Office of Pesticide Programs' Policy on The Determination of The Appropriate FQPA Safety Factor(s) For Use in The Tolerance-setting Process:

RESPONSE TO PUBLIC COMMENTS

OPP Docket OPP-00610

Office of Pesticide Programs
U.S. Environmental Protection Agency
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LIST OF ABBREVIATIONS

ADME	Absorption, Distribution, Metabolism, and Excretion
APA	Administrative Procedures Act
BMD	Benchmark Dose
ChEI	Cholinesterase Inhibition
CWS	Community Water Systems
CSFII	Continuing Surveys of Food Intakes by Individuals
DCI	Data Call-In
DNT	Developmental Neurotoxicity Test
Db UF	Database Uncertainty Factor
$ED_{05 \text{ or } 10}$	Effective Dose: central estimate on a dose associated with a 5% or a 10% response adjusted for background
FQPA	Food Quality Protection Act
FFDCA	Federal Food and Drug Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FEL	Frank Effect Level
LOAEL	Lowest-Observed-Adverse-Effect Level
MOE	Margin of Exposure
MOS	Margin of Safety
MRM	Multiresidue Method
NAFTA	North American Free Trade Agreement
NAPIAP	National Agricultural Pesticide Impact Assessment Program
NASS	National Agricultural Statistics Service
NASQAN	National Stream Quality Accounting Network
NAWQPA	National Water Quality Assessment Program
NFCS	Nationwide Food Consumption Survey
NHEXAS	National Human Exposure Assessment Survey
NOAEL	No-Observed-Adverse-Effect Level
OP	Organophosphorus Pesticides
PDP	Pesticide Data Program
PBPK	Physiologically Based Pharmacokinetics
PHED	Pesticide Handlers' Exposure Database
POD	Point of Departure
PND	Post Natal Day
PAD	Population Adjusted Dose
aPAD	Acute Population Adjusted Dose
cPAD	Chronic Population Adjusted Dose
RfC	Reference Concentration
RfD	Reference Dose
SHEDS	Stochastic Human Exposure Dose Stimulation Model

SRM	Single Residue Method
STORET	Storage and Retrieval Database
SF	Safety Factor
SOP	Standard Operating Procedure
UF	Uncertainty Factor
WOE	Weight-of-evidence

***Organizations**:*

AIHC	American Industrial Health Council
AWWA	American Water Works Association
CHPAC	Children's Health Protection Advisory Committee
CDC	Centers for Disease Control
CDPR	California Department of Pesticide Regulation
CMA	Chemical Manufacturers Association
FAO	Food and Agriculture Organization of the United Nations
HED	Health Effects Division, Office of Pesticide Programs, USEPA
HIARC	Hazard Identification Assessment Review Committee
HESI	ILSI's Health and Environmental Sciences Institute
ILSI	International Life Science Institute
ICCVAM	Interagency Coordinating Committee for the Validation of Alternative Methods
IWG	Industry Working Group
NAS	National Academy of Sciences
NCEA	USEPA's National Center Environmental Assessment
NHEERL	EPA's National Health and Environmental Effects Research Laboratory
NIEHS	National Institute of Environmental Health Sciences
NRC	National Research Council
NRDC	National Resource Defense Council
OCHP	EPA's Office of Children's Health Protection
OECD	Organization for Economic Cooperation and Development
OPP	EPA's Office of Pesticide Programs
OPPT	EPA's Office of Office of Pollution Prevention and Toxics
ORD	EPA's Office of Research and Development
OPPTS	EPA's Office of Prevention, Pesticides, and Toxic Substances
PMRA	Health Canada's Pesticide Management Regulatory Agency
SAP	Scientific Advisory Panel
USGS	U.S. Geological Survey

WHO World Health Organization

INTRODUCTION

The Food Quality Protection Act of 1996 (FQPA) significantly amended the Federal Food Drug and Cosmetic Act (FFDCA) under which EPA establishes "tolerances" (or maximum legal limits) for pesticide residues in food. In deciding to establish, modify, or leave a tolerance in effect, EPA must conclude that the tolerance is "safe." FFDCA sec. 408(b)(2)(A)(i). The term, "safe," means 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." FFDCA sec. 408(b)(2)(A)(ii). The FQPA amendments specifically directed EPA, in making the "reasonable certainty of no harm" determination to ensure that infants and children are adequately protected. FFDCA sec. 408(b)(2)(C)(ii)(I). The FQPA amendments also added the following:

> In the case of threshold effects, for purposes of clause [FFDCA sec. 408(b)(2)(C)] (ii)(I) an additional 10-fold 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 the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, 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.

FFDCA sec. 408(b)(2)(C). The provision quoted above is referred to as the "FQPA Safety Factor provision."

In March 1998, the U.S. Environmental Protection Agency (EPA) established an Agency-wide "10X Task Force" to address the implementation of the FQPA Safety Factor provision. Task Force members included high-level scientists primarily from the Office of Prevention, Pesticides and Toxic Substances, the Office of Research and Development, the Office of Solid Waste and Emergency Response, and the Office of Children's Health Protection. The 10X Task Force formed two working groups--the Toxicology Working Group and the Exposure Working Group. These groups each drafted a report containing recommendations for the implementation of the FQPA Safety Factor in their respective areas of review: *Toxicology Data Requirements for Assessing Risks of Pesticide Exposure to Children's Health* (US EPA 1999a) and *Exposure Data Requirements for Assessing Risks from Pesticide Exposure of Children* (USEPA 1999b).

The Office of Pesticide Programs (OPP) is responsible for implementing the requirements of FQPA in making its pesticide regulatory decisions. Accordingly, OPP developed interim guidance, which has been updated periodically since 1996, as to how it will comply with FQPA concerning the FQPA Safety Factor for protecting infants and children. In drafting the current guidance, OPP took into account the recommendations of the 10X Task Force as embodied in the above-mentioned documents. OPP's guidance consists of two revised documents: *The Office of Pesticide Programs' Policy on Determination of the Appropriate FQPA Safety Factor(s) for Use in the Tolerance-Setting Process;* draft version (USEPA 1999c) and *Standard Operating Procedures for the Health Effects Division FQPA Safety Factor Committee*; draft version (USEPA 1999d). The former paper explains the general policies that OPP proposed to follow in making determinations concerning the use of the FQPA Safety Factor, while the latter paper specified the detailed procedures that OPP would use in following these policies.

On July 8, 1999, the Agency published a Notice in the *Federal Register* announcing the availability of, and opportunity to comment on, the four documents relating to EPA's implementation of the FQPA Safety Factor provision (64 FR 37001). Copies of the documents made available for public comment also appear at: http://www.epa.gov/fedrgstr/EPA-PEST/1999/July/Day-08/p17315.htm. EPA subsequently extended the original 60-day comment period by 30 days to October 7, 1999 (64 FR 48617). EPA specifically invited the public to comment on sixteen questions, grouped into four broad categories:

General FQPA Safety Factor Issues

Question 1. The OPP guidance indicates that OPP will generally apply the FQPA Safety Factor only to food-use pesticides of "conventional" chemistry. Please comment on this approach. The guidance also indicates that different decisions about the need for, and size of, an additional FQPA Safety Factor may be appropriate for different durations of exposure and different exposed populations. Please comment on this approach. Finally, the guidance indicates that it would be appropriate to make only one FQPA Safety Factor decision for a single population/exposure period, even though such exposure might occur by different routes and pathways. Please comment on this approach.

Question 2. Is a weight-of-the-evidence approach to making FQPA Safety Factor decisions appropriate, taking into consideration the toxicology and exposure databases for a pesticide and the potential risks for the developing fetus, infant and child as well as other populations? If not, why not? Given the scope of the evidence which OPP intends to consider, are there any other types of information that OPP should consider in making its FQPA Safety Factor determinations?

Question 3. Do you agree with the view that the models and assumptions used by OPP in the risk assessment process, together with reliable data available on specific pesticides and other reliable, empirical data, typically do not understate risk? If not, under what circumstances do you believe OPP's current approaches to assessing risks from aggregate exposure to a single pesticide produce risk assessments that understate the risks to infants and children?

Question 4. Do you agree with OPP's view that the FQPA Safety Factor should be applied in addition to the interspecies and intraspecies uncertainty factors, but that the FQPA Safety Factor should not be applied in a manner that results in "double-counting" of uncertainties that are otherwise addressed in the toxicity and exposure assessments through, for example, the database uncertainty factor or conservative exposure models? If you disagree, why?

Toxicology Issues

Question 5. Please comment on OPP's proposed criteria for defining the core toxicology database.

Question 6. After having considered the recommendations from the FIFRA Scientific Advisory Panel and the Toxicology Working Group, OPP is beginning the process of calling in data for three studies (the acute and subchronic neurotoxicity studies in adult mammals and the developmental neurotoxicity study) for a subset of conventional chemistry food-use pesticides known neurotoxicants. In addition, OPP will be proposing to require the same set of studies for all conventional chemistry food-use pesticides in the revision of the 40 CFR 158 regulations. Please comment on this two-stage approach.

Question 7. The OPP policy guidance indicates that one of the critical issues is whether or not to apply an FQPA Safety Factor pending receipt of newly-required studies. There are a variety of possible approaches. One possible approach would be to apply the FQPA Safety Factor's database uncertainty component to gaps related to new core data requirements only where there are specific concerns regarding the pesticide pertaining to the data requirement. Alternatively, OPP could apply the default 10X factor (or some other additional factor) whenever a new data requirement is added and/or whenever a testing guideline is changed. Please explain how you think the FQPA Safety Factor provision should be implemented when OPP makes such changes. In commenting, please address whether OPP should apply the default FQPA 10X factor, some different yet additional factor, or no factor at all in the following circumstances:

- A minor change to testing guidelines.
- A major change to testing guidelines.
- An addition of a new required test.
- An addition of a new required test to core requirements.

Question 8. In the absence of the results from any of the studies to be required through Data Call-In (DCI) Notices (i.e., the acute and subchronic neurotoxicity studies in adult mammals and the developmental neurotoxicity study), what information from existing studies on a specific chemical would increase or decrease the concerns about the potential for prenatal and postnatal hazard, in general, and for neurotoxicity and developmental neurotoxicity, in particular? Which, if any, of the seven criteria discussed in Section V.A.1.a., footnote 4 and associated text of the OPP policy document is appropriate for judging whether there is increased concern about the potential for a pesticide to cause developmental neurotoxicity? Are there any other criteria which would be useful for informing this judgment?

Question 9. Please comment on whether you would expect that developmental neurotoxicity studies would, for a substantial number of chemicals, identify effects that are not detected in other studies and more fully characterize the potential risks of exposures during development. In addition, please comment on the sensitivity of these tests vis-a-vis other studies required and used for age-related comparisons for acute, intermediate, or chronic RfD derivation (e.g., prenatal developmental toxicity or multi-generation reproduction study, subchronic and chronic studies, etc.). Please explain the basis of your opinion.

Question 10. OPP's Guidance states that currently five studies (a multi-generation reproduction study, prenatal developmental toxicity studies in two species, and chronic toxicity studies in a rodent and non-rodent species) comprise the toxicity database necessary to produce a "high confidence RfD," and that some additional database uncertainty factor will be imposed if the database on a pesticide lacks one or more of these studies. OPP proposes to expand this core database to include the subchronic neurotoxicity study. Eventually, OPP also includes the acute neurotoxicity study in adult mammals and the developmental neurotoxicity study, once these studies have met the criteria for inclusion in the core toxicity database. Please comment on OPP's proposed approach to imposing a database uncertainty factor of 3X if one key study is missing from the database and a factor of 10X if more than one is missing.

Question 11. OPP is proposing to adopt the framework and its criteria/factors for assessing the degree of concern about the potential for prenatal and postnatal effects as recommended by the Toxicology Working Group. Please comment on the appropriateness of the proposed criteria/factors for use in this assessment process, and OPP's proposed approach for accommodating its concerns in the Reference Dose derivation and FQPA Safety Factor decision processes, in the near term, and in the longer term.

Question 12. When the hazard to infants and children is well-characterized, and the data show that infants and/or children are more susceptible than adults, under what circumstances, if any, should this information lead OPP to employ an additional Safety Factor?

Exposure Issues

Question 13. Subject to the qualifications expressed in the OPP policy document and the report from the Exposure Working Group, OPP believes that each of the Tiers for estimating exposure to a pesticide through food, in almost all instances, will not underestimate exposure to infants and children. Please comment on this conclusion, as it applies to each of the Tiers.

Question 14. OPP is developing a tiered approach to assessing the likelihood and magnitude of contamination of drinking water and its sources by a pesticide. As an interim approach, when direct assessment is not possible, is it reasonable and protective to regard the estimates generated by OPP's current screening methodology as upper bound pesticide concentrations for surface and ground water and to assume that this concentration generally will not be exceeded in drinking water?

Question 15. OPP is developing approaches to assess the likelihood and magnitude of exposure to pesticides in residential and other non-occupational use scenarios. When direct assessment is not possible, is it reasonable and protective to regard the estimates of exposure for the major residential and other non-occupational exposure use scenarios developed by OPP as upper bound estimates of the exposure received by infants and children from such use?

Question 16. In OPP's view, its aggregate exposure assessments generally do not underestimate the exposure to infants and children because the aggregate exposure is calculated by adding the high-end estimates of exposure to pesticides in food, to the high-end estimates of exposure to pesticides both in water and as a consequence of pesticide use in residential and similar settings. Please comment on this view.

Although EPA made four documents concerning the FQPA Safety Factor provision available for review and public comment, the Agency encouraged the public to focus particularly on the OPP Policy document. OPP also noted that, while it used the two papers produced by the Toxicology and Exposure Working Groups of the Agency's 10X Task Force in developing its guidance, the 10X Task Force was not planning to revise and reissue these documents following public comment. In addition, since the OPP Standard Operating Procedure was largely derived from the OPP guidance document, any changes in it following public comment should reflect changes in the revised guidance document.

OPP received about 825 public comments in response to the Notice of Availability. The comments came from a wide range of organizations and individuals interested in pesticide regulation including representatives of pesticide companies; organizations representing growers and other pesticide users; academicians and consultants; public health, environmental, animal welfare, and children's advocacy groups, as well as from foreign and state governments. The Agency also presented earlier drafts (which did not differ substantively from those that were made available for public comment) of the four documents for review by its FIFRA Scientific Advisory Panel (SAP), which also submitted comments (USEPA 1999l).

EPA has reviewed all of the comments and has grouped similar comments together. The remainder of this document contains EPA's summary of the comments and its responses to the comments. The comments are generally organized to follow the sixteen questions contained in the original Notice of Availability; the sequence of the questions has been changed to a slight degree to make the Agency's reasoning easier to understand.

COMMENTS AND RESPONSES

OPP received over 800 comments on this draft policy. These comments, along with a listing of each commentor and their affiliation, can be found at the FIFRA Docket which is located at: Crystal Mall #2, Room 119; 1921 Jefferson Davis Highway; Arlington, Virginia (http://www.epa.gov/pesticides/docket/).

I. General FQPA Safety Factor Issues

ISSUE 1. Applicability of FQPA Safety Factor to Conventional Chemistry Pesticides

The OPP guidance indicates that OPP will generally apply the FQPA Safety Factor only to food-use pesticides of "conventional" chemistry. Please comment on this approach.

Comment 1. A number of commentors (369, 761, 771, 773 and 776) questioned the proposal that the FQPA Safety Factor would generally apply only to food-use pesticides of "conventional" chemistry, apparently, in some cases, interpreting the proposal to say that *only* this category of substance would be covered and offering the opinion that this was too narrow a designation.

Response. EPA, in proposing that the need for making an FQPA Safety Factor decision would generally apply to food-use pesticides of *conventional chemistry*, meant those pesticides having a defined chemical structure. For the purpose of FQPA and the scope of the 10X policy, the term "pesticide" covers both active and other (i.e., inert) ingredients. The Agency had proposed that it would be possible to make an FQPA Safety Factor decision only in those cases where the required and necessary toxicology database would be sufficiently robust to allow or support the derivation of a hazard value, such as an acute or chronic reference dose (RfD), arguing that without such a hazard value, it would be inappropriate to conduct a quantitative safety factor analysis (i.e., determination to retain, remove, reduce, or increase the 10X FQPA Factor).

It was not the Agency's intention to constrain the FQPA Safety Factor decision process only to pesticides of "conventional chemistry," meaning only those with a defined chemical structure. At the time, OPP did believe, however, that the toxicity database for such chemicals would best lend themselves to *quantitative* FQPA Safety Factor decisions. Upon further reflection, and with additional experience, the Agency has realized that it, in fact, can and should (and, has) made FQPA Safety Factor decisions for a much broader range of

pesticides (both active ingredients and others). A sizeable proportion of these decisions will be only "qualitative" in nature (i.e., an evaluation of available information to determine the hazard concern for the young); others would be "quantitative," in that RfD or RfC values would be derived, then modified upward, downward or left unchanged, depending upon the nature and fullness of the available information.

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 (about 450 in number) and others, belong to many chemical classes. Some are mixtures. Some pesticides are registered both as an active and as an inert ingredient, albeit probably in different formulations (e.g., phenol and formaldehyde). Others are either whole foods or naturally-occurring constituents of food (e.g., soybean oil, ethylene and l-glutamic acid) or are food additives (e.g., oil of orange). Examples of classes more traditionally thought of as pesticide active ingredients are the organophosphorus and pyrethroid insecticides, the triazine herbicides, and the conazole fungicides. There also are several classes of biopesticide active ingredients (e.g., biochemicals such as formic acid; pheromones; plant growth regulators; natural insect growth regulators; and microbial pesticides such as bacteria and fungi). Most of the roughly 2500 other ingredients are divided up into four lists, categorized primarily by known or expected toxicity potential (List 1 having the potential for being the most hazardous and List 4 being the least, with List 3 substances being largely undefined as to their hazard potential). Tolerance exemptions have been granted for many actives and most inerts.

The chemical characteristics and anticipated toxicity potential of the pesticide (along with the proposed use pattern) dictate the kinds of toxicity data that would be needed to characterize its hazard profile. For those categories of food-use pesticides for which only a minimum toxicity database is deemed necessary, a "reasonable certainty [of] no harm" and the FQPA Safety Factor finding would be accomplished only in the qualitative sense, particularly for those for which an exemption from a tolerance would be granted. 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 protectants, microbial and some other biopesticides, as well as many inert ingredients.

Comment 2. One commentor (369) did not feel it is appropriate to limit the risk assessment policies outlined in the policy only to food-use pesticides, stating that they felt it is inappropriate to set two different sets of safety standards for the protection of children–one for food use pesticides and one for nonfood-use pesticides. They also believed that the same considerations should be applied to indirect exposures of fetuses and infants which may occur via pregnant or nursing women who may be occupationally exposed to either food-use or nonfood-use pesticides.

Response. The 1996 amendments to FFDCA (the tolerance-setting provisions) 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, under FFDCA section 408, the 10X Safety Factor provision is only applicable to those pesticide uses that need tolerances. Under FIFRA, the FFDCA section 408 safety standard, including the 10X Safety Factor provision, is only applicable to pesticide uses posing a dietary risk due to residue in or on food. Pesticides having only nonfood uses are not subject to these provisions. In addition, the FFDCA provisions state that, in assessing the aggregate exposure to the pesticide residue, aggregate exposure is considered to include dietary sources and other *nonoccupational* sources. The assessment of the risk that may accrue from occupational exposures should be conducted separately, under the provisions of FIFRA. The applicable FIFRA standard is that the use must not cause “any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use...”

Comment 3. Commentor 781 disagreed with the exclusion of consideration of exposures to fetuses of pregnant farmworkers in the risk assessment process for tolerance-setting. Exposures to these unborn children are not "occupational" and, hence, must be considered in determining the applicability of the 10X safety factor. Congress expressed concern for all children's pre- and postnatal development, without excluding any prenatal exposure which may have occurred in the course of a parent's employment. Indeed, section 408(b)(2)(C) of the Act makes no mention of excluding occupational exposures. Since Congress expressly excluded occupational exposures in other provisions, the absence of any "occupational" exclusions here should be regarded as dispositive of Congress' intent to fully protect all children.

Response. EPA believes that, for the purpose of implementation of the FQPA statutory language as it pertains to tolerance-setting, any exposures to the fetus or the child that result from its parent's employment are occupational exposures. To adopt the interpretation suggested by the Farmworker Justice Fund would essentially read the explicit limitation on considering occupational exposure out of the statute. Further, the limitation in section 408(b)(2)(D)(vi) regarding occupational exposures does apply to assessing children's risk to pesticides under tolerances because section 408(b)(2)(D)(vi) explicitly applies to all tolerance actions under the FFDCA.

Comment 4. Commentor 778 argued that FQPA mandates that EPA consider identifiable, highly exposed/sensitive subpopulations in making its statutory determinations. The commentor believes that farm children should be designated as such a subpopulation, and their exposures and risks should be separately evaluated under FQPA. Citing a 1998 NRDC petition and report "Trouble on the Farm," the commentor noted that the subgroup includes 320,000 children under the age of six, and hundreds of thousands of children who play or attend schools on or near agricultural land or have family members who work on farms. There are approximately one million children of adult farmworkers living in the United States. These children are exposed in ways other children generally are not and their exposures are higher than other children. Recognition of the unique exposures and risks of farm children is also consistent with environmental justice concerns for minorities and low income groups.

Response. By definition, there are subpopulations which may be more highly exposed or more sensitive to the effects of exposure than the average. Farm worker/farm family children may fall into this category by meeting one or both criteria. While EPA has not formally designated this group as a special category, it has been working to better understand the nature and magnitude of exposures that this group experiences, and, where data show differences, EPA will incorporate such information into chemical-specific aggregate exposure and risk assessments, as appropriate. This consideration would extend to cumulative risk assessment, should the chemical(s) under evaluation be deemed to share a common mechanism of toxicity. Overall, however, OPP believes that its exposure and risk assessment methodologies are conservative, i.e., do not generally underestimate exposure, for this subgroup. See also responses to Issue 16 under Comments 5 and 7.

The guidance also indicates that different decisions about the need for, and size of, an additional FQPA Safety Factor may be appropriate for different durations of exposure and different exposed populations. Please comment on this approach.

Comment 1. Two commentors (773 and 369) expressed support for the policy of determining the need for, and size, of the FQPA Safety Factor for different durations of exposure and different exposed subpopulations.

Response. These commentors agreed with the Agency approach and the Agency continues to believe that this approach is appropriate and necessary.

Finally, the guidance indicates that it would be appropriate to make only one FQPA Safety Factor decision for a single population/exposure period, even though such exposure might occur by different routes and pathways. Please comment on this approach.

Comment 1. Both commentors on this question (773 and 369) disagreed with the Agency's proposal of making only one FQPA Safety Factor decision for each population/exposure period combination. Both noted that there may be different endpoints of toxicity and differing qualities of the toxicity and exposure databases for the three possible routes of (aggregate) exposure (oral, dermal, and inhalation). They argued that, in light of these possibilities, it may be necessary (and, more appropriate) to make a different decision regarding the need for/size of the FQPA safety factor, on a route-specific, not an aggregate, basis.

Response. The Agency has identified three major subpopulations (i.e., infants, children, and women of child bearing age) that may require FQPA Safety Factor decisions. These three subpopulations were characterized, in part, because it was expected that different endpoints of toxicity might be of importance to each of these groups. Thus, tailored decisions for these subpopulations with regard to the nature and quality of the toxicity database and with regard to these specific endpoints would be addressed in the FQPA Safety Factor decision process.

The Agency disagrees with the commentors on how to handle the exposure questions. The Agency has interpreted as its mandate to the conduct of exposure assessment *in the aggregate* and, therefore, also to judge the nature and quality of the exposure database *in the aggregate*. Furthermore, it is indicated in OPP's guidance document on aggregate exposure risk assessment (USEPA 2001b) that only similar toxicological effects found for

different routes of exposure will be combined or aggregated. If the process is conducted properly, the decision outcome should be the same as if one were to make separate findings on a route-specific basis and then integrate these separate findings into an overall finding or on an aggregate basis from the beginning. In either case, if a deficiency were to be identified for one or more route/pathway, it should be highlighted and both a qualitative and quantitative judgment made as to the impact of this deficiency on the exposure assessment as a whole.

This particular discussion of decision-making in risk assessment brings to light how very important it is to develop a clearly-articulated, transparent risk characterization that includes a thorough description of the decision logic used to reach a conclusion, not simply a set of numbers which lack a context for their development.

ISSUE 2. Weight-of-Evidence Approach

Is a weight-of-the-evidence approach to making FQPA Safety Factor decisions appropriate, taking into consideration the toxicology and exposure databases for a pesticide and the potential risks for the developing fetus, infant and child as well as other populations? If not, why not?

Comment 1. Five commentors agreed that a weight-of-evidence (WOE) approach was appropriate in making FQPA Safety Factor decisions, but recommended that the Agency provide additional clarification and guidance regarding this concept and its application (L015, 369, 372, 773, 775). One of these commentors (L015) recommended that examples be provided to demonstrate how the toxicity and exposure information can be integrated in arriving at the safety factor decision for a pesticide. Additionally, the SAP supported a weight-of-evidence approach, since experience has shown the WOE approach to be especially useful when addressing complex issues such as those involved in this determination. They indicated that the full range of data and evidence should be considered in making safety factor decisions. The Panel did, however, express the need for definition of the term "weight-of-evidence" and for more clearly defined descriptions of the conditions of uncertainty that might lead to the application of safety factors of different magnitudes. Two commentors did not believe that a weight-of-evidence approach adequately satisfies the statutory language of FQPA (761/771, 778).

Response. EPA continues to believe that a weight-of-evidence approach is the most appropriate approach in determining the need for an FQPA Safety Factor.

The weight-of-evidence approach to data evaluation is a general scientific concept that promotes an integrative approach rather than item-by-item consideration of all information pertinent to the question or issue being addressed. It involves an assessment of the quality, adequacy, and consistency of the data and an integration of the scientific data and conclusions, with combined input from all relevant disciplines. The weight-of-evidence approach recognizes that initial views of one kind of evidence may change significantly when other information is brought into the interpretation. A key element of a weight-of-evidence approach is that no single piece of information determines the overall conclusion since all data are judged in combination.

The application of a weight-of-evidence approach is described in various Agency documents that address the evaluation of linear and nonlinear toxicity data that are used in assessing risk from chemical exposure. For example, an online Integrated Risk Information System (IRIS) document (USEPA 1999m) addresses the Reference Dose (RfD). A subsection (1.3.1.2 Weight-of-Evidence Determination) states that WOE is the culmination of the hazard identification step, and that it "summarizes the highlights of the information gleaned from the principle and supportive studies...to determine the extent to which a consistent, plausible picture of toxicity emerges." Similarly, the Agency's draft Guidelines for Carcinogenicity Risk Assessment contains a chapter (2.6 Weight-of-Evidence Evaluation for Potential Human Carcinogenicity), which defines a WOE evaluation as "a collective evaluation of all pertinent information so that the full impact of biological plausibility and coherence is adequately considered" (US EPA 1999f). The IRIS background document further provides a list of factors which could add to the weight-of-evidence that the chemical poses a hazard to humans, while the draft cancer guideline provides separate lists of factors (for human data, animal data, and other data, as well as for the weight-of-the-totality-of-evidence) that can be used to increase or decrease the weight. An example of the application of a weight-of-evidence approach as it relates to a specific body of data can be found in the OPP policy entitled *The Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides* (US EPA 2000a).

These background documents are useful as references that aid in the general understanding of a weight-of-evidence approach to data evaluation. However, none of these documents provides guidance that is directly applicable to the WOE approach used in determining the FQPA Safety Factor(s). This is because the FQPA-related weight-of-evidence approach includes consideration not only of toxicity data, but of all the information on both hazard and exposure in combination, to arrive at an integrated conclusion. This analysis involves close scrutiny of all available data, the study results, and data interpretation; it also incorporates carefully considered judgements regarding the completeness and adequacy of the databases as well as the quality and reliability of the data.

It is not possible to define every combination and permutation of toxicity and exposure information that might be evaluated in the course of reaching conclusions regarding the need for the FQPA Safety Factor. However, the revised *Standard Operating Procedures for the Health Effects Division FQPA Safety Factor Committee* (USEPA 1999d*)* will be used by OPP as a companion tool in the implementation of the WOE assessment. This document will provide guidance in the form of a list of questions which address in great detail the completeness of both the exposure and hazard information and any evidence of increased risks to infants and children. Illustrative examples appear in the SOP in order to provide further guidance regarding the manner in which the toxicity and exposure information can be integrated in arriving at the safety factor decision for a pesticide.

In determining the FQPA Safety Factor, the weight-of-evidence, the level of confidence, and residual uncertainties are used in interpreting the data that Agency scientists have already assessed to be reliable (or, not, as the case may be) and useful in the risk assessment. Given the complexity of this process, however, EPA agrees with the commentors that the decision process would benefit from the inclusion of examples and therefore is adding such material to the SOP document. EPA believes that the WOE approach, as described, is consistent with the language and intent of FQPA.

Comment 2. One commentor (775) suggested that EPA's criteria for determining whether sufficient information exists for determining whether the FQPA factor should be applied "indicate a move towards a checklist approach," notwithstanding the expressed intent to use a WOE approach.

Response. The Agency reiterates its intent to use a weight-of-evidence approach to its decisions about the FQPA Safety Factor. OPP does not provide a prescriptive list or a "checklist" of criteria but rather the revised guidance document generally describes factors and types of data that should be

considered in a weight-of-evidence analysis for evaluating the adequacy of information in characterizing risks to infants and children in order to guide the risk assessor in addressing a variety of different situations that might be encountered.

FIFRA Scientific Advisory Panel Comments

Comment 3. The SAP provided some assertions regarding the legal and policy aspects of the use of the FQPA 10X factor, defining the 10X factor as a comfort or policy factor, with minimal scientific basis.

Response. EPA does not agree with the assertion that there is minimal scientific basis to the determination of the FQPA factor. The revised guidance document clearly describes a process which is extensively informed by the science, including the weight-of-evidence assessment of the toxicity and exposure data for the pesticide under review. EPA considers statements by the SAP that purport to interpret the meaning of statutory provisions to be beyond the SAP's expertise.

Comment 4. The SAP recommended that the Agency consider published peer reviewed reports in the "open" literature in the weight-of-evidence assessment, and stated that a transparent characterization and usage of database uncertainty factors is needed when data of these types are taken into account in the risk assessment process. The Panel suggested that an SOP be developed for assessing available peer-reviewed literature reports of toxicity studies that fall outside currently required toxicology data sets. Additionally, it was recommended that the SOP might address the acquisition, evaluation, and weighting of peer-reviewed animals studies in the literature, as well as for human epidemiological data concerning the potential for health effects to occur following inadvertent/incidental chemical exposure.

Response. Current OPP practice includes the evaluation of information from the peer-reviewed literature, when appropriate and available, and this information is considered in the FQPA Safety Factor determination. The revised SOP will include a question regarding this topic, and OPP expects that the peer-reviewed literature will be searched and reviewed for pertinent information on toxicity and exposure (including human data, which might consist of case studies following accidental exposures and/or epidemiological studies) as standard practice in the development of a risk assessment. However, OPP recognizes that there is a lack of formalized procedures and process regarding this issue. As with any study, the quality of data should be taken into account.

An SOP is currently being developed in HED to address the use of peer reviewed literature in pesticide risk assessment, and the recommendations from the Panel will be helpful.

Comment 5. The SAP stated that OPP's decision logic is ambiguous, and that it is impossible to understand the relation between available evidence, its interpretation by experts, and the choice of a specific FQPA Safety Factor. It was suggested that the decision logic should flow from answers to a series of questions, two examples of which were provided by the Panel. In the first example, the questions related to the availability of specific toxicity and exposure data; in the second example, the questions related to what data or conservative default assumptions would be needed to "relieve the 10X safety factor."

The Panel concluded that the Agency should define assumptions that it will adopt and apply in the absence of perfect information, recommending that the Agency should approach the problem in the following sequence:

- Judgment regarding data sufficiency and quality.
- Judgment regarding application of conservative assumptions.
- Judgment regarding application of additional safety factor.

If the Agency concludes that data are insufficient or of poor quality, it has two options: (a) apply conservative default assumptions to estimate risk, or (b) do not apply conservative assumptions, but instead apply an additional safety factor.

The Panel recommended that relationships between any assumptions applied to uncertain information and the choice of specific safety factors should be explored more fully in case studies that explore the most difficult regulatory situations, e.g., where there must be a choice regarding the management of a pesticide that is registered for release to diverse environmental media, and for pesticides that act via a common mechanism with other chemicals. These examples would need to fully identify different sources of uncertainty, and then openly consider how its assumptions account for this uncertainty. The relations between uncertainty, default assumptions, and the choice of safety factors should be described.

Response. The revised SOP, which will be used as a tool in the process of determining the FQPA Safety Factor for each individual chemical being reviewed, will contain a series of questions regarding the nature and robustness of the available toxicity and exposure data. These questions are being carefully crafted to address, as completely as possible, all aspects of the information that could potentially contribute to the derivation of the FQPA Safety Factor(s) for that pesticide. EPA believes that this SOP will be more extensive than the examples provided by the Panel, and that a change in approach to this aspect

of the decision logic is not warranted.

The recommended approach to the problem of lack of sufficient information on a chemical, and the logic sequence that the Panel provided, is consistent with the approach OPP currently utilizes. The SOP will be expanded to include basic examples to illustrate the decision logic used in the determination of the FQPA Safety Factor. Every attempt was made to incorporate the information recommended by the Panel; nevertheless it is noted that most of the detailed logic that supports the default assumptions used to address recognized sources of uncertainty are extensively addressed as generic issues in other peer-reviewed OPP policy papers and documents, such as the residential exposure SOPs (USEPA 1999g), the common mechanism of toxicity guidance (USEPA 1999h), the aggregate (USEPA 2001b) and the cumulative risk assessment guidance (USEPA 2002) documents. As a matter of practice in OPP, individual chemical FQPA Safety Factor assessment documents make reference to these.

Comment 6. The Panel encouraged the Agency to formally revisit and review the core toxicology database every few years to ascertain if it is adequate, inadequate, or contains redundant or useless requirements. The Agency was also encouraged to examine its testing guidelines and where possible attempt to combine protocols to save animal and financial resources. The Panel recognized that the Agency has plans in this regard but wanted to further encourage and emphasize the need for this action.

Response. OPP is moving forward with efforts that are addressing these issues. Proposed revisions to 40 CFR 158, which includes the list of studies included in the core toxicology database, are being developed; a draft of Subpart W, which is a revised set of data requirements proposed specifically for antimicrobial pesticides, is soon to be released for comment. It should be noted that the Agency encourages the use of combined protocols for testing. While this approach is useful for first pass testing, it is more difficult to attain in the case of follow-up testing of reregistration/registration renewal. Thus, there also remains a need for stand-alone protocols to accommodate these situations. The Agency is, however, facilitating discussions (e.g., relative to development of the Endocrine Disruptor Screening Program) that will result in enhancement of endpoints in the current guideline studies, and, thus, more efficient utilization of animals on test.

Comment 7. Several members of the Panel expressed the opinion that improved

methods of neurotoxicity testing and validation of the assumptions regarding children's exposure would ultimately make the weight-of-evidence approach a stronger tool for risk assessment purposes. However, the Panel was concerned that, at present, too many gaps in the available databases exist in order to be confident in decisions made under this approach. Examples were provided of gaps in the knowledge regarding exposure and toxicity information applicable to children.

Response. OPP agrees with the Panel that, in some cases, there are gaps in the understanding of both the toxicity of a pesticide to children or the exposure of children to a pesticide. The Agency also agrees that additional data to evaluate potential toxicity and exposure could be valuable. (Obviously, as science and policy discussions advance, they will be incorporated into the process, as appropriate.) The significance of the data gaps, however, will vary from chemical to chemical and will depend, among other things, on the assumptions that OPP makes in the absence of data. Thus, OPP believes that its level of confidence in its decisions should take into account the full range of information available about each chemical. The Agency does not agree with a general assertion that the extent of its understanding of the risks of pesticides to children is so limited that it lacks any confidence in its decisions.

Comment 8. The Panel provided comment on three specific issues that could influence the weight-of-evidence analysis and FQPA Safety Factor determination:

First, the Panel expressed the opinion that the discussion of dose-response slopes and their use in the interpretation of concern for the effects that may be seen at lower doses, while statistically simple, is aimed in the right direction and suggests improved methods of analysis for noncancer endpoints. However, they also stated that the methods proposed provide only very limited evaluation of one very conservative issue, the assumption that noncancer endpoints have thresholds. Statistical methods exist for the evaluation of the shapes of dose-response curves that can provide objective information that would be useful in evaluating this hypothesis. While one can never get a definitive answer of whether a threshold exists or not, one can estimate the appropriate concern for the possible lack of a threshold. By applying methods which directly evaluate shape, this assumption can be strengthened (less need for the 10X factor) or weakened (suggesting possible need for the 10X factor).

Second, the Panel reminded OPP that NOAELs are not zero risk points; they are points at which there is greater than a 5% chance that the control and associated exposure group arise from the same distribution, and it is expected that there is still some risk at the NOAEL. The Panel felt that it is important to take this

issue into account when evaluating the need for the 10X safety factor. An example provided by the Panel: a NOAEL for which the possible risk (e.g., upper 95% limit) is 30% of the animals affected should have a very different bearing on the use of 10X safety factor than a NOAEL for which the possible risk is 1%. Therefore, failure to consider this issue in the evaluation could lead to substantial risks at doses considered safe, an anticonservative risk assessment and the failure to adequately protect the public when actions are based on such an assessment.

Third, the Panel commented on the dose-response nature of the data and the relative potency of response. They indicated that there is some confusion as to what kinds of data support the use of the 10X safety factor. For example, studies providing a strong dose-response relationship (increasing severity with increasing dose) creates greater concern for removal of the 10X safety factor. Yet, these studies generally provide the strongest information for clear identification of a low-risk exposure level and decrease the uncertainty in this estimate. Where dose-response data are inconsistent, only available for insensitive endpoints, or from studies of low statistical power, uncertainty is large and there is the possibility of unacceptable residual risk remaining after the application of the standard factors. Thus, the application of inconclusive dose-response information to 10X safety factor decisions is unclear.

Response. EPA agrees that the shape of the dose response curve, the characterization of the NOAEL, the dose-response nature of the data, and the relative potency of response are pertinent factors in the determination of the FQPA Safety Factor. These issues are relevant to the discussion on the weight-of-evidence approach for making judgments about the degree of concern for potential pre- and postnatal toxicity in humans (as summarized in the revised guidance document). The discussion on the dose response nature of experimental animal data has been expanded to address the Panel's concerns. The key lines of evidence or criteria considered in determining the degree of concern for potential pre- and postnatal toxicity are outlined and situations that could raise or lower a concern for the young are discussed.

Comment 9. The Panel stated that the analysis of the information used to support the addition of tests to the core list of studies for Tier 1 was incomplete, and went on to say that a careful analysis focusing not on NOAELs but on correlations of response patterns and magnitudes using more appropriate statistical tools would provide a clearer interpretation and provide greater scientific support for any eventual policy choice. Failure to do this analysis could leave serious gaps in the database which could lead to improper application of the 10X factor. In addition, because a NOAEL must be one of the administered doses, it is not clear that evaluations of whether certain studies lead to lower NOAELs can be properly

interpreted as providing more sensitive study endpoints. A more appropriate analysis would use a standardized measure of risk, such as the ED_{05} or ED_{10} and the bounds on this estimate.

Response. It is assumed that this comment is referring to the information derived from the *A Retrospective Analysis of Twelve Developmental Neurotoxicity Studies Submitted to the USEPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS)* (USEPA 1998c) and the role that the findings from this analysis had in the conclusion to consider redefinition of the core toxicity database. OPP recognizes the limitations in using study NOAELs to analyze the sensitivity of the endpoints; this issue was raised in the paper and during the HED presentation to the SAP in December 1998. However, the findings from this analysis alone did not form the basis of the proposal to move the neurotoxicity studies from the second to the first Tier of testing. (A more detailed discussion of this topic is included in the response to comments on Question 6 below.) Nevertheless, OPP agrees that the Panel's comments on appropriate data analysis have merit and will be considered when conducting future evaluation of more recently submitted DNT study data.

Given the scope of the evidence which OPP intends to consider, are there any other types of information that OPP should consider in making its FQPA Safety Factor determinations?

Comment 1. One commentor (776) raised a concern that studies in juvenile animals do not represent the action of pesticides on early-developing systems, such as neuronal migration and differentiation in the pre- and perinatal period of development.

Response. This comment may reflect a misunderstanding on why studies in adult animals are included in the core data set, as well as more traditional developmental studies. In the OPP guidance document, the childhood exposure period is defined as extending from preconception through adolescence (up to 18 to 21 years of age). Adult studies provide relevant information for this broad childhood age range, when organs may be fully formed, yet functionally immature. They also provide information on potential target organs that could then be further evaluated in the reproduction or other developmental studies (e.g., developmental immunotoxicity, developmental carcinogenesis, or endocrine toxicity studies). EPA may also compare the results from studies with adult animals to the effects observed in studies involving exposures to animals earlier in the developmental process. However, the adult studies were never intended to be used to substitute for studies with prenatal and/or early postnatal

exposures. OPP believes that a database that includes quality prenatal developmental, multigeneration reproductive, and adult neurotoxicity studies are important for an evaluation of potential risks to children. Additionally, the potential for effects on the developing nervous system should also be considered. Thus, 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 developmental neurotoxicity testing, which utilizes information about each chemical and its toxicity to develop a rational, science-based approach to the study design and testing strategy.

Comment 2. One commentor (773) recommended that, in the determination of the need for the FQPA Safety Factor, OPP "should be aware of the large body of data which led the 1993 NAS report to conclude that the existing 10X intraspecies uncertainty factor is generally adequate to protect infants and children."

Response. The1993 NAS study on *Pesticides in the Diets of Infants and Children* concluded that "quantitative differences in toxicity between children and adults are usually less than a factor of approximately 10-fold" (p. 3) and yet went on to recommend that an additional 10-fold uncertainty factor be applied to the risk assessment if animal studies demonstrated evidence of developmental toxicity, including postnatally (p. 9) (NRC 1993). Regardless of the content and apparent inconsistencies in the NAS report, OPP is staying abreast of ongoing research on age-related differences in response to toxicants. Pertinent data that were available at the time that the draft policy document was written are summarized in the 10X Task Force Toxicology Working Group report (US EPA 1999a). Since that time, a number of additional studies have been conducted, almost exclusively with pharmaceuticals. Unfortunately, the studies conducted to date do not fully resolve this issue, but do generally support the conclusion that any quantitative differences that may exist between the young and healthy adults are usually within an order of magnitude.

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Comment 3. The SAP noted that there are likely to be other types of data that will have to be considered that may improve the process within the next decade. Distinctions between particular types of toxicity data may become blurred. Eventually, due to the increased use of molecular biology in Tier 1 screening tests, such tools are likely to better predict toxicological responses in the future.

Response. The Agency acknowledges the promise of molecular based approaches (e.g., genomics, proteomics, bioinformatics, animal transgenic models) and the expanding role of mechanistic information in improving the ability to project human health risks for environmental agents. There is emphasis in the Agency's risk assessment approaches for such mechanistic information (e.g., the EPA's draft revisions for *Guidelines for Carcinogen Risk Assessment* (USEPA 1999f); and OPP's *Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity* (USEPA 1999h)). Although there is increasing effort to develop the use of gene profiles to predict adverse responses, the SAP rightly acknowledges that this technology is at an early stage of development for use in standard toxicology testing. The National Institute of Environmental Health Sciences has established a National Center for Toxicogenomics to help advance this technology. OPP is committed to keep abreast of new technologies and will follow the progress of molecular approaches and will incorporate them into our testing and risk assessment process as appropriate.

Comment 4. The SAP indicated that OPP should routinely obtain more (specific) information on a given toxicity finding by triggering other more definitive studies.

Response. OPP agrees that, in some circumstances, requiring more definitive studies on various toxicity findings may aid the regulatory process. Such triggered studies should include scientifically-sound methods and should be designed such that they could potentially provide key information relevant to the risk assessment of the pesticide under review. Historically, OPP has required the submission of such information on a case-by-case basis.

ISSUE 3. Overall Conservatism of OPP Risk Assessment Methodology

Do you agree with the view that the models and assumptions used by OPP in the risk assessment process, together with reliable data available on specific pesticides and other reliable, empirical data, typically do not understate risk? If not, under what circumstances do you believe OPP's current approaches to assessing risks from aggregate exposure to a single pesticide produce risk assessments that understate the risks to infants and children?

Comment 1. Citing a number of specific deficiencies, three commentors (761, 771,776 and L21) argued that, overall, OPP's risk assessment methods were generally inadequate. The commentors argued that: (1) the 1993 National Academy of Sciences study, *Pesticides in the Diets of Infants and Children*, found the Agency's historical practices deficient; (2) the public literature contains many examples of biological variability that exceed the size of the uncertainty factors historically used by EPA (10X interspecies and 10X intraspecies uncertainty factors); (3) OPP lacks data on the magnitude of critical exposures, such as inhalation of airborne indoor use pesticides and skin absorption of skin- applied insect repellents; (4) OPP ignores information showing that children consume significantly more drinking water for their size than adults; and (5) OPP does not consider the potential for pesticides to bioconcentrate in milk. In light of these flaws, the commentors argued that OPP should retain the FQPA Safety Factor in all circumstances; one of these commentors further asserted that when the FQPA 10X Safety Factor is retained, the Agency's risk assessments are adequately health protective for all identifiable populations.

The Scientific Advisory Panel noted there may be data on pharmaceuticals indicating variability in children, and between children and adults, that would aid in determining whether or not the uncertainty factors adequately account for variability in the general population.

Response. The 1993 NAS Study criticized a number of aspects of the risk assessment methods that OPP was using in the late 1980's, and suggested improvements. OPP has extensively revised and strengthened its scientific approaches to assessing pesticide risks, and thus, considers the conclusions of the NAS no longer to be completely applicable. For example, OPP now routinely evaluates the distribution of exposure to pesticide residues in food through the use of probabilistic models that take advantage of updated food consumption data and a vastly expanded pesticide residue database. OPP has also developed new approaches to estimating the levels of pesticide in surface and ground water that may be used for drinking water and incorporates any age-

related differences that may exist with respect to drinking water intake. OPP has improved its capability of estimating the exposure resulting from pesticide use in and around residences and similar sites. OPP has also made enormous strides in developing both its aggregate risk assessment and cumulative risk assessment methodologies. Further, OPP is obtaining a large body of additional data, particularly concerning residential pesticide use, that will improve its residential risk assessments. While there is always room for future improvement, OPP believes that its current methods are generally conservative.

OPP does not agree with the assertion that the traditional "10X intraspecies uncertainty factor" is generally not sufficient to protect infants and children, who may or may not be more sensitive than healthy adults to the adverse effects of a pesticide. The available information in the scientific literature seems to support the opposite view.

The 1993 NAS Report, for example, contains a variety of conclusions concerning whether the 10X intraspecies uncertainty factor generally accounts for the observed variability in sensitivity of children to the toxic effects of a pesticide. In the chapter discussing perinatal and pediatric toxicity, the NAS committee concluded:

> Differences in toxicity between young, and mature animals may be in either direction but are generally modest. The younger animal may be more sensitive or may be less sensitive than the older animal to comparable levels of exposure of toxic agents. The direction of these differences appears to be compound specific as well as age specific because toxicity may not vary linearly with age. In those instances where such measures as LD_{50}s are significantly different, the differences are usually less than one order of magnitude and often substantially less (pp.105-106).

However, the NAS also stated in its discussion of uncertainty factors:

> The other 10-fold *intra*species uncertainty factor is meant to cover variations within human populations, including genetic predisposition, poor nutrition, disease status and age (Babich and Davis 1981). A factor of 10 for intraspecies variation in susceptibility may be sufficient for any one element of interpersonal difference but may not be sufficient for multiple elements (p. 326, emphasis in the original).

On the whole, OPP interprets these and other similar statements in the NAS Report as meaning that for most chemicals, the very large majority of people, including children, respond similarly, and that the traditional 10-fold intraspecies uncertainty factor is sufficient to cover the variability 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 report of the Toxicology Working Group of the 10X Task Force supports a similar conclusion. That report included an extensive discussion of the literature on the general adequacy of the 10X intraspecies uncertainty factor. The available data from the literature on variability includes data primarily on pharmaceuticals. Various authors evaluated the *intra*species uncertainty factor using data from animal or human studies, as summarized by Dourson et al. (1996). The report noted that most assessments looking at a large number of chemical compounds had concluded that the traditional 10X factor appeared to "cover" 90% or more of observed human variability.

The report of the Toxicology Working Group, however, also pointed out that these assessments generally lacked information on the variation in sensitivity of children, compared to adults. The limited literature specifically comparing the sensitivity of children and adults seemed less conclusive, but suggested that variability between children and adults may be somewhat greater than variability among adults alone. For example, Renwick and Lazarus (1998) evaluated variability in response in children and adults, and indicated that, generally, infants and children do not represent a special subgroup from a kinetic point of view as young children frequently eliminate drugs and other chemical agents more readily than adults. They also showed, however, that marked differences in kinetic parameters for some agents, for example, as much as a five-fold reduction in clearance rates of theophylline in preterm infants versus adults, might result in a number of children not being covered by half the 10-fold factor that accounts for kinetic variability. Given that such differences between children and adults (or children of various ages) may exist because of differences in metabolic capacity or developmental stage of specific organ systems, these authors suggested that the focus should be on delineating the differences in sensitivity of developing organisms and on the variability in sensitivity compared with adults, as well as differences in the sources and extent of exposure. Renwick (1998) further evaluated the similarities and differences between children and adults as well as between young and adult animal models and humans, and reviewed comparative data on toxicokinetics. He suggested that the 10-fold inter- and intraspecies factors may be sufficient if developmental toxicity data are available. Because children tend to have a higher clearance rate for many xenobiotics compared with adults, this may compensate to some

extent for the potential increased sensitivity of the young during development.

The report of the Toxicology Working Group urged further research on the general issue and cautioned strongly against making decisions to reduce the 10X intraspecies uncertainty factor unless there is a robust understanding of the potential toxicity of the substance to the young, as well as adults. The Agency is closely following the research being done on this topic and is providing funds for several projects that address the issue of human variability. As additional information becomes available on this topic, we will consider it so that OPP will be better able to characterize the similarities and differences between children and adults and determine the adequacy of the intraspecies uncertainty factor for protecting children.

OPP notes that variability in a discrete biological function or process does not necessarily or even presumptively translate into equivalent variability in sensitivity to the toxic effects of a chemical. Because the occurrence of a toxic effect in humans is often a complex process that involves a number of pharmacokinetic steps as well as pharmacodynamics, human systems may attenuate the effects of the chemical in a variety of ways, thus narrowing the overall variability of human sensitivity. In other words, a chemical may affect people differently or to different degrees, but scientifically, one would expect such variation to be much smaller than the variability among the population with regard to an isolated biological parameter, especially a parameter that may have no biological relevance to the mechanism of chemical toxicity.

These overall conclusions clearly allow for the possibility that some compounds may produce an effect at lower levels in children than adults, or at lower levels in some adults than in other adults. But, EPA believes that the examples, cited by the commentors, of interindividual variability in human biological function greater than 10-fold are relatively rare exceptions, not the rule. Therefore, the Agency believes that available information does not support a categorical conclusion that the traditional 10X intraspecies uncertainty factor is insufficiently protective.

The Agency recognizes, however, that in specific circumstances information may indicate that humans will exhibit a greater range of sensitivity, and would conclude, in those cases, that additional protective factors are needed in the risk assessment. As discussed above, these decisions need to be made on a case-by-case basis. (See also the discussion, below, of EPA's approach to taking into account the potential impact of health conditions on sensitivity.) In addition, the Agency agrees with and adopts the 10X Task Force's conclusions on the need for further research, and for extreme caution in making decisions to reduce the intraspecies uncertainty factor. Finally, the Agency believes that

available literature underscores the need for careful consideration of the toxicity information on each pesticide for indications that children may be more than ten fold more sensitive than adults to its effects.

Contrary to the comments, OPP believes that it generally has a reliable database on which to estimate exposure from use of skin-applied insect repellents and airborne residues of indoor use pesticides. To the extent that data are limited, OPP uses models that make conservative assumptions about exposure. Therefore, OPP does not expect that its exposure assessments understate exposure in this regard.

Contrary to the comment, OPP has always taken into account data on the differences in drinking water consumption between children and adults. OPP's ability to assess drinking water exposure will be even better now that OPP has begun to use the very refined data in USDA's latest Continuing Study of Food Intake by Individuals (1994-1996, 1998) on the sources and amounts of water in the diets of people of different ages.

OPP also considers exposure to pesticides through milk. In addition to the results of tests that specifically study the potential for bioconcentration, OPP also has data on the presence of pesticide residues in milk and uses them, together with data on milk consumption, to evaluate exposure. OPP notes that data from USDA's Pesticide Data Program (http://www.ams.usda.gov/science/pdp/index.htm) show that milk rarely, if ever, contains measurable levels of a wide variety of pesticides.

In sum, OPP believes that it would not be scientifically credible to conclude that retention of the FQPA Safety Factor is automatically necessary in all cases to accommodate for age-related, intraindividual variability in sensitivity. Rather, as discussed above in Issue 2, OPP thinks that each pesticide risk assessment should be viewed on a case-by-case basis to determine whether the weight-of-evidence indicates that the FQPA Safety Factor should be retained, reduced, removed, or raised.

Comment 2. Several commentors (773, 775 and L005) indicated that OPP's current approach to risk assessment is inherently conservative and does not understate potential risk. They noted that many, if not most, of the steps in the risk estimation process appropriately are conservative and the overall result usually is risk assessments that adequately protect public health.

Response. OPP agrees that its approach to risk assessment is generally conservative, but in individual cases, OPP may not have sufficient information to insure that its exposure assessment is conservative. While OPP believes such circumstances are rare, each pesticide risk assessment should be evaluated carefully to determine whether the risk assessment is adequately protective. Therefore, OPP continues to believe that decisions about whether to retain the FQPA Safety Factor should be made on a case-by-case basis, taking into account the specific information available about the potential risks of the pesticide. See responses in Issue 2, above.

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Comment 3. Several members of the Panel expressed concern that it is difficult to make the judgment, from the existing information as presented, that OPP's proposed procedures for FQPA risk assessments are "sufficiently conservative and do not understate the risks to infants and children." Such a judgment requires a quantitative analysis of the likely residual risks that could remain after application of OPP's procedures to chemicals that prove "positive" for developmental effects and to chemicals for which the existing testing procedures fail to detect effects. For positive chemicals, it was emphasized that the animal/human "uncertainty factor" was, for the most part, a dosimetric adjustment factor that compensates for the fact that humans tend to eliminate toxicants at a slower rate than experimental animals (with middle values tending to be approximated by the ratio of human to animal body weights to the 1/4 power–about four-fold in the case of rats and seven-fold in the case of mice.) The generic average human/sensitive human factor of 10 fold would need to encompass somewhat more than three standard deviations in a possible lognormal distribution of human sensitivities in order to go from a 5% risk level consistent with observations of a NOAEL and a one in one hundred thousand or one in one million incidence of harm. Recent information on the spread of human interindividual variability for mild effects in adults gives some grounds for skepticism that a 10-fold factor will routinely encompass three standard deviations of a human population distribution of thresholds.

The proposal does not identify individuals that are inherently sensitive. For example, there are a variety of multifactorial diseases for which certain chemical agents could contribute to such conditions as Parkinson's disease, essential hypertension, or noninsulin-dependent diabetes mellitus. Such individuals could well be more sensitive to pesticide agents that lead to a number of secondary disorders as apparently different as neurotoxicity (e.g., diabetic neuropathy) and cancer (e.g., liver cancer). Therefore, there are conditions in which the current process may not be sufficiently conservative because these sensitivities are not likely to be tested for in the near future with new or established chemicals.

There is additional reason for concern for populations of children and developing fetuses. In general, OPP's current approaches could fail to yield risk assessments that are sufficiently conservative if one or more of the following circumstances applies:

- **Î** the battery of tests in rodents and other animals used does not effectively measure a wide enough array of higher-level neurodevelopmental or other developmental functions to detect important modes of action in people.

- **Ï** there is an insufficient allowance for human interindividual variability to cover the diversity of human sensitivities, which in some cases may be considerably broader than the diversity of sensitivities in experimental animal populations.

- **Ð** there are deficiencies in estimating high end exposures for infants and children.

- **Ñ** the single-chemical risk assessment techniques fail to capture the cumulative risks from chemicals with related or possibly interacting mechanisms of toxicity.

The Panel suggested that it is important to test the degree of protection likely to be afforded by OPP's risk assessment procedures by applying them on a hypothetical basis to the observations that would be routinely produced by the required pesticide testing protocols for an array of known "positive" developmental toxicants. Such materials would include methyl mercury, lead, some specific neuroactive noncoplanar PCB congeners, and an anticonvulsive agent with known human developmental toxicity. After application of OPP's procedures for determining reference doses to the test chemicals, quantitative risks could be estimated at the reference dose (and possibly below) and the judgments could be made of the advisability of retaining the FQPA uncertainty factor for such "positive" compounds.

Some Panel members expressed particular concern that pesticides that are used in homes, daycare centers and schools, food production, and pesticides contaminating water would be likely to lead to the greatest risk in underestimating exposure from all sources and routes, as well as drive the risk relative to multiple pesticides with similar modes of action. The limited exposure assessments are well outlined in the Agency's background document. Less well acknowledged are issues of short-term exposures at critical periods of development, including those inside the uterus, as they relate to endocrine disrupting chemicals and neurotoxicants. In the absence of improved knowledge about these exposures, there should be a very conservative approach to the protection of the fetus and child.

Models and assumptions employed require validation against empirical data when such data exist and prospectively (with the planning of new studies) when they do not. Considerable uncertainties surround exposure data, particularly in infants and children, and suggest proactive and expanded acquisition of data for validation.

Scenarios can likely be developed that would involve exposures to pesticides that will predict risks greater than risks predicted by the current approaches. Panel members differed whether such scenarios are considered. OPP must specify some target percentiles of the expected population distribution of exposure for routinely evaluating whether its standard procedures provide adequate protection for relatively highly exposed people with an adequate degree of confidence.

On the other hand, some Panel members thought that the current approaches are adequately conservative and, if properly applied, should be protective of infants and children. It is the Panel’s understanding that OPP will be taking into consideration potential exposures from all sources and, specifically, exposures during the entire span of human development. Further, according to OPP's interpretation of the FQPA, the default FQPA 10X safety factor must be used in the absence of reliable evidence justifying use of a different value. Use of the "risk cup" approach, which takes into account the concept of cumulative risk, i.e., the potential presence of residues of other pesticides with like mechanisms of action, adds to the conservatism of OPP's approach.

Response

Overall Response. The SAP's comments reflect different views on the question of whether OPP's risk assessments "typically do not underestimate risk." Not only does the range of the SAP's comments reflect the diversity of views expressed by the public, but the Panel's specific comments contain two themes that suggest why the members (and the public) may have reached different conclusions on whether OPP risk assessments do not understate risk. First, there appears to be an issue with regard to who should be considered in the assessment. Should EPA endeavor to protect the most sensitive individual or most highly exposed individual, or should the Agency focus on larger subgroups of the population? Second, there appears to be an issue about how confident OPP should be that the risks have been adequately assessed. Given the absence of data to characterize completely the degree of conservatism in OPP's risk assessments, it appears that members may have made different assumptions about the conservatism of the general assessment methodology. Both of these themes come together in the Panel's comments indicating various circumstances in which OPP's risk assessment methodology might underestimate risk for some people and pesticides.

Overall, OPP believes that the FQPA accords the Agency discretion in how it interprets the statutory provisions to ensure that pesticides in food are "safe." Therefore, OPP has considerable latitude in designing its risk assessment methodology to determine whether a specific pesticide's exposure meets the statutory safety standard. OPP has developed its risk assessment methodology, consistent with EPA policies and practices, to generate risk estimates which it believes are generally conservative, i.e., most, but not necessarily all assessments will tend to describe the upper bound or high end of the actual risk experienced by the exposed population, but the methodology may understate potential risk for a very small percentage of chemicals or portion of the exposed population.

Consequently, recognizing that there are many elements in a risk assessment, and that these elements differ from assessment to assessment, OPP believes that it is appropriate to review each assessment individually to see how all of the elements–hazard identification, dose response evaluation, and exposure assessment–tend to express potential risk. In the course of that case-by-case review, OPP can determine whether it is necessary to retain an FQPA Safety Factor or to make other adjustments to have reasonable confidence that risks are not underestimated, especially for infants and children.

Statutory Framework for Risk Assessment. In designing its risk assessment methodologies and making judgments about safety, OPP must follow the

provisions of FQPA. While the FQPA establishes a stringent, protective standard, that focuses particularly on children's health, OPP believes that the Agency has considerable discretion under that standard in how to interpret the statutory mandate. Specifically, FQPA requires OPP to determine whether exposure to a pesticide in food, water and through other, nonoccupational pathways is "safe," i.e., whether OPP can conclude that there is a "reasonable certainty of no harm" from such exposure. In addition, the statute directs EPA, in making the safety determination, to consider exposure to "major identifiable subgroups."

Collectively, these statutory provisions allow OPP to exercise judgment about how to implement the safety standard. Notably, FQPA does not require OPP to look at the most sensitive individual or the most highly exposed individual. Rather, the Agency may use its judgment to conduct the risk assessment in a manner that looks broadly at the whole population, giving particular consideration to the exposure of major identifiable subgroups. Similarly, the statute does not address in detail how OPP should assess exposure for the population in question. Finally, the statute does not specify complete certitude, but only a reasonable certainty of no harm. In sum, EPA interprets these provisions as allowing considerable discretion in designing its risk assessments and judging whether a particular exposure meets the statutory standard.

Specific Responses. The paragraphs below summarize and respond to the specific Panel comments.

Risks to individuals who, statistics predict, might be extremely sensitive. Some members of the SAP indicated that in a large population there is considerable interindividual variability in sensitivity, and that a dose which would affect one out of a million exposed individuals (or one in a hundred thousand) may be more than 10 times lower than the dose which affects 5% of the population. (The SAP comment appears to assume that a NOAEL established in animal studies generally corresponds to the dose which affects no more than 5% of the test group.) In a separate comment, the SAP encouraged OPP to establish "some target percentiles of the exposed population distribution" for evaluating risk.

OPP agrees with the Panel that, for some types of effects, there may be more than an order of magnitude difference between the level of a chemical affecting 5% and 0.0001% of exposed individuals. Such variability does not by itself, however, mean that the complete risk assessment for any particular pesticide understates its risk. It is equally important, for example, to consider the components of the exposure assessment and the impact of applying other uncertainty factors in judging the overall conservatism of the risk assessment. As noted above, these judgments need to be made on a case-by-case basis.

Further, OPP agrees with the Panel that the judgment of how conservative a risk assessment needs to be is, to some degree, a risk management judgment–how confident is the decision-maker that the identified hazards will not occur. While OPP has generally not established target percentiles for most of the risk assessments it performs, it issued a science policy paper recommending use of the 99.9th percentile of estimated acute exposure to pesticides in food as the starting point in estimating the threshold of regulatory concern (see *Choosing a Percentile of Acute Dietary Exposure as a Threshold of Regulatory Concern*; USEPA 2000c).

Sensitivity of individuals with special health conditions. The SAP identified a variety of "multifactorial" health conditions–Parkinson's disease, essential hypertension, or noninsulin-dependent diabetes–that could increase an individual's sensitivity to the toxic effects of a pesticide. Calling these people "inherently sensitive," some of the Panel members indicated that such people "could well be more sensitive" to the toxic effects of a pesticide.

Ordinarily, OPP does not take into account if and how a particular health condition may contribute to the impact of pesticide exposure. OPP generally assumes that the traditional intraspecies uncertainty factor (10X) is sufficient to cover such possible variation in sensitivity. OPP also generally requires information that would raise a reasonable concern about the possible link between a specific health condition and increased sensitivity to a particular pesticide. In cases where OPP has data to show that people with a particular health condition are more susceptible to the toxic effects of a pesticide, OPP will consider the information in its risk assessments and risk management decisions. For example, OPP received information establishing that many people were experiencing significant allergic reactions after having used Allercare™, a product marketed to control dust mites. OPP directed the registrant of Allercare to recall its products, and to reformulate the pesticide to remove the ingredient that caused the allergic response in users. As another example, OPP received information raising concerns about the potential for a biological pesticide, sp. *Burkholder cepacia*, to aggravate the health condition of individuals with cystic fibrosis. OPP conducted a thorough risk assessment

of this product, including a consultation with the SAP on this risk. In light of the assessment, the company withdrew its application for registration.

Unevaluated toxic effects. Some Panel members indicated that the currently required battery of animal toxicity studies does not effectively measure "a wide enough array of higher-level neurodevelopmental or other developmental functions to detect important modes of action in people." In connection with a similar comment, some of the SAP members noted that there was a way to evaluate more quantitatively whether risk assessment methods underestimated risks: after performing additional tests to evaluate these effects, OPP would need to compare the earlier (pretesting) risk assessments with assessments that took such studies into account. In the same vein, another SAP comment suggested conducting such a comparison with known neurotoxicants such as methyl mercury, lead, PCB congeners, etc.

OPP has tailored its data requirements for assessing the potential risks of particular pesticides to the characteristics and use patterns of the individual pesticide. Additionally, OPP may impose additional data requirements on a case-by-case basis through Data Call-In. As additional data are available, OPP will consider the findings and include them in the risk assessment as appropriate. Responses to Issues 6-10 describe the approach OPP uses to call in neurotoxicity data and the policies for using Traditional uncertainty factors and/or special FQPA Safety Factors in the absence of these data.

As to the suggestion by Panel members for conducting a series of comparisons for risk assessments performed before and after the inclusion of additional data or to a set of known neurotoxicants, this may be done in conjunction with the ongoing evaluations of the developmental neurotoxicity studies which have been submitted in response to the September 1999 chemical class DCI for all the cholinesterase-inhibiting organophosphorus pesticides with established tolerances.

Inadequately assessed high-end exposures for infants and children. The Panel suggested that EPA should collect empirical data to validate the models on which it bases exposure estimates.

OPP agrees that collection of empirical data to validate its exposure models could reduce uncertainty and strengthen its risk assessments. The Agency has made considerable progress in collecting data to validate and improve many of its models. These efforts are described in more detail in the responses to comments in Issues 13-16.

Unevaluated Exposure Scenarios. Some members of the Panel commented that because it is possible to identify exposure scenarios that OPP has not evaluated, it is possible to argue that OPP's risk assessment methodology may underestimate risk for people who might be exposed in such scenarios.

OPP agrees that there are certain hypothetical exposure scenarios that are not evaluated by current models. In Issue 15, OPP responds to public comments identifying a number of potential exposure scenarios allegedly not covered by current models, and discusses why OPP believes that these exposures are not likely to be significant or that the current models are adequate to estimate these exposures. The SAP did not identify any specific scenarios, and therefore OPP cannot comment on whether there are additional potential exposure scenarios not raised in the public comments. In addition, OPP has added to, or modified, the Residential SOPs (US EPA 1999g) since the SAP reviewed them in late 1998.

Critical exposure periods. Some members of the Panel expressed concern that OPP needed to adopt a "very conservative approach" to evaluating pesticides if exposure to the substance during a critical period of fetal development causes developmental toxicity.

OPP believes that it has a conservative approach to evaluating pesticides which produce toxic effects only if there is exposure during a critical period. Basically, OPP estimates acute exposure to women of childbearing age and assumes that a pregnant woman could receive an exposure at the high end of the range during a critical phase of the development of her fetus. Even though this approach most likely overstates the frequency of such exposures, OPP believes that it is an appropriately conservative approach.

Cumulative Risks Associated with Chemicals That Have a Common Mechanism of Toxicity. The Panel commented that EPA's risk assessments of individual pesticides may be insufficiently conservative if the pesticides share a common mechanism of toxicity with other chemicals. OPP agrees that FQPA requires the Agency to consider the cumulative risk of exposure to multiple chemicals that have a common mechanism of toxicity, and that failure to consider such potential risks could understate the potential risk. OPP, however, does consider whether pesticides have a common mechanism of toxicity and, if so, OPP evaluates the potential risks associated with exposure to them (see *Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity* (US EPA 1999h);*Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (US EPA 2002).

In sum, OPP agrees with the SAP that, in certain circumstances, its general approach to risk assessment may not be adequately conservative. Therefore, for each pesticide risk assessment, OPP attempts to identify any special circumstances that would necessitate a different approach. OPP risk assessments document specific steps that OPP has taken to address unique conditions involving the toxicity or exposure profile of a pesticide. In addition, at the conclusion of the risk assessment for a food use pesticide, OPP performs a weight-of-evidence assessment regarding whether to retain or modify the FQPA Safety Factor. OPP believes these kinds of steps are appropriate to take into account the possibility that the general approach to risk assessment should be modified.

ISSUE 4. Relationship of FQPA Safety Factor to Traditional Uncertainty/Safety Factors

Do you agree with OPP's view that the FQPA Safety Factor should be applied in addition to the interspecies and intraspecies uncertainty factors, but that the FQPA Safety Factor should not be applied in a manner that results in "double-counting" of uncertainties that are otherwise addressed in the toxicity and exposure assessments through, for example, the database uncertainty factor or conservative exposure models? If you disagree, why?

Comment 1. Commentor 778 (NRDC) asserted that Congress meant for OPP to do more than continue its traditional use of uncertainty factors.

Response. OPP is doing more than continuing its traditional use of uncertainty factors. As the Revised Guidance Document makes clear, the additional safety factor provision both codifies and expands traditional use of safety factors. NRDC does not explain how Congress' reference to the "completeness of the toxicity database" can be read as excluding traditional use of safety/uncertainty factors to address weaknesses in the toxicity database.

Comment 2. Commentor 778 (NRDC) pointed to the NAS 1993 "Kids' Study's" critique of the then-current EPA data requirements, NRDC's 1998 study of such data requirements, and EPA's proposed addition of several studies to EPA's Tier 1 toxicity testing requirements as grounds for retaining the additional 10X factor across the board.

Response. With respect to the 1993 NAS Report, it did include a number of recommendations for changes in existing toxicity testing as well as suggestions for new types of tests. During the time that this report was under development between 1988 and 1993, the Agency developed and implemented the use of several test guidelines for new study types (e.g., the developmental neurotoxicity and the acute and subchronic adult neurotoxicity). Since that time, the Agency has developed or upgraded several additional guidelines (e.g., upgrades to the multigeneration reproductive toxicity and prenatal developmental toxicity studies, enhanced evaluation of the immune system in the repeated dose studies and a stand-alone, short-term immune system assay). However, even at the time the Report was issued in 1993, the NAS did not take the view that any perceived deficiencies in the existing database were of such consequence that a full 10X safety factor was required across the board. For example, the NAS wrote:

> Although current uncertainty factors used to extrapolate toxicological data to humans provided for 10-fold variations between species and within the human population, additional protection for developmental toxicity may be required, depending on the toxicant of interest and the amount of testing that has been conducted. [emphasis added]

Similarly, the NAS report specified:

> [T]he committee recommends that an uncertainty factor *up to* the 10-fold factor traditionally used for fetal developmental toxicity should also be considered for postnatal developmental toxicity and when data from toxicity testing are incomplete.[emphasis added]

In both of these passages, the NAS committee clearly indicated that whether an additional factor was needed due to inadequate testing required a case-specific examination of the testing for the pesticide in question. Thus, even the NAS, the organization that recommended the use of an additional 10-fold safety factor, did not draw the conclusion advanced by NRDC.

EPA's Revised Data Requirements. NRDC argues that because EPA has announced it plans to add additional studies to the Tier 1 toxicity testing requirements, EPA has essentially concluded that the databases for all pesticides are incomplete and an additional 10-fold safety factor should be applied to all pesticides. NRDC appears essentially to be taking the position that should EPA consider requiring additional toxicity testing for any pesticide the statute automatically mandates application of an additional 10-fold uncertainty factor. EPA does not believe that the statute imposes such a rigid approach. Rather, the statute directs EPA to take into account the

completeness of the database and to evaluate what existing, reliable data indicate as to hazard and exposure. Moreover, as noted in the draft Policy Paper, Congress did not address the situation of what action would be appropriate where new toxicity testing requirements are imposed. Thus, EPA has some flexibility with regard to situations involving new testing requirements.

The approach that OPP will take when data have been requested, but are not yet available for assessment purposes is described in detail under Issue 7.

Comment 3. Commentors 369 (PMRA) and L015 (CDPR) agreed with OPP that it should take steps to avoid the double-counting of factors.

Response. As stated in the revised guidance document and in this Response to Comments document, Congress, in enacting the additional safety factor provision, was not creating an entirely new component of pesticide risk assessment. Rather, Congress was incorporating into the statute the existing risk assessment process that already involved use of "uncertainty" or "safety" factors to compensate for lacking toxicity data, while building upon that existing process. Frequently, the additional safety factor has been referred to as if it were a wholly new creation that operated independently from other traditional uncertainty/safety factors. This shorthand description of the additional safety factor increases the possibility that the additional factor could be applied in a way that overlapped with traditional safety factors and essentially resulted in double counting of factors designed to address database uncertainty and other components of data integrity. Thus, it is incumbent upon OPP to clearly identify why safety/uncertainty factors are needed so that OPP neither applies two safety factors to address one concern nor fails to apply any safety factor to address database uncertainty due to confusion as to what stage of the analysis such factor should be applied. The revised guidance document includes the principles and process of uncertainty/safety factor selection and application and these are also discussed in greater detail in this document under Issues 7, 11, and 12.

Comment 4. Commentor 372 (AWWA) noted that the positions set forth by OPP seem to be in line with their interests. It is important to note that the proposal for an additional safety factor to account for the possibility that infants and young children may in some instances not be protected with "reasonable certainty" by previous uncertainty factors has some basis in recent scientific research. These previous uncertainty factors accounted for known variations in human susceptibility and sensitivity, but this variation was estimated primarily from data in adults where a reliable database could be obtained. At the least, existing scientific evidence has not been analyzed systematically to demonstrate that the existing uncertainty factors are adequate in all cases. Until such an analysis is performed, it is reasonable for the Agency to apply an additional safety factor in cases where the application of traditional uncertainty factors cannot be shown with reasonable confidence to include variability across the entire human population.

The OPP needs to develop and clearly state a procedure of scientific review that will ensure the FQPA Safety Factor applied does not result in double counting of sources of uncertainty. Still missing from the discussion, however, is an explanation of how OPP will review the scientific merits of any proposed FQPA Safety Factor applied in a specific case. The presumption would be a SAP review, but this is not stated. Further, AWWA strongly encourages OPP to develop a formal process for making uncertainty decisions based on a hierarchy of questions that will give the regulatory manager the information needed to make decisions based on sound science. The structure of the questions should be supported by clearly defined Data Quality Objectives with data quality taking precedence over arbitrary scheduling deadlines.

The commentor stated further that, in its opinion, OPP fails to make clear several operational issues that could still result in double counting of uncertainty. OPP needs to clarify how an additional database uncertainty factor and an FQPA Safety Factor are related. Is the latter part of the former, or entirely separate? The document is not clear on this point. It also suggests that the FQPA Safety Factor might reflect more than an additional database uncertainty factor. This also leaves the reader unclear whether additional considerations will be reflected in risk characterization, whether some may be reflected in hazard characterization, and how the two points of characterization are related.

Response. OPP agrees that available data suggest that adults and children may display a range of sensitivities to different chemicals, and that for some chemicals, children may be more sensitive to the toxic effects of a chemical than adults. Therefore OPP agrees that application of the historical uncertainty factors may not always be sufficient to protect infants and children. As discussed above, however, the scientific data on variability in sensitivity of humans does not indicate the need for an additional uncertainty factor in most cases. See Issue 3, Comment 1.

OPP agrees that it needs a systematic approach to making decisions about the application of the FQPA Safety Factor. OPP accordingly is revising its Standard Operating Procedure to guide decision-making on individual chemicals. The SOP describes a very detailed process of collecting, organizing, and analyzing information that assures that all information is weighed appropriately. Although OPP does not think review of all its chemical-specific decisions by the SAP would be necessary, OPP has sought SAP advice on its guidance document and SOP, and would not hesitate to take specific FQPA Safety Factor decisions to the SAP if OPP believed the SAP's advice would be helpful.

OPP agrees that its approach to applying the FQPA Safety Factor should avoid "double-counting" and that it should clearly distinguish between considerations that are addressed by traditional uncertainty factors and those that arise as a result of concerns unique to the FQPA. OPP has revised its guidance document to make the differences clearer. The differences are also discussed in the material presented below in Issues 5 to 8.

Comment 5. Commentor 773 argued that OPP should not use the FQPA Safety Factor to cover any or all uncertainty factors other than the interspecies and intraspecies uncertainty factors (UFs). Rather, OPP should continue its prior practice with respect to applying database uncertainty factors. OPP should use its traditional approach to UFs for assessing risks to adults. But, because FQPA contains the Safety Factor provision, OPP must analyze whether there is a basis for reducing or removing the additional Safety Factor for children. However, this analysis should focus on the "important differences" in risks to children and adults. Specifically, the FQPA Safety Factor should be reserved for situations where: (1) pesticides pose particular safety concerns for children because of the nature and severity of the effects, the likelihood that children may be much more sensitive to the adverse effects than are adults, such that there is a reasonable apprehension that the traditional safety factors are insufficient to protect them; or (2) there is substantial uncertainty about the aggregate exposure, properly defined (i.e., exposure from food, and where reliable data exist, other sources).

Response. OPP agrees that its decisions to reduce or remove the FQPA Safety Factor should focus on whether there are important differences in risks to children and adults. The Agency, however, understands the comment to advocate a substantial narrowing of the scope of the FQPA Safety Factor that excludes toxicity database uncertainty concerns from the FQPA Safety Factor. Whether or not EPA agreed with such an approach as a policy matter, EPA does not see how such an approach can be squared with the language of the statute. The statute specifies that the FQPA Safety Factor is to "take into account...the completeness of the data with respect to...toxicity to infants and children." 21 U.S.C. §346a(b)(2)(C). Moreover, the NAS Report heavily emphasized that one of the reasons for an additional safety factor was toxicity database deficiencies.

Comment 6. Commentor 775 asserted that Congress intended that the FQPA Factor be a risk management factor for safety, not a risk assessment uncertainty factor. The policy document discusses at the length the Agency's belief that Congress intended that the FQPA 10X safety factor to function as an "uncertainty factor" and that the factor would serve to codify and extend EPA's practice of employing uncertainty factors in risk assessments. CMA believes OPP errs in its interpretation of Congress' intent. The language of FQPA makes clear that the 10-fold "margin of safety" is just that–a safety factor. OPP's discussion on the lack of difference between an "uncertainty factor" and a "safety factor" blurs the distinction between the purpose of and scientific rationales for applying such factors. An uncertainty factor is typically applied during the hazard and risk assessments to account for uncertainties and is incorporated into the resulting risk estimate. On the other hand, a safety factor is applied in setting a *safe* level of exposure. Congress

did not intend to interfere with the Agency's assessment of risks to children, but essentially directed the Agency to err on the side of safety in setting tolerances where it did not have sufficient data or there was clear evidence of pre- and postnatal toxicity and to take into account "completeness of the data with respect to exposure and toxicity to infants and children." Thus, CMA believes that the purpose of the FQPA factor is to provide an additional margin of safety to protect infants and children where warranted, and the factor should clearly be applied after the RfD is set, not as part of the RfD-setting process.

It is CMA's belief that application of an FQPA Safety Factor, regardless of its magnitude, must occur **only** after determination of the most scientifically supported RfD. The intent of the FQPA is that the application of the FQPA Safety Factor is a *risk management* policy decision that should be made when considering the overall *risk or lack of harm* that could occur following exposure to pesticides. Therefore, the decision to apply the FQPA Safety Factor would be made by the risk manager after reviewing the risk characterization. CMA believes that the **only**, and not just the "**final** decision on the FQPA factor be informed by the science presented in the risk characterization and recommendation." (64 FR 37007)

Response. The main point of the comment seems to be that the FQPA Safety Factor should not be used in setting the RfD but rather as some type of risk management tool for determining whether pesticides that otherwise had exposures within their RfD were nonetheless unsafe as to infants and children. Therefore, the comment urges OPP to apply the FQPA Safety Factor after it has derived the RfD.

OPP agrees that the final FQPA Safety Factor decision should be made after the RfD is derived, but it takes that position for a different reason than the one suggested by the comment. OPP sees value in keeping the RfD process consistent across the Agency, and thus does not intend to use those aspects of the FQPA Safety Factor that are unique to the policy concerns in the FQPA in establishing pesticide RfDs; rather, those types of safety factors are only used in establishing Population Adjusted Doses (PADs).

OPP does not agree with the comment that not differentiating between safety factors and uncertainty factors in its FQPA Safety Factor policy "serves to embed risk management decisions in the risk assessment process, undermines the scientific rigor of the risk assessment process, introduces unnecessary conservatism, and diminishes transparency." OPP has gone to great lengths to emphasize the importance of full and careful explanation of the basis for any additional safety/uncertainty factor used in assessing the risk posed by a pesticide. This commitment to the adequate explanation of OPP decisions insures that the concerns regarding diminished scientific rigor and

transparency should not arise.

Neither does OPP agree that Congress intentionally used the term “margin of safety” because it intended that it apply the additional margin of safety for infants and children in a fundamentally different manner than uncertainty factors are used. The comment claims that the term “margin of safety” is an unambiguous term that has acquired a clear technical meaning. According to the comment, an “MOS is a ratio between a hazard value (such as an RfD or, more correctly, a NOAEL) and an exposure(s) likely to be experienced.” An uncertainty factor, the comment asserts, is a wholly separate concept used to derive a hazard value such as a RfD. In fact, OPP’s experience in the regulation of pesticides has been that the derivation of hazard values such as RfDs and computation of MOSs or MOEs (Margins of Exposure) are equivalent processes. An RfD is calculated generally by dividing the appropriate NOAEL by various uncertainty (safety) factors. The RfD is then regarded as the “safe” dose and exposure is compared to the RfD to ensure that the RfD is not exceeded. An MOS (or margin of exposure, as it is more commonly referred to now) is calculated by dividing estimated or measured exposure into the appropriate NOAEL. The resulting MOS/MOE value is judged acceptable or not based on comparison to various uncertainty (“safety”) factors. Importantly, OPP has always assessed a specific pesticide risk using either a RfD approach or a MOS/MOE approach. Moreover, for a given effect of concern for a pesticide, the uncertainty (“safety”) factors used would be precisely the same whether the RfD or MOS/MOE approach were used. The two approaches are simply different ways of quantitatively expressing precisely equivalent results. For example, assume a risk assessment needs to be performed for a pesticide where an uncertainty/safety factor of 100 is appropriate, and the NOAEL is 10 and exposure is 0.05. In these circumstances, the RfD would be 0.1 (10/100), and exposure would only be 50 percent of the RfD. Under this situation, the MOS/MOE would be 200 (10/0.05), a value twice as high as necessary for a safety finding. Under either approach it is clear that exposure could double before a safety concern was raised. OPP is unaware of any instance where it has layered an MOS/MOE approach on top of a RfD or vice versa.

As previously noted, the overlap between the concepts of: (1) margin of safety or safety factors; and (2) uncertainty factors, is well-reflected in the legislative history of the FQPA. In fact, contradicting the argument of CMA, Congress referred to the traditional inter- and intraspecies uncertainty factors as safety factors and the new children's safety factor as an uncertainty factor (see H. Rept. 104-669, 41, 42; 1996).

CMA's argument that the statutory structure implies a clear distinction between uncertainty factors (used for risk assessment) and safety factors (used in risk management) is also unavailing. CMA argues that if Congress had intended the FQPA Safety Factor to be an uncertainty factor it would have included the factor in subsection (b)(2)(C)(i) which contains various risk assessment considerations and not (b)(2)(C)(ii). EPA suspects little can be read into placing the additional children's safety factor in a separate provision–after all, it was one of the key pieces of the legislation. More importantly, another provision of the statute demonstrates quite plainly that Congress did not draft the FQPA so as to maintain the sharp distinction that uncertainty factors were to be used only in risk assessment and safety factors were not. Subsection (b)(2)(D)–a subsection devoted entirely to enumerating factors to be considered in risk assessment–does not use the term "uncertainty factor" but instead mentions "safety factors." Moreover, safety factors are mentioned in a manner that clearly implies Congress was referring to the traditional inter- and intraspecies uncertainty factors used by EPA in extrapolating from animal data to human risk ("safety factors which...are generally recognized as appropriate for the use of animal experimentation data"). Thus, neither the statutory language in the children's safety factor provision, the structure of the statute, nor the legislative history supports CMA's argument.

Comment 7. Commentor 778 also raised the issue of terminology when it stated its belief that OPP incorrectly calls the statutory presumption an "FQPA Safety Factor;" in their view, it should be called an additional "margin of safety." By referring to the FQPA provision's requirement as an additional "safety factor," the comment claims that EPA is incorrectly trying to treat the FQPA provision as a variation on the traditional uncertainty factors. This, in turn, provides excuses for not retaining the FQPA margin of safety.

Response. Unlike the industry commentors who tried to develop a distinction between safety and uncertainty factors, and RfD derivation and margin of safety/margin of exposure approaches, NRDC claims there is a distinction between a margin of safety approach and a safety factor approach. According to this commentor, OPP uses the term "safety factor" so that it can treat the

additional margin of safety provision "as a variation on the traditional uncertainty factors." OPP explains elsewhere why it is appropriate to treat Congress' reference to safety factors to extend to what OPP has generally referred to in more recent times as uncertainty factors. This commentor, however, could rightly note that Congress used neither the term "safety factor" nor "uncertainty factor" in subsection (b)(2)(C)–the infants' and children's provision. Rather, Congress used the term "margin of safety." Any attempt to distinguish between a margin of safety approach and a safety factor approach, however, immediately flounders because the two terms are inextricably linked. As explained above in responding to Comment 6, OPP calculates a margin of safety or margin of exposure by dividing the appropriate NOAEL by estimated human exposure. The size of the resulting quotient represents the margin between human exposure and the exposure that yielded no adverse effects in experimental studies. The acceptability (i.e., safety) of the margin is evaluated by comparing to the safety ("uncertainty") factor deemed necessary to address such concerns as inter- and intraspecies variability (usually represented, in a default situation, by two 10-fold factors). Hence, when Congress dictates that the margin of safety should be 10-fold greater, it is saying that in addition to the traditional intra- and interspecies 10-fold safety/uncertainty factors, another 10-fold factor should be used. Because this additional 10-fold factor is to address safety, it seems a very small leap to label it a safety factor.

Comment 8. Several comments were received which make note of lack of clarity as to congressional intent when it crafted the language of the children's provisions in FQPA and/or OPP's implementation of the statute with regard to the "additional margin of safety."

Commentor 773 asserted that Congress was clearly misinformed about prior Agency practice regarding the extent of use of the 10X factor and mistakenly thought that the additional 10X was widely applied. Congress' misunderstanding is traceable to inaccurate statements in the 1993 NAS Report on *Pesticides in the Diets of Infants and Children*, which stated that EPA applied an additional10X "whenever toxicity studies and metabolic/disposition studies have shown fetal developmental effects." (This commentor also alleged that EPA further confused the issue by a letter provided to the House Commerce Committee during the debate over FQPA.) A Congressional report quoted that passage from the 1993 NAS Report to support inclusion of the 10X Safety Factor provision in FQPA and directed EPA to interpret the provision in furtherance of the NAS statement. Therefore, since Congress was trying to perpetuate what they understood to be existing practice, OPP should interpret the 10X provision to continue prior practice, as much as possible.

Commentor L016 stated that OPP should seek to implement the additional safety factor provision in a way that, as much as possible, continues the pre-FQPA approach. OPP should not presume there is a congressional mandate to add a new 10X factor in all or most cases. Congress clearly was misinformed about its prior practices and thought that the additional safety factor was already widely used, which was not the case.

Response. OPP agrees that special caution should be used in interpreting the legislative history pertaining to the 1993 NAS Report in regard to the Report's incorrect statement that OPP (and FDA's Center for Food Safety and Applied Nutrition, for that matter) routinely applied an additional 10-fold uncertainty factor where prenatal toxicity was identified. In fact, OPP has not blindly retained the additional 10-fold safety factor if pre- or postnatal toxicity is identified. Rather, it examines whether the pre- or postnatal toxicity shows that fetuses, infants, or children are more susceptible to the pesticide than adults, and the pre- or postnatal toxicity is particularly severe or has other characteristics that raise concerns regarding the adequacy of traditional safety factors . This approach is consistent with the concern reflected both in the statute and in the NAS Report concerning the potential heightened sensitivity of infants and children to pesticides.

Comment 9. Commentor 406 asserted that OPP has misinterpreted both the statutory language and Congressional intent of FQPA. Under section 408(b)(2)(A)(I) of FFDCA, OPP is to establish safe tolerances. In addition, section 408(b)(2)(A)(ii) defines the safety standard as a reasonable certainty of no harm. The latter term means exactly the existing regulatory practices of the FDA for food additives. While Congress added several minor modifications to the old FFDCA standard, the intent was for EPA to stay as close to FDA's practices under reasonable certainty of no harm standard as possible. This commentor recommends that OPP describe to Congress that regulatory toxicology practices in effect at FDA before FQPA protected infants and children. Instead, OPP has strayed far from this primary objective, acting as if the minor modifications in the FQPA were the primary intent and has set off on a tangent of creating new, unvalidated toxicology tests to measure pediatric endpoints.

OPP should cease inventing new regulatory practices and requiring new toxicology tests that in effect create a new standard. This thrust of OPP's policy development contradicts both statutory language and Congressional intent. If the standard protected children in the past, no reason exists to change the standard now. If OPP believes that children have higher exposures than adults, OPP should adjust tolerances to reflect the higher exposures, not the interpretation of toxicology data.

In the context of animal testing required before 1996, a one-hundred fold safety factor applied to the lowest no-effect level in a standard battery of animal tests adequately protected the developing human fetus and human neonates. No good reason exists to deviate from this practice. This commentor disagrees with the Agency's interpretation of both congressional language and intent about an extra 10-fold safety factor. Both language and intent about an extra 10-fold safety factor are ambiguous and sufficiently unclear that, in the face of a clear mandate to apply the "reasonable certainty of no harm" standard, OPP should incorporate the standard practice as policy. The standard practice will achieve safe levels for the human fetus and neonate.

Response. OPP would agree that the "reasonable certainty of no harm" standard applied by FDA since 1958 informs the content of the safety standard in the FQPA. However, Congress also imposed numerous other considerations and requirements on OPP in applying this safety standard. OPP's implementation of the "reasonable certainty of no harm" standard should take into account the whole of the congressional mandate included in the FQPA. OPP has attempted to remain faithful to the language of the children's safety factor provision in implementing decisions regarding this policy.

OPP is unsure what this commentor is referring to regarding "new, unvalidated toxicology tests to measure pediatric endpoints." No new testing protocols or guidelines have been developed directly as a consequence of the children's protection provisions of FQPA. Two study types–the multigeneration reproduction study and the prenatal developmental toxicity study–have been upgraded. While these two updated guidelines were not issued until after FQPA was passed in 1996, the work to improve their design began nearly a decade earlier, as did the work to develop the acute and subchronic neurotoxicity studies in adult animals and the developmental neurotoxicity study.

Comment 10. Commentor 778 argued that Congress clearly and knowingly inserted a presumptive additional margin of safety in FQPA to address the inadequacy of existing toxicity and exposure data for children. In their view, the 10X policy reverses the presumption in FQPA which strongly favors retention of the 10X. OPP erects too many hurdles to the decision to retain the 10X.

Response. OPP would agree that Congress included the additional 10-fold factor as a default position or presumption. The commentor does not cite any authority for the proposition that Congress intended this to be a "strong" presumption. In deciding whether to use a factor different than the additional 10X, OPP must be guided by the language of the statute. That language provides that OPP "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." The reference to "reliable data" indicates that Congress intended that any decision on changing the factor like other decisions under the FFDCA, should not be based on speculation. See Issue 16 below, for a discussion of the comments concerning the meaning of "reliable data." However, since "reliability" is a criterion with broad applicability under FFDCA section 408, it is difficult to argue that the requirement for reliable data creates a "strong" presumption. More important to judging the strength of the presumption is the standard Congress prescribed for when a different factor could be chosen. What Congress mandated was that a different safety factor was appropriate where the different factor would be "safe for infants and children." A standard such as "safe for infants and children" does not narrowly limit OPP's discretion but rather invokes the broad safety standard in section 408. Given that Congress gave OPP such a broad standard to apply in making decisions regarding changing the factor, OPP finds little support in the statutory language for the commentor's contention regarding a "strong" presumption.

OPP does not agree that it has reversed the statutory default position of including an additional safety factor. For the reasons explained in the draft policy document and in the revised guidance document, OPP believes that, when reliable data are available, it will be fully protective of human health to make a individualized determination of an appropriate additional factor for pesticides rather than simply rely on a default 10-fold factor. OPP also believes its policy on making such determinations is fully consistent with the discretion granted to determine that a different factor is appropriate.

Comment 11. Commentor 778 stated that OPP should revise its policy to assure that the decision about the FQPA Safety Factor is made on the basis of "no harm to children," rather than compliance with EPA's data requirements. By including the word "potential" in FQPA ["take into account potential pre- and postnatal toxicity..."], Congress did not intend to restrict the application of the additional 10X to chemicals for which greater sensitivity had already been demonstrated. The OPP policy takes the opposite approach, requiring there be some evidence of increased susceptibility.

Response. OPP's approach does not limit application of the additional 10-fold factor to situations where greater sensitivity or susceptibility has already been demonstrated. In general, there can be three possible scenarios for a given pesticide and potential sensitivity/susceptibility to infants and children: (1) there are sufficient data showing infants and children have increased sensitivity/susceptibility; (2) there are sufficient data showing no increased sensitivity/susceptibility to infants and children; and (3) data are insufficient to

demonstrate whether there is increased sensitivity/susceptibility to infants and children. In scenarios #1 and #3, OPP may decide to retain the default 10X children's safety factor or to assign a different safety factor greater than 1X. Scenario #3 particularly relates to the circumstance where there is the "potential" for increased sensitivity/susceptibility, and thus OPP is taking this statutory term into account. See additional discussion in the response to comments in Issue 7 (scenario #3) and Issue 11/12 (scenario #1), below.

Comment 12. Comments were received on the discussion in the proposed 10X Policy with regard to whether or not there were any directional constraints when making FQPA Safety Factor decisions.

Commentor 773 argued that several parts of the legislative history of the FQPA Safety Factor provision indicate that the additional factor cannot exceed 10. First, the House Committee report speaks of "an uncertainty factor up to the 10-fold factor traditionally used by EPA." Second, Dr. Goldman, EPA Assistant Administrator, wrote the House Commerce Committee that the proposed Safety Factor provision would allow EPA to impose "an additional margin of safety of up to ten" if risks to children required it. Third, the House floor debate referred to the flexibility given in the bill for EPA "to apply a safety factor of less than 10-fold" if such a factor would be safe for children. These specific passages, together with an absence of any language suggesting the use of a safety factor larger than 10X, indicate that Congress did not authorize the Agency to apply a factor greater than 10. Moreover, the draft policy provision would reverse prior Agency policy articulated shortly after enactment of FQPA that the FQPA Safety Factor can be no greater than 10X.

This commentor went on to say that if the database uncertainty factor is considered part of the FQPA Safety Factor, the overall factor should not exceed ten times the database uncertainty factor.

Response. OPP disagrees with the commentor's legal interpretation. The statute, on its face, does not limit the additional factor for the protection of infants and children to a maximum of 10X. To the contrary, the statutory language specifically uses a term ("different" margin of safety) that does not directionally constrain any decision in choosing the size of a factor replacing the default value. Moreover, as the commentor admits, the legislative history indicates the choice of the term "different" appears to have been a considered choice by Congress. Although earlier drafts of the bill more closely used the language from the 1993 NAS Report language recommending an additional safety factor of "up to 10X," the final version of the bill amended this phrasing by dropping the "up to" language and adding specific authority to assign a "different" factor. Moreover, it is interesting to compare the sentence in the final

bill granting authority to vary from the additional 10X factor with what appears to be its predecessor from the Clinton Administration proposal of 1994 (S.2084). The critical sentence from that bill specified:

> Notwithstanding this requirement for an additional factor, the Administrator may determine that a margin of safety for a pesticide chemical residue is considered ample for children and infants if, on the basis of reliable data, such margin will fully protect the public health (S.2084, 103d Cong., 2d Sess. §3; 1994; section 408(b)(2)(C) as revised).

This provision from the earlier bill clearly did contain a directional indication with regard to variation from the additional 10-fold factor. Thus, not only does the statutory language specifically authorize OPP to adjust the factor in either direction, but the history of that language suggests that was a conscious choice by Congress.

The commentor points to other legislative history to suggest Congress intended to bar OPP from exceeding 10X. First, it argues that when Congress dropped the "up to" language from the bill that change was "accompanied by agreement to preserve the 10X maximum by adding report language incorporating the NAS report's "up to 10X" explanation." It, however, cites no authority substantiating any such agreement. Moreover, although the NAS' "up to 10X" language does appear in the House Commerce Committee Report, it is simply as part of a long quote from the NAS Report (see H.Rept. 104-669, 43; 1993).

Second, the commentor cites to an EPA letter read into the Congressional Record in which EPA stated:

> [The children's safety factor] provision is consistent with current Agency risk assessment practices. We have been actively working to implement the NAS recommendations...In so doing, EPA scientists exercise their best judgment, based on reliable data, to determine whether studies accurately reflect the risk to children or if an additional margin of safety of up to ten is required (letter from US EPA Assistant Administrator Lynn Goldman to Chairman Thomas Bliley of the House Committee on Commerce, July 23, 1996).

This letter merely states that OPP practice of applying a factor of up to 10X is consistent with the statutory language. That is true. The plain language of the statute gives OPP the authority to remove the additional factor, set a lower additional factor, retain the additional factor, or set a higher additional factor. Any action to exercise any of those four options would be consistent with the statutory authorization.

Third, the commentor cites a statement in the congressional debate to the effect that the “bill does provide the additional flexibility to apply a safety factor of less than 10-fold....” Again, this statement is consistent with a reading of the statute as not imposing an upward directional constraint.

Fourth, the commentor claims that nothing in the legislative history mentions using a factor greater than 10X. However, OPP does not believe that the plain language of a statute can be countermanded simply because the legislative history does not explicitly state that the language means what it says.

Finally, the commentor points to a document concerning an additional safety factor for children prepared by OPP scientists for presentation to the FIFRA Scientific Advisory Panel in October, 1996. That document was released shortly after promulgation of the FQPA. In the document, OPP repeats the “up to 10X” formulation in the NAS Report. Although that document discusses the FQPA children’s safety factor provision, the original impetus for bringing the issue to the SAP had been the NAS Report and the SAP paper had been in production long before the passage of the FQPA. When the paper was revised in light of SAP comments and further reflection on interpretation of the statutory language, it was also amended to drop the description of the FQPA provision as requiring “up to” an additional 10X and to include the term “different” margin of safety (see USEPA 1997).

Accordingly, OPP concludes that nothing the commentor has cited in the legislative history or from any OPP interpretations provides any authority for overriding the plain language of the statute.

Comment 13. Commentor 372 recommended that if a benchmark dose (BMD) is used rather than a LOAEL, the uncertainty factor employed for use of a LOAEL rather than a NOAEL (typically a 10) should be smaller, since the BMD presumably provides a better estimate of the threshold than does the LOAEL.

Response. OPP agrees that a Benchmark Dose (BMD) may be a better approach to derivation of an RfD or RfC, but the Agency guidance on the use of BMD is not yet final. It is anticipated that the Agency's *Benchmark Dose Technical Guidance Document* (USEPA 2000d) will be finalized in early 2002, and when final, OPP will follow this guidance. This document, which was developed under the auspices of a Risk Assessment Forum Technical Panel, has received Agency review and is currently undergoing external review. It includes a chapter on using the BMD in dose-response assessment, and specifically addresses the application of uncertainty or adjustment factors to the point of departure (POD), the magnitude of which should be determined case by case.

II. Toxicology Issues

FQPA directs EPA to apply "an additional tenfold margin of safety...to take into account potential pre- and postnatal toxicity and completeness of the data with regard to exposure and toxicity to infants and children." The statute further provides that EPA may "use a different margin of safety...only if, on the basis of reliable data, such margin will be safe for infants and children." Thus, the statute directs EPA, for each pesticide, to focus on three points: (1) its potential pre-and postnatal toxicity to infants and children; (2) the completeness of its exposure database; and (3) the completeness of its toxicity database.

In the *Federal Register* Notice announcing the availability of the draft policy document and other related papers, the Agency posed a series of questions concerning the first and third points of the FQPA Safety Factor provision relating to toxicology (see Toxicology Issues: questions 5-10). This introduction provides a brief overview of OPP's approach to applying the factor concerning the completeness of the toxicology database. The Agency's response to the comments received on questions 5-10 posed by the *Federal Register* Notice of Availability follow the introduction.

Completeness of the toxicity database. Since the statute directs OPP to consider the completeness of the toxicity database for a pesticide, the draft guidance document devoted considerable attention to discussing what constitutes a complete toxicity database. Consistent with the basic approach of the overall guidance, OPP will make this decision on a case-by-case basis. Nonetheless, as discussed in more detail below, OPP has decided to apply in the revised guidance the following analysis, which draws on Agency-wide policy, public comments, and insights gained through several years' experience applying the FQPA Safety Factor provision. Because the FQPA safety factor provision regarding the completeness of the toxicity database is similar to the traditional database uncertainty factors used by the Agency to address inadequate or incomplete data, when deriving RfDs, OPP intends to use standard Agency practice by applying database uncertainty factors based on considerations of the available toxicity, toxicodynamic and toxicokinetic data. The traditional database uncertainty factors are intended to account for the potential for deriving an under protective RfD/RfC as a result of an incomplete characterization of the chemical's toxicity. Relying on the Agency's existing practice and policy of applying a database uncertainty factor will help ensure consistency in approach and that the RfDs produced by OPP and other EPA program offices should usually be the same for the same chemical.

The guidance document describes a set of factors considered in identifying the significance of missing data. Mandatory and conditional data requirements for pesticides are contained in 40 CFR 158. Further, OPP has long exercised its discretion to impose data requirements on pesticides beyond those contained in 40 CFR 158, and therefore also decides on a case-by-case basis if it needs additional special toxicity studies beyond those routinely or conditionally required for particular pesticides in order to evaluate the

potential hazards of the chemicals. 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 inadequate. This is similar to general Agency practice where the absence of core or routine required studies or required triggered or special studies generally prompts consideration of a traditional database uncertainty factor. While the Agency's general practice has been, as a default, to apply a traditional UF of 3X, if one core study is missing, or 10X, if more than one core study is missing, OPP intends to make this determination on a case-by-case basis considering *which* studies are missing, in addition to *how many* studies are missing. Having made a decision relating to the need for and size of the traditional database UF when studies are missing, OPP will generally not impose any special FQPA safety factor *with respect to the absence of those same studies* OPP believes that the use of the traditional database uncertainty factor in the manner described the policy statement should address any concerns about the "completeness of the toxicity database" pertaining to missing studies.

The absence of the Development Neurotoxicity (DNT) study as well as any other study important to evaluating effects in the young, will be considered under the traditional database uncertainty factor analysis like any other missing study. In other words, when data deficiencies 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. Thus, in addition to identification of toxicity information that is lacking, review of the available data may also provide information as to this potential. 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, route and duration of exposure. It should be emphasized that studies using adult animal may help inform the judgment about potential effects in the young and the need for additional studies. The size of any FQPA safety factor would depend on the degree of concern about the pesticide's potential to affect the young and would take into account the potency, severity, and persistence of the observed effects.

ISSUE 5. Definition of Core Toxicity Database

Please comment on OPP's proposed criteria for defining the core toxicology database.

Comment 1. Several commentors (369, 372) suggested that OPP's proposed criteria for defining the core toxicology database could be more clearly presented. There was some confusion on which of the recommendations of the Toxicology Working Group were being adopted by OPP. One commentor (776) fully supported OPP's proposal for the core toxicology database. Several others supported the proposal with certain qualifications. One commentor (369) stressed that one criterion for inclusion of a study in the core database should be that peer-reviewed and publicly available guidelines of validated study types (accepted by the scientific community) are available. Another commentor (773) agreed with the proposed core database, but stated that a study should be considered part of the core data set only if OPP has promulgated an appropriate regulation; a "Data Call-In" does not substitute for rulemaking.

Response. In recognition of the commentor's confusion about how OPP responded to the recommendations of the Toxicology Working Group concerning the definition of a "core toxicology database," OPP has substantially revised the Guidance Document to clarify its approach to evaluating the adequacy of the toxicity. Please see Section III of the revised guidance document; also see the introduction at the beginning of this section. It should be noted that the revised guidance responds to the Agency's RAF Technical Panel recent recommendation in its 2001 draft report that "The Technical Panel agrees with the Toxicology Working Group of the 10X Task Force (USEPA 1999a) 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." The 1993 NRC report on *Pesticides in the Diets of Infants and Children* (NRC 1993) indicated that additional protection for developmental toxicity (essentially an additional 10-fold factor) may be required, depending on the toxicant of interest and the amount of testing that has been conducted. The recommendation by the RfD/RfC Technical Panel is viewed as consistent with the NRC report on *Pesticides in the Diets of Infants and Children* (NRC 1993). This is because use of the uncertainty factors in the manner recommended by the Technical Panel addresses the NAS' concern regarding the completeness of data pertaining to the safety of infants and children. In many respects, the additional 10-fold factor for infants recommended by the NRC (NRC 1993) and by FQPA is similar to the traditional database uncertainty factor used by the

Agency to address inadequate or incomplete data (including data on pre- and postnatal toxicity) during the risk assessment process. OPP, therefore, believes that when data are inadequate to evaluate potential health risk to children or other potentially sensitive subpopulations, then the traditional uncertainty factors should be used to account for the uncertainty raised by incomplete data. The FQPA factor should be considered in the risk characterization and used to account for any residual concerns or uncertainties in either the hazard characterization or exposure assessment. Therefore, OPP does not make the distinction between core required data versus newly required data in the revised guidance. See response above.

Comment 2. Many commentors (L07, L29, L32, L033, 6-56, 58-191, 193-368, 370, 371, 373-400, 407-516, 518-522, 524-567, 569-614, 651-740, 742-760, 762-769, 774, 777, 779 780, 782-797, 799-802, 806, 807, 811, 812, 815, 817, 818, 820-823, 825, 828, 829) disagreed with OPP's proposal due to animal welfare concerns; increasing the number of toxicology studies in the core database would increase the use of animals. A large number of individuals repeated this concern through submission of a form letter.

Response. EPA is sensitive to public concerns about the use of animals in chemical testing and observes certain guiding principles in all of its testing programs. EPA is committed to avoiding duplicative testing, and to reducing the numbers of animals used, refining existing study types to mitigate pain and suffering and enhance the information gained from the existing guidelines, and replacing animals in testing when scientifically valid alternatives exist. OPP has taken every effort to include only the studies necessary to characterize the potential hazards to children as required by FQPA in the proposed core toxicology database. EPA encourages that toxicology studies be combined when possible to help reduce the number of animals. In addition, EPA is working within the framework of the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM), and, internationally, with the Organization for Economic Cooperation and Development (OECD) to ensure the scientific acceptability of alternative methods.

Although the Agency agrees that the use of animals in testing should be reduced, refined, and replaced whenever scientifically appropriate, as stated elsewhere in these responses to comments, OPP does not believe that the application of a 10-fold factor to the risk assessment for every chemical is an adequate alternative to animal testing. Identification of potential hazard, dose-response assessments, and evaluation of age-related differences in response to toxicological insult, all of which are critical aspects of risk assessment and FQPA factor determination, should include characterization through the use of

an integrated animal systems, i.e., *in vivo* testing given the complexity of the developing organism. This issue is discussed by Chengelis et al. (1995), who concluded, following the review of a number of publications that examined this topic, that mathematical models and simple cell culture systems cannot be used in place of intact animal models to predict toxicities in humans, since "the final expressions of toxicity in humans or animals are frequently the summation of extensive and complex interactions at cellular and biochemical levels." This can only be observed in a whole, intact animal system. Or, in the opinion of Chapin and Heindel (1993), "...*in vitro* methods are important for addressing specific mechanistic questions.... But without the demonstration of an *in vivo* effect at some point in the investigation, *in vitro* data are like a headless chicken: active, provocative, and attention-getting, but missing something quite important." OPP also points out that the 1993 NAS report (*Pesticides in the Diets of Infants and Children*) did not recommend that animal testing be replaced with a presumptive 10-fold factor, but actually suggested that more extensive animal testing be performed to evaluate potential toxicity to infants and children. Therefore, the OPP position, as presented in the 10X policy paper, is consistent with the NAS recommendations.

Comment 3. One commentor (369) requested clarification on whether OPP would consider the availability of data on cholinesterase activity for compounds known to inhibit this class of enzymes.

Response. For a cholinesterase-inhibiting pesticide, OPP thoroughly evaluates all available cholinesterase activity data as part of the hazard identification and dose-response assessment. These data, although not specifically addressed in all OPPTS guidelines, have been required of registrants since 1992, as specified in a Data Call-In (DCI) for adult neurotoxicity studies that was issued at that time. The need for adequate information on cholinesterase inhibition in young animals has been recognized by OPP. In order to address this concern for the cholinesterase-inhibiting organophosphorus pesticides, OPP has included a requirement for submission of comparative blood and brain cholinesterase measurements in dams and offspring in the September 10, 1999 DCI that was issued to require submission of developmental neurotoxicity studies (as well as any outstanding adult neurotoxicity data). OPP intends to include similar requirements in future DCIs that will be issued, in accordance with the process described in the 10X policy paper, for the other class of cholinesterase-inhibiting neurotoxic chemicals (e.g., the N-methyl carbamates). OPP also is encouraging the collection of enzyme activities in peripheral tissues. For further details on how OPP interprets these data in the risk assessment process, the reader is referred to the recently-issued OPP science policy paper entitled *The Use of Data on Cholinesterase*

Inhibition for Risk Assessments of Organophosphorus and Carbamate Pesticide (US EPA 2000a).

Comment 4. One commentor (778) stated that the proposed core toxicology database was inadequate to assess the potential hazards to children for several reasons including the lack of toxicology studies for assessing all developing systems, particularly the immune and endocrine systems, and the lack of toxicology studies that assess the organism throughout its life span. In addition, comments were made that potential developmental neurotoxicity should be assessed for all chemicals.

Response. OPP agrees with the commentor that, as scientific understanding of the potential toxicity of chemicals to humans grows, EPA needs to reexamine its policies regarding the types of data that are useful for risk assessment. With that in mind, in June 1999, the Agency's Risk Assessment Forum formed a Reference Dose (RfD) Technical Panel to reevaluate the Agency's RfD methodology. As part of this effort, the RfD Technical Panel is evaluating all of the toxicology test guidelines and study designs the Agency most frequently encounters in reference to the specific endpoints and life stages to determine which elements are adequately assessed and which are not. When this analysis is complete, the Agency will commence the updating of existing guidelines and/or development of new test guidelines.

Clearly the fields of toxicology mentioned in the comment–immunotoxicity, endocrine system effects, and developmental toxicity studies–are currently some of the more active areas for research and development of new testing methodologies. While there is a lot of new information, OPP does not think that, at this time, the scientific foundation exists for making most of these types of studies routine requirements. Nonetheless, EPA is moving to bring the research effort in these fields to a stage that would warrant its use in a regulatory context. Work is currently underway in the Agency to develop a testing protocol for developmental immunotoxicity. The Developmental Immunotoxicity Working Group, comprised of scientists from OPP, OPPT, ORD/NCEA, ORD/NHEERL, and OCHP participated in a meeting on developmental immunotoxicity testing held by ILSI/HESI in spring 2001 and continue to work with EPA's NHEERL laboratories in researching the techniques that could be validated to predict human hazard with respect to developmental immunotoxicity. With reference to the evaluation of the endocrine system, several new endpoints which often have a hormonally-mediated basis were incorporated into the updated two-generation reproductive toxicity test guideline issued in 1998. In addition, EPA is in the process of developing and validating other test guidelines to assess impacts on the endocrine system as an element of the implementation of the

FQPA-mandated Endocrine Disruptor Screening Program. Once these are validated, these tests will also be incorporated into OPP's data requirements, as appropriate. Until then, however, these studies are unlikely to be designated as a routine data requirement. Regardless of whether a study is a routine data requirement or not, when data gaps exist, in deciding to apply a database uncertainty factor, the risk assessor should consider the 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.

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Comment 5. The SAP felt that the Agency was justified in including the evaluation of the immune system as part of Tier 1. Guidelines for immunotoxicity testing already exist with regard to chemicals (OPPTS 870.780) as well as for the biochemical pest control agents (OPPTS 880 series). It is particularly significant that a functional test for immunity be included in this data set. A test that challenges the immune system to respond (such as the antibody response to sheep red blood cells) is appropriate. The assay that utilizes this antigen has undergone extensive validation. Furthermore, a considerable database exists with regard to pesticide exposure on this response in experimental animals.

The SAP recommended that the Agency consider a flexible science-based approach to the design and conduct of immunotoxicology studies by carefully considering the results from the other tests proposed in Tier 1 that identify other potential target organs and consideration of potential for recovery or transient effects. It is cautioned that currently, predictive animal models for autoimmunity are not well developed and the paucity of biological information on the developing immune system represents a limitation in the identification and inclusion of such endpoints into a testing protocol. The Agency should continue its efforts to develop and validate protocols that are designed to evaluate the potential for chemically-induced developmental immunotoxicity. The goal should be the creation of a carefully designed developmental toxicity study that incorporates the evaluation of functional immunity.

Response. OPP appreciates the Panel comments regarding the immediate need for adult immunotoxicity screening. As the Panel noted, OPPTS already has revised its repeated dose study guidelines to incorporate the evaluation of additional endpoints as an immune system screen. In addition, OPP will formally propose to include the in vitro screen as a Tier 1 requirement for certain

categories of food-use pesticides when it proposes revisions to 40 CFR 158 in the near future. The Agency agrees that a flexible, science-based approach to study design is necessary. The OPPTS 870.7800 immunotoxicity guideline states that "...the tests described in this guideline are intended to be used along with data from routine toxicity testing, to provide more accurate information on risk to the immune system. The tests in this guideline do not represent a comprehensive assessment of immune function."

The need for the creation of a guideline for the assessment of developmental immunotoxicity remains a priority in OPP, and work is underway in the Agency to develop a testing protocol for developmental immunotoxicity (see previous response to Comment 4.). Therefore, ongoing efforts within EPA continue to explore updates in the science and in available testing methodologies, with the expectation that guideline development will move forward as soon as feasible.

ISSUE 6. Approach to Calling in Neurotoxicity Data

After having considered the recommendations from the FIFRA Scientific Advisory Panel and the Toxicology Working Group, OPP is beginning the process of calling in data for three studies (the acute and subchronic neurotoxicity studies in adult mammals and the developmental neurotoxicity study) for a subset of conventional chemistry food-use pesticides known neurotoxicants. In addition, OPP will be proposing to require the same set of studies for all conventional chemistry food-use pesticides in the revision of the 40 CFR 158 regulations. Please comment on this two-stage approach.

Comment 1. Three commentors (369, 776, 778) supported the OPP decision to call in the data for the acute and subchronic neurotoxicity studies in adult mammals and the developmental neurotoxicity study, and additionally concurred with the two-stage approach as proposed in the 10X policy paper. Additionally, Commentor 773 agreed that it is reasonable, in principle, to require these types of studies for compounds either known to be neurotoxic or structurally related to neurotoxic compounds.

Response. Since the guidance document was presented to the SAP in May 1999, OPP has issued the first of the Data Call-Ins (DCIs), for 34 organophosphorus (OP) pesticides. The DCI (dated September 10, 1999) also included a list of neurotoxic chemical classes for which future DCIs will be generated. After the September 1999 DCI was issued, OPP and industry scientists met to discuss topics related to study design and conduct, focusing on specific requirements for the Developmental Neurotoxicity (DNT) study for the

specific chemicals included in the DCI. OPP has received and reviewed the draft DNT protocols for all the OPs that will undergo testing. OPP continues to work with industry to facilitate the prompt initiation of the required DNT studies.

Comment 2. A number of commentors (593, 709, 712, 755, L07, L32) opposed the addition of any animal testing to the standard battery of toxicity studies already required to support the registration of pesticides. In addition to this generic response, specific issues raised by commentors included opposition to the addition of any new study without a full review of the existing 19 animal tests required already (in accordance with guidelines drawn up by the NIH pursuant to the 1993 NIH Revitalization Act), to the proposed 21-day dermal toxicity study, and to the addition of the DNT study that the commentors assert will kill 1,200 animals per chemical (553, 709, 712, L32).

It was suggested by Commentor L32 that the 21-day dermal toxicity study should not be used to extrapolate percutaneous absorption in humans, but that data from human volunteers, from *in vitro* studies with human tissues and cells, and PBPK models can be used to more accurately describe the ADME profile of a specific chemical.

Commentors L32, 755, and L07 also stated the opinion that the addition of new animal tests will not provide a “reasonable certainty” of the safety of chemicals nor a “high level of confidence” that infants and children are adequately protected from risk to pesticide exposure. Further, Commentor 755 suggests that such tests would serve little purpose other than to provide dubious evidence to increase tolerance levels; therefore, there would be no need for these tests to be conducted.

Commentor 775 asserts that interspecies toxicity factors may vary by factors far greater than 10X, and that the safety of children would best be served by an improvement of systems that take into account the metabolism and toxicokinetics of the chemicals in human beings. Commentor L07 suggests that *in lieu* of animal testing, a 10-fold safety factor should standard be added for all pesticides.

Response. Contrary to the comments, OPP is not proposing to add a substantial number of new tests to its long-standing data requirements for registration/reregistration of food use pesticides the evaluation of neurotoxicity or other types of toxicity. As previously addressed in the Response to the second comment under Issue 5, OPP is identifying, for the most part, key study types from within the existing set of data already required and also is encouraging the chemical sponsor to combine two or more stand-alone study endpoint evaluations into single study designs, whenever feasible.

That said, it is emphasized that the 10X policy paper recommends that specific *currently available* toxicology studies be considered in evaluating the completeness of the toxicology database, but did not propose the immediate addition of any new, previously unavailable, animal study types to the database. OPP continues to believe that consideration of the specified animal testing, as described in the OPP 10X policy paper, will add significant value to the weight-of-evidence evaluation that supports the determination of "a reasonable certainty of no harm" to infants and children for any pesticide, and will increase the overall level of confidence regarding this scientific judgement.

OPP does not think that the scientific basis has been adequately established for using information from either *in vitro* studies with human cells or PBPK modeling in place of animal toxicity data. PBPK models are still under development and are not yet standard methods. OPP would consider such data on a case-by-case basis, the availability of such information would not lessen the need for animal toxicity data.

In response to the commentor who suggested that, *in lieu* of animal testing, the FQPA Safety Factor should be retained in all cases, OPP would respond by noting that if there were no toxicity data generated to provide information upon which a FQPA Safety Factor decision could be made, the legislative mandate to make a "reasonable certainty of no harm" finding could not be met for most, if not all, pesticide chemicals.

Comment 3. One commentor (788) suggested that any future developmental neurotoxicity testing should be conducted concurrently during the course of a two-generation reproductive toxicity study; such testing should only be required for new pesticides and currently registered ones which do not already have a two-generation reproduction study.

Response. As noted elsewhere in this document, OPP encourages the combining of testing, where practical. In this case, the Agency would find it acceptable for a sponsor to conduct the developmental neurotoxicity (DNT) study within the multigeneration reproduction study, *but only if the combined study includes evaluation of all of the elements cited in each individual protocol.* If it is apparent to the pesticide's sponsor that both the multigeneration reproduction study and the DNT would be needed to support the initial or continued registration of its chemical, the sponsor would be wise to consider the possibility of conducting a combined study.

The Agency disagrees with the suggestion that the DNT should not be required if a multigeneration reproduction study already exists. This study design, on its own, does not include an adequate evaluation of nervous system development and function.

Comment 4. Commentors 772 and 773 disagreed that the neurotoxicity studies should be conducted as Tier 1 studies, i.e., automatically required for all classes of conventional chemical food-use compounds. Commentor 773 states that, until issues regarding study design and interpretation are resolved, OPP should proceed cautiously.

Commentor 772 provided additional extensive comments on this issue:

This commentor endorses a tiered testing approach so that additional animal use, neurotoxicology testing resources, and EPA resources are focused on those chemicals that actually represent a hazard. Neurotoxicological evaluations should follow a tiered testing strategy in which the initial Tiers identify a hazard and subsequent Tiers characterize any hazards that are identified.

Subchronic neurotoxicity tests in adult rodents should not be required for all active ingredients. This study was designed to be, and has traditionally been, a Tier II study. Conversely, the standard subchronic toxicology test has been a Tier I requirement for many years. The latter test has been recently revised to include formal neurobehavioral evaluations and enhanced clinical observations that provide enhanced screening-level information to make an informed judgment about neurotoxic potential. The adult neurotoxicity test battery could be triggered if the screening data from the standard 90-day toxicology test suggest that a neurotoxic hazard exists.

The acute neurotoxicity test in adult rodents should not be required for all active ingredients. Instead, EPA should develop a first Tier acute toxicity test that evaluates multiple toxicity endpoints. EPA should expand the requirements of the

currently required acute oral toxicity study to include controls and additional dose levels so that a reliable acute NOEL can be established. EPA recently provided more detail in the description of clinical observations in the acute oral toxicity test guidelines. These clinical observations can be conducted frequently which is an important advantage over the endpoints required by the acute neurotoxicity study in screening for acute effects. The acute neurotoxicity study could be triggered if either the acute or subchronic repeated dose study suggests that a neurotoxic hazard exists.

The developmental neurotoxicity (DNT) test should not be a requirement for all pesticide active ingredients. Instead, EPA can enhance the standard reproduction toxicity study to include endpoints that provide additional focus on developmental neurotoxicity. EPA's proposal to require the DNT test as a first Tier test for all pesticides is inadequately justified. EPA notes that Goldey et al. (1995) showed that 50-70% of pesticides causing developmental neurotoxicity did not alter traditional developmental landmarks and growth indices. Further, Goldey et al. (1995) classified chemicals as a developmental neurotoxicant if they affect any of the neurological domains, regardless of their mechanism or duration of action on the nervous system. Goldey at al. (1995) then determined if any of these chemicals had effects in the Chernoff/Kavlock assay which has limited *in utero* exposures and limited data collection during the early postnatal period. This comparison overstates effects as evidence of developmental neurotoxicity and underestimates the screening ability of currently required developmental and reproductive toxicity studies. The outcome of this comparison does not support the conclusion that all compounds should therefore be subjected to the DNT battery. In fact, a major conclusion from Goldey et al. (1995) is that “the importance of exposure periods that span the development of the nervous system (which in rodents extends well into the postnatal period) cannot be overemphasized in the hazard identification of potential developmental neurotoxicants.” An alternative interpretation of Goldey et al. (1995) is that a standard reproduction toxicology study will more effectively screen for potential developmental neurotoxicants than the Chernoff/Kavlock assay.

The commentor also disagrees with the EPA interpretation of *A Retrospective Analysis of Twelve Developmental Neurotoxicity Studies Submitted to the USEPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS)*, a review of the results of DNT tests for 12 neurotoxicants (USEPA 1998c). EPA partitioned the data for the 12 chemicals in various ways to support the need for DNT tests for all chemicals. But EPA ignored the key outcome that the DNT tests did not cause a single chemical on the list of 12 to be regulated at lower exposure levels than the levels determine by other more traditional toxicology tests.

Response. 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. This includes 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 developmental neurotoxicity 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 developmental neurotoxicity 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.

OPP intends to seek comment on whether the acute and subchronic neurotoxicity studies in adult animals be routine data requirements. These studies are currently conditionally required ("triggered" by some special characteristic of the pesticide or by potential use and exposure patterns or by the results of the required studies) but are viewed as important data, given the well established experience with these studies and their value in characterizing neurotoxicants.

Issues raised by Commentor 772, regarding the interpretation of the retrospective analysis of DNT studies submitted to OPPTS, are addressed in depth in the OPP response to comments on Comment 9.2. The argument that the DNT studies examined did not provide any information that was critical in the regulation of the specific chemicals examined is not, in fact, correct. Additionally, *A Retrospective Analysis of Twelve Developmental Neurotoxicity Studies Submitted to the USEPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS)* (USEPA 1998c) provides extensive discussion regarding the use of the DNT study in risk assessment, and affirming the value of the study for this use.

Comment 5. The commentor also recommended that an acute toxicity test be developed which would allow a dose-response assessment and could potentially provide endpoints for acute dietary risk assessment.

Response. There are efforts underway, both domestically and internationally, to develop a single-exposure toxicity test guideline that would evaluate a wider variety of endpoints than does the current acute neurotoxicity protocol. This test would be used when the need for an acute dietary risk assessment was identified. This determination would be made upon evaluation of toxicity information gathered in the first Tier of mandatory testing for a food-use pesticide. A draft guideline was prepared at the recent WHO/FAO Joint Meeting on Pesticide Residues. This document, along with a commitment to serve as sponsor for the development of an OECD guideline, was forwarded to the manager of the OECD Test Guidelines Programme, for that organization's consideration. These two items can be found on the WHO website at (http://www.who.int/pcs/jmpr/jmpr.htm).

Comment 6. Commentor 772 endorses the use of the reproduction toxicity study to screen for developmental neurotoxicity instead of OPP's proposal to required an extensive DNT battery for all active ingredients for several reasons:

The reproduction study involves an extensive assessment of effects on reproduction, behavior, and growth and development of the offspring. Such information involving maternal and neonatal toxicity would add considerably to the ability to interpret neurobehavioral changes in the developing animal.

Unlike the DNT study, the duration of exposure in the reproduction toxicity study is most relevant to human exposure. Each chemical would be administered continuously for an extended period of time, thereby providing the greatest opportunity to detect possible effects on the developing nervous system by the anticipated route of exposure.

The reproduction toxicity study design already includes examinations of selected F1 and F2 offspring at weaning (postnatal day 21) that are relevant to neurotoxicity assessment: thorough necropsy examination of all P and F1 parental animals; histopathology evaluation of reproductive organs, pituitary, adrenal glands and target tissues; and endpoints such as weekly clinical observations, body weight and food consumption measurements, clinical chemistry, and hematology.

A stand-alone DNT study uses a large number of animals. By obtaining additional information from animals that are already being used in a reproduction study, the proposal to enhance the protocol helps to reduce the number of animals while not negatively impacting the ability to identify a developmental neurotoxicity hazard. If screening-level developmental neurotoxicity information triggers further investigation, the plan ensures that additional animal use is focused on those chemicals that actually represent an hazard.

The commentor endorses the following specific enhancements to the reproduction study:

- Greater detail for clinical observations and functional tests of the offspring. These enhancements would include observations that are performed while the animal is outside the home cage, preferably in a standard arena, and the use of rating scales for certain behavioral/neurological clinical signs.

- Brain weight measurements on postnatal day 21 and day 60 (already required).

- Histological examination of the brain at postnatal day 21 and of the central and peripheral nervous system at day 60.

- A test of cognitive function to determine whether there is evidence of potential effects on learning and memory.

- A longer duration of exposure (from premating through PND 21) than that used in the guideline developmental neurotoxicity study design. The longer duration of exposure includes a period that involves continued development of the nervous system (already required).

EPA should convene a workshop to discuss the details of a study design to screen for developmental neurotoxicity. The participants should examine how best to enhance the design of the reproduction toxicity study to create a first Tier screen for neurotoxic potential.

The requirement for careful clinical examination during standard subchronic and

chronic toxicity studies provides good guidance needed to screen animals for neurobehavioral effects. However, the number of animals required and frequency of evaluation should be amended so that the necessary toxicology evaluations can be appropriately conducted in a manner that is not unnecessarily burdensome. EPA requires a clinical examination be made at least once prior to the initiation of treatment and once weekly during treatment in all animals. The commentor embraces the detailed description of clinical examination, but believes that it is more appropriate to conduct these evaluations monthly in the subchronic study and quarterly in the chronic study. Of course, the health status of all rats would continue to be monitored through the daily mortality checks and weekly cage-side observations.

Response. OPP agrees with the commentor that the two-generation reproduction study can be expanded to accommodate developmental neurotoxicity testing. Since the developmental neurotoxicity study guideline was finalized in 1991, the Agency has clearly indicated that, although the DNT guideline describes a stand-alone study, a well-conducted combined DNT/reproduction study would be considered adequate to meet regulatory requirements. OPP sees no benefit in conducting a combined study if a valid reproduction study already exists, and, in fact, would consider a combined study in such a situation to be a waste of resources. The guideline itself contains language that states this to be the case: "This protocol may be used as a separate study, as a follow up to a standard prenatal developmental toxicity and/or the (repeat dose) adult neurotoxicity study, or as part of a two-generation reproduction study, with assessment of the offspring conducted on the second (F2) generation." [OPPTS 870.6300 (c)]. Both the availability of a stand-alone protocol and the authorization to conduct the study in a combined protocol, are necessary to accommodate the testing needs for all pesticide chemicals, whether related to registration or reregistration actions.

There are reasons that a combined two-generation reproduction/developmental neurotoxicity study would be particularly useful, and many of these considerations have been described in the comments. These include evaluation of a population of offspring with maximized exposure duration (i.e., that have been treated throughout pre- and postnatal life), assurance that steady state levels of test substance in the animals have been achieved prior to neurotoxicological testing, evaluation of neurobehavioral effects within the larger context of assessments of maternal and neonatal toxicity offspring growth and development, and better utilization of animals already on study.

The proposal for enhancements to the reproduction study that are designed to screen for developmental neurotoxicity includes functional observation battery (FOB) assessments of pups, brain weight measurements at two time points, qualitative neuropathology at two time points, and learning and memory testing. The proposal does *not* include assessments of the ontogeny of motor activity or auditory startle habituation (two particularly sensitive endpoints, as demonstrated in USEPA 1998c), mention of a second time point for learning and memory testing, or a quantitative evaluation of brain development in the neuropathology examination. With the addition of these few missing items, the commentor's proposed "enhanced reproduction study" would be equivalent to a combined reproduction/DNT study.

The developmental neurotoxicity study protocol provides an assessment of a wide selection of endpoints and time points in order to maximize the potential for detection of effects on the developing nervous system. By reducing the number of sensitive endpoints examined or by dropping the assessment of ontogeny of nervous system development, as is proposed in the enhanced reproduction study, the likelihood of detection of developmental neurotoxic potential would be greatly reduced. Therefore, OPP considers the guideline DNT study to be the representative screening assessment for developmental neurotoxic potential, whether conducted as a stand-alone protocol or when incorporated into a standard two-generation reproduction study. In addition, OPP believes if the DNT is incorporated into the multigeneration reproductive toxicity study, the combined study should incorporate all of the endpoints required in the stand-alone DNT, as well as all of those required in a stand-alone multigeneration reproduction study. Only under these circumstances would the combined study to be considered an acceptable study.

Comment 7. Commentor L015 stated that, as part of the guideline development process, EPA's criteria for interpretation of the results of the studies should be developed and subjected to public comment.

Response. OPP scientists review all toxicology study data (including the developmental neurotoxicity study) in detail, and interpret the findings utilizing time-honored principles of basic scientific data analysis. These reviews are conducted according to applicable peer-reviewed Agency risk assessment guidance that specifically address the interpretation of data, e.g., the *Guidelines for Developmental Toxicity Risk Assessment* (USEPA 1991) and the *Guidelines for Neurotoxicity Risk Assessment* (USEPA 1998a). (Several other peer-reviewed Agency guidelines also exist for other endpoints of toxicity.) Further, to provide consistency in the reporting of developmental neurotoxicity studies, OPP (in cooperation with Health Canada PMRA) has recently created a standardized format that can be utilized in the generation of Data Evaluation

Reports.

Regarding chemical-specific issues of data interpretation, OPP has committed to reviewing the results of submitted developmental neurotoxicity studies, within the context of each chemical toxicity database (including the adult acute and subchronic studies, as well as the prenatal developmental studies and the multigeneration reproduction study), in an external peer review process. The first such review was conducted in December, 1998, when the FIFRA Scientific Advisory Panel reviewed the Retrospective Analysis of Twelve Developmental Neurotoxicity Studies Submitted to OPPTS. As more DNT studies are submitted to OPPTS, subsequent reviews and analyses will be conducted consistent with scientific principles. This process will be transparent and will include an opportunity for public comment on HED's interpretation of the study data and conclusions.

FIFRA Scientific Advisory Panel Comments

Comment 8. The Scientific Advisory Panel members agreed that the two-stage approach for expanding the newly required test methods appears to be logical. However, they expressed some concerns regarding what was seen as a collapse of toxicology testing requirements into a single tier system. One member of the Panel argued that such a system would not encompass all of the concerns that one would have for purposes of dose-response assessment. Broad screening studies should be used to identify hazard, and then a second tier of studies should be used to specifically aim at establishing a dose-response relationship for endpoints most useful for making a regulatory decision.

Response. The order of toxicological test conduct is not specified by the Agency, but rather selected by the pesticide's sponsor. It is highly unlikely that a sponsor/registrant will conduct all required toxicology studies simultaneously for any specific pesticide chemical. Generally, the less-complex, shorter-duration studies are conducted first. Therefore, information from other studies in the database (e.g., acute, mutagenicity, subchronic, range-finding, chronic/carcinogenicity, prenatal developmental, and/or reproduction studies) will generally be available to contribute to study design and dose-setting decisions for more complicated studies such as the DNT.

Comment 9. The SAP stated that, at present, the need for the developmental neurotoxicity test seems to rest largely on the premise that it is at times the "most sensitive" response from a dose-response perspective. The same argument could be attributed to the endocrine system or even control of intermediary metabolism

(e.g., cholesterol synthesis). Clearly, sensitivity arises from specificity in the measurements one can identify to detect adverse effects and functional endpoints with other organ systems. It was the opinion of the Panel that nervous system evaluations come to the forefront because functional measurements are so much richer than those evaluations applied to other organ systems. The opportunity to refine the developmental neurotoxicity testing battery should not be missed. While the endpoints in the current battery assess the integrative functioning of the sensory, motor, and cognitive systems with supportive neuromorphology measurements, the limited exposure via the mother/dam may not provide adequate or accurate levels of exposure to the offspring to assess neurotoxicity. Aspects of the dosing paradigm to consider are the extension of exposure to postnatal day 21 (consistent with the OECD guidelines), direct administration of the compound to the offspring after birth, and shorter intervals of exposure, including direct acute exposure during development.

Response. OPP agrees with the Panel's assertion that the most sensitive response in offspring could reside in a physical or functional endpoint in a tissue or organ system which is not yet evaluated in depth within the context of existing guideline toxicology studies. The availability of validated testing protocols for the assessment of every possible biological endpoint, however, is not realistic. (It is noted that several of the endpoints mentioned by the SAP are identified in the 10X policy paper, for the development of further guidance.) The DNT study is an exception, having been subjected to extensive scientific evaluation over a decade ago, (as reported by Kimmel et al. 1990 in a special issue of *Neurotoxicology and Teratology*, entitled Qualitative and Quantitative Comparability of Human and Animal Developmental Neurotoxicity) and having been peer reviewed by the FIFRA Scientific Advisory Panel, as well as through a formal public comment process, prior to guideline finalization.

An analytical review of the developmental neurotoxicity studies that had been received and evaluated by OPPTS from the time that the guideline was developed until late 1998 was presented to the SAP in December 1998. Issues relevant to potential guideline update and improvement were discussed in that analysis and in the Panel members' responses to questions from OPP. Since that time, OPP has, through a cooperative agreement, participated in a project coordinated by ILSI Risk Sciences Institute to address many of these same issues. Efforts to coordinate and harmonize with guideline development efforts by the OECD, which also address some of these revision concerns, are also ongoing.

While OPP has determined that DNT guideline revision activities should proceed formally in the context of the OECD guideline development process, OPP scientists have attempted to address some of the more immediate

concerns in the Data Call-In process, particularly in areas where there appears to be preliminary agreement that change/upgrading is needed. Specifically, the DCI language that was issued for the organophosphorus (OP) pesticides on September 10, 1999 has included modifications or additional requirements for the conduct of the DNT study for this class of substances, including the following:

- extention of the duration of dosing beyond postnatal day 10 to postnatal day 21;
- the need for a reliable estimate of the presence of test substance in the milk, with a directive to consider other methods of exposure, including the possibility that direct administration to offspring may be necessary;
- an increase in the number of animals evaluated for neuropathology;
- comparative evaluation of cholinesterase inhibition and behavior in young organisms and adults.

The additional requirements, and the way in which these requirements will need to be addressed in the protocols for these specific DNT studies, will respond to the concerns raised by the Panel, at least for the OPs. Future DCIs, for other chemical classes, are similarly expected to address these concerns, along with any other chemical-specific considerations that are identified.

Comment 10. The SAP commented on the fact that the Agency is beginning the process of calling in data for the developmental neurotoxicity study for a subset of conventional chemistry food-use pesticides known to possess neurotoxic potential. They stated that there is a certain logic in using known neurotoxic pesticides as the initial test cases from which to gain knowledge and experience in the evaluation of data from the newly required neurotoxicity studies. That is the case because there should be a greater likelihood of at least some degree of neurotoxic effects observed in tests of this subset of pesticides. However, there is also the likelihood of bias from this data set of known neurotoxicants. Alternatively, the Agency should consider that selecting a few pesticides from the universe of those that do *not* act by neurotoxicity mechanisms could be instructive for comparison with representative samples of the neurotoxicants (e.g., organophosphates, carbamates and synthetic pyrethroids) in the developmental neurotoxicity studies. This would allow the Agency to more accurately assess the sensitivity gained with the developmental neurotoxicity data.

Response. OPP recognizes the challenges that will present themselves when the DCI-initiated developmental neurotoxicity study data for the neurotoxic

pesticides become available for review and analysis. Analysis of the results of these studies alone will not be able to fully address the question of whether the DNT study should be conducted routinely for all chemicals. Nevertheless, these data, although biased towards the expectation of detection of an effect on the neurological system, will aid in identifying differences in response between the adult and developing animal. Therefore, the data will provide an answer to the question of whether this specific, newly-added trigger for DNT testing was predictive of differences in sensitivity. It is further noted that there have been a number of pesticides that have been identified over the past decade as meeting various criteria that would suggest that a DNT study should be performed. Some of these chemicals are not considered to be neurotoxicants in the classic sense (e.g., their principal mode of pesticidal action). Data from these chemicals, which will also be called in through the DCI process, should provide some basis for scientific comparison, but may still not definitively address the question of whether the DNT study should be routinely conducted for all chemicals. OPP plans to issue DCIs for some of these during the early phases of the DCI process.

ISSUE 7. Application of an FQPA Safety Factor Pending Receipt of Newly-Required Studies

The OPP policy guidance indicates that one of the critical issues is whether or not to apply an FQPA Safety Factor pending receipt of newly-required studies. There are a variety of possible approaches. One possible approach would be to apply the FQPA Safety Factor's database uncertainty component to gaps related to new core data requirements only where there are specific concerns regarding the pesticide pertaining to the data requirement. Alternatively, OPP could apply the default 10X factor (or some other additional factor) whenever a new data requirement is added and/or whenever a testing guideline is changed. Please explain how you think the FQPA Safety Factor provision should be implemented when OPP makes such changes. In commenting, please address whether OPP should apply the default FQPA 10X factor, some different yet additional factor, or no factor at all in the following circumstances:

- *A minor change to testing guidelines.*
- *A major change to testing guidelines.*
- *An addition of a new required test.*
- *An addition of a new required test to core requirements.*

Comment 1. Several commentors (372, 773, 781, L016) supported the proposed redefinition of the "core" toxicology database. Commentor 372 (American Water Works Association) stated that the clear criteria OPP laid out for electing to require a new methodology as part of the core toxicology database, represent sound science. Specifically, Commentor 372 indicated strong support for what they interpreted to be the OPP position, i.e., that new kinds of toxicological studies will not be placed into the core toxicology database until it is clear that those studies provide information that is essential in deciding whether infants and young children are more susceptible/sensitive than the rest of the population. It was the opinion of this commentor that if new studies (e.g., different kinds of neurotoxicity assessments) are required as part of the core toxicology database, it will be increasingly difficult for OPP to justify any numerical value for the FQPA Safety Factor other than 10 until specific pesticides are reevaluated using the data from the new studies. Additionally, Commentor 372 suggested that such broad application of the 10-fold FQPA factor might be necessary even if the new studies do not significantly improve the ability of the Agency to determine whether existing Reference Doses (RfDs) are protective of infants and young children.

One commentor (781) interpreted the draft 10X guidance document to state that an FQPA Safety Factor would only be applied for missing data if those data were considered to be part of the minimum core data requirements, and on that basis disagreed with the use of the redefined core data set.

Commentor 776 recommended that EPA include the DNT study in the list of core toxicology data that would lead to the application of a database uncertainty factor if they were missing in the database.

Response. As discussed in responses to comments above, OPP does not retain the distinction between core required data versus newly required data in the revised guidance. The absence of any study important to evaluating effects in the young will be considered under the traditional database uncertainty factor like any other missing study. In other words, when data deficiencies 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. Thus, in addition to identification of toxicity information that is lacking, review of the available data may also provide information as to this potential. In deciding whether to retain the default 10X factor or 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, route and duration of exposure. It should be emphasized that studies using adult animals may help inform the judgment about potential effects in the young and the need for additional studies. The size of any FQPA safety factor would depend on the degree of concern about the pesticide’s potential to affect the young and would take into account the potency, severity, and persistence of the observed effects. Also see Section III of the Revised Guidance Document.

Notwithstanding commentor 781's characterization of the draft policy paper regarding the application of the FQPA Safety Factor in situations where data are missing, in the revised guidance document, the absence of developmental neurotoxicity study would be treated like any other missing data.

Furthermore, OPP recognizes the need to improve and revise its data requirements for pesticides. Since the promulgation of FQPA, there have been a number of activities 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. This includes 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 and a more systematic evaluation of toxicokinetics. For example, OPP plans to publish proposed revisions to its pesticide data requirements regulation, 40 CFR 158, and expects to ask for comment on including the developmental neurotoxicity study as a standard requirement or using a logic- and information-based approach that would aid in designing a mechanistic approach to evaluate developmental neurotoxicity and/or other functional effects based on what is known about the pesticide.

Comment 2. Retention of the full 10X FQPA factor in the absence of any single piece of toxicity or exposure data that could reliably inform the Agency about potential risks to infants and children was supported by several commentors (761, 771, 778, L021). The commentors stated specifically that the absence of a newly-required study, or one that is required by Data Call-In, should in all cases immediately lead to the retention of a 10-fold uncertainty factor. Commentor 778 rejected the EPA criterion that the absence of a newly-required study should lead to retention of some database uncertainty factor only if the new data are so "key as to warrant an additional uncertainty factor;" Commentor 771 stated that data deficiencies should never be regarded as "minor," and Commentor 781 disagreed with the use of a defined "core" toxicology data set in determining the need for an FQPA factor. Reasons for retention of the full 10X FQPA factor (as cited in the comments) included: (1) that application of the 10X in the absence of any data is a statutory mandate (761, 771, 778, L021); (2) that the retention of an FQPA Safety Factor would provide industry with an incentive for developing the data and submitting missing studies to the Agency as quickly as possible (761, 771, 778); and (3) that the need for a 10X factor is supported by comparisons of human and rodent data for pharmaceuticals and specific neurotoxic pesticides (L021). According to Commentor L021, there is at least a 6000-fold difference in response to pharmaceuticals among humans. Additionally, Commentor L021 asserts that for lead, PCBs, and mercury, neurotoxicity testing in rodents consistently underestimates the dose that can affect the developing animal, and the developmental neurotoxicity study in rodents can fail to identify effect levels in humans, by a factor of greater than 10-fold.

Response. The draft policy clearly indicated that OPP first assumes that the full 10X FQPA Safety Factor is applied for each food-use pesticide. A subsequent weight-of-evidence analysis of the available toxicity and exposure data may justify the use of a different (lesser or greater) factor for each chemical. OPP believes that this approach is consistent with the statutory requirement of FQPA.

The retention of a 10-fold traditional database uncertainty factor for missing toxicity studies or a safety factor for missing exposure data would generally provide the regulated industry with an incentive to quickly conduct and submit the missing studies. However, a desire to provide industry with an incentive to quickly produce studies should not trump all other considerations, particularly since OPP has adequate statutory mechanism to insure that data are provided in a timely manner.

As previously addressed in the OPP response to comments on Issue 2, the position that a uniform 10-fold safety factor is needed in every pesticide risk assessment to protect infants and children, based upon pharmaceutical data and selected neurotoxic pesticide data, is not an accurate representation of emerging scientific information on this issue. Discussion on the adequacy of the 10-fold intraspecies factor to address age-related differences in pharmacological and toxicological responses can be found in the 10X Task Force Toxicology Working Group Report, which summarized information available at the time it was drafted (USEPA 1999a). Since that time, additional studies have been conducted to further evaluate this issue and appear to reaffirm the adequacy of the 10-fold intraspecies factor, in the vast majority of cases.

Commentor L021 cited a paper by Rice et al. (1996) to demonstrate that studies in animals appear to underestimate the risk to humans for lead, methyl mercury, and PCBs. In that paper, utilizing what information was available for each of these three neurotoxic substances, the external (administered) dose in animal studies was compared to the estimated intake level in humans and then contrasted with the observed internal dose (i.e., body burden, as represented by substance levels in various tissues) in humans. This commentor asserts that for lead, PCBs, and mercury, neurotoxicity testing in rodents consistently underestimates the dose that can affect the developing animal, and the developmental neurotoxicity study in rodents can fail to identify effect levels in humans, by a factor of greater than 10-fold.

OPP does not think that the analysis by Rice et al. (1996) supports the commentor's conclusion. First, the comparison does not appear appropriate. A more precise approach might have been to compare internal dose (tissue levels) in both animals and humans, and contrast this information with known administered dose in animals and precise analytical measurements of exposure in humans. (OPP notes that obtaining such data is not practical for the regulation of most pesticides, since precise data on internal dose are seldom available.) Second, it is also noted that the chemicals represented in this analysis were selected because of their known potent neurotoxic potential to humans, which is mediated and exacerbated in part by their specific chemical-physical properties (i.e., long half life) and toxicokinetic disposition following exposure (i.e., accumulation in the body). Therefore, OPP concludes that the results of this analysis should not unduly influence policy development for the regulation of pesticides (although if a similar chemical profile were observed in any pesticide undergoing OPP review, it would be addressed appropriately in the risk assessment).

Additionally, OPP believes that the above example from Rice et al. (1996) is more of an exception than a typical example and it is inappropriate to use this limited analysis of extremely potent neurotoxic chemicals to suggest that animal testing cannot, as a general rule, be used to adequately predict human hazard and dose response for the purposes of risk assessment. In fact, the opposite position, that other organisms can serve as accurate predictive models of toxicity in humans, is a key assumption in modern toxicological testing (see standard toxicology textbooks such as Casarett and Doull's *Toxicology* (Casarett and Doull 1995), Hayes' *Principles and Methods of Toxicology* (Hayes 2000), and *Regulatory Toxicology* by Chengelis et al. 1995). Standard risk assessment practices, which rely upon dose response information generated in animal studies and known or anticipated exposure levels to humans, are described in multiple Agency policy documents, such as the guidelines for developmental (USEPA 1991), reproductive (USEPA 1996a), and neurotoxicity (USEPA 1998a) risk assessment, and in numerous scientific analyses and commentaries on the risk assessment process that exist in the peer reviewed literature such as the 1983 and 1994 NAS/NRC reports (NRC 1983 and NRC 1994)

In summary, OPP believes that the best approach to the determination of an appropriate FQPA Safety Factor for any pesticide will involve a case-by-case weight-of-evidence analysis of all available toxicology and exposure data, rather than a blanket application of a 10-fold FQPA factor for all pesticides. Such an approach is scientifically defensible and consistent with current Agency practices.

Comment 3. There were several comments (772, 773, L011, L016) that focused on the timing of the decision to retain an FQPA Safety Factor when new data requirements were imposed (either as the result of redefining the core toxicology database, or of issuing a Data Call-In). The opinion of these commentors was that OPP should first communicate the need for the data requirement, and then allow a sufficient amount of time for the registrant/sponsor to conduct the study before imposing an additional database uncertainty factor or FQPA Safety Factor on the basis of the completeness of the toxicity database.

Commentor 773 stated that there are legal and policy considerations that argue for allowing pesticide registrants adequate time to conduct a newly required study before OPP concludes that, in the absence of the study, the toxicology database is "incomplete" and retains the FQPA Safety Factor. For a long time, the statutory scheme has allowed EPA to impose data requirements and to apply sanctions if the new data were not submitted in a timely fashion. The statutory scheme also made it clear that companies were to be allowed adequate time to generate the required data before the sanctions were applied. Nothing in the FQPA or its legislative history indicates any Congressional intent to change this basic scheme.

Additionally, Commentor 773 predicts that serious market disruptions are likely to occur if OPP takes any other approach. If the new study requirement immediately triggers the additional FQPA Safety Factor, some portion of the use of the pesticide may need to be eliminated. Yet once the study is completed, it may appear that the additional FQPA Safety Factor was unnecessary, allowing the uses to be reinstated.

Several commentors took the position that a decisive element in considering whether the completeness of the data mandates retention of the additional safety factor is whether pesticide manufacturers have been given adequate time to produce any needed data. Commentor 773 writes:

OPP may determine that a study is needed to replace or supplement a previously accepted study (e.g., to address recent revisions in the guidelines or a recent reinterpretation of the earlier study), or that it wants a particular kind of study not previously required for a category of pesticides (e.g., a developmental neurotoxicity study). In such a situation, however, no additional safety factor should be applied merely because the study has not been conducted, until the need for the study has been announced and sufficient time to conduct and submit the study has been provided.

As a basis for this position, this commentor cites the FIFRA and FFDCA provisions addressing regulatory requirements for data requirements and regulatory procedures for requiring the submission of data in connection with existing registrations and tolerances. The commentor allows OPP may retain the additional safety factor for a pesticide if there is evidence suggesting that the pesticide may cause adverse effects at lower levels than seen in the existing database.

Response. As explained in the Introduction appearing before Issue 5, OPP proposed dividing the universe of toxicity data requirements into routinely required (of which some are also core) studies and conditionally required studies. In the revised guidance document, OPP does not make the distinction between core required and conditionally required studies in considering the need for a database uncertainty factors, as discussed above.

If the absence of any missing data raises concern, whether it is considered to be part of or not to be part of the routine toxicology database, then either the default 10X factor would be retained or a traditional database uncertainty factor would be applied using a weight-of-evidence approach. Thus, OPP disagrees in part with the commentors: OPP does intend to apply a FQPA factor (either the default value or a traditional database uncertainty factor) due to the absence of a "supplementary" toxicity study if its absence raises concern about the adequacy to evaluate potential effects in the young. OPP considers the FQPA Safety Factor to encompass the traditional database uncertainty factors. As explained in Section III of the guidance document, OPP has developed some broad criteria to guide its general decision-making about the significance of missing data. OPP would make the decision on a case-by-case basis.

If Agency scientists conclude, based upon available information on a pesticide, that the absence of a certain study is critical to the assessment of potential hazard to infants and children, then a traditional database uncertainty factors would be applied (assuming reliable data allow OPP to conclude that such factor is safe for infants and children), which would address the FQPA safety factor. A DCI, addressing the specific study(ies) that are expected to inform the scientific assessment, could be issued prior to or following the FQPA factor determination. OPP believes that delaying the application of an uncertainty or a safety factor to a risk assessment until identified critical missing data are submitted to the Agency would not be consistent with the application of the FQPA Safety Factor provision.

OPP agrees with the commentor that its approach to applying the FQPA Safety Factor should be consistent with the FIFRA and the FFDCA provisions authorizing OPP to establish data requirements for pesticide registration applications and tolerance petitions. Further, there are provisions in both statutes mandating that OPP require registrants, pesticide manufacturers, or others to keep databases on existing pesticides up to date. These Data Call-In procedures specify that data submitters must be given sufficient time to submit additional data before the sanctions in these provisions (which are designed to ensure compliance with Data Call-Ins) are applicable.

These Data Call-In provisions, however, do not address what inferences OPP should make regarding pesticide safety while data are being produced. OPP does not interpret the extreme sanction (suspension of registration or tolerance) included in the Data Call-In provisions for not taking appropriate steps to submit the data as barring OPP from making health protective assumptions for risk assessment conducted while the data are outstanding. Further, as noted in the draft policy, the children's safety provision also was silent concerning how the completeness of data consideration should be applied in circumstances involving new or revised data requirements.

OPP believes the primary guiding principle for interpreting the FQPA Safety Factor provision should be the paramount importance of protecting the health of infants and children. Further, the statutes' data collection provisions, including the enforcement mechanisms in these provisions, do not, on their face, elevate the concerns of pesticide manufacturers over the protection of infants and children. Although whether pesticide manufacturers have had sufficient time to produce data may have some relevance to the safety factor decision, this consideration should not automatically trump the need to protect infants and children. That does not mean that any data deficiency, no matter how small, should be used to justify retaining the full 10-fold safety factor. Thus, OPP can agree with IWG that "no additional safety factor should be applied merely because [a] study has not been conducted...." As OPP noted in the draft policy notice, taking such an expansive approach to implementation of the children's safety factor provision may actually be counterproductive in terms of collecting the best scientific data on pesticides. If any change in data requirements has the effect of requiring that an additional 10-fold factor be applied to all pesticides, OPP might very well be overly hesitant to require new studies in order to keep the pesticide database up-to-date.

Comment 4. A number of specific comments were received regarding the appropriateness of retaining an uncertainty factor for studies that may be required as a result of a redefinition of the core toxicology database or through a Data Call-In. One commentor (L011) stated that retention of the FQPA factor based solely on a change in data requirement(s) seems unfair and should not be necessary unless additional data can show that the margins of safety are not sufficient. Several other commentors focused their comments on the appropriateness of applying an FQPA factor based upon the lack of adult and/or developmental neurotoxicity studies. Commentor L015 stated that the absence of DNT and adult neurotoxicity studies justifies an uncertainty factor, but the magnitude of this factor should be decided on an individual basis. Commentor 773 disagreed with OPP's stated policy of using a database uncertainty factor greater than one when a subchronic neurotoxicity study has been triggered, but is absent. The commentor stated that OPP did not provide an adequate explanation of this policy and that, in some cases, registrants have not been notified that such studies are required. Commentor 772 stated that it is not necessary to automatically add a database uncertainly factor when the DNT test is missing. This position was based upon the outcome of the retrospective study in *A Retrospective Analysis of Twelve Developmental Neurotoxicity Studies Submitted to the USEPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS)* (USEPA 1998c), which demonstrated that the DNT studies received by OPPTS have not caused a single chemical on the list of 12 to be regulated more stringently than any other standard toxicology tests. The commentor concluded that the traditional uncertainty factors of 100X appear to be sufficiently protective for potential developmental effects, or at a minimum, that an automatic database uncertainty factor for chronic risk assessment is not needed when a developmental neurotoxicity study is missing.

Response. OPP believes that the decision to apply an FQPA factor cannot be based on whether or not the margins of safety are sufficient (as proposed by Commentor L011). This proposal is flawed in that it does not consider the uncertainty that results from the absence of any study that is considered critical in the assessment of hazard to infants and children. Sufficient margins of safety cannot be determined unless hazard is fully characterized or unless the impact of uncertainties has been addressed.

OPP agrees with Commentor L015, with the following clarification: that the absence of the DNT and the two adult neurotoxicity studies may justify an uncertainty factor, but that the magnitude of the factor should be determined on a case-by-case basis for each chemical. (See comments and responses in Issue 8.)

OPP has stated the intent to use a database uncertainty factor of greater than one when a subchronic neurotoxicity study has been triggered, but is absent. The fact that the study has been triggered indicates that the Agency has determined that there is an issue of concern that could be addressed by the subchronic neurotoxicity study for the specific pesticide under review. 40 CFR 158 already specifies that the acute and subchronic neurotoxicity study are required for neurotoxic chemicals; therefore, sufficient notification of the triggered requirement for this study has already been provided to registrants. As with the subchronic study, OPP has concluded that the absence of a triggered acute neurotoxicity study from the database does prompt concerns relating to the "completeness of the toxicity database" in regard to the safety of infants and children and will be taken into consideration in FQPA Safety Factor decisions.

Issues raised by Commentor 772, regarding the interpretation of the retrospective analysis of DNT studies submitted to OPPTS, are addressed in depth in the OPP response to comments in Comment 9.2. The argument that the DNT studies examined did not provide any information that was critical in the regulation of the specific chemicals examined is not, in fact, correct. Additionally, *A Retrospective Analysis of Twelve Developmental Neurotoxicity Studies Submitted to the USEPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS)* (USEPA 1998c) provides extensive discussion regarding the use of the DNT study in risk assessment, and affirming the value of the study for this use.

Comment 5. Commentor 369 supported the general approach of applying an additional safety factor in the absence of newly required studies, provided that a specific concern for the endpoint addressed by the study in question has been identified. This step would then apply regardless of whether a newly required study is missing or whether changes have been made to an existing guideline. The factor applied could be either the database uncertainty factor and/or an FQPA Safety Factor for residual concerns about the adequacy of the database. Commentor 773 also indicated that this approach may be appropriate.

As a related issue, Commentor 776 recommended that the Agency revisit the organophosphate (OP) pesticides, since the 10X factor was not added to them even though the developmental neurotoxicity studies were required.

Response. The approach described by Commentor 369 is, in general, that which OPP uses to determine how the absence of new data requirements will be considered in the FQPA Safety Factor evaluation. FQPA decisions that result from this approach are informed by a weight-of-evidence assessment of scientific data and an evaluation of residual uncertainties.

OPP agrees that the one particularly critical consideration for a safety factor determination is what existing evidence tells us about the pesticide. Thus, when additional data are needed on a pesticide, OPP examines whether that data requirement is being imposed because of a general desire to upgrade pesticide testing or because of some specific concern regarding the pesticide that was identified in the testing that had already been completed. General increases in the information needed to support pesticide registration or reregistration (which could be comprised either of a generic increase in required studies or of updates/revisions to existing testing guidelines) could be initiated by an evolving understanding of the pharmacological or toxicological sciences, or by the realization that the information provided is critical to an adequate understanding of potential hazard. Specific concerns that could elicit the request for additional information might include, for example, the observation of an effect which is not fully characterized, or the observation of a pattern of effects across the toxicological database that suggests that evaluation of previously unexamined endpoints is necessary to fully characterize hazard and dose-response. Such specific concerns could be identified for an individual chemical, for a chemical class, or for multiple chemicals with related modes of action.

Where the specific concern suggests that risk to infants and children may be underestimated, the lack of the study would weigh heavily in favor of retaining some or all of the FQPA factor. In such circumstances, there is a greater chance that the needed data may identify a lower regulatory dose level than observed in other studies in the chemical database, or demonstrate that young animals are more susceptible than adults to effects of the pesticide, leading to a more health protective approach to risk assessment (as opposed to demonstrating that the additional factor was not necessary). Where additional data requirements are being imposed more generically, it may be less likely that there is a specific concern regarding the underestimation of risk to children, and if so, there would be less need for the retention of an additional safety factor.

Comment 6. One commentor (773) stated that clarification is needed regarding

whether the lack of a developmental neurotoxicity study would be the basis of the decision to apply the FQPA Safety Factor.

Response. The presence or absence of a developmental neurotoxicity study will be part of the weight-of-evidence determination for another component (Residual Concerns) of the FQPA Safety Factor. A more extensive discussion of this issue is presented in the Response to Comments 4 and 5 above.

ISSUE 8. Criteria Indicative of Increased Concern for Pre- and Postnatal Hazards

In the absence of the results from any of the studies to be required through Data Call-In Notices (i.e., the acute and subchronic neurotoxicity studies in adult mammals and the developmental neurotoxicity study),

- *what information from existing studies on a specific chemical would increase or decrease the concerns about the potential for prenatal and postnatal hazard, in general,*
- *and for neurotoxicity and developmental neurotoxicity, in particular?*
- *which, if any, of the seven criteria discussed in Section V.A.1.a., footnote 4 and associated text of the OPP Guidance Document is appropriate for judging whether there is increased concern about the potential for a pesticide to cause developmental neurotoxicity?*
- *are there any other criteria which would be useful for informing this judgment?*

Overview:

The draft policy contained a list of seven criteria that OPP proposed to apply on a case-by-case basis to evaluate whether the database on a pesticide suggests reason for concern that the chemical may cause developmental neurotoxicity. The criteria were that the substance has been shown to:

- Î cause central nervous system (CNS) malformations following prenatal exposure;
- Ï affect brain weight in offspring, which does not appear to be related to general

growth retardation, following pre- and/or postnatal exposure; cause neuropathology in developing or adult animals or neuropathy in humans;

Ð cause persistent functional changes in the offspring which may be the result of effects on the nervous system;

Ñ act to significantly alter hormonal responses associated with the development of the nervous system, leading to significant developmental effects (e.g., effects on sexual maturation);

Ò act as a neurotoxicant in insects, unless other information about the chemical, such as pharmacokinetic and pharmacodynamic data, demonstrate the inappropriateness of such testing; or

Ó cause evidence of adverse effects in tests of cognition, memory, and other higher brain functions.

Comment 1. Most of the comments received on this issue focused on characterizing an increased or decreased concern about potential neurotoxicity. Those commentors (369, 773, 776, SAP) who offered their perspective on neurotoxicity specifically expressed agreement, in principle, with the criteria that OPP proposed as indicating an increased concern for neurotoxicity and developmental neurotoxicity, and also to be used in "triggering" the requirement for the developmental neurotoxicity study.

Two commentors (773, 776) provided suggestions for additional information that could be considered that would lead to an increased as well as decreased concern for developmental neurotoxicity. Commentor 773 reaffirmed the principle that if existing data show neurotoxic effects, that would increase the concern for other manifestations of neurotoxicity and/or developmental neurotoxicity. Evidence of nondevelopmental effects known to have developmental consequences, such as effects on thyroid function would also increase concern. On the other hand, this commentor argued that the absence of data showing these effects would lessen the concern for developmental neurotoxicity. Commentor 776 also noted that changes in thyroid status, particularly hypothyroidism during pregnancy and its potential for adverse impact on neurodevelopment of the fetus, would provide an indicator for increased concern. They also suggested that noting brain weight as it relates to body weight, generally, in studies would be helpful.

Commentors 369 and 773 agreed with criteria 1-5 and 7. Both commentors questioned the specificity of criterion #6, relating to neurotoxicity in insects. Commentor 773 asserted that this criterion was "inappropriately overbroad." In

addition, the commentor suggested that a weight-of-evidence approach should consider all available information and not rely on a single criterion to make judgments about potential developmental neurotoxicity or level of concern. Commentor 369 recommended that criterion #6 be changed to include evidence of neurotoxicity in any species rather than simply insects. This commentor also agreed with criterion 7 in principle, but expressed doubt about whether it was likely to be useful given the paucity of validated test guidelines that address cognition, memory and higher brain function.

FIFRA Scientific Advisory Panel Comments

The FIFRA SAP agreed with the seven criteria, but stated that clarification was needed on how the criteria would be weighted for decision-making. The FIFRA SAP also provided ten additional criteria that might be useful. The ten additional criteria include that the substance has exhibited:

- inhibition of cell division (e.g., colchicine);
- specific toxicity/lethality for dividing cells (e.g., ionizing radiation);
- changes in neuronal migration (e.g., methyl mercury);
- neuroreceptor/neurotransmitter agonism or antagonism;
- molecular resemblance or parent compounds or predictable metabolites to known neurotoxins (e.g., gamma diketones such as 2,5-hexanedione, certain nitriles/cyanide compounds, some metals and organometallic compounds such as alkylmercury, lead, manganese, cholinesterase inhibitors);
- high lipophilicity conducive to concentration in lipid bilayers important for neural functioning (e.g., PCBs);
- identification of decreased biological factors in the adult that could present a problem in the developing organism (e.g., decreased cholesterol with carbon disulfide could be significant for the developing nervous system due to its high demand for cholesterol);

- mode of action on the target species and its relationship to the human system, whether directly or via an associated mechanism or human homologue;

- mutagenicity, clastogenicity, or carcinogenic responses may increase concerns as well because of the implications that these effects have for low dose extrapolation; and,

- clear positive results from the two-generation reproduction studies and prenatal developmental studies in the absence of maternal toxicity would increase concern about pre- and postnatal hazards.

Response. As noted above, OPP is appreciative of the general support expressed for the proposed criteria, and would like to take this opportunity to clarify that the weight-of-evidence approach does include consideration of all available information. While some might wish for more specific articulation in how a weight-of-evidence approach might be applied, it clearly is case-specific. It would be difficult, and, probably, not particularly useful to try to apply it in the abstract. Examples of application of this decision logic can be found in OPP's Hazard Identification Assessment Review Committee reports on individual chemicals.

The first five criteria had been reviewed previously by the FIFRA SAP (USEPA 1998d and USEPA 1998e) as indicators of developmental neurotoxicity potential that would trigger a DNT study. Based on this review and subsequent discussions, OPP proposed two additional criteria (6 and 7). Criterion 6 ("acts as a neurotoxicant in insects") had been recommended for inclusion by an earlier SAP and was proposed due to concerns for pesticides that had been designed to target the nervous system, albeit in insects. This criterion was informed by the knowledge that many of the traditional classes of insecticides functioned via a neurotoxic mechanism that also was common to mammalian species, including the human. OPP agrees that the criterion "acts as a neurotoxicant in insects" is too narrow and has broadened this criterion to include neurotoxicants in any species, with an obvious focus on mammalian species (see Table 3 in the revised guidance document). With reference to criterion 7 ("cause evidence of adverse effects in tests of cognition, memory, and other higher brain functions"), OPP agrees that this criterion would not often be used, at least in the near term, given the general paucity of data evaluating these endpoints. However, OPP would like to point out that test guidelines do exist that assess cognition and memory, and, when available, these data may prove very useful in assessing potential concerns for developmental neurotoxicity.

OPP's analysis of the SAP's proposed additional criteria, which are now proposed for use in determining a level of concern for developmental neurotoxicity potential, reveals that several are not so much new criteria but rather more detailed descriptions of types of information and specific modes of action that can be combined within the context of OPP's proposed seven criteria to provide more clarity. Some of them appear to be more suitable for addressing pre- and postnatal hazard concerns, in general (SAP's #1, 2, 7, 8, 9, 10). In the revised guidance document, OPP has modified the list of criteria to take the SAP's recommendations into account. The revised set, which addresses concerns for developmental neurotoxicity specifically, not developmental toxicity generally, includes that the substance (and/or a 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:
  - Structure-activity relationship to known neurotoxicants
  - Altered neuroreceptor or neurotransmitter responses
  - Altered hormonal responses

OPP recognizes that there has been an apparent inconsistency in the past with the practical application of the procedures when the developmental neurotoxicity study was required for conventional food-use pesticides with neurotoxic mechanisms (as noted by Commentor 776). The 1999 draft policy stated that, in response to well-supported scientific recommendations, two

criteria would be added to a previously-defined list of five criteria that are used, either individually or as part of a weight-of-evidence assessment, establish concern for developmental neurotoxic potential. When a specific cause for concern is identified and the developmental neurotoxicity study has not yet been submitted to the Agency, the scientific uncertainty regarding the risk assessment for infants and children and the possibility that the findings from the (absent) DNT study might result in a lower regulatory value (i.e., RfD or PAD), would initiate retention of some or all of the FQPA Safety Factor. Although the five previous triggering criteria were used in this manner, OPP delayed utilizing the two new criteria in the same way, while awaiting public input on the issue. OPP has not, by virtue of this delay, intended to suggest that these two considerations were less critical or concern-worthy aspects of the weight-of-evidence evaluation. Rather, OPP has both explicitly and implicitly recognized the importance of the DNT study in hazard characterization, and has (as described in the revised guidance document) begun the process of requiring the DNT studies for neurotoxic pesticides via the DCI authority under FIFRA and the FFDCA. The first DCI, requiring submission of the developmental neurotoxicity study and the supporting adult acute and subchronic neurotoxicity studies for the cholinesterase-inhibiting organophosphorus chemicals, was issued by OPP on September 10, 1999. Data Call-Ins for these same three studies on other classes of neurotoxic pesticides will be issued in the future.

A weight-of-evidence decision regarding the application of the database uncertainty factor to account for the absence of any study including the absence of a DNT should be used for consideration of the traditional database uncertainty factor. In the case of a missing DNT, a number of factors (as described in the revised policy) 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. 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 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 for example: 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. These considerations or factors 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.

Comment. One commentor (776) suggested that information on exposure patterns may be useful to increase concern. They suggested that special attention should be given to particular use patterns such as topical (skin) application and residential uses or residues in drinking water–any situation where one might expect children and pregnant women could be exposed. In contrast, another commentor (773) suggested that exposure information may decrease concerns, that is, for those use patterns that would make exposure of children unlikely.

Response. In both the draft and revised guidance documents, OPP states that exposure information is taken into account in making decisions about the FQPA Safety Factor. While the potential for exposure to children and pregnant women is a consideration in the FQPA Safety Factor finding, Issue 8 relates to a section of the guidance document that addresses issues only of hazard assessment. While exposure is not a consideration at this point in the process, OPP does take use information and activity patterns for children, among other factors, into account when performing exposure assessments, which then are combined with hazard assessments to produce risk assessments.

ISSUE 9. Expectations about the Results of DNT Studies

Please comment on whether you would expect that developmental neurotoxicity studies would, for a substantial number of chemicals, identify effects that are not detected in other studies and more fully characterize the potential risks of exposures during development. In addition, please comment on the sensitivity of these tests vis-a-vis other studies required and used for age-related comparisons for acute, intermediate, or chronic RfD derivation (e.g., prenatal developmental toxicity or multi-generation reproduction study, subchronic and chronic studies, etc.). Please explain the basis of your opinion.

Comment 1. Commentors 773 and 776 agreed that the DNT study would identify effects that are not detected in other studies, particularly since the study evaluates endpoints (e.g., functional endpoints) that are not measured in other tests. Commentor 773, however, expressed the opinion that this fact does not justify

making the DNT study a routine Tier 1 requirement.

Response. OPP agrees that the DNT study will likely detect effects not observed in other studies. *A Retrospective Analysis of Twelve Developmental Neurotoxicity Studies Submitted to the USEPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS)* (USEPA 1998c) demonstrated this to be the case, even within the small number of studies examined. 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 developmental neurotoxicity testing, which utilizes information about each chemical and its toxicity to develop a rational, science-based approach to the study design and testing strategy.

FIFRA Scientific Advisory Panel Comments

Comment 2. Commentor 369 stated that it is not yet possible to predict how the results of these developmental neurotoxicity studies may impact the final risk assessments. The impact will depend entirely on the nature and dose response of the effects observed.

The SAP stated that consensus among the Panel members could not be developed regarding whether NOAELs from developmental neurotoxicity studies would be lower than from historically required studies. One member argued strongly that the NOAELs or more appropriate benchmark doses identified by the developmental neurotoxicity studies will be lower than those detected by the present tests for a substantial number of pesticides. This member's prediction was based on the fact that the effects of many teratogens (e.g., psychoactive compounds, antiseizure medications, anticarcinogens, metals, radiation, retinoids, folate levels, etc.) are already known to be detected at lower doses with these tests than with the ones presently required. Another member did not accept the notion that the number of chemicals with effects occurring at lower doses would be large, but agreed that those identified would represent an important group. In addition, the analyses already presented by the Agency (USEPA 1998c) indicate that NOAELs identified by the use of developmental neurotoxicity testing are often not likely to be lower than those characterized by prior testing methods. The Panel is aware that only one of 12 chemicals showed developmental neurotoxicity effects at lower doses than were observed with the prior standard testing protocol. However, the Panel expressed caution that the results from testing the 12 pesticides could not be applied to a broader set of pesticides.

Response. OPP agrees with Commentor 369 in stating that it is not yet

possible to predict exactly how the results of these developmental neurotoxicity studies may impact any particular risk assessments.

The SAP appears to have misunderstood the concerns of OPP regarding the analysis of the DNT studies, citing the fact that only one of the 12 pesticides examined showed developmental neurotoxic effects at a lower dose than the dose level at which effects were observed with current standard testing. The OPP position on this issue is that even though only nine DNT studies on pesticides were available for review and analysis (out of a total of 12 studies), one of these nine DNT studies demonstrated developmental neurotoxic effects at a lower dose than were observed with current standard testing for chronic effects which may reduce the confidence that the traditional testing paradigm is generally adequate for the assessment of potential toxicity to infants and children.

It is inappropriate to assume that there would be many cases in which the NOAEL from a DNT would be lower than one from a chronic study. After all, the DNT reflects exposures that are not chronic in nature, but subchronic, at best. A more appropriate comparison might be made with NOAELs from studies of subchronic exposures such as a 28- or 90-day repeated dose study or the two-generation reproduction study in which the offspring of the first generation are exposed for a total of about 120 days.

Comment 3. One Panel member questioned the wisdom of moving tests of central nervous system function into Tier 1, with no plans for testing the functions of other organ systems. Another question regarding the proposed battery was whether it is intended as a screen or as research. It was stressed that the results of the developmental toxicity study must be usable for risk assessment.

Several members supported the idea that the Agency needs to improve and refine the proposed neurotoxicity battery. Because new factors in development are being discovered at a rapid rate, the Agency needs to be flexible, and the pace of development, validation, acceptance, and implementation of new protocols needs to be increased.

Response. OPP does not believe that there is any justification to delay the inclusion of the tests of adult central nervous system function in Tier 1, based upon the lack of availability of testing guidelines that address specific functional aspects of every other organ system. Such an approach would be neither logical nor scientifically supportable. It is additionally noted by OPP that guidelines already exist for at least some aspects of structure and function for developing organ systems thought to be critical for risk assessment purposes and most of these studies are required already in Tier 1 (per 40 CFR 158) for the registration of conventional food-use pesticides. For at least one other system, i.e., the reproductive system, an extensive evaluation of the effects on function, including those that may arise from developmental exposure is routinely conducted.

The use of the developmental neurotoxicity study to select endpoints for use in risk assessment in OPP was addressed in some detail within the retrospective analysis of twelve DNT studies cited above; this document was reviewed by a FIFRA Scientific Advisory Panel in December, 1999 (USEPA 1998f). On a broader Agency-wide level, the use of the results of the DNT study in risk assessment is also addressed in the *Guidelines for Developmental Toxicity Risk Assessment* (USEPA 1991) and the *Guidelines for Neurotoxicity Risk Assessment* (USEPA 1998a).

ISSUE 10. Policy for Database Uncertainty Factors

OPP's guidance states that currently five studies (a multigeneration reproduction study, prenatal developmental toxicity studies in two species, and chronic toxicity studies in a rodent and non-rodent species) comprise the toxicity database necessary to produce a high confidence RfD, and that some additional database uncertainty factor will be imposed if the database on a pesticide lacks one or more of these studies. OPP proposes to expand this core database to include the subchronic neurotoxicity study. Eventually, OPP also includes the acute neurotoxicity study in adult mammals and the developmental neurotoxicity study, once these studies have met the criteria for inclusion in the core toxicity database. Please comment on OPP's proposed approach to imposing a database uncertainty factor of 3X if one key study is missing from the database and a factor of 10X if more than one is missing.

Comment 1. One commentor (372) expressed the need for further clarification on whether the adequacy of the database will be the primary consideration in selecting the numerical value of the FQPA Safety Factor, and suggested that OPP include a single section in the document that clearly outlines the issues that will be considered in the decision-making.

Response. While the guidance document discusses the use of a database uncertainty factor in cases where the toxicity database may not be adequate for the derivation of high confidence reference values, the adequacy of the toxicology database is NOT the sole focus for consideration in selecting the numerical value of the FQPA Safety Factor. It is but one of three areas of consideration, each given weight as appropriate to the pesticide under review. As the guidance document states in a number of places, the FQPA Safety Factor determination is premised on the application of a weight-of-evidence approach which considers not just the adequacy of the data as it relates to toxicity, but also the nature of the toxicity data for informing a judgment with regard to the determination of the potential for pre- and postnatal and to the adequacy of the database as it relates to the assessment of exposure. Discussion of the weight-of-evidence approach can be found in the guidance document chapters II, IV, and VI.

Comment 2. One commentor (773) agreed with OPP's proposal to use a 3X if one study was missing and a 10X if more than one were missing. Another commentor (372) agreed in principle, but suggested clarification as to why these numerical values were chosen. Another commentor (369) agreed in principle, but thought the choice was too prescriptive; a suggestion was made to provide more

general guidance on how the database would be included in a more general weight-of-evidence approach. Several commentors (761, 771) stated that the factor should be at least 10X since OPP does not have "reliable" data to do otherwise. One commentor (778) stated that the question is whether OPP has complete and reliable data to assure no harm to children, not whether a sufficient number of studies exist.

Response. OPP's proposed approach to imposing a database uncertainty factor of 3X if one key study is missing from the database and a factor of 10X if more than one is missing was based on EPA's longstanding RfD process which identifies five uncertainty factors and one modifying factor that may be applied to the NOAEL or BMD to derive an RfD (US EPA 1994). The maximum default value for each of these factors is 10, although sometimes a different factor (most often 3X) is used depending on the nature and quality of the information available on the pesticide. Upon further reflection with an additional year of experience in making FQPA Safety Factor determinations, OPP agrees with Commentor 369 that the approach of applying a 3X if one study is missing and a 10X if more than one study is missing is too prescriptive and is inappropriate for a guidance document. OPP has revised the guidance document and will use a weight-of-evidence approach in decisions regarding the size of the database uncertainty factor, when it is deemed appropriate to impose one. OPP will base the decision regarding the size of the database uncertainty factor on *which* studies are missing in addition to how many studies are missing (see chapter III).

With respect to the question of reliable data, it is OPP's position that the reliable data requirement in the infants and children's provision does not mandate 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 (also see response to comments under Issue 17).

Comment 3. One commentor (775) expressed concern over the use of the term "high confidence RfD" and the potential implications for public perception. The commentors stated that the term "high" or "low" confidence should be restricted to the database as opposed to the RfD.

Response. OPP would like to clarify that the terms "high confidence RfD" and "low confidence RfD" are terms that have been used by the Agency for nearly two decades. A detailed description of the Agency RfD derivation process and guiding principles can be found on the Agency IRIS website (see http://www.epa.gov/iriswebp/iris/rfd.htm). Designation of high, medium, or low

confidence as it applies to an RfD (or RfC) is based on a number of factors including the adequacy of the core database, consistency of response, and route of exposure. In the guidance document for the RfD Process, it indicates that the EPA is attempting to standardize its approach to determining RfDs. The RfD Work Group has developed a systematic approach to summarizing its evaluations, conclusions, and reservations regarding RfDs in a 'cover sheet' of a few pages in length. The cover sheet includes a statement on the confidence (high, medium, or low) the evaluators have in the RfD. High confidence indicates the judgment that the RfD is unlikely to change in the future because there is consistency among the toxic responses observed in different sexes, species, study designs, or in dose-response relationships, or that the reasons for existing differences are well understood. High confidence is often given to RfDs that are based on human data for the exposure route of concern, since in such cases the problems of interspecies extrapolation have been avoided. Low confidence indicates the judgment that the data supporting the RfD may be of limited quality and/or quantity and that additional information could result in a change in the RfD.

ISSUE 11/12. Applying the FQPA Safety Factor Clause Relating to Potential Pre- and Postnatal Toxicity

OPP has decided to combine the comments and responses to the following two questions in the same section because they both relate to the interpretation and application of the clause in the FQPA Safety Factor provision directing EPA to take into account "the potential pre- and postnatal toxicity of" a pesticide in deciding whether infants and children are adequately protected. As summarized below and then discussed in more detail in the Agency's responses to comments, OPP thinks that the decisions about retaining the default 10X factor and the need for, and size of, different FQPA Safety Factor should reflect both the level of concern for pre- and postnatal effects and the level of certainty about the hazard relative to other toxic effects.

Issue 11. Criteria for Assessing Concerns about Potential Pre- and Postnatal Effects

OPP is proposing to adopt the framework and its criteria/factors for assessing the degree of concern about the potential for prenatal and postnatal effects as recommended by the Toxicology Working Group. Please comment on the appropriateness of the proposed criteria/factors for use in this assessment process, and OPP's proposed approach for accommodating its concerns in the Reference Dose derivation and FQPA Safety Factor decision processes, in the near term, and in the longer term.

Issue 12. Interplay of Certainty about Hazard and Increased Sensitivity of Infants or Children

When the hazard to infants and children is well-characterized, and the data show that infants and/or children are more susceptible than adults, under what circumstances, if any, should this information lead OPP to employ an additional safety factor?

Summary of OPP Approach to the Weighing of Potential Pre- and Postnatal Toxicity

Concern for Potential Pre- and Postnatal Toxicity to Infants and Children. Because the statute directs EPA, in making decisions about the FQPA Safety Factor, to consider the "potential pre- and postnatal toxicity [of a pesticide] to infants and children," the guidance document sets forth factors that would increase or decrease the Agency's concern that a pesticide has the potential to cause toxicity to infants or children that has not been adequately evaluated. Consistent with the basic approach of the overall guidance, OPP will make this decision on a case-by-case basis, taking all available, relevant information on toxicity and exposure into account to evaluate whether the young are more sensitive or susceptible to the toxic effects of pesticides than adults. OPP will evaluate whether the standard approach for determining an RfD or RfC–using available data on toxicity and exposure and applying the traditional uncertainty and modifying factors–provides assurance that infants and children will be adequately protected, or alternatively whether the default FQPA Safety Factor should be retained or a different FQPA safety factor adopted. As discussed in more detail below, risk assessors should apply the following analysis which draws on Agency-wide policy, public comments, and insights gained through several years' experience applying the FQPA Safety Factor provision.

Î When the available database permits, risk assessors should determine the

Reference dose(s) or RfD(s) for a pesticide by selecting an appropriate toxicity study and applying traditional uncertainty or modifying factors to the highest dose level in that study at which no adverse effects were observed (the NOAEL). As cited and explained in the revised guidance document, the risk assessor should choose the appropriate toxicity study taking into account established EPA policies and practices on the determination of a RfD.

Ï Since the determination of an RfD involves consideration of a number of issues that OPP associates with increased concern for toxicity of a pesticide to infants and children, the subsequent FQPA safety factor analysis relating to these issues should focus on whether those issues have been adequately addressed in the RfD derivation process. Specifically, risk assessors should evaluate whether the RfD process adequately took into account any data indicating that young animals are more sensitive to the toxic effects of a pesticide than mature animals or are susceptible to a different array of toxic effects than mature animals. If younger animals appear to display increased sensitivity or susceptibility, the risk assessor should determine the degree of concern for potential toxicity, using the factors presented in the guidance document. The risk assessor should not recommend retention of the default FQPA safety factor or application of a different FQPA safety factor on a routine basis solely because some kind of pre- or postnatal toxicity is observed or there is an apparent difference in sensitivity.

Ð After having determined the RfD(s) for a pesticide and the degree of concern for observed pre-/postnatal toxicity (increased sensitivity or susceptibility) the risk assessor should identify any residual concerns relating to the potential toxicity of the pesticide to infants and children which will inform the final decision to retain the default FQPA Safety Factor or adopt a different FQPA safety factor.

Comment 1. One commentor (369) questioned how the degree of concern for children's health risks would be integrated into the selection of uncertainty factors in establishing RfDs and PADs. Three commentors (773, L016, L005) suggested that the appropriate consideration for degree of concern should be whether infants and children are more than 10 times more sensitive than adults. One commentor (776) questioned whether a high degree of concern for one of the criteria would be enough to judge concern for pre- and postnatal toxicity. One commentor (773) indicated that all criteria that relate to factors considered in the current uncertainty factors should be eliminated, and asserted that the proposed criteria mandate "double-counting" by focusing on factors that are already considered in the traditional uncertainty factors.

Response. The criteria for degree of concern for potential pre- and postnatal toxicity in humans were developed by the Toxicology Working Group simply to provide more detail on the issues that should be considered when evaluating the available data to determine the overall degree of concern for such effects. Most of these criteria already are considered in the development of the RfD and RfC, but are not specifically detailed in the Agency's risk assessment guidelines for developmental toxicity (or, any other endpoint of toxicity, for that matter). Therefore, historically, they may not have been considered explicitly when a hazard characterization is being developed for an environmental agent. As part of a weight-of-evidence approach to evaluating the potential of pesticides to produce pre- and postnatal toxicity, OPP will consider the information on all of these issues before making a determination about the degree of concern for potential pre- and postnatal toxicity in humans. If data are not available, for example, on toxicokinetics, then assumptions must be made about whether, and how, data indicating hazards for developmental effects in the species tested are relevant to humans. Although OPP believes that the intraspecies (that is, human to human) uncertainty factor is protective for any age-related differences in sensitivity in most cases, no single criterion drives the decision about relative sensitivity of the young versus adults; rather it comes from a consideration of all of the criteria in a weight-of-evidence approach. This latter step–employment of the modifying factor for this purpose–is not currently a component of the Agency's "formal" procedure for deriving RfDs/RfCs. How to formalize this step is being further addressed by EPA's RfD Technical Panel. Since there is no formal Agency guidance, OPP has chosen to account for a high degree of concern and other uncertainties not addressed by the inter- and interspecies uncertainty factors by applying an FQPA Safety Factor greater than 1X. The size of this component of the overall FQPA Safety Factor should take into account any other factors that are applied in the RfD/RfC process, thus avoiding double-counting. It is determined on a case-by-case basis, driven by existing information (or, lack thereof). The FQPA Safety Factor and some of the uncertainty factors applied in the derivation of the RfD/RfC are not mutually exclusive, but are complementary in their attempts to account for all uncertainties and the degree of concern.

Comment 2. One commentor (776) questioned the criteria, particularly giving effects of longer latency a low degree of concern, since the effects of developmental toxicants may not manifest themselves until systems are fully mature and functional.

Response. The issue of latency of time to manifestation of effect was raised in the criteria for degree of concern only in the case where organ systems have matured to the point of being functional and similar types of effects are likely to be seen in adults and the young, although to a different extent. In this case, if the effects in adults are seen at a lower dose and occur sooner (shorter latency) than in the young, this would constitute a lower degree of concern for children, because this pattern of response would indicate lesser sensitivity in young than adult animals. This has nothing to do with the long latency effects that may occur as a result of early life exposure to a developing organ system that has not matured and that do not occur as a result of adult exposure, e.g., effects that may be seen in adulthood or old age that are the result of early nervous system or other organ system impairment during development.

Comment 3. Three commentors (369, 372, 773) stated the need for clarification on why both a steep slope and a shallow slope would raise the degree of concern.

Response. OPP's initial policy considered both a steep slope and a shallow slope to be of concern, but for different reasons. The discussion of steep and shallow slope has been removed from the revised document. The discussion focuses on the certainty surrounding the identification of the point of departure (usually a NOAEL) that is used to derive the RfD. 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.

There is also discussion on the degree of concern with respect to where in the dose-response curve effects are seen. For example, the degree of concern could 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.

Comment 4. Two commentors (773, 372) questioned the statement that the concern is higher if the increment between the NOAEL and LOAEL is large, indicating that if anything, the larger the increment, the more conservative the NOAEL, providing a greater level of assurance that the RfD is protective.

Response. See response to Comment 3.

Comment 5. Two commentors (369 and 773) indicated that the criteria on pre- and postnatal toxicity should include the element of relative severity of effect in young versus adult animals, particularly for similar types of effects, as well as the permanence and life-threatening nature of the effects. One commentor (773) also suggested that the relevance of relative young to adult sensitivity data collected at high dose levels for predicting potential differences at low doses should be included in the criteria.

Response. OPP agrees that relative severity in young versus mature animals where the effects are of a similar type should be included as a criterion. Severity would also include consideration of permanence and life-threatening nature, but these are not requirements for whether or not the effects should be considered adverse. The issue of high to low dose relevance would be part of the consideration of relevance of the experimental animal data to humans, particularly as related to toxicokinetic and mechanism of action considerations.

Comment 6. One commentor (773) indicated that OPP should recognize that human data relating to reproductive toxicity will rarely, if ever, be available and, therefore, the lower degree of concern should focus on whether available information supports a conclusion that "no effects occur at the level of potential human exposure."

Response. OPP agrees with the assertion that there is a paucity of human studies which investigate the potential for effects on reproduction. Nonetheless, OPP does not agree with the statement that there should be a lower degree of concern if the available information supports a conclusion that "no effects occur at the level of potential human exposure." Absence of evidence does not constitute evidence of absence of an effect. Proving no effect in humans is very difficult, and even data showing no effects from limited human studies are usually not adequate to indicate an absence of human effects, unless a wide range of reproductive and developmental outcomes has been evaluated.

Comment 7. One commentor (773) asked for clarification of the difference between the criteria for "relative potency of response" and "pre- and postnatal toxicity in animal studies." There was also a suggestion that the criteria for "dose-response nature of the experimental animal data" should be limited to data on reproductive and developmental toxicity.

Response. The criteria for pre- and postnatal toxicity in animal studies are part of the hazard identification/characterization process and allow a qualitative evaluation, whereas relative potency of response is more quantitative in nature, having to do with the incidence and intensity of response over the dose-response range, as well as the comparative doses in young and adult animals at which effects are seen.

OPP disagrees that the data for dose-response evaluation should be limited to reproductive and developmental toxicity data. Data from all available toxicity studies, whether conducted with neonatal/juvenile or adult animals, should be considered for several reasons. For example, adult data are important in identifying potential target organs that may also be affected when exposures occur in children whose major organ systems have already formed but are functionally less mature than in adults. Because children include adolescents up to 18-21 years of age, adult data also will provide important information about potential target organs during this time period as well. Adult data also may provide information on target organs to evaluate in the reproduction studies or other developmental studies for similar target organ effects, e.g., developmental immunotoxicity, developmental carcinogenesis, or endocrine toxicity studies. In addition, adult data provide relative potency information when comparing or estimating differences between children and adults.

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Comment 8. The SAP commented that there needs to be some relatively well-considered process for establishing factors for different outcomes in a severity-of-effect determination.

Response. OPP has already incorporated limited consideration of the severity of effects into the factors for judging the level of concern for potential pre- and postnatal toxicity. In general, “severe” effects are those which are enduring and either life-threatening or involve serious impairment of an organism’s ability to function effectively. Less severe effects lack these characteristics. The presence of severe effects contributes to an overall higher level of concern.

OPP, however, is reluctant to undertake any more specification of the weight to be given to the type of toxic effect observed in animal studies for a combination of reasons. First, while there is often similarity in response between animals and humans, there are sufficient instances in which the responses differ qualitatively, as well as quantitatively, that it may not be sufficiently protective of public health to systematically give less weight to less severe effects. Second, there is considerable lack of societal acceptance of the

notion that humans should be assumed to tolerate exposures which have caused adverse effects in animals, even if the effects are not particularly severe. Finally, the range of toxic effects caused by chemical exposure is quite large, and as a practical matter, it would be nearly impossible to gain general agreement on how to assign different effects to a point along the continuum from mild to severe.

Comment 9. The SAP endorsed the criteria developed for degree of concern, in general, but suggested additional criteria for toxicokinetics and mechanism of action, indicating that the lack of adequate data would add some degree of uncertainty and should fall between the higher and lower extremes. They also indicated that in cases where there are clear toxicokinetic differences between humans and the experimental animal, the agent may not have been adequately tested in a relevant species and may be indicative of important missing information.

Response. OPP agrees with the SAP that criteria should be added which would describe a moderate degree of concern in the areas of toxicokinetics and mechanism of action. The proposed table has been modified and the text of the revised guidance document has been expanded to address these points.

Comment 10. One commentor (773) asked for clarification of whether the policy means that: (1) the additional 10X would be applied to the NOAEL from a study in which young animals showed more sensitivity to effects than adults, only if the NOAEL was the lowest NOAEL from the available toxicity database; or (2) the additional 10X would be applied to the lowest NOAEL from the available toxicity database, if the database contained any study in which young animals showed more sensitivity to effects than adults. The commentor stated that based on recent decisions, it appears that OPP is using the second approach.

One commentor (773) indicated that OPP's justification for applying an additional 10X when children appear to be the most sensitive age group–"that OPP wants a greater level of certainty that children and infants will be adequately protected" --is an inadequate explanation for departing from its practice and policy for the first year and a half after passage of the FQPA. OPP needs to explain why it now concludes that the traditional 10X intraspecies factor is not sufficient to protect the young, and why it departs from the approach used elsewhere in EPA, in other federal agencies, and by regulatory organizations throughout the rest of the world. This commentor and others (e.g., L005) argued that an additional FQPA safety factor should be used only to compensate for the extent to which the expected sensitivity difference exceeds the traditional 10X intraspecies factor, and that no additional factor is needed in cases where the hazard to children is well-characterized and is considered in the selection of the toxicity endpoint used in calculating the RfD.

Commentor L005 further noted that an additional uncertainty factor could be applied on a case-by-case basis, such as where there is inadequate toxicological information or for those pesticide residues producing severe and irreversible developmental or reproductive effects. The additional FQPA Safety Factor should not be applied in all cases simply because a pesticide causes prenatal or postnatal effects, or merely because the NOAEL for such effects is the lowest NOAEL.

Another commentor (776) indicated that the additional factor should be used in all cases when the hazard to children is well characterized, and the data show that infants and children are more susceptible than adults, and if the NOEL from the most sensitive endpoint from developmental studies has not been used to effect regulation.

Alternative options were presented by two additional commentors. Commentor 369 stated that its approach is to employ an additional safety factor when the data set indicates that infants/children are more susceptible, and this is applied when the study where the effect is noted is used in the risk assessment and setting of any reference doses. They also indicated that when an endpoint from another study is selected, the NOAEL selected may provide protection of infants and children, but if not, an additional safety factor of equal or less magnitude may be considered to ensure the required margin of safety for the protection of all subpopulations. One commentor (L005) suggested that if developmental and reproductive toxicity studies demonstrate that in utero or neonatal exposure results in severe adverse effects while the same dose has no effect in the adult animal, then in the absence of human data, an added safety factor to account for the possible increased sensitivity of human infants and children may be warranted.

The SAP suggested that OPP's approach could be made more readily

understandable by inclusion of one or more flow charts in the Agency's background document. These should highlight decision points, the kinds of inputs considered at each such point, and the possible alternative outcomes. Separate charts could, for example, illustrate the past, current, and proposed approaches, and should illustrate the entire process, including the incorporation of exposure data, leading to the final regulatory outcome.

Response. In response to commentor (773), if a decision is made to retain the default FQPA safety factor or apply a different FQPA safety factor, that factor would be applied to the NOAEL (or BMD) selected as the basis for deriving the RfD.

The timeline below outlines the approach to selecting the appropriate FQPA Safety Factor for use in human health risk assessments and the major events which induced changes in the approach used by OPP.

August 1996	The Food Quality Protection Act is passed unanimously by Congress.
October 1996	First draft of the 10X Policy/Guidance Paper is presented to the FIFRA Science Advisory Panel.
March 1997	10X Policy/Guidance Paper Revised Including Response to SAP Comment
February 1998	First organizational meeting of the Health Effects Division (HED) FQPA Safety Factor Committee is formed and the working Standard Operating Procedure (SOP) drafted.
March 1998	Second draft of the 10X Policy/Guidance Paper is presented to the FIFRA Science Advisory Panel.
May 1999	Third draft of the 10X Policy/Guidance Paper *The Office of Pesticide Programs' Policy on Determination of the Appropriate FQPA Safety Factor(s) for Use in the Tolerance-Setting Process* (USEPA 1999c) is presented to the FIFRA Science Advisory Panel along with the revised SOP.
July 1999	Third draft of the 10X Policy Paper and revised SOP are issued for Public Comment (64 FR 37001, Docket No. 37001).

Since the enactment of the FQPA in August 1996, there have been a

number of changes in OPP's approach to implementation of the FQPA Safety Factor provision. These changes resulted from the continued examination of the law and the policy and their implications for OPP and other EPA offices, as well as from the input of other agencies, the regulated community, and public and environmental advocacy groups. In 1996, OPP began to implement the FQPA Safety Factor provision. By the time of the March 1998 presentation to the Scientific Advisory Panel, a number of conceptual and practical differences had emerged, and OPP had made some changes to its application of the FQPA Safety Factor.

First, there was a change in the timing of the determination of the need for the FQPA Safety Factor within the overall risk assessment process. While the FQPA Safety Factor was recommended and applied initially during the hazard and dose response evaluation, now it was being determined during the last phase of the risk assessment process–risk characterization–taking into account both the hazard and exposure information on the chemical, as the law instructs the Agency to do. In order to implement this process with efficiency and consistency, the Office of Pesticide Programs' Health Effects Division (HED) formed the FQPA Safety Factor Committee, which developed a Standard Operating Procedure for making safety factor determinations.

Second, it was concluded that the FQPA Safety Factor–to the extent it went beyond traditional uncertainty factors–should be determined *after* the calculation of the RfD values, whereas previously it had sometimes been applied during the calculation of the RfD. The concept of the Population Adjusted Dose (PAD) was implemented in HED to accommodate this two-step process, and to differentiate decisions under the FQPA from decisions by other Agency offices and elsewhere that relied solely on uncertainty factors utilized historically in risk assessment practices. Additionally, it was determined that the Safety Factor decision would be made only for appropriate populations (infants and children and women of bearing age) and exposure scenarios/durations, rather than the population at large.

Third, it was made clear that the default 10X FQPA Safety Factor was automatically included in each risk assessment, and that this factor could only be replaced by a different FQPA Safety Factor if, after a full examination of both the toxicity and exposure databases, it was found that reliable data demonstrated such different factor to be safe for infants and children.

Fourth, the FQPA Safety Factor, which, to that point in time, generally had been applied to accommodate uncertainty concerns alone, was now clearly defined as addressing issues of both uncertainty and sensitivity/susceptibility. The practical application of this concept had been molded by an OPP policy

decision to retain the default FQPA 10-fold Safety Factor or apply some different FQPA safety factor greater than 1X when any evidence of sensitivity/susceptibility was observed in the hazard database, regardless of the degree of concern. Admittedly, one might argue that this has led to some instances of overprotection as an additional safety factor was applied to a study NOAEL that adequately characterized the sensitivity (variability) of the effect in the young.

The May 1999 draft OPP 10X policy document attempted to clarify these concepts, while at the same time addressing the recommendations of the 10X Task Force. It is apparent from comments received both from the SAP and the public that OPP has not been fully successful in communicating its practices in a clear and transparent manner. OPP believes that there is little value in developing a comparison of past, present and future practices, as suggested by the SAP, but it is incumbent on the Program to present clearly, and in as great detail as practicable, a discussion of the general approach this guidance describes. It should be noted that there are no plans to revisit past decisions, simply for the purpose of determining, in the abstract, whether or not residual overprotection may have occurred. OPP will attempt here, and through the revised guidance document, to provide greater detail and transparency. The revised Standard Operating Procedure (SOP) will also include several examples of the application of the FQPA Safety Factor determination process for specific chemicals.

Comment 11. Commentor 773 offered the suggestion that EPA implement the additional Safety Factor provision in a manner that uses the concept of "trial Population Adjusted Doses" that would then guide the eventual selection of the final PADs for different age and gender groups and durations of exposure. In employing this approach, the commentor would propose that OPP should apply any additional FQPA Safety Factor only to the appropriate toxicity end point, i.e., the endpoint for which available data suggest that traditional uncertainty factors would not be adequately protective. Thus, the decision about the application of the FQPA Safety Factor should depend on the specific risk scenario. The application of the FQPA Safety Factor would depend on whether the reason is (1) a risk of developmental toxicity, or (2) a risk of increased "susceptibility" [sic] to nondevelopmental effects.

Further, if the reason for an additional FQPA Safety Factor is an observed developmental effect, OPP should produce a "trial PAD" by applying the safety factor, along with other appropriate uncertainty and modifying factors, to the NOAEL for that effect in the study in which it was seen. If the resulting PAD is the lowest for a relevant subpopulation, it should be used as the scientific benchmark of safety. Alternatively, if another toxicity study, relevant to the subpopulation, has a lower

NOAEL, such that the application of traditional uncertainty and modifying factors produces an RfD lower than the "trial PAD," then that RfD (without an further reduction by an FQPA Safety Factor) should govern. For example, concern about a developmental effect such as supernumerary ribs should not prompt application of an FQPA Safety Factor to an RfD calculated from the NOAEL for a brain cholinesterase inhibition (ChEI) effect in an acute neurotoxicity study. There is no biological reason to think that the unrelated developmental effect makes the RfD derived from the ChEI effect inadequate or that the ChEI effect makes the unrelated developmental effect of more concern.

Commentor 773 goes on to argue that, in some cases it may be appropriate to consider applying an FQPA Safety Factor based on concerns about potential developmental toxicity, based on data from a test other than a developmental or reproductive toxicity study. (For example, a chronic dosing study might show effects on the thyroid function that could trigger developmental effects not seen in other tests.) If so, OPP should construct a trial PAD appropriate for the subpopulation and duration of exposure, and compare it to the RfD otherwise calculated for the group. This step would resemble the approach described above.

Response. OPP agrees with the basic theoretical concept of "trial Population Adjusted Doses" which could guide the eventual selection of the final PADs for different age and gender groups and durations of exposure. A similar type of comparison has been used informally by OPP when evaluating individual pesticides. It is noted, however, that the commentor has omitted any consideration of FQPA's mandate for adequacy of the exposure data in its calculation of a final PAD. OPP also agrees with the commentor that the FQPA Safety Factor decision should depend upon the specific risk scenario that is being evaluated and has made its FQPA safety factor decisions considering this information. For example, when a safety factor is required for risk to a specific population subgroup (e.g., infants and children and/or women of childbearing age) or particular duration of exposure.

However, since the Population Adjusted Dose is calculated as the Reference Dose divided by the final FQPA safety factor required; and since the final FQPA safety factor must take into consideration not only toxicity but exposure considerations; it is not, in practice, feasible to perform a true Trial PAD analysis for a specific population subgroup or duration of exposure at the time of establishing RfDs and other toxicity endpoints. OPP believes that the better approach is that described in the revised guidance document (see Chapters II and VI), wherein OPP will: determine the RfD(s) for a pesticide according to Agency policies and practices; evaluate whether the available data indicate that young animals are more sensitive or susceptible than mature animals; determine the degree of concern for potential toxicity or data gaps;

identify any residual concerns or uncertainties relating to the potential toxicity of the pesticide or relating to exposure to infants and children; and then base the final decision to retain or modify the FQPA Safety Factor on the overall risk characterization.

III. Exposure Issues

ISSUE 13. Conservatism of Exposure Assessments for Residues in Food

Subject to the qualifications expressed in the OPP policy document and the report from the Exposure Working Group, OPP believes that each of the tiers for estimating exposure to a pesticide through food, in almost all instances, will not underestimate exposure to infants and children. Please comment on this conclusion, as it applies to each of the tiers.

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Comment 1. One commentor (773) indicated that the current tiered approach to dietary risk assessment almost always overstated the actual dietary risk from pesticide residues in food. This commentor also disagreed with the qualifications on data and methodology included in the document. However, the SAP indicated that current methods might underestimate possible dietary exposures, particularly for infants and children and discusses a number of factors in the assessment that would impact that likelihood including: age of data; sample size of age classes; demographic stratification; accuracy of recipe files; use of percent crop treated data; changes in marketing and processing; water; and pesticide residue data.

Response. OPP uniformly attempts to develop the best estimate of exposure to pesticides in foods possible, using all available data and the best methods possible. OPP encourages the continued development and improvement of methodologies and tools to improve the ability to accurately estimate the potential for exposure to pesticides in foods.

With regard to specific factors cited by the SAP as potentially impacting the outcome of OPP's dietary risk assessments, OPP has already attempted to address a number of these. With regard to the age of consumption data used in the assessments, OPP has recently completed a cooperative effort with USDA to translate the most recent data available from the Continuing Survey of Food Intakes by Individuals. These data were collected during the period from 1994-1996, with additionally sampling in 1998 to increase the numbers of children 12 years or younger in the survey. The additional data were collected specifically to address the issue of limited numbers of children present in previous surveys and to allow OPP to better meet its mandate under FQPA. The number of children under six years of age were approximately doubled, greatly enhancing the

confidence in estimating food consumption patterns for this age group. These data are now being introduced into the OPP risk assessment process. Demographic characteristics of respondents to the CSFII were collected in sufficient detail to permit the evaluation of the differing consumption patterns by age group, income level, region and season. However, due to the variety of ethnic groups responding to the survey, the ability to evaluate differences in food consumption based upon ethnic group is limited. In all but a few cases, too few of any ethnic group are identified to permit evaluation of differences with any degree of confidence. The SAP has raised the issue of the accuracy of recipe files to convert consumption of foods to consumption of commodities. This conversion is a potential source of uncertainty. However, USDA took great care in researching the most appropriate decisions in developing recipes to reduce to the extent possible the potential errors in the process. Prior to the translation step, the recipe files and their underlying conventions were peered reviewed by experts in the fields of food and nutrition and risk assessment to seek further guidance on possible errors in the translation process.

The SAP indicated discomfort with the manner in which percent crop treated data are used to adjust the food risk assessment. The percent crop treated data used in OPP assessments reflects a synthesis of data from a variety of sources, not a single data source to which the reader can be referred. OPP takes this approach to offset strengths and weaknesses in each of the data sources used and to permit a check of the results of each database based upon its consistency with others. To this extent, the percent crop treated value used in OPP risk assessment is in many ways strengthened relative to reliance on any single source of information. When relying on monitoring data, OPP uses the percent crop treat value in acute dietary risk assessments of individual chemicals to correct for the number of nondetectable residue values reported for the possibility that the commodity may not have been treated. All detectable residues are retained as they were reported and only the proportion of nondetects is adjusted. Therefore, the potential for significant impact on the outcome of the assessment, particularly at the upper ends of the exposure distribution, is minimal. When monitoring data are not available to estimate exposure to pesticides in foods, OPP may use residue field trial data combined with the percent of crop treated data to calculate anticipated residues in foods. Residue field trial data reflect maximum application rates shortest preharvest interval allowed on the label. Therefore, the upper end of pesticide residues likely to be encountered. In addition, percent crop treated data used in the assessment reflect the likely maximum values based upon agricultural use statistics produced by public and private sources. As a result, underestimation of exposure to pesticides in foods is unlikely. To the extent that regional distributions of residues vary within a commodity, this factor can be addressed by limiting the scope of the input data to focus on data reflecting the nature of

this special case. However, in OPP's experience, this rarely occurs. Within available monitoring data, little variation between collection points has been observed. To further characterize any possible differences due to production area, OPP has undertaken an analysis of available PDP data to definitively evaluate any evidence of difference based upon region of production, domestic vs foreign source and a variety of the factors.

The SAP suggested that the product form and processing should be factored into the dietary risk assessment. Product form and processing *are* carefully factored into the risk assessment process, particularly with regard to the potential for concentrating or reducing the amounts of pesticide residues in processed foods. These data are used to the extent that they are available and their submission by the regulated community is encouraged by OPP.

The SAP indicated that drinking water and water in foods should be included in the risk assessment. With regard to consumption figures for water used for these purposes, OPP does now incorporate into its risk assessment process consumption of water from CSFII 1994-1996, 1998 using the Office of Water's extraction of these data. These data were peer reviewed by the Science Advisory Board and found to be acceptable. These consumption data are sufficiently robust to permit a reliable estimate of exposure in water when used in conjunction with reliable drinking water concentration estimates.

Comment 2. Commentor 405 questioned whether a sufficient number of individual consumption days were available in the CSFII to permit estimation of the 99.9th percentile of exposure.

Response. OPP has discussed the rationale for why this data set permits a credible estimation of this percentile of exposure at length in a paper titled *Choosing a Percentile of Acute Dietary Exposure as a Threshold of Regulatory Concern* (US EPA 2000c). See also the response to Comment 1, Issue 13, above.

Comment 3. Commentor 405 expressed support for OPP in its pursuit of the capability to conduct chronic probabilistic assessments, reflecting variability in use patterns and consumption over time.

Response. While OPP believes that the current deterministic approach will not underestimate chronic exposure to residues in food, it encourages the collection of appropriate longitudinal consumption data and use/usage data to make reliable chronic probabilistic assessment possible. The method of Nusser

(1994) cited by the commentor was developed to extrapolate from short term consumption of nutrients to longer term likely consumption patterns. Because of the distribution of nutrients in foods, most nutrients are consumed almost daily, making correction for likely daily intakes possible. However, food frequencies are much less reliable in that a given food may be eaten only occasionally or never reported during a given period of a consumption survey. This information can not be construed to indicate that the food is never or rarely eaten, nor does consumption on all days of the survey reflect necessarily that the food is eaten every day. Because of this food frequency issue, the method of Nusser is not readily adaptable from nutrients to foods.

Comment 4. Commentor 405 also recommended that guidance be developed for extrapolation from field trial data on parent products to metabolites of concern.

Response. Because the Agency requires field trial data on the parent compound and all of the identified metabolites of regulatory concern, this extrapolation is not often required. Nonetheless, while no formal guidance is in place, OPP does perform this extrapolation using available metabolism data in lieu of empirical data for residue levels of the metabolite in those rare cases where doing so is appropriate (i.e., when ratio of residue levels of parent and metabolite remains constant as the residues decline).

Comment 5. Commentor L005 argues that exposures from residues in food and exposures from other sources should not be combined because the estimates for exposures from other sources fail to meet the criterion of "reliable."

Response. OPP has argued that screening level assessments for other routes should not automatically be combined quantitatively with highly refined assessments of residues in food. Rather, the screening level assessments should be evaluated in tandem with the refined assessment of residues in food to develop an understanding of the overall level of concern for a pesticide from all appropriate routes and to identify likely areas for further concentration. OPP is working aggressively to develop improved methods for estimating residential exposure and drinking water concentration levels. An approach using data from a pesticide with a similar use pattern as a surrogate for other, less well documented pesticides is being developed for residential exposure assessments. This approach is comparable to the use of surrogate data in PHED to estimate some aspects of worker exposure. In the drinking water arena, OPP is pursuing the use of modeling in conjunction with monitoring data to develop a tiered approach which would result in more realistic estimates of pesticide residue concentrations in drinking water.

Comment 6. Commentor 778 indicated that OPP should retain the full 10X uncertainty factor for cases in which limited information for food consumption are available.

Response. As discussed in *Choosing a Percentile of Acute Dietary Exposure as a Threshold of Regulatory Concern* (US EPA 2000c), OPP believes that adequate consumption data are available to estimate pesticide exposure to residues in food for all of the subgroups upon which we currently regulate.

Comment 7. Commentor 776 also suggested that an uncertainty factor be applied when exposure data are missing, citing breast milk accumulation and farm area well water as examples.

Response. In the case of farm area well water, OPP believes that the conservative, upper bound estimates resulting from ground water modeling would be protective of this exposure.

OPP is aware of the concern for exposure to infants in breast milk, but rarely has adequate residue data on human breast milk to assess this potential source of exposure. If data suggest that exposure by this route is not adequately estimated, OPP will consider this issue in the judgement as to whether reliable data are available to permit removal or reduction of the factor. In lieu of empirical data, the Agency may use data from required ruminant studies, metabolism studies, and information regarding the physical/chemical characteristics of the pesticide to estimate residues in human breast milk.

FIFRA Scientific Advisory Panel Comments

Comment 8. The SAP indicated that OPP should endeavor to improve the understanding of food consumption patterns for infants and children in order to reduce the uncertainty of assessments for those age groups.

Response. OPP agrees that it is very important to have the fullest understanding of children's food consumption patterns. To this end, OPP actively supported the collection by USDA of supplemental food consumption data for children and has incorporated these data into the risk assessment process.

Comment 9. The SAP also recommended improving the ability to understand the nature and quantity of pesticides in food stuffs for which little monitoring or residue field trial data are available.

Response. Again, OPP agrees and has implemented practices by which data from similar chemical/crop combinations are used as surrogates for those with less robust data sets. In addition, USDA's Pesticide Data Program (PDP) continues to evolve, with new chemicals and commodities being added to the sampling scheme (http://www.ams.usda.gov/science/pdp/index.htm). Usually, good field trial data are available as well, given that they are required to be generated in support of registration and/or reregistration.

Comment 10. The SAP questioned the manner in which percent crop treated data are used to adjust the dietary risk assessment. The panel pointed out that these data are commonly employed to adjust chronic exposure and risk estimates but are not available for public review.

Response. OPP's pesticide use-related data come from a variety of sources for both agricultural and nonagricultural pesticide uses. Sources of use-related data fall into five general categories: (1) other government entities that produce pesticide-use data (e.g., USDA's National Agricultural Statistics Service (NASS) and the National Agricultural Pesticide Impact Assessment Program (NAPIAP)); (2) data submitted by registrants, user organizations and other interested parties; (3) proprietary data purchased from vendors whose business is to obtain pesticide-use data; (4) the scientific literature; and (5) miscellaneous Agency contracts and sources (For further details see *The Role of Use-related Information in Pesticide Risk Assessment and Risk Management*, USEPA 2000e).

The percent crop treated data used in OPP assessments reflect a synthesis of data from a variety of sources, not a single data source to which the reader can be referred. OPP takes this approach to bolster the strengths and offset the weaknesses there may be in any one of the data sources used and to permit a check of the results of each database based upon its consistency with others. Consequently, the percent crop treated values used in OPP risk assessments are, in many ways, strengthened relative to those relying only on a single source of information. The residue monitoring surveys such as the USDA Pesticide Data Program (PDP) are used to corroborate the percent crop data since the statistically representative sampling scheme represents commodities both treated and untreated.

Comment 11. The SAP asserted that regional distributions of residues vary within a commodity.

Response. In fact, little variation between collection points has been observed in the available monitoring data. OPP has begun an analysis of the available PDP data to further characterize any possible differences due to production area including domestic versus foreign sources and other factors. Preliminary results indicate some differences between domestic vs. foreign sources, which are taken into consideration when the Agency undertakes risk mitigation measures.

Comment 12. The SAP and Commentor L005 indicated the product form and processing should be factored into the dietary risk assessment.

Response. The consideration of product form and the effects of processing of raw agricultural commodities has long been an element in the dietary risk assessment process. Processing studies are required under 40 CFR 158.240. These data provide information on how processing can affect the levels of residues expected in final food forms. Processing and product form are carefully factored into the risk assessment process, particularly with regard to the potential for concentrating or reducing the amounts of pesticide residues in processed foods.

Comment 13. The SAP considered the sampling design of federal surveys of pesticide residues found in imported and domestically produced foods to be a "significant source of uncertainty in dietary exposure estimates" since: (1) the number of specific pesticide-food samples are small relative to the volume of food in the marketplace; (2) processed foods receive limited attention from FDA and USDA; (3) pesticides that require individualized tests are more rarely sampled than pesticides detectable via multiresidue screens; (4) an increasing proportion of the US food supply is imported; and (5) blending portions of crops selected from different pieces of fruit, or from different crates or shipments will systematically underestimate pesticide residue levels.

Response. OPP disagrees with the SAP on this point because: (1) monitoring program sampling is statistically designed to represent residues throughout the entire food supply; (2) processing studies are required as part of the data set for registration and/or reregistration of each food use pesticide and the monitoring programs sample many of the major processed foods (e.g., juices, frozen and canned fruits and vegetables, etc.); (3) OPP only uses monitoring data if there is a sufficient number of samples collected in a manner that represents the food

supply adequately, and thus if there are not enough samples for a particular pesticide/use combination in the monitoring database, OPP will rely on field trial data; (4) monitoring programs collect samples at distribution centers (warehouses or supermarkets) or ports of entry which contain both domestic and imported commodities; and (5) OPP has developed a decompositing method which allows an estimate of residues in single servings (e.g., one orange or one apple). See *Use of the Pesticide Data Program (PDP) in Acute Dietary Assessment*, USEPA 1999i). Additionally, numerous single-serving surveys have been conducted both in USDA's PDP and by industry task forces. In conclusion, OPP notes that federal monitoring programs have been expanded to include those foods most consumed by children including milk and grains.

Comment 14. SAP also raised the issue of accidental contamination of food but agrees that it does not make sense to develop a national regulatory program around such extremes. However, the Panel also noted that the program should identify the minimum size of the group that might be impacted by usual consumption of foodstuffs at some maximum level of probable contamination.

Response. OPP does not make decisions to grant, modify or revoke tolerances, considering scenarios which may reflect the misuse of pesticides. There, obviously, could be ways by which misuse could occur, and it would be virtually impossible to address them in any sensible way in setting tolerance levels. That is why there are regulatory monitoring systems in place (e.g., FDA surveillance and compliance programs) designed to prevent contaminated food from entering the channels-of-trade. Additional tolerance and pesticide misuse enforcement is conducted by individual states. USDA PDP program conducts monitoring for pesticide residues in major foods consumed by children and reports violative residues to FDA. OPP understands that accidental contamination and/or intentional misuse may occur but this would not likely affect potential exposure to the population as a whole.

ISSUE 14. Conservatism of Drinking Water Exposure Assessments

OPP is developing a tiered approach to assessing the likelihood and magnitude of contamination of drinking water and its sources by a pesticide. As an interim approach, when direct assessment is not possible, is it reasonable and protective to regard the estimates generated by OPP's current screening methodology as upper bound pesticide concentrations for surface and ground water and to assume that this concentration generally will not be exceeded in drinking water?

Comment 1. One commentor (778) stated that EPA does not have "reliable data" to support using anything other than the additional 10X margin of safety when estimating the exposure risks in drinking water since sufficient monitoring data and/or adequate pesticide-specific data are usually lacking. To the contrary, two other commentors (773 and 405) asserted that since the ecological fate models grossly overestimate potential exposure from residues in drinking water and the output represents highly conservative estimates (similar to Tier 1 or 2 analyses for assessment of residues in food), an additional FQPA uncertainty factor is not needed.

Response. The peer reviews conducted by the FIFRA Scientific Advisory Panel in 1997 and 1998 agreed with OPP's view that the screening level modeling outputs can in general be viewed as high-end estimates of potential pesticide concentrations in drinking water. Further, these peer reviews supported OPP's use of this approach for purposes of rapid, cost-effective screening of pesticides for drinking water-related dietary concerns. An additional safety factor to account for uncertainty around the accuracy of the screening level drinking water estimates is therefore not typically warranted. However, in cases where OPP is placing greater emphasis on what, in reality, is a very limited amount of drinking water monitoring data for a compound and is de-emphasizing the screening level model-based outputs in its drinking water assessment, there is reason to consider the application of an additional safety factor to account for uncertainty associated with using a limited monitoring data set. (See also response to comment 4, below, for more discussion of why this is important.)

The long-term goal of OPP is to go beyond screening level drinking water assessments, to go beyond the use of limited monitoring data with the application of a safety factor, and to go beyond requiring pesticide-specific drinking water monitoring data collection. The long term goal is for OPP to have the capability to develop accurate predictions of pesticide concentrations in drinking water resources at particular locations where a pesticide is used. These predictions can then be combined with data on the distribution of water consumption values across the population in order to produce distributions of human exposure values associated with ingestion of drinking water from different sources in different locations. The drinking water exposure distributions can then either be combined with food-related exposures in some probabilistic fashion, or, OPP could simply select a "reasonable worst case" drinking water exposure value from a distribution and combine this value with the food-related exposure values. In March 2000, OPP and the United States Geological Survey (USGS) brought two regression-based models to the Scientific Advisory Panel (SAP) which if realized would allow for the prediction of pesticide levels at surface water-based community water system intakes. The March SAP was very favorable in its review and comments and strongly encouraged the program to continue down this path (USEPA 2000f).

Much progress has been made over the past year in refining the models used for drinking water assessments. For example, in the case of surface water, OPP has replaced the field pond scenario used in screening assessments with an "index" reservoir based on an actual drinking water reservoir in its Tier 2 screening assessments. The model has also been adjusted for the percentage of the watershed feeding the reservoir that is actually in agricultural production in order to more realistically reflect watershed-scale use. OPP also plans to incorporate the "index" reservoir and percent crop area in the Tier 1 surface water screening assessments. As indicated above, in the longer term, OPP is working to develop and validate more sophisticated approaches for estimating pesticide exposure in drinking water, including the use of watershed-scale models and regression models which more accurately capture basin-area processes and would be more appropriate for use in quantitative human health risk assessments (For further details, the reader is referred to the document entitled *Estimating the Drinking Water Component of a Dietary Exposure Assessment* (US EPA 1999j).

Comment 2. Two commentors (773 and 405) agreed that since the estimates of pesticide concentrations in drinking water are high end or upper bound values, such estimates should be used only for screening purposes and should not be combined with estimates of food exposure to produce an aggregate exposure estimate. Commentor 405 suggested that the approach for determining potential exposure from drinking water should be consistent with determining potential exposure from foods when using highly conservative assumptions (e.g., tolerance-level residues, 100% crop treated), the 99.9th percentile of exposure is not an appropriate regulatory target. Instead, regulating at a lower percentile of exposure would be highly protective of infants and children when the results of such screening models are used.

Response. As previously stated (see Issue 13), under some circumstances it may not be appropriate to quantitatively combine certain tiered assessments. It is recommended that screening level assessments, for example, be evaluated in tandem with the highly refined assessments to develop an understanding of the overall level of concern for a pesticide from all appropriate routes and to identify likely areas for further data development. OPP is pursuing the use of improved modeling in conjunction with monitoring data to develop a tiered approach which would result in more realistic estimates of pesticide concentrations in drinking water.

Comment 3. Commentors L005 and 405 suggested that the consumption data on drinking water (i.e., tap water) as well as commercial processing and bottled water provided by the CSFII be considered as equally "reliable" as the consumption data reported for any other foods in the surveys. Additionally, Commentor 405 suggested that drinking water be included in the USDA PDP and that finished drinking water (i.e., not raw surface or ground water) be considered as any other commodity reported in the USDA surveys.

Response. OPP has incorporated water consumption data from CSFII 1994-1996, 1998 into its risk assessment process using the Office of Water's extraction of these data. These data were peer reviewed by EPA's Science Advisory Board and found to be acceptable. These consumption data are sufficiently robust to permit a reliable estimate of exposure in water when used in conjunction with reliable drinking water residue concentration estimates.

On June 6, 2000, OPP scientists gave a presentation to the Scientific Advisory Panel concerning a national drinking water survey design for collecting data appropriate for assessing chronic exposure. Based on the feedback from the June 2000 SAP, it appears that there would be a number of limitations on the use of a "PDP-type" approach to drinking water monitoring (i.e., the collection of finished water samples using the basic statistical design framework of the PDP) for drinking water. During OPP's consultation with the SAP, the Agency discussed design options and a proposed survey design framework for assessing annual average pesticide concentrations in surface-derived drinking water. The population of interest in the survey for a particular pesticide was defined as the community water systems (CWSs) using surface-derived drinking water with the target pesticide used in the watershed. The SAP generally endorsed the Agency's recommended design structure and recommended that at least some CWS's in the study be monitored for three years to assess year-to-year variability. The SAP also recommended that more emphasis be placed on raw water samples than finished water samples because of the complexity introduced in temporally paired sampling in a water treatment facility. They urged the Agency to investigate the impact of treatment on pesticide concentrations in finished water and take the approach of scientifically determining the impact of different "units" of the treatment "train" on different types of pesticides and to use these data to develop appropriate water treatment factors to account for water treatment effects on pesticide removal and transformation. Finally, the SAP recommended that the Agency initiate a pilot scale study to test the framework design and agreed with adding the census approach to the framework for very large systems (USEPA 2000g).

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Comment 5. The SAP agreed in prior reviews that the water modeling approach is sufficiently conservative but notes that the models appear to be most useful for identifying those pesticides that are unlikely to reach water in appreciable concentrations. Departure from the upper-bound estimates by virtue of examining exposure in current databases must be done with caution. In many of the databases used as a source of monitoring data, it is not possible to identify the source of drinking water because many cities depend upon several sources. Bias has also been introduced because negatives may simply come from areas where a pesticide was not used. Information on drinking water samples seldom identifies the treatment processes used in sampled drinking water systems which is absolutely necessary to understand before monitoring results can be generalized–even to other systems that use the same source water. Consequently, it is probably not appropriate to rely on databases to determine the potential of a pesticide to impact drinking water. It would seem that the way that this question can

be answered with rigor is to design studies to specifically evaluate this question. Dependence upon existing or even future databases that may be more representative may, in fact, not represent the use patterns associated with a particular pesticide, even though the database could be representative for the country as a whole.

Another issue raised was that significant exposures to pesticides are likely to be episodic. Large systems are unlikely to end up with significant exposures for many reasons. Better water treatment and large volumes increase the likelihood of dilution and other considerations. Small systems could be exposed to a spill located close to source, encounter storm events that might introduce particulate matter into the water, have high levels of local irrigation, etc., that all increase the vulnerability of drinking water to pesticides.

Response. OPP believes its risk assessments would be strengthened by additional monitoring data and in parallel, the development of improved predictive models and approaches for producing more accurate estimates of pesticide residue concentrations in drinking water. OPP agrees that relying on limited monitoring data in lieu of current screening level model-based estimates OR placing more emphasis on limited monitoring data over screening level estimates should be done with caution, because there is a possibility that the results of limited monitoring efforts would underestimate concentrations to which a significant number of people could be exposed in drinking water. OPP recognizes that, if it is unable to interpret limited monitoring data as to how well it represents use of the pesticide, that it could misestimate actual exposures when relying on these measurements in its risk assessment. This suggests the need for OPP to consider including an additional safety factor for drinking water exposure in those cases where OPP is relying on or placing more emphasis on limited monitoring data as the basis for a determination that there is no significant risk posed by exposure to a pesticide through the drinking water route.

Efforts currently underway to collect additional monitoring data include requesting monitoring and runoff studies on individual pesticides from their sponsors, working with the U.S. Geological Survey (USGS) to obtain more regional- and national-scale monitoring data on multiple pesticides in reservoirs and other surface water-based sources, and exploring design considerations for a national survey of pesticides in drinking water with various government agencies and industry groups and associations.

ISSUE 15. Conservatism of Residential Exposure Assessments

OPP is developing approaches to assess the likelihood and magnitude of exposure to pesticides in residential and other non-occupational use scenarios. When direct assessment is not possible, is it reasonable and protective to regard the estimates of exposure for the major residential and other non-occupational exposure use scenarios developed by OPP as upper bound estimates of the exposure received by infants and children from such use?

Comment 1. One commentor (369) indicated that the level of certainty in the residential SOP-based assessments, particularly with regard to the number of replicates available in the Pesticide Handlers' Exposure Database (PHED), was not adequate to permit characterization of whether estimates of exposure were conservative or not with any certainty. In particular, the commentor pointed to the departure from the NAFTA criteria for subsetting PHED data which require a minimum of 15 replicates to be classified as grades A and B for estimation purposes.

Response. OPP acknowledges that some of the data sets in PHED fall short of this criterion. However, where user-controlled input variables are high end values, it is unlikely that the SOPs will underestimate residential exposures. OPP agrees that the risk assessor must characterize the amount and quality of data supporting each estimate and highlight areas of concern or uncertainty for the risk manager. OPP also encourages the production of additional exposure data that may be used to bolster this valuable tool and to reduce the uncertainties in the residential risk assessment process.

Comment 2. Commentor 369 also noted the existence of other models such as CONSEXPO and TherDbase which may be useful in estimating residential exposure. The commentor encourages the validation of these models.

Response. OPP is aware of these as well as other models that are currently under development and joins the commentor in encouraging validation be undertaken. The reader should note, however, that TherDbase is no longer a supported product.

Comment 3. Commentor 369 also noted that some pathways (e.g., track-in from turf) have not been quantitatively characterized in the SOPs and recommends that these scenarios be researched to close this information gap.

Response. OPP is looking at other sources of exposure for children that may be associated with pesticides used in and around the home, including dust/dirt containing pesticides tracked into the home and related routes of possible exposure. These routes of exposure, available research, and methods for assessing these kinds of exposures were presented to the SAP in September 1999. The Panel comments and conclusions can be found in the final report of the meeting (USEPA 1999k).

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Comment 4. The Scientific Advisory Panel commended the10X Task Force Exposure Working Group for the background document they developed, acknowledging that it advocated a number of major steps forward in the exposure assessment process that would help overcome some of the shortcomings in OPP's Residential Exposure standard operating procedures (SOPs), including the incorporation of probabilistic approaches, the recognition of narrowly defined age groups relevant to specific exposure-related behaviors (i.e., prenatal, crawlers, young toddlers, etc.), movement of pesticides across media (e.g., deposition on nontarget surfaces), and recognition of the importance of receptor-based (as opposed to source-based) exposure assessments that examine important exposure issues from the perspective of how and where children spend time. The Panel urged OPP to fully integrate the above steps into the exposure assessment process for nondietary exposures. The SAP remarked that the production of this document, nearly two years after the initial residential SOP protocols were developed, is a reversal of the order in which these activities should have taken place, meaning that it is difficult to answer the question put forward to the Panel because the question implies that it is possible to judge or determine through empirical or semiempirical techniques if the scenarios as articulated in the document are reasonable and protective.

Response. When the *Standard Operating Procedures (SOPs) for Residential Exposure Assessments* (USEPA 1999g) were originally developed they were intended to serve as a screening level tool for use in deterministic risk assessments and not to be used in probabilistic assessments. The best available data were used at the time and, in many cases, the level of refinement was limited by the data that were available. OPP is currently engaged in many efforts to develop further improvements to the risk assessment process. These include utilizing new data sources characterizing activity patterns and behaviors relating to pesticide use in the home, incorporating data into risk assessments as distributions rather than point estimates, and better defining scenarios characteristics in the SOPs. The key factors for adding these refinements to our process are the availability of appropriate data and also the development of

appropriate risk assessment methodologies.

OPP has funded, through a cooperative agreement, the development of a probabilistic model called Lifeline which incorporates residential exposures. It is also working in various capacities with the developers of several other probabilistic models that include a residential component. One such model is Residential SHEDS-Pesticides model, a two-stage Monte Carlo model for estimating children's exposure to pesticides via the dermal and nondietary ingestion routes developed by EPA's Office of Research and Development (ORD). Another model is Calendex from Novigen Sciences.

OPP assisted in the planning and execution of a technical workshop held July 26-27, 2000 and sponsored by the Agency's Risk Assessment Forum entitled Workshop on Issues Associated with Considering Developmental Changes in Behavior and Anatomy When Assessing in Children (http://www.epa.gov/ncea/raf). This workshop involved discussions about available data and research to help characterize age-related changes in behavior and exposure factors of children to help improve children's exposure and risk assessment. Movement of pesticide residues across media and the development of receptor-based exposure models are also key components to future OPP efforts related to residential risk assessment. As new and better data become available from academia, ORD, and industry, the treatment of these issues in our risk assessment process will become more refined. OPP will use mechanistic data, such as track-in information, indoor air emission terms, and residential use data, to better understand multimedia issues. OPP will also consider survey and videography information to understand how behaviors contribute to children's exposure in order to develop receptor-based approaches. Finally, OPP will use population-based monitoring data, such as those being developed through the National Human Exposure Assessment Study (NHEXAS), to establish "real-life" exposure levels with which to validate the models.

Comment 5. The SAP also noted that the decision whether scenario-based residential and other nonoccupational exposure assessments are sufficiently conservative so as to not underestimate exposures hinges on several issues:

< Whether the scenarios chosen are exhaustive, i.e., have included every potential exposure scenario and have not overlooked cross media transfer.

< Whether measurement and assessment data and exposure factors are accurately characterized.

< Whether exposure factors based on data and default assumptions have been chosen in a consistent manner and reflect within individual variability in behaviors so that assessors know whether or not contact rates and durations are truly upper bound.

< The timing of exposures relative to one another, given that many pesticide applications take place on a seasonal basis. It is possible that exposures by more than one scenario (e.g., turf applications and wading pool exposures) can take place within a day or days of each other.

Concerns were raised by the SAP and other commentors regarding the inadequacy of the residential SOPs, particularly weaknesses in assumptions about hand-to-mouth and object-to-mouth activities and ingestion of dust, soils, and turf. According to these commentors, the goal should be to use the median values of well articulated exposure distributions (e.g., body weights or surface areas, for example) along with conservative but defensible upper-bound estimates where chemical-specific data do not exist (e.g., 100% inhalation absorption).

Response. The SAP appears to be raising two points: the adequacy of the measurement and assessment data and exposure factors defined in the (revised) Residential SOPs and the ability of an assessor to properly assess aggregate exposures which may occur in the real world. On the first point, in order to ensure that the standard of "reasonable certainty of no harm" was established in the risk assessments completed by OPP, the original *Standard Operating Procedures (SOPs) for Residential Exposure Assessments* (USEPA 1999g) were developed using a deterministic approach to exposure assessment that intentionally produced bounding estimates. This approach is based on conservative assumptions and, the Agency believes results in exposure estimates for a single exposure pathway that are sufficiently protective. The residential SOP's represent the best 'state-of-science' possible at this time. OPP disagrees with the implication by the commentor that the measurement and assessment data and exposure factors are not accurately characterized by the Residential SOP's. Indeed, OPP has expanded considerably the number and types of residential exposure scenarios included, e.g., the number of hand-to-mouth contacts per hour has increased, and relied upon conservative assumptions in the face of uncertainty (see *Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment*; USEPA 1999n).

As previously stated, other efforts within the Agency to further improve

exposure estimates, including the development of the Residential Stochastic Human Exposure and Dose Simulation Model for Pesticides (or Residential-SHEDS model) by the Office of Research and Development. A publication describing this model framework and presenting a case study application of the model is on NIEHS' Environmental Health Perspectives web site (http://ehpnet1.niehs.nih.gov/docs/2000/108p505-514zartarian/abstract.html), and the manuscript published in the June issue of *Environmental Health Perspectives* (Zartarian et al. 2000). A peer review of the SHEDS-Pesticides model will be conducted in the near future.

The second point raised by the SAP is the ability of an assessor to adequately perform and characterize an aggregate exposure which includes the residential pathway. OPP points to the revised guidance for conducting aggregate exposure risk assessments (US EPA 2001b) which articulates the Agency's framework in which to evaluate aggregate exposure. The fundamental approach of the guidance is a move toward population-based exposure and risk assessment which is comprised of data representing "coherent individuals" in the population. By "coherent individual," OPP refers to the use of various data sets or professional judgment to represent individuals in the population which are spatially and temporally linked to, and demographically consistent with, each individual. This 'linking' of data sets, each data set possibly playing a part in defining the total aggregate exposure to the individual in the population, or use of professional judgement to define likely linkages, will ensure the use of all relevant exposure scenarios, timing of exposures, and move closer to reflecting the interindividual variability accurately. In this way, aggregate exposure assessment can be used to analyze the (representative) total population. OPP is confident that the use of such data sets which are based on an individual can be developed using available data sources which adequately and accurately assess the temporal, spatial and demographic characteristics of a representative population within an aggregate assessment.

ISSUE 16. Overall Conservatism of Exposure Assessments

In OPP's view, its aggregate exposure assessments generally do not underestimate the exposure to infants and children because the aggregate exposure is calculated by adding the high-end estimates of exposure to pesticides in food, to the high-end estimates of exposure to pesticides both in water and as a consequence of pesticide use in residential and similar settings. Please comment on this view.

Comment 1. Commentor 773 (pp. 7, 36, 56) states that the models OPP currently uses to estimate drinking water and residential exposure are so conservative that they are extremely unlikely to underestimate exposure, and that is a good reason for not applying an additional FQPA uncertainty factor because of nonfood issues. OPP should, however, change its approach to calculating aggregate exposure. OPP should not incorporate deliberate overestimates of pesticide exposure into assessments just for the purpose of avoiding the use of an additional 10X Safety Factor.

This commentor (p.56) agrees that the current OPP estimates of exposures from residential pesticide use are high end, upper bound values, but disagrees with OPP that such estimates should be combined with estimates of food exposure to produce an aggregate exposure estimate. Such estimates should be used only for screening purposes.

Commentor 369 concurred that a simple additive approach to aggregate exposure (i.e., summing high-end estimates for food, water and residential) would not likely underestimate exposure to infants and children. However, as the Agency moves toward probabilistic approaches, it will be important that the level of confidence in the inputs is high; the methodological and data development currently underway will eventually increase the level of certainty associated with these inputs.

Response. OPP bases its exposure estimates on a variety of models which reflect the various pathways through which exposure could occur. These models utilize the data described in 40 CFR: residue chemistry data (40 CFR 158.240) used in dietary food risk assessment; environmental fate data (40 CFR 158.290) used in dietary drinking water risk assessment; and reentry protection data (40 CFR 158.390) used in residential (nonoccupational) risk assessment.

Many other data sources, modeling techniques, and other resources are available to supplement the guideline exposure studies submitted to the Agency and together allow consideration of all potential exposure pathways.

Additional data sources for dietary food risk assessment may include:

Food and Drug Administration (FDA) Regulatory monitoring data (crop surveillance and compliance data); United States Department of Agriculture (USDA) Pesticide Data Program monitoring data; State monitoring data; FDA Total Diet Survey; and consumption data from the USDA Nationwide Food Consumption Survey (NFCS) and Continuing Surveys of Food Intakes by Individuals (CSFII).

Additional data sources for dietary drinking water risk assessment may include monitoring data from: 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 STORET database; the OPP Pesticides in Groundwater Database; and the National Pesticide Survey.

Additional resources for residential (nonoccupational) risk assessment include: the Pesticide Handler Exposure Database (PHED); the Exposure Factors Handbook; and the OPP Standard Operating Procedures (SOPs) for Residential Exposure Assessments; chemical-specific use/usage data from OPP Biological and Economic Analysis Division; and Center for Disease Control (CDC) biomonitoring or epidemiology data.

Collectively and individually, these data sets have both strengths and limitations. EPA believes that its approach to using these data is generally conservative, i.e., unlikely to underestimate potential exposure. On a case-by-case basis, however, EPA will examine a particular exposure assessment to determine–in light of the particular data used and the methods of combining the data–whether the assessment may understate exposure.

Comment 3. 778 (NRDC), p. 8. The absence of child-specific exposure data is sufficient reason to apply the FQPA 10X margin of safety. It is not appropriate to argue that incomplete, limited information or data may be used to develop an estimate that does not understate exposure and therefore that the Agency may ignore the statutory mandate to apply the 10X.

Response. See the response to comments under Issue 17 below.

Comment 4. 778 (NRDC), p. 3. The “completeness” of the exposure database under FQPA is different from the adequacy of the database to support registration.

Response. See the response to comments under Issue 17 below.

Comment 5. 781 (Farmworker Justice Fund; p.6) could not agree with the Agency's blithe assumption that "it is not underestimating exposure to infants and children or to the general population" and that "the FQPA Safety Factor would not be needed to address uncertainties in the exposure database." The 1993 NAS Report, *Pesticides in the Diets of Infants and Children*, raised many concerns about the quality of EPA's pesticide residue data and problems with the reliance on "average" (adult) exposures. Nor has the Agency accurately modeled children's exposure to pesticides at home, in school, or through drinking water. Given the deficiencies found by the NAS report, the scant actual data, and the untested nature of EPA's assumptions, it cannot be said that the exposure data is complete for the general population of infants and children.

Response. OPP exercises great care in ensuring that its estimates of exposure to infants and children are health protective. A number positive steps have been taken to improve the risk assessment process and the quality of available data since the issuance of the 1993 NAS Report. OPP now has extensive, age-specific food consumption data for infants and children. This is combined with monitoring data designed to target pesticide residues in the major children's foods. USDA's Pesticide Data Program generates nationally representative data defining pesticide residues with great precision. Exposure to pesticides in foods is estimated using the full range of the distributions of food consumption and pesticide residues, including information specific to childhood exposures. Water concentration estimates used in OPP risk assessments currently reflect high end values, making underestimation of exposure to pesticides in drinking water unlikely. OPP also includes a number of conservative assumptions in its residential exposure assessments to ensure that exposures in the home are not underestimated. These conservative assumptions produce estimates of exposure that are sufficiently health protective to encompass exposures to children in a variety of settings including farming areas.

Comment 6. 781 (Farmworker Justice Fund), p. 6-7. The inadequacy of data concerning exposures to the general population of infants and children is compounded many fold for the children of farmworkers. These children face many more exposures from drift, take-home exposure and direct exposure in the fields. Since neither the EPA's actual data nor its assumptions adequately take into account the exposures of farmworker children, the exposure database for virtually all pesticides must be viewed as incomplete, necessitating at least the imposition of a 10X safety factor.

Response. See the response to comment 7 below.

Comment 7. 781 (Farmworker Justice Fund). Farmworker children should be a sentinel population in determining the adequacy of the exposure data. Farm children experience a wider range of exposures to pesticides than most other children (e.g., playing/walking in fields, spray drift, parents' contaminated clothing, fruits/vegetables from the fields, dust in homes, spray drift at school, drinking water). Children of rural residents may be viewed as a second significant subpopulation because they share some of the same sources of exposure. In support, the commentor, cited several exposure studies. Because of the significant body of data demonstrating the extent of pre- and postnatal exposures of farmworker children to pesticides, farmworker children should be deemed a sentinel population by EPA for purposes of determining the adequacy of the exposure database for purposes of applying the 10X safety factor.

Response. Again, OPP agrees that it is important to assess whether farm worker children are currently at risk and to address that risk. However, OPP has no information indicating that exposures to farm worker children differ significantly from exposures to children in the population at large. OPP includes a number of conservative assumptions in its residential exposure assessments to ensure that exposures in the home are not underestimated. Thus, for pesticides registered for residential uses, these conservative assumptions produce estimates of exposure that generally encompass exposures to children in a variety of settings, including farming areas. Since FQPA was passed, the Agency has generally been examining the special vulnerabilities of children, has adopted specific policies (such as the 10X policy) to protect children when available information indicates such vulnerability, and has been developing specific methods for estimating risks to children resulting from exposure to registered pesticide uses. Specific to farm worker children, EPA is continuing to seek and evaluate information as to whether certain activities of children, such as playing on lawns, are analogous to exposures that farm children may receive. EPA is also developing with USGS a project to gather data on farmworker exposure to pesticides from their drinking water sources. The issue of exposure to farm worker children was included in the presentation to the SAP in September 1999. The Panel comments and conclusions can be found in the final report of the meeting (USEPA 1999k).

Comment 8. The SAP postulated that combining data of varying quality (i.e., food, water, nondietary) with widely different confidence intervals affects the end result. Deterministic approaches are not necessarily always more conservative than assessments that use distributional approaches, especially when the data sets for concentration, contact rates, and duration are robust. This is not a reasonable view in light of the severe defects in the assessment of nondietary exposures of the fetus, infants, and children. As a result, there is no confidence in the assessment of aggregate exposure.

Response. OPP disagrees with the SAP that there is no confidence in the assessment of aggregate exposure due to the combining of data of varying quality. OPP agrees that aggregate exposure assessment may include data of different quality, collected for different purposes, and that such data can be treated both as distributional and as point estimates of exposure. However, the goal of the aggregate assessment is to give as accurate and reasonable an estimate of distributions of risks as possible, without underestimating the upper tail. Others have commented on and expressed support for OPP's use of different types of data sets for the purpose of aggregate assessment in the past. For example, the ILSI panel and previous SAPs have stated that it is acceptable to combine probabilistic and deterministic types of data in the food pathway.

OPP believes that a full understanding of the uncertainty and a careful characterization of the results is vital when combining different types of data. OPP agrees that sensitivity analyses are key to fully understanding the combined data distributions. OPP also agrees that it is most appropriate to use central tendency values when defining deterministic values. The definition and description of data distributions is addressed in an accompanying OPP Science Policy document entitled *Guidance for Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs* (US EPA 1998b) OPP is investigating the use of two-stage Monte Carlo techniques for use in probabilistic assessment models which will aid the Agency in quantifying the uncertainty and variability of the estimates.

ISSUE 17. Reliable Data

Several commentors raised the issue of how the terms “reliable data” and “reliable information” in the FQPA should be interpreted. Although these comments address the application of the children’s safety factor, the statutory interpretation issues raised by these comments have implications for many other aspects of implementation of the FQPA. Because this interpretational issue should not be viewed in isolation, OPP has attempted to address below all of the comments provided on this issue. OPP first discussed these issues in the Response to Comments document for the Aggregate Exposure policy in December, 2001. The FQPA Implementation Working Group (IWG) submitted further comments on these issues in a letter responding to the Aggregate Exposure Policy Response to Comment document. IWG Letter to Stephen Johnson and Robert Fabricant (January xx, 2002) [hereinafter cited as “IWG Letter”]. IWG asserted that OPP mischaracterized its earlier comments on these issues and did not respond adequately to them. This Response to Comments document addresses these latest comments from IWG as well.

The two primary statutory provisions cited by commentors are the general definition of safety in section 408(b)(2)(A)(ii) and the language in section 408(b)(2)(C) addressing when it is appropriate for OPP to select an FQPA Safety Factor “different” from the additional tenfold factor to protect infants and children. Section 408(b)(2)(A)(ii) states:

> [T]he term “safe”...means that [EPA] has determined 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 exposure for which there is reliable information.

Section 408(b)(2)(C) provides that:

> Notwithstanding such requirement for an additional margin of safety, [EPA] 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.

Another relevant provision is subsection (b)(2)(D)(i) which provides that in making tolerance decisions:

> [EPA] shall consider, among other relevant factors, ...the validity, completeness, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue....”

Industry Comments

Essentially, industry's view is that the "reliable information" language in section 408(b)(2)(A)(ii) is a screen, or gatekeeper, for both whether nondietary exposure can be considered as part of a pesticide's aggregate exposure for the purpose of making the safety determination and whether nondietary exposure can be considered in judging the completeness of the exposure database for children's safety factor purposes. According to IWG (whose views were repeated in comments from others, e.g., Commentor L016 (Michigan Farm Bureau) [hereinafter cited as IWG 10X Comments], Congress' intent in including the "reliable information" language in section 408(b)(2)(A)(ii) was to ensure that data on pesticide exposure, other than exposure through residues in food, would only be taken into account in assessing aggregate exposure if there exist data providing "a reasonable estimate of the actual, real-world level of exposure to the pesticide...includ[ing] information on the distribution of the exposure, so that probabilistic estimates of aggregate exposure can be made" (IWG 10X Comments at 39). Moreover, IWG argues that the reliable information language in section 408(b)(2)(A)(ii) not only serves as a screen for what information is considered in calculating aggregate exposure but also as a gatekeeper for what exposure scenarios should be considered in determining, for children's safety factor purposes, the completeness of the exposure database.

As stated by IWG, "[w]e do not think that Congress meant that when [OPP] is assessing the acceptability of the risk from a well-defined exposure, it should have to add a 10X factor to account for some other possible exposure for which there are no reliable data" (IWG Roadmap at VIII-7). Thus, IWG asserts that if OPP does not have reliable information on a nonfood exposure scenario, that exposure scenario should be completely excluded from the frame of reference in making safety factor decisions. In other words, IWG does not believe that the "reliable data" test for assigning a different FQPA Safety Factor even comes into play as to nonfood exposure scenarios lacking reliable information *precisely because OPP does not have reliable data on this exposure scenario*. IWG states, however, "that in some circumstances there might be enough quantitative information [on nondietary exposure] to satisfy [the "reliable information" requirement]...but there still might be some need for an additional uncertainty factor." IWG Letter at xx. Further, IWG states that "[i]n the unlikely event that important information on exposure via food residues is missing, and such information might show a significant risk to infants or children that is not accounted for by normal use of probabilistic exposure assessments in assessing food-based risk, then [OPP] has the authority to retain an additional FQPA safety factor to address that uncertainty." (IWG 10X Comments at 40).

Given this legal interpretation, IWG criticizes OPP's approach of using models to insure that exposure is not underestimated for drinking water and residential exposure issue. OPP has relied on such models to conclude that it has "reliable data" on exposure issues in making decisions on the children's safety factor. IWG claims that this approach is unnecessary because "[m]odels designed to produce conservative overestimates, and the overestimates that they generate, cannot be considered 'reliable information' for purposes of the 'aggregate exposure' computation..." (IWG 10X Comments at 39).

There are several building blocks to the IWG's legal interpretation. First, IWG asserts that the phrase in subsection (b)(2)(A)(ii) "for which there is reliable information" applies not to the requirement to consider "all anticipated dietary exposures" but only to consideration of "all other exposures..." Thus, according to IWG, subsection (b)(2)(A)(ii) imposes a reliability test on nondietary exposures but no such test on dietary exposures. IWG claims that Congress chose not to impose a "reliability criterion" on dietary exposure information because Congress was aware of the quality of the data on such exposure already in OPP files and the reliability of government residue monitoring programs. Second, IWG contends that the term "dietary exposure" only extends to pesticide residues in food and not residues in drinking water. Thus, IWG argues that the reliability criterion attaches to exposure to pesticide residues in drinking water. Although IWG admits that "water is often thought of as a component of the diet," IWG asserts that the language of the statute and a pre-FQPA action by OPP and FDA suggest that drinking water is not included in the term dietary exposure. (IWG 10X Comments at 38-39. The statutory language IWG cites is section 408(b)(2)(D)(vi) that describes aggregate exposure as "including dietary exposure under the tolerance and all other tolerances in effect for the pesticide chemical residue, and exposure from other nonoccupational sources." The OPP/FDA action noted is the joint agency interpretation following passage of the Safe Drinking Water Act that the term "food" in the FFDCA does not include drinking water.

IWG does not contend that this legal interpretation is compelled by the statute; however, it does assert that its interpretation is a permissible one. It claims that "[i]t would be extremely arbitrary for OPP to proceed to use worst-case model estimates without stating publicly whether it has the legal authority to do so, and whether it would be good policy" (IWG 10X Comments at 40).

NRDC Comments

NRDC takes a dramatically different approach to the terms "reliable data" and "reliable information" as they are used in subsections 408(b)(2)(C) and 408(b)(2)(A)(ii), respectively. NRDC argues that OPP has inappropriately merged the concepts of reliable data and reliable information. Although NRDC does not explain how it would define either of these terms, it does make clear that it believes "reliable information" sweeps more broadly than "reliable data." Importantly, as to the children's safety factor, NRDC asserts that exposure estimates based on models are not data. According to NRDC such model estimates are information–information that must be considered in calculating aggregate exposure–but not data sufficient to address concerns about the completeness of the exposure database and not reliable data sufficient to justify choosing a different safety factor than the additional tenfold children's safety factor.

In support of this argument NRDC points out that in two places, section 408(b) refers to both data and information in a single provision. See §408(b)(2)(E)(i) and (b)(2)(F).

Response. The IWG's and NRDC's approaches to the terms "reliable data" and "reliable information," exposure estimates from models, and the children's safety factor could not be more polar. IWG claims OPP's existing models for drinking water and residential exposure may not be considered as reliable information and, therefore, IWG would not include such model estimates of exposure in aggregate exposure. Further, IWG believes that exposures excluded from consideration under aggregate exposure are irrelevant to the children's safety factor decision and, thus, in their view, the inability of a model to yield reliable information for an exposure scenario would not necessitate retention of an additional tenfold safety factor due to incompleteness of the exposure database. In contrast, NRDC argues that model estimates are reliable information but not reliable data. Thus, NRDC would include model estimates in calculations of aggregate exposure and would conclude that, if OPP is using a model to estimate exposure, reliable data do not exist to permit removal of the additional tenfold children's safety factor.

OPP views both of these positions as extreme and cannot agree with either one. Each of the points raised by the commentors is discussed fully below.

The Reliability Requirement and Aggregate Exposure. OPP believes that IWG misreads the statutory requirements pertaining to reliable information on aggregate exposure. The IWG argues that Congress, by inserting the reliable information requirement in that provision, was erecting a special standard of reliability applicable to nondietary exposures whereas no reliability requirement was applied to dietary exposures. (See IWG 10X Comments at 38 ("Regarding dietary exposure, the statute does not impose a 'reliable information' requirement.")) Not only does this special standard have a role as a gatekeeper for what nondietary exposures may be included in aggregate exposure, but, according to IWG, the "reliable information" requirement has a substantive content as well. IWG asserts that the "reliable information" requirement mandates that nondietary exposure data must demonstrate not just the magnitude of exposure but the magnitude of "actual, real-world exposure levels" including "information on the distribution of the exposure, so that probabilistic estimates of aggregate exposure can be made." (IWG 10X Comments at 39).

IWG's theory that the "reliable information" requirement serves as gatekeeper for aggregate exposure is not necessarily problematic by itself. However, when this gatekeeper argument is coupled with IWG's interpretation of the scope of the "reliable information" requirement (i.e., the "reliable information" requirement has a specific substantive scope addressing the magnitude of exposure), IWG's approach becomes implausible. There is no basis in the language of the statute for giving an evidentiary type of requirement–reliability–a substantive content. Moreover, IWG's interpretation is difficult to square with the structure of the FQPA and particularly the reliability requirements in subsections (b)(2)(D)(i) and (b)(2)(C). Finally, IWG's approach runs counter to the clearly-expressed congressional intent to provide additional protection to infants and children when there are concerns about the completeness of the exposure database. These issues are discussed in more detail below.

To What Exposure Data Does the "Reliable Information" Requirement Apply? OPP thinks that the better interpretation of subsection (b)(2)(A)(ii) is that the "reliable information" requirement applies only to nondietary exposure and not dietary exposure. IWG believes strongly that this is so. IWG Letter at 3 (describing as "untenable" the notion that the reliable information requirement applies to dietary exposure); IWG 10x Comments at 38 (Regarding dietary exposure, the statute does not impose a "reliable information" requirement.). OPP also thinks that the statutory language is sufficiently ambiguous that phrase in subsection (b)(2)(A)(ii) referencing "reliable information" could be interpreted as applying to both dietary and nondietary exposure and thus reinforces the reliability consideration in subsection (b)(2)(D)(i). Nonetheless, OPP prefers the first interpretation to the second because it appears to be the more natural construction of the language in subsection (b)(2)(A)(ii). Further, as the

discussion below will show, OPP's interpretation of the meaning of the "reliable information" requirement supports the reasonableness of the first interpretation because it allows this requirement to mesh in an understandable fashion with the reliability mandate in subsection (b)(2)(D)(i) and the "reliable data" requirement in the children's safety factor provision.

Under OPP's preferred interpretation, OPP can, in theory, agree with the gatekeeper argument advanced by IWG regarding the "reliable information" language in subsection (b)(2)(A)(ii)–namely, if the "reliable information" requirement is not met for nondietary exposure, OPP should not assume that such exposure will occur in its estimation of aggregate exposure. However, as discussed below, because OPP disagrees with IWG concerning the "substance" of the reliable information test, OPP differs with IWG on how this test should be implemented.

What Qualifies as Reliable Information? OPP believes that the key to interpreting the meaning of the "reliable information" requirement are the plain language of that provision and the other statutory provisions bearing on the issue of reliability. The common meaning of "reliable information" is information that is trustworthy, or in the scientific sense, information that is reproducible. However, both the construction of subsection (b)(2)(A)(ii) as well as other provisions in the statute addressing reliability convince OPP that the "reliable information" requirement in subsection (b)(2)(A)(ii) does not simply impose a general trustworthiness standard to all aspects of nondietary exposure information.

As noted above, the better interpretation of subsection (b)(2)(A)(ii) is that the "reliable information" requirement applies only to nondietary exposure and not dietary exposure. Ordinarily, one would presume that Congress would be concerned about the reliability of any exposure data, whether dietary or nondietary, forming the basis of an OPP safety finding. This differential application of the "reliable information" requirement, therefore, must reflect a congressional conclusion that, at least as to some aspect of exposure data, a demonstration of reliability was important when such data concerned nondietary exposure but was unnecessary regarding dietary exposure.

OPP used this principle as a guide in interpreting the "reliable information" requirement in subsection (b)(2)(A)(ii). In other words, OPP sought an interpretation of the "reliable information" requirement that focused on reliability issues that are likely to be unique to nondietary exposure. In OPP's judgment, the reliability question that is unique to nondietary exposure in the pesticide tolerance context is whether exposure is *occurring* by the nondietary route. Because the FFDCA concerns tolerances, or maximum residue levels for

residues in food, it can be presumed that any tolerance action involves exposure through the diet. See 21 U.S.C. §346a(a) (describing the scope of section 408 as extending to "any pesticide chemical residue in or on a food ...."). In such circumstances, no reliable information is required to show that exposure can *occur* by the dietary route. On the other hand, that a tolerance permits residues in food does not mean that there is human exposure through nondietary channels (e.g., oral exposure to pesticides of young children from hand-to-mouth behavior in areas in or around homes where pesticides have been used). For example, many pesticides registered for use in agriculture have no permitted uses in residential settings that could lead to nondietary exposure. Thus, it is logical to demand reliable information that nondietary exposure can occur by the nondietary route prior to considering such exposure in making a safety determination. Accordingly, OPP interprets the "reliable information" requirement as being directed primarily at identifying *whether exposure occurs* by a certain pathway or route (i.e., nondietary). Such an interpretation meshes well with the statutory language because the provision in question specifically includes the reliable information requirement in the context of mentioning the *routes* of dietary and nondietary exposure.

OPP's interpretation also harmonizes the "reliable information" requirement in subsection (b)(2)(A)(ii) with the mandate in subsection (b)(2)(D)(i) for OPP to consider the "reliability" of data in making safety determinations. Although at first blush there appears to be some tension between subsection (b)(2)(A)(ii) imposing a reliability requirement only on nondietary data and subsection(b)(2)(D)(i)'s direction to consider the reliability of data generally, any such tension is relieved by limiting the reliability inquiry in subsection (b)(2)(A)(ii) to an issue–whether exposure is occurring by the route in question–for which no reliability inquiry is necessary as to dietary exposure based on the regulatory action involved–i.e., setting maximum pesticide residue levels in food. As is appropriate, questions regarding the magnitude and distribution of dietary exposure still would fall under subsection (b)(2)(D)(i)'s reliability inquiry.

IWG takes a quite different approach. It asserts that, because OPP has specific and reliable information on the actual residue levels and distribution of those residues in food, the reliable information requirement must have been intended to assure that OPP had a similar type of reliable information on nondietary exposure. In IWG's words, "[f]or information to be considered reliable..., it must provide a reasonable estimate of the actual, real-world level of exposure to the pesticide ...[including] information on the distribution of the exposure, so that probabilistic estimates of aggregate exposure can be made." IWG Letter at xx; IWG 10X Comments at 39. IWG does not believe that this very specific and substantive construction of the term "reliable information" as it applies nondietary exposure implies that OPP is without power to investigate

the reliability of data on the levels and distribution of dietary exposure. Rather, IWG asserts that OPP can demand reliable information on dietary exposure based on the mandate to consider data reliability in subsection (b)(2)(D)(i) and OPP's data regulations and guidelines. Further, IWG states that "missing" data pertaining to infants and children can be addressed through retention of the additional safety factor for the protection of infants and children, as provided in subsection (b)(2)(c).

In OPP's view, IWG does not provide an adequate explanation for its infusion of the term "reliable information" with a specific, substantive content. First, it is a considerable leap to interpret a general statutory term regarding essentially an evidentiary issue ("reliable information") as imposing a substantive requirement of the type of information that must be submitted (information on the "actual, real-world level" and "distribution" of residues). OPP is reluctant to preclude consideration of "reliable information" concerning nondietary exposure that does not fit IWG's specific substantive construction of that term without reference to some language in the statute or legislative history that supports IWG's interpretation. IWG provides no such support.

Second, OPP questions the accuracy of factual premise to IWG's argument–that OPP has data on "actual, real-world level" and "distribution" on all pesticides used on food. Actually, there is a fair amount of variability in the quality of data OPP has on pesticide residues in food. Although OPP does have very specific and detailed information concerning the "actual, real-world" residue levels and distribution of those residues for many agricultural pesticides, this is certainly not true as to all pesticides used on food. For many pesticides, OPP may have little or no data on actual residues from monitoring of food in distribution channels (especially as to new pesticides) but instead OPP must depend on residue data from residue field trials. Residue levels measured in such trials are higher, often significantly so, than the actual residue levels to which consumers are exposed and such studies may provide limited information concerning the distribution of residue levels.[1] IWG's factual premise is also weakened by its concession that it is perfectly appropriate–even required–that OPP evaluate the reliability of data pertaining to pesticide residues in food. IWG Letter at 4. After all, IWG's interpretation of the "reliable information" requirement is based on the proposition that the statute imposed no "reliable information" requirement on dietary exposure because "there was no general need for concern about whether available information on exposure from food residues is reliable." IWG Comments at 4.

[1]IWG does not address how its "reliable information" test–information comparable to that on dietary exposure – can be consistently applied in the face of this wide variation with regard to exposure information on food.

Third, OPP does not believe that IWG has provided an adequate explanation of how the "reliable information" requirement in subsection (b)(2)(A)(ii) can comfortably be integrated with the mandate to assess data reliability in subsection (b)(2)(D)(i). Given IWG's definition of the "reliable information" requirement as demanding reliable information on the actual level and distribution of residues, it seems inconsistent to assert, on one hand, that "[r]egarding dietary exposure, the statute does not impose a 'reliable information' requirement," IWG 10X Comments at 38, and to argue, on the other hand, that the reliability mandate in subsection (b)(2)(D)(i) and OPP regulations and guidelines mandate that OPP test the reliability of dietary information on the level and distribution of pesticide residues.[2]

Further, IWG does not address the considerable interpretational problem posed by its construction of subsection (b)(2)(D)(i). If, in fact, the statute does impose an unqualified reliability test on the level and distribution of dietary exposure information through subsection (b)(2)(D)(i), that same provision would impose a similar test on nondietary information rendering the "reliable information" requirement in subsection (b)(2)(A)(ii) wholly superfluous. Similarly, OPP believes that all of IWG's attempts to describe alternate general sources of authority to investigate the reliability of dietary exposure data tend to undermine its attempt to give the "reliable information" requirement a specific, substantive content because these other sources are based in the end on OPP's broad authority to require the submission of data or authority not limited to data on residues in food.

Finally, OPP does not accept the IWG view that Congress did not impose a "reliable information" requirement on dietary exposure information because it intended that a lack of reliable information on such exposures be addressed through the retention of the additional ten-fold factor for the protection of infants and children. The IWG approach unreasonably restricts OPP's ability to deal with issues relating to the reliability of dietary exposure data. Specifically, under IWG's approach, OPP's only recourse (unless IWG's theory that subsection (b)(2)(D)(i) provides a redundant reliability requirement is accepted), when dietary exposure data is judged unreliable, becomes retention of the additional

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[2]In fact, some statements by IWG seem to leave little room for the subsection (b)(2)(D)(i) reliability mandate as to dietary exposure: "If [OPP] is correct [in interpreting the term "dietary" as including drinking water], then drinking water exposure *always must* be determined and the aggregate of food and drinking water exposure *must* be tested against the FQPA safety criterion in making decisions on food tolerance, *without regard to the reliability of the information on drinking water exposure.*" IWG, Comments on Guidance for Performing Aggregate Exposure and Risk Assessments (February 10, 2000) (emphasis added).

10x factor for the protection of infants and children.[3] In contrast, OPP's interpretation provides OPP with the flexibility to reject all or part of dietary exposure data with reliability problems and deny a tolerance petition as unsupported or to use all or part of such data in conjunction with an additional factor for the protection of infants and children. Because the additional children's safety factor is designed to provide increased protection for infants and children in response to concerns regarding, among other things, the completeness of the exposure database, OPP believes the children's safety factor should be implemented in a manner that provides additional protections for infants and children and not as a substitute for standard administrative practices such as demanding that reliable information support safety determinations on tolerances. Further, OPP is reluctant to rely on a provision that is premised on a concern about the completeness of the exposure database as supporting an interpretation of another portion of the statute that would bar OPP from taking into account certain potential pesticide exposures unless a very specific and stringent reliability test was met.

Application of the Reliability Requirement in Subsection (b)(2)(A)(ii). As indicated, OPP's preferred interpretation of the reliability requirement in subsection (b)(2)(A)(ii) is that is directs OPP to consider whether there is trustworthy and reproducible information on whether there is exposure occurring by the nondietary pathway in assessing the aggregate risk imposed by a pesticide. If OPP concludes there is no reliable information showing exposure by a nondietary pathway, OPP will not assume that there is nondietary exposure to the pesticide. If OPP finds that reliable information does show exposure by a nondietary route/pathway, OPP must take such exposure into account in assessing the aggregate risk posed by the pesticide whether or not OPP is able to quantify with precision the level of such nondietary exposure.

As to reliable data bearing on whether exposure occurs by a given route/pathway, OPP believes that information can reliably demonstrate exposure by a given route/ pathway even if OPP does not have data documenting the magnitude of exposure levels to humans. For example, OPP has a large body of data showing that pesticide exposure can occur when there is residential use (e.g., insecticides are applied as a crack or crevice spray in a dwelling or other occupied structure, applied to the lawn, etc.). Further, OPP has compiled extensive data detailing the physical properties and

[3]This argument becomes more problematic when it is considered that IWG also argues that the children's safety factor cannot exceed 10X. IWG 10X Comments at 10. Thus, if OPP had only unreliable data on dietary exposure and OPP had reason to believe that such data was likely to understate exposure by greater than tenfold, OPP would still be limited to no more than use of a 10X safety factor to protect infants and children.

characteristics of those pesticides that potentially may result in human exposure under this use scenario. Thus, where the physical properties and characteristics of a specific pesticide, when considered in light of the generic data OPP has on pesticide exposure in nonoccupational residential settings, show that it is likely that the presence of that pesticide will result in human exposure if used in under a given scenario, OPP would have reliable information showing such nondietary exposure. (See also the additional discussion on models and the reliability requirements below.)

IWG expresses the concern that OPP's interpretation "creates the real and scary possibility that OPP will feel free to conclude, without any good reason, that high levels of nonfood residues might occur, and that OPP will then feel free to include those speculative, high-level residue values in aggregate exposure calculations." IWG Letter at 4. OPP does not see the basis for such a conclusion. OPP made clear in the Aggregate Exposure Response to Comments document that the "reliable information" requirement mandated that OPP have accurate and reproducible information that nondietary exposure was occurring prior to taking such exposure into account in aggregate exposure. Nothing in this interpretation would permit OPP to make unreasonable conclusions about the level of nondietary exposure in tolerance actions. Similarly, OPP does not believe that any aspect of its approach to the children's safety factor provision would sanction OPP reliance on unreasonable or speculative exposure assessments.

The Reliability Requirement in Subsection (b)(2)(A)(ii) and the Children's Safety Factor. Once the limited nature of the reliability requirement in subsection (b)(2)(A)(ii) is recognized, OPP can agree with IWG that if OPP does not have reliable information showing that exposure is occurring by a nondietary route/pathway, OPP generally should be able to conclude that as to nondietary exposure OPP has sufficient reliable data to ensure the safety of infants and children in regard to the tolerance in question. Although OPP is not certain that the gatekeeper role the "reliable information" requirement plays for aggregate exposure applies with equal effect in section (b)(2)(C), as a practical matter, under OPP's approach it is unlikely to make a significant difference.

OPP's major difference with IWG in regard to the children's safety factor provision turns, once again, on what constitutes "reliable information" showing that exposure is occurring by a nondietary route/pathway. IWG asserts that such a showing cannot be made absent a database demonstrating actual, real-world exposure levels and the distribution of those levels sufficient to conduct a probabilistic risk assessment. As explained above, OPP believes that the reliable information threshold is crossed once it can be shown that exposure is more likely to occur than not by the route/pathway in question, whether or not the

information can precisely define the level or distribution of exposure. The effect of IWG's interpretation of the "reliable information" requirement combined with its assertion that this requirement serves as a strict gatekeeper to what exposure scenarios can be considered in the "reliable data" inquiry in the children's safety factor is that, for all practical purposes, the children factor provision's concern with the completeness of the exposure database is obviated for nondietary exposure. Under the IWG's approach, it is difficult to imagine a scenario that would justify retaining an additional safety factor due to concerns regarding the database on nondietary exposure. If the database contains "reliable information" on the nondietary exposure–meaning in IWG's words "a reasonable estimate of the actual, real-world level of exposure to the pesticide...includ[ing] information on the distribution of the exposure, so that probabilistic estimates of aggregate exposure can be made"–it would seem that the nondietary exposure database is complete and therefore no additional safety factor is warranted with regard to nondietary exposure. If the database does not reliably address the magnitude or duration of exposure, then "reliable information" requirement would bar consideration of nondietary exposure as a potential concern bearing on the completeness of the database with regard to the need for a additional safety factor. Instead, the IWG approach would suggest that "reliable data" support removing the additional safety factor. In effect, under the IWG approach, the absence of "reliable information" on the magnitude or distribution of nondietary exposure necessarily means that there is "reliable data" on nondietary exposure such that the additional safety factor for the protection of children is unnecessary, and can be removed, so far as concerns any risk to infants and children from nondietary exposure.

In its latest comments on this issue, IWG takes exception to this characterization of its position. IWG claims that this conclusion was neither explicit nor implicit in its comments. According to IWG, "[w]e said–clearly–that if there is not reliable information on a no-food exposure route, that route should not be included in aggregate exposure and thus should not be regulated under section 408 until better information was available." Id. In its letter, IWG now allows that if the "reliable information" test is met for nondietary exposure (i.e., there is reliable information on the actual level and distribution of exposures), there could be circumstances where "there still might be some need for an additional uncertainty factor." IWG asserts, however, that its prior comments were not addressing this issue but "were pointing out our very urgent concern that OPP's approach would allow, and even require, the inclusion of gross overestimates of nonfood exposure in tolerance reassessments...in order to avoid the possibility of having to use an exposure uncertainty factor." Id.

After carefully rereading all of IWG's comments on OPP's aggregate exposure and children's safety factor policies, IWG's Roadmap paper, and

IWG's recent letter, OPP believes that it has fairly characterized IWG's approach to "reliable information," aggregate exposure and the children's safety factor provision. IWG may not have used the same words OPP did in describing IWG's position but the clear effect of IWG's interpretation of "reliable information" on aggregate exposure leads precisely to the result described above.

IWG is quite clear that information bearing on nondietary exposure which cannot meet IWG's interpretation of the "reliable information" requirement (because it does not provide information on the "actual level" or "distribution" of pesticide residues) is excluded from the FQPA's "aggregate exposure" concept used to judge the safety of pesticide tolerances. IWG Comments at 39. IWG is equally clear that nondietary exposure information excluded from aggregate exposure should not be relied upon as a justification for retention of the additional 10X safety factor for the protection of infants and children. IWG Comments at 39-40. Moreover, according to IWG, the inquiry under the Children's Safety Factor provision as to whether there are "reliable data" to remove the additional safety factor should focus on "whether there is sufficient reliable data about toxicity, about dietary exposure, and about the other kinds of exposure *that qualify for inclusion in the aggregate exposure assessment*...." IWG Roadmap at VIII-7 (emphasis added). Thus, the "reliable data" inquiry in the Children's Safety Factor Provision, according to IWG, is applied to a narrower set of data–the set of data defined by the "aggregate exposure" concept and its integral test of "reliable information" for nondietary exposure data–than the "reliable information" requirement.

In other words, IWG's position seems, essentially, to be that the issue of nondietary exposure does not even appear on the radar screen in applying the children's safety factor if information on nondietary exposure is judged unreliable when OPP assesses aggregate exposure. OPP grants that IWG's approach does not directly maintain that "unreliable information" under subsection (b)(2)(A)(ii) is "reliable data" under subsection (b)(2)(c). But, by making aggregate exposure and the reliable information requirement a screening mechanism for the scope of the reliable data requirement in the children's safety provision, IWG's approach would compel OPP to conclude that it has "reliable data" for decisions involving the children's safety factor in situations where OPP has concluded that it does not have "reliable information" on nondietary exposure. In these circumstances, whether or not OPP could make the "reliable data" finding would depend entirely on issues unrelated to nondietary exposure. Thus, according to IWG, OPP's conclusion on the unreliability of the nondietary exposure data necessarily means that it has "reliable data" to make a safety finding for children as far as nondietary exposure is concerned. In essence, OPP would be concluding that it has "reliable data" showing there is no

nondietary exposure. Importantly, because of the high hurdle at which IWG has pegged the "reliable information" requirement, an OPP conclusion that it has reliable data to show no nondietary exposure is compelled in circumstances where OPP does not have data showing actual real-world exposure levels and the distribution of those levels but does have data definitely showing such exposure is occurring.

The first and foremost legal difficulty with this strict linkage of the scope of the "reliable data" inquiry under the children's safety factor provision to how IWG has defined "aggregate exposure" is that, as explained earlier, the statute contains no language defining "reliable information" in the demanding, substantive manner put forward by IWG. Further, IWG's approach to aggregate exposure and the "reliable information" requirement is at odds with Congress' expressly-stated concerns regarding exposure in the children's safety factor provision. According to IWG, where there is not reliable information on nondietary exposure "that route [of exposure] should not be included in aggregate exposure and thus should not be regulated under §408 [which includes the children's safety factor provision] *until better information is available*." IWG Letter at 6 (emphasis added); accord IWG 10X Comments at 40. Congress explicitly specified, however, that the children's safety factor is to be added to "to take into account...completeness of the data with respect to exposure...to infants and children." 21 U.S.C. §346a(b)(2)(C). The conflict is clear: IWG's gatekeeper approach to aggregate exposure and the children's safety factor provision based on its strict reading of the "reliable information" requirement cancels, to a large degree, the congressional intent to take a more protective approach when exposure data are missing or inadequate. Under IWG's approach, there are likely to be numerous situations where nondietary exposure data will be excluded from aggregate exposure on reliability grounds but the children's safety factor will be deemed unnecessary despite the fact that there is not complete data on nondietary exposure.

For all of the above reasons, OPP believes that: (1) it has characterized IWG's position accurately; and (2) IWG's position on the "reliable information" requirement and the interaction of this requirement and "aggregate exposure" and the children's safety factor is unreasonable.

Models and Reliable Information/Data. OPP objects to the IWG's claim that OPP's models for drinking water and residential exposure will not produce "reliable information" and NRDC's similar conclusion regarding models generally and "reliable data." After all, any exposure estimate is a model of some sort. It is a false dichotomy to suggest that models and data (or information) are opposite extremes. Rather, models, as "users" of both empirical data and assumptions based upon empirical data and informed by

scientific judgment, allow scientists to generalize from a less than perfect data set (and data are never perfect). For example, short of measuring the pesticide residues in every sip of water and every bite of food as it is being consumed, OPP must model or estimate exposure values for residues in drinking water and food. The need for models exists whether the exposure estimate is based on monitoring values in drinking water and food, residue values from field studies, or data on a pesticide's properties and characteristics which are used to predict anticipated residue levels in water and food. Monitoring data may produce a more realistic and reliable estimate of exposure, but the reliability of any method of estimating exposure will have to be evaluated based on what data the method relies upon.

The IWG is more concerned with a particular drinking water model (the farm pond model) and the residential exposure SOPs than models generally. IWG asserts that these models cannot produce reliable information because they are designed to overestimate exposure. In contrast, IWG notes that it "has supported the use of models in estimating drinking water and residential exposure in its comments on those science policy papers, although it has asked that the models and their outputs be reasonably likely to allow decent estimates of actual exposure if they are to be used for purposes other than screening." IWG Letter at 5. Similarly, NRDC has expressed concern with the accuracy of OPP models, particularly with regard to nondietary exposure.

OPP is aware of the criticisms that have been leveled at these screening level models by IWG and continues to take steps to improve the drinking water modeling techniques used in FQPA risk assessments (US EPA 1999j and US EPA 1999g). As with IWG's criticisms, OPP has taken steps to address the inadequacies identified by NRDC (USEPA 1999k). As indicated in Aggregate Exposure Response to Comment document, OPP will continue to take under consideration any concerns raised regarding whether its exposure models overstate exposure. Whether any particular model, when used to estimate exposure for a particular pesticide, produces estimates of sufficient quality for those estimates to be quantitatively considered in an estimate of aggregate exposure involves a case-by-case inquiry. OPP would reiterate, however, that the inability of a model to produce a fully reliable quantitative estimate of "actual real-world" exposure levels and the distribution of those levels would not mean that safety evaluations can disregard reliable information showing such exposure does, or will, occur.

The Diet Does Not Include Drinking Water Argument. Given the common, everyday meaning of the term diet as including both food and water, IWG would have to find some fairly explicit statutory language to support its claim that "dietary exposure" does not include exposure form drinking water. This IWG

cannot do.

IWG cites to subsection (b)(2)(D)(vi) describing aggregate exposure as "including dietary exposure under the tolerance and all other tolerances in effect for the pesticide chemical residue, and exposure from other nonoccupational sources" as supporting its position. IWG argues that this language "surely is susceptible of the reading that 'dietary exposure' includes precisely and only those exposures 'under...tolerances.'" IWG Letter at 6. IWG asserts that if the term dietary is read as including food and water, the inclusion of the term "dietary" in this phrase is superfluous. OPP does not find this argument convincing. Although perhaps this language can be read in the manner IWG describes, it is not a compelled reading. Another reading is that the language is meant to capture only that aspect of dietary exposure that occurs "under...tolerances." IWG's protest that OPP's interpretation of dietary as applying to both food and water renders the term dietary as meaningless in this provision can be equally leveled at IWG's interpretation. IWG states that "drinking water exposures definitely are not 'under...tolerances,'" and thus appears to take the position that the only exposure under a tolerance can be an exposure in food. IWG Letter at 6. If that is the case and the term "dietary" means food, the inclusion of the term "dietary" in the phrase "dietary exposure under the tolerance" adds nothing to the meaning of the phrase. In the final analysis, the statutory language in subsection (b)(2)(D)(vi) is too opaque to justify abandoning the commonsense reading of the term "dietary."

IWG next argues that, because OPP has decided that it will not write tolerances for pesticides in drinking water because drinking water is not food, "drinking water exposures definitely are not 'under...tolerance,' and thus at least arguably are not 'dietary' within the meaning of the statute." IWG Letter at 6. Because this argument is based on IWG'S prior contention that the language addressing dietary exposure under tolerances in subsection (b)(2)(D)(vi) must be read in a certain fashion, it is not convincing for the reasons stated above.

IWG further asserts that it would have been reasonable for Congress to treat similarly exposure to pesticides in drinking water and exposures to pesticides from residential pesticide applications, rather than grouping drinking water exposures with exposures to pesticides in food. OPP does not disagree with the proposition the Congress *could* have reasonably chosen such an approach; however, as noted, there is no explicit language in the statute drawing this distinction and OPP is not convinced that anything in the statute suggests this approach.

Also unpersuasive is the IWG's argument that because OPP and FDA have treated drinking water as not a "food" under the FFDCA, drinking water is not part of the diet. This argument fails to recognize that the question is not whether water is food, but whether water is part of the diet. Furthermore, OPP and FDA decided to interpret the term "food" as not encompassing drinking water based on their conclusion that Congress' passage of the Safe Drinking Water Act was an implied repeal of OPP and FDA's tolerance setting authority over pesticides in drinking water under the FFDCA. See 44 FR 42775 (July 20, 1979). However, here, there has been no action by Congress that would suggest that the term "dietary" should be read in other than its dictionary sense.

Finally, IWG requests that OPP acknowledge that its interpretation of the term "dietary" is not legally compelled and explain its policy basis for that interpretation. Whether or not OPP's interpretation of "dietary" is legally compelled, OPP would note that whether drinking water is part of dietary exposure or not holds great significance only if IWG's interpretation of the "reliable information" requirement is accepted. Because, as explained above, OPP views IWG's interpretation of the "reliable information" requirement as unreasonable, OPP sees no reason to go beyond commonsense interpretation of the term "dietary."

The Difference Between Information and Data. Although NRDC claims the statute draws a clear distinction between "data" and "information," NRDC does not explain or elaborate on that distinction other than to state that, in the context of drinking water exposure, data means "monitoring data" and not exposure estimates from models. NRDC does not address the fact that OPP's drinking

water models are based both on generic environmental and pesticide data and empirical data on a pesticide's specific properties and characteristics.

OPP would note that the dictionary defines data and information by cross-referencing between these terms and thus information is defined as data and data is defined as information. See, e.g., Webster's New World Dictionary (2d College Ed. 1976). Given this overlap, it seems unlikely Congress intended OPP to make critical regulatory decisions by dissecting the fine distinctions between the terms "data" and "information." In any event, even if the term "data" is regarded somehow as only capturing some type of information derived from a scientific study, OPP believes its models are based on information meeting this description.

In sum, OPP disagrees with the major policy implications that both the IWG and NRDC ascribe to the terms "reliable data" and "reliable information" based on either a rather hyper-technical reading of the statute or little more than mere speculation. OPP has been unable to find any legislative history, and the commentors have cited none, that supports the notion that the use of the term "reliable information" or "reliable data," or the use of the term "data" instead of "information" and vice-versa, were intended to have far reaching policy significance. OPP believes Congress' inclusion of the terms "reliable data" and "reliable information" had a much more prosaic purpose–Congress merely wanted to reconfirm that reliability is a necessary criterion for any data or information, or model based on data or information, used in risk assessment under the FFDCA.

Scope. OPP believes that there exist two more reasonable interpretations regarding the scope of the reliability requirement in subsection (b)(2)(A)(ii). Both of these interpretations are more consistent with the general principles of administrative law and practice and with the other language of the statute. They take into account both the "reliable information" requirement in subsection (b)(2)(A)(ii) and the requirement in subsection (b)(2)(D)(i) that OPP consider "the validity, completeness, and *reliability* of the available data from studies of the pesticide chemical and pesticide chemical residue."

The first, and OPP's preferred interpretation, is that the reliable information requirement in subsection (b)(2)(A)(ii) is directed primarily at identifying whether exposure occurs by a certain pathway or route (i.e., nondietary) and that the reliability consideration in subsection (b)(2)(D)(i) more broadly insures that exposure estimates (addressing the magnitude and distribution of exposure) are reliable, whether that exposure is dietary or nondietary. Two reasons support this interpretation. First, the "reliable information" requirement in subsection (b)(2)(A)(ii) is in a clause specifically discussing routes/pathways of exposure ("dietary exposure and all other exposures"). Second, as discussed above, reading the reliable information requirement more broadly contradicts the direct command of subsection (b)(2)(D)(i) (consider the reliability of data) by implying that reliability is not a pertinent consideration as to dietary exposure data, and does so in a manner that appears to condone arbitrary agency decision-making. On the other hand, the more narrow (route-specific) construction of the reliability requirement in subsection (b)(2)(A)(ii) can logically be squared with subsection (b)(2)(D)(i). It makes sense for Congress not to have imposed a reliability requirement on the question of whether exposure *occurs* by the dietary route/pathway. After all, this statutory section addresses setting maximum levels for pesticide residues in food, an important part of the diet. Setting a tolerance level for a pesticide residue in food presupposes that there will be some exposure to the pesticide through the dietary route/pathway. For these exposure issues under section 408, reliability considerations apply principally, if not entirely, to the question of amount of exposure.

Either of these two interpretations is more reasonable than IWG's interpretation because they do not impute to Congress an intent to authorize arbitrary action by an administrative agency (i.e., the agency may rely on unreliable data). In the absence of a clearer statutory pronouncement, or at least some support in the legislative history, OPP is unwilling to endorse an approach that presumes such congressional intent. OPP prefers the first interpretation to the second because it appears to be the more natural construction of the language in subsection (b)(2)(A)(ii) and because it gives some separate purpose for the inclusion of the reliability language in subsection (b)(2)(A)(ii). That purpose is to direct OPP to examine whether some trustworthy information is available to show that exposure would occur (or is occurring) by the nondietary pathway.

The Substance of the Reliable Information Requirement. The common meaning of "reliable information" is information that is trustworthy, or in the scientific sense, information that is reproducible. Accordingly, OPP believes that the reliable information requirement in subsection (b)(2)(A)(ii) simply is designed to ensure that information considered by OPP is trustworthy and reproducible. (OPP sees a similar role for the reliability consideration in

subsection (b)(2)(D)(i).) IWG's argument that OPP should depart from this plain meaning of the term "reliable information" and impute a more substantive role for the reliability requirement is unpersuasive.

IWG argues that the general language in the subsection (b)(2)(A)(ii) establishing a reliability criterion for nondietary exposure imposes more than some type of reproducibility test. According to IWG, the reliable information requirement substantively defines what the information must show and the specificity of the information itself. IWG states that "[f]or information to be considered reliable..., it must provide a reasonable estimate of the actual, real-world level of exposure to the pesticide...[including] information on the distribution of the exposure, so that probabilistic estimates of aggregate exposure can be made." IWG's logic is as follows: (1) Congress has imposed no reliability requirement on dietary exposure data; (2) IWG claims this was because OPP often has data on the actual, real-world levels of pesticide residues on food including data on the distributions of those residue levels; and, thus, (3) there is a "strong implication" that for information on the nondietary route/pathway to be reliable it must be comparable to the information OPP has on dietary exposure.

Each of the three steps in this argument, however, is faulty. The first premise–that there is no reliability requirement pertaining to dietary exposure data–has already been shown to be untenable if asserted broadly (i.e., not just applying to whether there is exposure by a given route), as the IWG comment does. As noted, it is illogical to suggest that Congress removed any constraint regarding the need for reliable information on dietary exposure data pertaining to the magnitude and distribution of exposure. Second, IWG's claim that the lack of a reliability requirement as to dietary exposure data is due to the nature of the data that OPP collects on dietary exposure is nothing more than speculation. IWG cites no authority to support this proposition. Moreover, as noted above, there is an alternative and logical reason appearing on the face of the statute as to why Congress might not have imposed a reliability criterion on exposure through the dietary route– this statutory section addresses setting maximum levels for pesticide residues in food. Given this explanation based on the statutory structure there is no need to speculate concerning other motivations. Finally, even if the first two steps of IWG's argument are correct (that there is no reliability requirement pertaining to the magnitude and distribution of dietary exposure and that dropping that requirement is due to the quality of OPP's exposure data on food), it does not follow that data on nondietary exposure must be comparable to food exposure data collected by OPP. At most, there would be an implication that one type of data–data on actual real-world levels of pesticides including information on the distribution of residue levels–would be considered reliable. It would not preclude other data

from meeting the reliability requirement.[4]

ISSUE 18. Policy or Rule

Overview. OPP requested comments on how this policy could be structured so as to provide meaningful guidance without at the same time imposing binding requirements on either the government or outside parties. OPP received a few comments on this issue relating to inclusion of data requirements in regulations and the need to define a "core" data set by regulation. OPP will also take this opportunity to respond to a petition from pesticide manufacturer and grower groups requesting, among other things, rulemaking that "lay[s] out the circumstances in which an additional safety factor will be imposed" and specifies "the data that EPA may require in order to decide whether, in establishing tolerances, an additional safety factor is needed to protect infants and children." Petition for Rulemaking to Develop Policies and Procedures for Implementing the Food Quality Protection Act of 1996 32 (May 22, 1998). The petition asserts that a series of EPA documents has "effectively established guidelines for implementation of the tenfold factor...." Id. One of the documents cited is the draft version of 10X policy paper. The pesticide manufacturer and grower groups have also filed a lawsuit against EPA that claims that EPA "has consistently used its FQPA safety factor policy in a binding and unvarying manner...." Fourth Amended Complaint, p. 33 American Farm Bureau Federation, et al. v. EPA, Case No. 1:99CV01405 RCL (D.D.C.). Therefore, these groups assert this alleged use of the policy is unlawful in that EPA is treating the policy as if it is a legislative rule under the Administrative Procedures Act (APA) without complying with the APA procedures for promulgating such rules.

Comments. IWG urged OPP to "propose and finalize 40 CFR 158 amendments to specify Tier I toxicology and exposure data requirements, as well as higher-tier requirements." IWG comment at 48. IWG asserted that "interested parties need a single, readily available, authoritative source for this information...." Id. IWG also argued that the policy's definition of a core data set must be set out in regulations. According to IWG, the "Administrative Procedure Act requires that test requirements of general applicability be promulgated by rulemaking." Id. at 47.

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[4]IWG does not address the difficult interpretation raised by such an approach concerning how OPP is to decide what nondietary data is comparable to dietary exposure data. Despite IWG's claims to the contrary, OPP has several gradations of data on actual, real-world pesticide residue levels in food. For some pesticides, OPP has full-blown studies from retail markets; in other cases, it may have varying amounts of monitoring data; and, in many cases, it may have only data from the crop field trials. The amount of distributional data OPP has on pesticide residues in food is also variable.

Petition. The pesticide manufacturer/grower petition requested that the Agency undertake rulemaking on a number of topics including implementation of the children's safety factor and the data requirements relevant to making safety factor decisions. The petition urged that specifying data requirements relevant to the safety factor decision was important because it gave pesticide registrants notice as to what data needed to be prepared to avoid EPA finding the gaps in the toxicology database necessitated retention of the children's safety factor.

The petition also lists various generic policy and legal reasons for issuing rules regarding FQPA implementation. The policy reasons include: (1) a rule provides greater transparency because the Notice and Comment process will provide formal notification of EPA's views; (2) rulemaking will give all parties a chance to participate in the development of policy not just those invited to Agency advisory committees; (3) in a rulemaking EPA must respond to public comments on the public record and must provide a concise statement of the basis and purpose for the rule; (4) a rule provides certainty and stability because rules are subject to judicial review and legal issues can be resolved once and for all; (5) the advisory committee process and SAP review of policies has not adequately provided for public participation; and (6) rulemaking on individual tolerances has not been an adequate substitute for generic rulemakings. The legal reasons listed in the petition include: (1) that FQPA policies 'impose obligations' and have 'significant effects on private interests' and thus are, in fact, legislative rules requiring Notice and Comment procedures; and (2) the FQPA "requires EPA to use Notice and Comment rulemaking to establish general requirements or procedures for implementing the key provisions of the FQPA." Pet. at 15

Legal Challenge. In the course of the American Farm Bureau Federation lawsuit, the pesticide manufacturer and grower industry plaintiffs have cited portions of the draft Safety Factor Policy that they consider to impose binding requirements. Specifically, the plaintiffs state:

The Safety Factor Policy "describe[s] the policies *employed by* the Office of Pesticide Programs in making a determination regarding the FQPA Safety Factor *when developing aggregate risk assessments and regulatory decisions* for single active ingredient pesticides." Safety Factor Policy at 10 (emphasis added). The Policy goes on to "describe the factors/issues related to exposure assessment and the completeness of the exposure database that *must be considered when making an FQPA Safety Factor finding.*" Id. at 45 (emphasis added); see also id. at 45-53. EPA's *default* position is that a database uncertainty factor *will always be applied* when the toxicology database lacks one or more of [certain] types of studies. Id. at 55 (emphasis added). Under the Safety Factor Policy, "the absence of detailed and specific exposure data *would require* the application of an additional safety factor unless OPP can determine that the available data and its assessment

methodologies give a high degree of confidence that exposure to infants and children is not underestimated." Id. at 8 (emphasis added).

. . . .

Notice and comment are also required because the two Science Policies make significant changes in prior EPA practice and policies. It is axiomatic that an agency's change in existing policy constitutes a legislative rule requiring Notice and Comment. [cites omitted]

. . . .

The Safety Factor Policy likewise marks a dramatic change in EPA policy. As the Policy itself indicates, it "*for the first time*, addresses the question of how additional safety factors should be applied in situation where a toxicology database is considered incomplete given changes in data requirements." FQPA Safety Factor Policy at 19. [emphasis added by plaintiffs]. The Policy further states that it effectuates "several changes in [EPA's] approach to the assessment of the completeness of the toxicology database" and acknowledges that "application of these criteria leads OPP to expand immediately the scope of the core database it has historically considered." Id. at 29-30.

. . . .

EPA's assertion that "the plain language of the policies makes clear that EPA does not intend to bind itself" is demonstrably false. The policies themselves contain no such indication. The general disclaimer EPA cites is found only in the *Federal Register* Notices, not the policy papers themselves.

Response. The comments, petition, and lawsuit present two overall concerns. First, commenters urge OPP to update its 40 CFR 158 data requirements. OPP agrees that these regulations should be amended and plans to propose amendments to the rule soon. Second, the pesticide manufacturing industry and growers have argued that OPP must promulgate its children's safety factor policy as a rule. The remainder of this response addresses this question.

After considering the comments, the petition, and the arguments raised in the lawsuit, OPP has decided to issue the Safety Factor Policy as an interpretive rule and nonbinding policy guidance, not as a binding legislative rule. Accordingly, OPP denies the petition from the pesticide manufacturers and growers to the extent it sought rulemaking regarding this policy.

Several of the matters addressed in the policy concern legal questions. Because these legal issues were resolved through interpretation of the statute, OPP believes it is authorized under the APA to speak to these questions through the means of an interpretive rule rather than a legislative rule. See General Motors Corp. v. Ruckelshaus, 742 F.2d 1561, 1565 (D.C. Cir. 1984) (*en banc*), *cert. denied*, 471 U.S. 1074 (1985). Examples of the interpretive issues in the policy include questions such as what safety factors are the children's safety factor intended to be in addition to and what constitutes reliable information or data.

The bulk of the policy document does not involve interpretational issues but rather describes OPP's views regarding the science and policy considerations that bear on its decisions regarding the children's safety factor. OPP describes in great detail the considerations that pertain to each of the three reasons the statute enunciates for application of an additional 10-fold safety factor. For the most part, these considerations involve science judgments of high complexity. Certainly, final decisions which involve a weighing of all three factors require OPP decision-makers to take into account a wide array of considerations. Because safety factor decisions involve such a complex of factors, many related to difficult science assessment issues, OPP has decided that this policy should not be cast in the form of a binding legislative rule. There is simply no adequate way to capture the multifaceted considerations involved in safety factor decisions in a rigid rule format. Moreover, because the science issues that form the basis for so many of the considerations are rapidly evolving as more and more data becomes available, any rule-like formulation would either quickly be outdated or would necessarily be so heavily caveated as to serve little purpose. Nonetheless, OPP does not believe that decisions on the children's safety factor should be made in a vacuum. Adopting this policy serves the important goal of helping to insure consistency in OPP decision-making by regularizing, to a large degree, the process and considerations that will be used in decision-making. At the same time, using a policy, as opposed to a rule, to accomplish this goal, leaves OPP with the flexibility to react to rapidly changing scientific developments.

So that there is no misunderstanding regarding the nonbinding nature of the policy, OPP has included in the introduction to the policy a clear explanation of the manner in which the policy will be used and of the opportunity for affected

parties to assert their views regarding the proper considerations in safety factor decision-making.

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.

This position is consistent with the manner in which the Agency generally approaches complex risk assessment issues and has resolved questions regarding other science policies under the FQPA. Thus, EPA's views on major risk assessment topics have been issued as policy guidances not binding rules. See e.g., *Guidelines for Carcinogen Risk Assessment* (USEPA 1986; 51 FR 33992); *Guidelines for Reproductive Toxicity Risk Assessment* (USEPA 1996a; 61 FR 56274); *Guidelines for Exposure Assessment* (USEPA 1992; 57 FR 22888); and *Proposed Guidelines for Carcinogen Risk Assessment* (USEPA 1996b; 61 FR 17960). Similarly, OPP's FQPA policy addressing the selection of the population percentile used in calculating the threshold of

regulatory concern in acute risk assessments was issued as a policy not a rule. (See EPA 2000c). In their petition, the pesticide manufacturers and growers cited to one EPA proposed rule that included "models and assumptions for estimating public exposure" concerning certain air emission standards. See 59 Fed. Reg. 15504 (April 1, 1994). However, OPP would note that when that rule was finalized, the portions addressing risk assessment were omitted. 61 Fed. Reg. 68384 (December 27, 1998).

OPP found none of the arguments set forth in the rulemaking petition from the pesticide manufacturers and growers to be persuasive. Each of those arguments is addressed in turn below.

Transparency. The petition argued that a rule would provide greater transparency because there would be formal notification of all parties concerning the rulemaking. However, this formal notification concern was met by the procedure OPP followed in developing this policy. OPP published Notice of the draft policy in the *Federal Register* (64 FR 37001). That Notice provided a concise summary of the policy and requested public comment on the policy. Further, OPP put a full copy of the policy on its Internet Web site and generally made copies available to the public.

Public Participation. The petition argued that a rulemaking would allow all affected parties to participate not just advisory committee members. That concern, however, has also been met by OPP's public comment process. As noted, OPP received over 800 comments on this draft policy.

Response to Comments. The petition expressed a concern that without a requirement to respond to comments and to provide a statement of the basis and purpose for the policy, OPP would not in fact produce such documents. OPP, however, believes that its policy document clearly articulates the basis and purpose of the policy and that this Response to Comments document has adequately addressed all significant comments.

Judicial Review. The petition argued that a rule provides certainty and stability because unlike a policy document it would be subject to judicial review. Generally, policy statements are not reviewed as ripe for review until they have been applied to a concrete regulatory action. Similarly, generic rules are often found unripe on the same grounds. On occasion, courts will review a generic rule in the absence of a concrete application of the rule where a challenge to the rule presents purely legal questions and there would be hardship to the challenger in delaying review. This policy does include several legal interpretations of the FQPA. However, OPP believes that many of these interpretations are of the variety that judicial review of the interpretation would

benefit from application of the interpretation in a concrete context (e.g., OPP's determination of whether specific data constitutes "reliable data"), and, thus, whether the interpretations are included in the policy as interpretive rules or promulgated as binding legislative rules, is likely to have little effect on their reviewability. Moreover, to the extent the policy contains legal interpretations, those legal interpretations are arguably subject to judicial review if ripe. Codifying the interpretations does not necessarily affect their ripeness. Thus, this consideration does not appear to strongly support issuance of the policy as a rule.

Advisory Committee Process and SAP Review. The petition claimed that Agency attempts to get outside input into its policies through various advisory committees and the FIFRA SAP have been inadequate. OPP believes the advisory committee process and SAP review have provided important input. However, to the extent these processes have provided only a limited forum for public participation, the Notice and Comment process for the policy has addressed any such concern.

Individual Tolerance Rulemakings. The petition argued that OPP has not opened its policies up for comment in rulemakings addressing individual tolerances. The petition also implies that application of OPP policies in the context of such tolerance actions is not subject to judicial review. Pet. at 24. Although OPP has not specifically requested comments on its policies in tolerance actions, such comments would certainly be appropriate to the extent the policy formed part of the basis for OPP's decision. Moreover, the petition is clearly incorrect if it is suggesting that the lack of an explicit request for comment on policies underlying a specific tolerance decision somehow insulates the policy's application from administrative and judicial review.

Similarly, OPP found none of the legal reasons contained in the lawsuit filed by associations representing pesticide manufacturers and growers to have merit.

Policies Impose Obligations. The industry associations argued that FQPA policies generally and the *Children's Safety Factor Policy* specifically impose obligations and have significant effects on regulated parties and thus these policies are binding rules and must be promulgated following Administrative Procedure Act (APA) requirements. OPP has attempted to make clear that the *Children's Safety Factor Policy* does not impose binding obligations on either regulated parties or the government both in the policy document and in this response to comments. Further, OPP does not believe that the policy itself has significant effects on regulated parties because it does not impose any rights or obligations. Rather, the policy provides nonbinding guidance on one aspect of

pesticide risk assessment. It is true that the considerations in the policy when taken into account in an individual risk assessment for a pesticide may affect the ultimate decision on that pesticide. In this regard, this policy is similar to other policies and numerous decisions not covered by policies that can affect the outcome of a risk assessment. Yet, OPP has made clear that it is not the *Children's Safety Factor Policy* that decides what safety factor is appropriate for a given pesticide. The considerations discussed in the policy remain open to question from interested parties. Moreover, OPP does not believe that any policy or other decision that may have a substantial affect on a risk assessment must, because of that potential effect, be promulgated as a rule. If this were true, OPP could only issue risk assessment policies addressing insignificant matters. Courts addressing disputes regarding whether agencies have treated policies as rules have not envisioned such a narrow role for policy statements. For example, in Community Nutrition Institute v. Young, 818 F.2d 943 (D.C. Cir. 1987), the DC Circuit noted:

> Our holding today [that FDA's action levels have been treated by FDA as binding] in no way indicates that agencies develop written guidelines to aid their exercise of discretion only at the peril of having a court transmogrify those guidelines into binding norms. We recognize that such guidelines have the not inconsiderable benefits of apprizing the regulated community of the agency's intentions as well as informing the exercise of discretion by agents and officers in the field. It is beyond question that many such statements are nonbinding in nature and would thus be characterized by a court as interpretative rules or policy statements.

Id. at 949. Finally, it is worth noting, that a risk assessment, is not itself a regulatory action. Although a risk assessment may serve as the basis for a tolerance rulemaking under the FFDCA, a risk assessment does not have formal legal consequences. A guidance for conducting some aspect of a risk assessment is even further removed from regulatory consequences.

FQPA Requirement for Rulemaking. The petition claimed that section 408(e)(1)(C) requires that general procedures for implementing section 408 must be promulgated as rules. The language of section 408(e)(1)(C), however, is clearly permissive–"EPA *may* issue a regulation... " (emphasis added). This language authorizes OPP to establish rules for "general procedures and requirements to implement this section;" it does not mandate such rules.

Binding Language in the Children's Safety Factor Policy. OPP has made several changes in the document in response to arguments in the litigation regarding binding language. First, and most importantly, OPP agrees with the pesticide and grower associations that OPP should include in the policy itself, as opposed to the *Federal Register* Notice soliciting comment on the draft policy, an explicit statement regarding the nonbinding nature of the policy. The policy now contains a detailed caution to agency personnel in this regard and an explicit invitation to affected parties to comment on individual decisions. Second, the associations cited two instances where inappropriate mandatory language was used. The first of these appeared to make it mandatory that OPP staff consider certain factors in making the safety factor decision. DRAFT SFP at 45 ("the factors/issues...that must be considered when making a FQPA Safety Factor Finding"). OPP believes it is important, that for consistency's sake, agency reviewers, in general, take into account similar considerations in making safety factor determinations. Yet, OPP recognizes that not every listed consideration will apply in every instance and, in some cases, factors not mentioned in the policy should be examined. Further, OPP would reiterate that since this is a policy, it does not carve into stone the listed considerations as definitively relevant to the safety factor determination. Interested parties remain free to argue to the Agency that a consideration mentioned in the policy is inappropriate in general for safety factor determinations. OPP has amended the language of the policy in an attempt to capture these concepts. The second mandatory statement pertained to the use of a safety factor where core toxicology data are missing. The draft policy stated that the "default position" is that a factor "will always" be applied in those circumstances. Id. at 55. This framing of a default position could be misleading and so OPP has amended the language to make clear that the default position in these circumstances is, in fact, a true default position–i.e., an initial position that is subject to change after consideration of case-specific factors.

Two other statements cited by the associations, OPP concluded, were not problematic. First, the associations seemed troubled because the draft policy stated that it described policies that "employed" by the OPP in making safety factor decisions. OPP believes that it is important for consistency's sake that OPP staff make safety factor decisions in the context of the safety factor policy. Because the policy guides discretion without narrowly cabining it, OPP believes

the policy is not a rule, and that it can require its staff to not abandon the context of the policy without providing an adequate explanation for the alternate approach. Second, the associations cited as problematic the following statement: "the absence of detailed and specific exposure data would require the application of an additional safety factor unless OPP can determine that the available data and its assessment methodologies give a high degree of confidence that exposure to infants and children is not underestimated." Id. at 8 (emphasis added by associations). OPP believes that this is a fair interpretation of the legal standard in section 408(b)(2)(C) and, as such, does not run afoul of any APA constraints on legislative rulemaking.

Significant Change in Policy Requires a Legislative Rule. In their lawsuit, the pesticide and grower associations also contend that because the Children's Safety Factor Policy contains some variations from earlier policies on this question, it must be promulgated as a legislative rule. OPP disagrees. The essence of a policy statement is that it is not binding on the agency; thus, the agency remains free to act in variance with the policy so long as it explains its change in course. See Syncor Int'l Corp. v. Shalala, 127 F.3d 90, 94 (D.C. Cir. 1997) ("The agency retains the discretion and the authority to change its position–even abruptly–in any specific case because a change in its policy does not effect the legal norm."). OPP's earlier positions on application of the children's safety factor are contained in nonbinding guidance not legislative rules, so it is fully appropriate for OPP to revise its policy positions by use of a policy statement, not a legislative rule.

Categorization of Data as "Core," "Routinely Required," or "Newly Required." One commenter objected to OPP's use of categories for describing data, stating that such categories could only by established by rule. These categories have been dropped from the revised document.

ISSUE 19. Additional Comments

A few comments were received which did not fit into any of the Issue categories. They are captured here.

Determination of NOELS versus NOAELs

Comment 1. Several commentors (761, 771, 778) expressed the opinion that the FQPA mandated the use of the NOEL, rather than the NOAEL, in establishing reference doses; the House Commerce Committee Report, H. R. 104-669, Part 2 p. 9 (July 23, 1996) was cited in support of this position. One further assumption leading to this conclusion was that nonadverse effects may occur at lower dose levels than adverse effects; therefore, the NOEL will likely provide the most sensitive endpoint and dose for pesticide regulation.

Response. OPP does not believe that the FQPA mandates that OPP, in evaluating animal studies, use a NOEL instead of a NOAEL. The statute does not mention either term. The legislative history does at one point use the term NOEL but that legislative history does not indicate that Congress intentionally used the term NOEL because it did not think it appropriate for OPP to consider the NOAEL. H. Rept. 104-669, 104th Cong., 2d Sess. 41 (1996). In fact, Congress appears to have assumed NOELs are NOAELs. For example, in defining "threshold effect" Congress stated that this "is an effect for which the Administrator is able to identify a level at which the pesticide chemical residue will not cause or contribute to any known or anticipated harm to human health." Id. (emphasis added). If Congress had intended that threshold effects be based on NOELs rather than NOAELs, it would not have used the word "harm" in defining the effect.

Congress seems to have used the term NOEL because it was common usage for OPP at that time FQPA was passed. However, prior to 1998, in OPP's discussion of the hazard identification process of evaluating pesticide toxicity, the term NOEL was used to describe the dose level at which no significant adverse effects were noted. OPP's terminology was not consistent with the rest of the Agency, as illustrated in EPA's Integrated Risk Information System (IRIS). This system included more hazard terms than OPP generally employed, including NOAEL, LOAEL, and FEL (Frank Effect Level). On September 2, 1998, this apparent semantic inconsistency was eliminated by HED Standard Operating Procedure (SOP) 98.3 which indicated that OPP would commence using the terms NOAEL and LOAEL in their scientific reviews and documents. It also stated, "In a practical sense, the terms NOEL and NOAEL have been used interchangeably in OPP. As a general rule, OPP would

consider as appropriate for hazard identification and risk assessment only those effects which are adverse or potentially adverse. This inclusion of the term NOAEL should not change any of our hazard endpoints for regulation but add to the quality of the risk assessment."

Blue Ribbon Panel on 10X and "Reliable Data"

Comment 2. One commentor (778) stated that EPA should convene a "blue-ribbon" panel under the auspices of the Children's Health Protection Advisory Committee to assist in determining when there are "reliable data" on which to base a decision to use anything other than the additional 10X margin of safety mandated by FQPA.

Response. OPP agrees with the commentor that independent, external, scientific peer review of its policy on the FQPA Safety Factor provision can add significant value. But, the Agency does not agree with the particular recommendation that an external peer review group separate from the FIFRA SAP should be convened to consider this policy. The Agency has already obtained extensive external peer review from its legislatively-mandated advisory group. OPP believes that it is appropriate to continue using this established advisory group which provided the earlier reviews.

OPP has consulted substantively with the FIFRA Scientific Advisory Panel on four occasions about its interpretation and application of the FQPA Safety Factor provision: October 29, 1996; March 25, 1998; July 30, 1998 (update only); December 8, 1998; and May 25, 1999. The most recent SAP consultation focused on drafts of the documents made available for public comment by the *Federal Register* Notice of Availability published on July 8, 1999. The SAP's comments appear in its final report on the meeting and are available at: http://www.epa.gov/scipoly/sap/1999/may/final.pdf). (These comments are also addressed in this comment and response document.) The Agency also notes that, shortly after publication of the *Federal Register* Notice of Availability, OPP provided the Science subcommittee of the Children's Health Protection Advisory Committee (CHPAC) an extensive briefing on the policy and supporting documents. Neither the CHPAC nor any of the individual members of the Science subcommittee submitted written comments on the FQPA Safety Factor Policy or accompanying documents.

The Agency believes that it is appropriate to continue to use its SAP to address new and unresolved science issues relating to the implementation of the FQPA Safety Factor provision. Future consultations can build on the strong foundation of knowledge and understanding achieved through previous interactions.

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