RESPONSE TO PUBLIC COMMENTS ON THE OFFICE OF PESTICIDE PROGRAMS'

Guidance on Cumulative Risk Assessment of Pesticide Chemicals that have a Common Mechanism of Toxicity

(Issued for Public Comment June 30, 2000)

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

AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase inhibition
BMD	Benchmark Dose
CAG	Cumulative Assessment Group
CARES	Cumulative and Aggregate Risk Evaluation System
ChE	Cholinesterase
ChEI	Cholinesterase inhibition
CMG	Common Mechanism Group
CSFII	Continuing Surveys of Food Intakes by Individuals
CWS	Community Water Systems
ED	Effective Dose
ED_{10}	Central estimate on a dose associated with a 10% response adjusted for background
FFDCA	Federal Food Drug and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
LED	Lowest Effect Dose
LOAEL	Lowest-Observed-Adverse-Effect-Level
LOEL	Lowest-Observed-Effect Level
MOE	Margin of Exposure
NAWQA	National Water Quality Assessment Program
NOAEL	No-Observed-Adverse-Effect Level
NOEL	No-Observed-Effect Level
OP	Organophosphorus Pesticides
PAD	Population Adjusted Dose
PD	Pharmacodynamics
PDP	Pesticide Data Program
PK	Pharmacokinetics
POC	Point of Comparison
POD	Point of Departure
RfD	Reference Dose
RPF	Relative Potency Factor
SF	Safety Factor
SOP	Standard Operating Procedure
UF	Uncertainty Factor

Organizations:

ACPA	American Crop Protection Association
ADA	Arizona Department of Agriculture
CEHN	Children's Environmental Health Network
CU	Consumers Union
DPR	Department of Pesticide Regulation, California
FDA	U.S. Food and Drug Administration
ILSI	International Life Science Institute
IWG	Implementation Working Group
NCAMP	National Coalition Against the Misuse of Pesticides
NRC	National Research Council
NRDC	National Resource Defense Council
OPP	Office of Pesticide Programs, USEPA
PMRA	Pesticide Management Regulatory Agency, Canada
SAP	FIFRA Scientific Advisory Panel
USEPA	U.S. Environmental Protection Agency
USGS	U. S. Geological Survey
WWF	World Wildlife Fund

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 particular, the FQPA amendments require the Agency to consider the cumulative effects of any pesticides and other substance that have a common mechanism of toxicity (see *Section 408(b)(2)(D)(v)*). The Office of Pesticide Programs (OPP) is responsible for implementing the requirements of FQPA in making its pesticide regulatory decisions. Accordingly, OPP developed draft guidance that describes the process that OPP risk assessors should use for performing cumulative risk assessments. Public release of this guidance increases the transparency of approaches OPP will use for performing cumulative risk assessments.

OPP sought input from scientific experts before drafting guidance for conducting cumulative risk assessment. OPP, through its cooperative agreement with the International Life Science Institute/Risk Sciences Institute (ILSI), sponsored two workgroup meetings. ILSI convened a Workshop on Aggregate Exposure Assessment in 1998 to describe the state of the art with respect to methods and issues (ILSI, 1998). Later, ILSI convened another workshop and published a report on a framework for cumulative risk assessment which explores the methods and data (ILSI, 2000).

In September 1999, OPP sought comment from the FIFRA Scientific Advisory Panel (SAP) on the hazard and dose response portion of its draft cumulative guidance, and again December 1999 on the exposure and risk characterization chapters of the draft guidance document (USEPA, 1999a; USEPA, 2000a). Additionally, the concepts and methods that OPP will consider in conducting cumulative risk assessment have been applied to actual datasets on common mechanism chemicals. In a pilot analysis of 24 organophosphorus pesticides (OPs), OPP demonstrated in detail the methods and parameters that should be considered in estimating cumulative risk associated with common mechanism pesticides by multiple pathways of exposure. The hazard and dose-response assessment, and the exposure analyses of this pilot were presented to the SAP for comment in September and December 2000 (USEPA, 2001a; USEPA, 2001b). OPP revised its approach to the dose response assessment of the OPs based on comments provided by the SAP (USEPA, 2001d).

On June 30, 2000, the Agency published a Notice in the *Federal Register* (65 FR 40644) announcing the availability of, and opportunity to comment on "Guidance on Cumulative Risk Assessment of Pesticide Chemicals that have a Common Mechanism of Toxicity" (USEPA, 2000b). EPA subsequently extended the original 60-day comment period by 30 days.

EPA specifically invited the public to comment on fourteen questions, grouped into nine issues:

Issue 1. Selection of Chemicals for a Cumulative Risk Assessment

Chapter 3 of the draft science policy paper emphasizes that all chemicals that have been initially grouped by a common mechanism of toxicity are not necessarily appropriate for inclusion in a final cumulative risk assessment. There are both hazard and exposure considerations.

> **Question 1:** Does Chapter 3 clearly present additional hazard considerations that are needed to determine those chemical members which should be included in the final cumulative risk assessment?

Issue 2. Selection, Normalization, and Adjustment of the Point of Departure for Cumulating the Common Toxicity

As discussed in Chapter 5.1-5.2, a point of departure or POD (i.e., a dose or exposure metric corresponding to some fixed marker of toxicity) should be selected to sum the combined exposure for the chemical group. To the extent possible, the PODs should reflect a uniform measure of the common toxic effect, which is produced by a common mechanism of toxicity, across the chemical members. A benchmark dose (BMD) approach is preferred to derive the PODs for each chemical member.

> **Question 2:** In single chemical assessments, the Agency uses the upper-bound estimates (i.e., the lower confidence limit on dose) for both cancer (called the Lowest Effect Dose or LED) and noncancer BMD assessment. The concern has been raised, however, that summing upper-bounds of multiple compounds may result in a exaggerated risk. Do you agree that it is more appropriate to sum the central estimates (i.e., effective dose or ED) rather than combining upper-bounds in the cumulative risk assessment of multiple chemicals? If not, why not?

Issue 3. Incorporation of Group Uncertainty Factors

As discussed in Chapter 5.3, traditionally one or more of the uncertainty factors (UF) are used to derive a Reference Dose (RfD) for a single chemical. There are five UFs that are considered to account for the following extrapolations:

- UFL for the lowest-observed-adverse-effect level (LOAEL) to no-observed-adverse-effect level (NOAEL);
- UFS for subchronic NOAEL to chronic NOAEL;
- UFA for experimental animal to humans;
- UFH for interhuman variation; and
- UFD for an incomplete database to complete database.

It is proposed that the extrapolations of LOAELs to NOAELs or subchronic NOAELs to chronic NOAELs be applied as adjustments of a chemical's POD before estimating the cumulative risk. These adjustments are meant to be based on some scientific data that permits a reasonable extrapolation or interpolation rather than applied solely as a science policy default decision. EPA further proposes that other traditional UFs be treated as a composite “group UF" that pertains to the chemical members as a whole. Thus, the intraspecies and interspecies UFs and the database completeness UF are applied as a composite group factor after cumulative risk is estimated (i.e., not before on each chemical's POD). The rationale of the group UF is based on the premise that these factors should be viewed for the group as a whole given that all the chemicals are anchored by a common toxic effect produced by a common mechanism. Additionally, one is not simply evaluating risk in the context of a single chemical data base but the database for all the chemicals in the assessment. The advantage of a group UF is that it allows one to separate the resulting risk that is based on scientific adjustments from judgmental policy decisions to account for uncertainty. Finally, EPA proposes that an FQPA Safety Factor (SF) decision be applied for the group rather than on individual pesticides.

> **Question 3:** Do you agree with this approach, and does the draft science policy paper clearly describe the rationale and guidance for the implementation of chemical specific adjustment factors and of a group UF for the cumulative risk assessment? Has the draft guidance clearly presented the limitations and strengths of the group UF approach?

Issue 4. Methods for Estimating the Cumulative Toxicity

As discussed in Chapter 5.6, one of the steps in the cumulative risk assessment process will be to select a method to cumulate dose or exposures. This method will serve to normalize differences in the toxic potencies among the chemicals in the cumulative assessment. Precedence in the Agency's 1986 and revised 1999 “Guidance for Conducting Health Risk Assessment of Chemical Mixtures" (USEPA, 1999b) describes several techniques for estimating risk to multiple chemicals. The cumulative guidance focuses on the component-based dose addition methods used in the EPA's chemical mixture assessment guidance document. Two methods, a margin of exposure (MOE) approach and an approach using relative potency factors (RPFs), are presented.

Question 4a: Do you agree that both methods are valid to consider for estimating cumulative risk associated with exposures to chemical that cause a common toxic effect by a common mechanism? Has the draft document clearly described these two approaches and their strengths and limitations? Are there other methods that OPP should consider?

Question 4b: EPA anticipates that most mechanisms of toxicity encountered currently will be nonlinear dose-response relationships. Nevertheless, for mechanisms of toxicity consistent with linear dose-response relationships, do you agree that using the RPF approach by summing the slopes of the dose-response curves is an appropriate method? If not, what methods would you recommend for low-dose linear extrapolations of risk?

Issue 5. Case Study

In Appendix A of the draft science policy paper is a case study on OPs.

Question 5: Does this case study provide a clear example of the application of the hazard and dose-response elements of the draft guidance?

Issue 6. Input Parameters

There are several types of data available for pesticide exposure assessment (e.g., field trial data, monitoring data, percent crop treated, label usage). For the food pathway, monitoring data are available from the USDA Pesticide Data Program (PDP). OPP conducts the majority of its drinking water assessments by calculating a screening level value. Similarly, residential assessments are conducted using the draft residential Standard Operating Procedures (SOPs) which also provide a screening level assessment (USEPA, 1997). Thus, given PDP, the assessment of the food pathway will, in many cases, be based on higher quality data than for the residential and drinking water pathways where usually only screening values are available. Because of the different quality of data that will be encountered when conducting a cumulative exposure assessment, the concern is raised that the value and benefit of high quality monitoring data will be lost if combined with extrapolated exposure values from screening models.

Question 6.1: Please comment on how this concern could be addressed. For instance, should OPP at this time conduct separate pathway assessments for food, drinking water, and residential exposures so as to avoid combining higher quality monitoring data with more limited screening level data?

Question 6.2: Please comment on whether there are other means of dealing with existing data to reduce the uncertainties about exposure values derived from screening approaches.

Question 6.3: Please comment on whether and how OPP could incorporate quantitative uncertainty analyses in the overall cumulative risk assessment when OPP uses data of varying quality.

Question 6.4: Is it appropriate to extrapolate food exposure from residue field trials and use/usage information if food monitoring data such as USDA's PDP data are not available?

Issue 7. Deferral Criteria

OPP is proposing that deferral criteria be applied to “negligible" sources of risk in a full cumulative risk assessment (65 FR 40649). OPP believes that this approach will permit a better focus on the more important sources of risk. It will also assist the risk manager in understanding and evaluating sources of risk that may provide the greatest benefit with risk mitigation activities.

Question 7.1: Please comment on whether the deferral criteria discussed in Chapters 4 and 6 appear to be reasonable. Are there other exclusionary criteria that should be considered?

Question 7.2: Should OPP establish more specific criteria, for example, not only the magnitude of the exposure resulting from a particular chemical, use pattern or pathway, but also the size of the exposed population group?

Issue 8. National and Regional Exposures

The potential for people to encounter overlapping exposures to different pesticides will be influenced by many factors. One important consideration is the geographic effects and seasonal uses of pesticides. Thus, a framework is proposed for assessing different pathways of exposure that are essentially driven by these considerations. OPP believes that the food pathway should be approached on both a national and regional scale to account for both national and regional distribution of treated commodities. However, the OPP believes that residential and drinking water pathways are more appropriately dealt with on a regional or multistate basis, since there is no single, national source of drinking water; and residential exposures may be driven by regional use patterns.

Question 8.1: Please comment on whether the concept of developing a series of cumulative assessments on a geographic scale for different pathways is reasonable.

Issue 9. Case Study

Cumulative risk assessment is at an early stage of development. Furthermore, there is very limited experience in conducting such assessments. Thus, the development of case studies using actual data are critical to refining useful and practical guidance, and to identifying future research and testing needs. OPP is taking a stepwise approach to the development of such case studies by starting with simple examples and moving toward more complex situations. Attached is a case study that uses actual food residue data on three pesticides and evaluates only a single pathway/route/duration of exposure. Certain assumptions were made in the case study. In single chemical exposure assessment, for example, nondetects are assumed to be one half the level of detection and composite samples are decomposited. In this case study, for illustrative purposes, nondetects were assumed to be zero, the samples were not decomposited, and surrogate data were not used.

> **Question 9.1:** Given that an important goal of the cumulative assessment is to reliably determine sources of concern from a multichemical exposure, please comment on to what extent is it appropriate to apply standard practices and assumptions used in single chemical assessments.

OPP received 13 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, and children's advocacy groups, as well as from foreign and state governments. OPP also presented earlier drafts of its cumulative guidance (which did not differ substantively from those that were made available for public comment in 2001) for review by SAP, which also submitted comments (USEPA, 1999a; USEPA, 2000a).

OPP has reviewed all of the comments and has grouped similar comments together. The remainder of this document contains OPP's summary of the comments and its responses to the comments. The comments are generally organized to follow the questions contained in the original *Notice of Availability*.

This science policy paper is intended to provide guidance to EPA personnel and decision-makers, and to the public. As a guidance document and not a rule, the policy in this guidance is not binding on either EPA or any outside parties. Although this guidance provides a starting point for EPA risk assessments, EPA will depart from its policy where the facts or circumstances warrant. In such cases, EPA will explain why a different course was taken. Similarly, outside parties remain free to assert that a policy is not appropriate for a specific pesticide or that the circumstances surrounding a specific risk assessment demonstrate that a policy should be abandoned.

COMMENTS AND RESPONSES

ISSUE 1. Selection of Chemicals for Cumulative Risk Assessment

Chapter 3 of the draft science policy paper emphasizes that all chemicals that have been initially grouped by a common mechanism of toxicity are not necessarily appropriate for inclusion in a final cumulative risk assessment. There are both hazard and exposure considerations.

Question 1: Does Chapter 3 clearly present additional hazard considerations that are needed to determine those chemical members which should be included in the final cumulative risk assessment?

1.A Hazard Identification Process

1.A.1 Comment: The SAP (in September 1999) recommended that the selection process used to identify chemicals for inclusion in a Common Mechanism Group (CMG) should be subject to external peer review (given the possible significant regulatory consequences of selection to a CMG). The panel also indicated that Chapter 3 of the draft guidance document, "Hazard Assessment and Characterization," adequately presents hazard considerations for inclusion of a chemical in a CMG. While many of the additional hazard considerations for inclusion of a chemical in a Cumulative Assessment Group (CAG) are also presented, members of the SAP recognize that there are other additional hazard considerations remaining to be clearly defined in order for chemicals to be appropriately selected for a CAG. Factors to consider in the refinement of additional hazard considerations include the following:

a. There should be consideration of issues of exposure and the likelihood of co-exposure to chemicals in a CMG.

b. There should be consideration of the pharmacokinetics (PK) and pharmacodynamics (PD) of the entire mechanism of action of each chemical in a CMG in order to distinguish between common PK and common PD when making comparisons within the CMG.

c. It should be determined if dose-response data for each chemical are adequate to allow for: (1) an acceptable degree of confidence in points-of-departure; and (2) assessment of whether or not individual chemicals have parallel dose-response curves. Parallel dose-response curves are required for dose-addition, the default method for estimation of cumulative risk in the proposed guidance.

Agency Response: As to the use of peer review on judgments about grouping chemicals by a common mechanism of toxicity, OPP has made use of scientific workshops, as well as formal peer review by the SAP. In 1994, the Administrator of EPA published formal guidance for peer review of EPA scientific work products that increases the amount of peer review for risk assessments as well as other work. OPP will consider that guidance in making decisions regarding common mechanism. However, not every assessment pertaining to the grouping of chemicals by a common mechanism of toxicity will merit the same level of peer review. For example, in some cases the mode of action may have already been established by development of a large body of research information and characterization of the phenomenon over time. There will have been development of an Agency policy, e.g., male rat thyroid disruption, or a series of previous assessments in which both the mode of action and its applicability to particular cases has been explored, e.g., urinary bladder stones. If so, the assessment and its peer review can be focused on the evidence that particular chemicals act via this mechanism of toxicity. In other cases, the mechanism of toxicity previously may not have been the subject of an Agency document. If so, the data to support both the mechanism of toxicity and the activity of the chemicals with respect to it should be the subjects of EPA assessment and subsequent peer review.

The SAP agrees that the "Hazard Assessment and Characterization" of the draft June 2000 guidance adequately presents hazard considerations for inclusion of a chemical in a CMG. The revised guidance (Sections 4, 7and 8) incorporates the SAP recommendations regarding other additional hazard considerations (e.g., pharmacokinetics and pharmacodynamics, considerations of parallel dose-response curves) that should be considered in appropriately selecting chemical for the quantification of cumulative risk, as well as issues of exposure and the likelihood of co-occurrence. The revised document also discusses in Section 7, the factors and statistical analysis that should be considered in evaluating the dose-response data for each chemical and degree of confidence in both determinations of relative potencies and points-of-departure.

1.A.2 Comment: IWG (06) indicates that the cumulative risk policy appears to mix or confuse what should be two independent processes: deciding which compounds belong properly in a CMG, based on hazard identification data and mechanistic data; and deciding which of the CMG compounds should be excluded from the CAG on the basis of minimal risk concern. The 1999 Common Mechanism Document (which did not use the term CAG) went to some length to make it clear that a careful assessment of data and hypotheses will be needed to refine the initial candidate list before the final CMG members are known. According to that document, it is only after considerable winnowing that the Agency can "determine, through the in-depth review" that a set of substances cause a common toxic effect by a common mechanism [and thus] will be considered for cumulative risk assessment. In the cumulative risk policy, which uses both terms CMG and CAG concepts, there is confusion about the design and the purpose of the winnowing process. It appears that compounds can be included in the CMG on the basis of flimsy evidence, weak data, or hypothesis, and then omitted from a CAG or "deferred" because of that very flimsiness. IWG recommends that OPP not treat a compound as being part of a CMG unless there is persuasive reason for including it. In addition, IWG further points out that the list of factors in Table 3-1, page 30 inappropriately and confusingly mixes issues regarding strength of evidence that various chemicals have a common mechanism of toxicity and should be included in the CMG with issues concerning the strength of the evidence that numerical calculation of risk are correct or concerning what SFs are appropriate.

> **Agency Response:** The Agency agrees with IWG, that chemicals grouped by a common mechanism of toxicity should follow the weight of evidence approach outlined in OPP's policy entitled "Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity" (USEPA, 1999c). In addition, the Agency has developed a framework for evaluating a chemical's mode of action for carcinogenesis (USEPA, 1999d), which is widely embraced by the scientific community and adopted by the World Health Organization. This framework also provides a rigorous approach for making decisions regarding an agent's mechanism of toxicity. Thus, OPP's cumulative guidance document also refers to that as additional guidance for establishing a mechanism of toxicity.

OPP agrees that chemicals should not be grouped by a common mechanism on weak or "flimsy evidence," and that determining the CAG should not be based on chemicals that did not have sufficient evidence to be grouped by a common mechanism. Language in the draft 2000 document which may have implied this has been removed from the revised document. However, the hazard considerations for defining the CAG or removing a chemical from the quantification of risk involve a more detailed analysis of pharmacokinetic and pharmacodynamic processes that emerges as one enters dose-response analysis for a cumulative assessment or simply because its toxic potency is considered to present a minimal hazard.

1.A.3 Comment: DPR (09) views this document to provide a concise list of considerations for CAG selection, but because of the complexity of these considerations, it is not clear regarding the extent to which they would impact the final selection of the CAG. Case studies would be useful to illustrate their application.

Agency Response: The revised guidance has incorporated a separate section on defining the CAG (see Section 6). OPP does not intend to develop additional case studies but will begin conducting cumulative risk assessments on identified CMGs. OPP is currently preparing a preliminary risk assessment on OPs that will illustrate the decision logic and critieria applied in defining a CAG.

1.A.4 Comment: A commenter (BPFJF-05) states that EPA should not use common mechanisms of toxicity as a filter to decrease the number of chemicals it considers in a given CAG. The current Guidance on Cumulative Risk requires that chemicals share both a common toxic effect and a common mechanism of toxicity to be considered in a CAG. In the real world, a liver cannot tell the difference between two cancer causing chemicals because of the biochemical route each chemical takes to cause that cancer. In other words, if a number of pesticides and other substances cause liver cancer via a number of different pathways the end result is the same, a diseased liver. The commenter cites atrazine as an example.

Agency Response: FQPA amendments requires that the Agency to consider the cumulative effects of any pesticides and other substance that have a **common mechanism of toxicity** (see *Section 408(b)(2)(D)(v)*). It is those chemicals that cause the same toxic effect at the same site via the same biochemical pathway that are likely to result in a cumulative risk at environmental exposure levels. This is because dose additivity is more

likely to apply to common mechanism of toxicity agents and not to those agents that operate via a different chemical pathway or may operate at a different site. Chemicals acting by different mechanisms of toxicity may still interact in some way to change the total risk (e.g., potentiation, synergy, antagonism), but an ED of those chemicals would have to be achieved for those interactions. This type of interaction is beyond the scope of FQPA.

1.A.5 Comment: This commenter (BPFJF-05) states that in assessing cumulative risk, EPA needs to consider the fact that different endpoints have been shown to influence one another. For example, if a chemical causes a suppression of the immune system this could cause an increase in the risk of cancer. The draft guidance follows EPA's standard procedure of selecting endpoints and considering them in isolation from other toxic effects. Looking at each endpoint individually ignores the complicated set of interactions that occur within a body exposed to a variety of toxic chemicals.

Agency Response: To the extent data exist to show that different chemicals' toxicity may, acting in combination, cause more toxic response than either chemical acting in isolation, EPA will use such information in its risk assessments. Such data generally are not available. See also response to Comment 1.A.4.

1.A.6 Comment: PMRA (L02) points out that in discussing factors to be addressed in determining which members of the CMG should be included in the cumulative risk assessment, questions are raised about the saturation of metabolic pathways. Given that the EPA test guideline OPPTS 870.7485 requires only single low-dose testing in metabolism/pharmacokinetic studies at tier 1, it would seem that data adequate to determine the dose level required to saturate metabolic pathways would often not be available.

Agency Response: The cumulative dose response modeling should not focus on those high doses causing metabolic saturation. OPP does agree that pharmacokinetic information would be helpful in refining the dose-response modeling for cumulative risk assessment. Although the type of pharmacokinetic data that would be useful to the cumulative risk assessment process is not a data requirement for pesticides under 40 CFR 158, OPP has recently initiated a number of activities to evaluate Part 158 data requirements for pesticides. Part of this re-examination of testing will include consideration of those data needed for cumulative risk assessment. Nevertheless, OPP has emphasized the value of both pharmcokinetic and pharmcodynamic data in estimating cumulative risk

and thus encourages the generation of such data.

1.A.7 Comment: NRDC objects to EPA's criterion that some subset of the active ingredients within CMG might pose risk through another, more toxic mechanism. EPA envisions circumstances where these active ingredients might be pulled out of the CMG because they are likely to be regulated more strictly under the second common mechanism. It would be unscientific and less than health protective for the Agency to remove the second set of chemicals from the initial cholinesterase CMG until it actually restricts the use and exposures to those chemicals through enforceable regulatory actions. As long as the chemicals remain in use, they will be contributing to cholinesterase inhibition, and hence there is no basis to remove them from the cholinesterase CMG. The presumption that the second set of chemicals will be regulated more strictly as a result of the more sensitive, second common mechanism is conjecture on EPA's part.

Agency Response: OPP agrees that in general all chemicals should be included in the quantification of cumulative risk assessment, unless there is a clear basis for concluding that the potential contribution to cumulative risk is negligible. Accordingly, OPP has revised the text of the guidance to reflect this position.

1.B Mechanism versus Mode of Action

1.B.1 Comment: One commenter (ACC-02) indicated that OPP should use more rigorous criteria for defining common mechanism chemicals, and that a common mechanism group should be based on the chemicals' mechanism of toxicity and not on their mode of action. The SAP (September 1999) indicated that in order to be consistent with terminology used in the FQPA, the Agency erroneously uses "mechanism of toxicity" and "mode of action" as equivalent terms instead of using the terms according to their commonly accepted definitions. The SAP recommended that the Agency use "mode" to address what FQPA calls "mechanism," and the Guidance should justify the Agency's usage of conventional terminology.

Agency Response: OPP believes that it does apply rigorous criteria concerning its common mechanism of toxicity determinations by following the approach described in "Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity" (1999c). This guidance document was reviewed by the SAP and the public, and revised accordingly. Furthermore, the revised cumulative guidance also refers to the Agency's framework for evaluating a

chemical's mode of action as complementary guidance (USEPA, 1999d). This mode of action framework also provides a rigorous approach and has been adopted by the World Health Organization and is embraced by the scientific community.

FQPA uses the term "mechanism of toxicity" in subsection (b)(2)(D)(v) to describe substances that should be considered as to their "cumulative effects." That term is not further defined by the FQPA other than through the context in which it appears–i.e., as describing those substances that should be considered as to their potential "cumulative effects." Since the passage of the FQPA, however, a similar term–"mechanism of action" has been used in some Agency-wide guidance documents as a term of art with a fairly specific and narrow meaning. For example, the 1999 draft "Guidelines for Carcinogen Risk Assessment" (USEPA, 1999d) drew the distinction between a "mechanism of action" and a "mode of action" for carcinogenicity as follows:

> Understanding an agent's "mode of action" means understanding the general sequence of events by which it causes effects on cell growth control that result in cancer. "Mode of action" is used rather than "mechanism of action" which is a term that implies complete knowledge of the steps of carcinogenesis at the molecular level, a level of understanding that currently does not exist for any agent.

OPP is confident that, as a scientific matter, an understanding of a substance's mechanism of toxicity at the level described by the term "mode of action" as used in the 1999 draft "Guidelines for Carcinogen Risk Assessment" (USEPA, 1999d) is generally sufficient to reach a conclusion as to whether exposure to the substance is likely to result in cumulative effects with from exposure to other substances. Although understanding the precise "mechanism of action" would be helpful, it generally is not needed for a conclusion regarding potential cumulative effects.

OPP does not believe that "mechanism of toxicity" should be interpreted as narrowly as EPA has used, in recent years, the term "mechanism of action." To do so would exclude, without scientific basis, substances likely to have cumulative effects from consideration through a cumulative risk assessment. The statutory language does not suggest that a narrowed approach is favored. Presumably, subsection (b)(2)(D)(v) was added to emphasize to EPA the importance of evaluating the potential cumulative effects of substances and not to create a rigid guideline regarding which substances could be considered to have such effects. Importantly, it is unlikely that complete knowledge of how an agent causes its toxicity will exist, certainly for the near term and thus adopting the recent, narrow definition of "mechanism of action" for the FQPA term "mechanism of toxicity" would render subsection (b)(2)(D)(v) a nullity. Moreover, there is no evidence in the legislative history that Congress understood the term "mechanism of toxicity" to have a precise meaning, and the whole tenor of the FQPA enactment evinced an intent to avoid writing overly prescriptive scientific concepts into the statute. For example, FQPA was repeatedly hailed as allowing "sound science to prevail," 142 Cong. Rec H8146 (July 23, 1996) (statement of Rep. Buyer), id. at H8144 (statement of Rep. Condit); id. at H8143 (statement of Rep. Dingell) , and for taking "advantage of the latest scientific advances to maintain our food safety, while not being bound by those very advances to impossible-to-enforce laws." Id. at H8147 (statement of Rep. Camp); Id. at H8141 (statement of Rep. Roberts) (The new law would "provide wide latitude for the Environmental Protection Agency to adapt its regulatory system to meet the constantly improving scientific information that is available.").

For these reasons, OPP believes that the FQPA term "mechanism of toxicity" should be interpreted to embody the concept described recently in Agency documents as "mode of action." In its initial guidance on common mechanism determinations, OPP took precisely this position. The Agency has interpreted the legislative language to mean "mode of action." A "mode of action" is defined as "*the major steps leading to an adverse health effect following interaction of a pesticide with biological targets. All steps leading to an effect do not need to be specifically understood. Rather, it is the identification of the crucial events following chemical interaction (with biological targets) that are required in order to describe a mechanism of toxicity"* (U.S. EPA, 1999c).

1.B.2 Comment: IWG (06) points out that much of section 3.1 of the June 2000 Cumulative Risk Guidance essentially duplicates or restates material from the common mechanism guidance. IWG, therefore, recommends that consideration be given to either merging the two documents or otherwise eliminating the redundancies. IWG further points out that there are conflicting statements between the June, 2000 Cumulative Risk Guidance document and the 1999 Common Mechanism Guidance Document. For example, on page 19 of the cumulative risk policy it says that a CMG is a group of pesticides determined to cause adverse effects by a common mechanism of toxicity, but erroneously omits two of three key elements—common site and common effect as described in the Common Mechanism Guidance. It is very important that there be no confusion or inconsistency with respect to the definition of CMG.

> **Agency Response:** The revised cumulative guidance document now simply refers to the separate guidance developed for grouping chemicals by a common mechanism of toxicity (see Section 2). OPP agrees that a common site and common effect as described in the Common Mechanism Guidance are key elements of that decision, which are stated in the Common Mechanism Guidance. OPP will follow that 1999 guidance in making judgements about common mechanisms of toxicity.

1.C Need for Additional Toxicity Data

1.C.1 Comment: The World Wildlife Fund (WWF-03) indicated that cumulative risk assessment should move ahead even with the presence of data gaps. Because pesticides can be registered with the presence of data gaps, the same should be held true for cumulative risk assessment.

On the other hand, the Implementation Working Group (IWG-06) raised the concern that the cumulative risk policy gives the impression that useful cumulative risk assessments can be conducted now, without explicitly acknowledging that additional data and further work are needed in a number of areas. This is particularly true of the hazard assessment side of the process; the limitations in data on nonfood exposure are covered as well (see comment below under issue 6 input parameters). IWG points out that the Agency also admits it lacks the kinds of toxicity data that would allow the Agency to calculate with confidence the relative toxicity of compounds and the cumulative effect of concurrent exposure to low levels of several such compounds. The statute says that EPA “shall consider...available information concerning the cumulative effects of ...substances that have a common mechanism of toxicity,” but the Cumulative Risk Policy makes it clear that at this time the approach to cumulative risk assessment will of necessity have to be based to a very large extent on toxicity assumptions. The document’s treatment of virtually every hazard assessment

issue contains: (1) a discussion of the ideal approach that would be used if proper toxicity data were available; (2) a statement that these data are not available; and (3) a statement of the inferior approach that will be used instead of the desirable approach because of lack of the needed data. This is true for each of the following areas:

- use of NOAELs to estimate relative potency and points of departure for extrapolating risk;
- use of assumptions to extrapolate LOAELs to NOAELs;
- use of the assumption when data on one compound are not available for what is considered the most sensitive species;
- use of assumptions to allow toxicity values from tests regarding one exposure route to represent values for another exposure route; and
- use of the assumption that the CAG chemicals behave similarly in terms of primary physiologic process (absorption, metabolism, distribution, elimination) as well as the toxicologic processes.

IWG recommends that the Agency discuss the undesirable compromises and assumptions that must be made because the existing databases were not developed with cumulative risk assessment in mind; and further recommends that the Agency discuss the steps that might reasonably be taken to obtain new toxicity data that would eliminate the need for many of these compromises and assumptions.

Agency Response: In its 1994 report on risk assessment, the National Research Council (NRC) supported continued use of default assumptions in the face of little or no data (NRC, 1994). The NRC report thus validated a central premise of the approach to risk assessment in general that EPA had evolved in preceding years–the making of science policy inferences to bridge gaps in knowledge–while at the same time recommending that EPA develop more systematic and transparent guidelines to inform the public of the default inferences EPA uses in practice. The cumulative guidance indicates that it will update the current guidance appropriately in light of evolving scientific information and experience in practice in applying the guidance. The assumptions described in OPP's guidance are consistent with Agency-wide science and policy, and thus are viewed as appropriate. The revised guidance, however, encourages research and analysis that would lead to new risk assessment methods and data for both hazard and exposure . For example, the document encourages the collection of exposure data to make reliable probabilistic assessments possible. It mentions that OPP would depart from the assumption of additivity if there

were data that would replace the default method. It encourages the development of dose-response data by indicating that modeling is the desired approach and the use of NOAELs is the least desired default approach.

While some chemical groups may have a sufficient basis for conducting a cumulative assessment, OPP acknowledges that other common mechanism groups may not. The sufficiency of data will have to be determined on a case-by-case basis because each common mechanism group will likely have unique issues and data needs. Finally, in any risk assessment, data deficiencies and gaps are likely because it is rare that all ideal information is available. Thus, the document stresses the importance of risk characterization (Section 11) and the description of the level of confidence in the assessment as well as the key uncertainties and assumptions.

1.C.2 Comment: In the draft document EPA makes reference to the use of human data in relation to dose-response assessments or the possibility of reducing the interspecies UF. In light of recent EPA decisions regarding the use of human data, could these sections be clarified by including some qualifying statements about the suitability of using such data (PMRA-L02)?

Agency Response: In Chapter 4.6 of the revised document, guidance is provided on the role of human information in assessing cumulative risk. The revised document points out that both the design and the execution of research with human subjects must be rigorously reviewed and found to meet the highest standards of scientific merit and ethical conduct before the resulting information is relied on in an EPA risk assessment. OPP's standards for scientific and ethical acceptability of human studies are currently under review.

ISSUE 2. Selection, Normalization and Adjustment of the Point of Departure for Cumulating the Common Toxicity

As discussed in Chapter 5.1-5.2 (page 40648), a POD (i.e., a dose or exposure metric corresponding to some fixed marker of toxicity) should be selected to sum the combined exposure for the chemical group. To the extent possible, the PODs should reflect a uniform measure of the common toxic effect, which is produced by a common mechanism of toxicity, across the chemical members. A BMD approach is preferred to derive the PODs for each chemical member.

Question 2: In single chemical assessments, the Agency uses the upper-bound estimates (i.e., the lower confidence limit on dose) for both cancer (called LED) and noncancer BMD assessment. The concern has been raised, however, that summing upper-bounds of multiple compounds may result in a exaggerated risk. Do you agree that it is more appropriate to sum the central estimates (i.e., ED) rather than combining upper-bounds in the cumulative risk assessment of multiple chemicals? If not, why not?

2.A Endpoint Selection Process

2.A.1 Comment: Several commenters (IWG-06, Novartis-04) agreed with OPP that the hazard identification issues are different from those involved in RfD derivation, and that only factors relating to the common toxic effect should be considered. Furthermore, these commenters agreed with EPA that to the extent possible, a common endpoint derived from the same type of study using comparable methodology, species, sex of animals, duration and route of exposure be used to establish the relative potency of the chemicals.

Agency Response: The commenters agree with the Agency's approach to not using each chemical's RfD to derive RPFs and points of departure. The commenters further agree with the Agency's approach of basing relative potency determinations on a common and uniform basis by using, to the extent possible, the same endpoint and species/sex from studies of comparable methodology.

2.A.2 Comment: IWG (06) points out that it is preferable to use an endpoint for cumulative assessment that either measures an adverse effect directly or measures one of the events that leads directly to an adverse effect, and that the common endpoint definitely should not be a mere biomarker of exposure. This comment is made in regard to the use of blood cholinesterase inhibition (ChEI), where the Agency states in its 2000 cholinesterase policy document is not an adverse effect and is used only as a surrogate when data on possible adverse effects are missing for a particular compound.

Agency Response: Acetylcholinesterase inhibition (AChEI) in the nervous system is viewed as the key event in the mechanism of toxicity for cholinesterase-inhibiting pesticides. Thus, direct measures of AChEI in the neuronal tissues (i.e., central and peripheral nervous system) would be the preferred choice for characterizing potential cumulative risk for this class of pesticides. When OPP is conducting cumulative risk assessments on cholinesterase inhibitors, OPP will refer to its Science Policy on "The Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides," which states that:

> RBC measures of acetylcholinesterase (AChE) are generally preferred over plasma measures of cholinesterase (ChE) activity because data on red blood cells may provide a better representation of the inhibition of the neural target enzyme, AChE. OPP may use plasma ChEI data under certain circumstances, such as if red blood cell data are insufficient, of poor quality, or unavailable; if there is a lack of dose-dependency for the red blood cell AChEI; or, if the dose responses for inhibition of plasma ChE more closely approximate those for AChE inhibition in the nervous system than do the dose responses for RBC AChEI (USEPA, 2000c). OPP will develop relative potencies and points of departure for RBC, plasma, and brain ChEI as the data allow. In selecting one of these tissues, OPP will use its 2000 policy on the use of ChEI data. OPP recently sought SAP comment on its approach to the dose response assessment of the cholinesterase-inhibiting OPs based on previous comments provided by the September 2000 SAP review (USEPA, 2001a). This analysis illustrates how OPP applied its ChE policy.

2.B Calculation of Relative Potency

2.B.1 Comment: Two commenters (IWG-06, Novartis-04) indicated that OPP should use a process for calculating PODs from combined data based on normalized estimated doses like that described by Wilkinson et al., (2000). Novartis stated that EPA should normalize PODs on the basis on EDs, and that EDs are preferred over NOAELs.

> **Agency Response:** OPP agrees with the commenter, and has incorporated in its revised guidance document for cumulative risk assessment a section on combining response data (see Section 7.2.1.4). OPP recently illustrated how multiple datasets can be combined to derive more robust relative potency and BMD estimates for ChEI data on OPs (USEPA, 2001c).

2.B.2 Comment: IWG (06) and Novartis (04) note that ideal data sets for calculating relative potency (i.e., experimental data for each CAG member for all relevant exposure routes and durations, measures of the appropriate toxicity endpoint in the same animal species by means of standard procedures and employing a number of dose levels over a wide range) generally do not exist for most compounds. IWG further notes that such data have never been requested by EPA. These commenters further state that for some kinds of endpoints such as chronic toxicity the cost of obtaining such ideal data set would be extremely high. Thus, methods are needed for estimating aggregate and cumulative toxicity by use of data that either are available already or are reasonably obtainable as supplemented by assumptions that are necessary and appropriate.

> **Agency Response:** OPP agrees with the commenters that ideal data sets for some compounds are not likely to be available for calculating relative potency. However, OPP has demonstrated how existing hazard and exposure data can be modeled with current tools. Thus, methods are available for estimating aggregate and cumulative toxicity. OPP will apply assumptions that are necessary and appropriate and consistent with Agency policy and practice.

2.B.3 Comment: IWG (06) notes in their comments that EPA, at the July 2000 Technical Cumulative Risk Briefing, indicated for the RPF approach that for the foreseeable future the index chemical's NOAEL would be used as the POD instead of estimated dose (ED_xs). They also indicated in their comments that no explanation is given of the rationale or criteria to be used in selecting an index chemical.

> **Agency Response:** In the revised cumulative guidance, OPP states that the preferred POD for the index compound is a BMD derived from modeling the data. However, some data sets may not be amenable to modeling, and therefore, OPP would take the standard approach of using a NOAEL (see Section 7.2.3). The revised guidance document has also incorporated a section on criteria for selecting the index chemical (see Section 7.2.2). OPP also states that the most important consideration in selecting an index compound is that high quality dose-response data are available for the common toxic effect/species/sex and for the exposure route/pathways of interest. Furthermore, the index chemical should have a biological and toxicological profile pertaining to the common mechanism of toxicity that is representative of the other chemical members. It is preferable to have one index compound to scale the potencies across all routes/durations of interest.

2.B.4 SAP Comment: The SAP (September, 1999) agreed that, in order to avoid compounding conservativism, it is appropriate to sum the central estimates (ED_xs) rather than combining upper-bounds in the cumulative risk assessment of multiple chemicals. For the particular purpose of assessing relative potency, central estimates are better since they provide unbiased estimates of the relative contribution of components of a mixed exposure. The issue is not just conservatism with regard to overall risk, but is also determination of the contributions of each agent in the right proportions. Depending on the exposure levels, it is not necessarily conservative to use LEDs for each agent when doing relative potency as one can overemphasize the contribution of a low-potency, low-exposure chemical and hence underemphasize the risk from a more potent, higher exposure one.

One Panel member noted that the proposed guidance did not clearly establish whether the effect of using the lower confidence limit for each agent would significantly increase the SF, and if so, by how many fold. The derivation of a RfD (using ED as a benchmark for cumulative risk from two agents) higher than the most potent of two compounds used in combination (moderately high potency and moderately low potency) would be perverse. More detailed consideration of this issue needs to be included in the guidance document. This question raised the following concerns from Panel members:

a. Using central estimates does not provide a means for considering uncertainty associated with variability in the dose-response data; the proposed guidance intends to address this through application of a database UF (UFD) after assessment of cumulative hazard; will the method of selecting this UFD be scientifically sound enough to make use of central estimates defensible?

b. The proposed guidance does not thoroughly address the impact of using upper-bound estimates in cumulative risk assessment; i.e., to what degree would the SF potentially be exaggerated?

Agency Response: The SAP agrees with OPP that it is appropriate to sum the central estimates (ED_xs) rather than combining upper-bounds in the cumulative risk assessment of multiple chemicals. OPP does not intend to increase safety or UFs because central estimates are used rather than the lower confidence limits for each agent. The revised guidance states that confidence intervals or limits should be included as part of the dose response analysis because they can be valuable for evaluating the influence of variability on the potency estimates. They will also aid in describing the confidence in or uncertainty for the resulting dose-response estimates. UFs will be used to primarily address data base deficiencies or making adjustments of each chemical's toxic potency value so as to put it on a common basis with the rest of the chemical members.

2.B.5 Comment: CU (08) supports the point of comparison (POC) approach as a general rule; however, in the real world EPA will not have access to such a homogenous set of toxicology studies across a large CAG like the OP's and carbamates. Toward this end, the commenter urges the Agency to adopt as one of its general rules that in the absence of comparable toxicity data, a weight-of-evidence approach be used to estimate RPFs.

Agency Response: The revised guidance indicates that a common basis should be used to determine relative toxic potencies among the chemical members of the CAG **to the extent possible.** OPP acknowledges that ideal data may not be available and thus it may be necessary to mix sexes or species. However, the document goes on to say that if mixing of species/sexes, endpoints, or measures of potency is necessary, then additional uncertainties are introduced to the assessment and must be clearly noted, and some characterization of their impact on the total cumulative assessment should be given.

2.B.6 Comment: Regarding which method ought to be used–central estimate of an ED or lower-bound of an ED–DPR (09) believes that the choice is dependent on the methods used for estimating cumulative toxicity. When following the Cumulative Margin of Exposure Method, the draft document's rationale (Section 5.1) for using ED is reasonable. However, when following the RPF method, there's an advantage in using the LED.

Agency Response: OPP disagrees with the commenter concerning the RPF approach. The commenter is not clear why the LED would be an advantage. OPP indicates in its revised guidance that when comparing potency among the chemical members of the CAG, the POC should be based on central estimates should be used. The guidance indicates that both the central estimate (BMD) and the 95% lower confidence limit on a dose (BMDL) should be presented to provide the risk manager with the magnitude of uncertainty associated with the POD used to estimate the cumulative risk.

2.C Other Comments

2.C.1 Comment: One commenter (PMRA-L02) raised issues concerning the determination human equivalent doses.

Agency Response: OPP will follow the Agency policies and practices for determining human equivalent doses. The revised guidance refers to these Agency policies.

ISSUE 3. Incorporation of Group Uncertainty Factors

As discussed in Chapter 5.3, traditionally one or more of the UF are used to derive a n RfD for a single chemical. There are five UFs that are considered to account for the following extrapolations: LOAEL to NOAEL (UFL), subchronic NOAEL to chronic NOAEL (UFS), experimental animal to humans (UFA), interhuman variation (UFH), and incomplete database to complete database (UFD). It is proposed that the extrapolations of LOAELs to NOAELs or subchronic NOAELs to chronic NOAELs be applied as adjustments of a chemical's POD before estimating the cumulative risk. These adjustments are meant to be based on some scientific data that permits a reasonable extrapolation or interpolation rather than applied solely as a science policy default decision. EPA further proposes that other traditional UFs be treated as a composite ``group UF'' that pertains to the chemical members as a whole. Thus, the intraspecies and interspecies UFs and the database completeness UF are applied as a composite group factor after cumulative risk is estimated (i.e., not before on each chemical's POD). The rationale of the group UF is based on the premise that these factors should be viewed for the group as a whole given that all the chemicals are anchored by a common toxic effect produced by a common mechanism. Additionally, one is not simply evaluating risk in the context of a single chemical data base but the database for all the chemicals in the assessment. The advantage of a group UF is that it allows one to separate the resulting risk that is based on scientific adjustments from judgmental policy decisions to account for uncertainty. Finally, EPA proposes that an FQPA SF decision be applied for the group rather than on individual pesticides.

Question 3: Do you agree with this approach, and does the draft science policy paper clearly describe the rationale and guidance for the implementation of chemical specific adjustment factors and of a group UF for the cumulative risk assessment? Has the draft guidance clearly presented the limitations and strengths of the group UF approach?

3.A Questions about the Group Uncertainty Factors and Safety Factors

3.A.1 Comment: Several public commenters (PMRA-L02, ACC-02, etc.) expressed concern regarding how OPP will apply group UFs in cumulative risk assessment. The comment was made that OPP should provide an illustration or examples of the application of group UFs in cumulative risk assessment. Furthermore, the comment was made that there was a discrepancy between what was stated about the database UFs in the June 2000 Cumulative Risk Guidance Document and what was said at the July 2000 Technical Cumulative Risk Briefing.

Agency Response: OPP has developed a separate paper containing guidance for the application of uncertainty and SFs that it will circulate for additional public comment (USEPA, 2001g). At this time OPP does not include specific examples but instead provides general guidance. As OPP continues to develop cumulative risk assessments on specific common mechanism groups, specific examples will emerge.

3.A.2 SAP Comment: The SAP (September, 1999) generally supports the use of group UF approach as presented in the proposed guidance. The Panel recognizes the effort made in the Guidance Document to distinguish aspects of the UFs that adjust results to put them on a comparable footing (and thus should go before combination) from those aspects that express uncertainty about application of the final result to human risk (and hence should go after combination). This distinction represents an important advancement by the Agency and a contribution to the development of cumulative risk methodology. It would be helpful if a further discussion pointed out that all UFs are partially a means of extrapolation (i.e., applying a needed adjustment) and partially an allowance for the uncertainty in the size of that adjustment. The method proposed in the document emphasizes the extrapolation aspect of factors for LOAEL-to-NOAEL and subchronic-to-chronic factors in that they are needed to adjust different studies to put the endpoints on equal footing before combination. It emphasizes the allowance-for-uncertainty aspect of the inter- and intraspecies adjustments and completeness factor in that these are a product of the uncertainty in relative effect of the agent among species and among differently sensitive humans. In fact, both sets of factors may contain some aspects of adjustment and some aspects of uncertainty.

Specific concerns from Panel members are as follows:

a. Group application of a UFA (experimental animal to human extrapolation factor) is problematic if both human and animal data are used in cumulative risk assessment; there should be a method of adjustment which accounts for the possibility of important interspecies differences for the individual chemicals in the CAG.

b. One member strongly disagreed with use of a UFD for a CAG as a whole as this may not be satisfactory when dose-response relationships are not well-established for all chemicals in a CAG; the contribution of each chemical to uncertainty associated with the CAG is a function of relative exposure; it would be most practical to apply UFDs to individual chemicals prior to cumulative hazard assessment as the adjustments that would be necessary, based on exposure factors, from one cumulative risk assessment to another would likely be unworkable.

c. Serious critical evaluation of the use of Group UFs as put forward in the proposed guidance will depend on its application to real world examples.

d. One member suggested the proposed guidance be more explicit in its discussion of how uncertainty propagates through cumulative assessment.

e. In response to the third part of question 3, one member failed to find clear presentation of the strengths and weaknesses of the group UF approach in the proposed guidance.

f. One member suggested that additional thought be given to the issue of interspecies UFs and whether they should be applied at the outset individually (i.e., PODs for individual compounds) or applied as a group after the fact. Difficulties arise when the database includes studies comprised of both human and animal data for some compounds, but only animal data for others. In cases where correction needs are determined and must be made by extrapolation from animal to human, it is not enough to know that there is an identical mechanism of action in both species. Metabolism can differ greatly across species, and even from individual to individual, on a compound by compound basis which is not readily predictable from analysis of chemical structure. Therefore, even when human data are available for most compounds, and these data demonstrate equivalent sensitivity between humans and rats, it may still be necessary to acknowledge that remaining compounds in the CMG might differ markedly across species. Differences in sensitivity should be accommodated either by adjusting PODs for those compounds, or by applying a weighted correction factor "after the fact" to the whole group, in a manner reflective of relative risk (perhaps as determined by MOE for the individual compound as a fraction of the combined MOE).

Agency Response: The SAP supports OPP's approach of distinguishing between those UFs which apply to all the member of the chemical group versus those UFs that should apply to individual chemical members as adjustments. OPP agrees that both group and chemical-specific UFs may contain some aspects of adjustment and some aspects of uncertainty. OPP has developed a separate paper containing guidance for the application of uncertainty and SFs during cumulative risk assessment that it will circulate for additional pubic comment (USEPA, 2001g). The revised guidance indicates that cumulative risk should be based on the same species, to the extent possible. If a different species is used for a chemical member, the guidance acknowledges that this may introduce uncertainty, and that adjustments to account for the possibility of species differences will be made on individual chemicals in the CAG, or that uncertainty will be noted in the risk characterization. Furthermore, an UFD, UF for database deficiencies, should be dealt with on each chemical

in adjusting its relative potency. But OPP anticipates that it will rarely need to apply an UF as a group composite factor to account for database deficiencies. If there are substantial database issues with the CAG as a whole, questions should be raised as to whether a cumulative risk assessment can be reliably conducted. Nonetheless, care must be taken to avoid the "double-counting" of safety/UFs (redundant use of UFs) in the cumulative risk assessment.

3.A.3 Comment: IWG (06) agrees with the Agency that when several chemicals share a common mechanism of toxicity, EPA may be able to use data from tests on some of the chemicals to lessen or remove uncertainties arising from missing or inadequate studies on other chemicals. This should avoid the need to apply UFs for such problems as lack of a NOAEL in a particular study, and use of an unrealistically low NOAEL caused by large differences in test doses. IWG goes on to further suggest that EPA consider the possibility of including some other adjustments that may modify the impact of the group UF in a chemical specific way. For example, if a POD is derived from animal data, and if for a single CAG chemical the relationship between animal and human potency is known to differ from the default 10X interspecies factors, there should be a way to adjust the RPF to recognize this. EPA should incorporate data-derived judgements about the proper value for the group UF to the fullest extent possible.

Agency Response: OPP indicates in its guidance for interspecies differences, a factor of 10-fold is usually applied as a default assumption, but when specific data indicate that humans are less sensitive than animals, the interspecies group UF of 10-fold may be reduced. OPP would need to examine the entire database, and usually studies on a single chemical would not be sufficient to reduce the standard UFA for the CAG. See the SAP comments in 3. A. 2.

3.A.4 Comment: The IWG (06) points out that at the July 2000 Technical Cumulative Risk Briefing on the June 2000 Cumulative Risk Guidance, the UFs were divided into two categories “chemical specific adjustments” and “composite group” UF or SF. IWG further notes that the chemical adjustment factors are not UFs as traditionally defined. In fact, they would be more aptly termed adjustment factors because the are used to adjust chemical data to derive relative potencies. Thus, a better term for the Database Problems Factor (as shown on slide 66 of the briefing as a UFs) would be the Database adjustment factor. IWG further notes that the EPA also should commit in writing to what its representatives said at the July 2000 Technical Cumulative Risk Briefing: that it will not use uncertainties attributable to harmonization of CAG compounds as a basis for adding an additional UF when calculating group RfDs.

> **Agency Response:** OPP disagrees with the commenter that it should introduce new terminology to describe the different application of UFs in the cumulative risk assessment process. As long as OPP explains clearly its decisions to use an UF–either at the chemical-specific level or for the entire CAG–OPP expects its approach will be sufficiently transparent to ensure that the basis for application of the UF will be apparent. In addition, such transparency should preclude the kind of “double counting” referred to in the comment because the analysis of the basis for application of the UF will make "double counting" obvious to the assessor.

3.A.5 Comment: Page 48 of the draft document lists three extrapolations: high to low dose, animal to human and route-to-route. PMRA (L02) asks if would it be appropriate to also add a fourth extrapolation, that of adult to child responses?

> **Agency Response:** OPP agrees that when adult animal data are used for cumulative risk an extrapolation of adult to child responses is made. A default factor of 10 is applied to account for human variability and to protect potentially more sensitive populations including children, as well as another default factor 10 to account for the animal to human extrapolation. OPP will apply an additional FQPA SF to protect children unless reliable data show a different factor would be safe. OPP will reduce the standard 100-fold factor if sufficient data allow. OPP believes this is clear in the guidance document.

3.A.6 Comment: NRDC (L05) commented that when the database for a certain pesticide is incomplete, the UF_D should be applied to the exposure/risk estimates impacting just that chemical. Imposition of the UF_D for one chemical, however, in no way precludes imposition of another UF_D to the CMG group, or retention of the added FQPA 10X factor. EPA must not confuse the UF_D with the additional FQPA margin of safety, which encompasses not only "completeness of the data," but is also intended to include both children's likely greater vulnerability and exposure. NRDC suggests that EPA develop simple guidelines differentiating when the UFD will be applied to the CMG as a whole, and when it will be applied to one or more active ingredients in the CMG.

Agency Response: See response to 3.B.4.

3.B Susceptible Subpopulations and the Intraspecies Factor

3.B.1 Comment: WWF (03) thinks that the general theme of the cumulative risk assessment process is avoidance of SFs, and calls for EPA to enact the FQPA's provision for an addition 10-fold SF. WWF believes that the draft guidance contains strong limitations on the circumstances where EPA will retain added SFs and there are elaborate steps to avoid overestimation of exposure. For example, they raise the concern about the RPF approach given the definition and assumption of TEFs all chemical constituents acting via all routes and on all biological targets, as a means to selectively guard against the introduction of unproven sources of exposures.

Agency Response: OPP's goal with respect to the use of UFs is to assure that the resulting risk assessment does not underestimate risk. In addressing this goal, OPP intends that its cumulative risk assessment guidance describe an appropriately science-based approach to the use of UFs. OPP does not regard its guidance as either promoting or discouraging the use of UFs, except to the extent that the particular circumstances of a specific risk assessment would warrant. In addition, OPP will release a discussion document that arrays the many considerations surrounding application of the FQPA SF in the context of a cumulative risk assessment. OPP will request public comment on this topic at the time of the release.

Contrary to the implication of the commenter, discussion of the distinction between TEFs and RPFs was included to clarify the use of an RPF approach requires **less** rigorous evidence of common effect, that is, commonality for only one effect whereas the TEF approach requires evidence of commonality for **all** effects and is therefor less inclusive.

3.B.2 Comment: IWG (06) raises the issue that the June 2000 Cumulative Risk Guidance in Sections 3.4 in Table 3-1 and Table 3-2 contains statements about potentially sensitive and susceptible populations. IWG questions inclusion of such statements in that part of the document. IWG does think however, that the topic is appropriately addressed on page 74 in the context of determining the appropriate group UF. The earlier references are confusing and unnecessary and should be omitted. In a similar vein, on page 5, the document says "all dose-response assessment should include consideration of their relevance by addressing whether key studies reflected dosing of adult age animals only." IWG questions the purpose of this statement in this document, and the meaning of this language as is the relationship of the sentence to cumulative risk assessment. Is this a nod to political correctness or is it eluding to the deficiency of EPA data requirements? As the Agency has pointed out repeatedly, the 10X intraspecies UF is intended to account for possible differences in susceptibility due to age among other factors.

> **Agency Response:** OPP revised its guidance document to reword the statements identified in the comment. In doing so, OPP has clarified that it intends to consider the potential that infants and children may be more sensitive to the common mechanism of toxicity exhibited by the members of the CAG than are adults. If data suggest potentially increased sensitivity, OPP will weigh this information, along with other relevant information, in deciding whether to apply the default FQPA SF or whether reliable data support either no or some other UF.

3.B.3 Comment: Another commenter (ACC-02) believes that the decision to apply the FQPA SF as a group UF should be undertaken judiciously, since EPA's current risk assessment process is inherently conservative and, in most cases, adequately takes children into account. Application of the FQPA SF will not necessarily provide a greater public health benefit than the already conservative risk assessment/risk management approaches employed by EPA.

> **Agency Response:** OPP will issue for public comment a separate paper containing guidance for application of the FQPA 10X SF. See response to Comment 3.B.4.

3.B.4 Comment: CU (08) supports the concept of applying a single group UF. However, the commenter is concerned that in doing so EPA may be ignoring the FQPA 10X SF provision, noting that in some of the document's discussions on group UF the 10X factor is not always mentioned. According to the commenter, the document needs to be very clear and consistent regarding when and why an additional FQPA UF will be included in the cumulative risk assessment group UF.

Another commenter (NRDC-L05) points out that the guidance EPA undermines one of FQPA's most important health protective provisions by limiting the circumstances when the Agency will retain an added safety factor. Beyond any good scientific or public health reason, EPA threatens to require that all pesticides within a CMG be shown capable of inducing heightened toxicity in young animals before it retains an additional FQPA margin of safety to protect children. Broad application of the 10X safety factor makes complete sense given that FQPA was written in response to the 1993 NAS report, "Pesticides in the Diets of Infants and Children." FQPA specified a presumptive, added margin of safety specifically because the kind of data that EPA collects on individual pesticides may be inadequate to show conclusively when young animals are, in fact, at greater risk than adults.

> **Agency Response:** OPP has not included discussion of the FQPA 10X SF in this document. Instead, a separate document will be issued describing the issues surrounding application of the FQPA 10X SF to a cumulative risk assessment and how this problem differs from application in a single chemical assessment. OPP will request public comment on factors to be considered in developing an FQPA SF decision at that time.

3.B.5 Comment: CU (08) states that the application of the FQPA SF should not be limited to the toxic effect underlying the CAG. Rather, it should be applied in cases where there is increased susceptibility to the young, as demonstrated in developmental neurotoxicity testing, regardless if this is the most sensitive endpoint. One commenter (NRDC-L05) objects to the statement in Chapter 6: "Particular attention should be paid to whether the increased sensitivity in the young is related to the endpoint that reflects the common mechanism." The purpose of such "particular attention" is presumably to discount the relevance of any evidence that the second mechanism should influence the magnitude of the FQPA margin of safety. The commenter objects to EPA's narrow reading of this key provision. There is no scientific or public health reason for EPA to require that all pesticides within a CMG display heightened toxicity to young animals before imposing an added safety factor.

Agency Response: OPP disagrees with the commenter. Application of the FQPA SF should pertain to the common mechanism of toxicity, but not necessarily to the common toxic endpoint that is used in the cumulative risk assessment. OPP will issue for public comment separate guidance for application of the FQPA 10X SF.

ISSUE 4. Methods For Estimating Cumulative Toxicity

As discussed in Chapter 5.6, one of the steps in the cumulative risk assessment process will be to select a method to cumulate dose or exposures. This method will serve to normalize differences in the toxic potencies among the chemicals in the cumulative assessment. Precedence in the Agency's 1986 and revised 1999 "Guidance for Conducting Health Risk Assessment of Chemical Mixtures" (EPA, 1999b) describes several techniques for estimating risk to multiple chemicals. The cumulative guidance focuses on the component-based dose addition methods used in the EPA's chemical mixture assessment guidance document. Two methods, an MOE approach and an approach using RPFs, are presented.

Question 4a: Do you agree that both methods are valid to consider for estimating cumulative risk associated with exposures to chemical that cause a common toxic effect by a common mechanism? Has the draft document clearly described these two approaches and their strengths and limitations? Are there other methods that OPP should consider?

Question 4b: EPA anticipates that most mechanisms of toxicity encountered currently will be nonlinear dose-response relationships. Nevertheless, for mechanisms of toxicity consistent with linear dose-response relationships, do you agree that using the RPF approach by summing the slopes of the dose-response curves is an appropriate method? If not, what methods would you recommend for low-dose linear extrapolations of risk?

4.A Cumulative Margin of Exposure and Relative Potency Factor Methods

4.A.1 Comment: Several commenters (PMRA-L02, Novartis-04) and the SAP (USEPA, 1999a) agreed that both the cumulative MOE and RPF approaches are appropriate for cumulating the hazard of common mechanism chemicals, and that both will yield similar results if the same PODs are used and UFs are applied as a group composite factor at the end of assessing cumulative risk. IWG (06) notes that as stated on page 67 of the June 2000 Cumulative Risk Guidance, it is misleading to describe the cumulative MOE approach simply as the reciprocal of the hazard index method because the HI method includes chemical specific UFs in its calculation.

Agency Response: The commenters agree with OPP's statement about the cumulative MOE and RPF approach. OPP agrees with IWG that the cumulative MOE should not be described simply as a reciprocal of the hazard index approach because it includes chemical-specific UFs. This has been deleted from the revised guidance.

4.A.2 SAP Comment: SAP (USEPA, 1999a) further suggested that some effort should be expended to assess the accuracy of these two methods (RPF and MOE) and the assumptions that underlie each method and to rigorously compare the methods; analysis of appropriate hypothetical data sets may help identify factors that could introduce significant error. The proposed guidance should clarify if both of these methods will be applied to each cumulative risk assessment. If not, what criteria will be used to select one method over the other?

The proposed guidance does describe strengths and limitations of the two methods. There are actually two separable issues to consider in combining toxic responses by these methods: (1) calculation of relative potency among the agents in question (i.e., the fraction of the total risk coming from each agent); and (2) the absolute degree of potency (i.e., the total risk). If one acknowledges that each agent's individual toxicity is determined with experimental error, and that the degree of such error may vary among agents, then the two methods differ in their sensitivity to such error. The relative potency method incorporates any error in the determination of the absolute potency of the index chemical into the calculation of all the relative potencies, and so it is a good idea to use the best characterized agent as the index. The MOE method spreads the effects of error among all the agents, since no single one need be chosen as the index. This makes the result less vulnerable to the error in one particular agent's dose-response determination, but it also means that the overall error is from a combination of the better- and worse-estimated curves (in a sense, averaging the error over them) and not just of the curve thought to have the least error. Further discussion of the sensitivity of each method to experimental errors in determination of points-of-departure is warranted. Proportionality of differences in MOEs should not be interpreted as proportionality in differences in risk. The temptation to act as though an MOE 10-fold larger implies a risk 10-fold lower should be avoided. If dose-response curves are not estimated (e.g., if only NOAELs are used of if PODs are presented without presenting the fitted curves they are derived from), then relative risks at different levels of exposure cannot readily be compared. Some difficult examples of cumulative risk assessment that require application of UFs might be informative for comparing strengths and limitations of the methods of MOE and RPF.

The Panel did not specifically propose other methods for the Agency to consider. However, the Panel did ask for more information on methods that were rejected for cumulative risk assessment. One Panel member recognizes that the Agency needs to avoid two unsatisfactory extremes: (1) insisting on "ideal" methodology which cannot be used with available data; and (2) accepting a "purely practical" methodology with poor scientific rationale, which offers no way to improve risk analyses when better data become available. The best compromise is to define methodology with reference to the data that are desired and can ultimately be provided. Such a methodology allows for the frequent

cases when ideal data are lacking and analyses must use practical surrogates. For example, rather than base risk assessments on NOAELs, one could base them on BMDs, while allowing use of NOAELs when BMDs are not available. This strategy encourages the generation of better data, it allows policy choices to evolve as the science improves, and it puts less-than-ideal analyses in their proper perspective.

Agency Response: OPP agrees generally with the SAP comment. OPP refers to the Agency's recent "Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures" (USEPA, 2000d) for a detailed discussion of the types of approaches that exist for determining the joint risk of multiple chemicals. The revised cumulative guidance document discusses only the RPF method; OPP does not anticipate using the MOE approach, either in combination with the RPF approach or by itself. At this time, OPP prefers the RPF approach as a standard method because it can utilize dose-response information to provide an estimate of the common toxicity, and thus allows for the quantification of exposure as it relates to the joint risk of the CAG. The RPF method evaluates the equivalent index chemical exposure on its dose-response curve in order to estimate the risk of the CAG. Thus, OPP emphasizes in the revised guidance that it is essential that the index chemical be well characterized (qualitatively and quantitatively) because any imprecision in its data is compounded with every chemical against which it is compared.

The guidance clearly describes criteria for selection of an index compound. The most important consideration in selecting an index compound is that high quality dose-response data are available for the common toxic effect/species/sex and for the exposure route/pathways of interest. Furthermore, the compound should be well characterized for the common mechanism of toxicity, and the common mechanism of toxicity should be its principal toxicity. The index chemical should have a toxicological profile for the common toxic effect(s) that is representative of the other chemical members. It is preferable to have one index compound to scale the potencies across all routes/durations of interest.

OPP will use dose addition and prefers the RPF approach at this time and believes that the incorporation of bench mark techniques to increase the accuracy of estimating PODs will greatly reduce the potential error referenced by the SAP. As indicated in the revised guidance, OPP will use an alternative approach that is more appropriate when data permit. OPP will continue to gain experience with cumulative risk, and OPP anticipates that data and methods will continue to evolve, thus OPP may update this revised guidance or provide supplementary materials as appropriate.

4.A.3 Comment: One commenter (Novartis-04) indicated that PK differences (time, rate, recovery, etc.) among chemicals should be included in the cumulative risk assessment process as part of the dose-response assessment software.

Agency Response: OPP agrees with the commenter that PK information should incorporated into the cumulative assessment to the extent possible and as data allow. The revised guidance makes reference to this in several sections of the document.

4.A.4 Comment: PMRA (L02) believes that the descriptions of the two methods can be clarified; they pointed out that it is not clear how the individual MOE's are combined.

Agency Response: The revised guidance only discusses the RPF method (see response to Comment 4.A.2). Even with the RPF method, MOEs are used to integrate the risk across multiple pathways of exposure. This is explained in Chapter 10 of the revised guidance. OPP will express the total pesticide residues for the CAG in terms of the Index Chemical using the RPF method. This approach requires conversion of the residues of each member of the CAG to concentration equivalents of the index chemical. This can be done using RPFs developed to normalize the toxic response of each pesticide to the toxicity of the index chemical. The POD (e.g., an ED_{10} or NOAEL) for the index chemical is then used to calculate route-specific MOEs for the CAG. OPP uses MOEs for aggregating the risk posed by exposure to a single pesticide via multiple pathways (USEPA, 2001h) and has extended this approach to estimating the cumulative risks of multiple chemicals. Route-specific MOEs can be used and combined to generate a total MOE while preserving the route-specific nature of the risk estimates. This method is illustrated in “Cumulative Risk: A Case Study of the Estimation of Risk From 24 Organophosphate Pesticides” (USEPA, 2000e).

4.A.5 Comment: CTRAPS (19) points out that EPA’s draft document does not

adequately explain how relative potencies will be estimated–the guidance lacks an adequate mathematical description of relative potency.

> **Agency Response:** OPP disagrees with the commenter. OPP believes that the guidance document clearly explains how relative potency is calculated. Furthermore, OPP has recently provided a detailed analysis for how relative potency is calculated for the OPs (USEPA, 2001d). The SAP has commented on this analysis and has recommended additional refinements which OPP is currently considering. See website referenced above.

4.A.6 Comment: CTRAPS (19) disagrees with the TEF approach, pointing out that it has received extensive criticism by scientists outside the Agency. The commenter states that the TEF approach will not work with substances that bind to the same receptor; this is not likely to occur with the OP's. However, OPP intends to apply the proposed guidance to all common mechanism groups, not just those with mechanisms involving enzyme inhibition. The commenter suggests reference the scientific literature on isoboles as it provides extensive justification regarding the use of relative potency.

> **Agency Response:** Because the commenter fails to explain why the RPF approach would be inappropriate, OPP will continue to use the RPF approach which the September 2001 SAP indicated is an appropriate approach for estimating total risk to common mechanism chemicals.

4.B Assumption of Dose Addition and Proportionality of Dose-Response Curves

4.B.1 Comment: Although the SAP (September, 1999) indicated that the MOE method and the RPF method are clearly useful methods to apply in initial investigations of cumulative risk assessment, the validity of these methods remains to be determined. Since both methods are based on dose-addition, they are conceptually valid only when the dose-response relationships for the individual chemicals are parallel. PMRA indicated that common mechanism chemicals may not necessarily exhibit parallel dose-response curves. SAP and PMRA indicated that the guidance document needs to discuss the impact of nonparallel dose-response curves on cumulative risk assessment.

The SAP (September, 1999) further recommended that the assumptions underlying the use of the cumulative MOE and RPF methods should be explicit in the proposed guidance and should at least clarify: (1) whether or not the dose-response curves for members of a CMG are assumed to be parallel; and (2) if dose-response curves are assumed to be parallel, what is the impact for assessment methodology if the curves are not parallel?

Agency Response: Additional discussion has been added to the revised document regarding the assumption of dose additivity In Chapter 7.6, the revised document emphasizes that the cumulative dose-response assessment should include a discussion concerning the applicability of the assumption of dose additivity and proportionality of the dose-responses among the CAG, and the document discusses the factors or information that needs to be evaluated (e.g., information on chemical interactions among the CAG, as well as a statistical examination of whether the dose-response curves for each chemical member of the CAG are consistent with the assumption of dose additivity). The document indicates that if evidence exists that is judged to disagree with dose addition, particularly at low doses, then the chemical(s) in question should be reevaluated for inclusion in the quantification of cumulative risk. Furthermore, the revised document acknowledges (Chapter 7.1) that although simple dose addition assumes no chemical interactions, in reality, common mechanism chemicals may not behave ideally (i.e., display the exact same pharmacokinetics and pharmacodynamics). It further acknowledges that dose addition may be limited to some range of exposure conditions (dose level and frequency, as well as route), and thus dose addition is an Agency default assumption, and when applied it is only an approximation of the joint chemical risk. OPP clearly indicates in the revised document that it will use an alternative approach that is more appropriate when data permit.

4.B.2 Comment: Several commenters (ACC-02; Novartis-04) raised issues concerning the use of dose addition methods to estimate cumulative risk. Two commenters (IWG, Novartis) stated that in the absence of data, it is prudent to assume dose additivity at low dose. These commenters further recommend that EPA provide registrants with an opportunity to demonstrate experimentally that exposures below a threshold level result in a zero or negligible delivered dose at the target site because of metabolic and other processes that prevent low doses of the compound from reaching the target site. Another commenter (ACC-02) recommended the use of response addition as a default (rather than dose addition) in assessing chemicals effects below the NOAEL.

Agency Response: The revised document now indicates that, when data

allow, OPP risk assessors should consider alternative approaches rather than simply use dose addition. The Agency encourages the development of any data that would reduce uncertainties and refine estimates of cumulative risks. Agency policy recommends the use of the assumption of additivity at low doses.

4.C Low Dose Linear Extrapolations

4.C.1 Comment: The SAP (September, 1999) accepted EPA's proposal to use the RPF approach by summing the slopes of the dose-response curves when linearity has been established in dose-response relationships. Several commenters (IWG-06, Novartis-04, DPR-09) raised concern, however, about using the RPF method to estimate linear cancer risk as described on page 60 of the draft guidance document. IWG and Novartis indicated that the issues of low dose linearity and common mechanism of carcinogenesis are complex, and thus recommends that this issue not be a part of the cumulative risk guidance, and that it is better to defer making a specific recommendation for these situations at least until the Agency has finalized its cancer guidance policy. DPR (09) finds the expression “summing the slopes of the dose-response curves” for the assumed linear dose-response relationships to be problematic. Technically, what is being “summed” is not the “slopes,” but an expression of response (MOE or cancer risk) or dose (or exposure). And, recognizing that most dose-response relationships are nonlinear does not necessarily contradict the assumption of linearity at the low-dose range.

Agency Response: The statement quoted in the comment has been deleted and the document now includes a statement that focuses on guidance for pesticide chemicals that act by a common mechanism of toxicity. It is anticipated that most mechanisms of toxicity that have been elucidated will be consistent with nonlinearity or threshold biological phenomena. The dose-response methods presented in this guidance are more applicable to these situations.

ISSUE 5. Case Study

In Appendix A of the draft science policy paper is a case study on OPs

Question 5: Does this case study provide a clear example of the application of the hazard and dose-response elements of the draft guidance?

5.A.1 Comment: PMRA (L02) comments that the case studies present a good explanation of the basic steps involved in assessing the hazard and dose-response of each chemical and identifying their POD's and UFs. However, at times, the conclusions drawn for the three chemicals are not consistent and/or do not seem to be supported by the data that is presented.

Agency Response: OPP has removed this case study on three OPs via the dietary food exposure from the revised document. OPP does not intend to develop additional case studies but will begin conducting cumulative risk assessments on identified CMGs. The revised document refers to a more updated and comprehensive analysis on OP pesticides.

5.A.2 SAP Comment: The SAP (September, 1999) agreed that the use of case studies to illustrate application of the proposed guidance to cumulative risk assessment is a valuable addition to the proposed guidance document. It was agreed that the straightforward case study provided for review gave a general feel for the Agency's weight-of-evidence approach; however, all Panel Members considered this example too simplistic. A more complex, realistic case illustrating application of UFs and considerations of sensitive subpopulations would provide much better guidance. Panel members suggested the following:

a. Providing more than one case study should be considered.

b. Correlating case study examples with technical guidance chapters would allow the proposed guidance to illustrate points as they are being developed in the text.

c. The case study examples should clearly identify the portions of the cumulative risk assessment approach that are based on science and those portions that are based on policy.

d. In quantifying cumulative risk, the example states (e.g., page 92) that, " In practice, the risk data for each pathway would be combined over time and presented as a distribution." There are significant technical issues that need to be addressed and resolved before this can be accomplished. Additional detail on this aspect needs to be provided.

e. A UfD was not applied in this example. The rationale for this decision needs to be included in the example.

Agency Response: OPP does not intend to develop additional case studies but will be conducting cumulative risk assessments on identified CMGs. OPP has removed this case study on three OPs via the dietary food exposure from the revised document. Instead the revised document refers to a more updated and actual cumulative analysis on OP pesticides.

ISSUE 6. Input Parameters

There are several types of data available for pesticide exposure assessment (e.g., field trial data, monitoring data, percent crop treated, label usage). For the food pathway, monitoring data are available from the USDA PDP. OPP conducts the majority of its drinking water assessments by calculating a screening level value. Similarly, residential assessments are conducted using the draft residential SOPs which also provide a screening level assessment. Thus, given PDP, the assessment of the food pathway will, in many cases, be based on higher quality data than for the residential and drinking water pathways where usually only screening values are available. Because of the different quality of data that will be encountered when conducting a cumulative exposure assessment, the concern is raised that the value and benefit of high quality monitoring data will be lost if combined with extrapolated exposure values from screening models.

Question 6.1: Please comment on how this concern could be addressed. For instance, should OPP at this time conduct separate pathway assessments for food, drinking water, and residential exposures so as to avoid combining higher quality monitoring data with more limited screening level data?

Question 6.2: Please comment on whether there are other means of dealing with existing data to reduce the uncertainties about exposure values derived from screening approaches.

Question 6.3: Please comment on whether and how OPP could incorporate quantitative uncertainty analyses in the overall cumulative risk assessment when OPP uses data of varying quality.

Question 6.4: Is it appropriate to extrapolate food exposure from residue field trials and use/usage information if food monitoring data such as USDA's PDP data are not available?

6.A Lack of Information and Using Screening Approaches for Nonfood Exposures

6.A.1 Comment: IWG (06) states that to yield reasonably accurate estimates, a cumulative pesticide risk assessment must take into account: the way(s) in which a population or subpopulation or persons might be exposed to one or more pesticides; the period during which exposures of various sorts might occur and the extent of overlap; the levels of pesticide residues to which persons could be exposed; the extent to which residues are ingested, inhaled, or dermally absorbed; and the extent (concentration and duration) of exposure that occurs at the internal site at which the common toxic effect occurs. In an assessment that is intended to reflect reality, each of these factors should be incorporated as a probability distribution.

Agency Response: OPP generally agrees. Most model inputs should be represented by distributions to the extent possible. Where the shape of the distribution is uncertain, a uniform distribution should be used to allow expression of the full range of data in the resulting risk assessment. This approach to data use is consistent with advice received from the SAP in its review of the OP Cumulative Risk Assessment Case Study in December 2000.

6.A.2 Comment: IWG (06) notes that assumptions that do not underestimate exposure are bounding assumptions. EPA should acknowledge that, if it does use such assumptions, the results can be used properly in screening assessments but not in attempts to estimate actual quantitative risk. However, if too many such assumptions are used, the assessments become useless even for screening purposes.

Agency Response: OPP disagrees that assumptions which do not underestimate exposure are "bounding assumptions." Assumptions that do not underestimate exposure may reflect realistic estimates of anticipated exposures. In addition, it is common to combine bounding estimates of one variable with an estimate of the central tendency of another parameter in algorithms that produce a reasonable high-end value. In general, OPP will use the best data available and will employ the data in a manner that neither underestimates potential exposure nor produces gross overestimates of exposure. Finally, assessments that overestimate potential exposure, even significantly, can be useful for screening purposes if the resulting estimate is considered to be acceptable.

6.A.3 Comment: The commenter (IWG-06) disagrees with EPA's policy of using one-half the level of detection for pesticide residues that are nondetect. They state that when doing cumulative risk assessments, using this assumption in a CMG could grossly overstate the likely residues. Typically, a particular crop site would not be treated with multiple compounds from a given CMG, and it is extremely unlikely that any field would be treated with more than two or three members of a CMG within a single growing season.

> **Agency Response:** It is OPP's intention to evaluate the appropriate treatment of nondetectable residues on a case-by-case basis. This decision will be based upon evaluation of the data available and the use of sensitivity analyses to determine the impact of this assumption on the outcome of the cumulative risk assessment. To the extent that the results of the risk assessment are markedly affected by the treatment of nondetectable residues, the impact must be characterized as an uncertainty in the results and factored into any risk management decisions that may arise from the use of the cumulative assessment.

6.A.4 Comment: IWG (06) believes that using residue data from field trials (as opposed to monitoring data) results in unrealistic compounding of conservatism in the final exposure estimates.

> **Agency Response:** OPP agrees that this could be true in the case of a cumulative risk assessment and has no plans at this time to use field trial data in upcoming assessments. However, this decision may prove problematic in incorporating new active ingredients or significant new use patterns into an existing cumulative risk assessment. OPP will continue to consider methods for prospective estimation of the impact of new materials on cumulative risk.

6.A.5 Comment: The draft guidance states that "pesticide concentrations in raw water with adjustments for the effects of blending and treatment" can supplement direct tapwater measurements. IWG (06) agrees with this approach *if* "raw water" is defined as water sampled at or near the Community Water System (CWS) intake (rather than in streams far from the intake), or *if* adjustments for blending/treatment are done well.

Agency Response: OPP recently released for public comment a science policy paper concerning the impact of drinking water treatment on the levels of pesticide residue in drinking water. In the paper, OPP indicated that it would generally conclude that most commonly used methods of treatment had little or no impact on pesticide levels, and that in the absence of data on such impacts, would assume that measurements of pesticide levels in raw water provided a reliable indication of the levels of potential human dietary exposure via drinking water. In using raw water values, OPP will consider how and where the data were collected in order to characterize the relevance of monitoring data.

6.A.6 Comment: Several commenters (IWG-06, Novartis-04) agreed with EPA that highly refined information on exposure through the food pathway should not be combined with screening level or high end estimates of exposure through other pathways. Novartis notes that adding worst-case estimates will produce a number that usually will be meaningless and unhelpful, even for purposes of screening because of the compounded conservatism it involves. These commenters raised the issue of data availability and quality, and the basis for combining exposures across multiple pathways. IWG indicated in their comments that EPA should acknowledge in most cases it lack sufficient information on residue levels and human behavior patterns to do more than establish upper-bound, worst case screening estimates for drinking water and residential exposures. EPA sets forth no detail about how it proposes to include drinking water and residential or nonoccupational exposures. It should obtain public comments on this exceedingly complex task.

PMRA (L02) called for further guidance on how uncombined cumulative risk assessment pathway are used. Some commenters (IWG-06) felt that the language in the June 2000 Cumulative Risk Guidance is ambiguous with respect to integrating multiple pathways of exposure. For example, it could be interpreted that cumulative risk assessments will not be performed until aggregate assessments have been done for all exposure routes for each compound. If this is what it means, EPA must explain whether quantitative aggregate risk assessment will be performed without waiting for needed refined data, or will not be performed until EPA has obtained refined data for all exposure routes. On the other hand, it could be interpreted that cumulative exposure assessments will be performed and regarded as completed, before refined data on nonfood pathways are obtained.

Agency Response: OPP intends the cumulative risk guidance to impart to the reader an understanding of the basic concepts underlying the conduct of a cumulative risk assessment and to point out issues that must be addressed in the assessment. The specifics of combining routes of exposure will vary considerably from case to case depending upon the nature of data available for characterizing and estimating exposure. As such, the guidance is not intended to be a "how-to document" for the conduct of cumulative risk assessments. Rather, the details of each assessment will be determined on a case-by-case basis. OPP anticipates that, for the foreseeable future, cumulative risk assessments will be subject to a public comment period to allow critique of methods and data used, much as the OP aggregate assessments have been. In this way, OPP anticipates that the cumulative risk process will expand with experience, with the public developing an awareness of the necessary considerations and methods as they continue to develop. A detailed example of the process by which different routes of exposure may be combined was presented in the Cumulative Risk Assessment Case Study that was presented to the SAP in December, 2000. Further examples will be come available as OPP begins the task of performing cumulative risk assessments for regulatory purposes and requests public comment on those assessments.

6.A.7 Comment: IWG recommends that EPA acknowledge the principle that there may be a need for more than one round of both aggregate and cumulative assessments. EPA should embrace the idea that it can perform a single chemical assessment or multiple chemical assessment on the exposure pathways for which it has reliable information at a particular time, and later perform reassessments when it obtains reliable information on additional exposure pathways. Doing so would allow the description of the assessment processes could be greatly simplified. EPA also should embrace specifically in the cumulative risk content—as it has in other areas—the idea that it may determine a risk to be acceptable by use of worst-case exposure assumption even though it cannot use such assumption as the basis of a finding that an exposure for a tolerance is unacceptable.

Agency Response: OPP anticipates that in some cases, it will prepare more than one cumulative risk assessment for the same CAG, with subsequent versions incorporating data to permit more realistic estimates of exposure or hazard. This may occur either because the initial cumulative risk assessment only provided screening estimates of exposure or because new studies became available after completion of the initial assessment. In general, OPP agrees with the commenter that it will not base its regulatory decisions on a screening level assessment when data are available to conduct a more realistic risk assessment.

6.A.8 Comment: WWF (03) comments that EPA's concern regarding drinking water data can be overcome by using real world data instead of the Agency's current conservative estimates. There is currently a great deal of real world data available documenting mean and maximum pesticide residues in various sources of drinking water throughout the nation. EPA could lend credibility to the process by endeavoring to use this real world information for its cumulative risk assessments of pesticides in drinking water, rather than awaiting the development of speculative modeling data. NRDC (L05) supports the use of water modeling to set priorities for further drinking water monitoring studies. However, the Agency's long-term goal should be development of a database of actual residues in drinking water on a regional basis that can be incorporated directly into Monte Carlo assessments of exposure and risks, with drinking water treated in essentially the same way as other foods and drinks. However, until such data are available, FQPA requires EPA to retain an added safety margin to account for possible water-based exposures.

Agency Response: OPP is committed to improving its models for estimating water concentrations of pesticides. This process involves the use of properly collected monitoring data to support the construction of accurate, prospective models that will permit detailed estimation of anticipated pesticide concentrations both from existing uses and new uses of pesticides. OPP anticipates the release of a guidance document outlining a tiered approach to estimation of drinking water concentrations using existing models. The outputs of the models will be compared to existing monitoring data as a part of the risk characterization process. In the meantime, OPP will continue to pursue methods development and, as new methods become available, to incorporate them into the risk assessment process

6.A.9 Comment: CU (08) argues that FQPA provides a clear remedy when the Agency feels that the available data and methods are unreliable–impose an additional UF. Accordingly, the Agency should include such additional exposures and chemicals in a cumulative risk assessment by some combination of three actions: (1) reserve a portion of the 'risk cup' for uncertain exposures and risks; (2) estimate such exposures and risks with the best data/methods available; and (3) impose an added group UF to account for these additional exposures and risk.

> **Agency Response:** OPP currently takes steps in its single-chemical assessments to ensure that estimates of risk do not understate risk potential. These steps include seeking the best available data for use in assessments and, where data are limited, using surrogate data for similar use patterns or using health protective, data driven assumptions to estimate exposures. OPP will use the same types of processes in conducting cumulative risk assessments to ensure that it can meet the standard of reasonable certainty of no harm required under FQPA. Nonetheless, any remaining uncertainties regarding exposure will be considered in OPP's FQPA SF analysis.

6.A.10 Comment: CEHN (10) comments that the Agency needs to describe how it will deal with the differential quality and quantity of data while attempting to use a weight-of-the-evidence approach.

> **Agency Response:** The risk characterization phase is the appropriate place in the risk assessment to make overt issues of differential data quality and the potential impact on the results of the risk assessment. The risk assessment should present the best estimate of risk that can be developed with the available data. The application of risk management judgments should be made in light of all of the many considerations of data quality and potential biases or uncertainties in combining the data during the risk assessment process.

6.A.11 Comment: CEHN (10) comments that given the fact that quantitative inclusion of exposure to pesticides in drinking water will be limited for the near future, EPA must fund additional research in this area so that the data gaps can be closed as soon as possible.

Agency Response: OPP believes that it currently has sufficient information about most pesticide active ingredients to generate model-based estimates of pesticide residues in surface water and ground water. Using these estimates, together with monitoring data, OPP expects that there is an adequate basis to develop estimates for inclusion in upcoming cumulative risk assessments. Nonetheless, as noted above, OPP is constantly seeking to improve its methodology, and therefore is providing substantial support for ongoing research by USGS into improved modeling techniques. In addition, when OPP identifies data gaps for specific chemicals, it requires the appropriate pesticide companies to generate the necessary information.

6.A.12 Comment: The commenter (CEHN-10) is pleased that EPA is recognizing the importance of geographic variation. In addition, the commenter believes that the Agency also needs to factor in the differences in origin of foodstuffs by season of the year.

Agency Response: OPP has extensive experience with analyzing both the Continuing Surveys of Food Intakes by Individuals (CSFII) and PDP data that provide the underpinnings for the food risk assessment. Our experience with the CSFII data indicates that overall there is little impact on consumption due to import of commodities from abroad and extensive storage capabilities, making most commodities available throughout the entire year in either fresh or processed form. In addition, PDP suggest only modest variation in residue levels within most commodities across seasons. OPP is confident that seasonal variation and source are minor contributors to the variability in risk throughout the year.

6.A.13 Comment: NRDC (L05) points out that in considering geographic variation in exposure EPA has failed to consider one of the most obvious sources of geographic variation in exposure: children's exposures in or near farms. Exposure sources common to agricultural communities (and currently largely ignored by EPA's risk assessments) include, among other things: spray drift, higher indoor concentrations of pesticides, contaminated soil in play yards, parks, and playgrounds, etc.

Agency Response: The cumulative guidance document calls for consideration of significant sources of exposure. EPA is working to improve its ability to evaluate significant sources of localized exposure from all appropriate pathways.

6.A.14 Comment: NRDC (L05) states that instead of making a determination up

front about which exposures and chemicals to exclude from the cumulative risk assessment, EPA should include in the assessment at a minimum all dietary exposures and all foreseeable nondietary exposures in water and urban, residential, and agricultural settings from existing uses, focusing its effort toward refining assessments and crafting risk mitigation measures on known risk drivers.

> **Agency Response:** The issued guidance requires that all sources of exposure should be considered initially. It then points out that insignificant contributors to risk should be excluded only for cause so that a more realistic estimate of exposure and risk can be made.

6.A.15 Comment: NRDC (L05) commends the Agency for recognizing that the data supporting dietary exposures and risk are typically of high-quality and adequate to support refined assessments of the risks stemming from this key pathway. The commenter also agrees that EPA should base dietary risk assessments on all the residues found on an individual food sample, or in an individual sample of drinking water. And, the commenter supports the Agency's proposal generally to not use field trial data in estimating exposures in a cumulative assessment.

The commenter added that in the interim, in cases where EPA determines that there is inadequate dietary exposure data relevant to all food uses being considered in a cumulative assessment, FQPA provides the Agency with clear-cut direction on what to do: it should retain the added margin of safety to better protect infants and children.

> **Agency Response:** EPA agrees that an important consideration in determining the FQPA SF is the completeness of the exposure data. Thus, OPP would consider retaining the default FQPA SF unless the best available data and assessment methodologies do provide confidence that exposure to infants and children is appropriately estimated. See response to comment 3.B.4.

6.A.16 SAP Comment: The SAP (December, 1999) indicated that when conducting a cumulative risk analysis that utilizes data from multiple sources of different strengths, the data quality should be clearly stated and the input parameters documented regarding quality and reliability of data. If the data are quantitative, they can be used to weight the results of the assessment using methods analogous to the dose response assessment. Alternatively, qualitative data should be assigned at the point the data enters into the assessment and the quality labels used to assess the overall process in the risk characterization step. Given the lack of data in either event, it will be necessary to develop and use

models that propagate uncertainty and distinguish that from variability to perform quantitative estimates of exposure and effectively use existing input parameters.

As new quality data become available where they were absent for pathways leading to exposure, a reassessment should be conducted. The Agency should develop some criteria or process that permits reassessment, e.g., it might be stated in the initial assessment when and under what circumstances this might occur.

There will always be considerable variance in the quality of data that are combined to estimate cumulative exposure and risk. Data quality thresholds should be established for each pathway and when these are not met, default assumptions that are conservative (i.e., that assume high exposure) should be used to estimate exposure and risk. Within each pathway where numerous types of data are often combined, quality thresholds should be defined for each type. If the quality threshold is not reached, the Agency should revert to conservative default assumptions. The effect of such defaults should be tracked using uncertainty analysis to make evident the contributions of defaults and to point out places where provision of further data could significantly alter and improve the analyses.

In designing the process of assessing cumulative risk, it would be beneficial to describe more useful categories than merely food, drinking water, and residential, since there are many potential exposure scenarios within each of these pathways. It is likely most useful to frame the analysis in terms of sensitive subpopulations and devote resources to better characterizing the uncertainties for the sensitive subpopulations. Use of initial scientific judgement on chemicals and pathways would allow the Agency to devote resources to “worst-first” cases, so that the most egregious potential errors from combining data of varying quality could be avoided.

Available data will always be uncertain reflections of real-world patterns of exposure. Given this conclusion, the Agency should use the best available data and attempt to estimate the magnitude of uncertainty as best it can for each type of data employed in the exposure assessment. The capacity to test the sensitivity of its exposure estimates to differing assumptions and different data sets should be developed. This should be done in a way that is transparent and graphic. The Agency might consider the construction of a simple spreadsheet model that would identify each factor that contributes to exposure and risk. Such a model could easily allow the user to change assumptions or data sets, while viewing the effect upon total exposure graphically. This type of interactive sensitivity analysis quickly demonstrates the relative importance of different contributing factors. The Agency should strive to reduce uncertainty among variables that contribute significantly to cumulative exposure.

Agency Response: OPP is committed to using the best available data and methodology for estimating risk. OPP agrees that the uncertainty in a cumulative risk assessment should be characterized to the extent possible. At this time, a qualitative scheme such as proposed by the SAP is a reasonable approach to characterizing the uncertainty until quantitative methods are available. Assessments will be revisited as new applications for use or new active ingredients are submitted for registration. In addition, reregistration actions will be revisited on a periodic basis to permit updating of the assessments and incorporation of new data and up to date use information.

OPP is committed to seeking the best data available for inclusion in all risk assessments. Where surrogate data from another chemical is of better quality and is a reasonable substitute for chemical specific data of lesser quality, it is often used to improve the accuracy of the risk assessment. OPP acknowledges that risk assessments must often address a variety of concerns regarding differences in exposure experienced by a variety of subpopulations, some with unique exposure considerations. As a result, OPP risk assessments evaluate a number of age groups, both genders, regional aspects of residential and water exposures and a number of sub-scenarios that further break down the larger areas of food, drinking water and residential exposures. The process by which special subgroups are identified will continue to improve as OPP gains experience in this area. Current OPP assessments attempt to incorporate the full range of exposures from as many sources as can be accommodated to ensure that sensitive subpopulations are represented in the risk assessment. OPP agrees that sensitivity analyses will be an important tool in ensuring that the most important aspects of the risk assessment receive priority in data development and are subjected to the appropriate level of scrutiny in the risk characterization process.

6.B Determining Residue Levels and Co-Occurrence

6.B.1 Comment: The draft guidance suggests that model-based estimates of pesticide concentrations in raw water may be useful, not only for determining levels of individual compounds but also for measuring frequency and levels of co-occurring CMG compounds. IWG (06) believes that this statement is overly broad and perhaps promises more than current modeling ability allows.

> **Agency Response:** OPP recognizes the difficulties in determining co-occurrence using modeling of pesticide concentrations in water and agrees that great care needs to be exercised when making estimates of co-occurrence of pesticides in water. However, OPP has extensive data describing the use of pesticides on crops across the U.S., including the times of application and re-application, the rates of pesticides applied and the pest pressure prompting the applications. Using such data, OPP believes that it is reasonable to estimate the likelihood of multiple pesticides being applied in a given area at the same time. In addition, these data permit estimation of likely applications in any particular area throughout the year, permitting development of an annual profile of likely water concentrations. In conducting a cumulative assessment, OPP will use these data to provide the best possible estimate of co-occurrence and produce a reasonable, health-protective estimate of co-occurring pesticides and the resulting risk. Existing monitoring data and the recorded occurrences of multiple pesticides in those data will be used as a check on the accuracy of developing methods. OPP anticipates that it will seek public comment on, among other aspects of its cumulative risk assessment, the manner in which it has employed use data to estimate co-occurrence.

6.B.2 Comment: The commenter (IWG-06) questions EPA's ability to establish co-occurrence, stating that the type of data needed to do this may not exist.

> **Agency Response:** See response to Comment 6.B.1. OPP agrees that in many cases data which demonstrate co-occurrence may not be available or are very limited. The guidance document describes the kinds of data and information that can be used to determine the likelihood of co-occurrence in water.

6.B.3 Comment: Novartis (04) supports the Agency position that the use of monitoring data (e.g., PDP, FDA compliance testing, or market basket data) in which co-occurrence was measured provides the only basis for conducting a cumulative food exposure assessment that describes co-occurrence with any degree of certainty. EPA currently lacks a reasonable, defensible methodology for estimating overlapping pesticide residues occurrence *for water*. Such methodology would have to extrapolate from data on use areas, use rates, season of application and many other factors. The combination of these conservative residue values would be highly speculative and introduce sufficient uncertainty as to make the cumulative risk assessment unreliable for regulatory purposes.

> **Agency Response:** See response to Comment 6.B.1 and 6.B.2. While preferable, OPP does not agree that monitoring data which measures co-occurrence in food is **the only** basis for conducting a cumulative risk assessment. The use of residue field trial data along with other information on actual use rates, use areas, frequency treatment and other factors will allow for approximations of co-occurrence and cumulative risk. Although actual monitoring data would provide more refined estimates, estimates based on residue field trial data are still useful for identifying importance sources and contributors of cumulative risk. Alternatively such assessments may better guide what monitoring data are needed.
>
> Furthermore, OPP believes that the use and adaptation of existing modeling techniques will permit reasonable, descriptive estimation of pesticide residues in drinking water. OPP will issue guidance on refining existing estimates later in FY2002. In the meantime, OPP is committed to developing more refined modeling techniques using monitoring data to support the process. The extent to which existing techniques introduce bias or uncertainty into the assessment will be described in the risk characterization.

6.B.4 Comment: Novartis (04) notes in their comments that EPA believes that USGS National Water Quality Assessment Program (NAWQA) databases of pesticides in ambient surface water might provide evidence of co-occurrence of pesticides in tap water. However, most of these data are from sites that are far from CWS intakes and thus are not very predictive of tap water levels. Novartis further notes in their comments that they agree with EPA that it is desirable to use direct measurement of pesticide concentrations in tap water. However, increasingly a single source of tap water does not supply all or even most of the water consumed by an individual. The guidance document states that measurements of “pesticide concentrations” in raw water with adjustments for the effects of blending and treatment can supplement direct tap water

measurements. Novartis agrees that this approach should be used as a lower tier screening tool, if raw water is defined as water sampled at or near the CWS intake (rather than e.g., in small streams far from the intake), and if adjustment for blending/treatment are done properly. Under such conditions, Novartis thinks that monitoring of CWS intake water could be used for estimating levels of individual compounds at the monitored sites (and also, perhaps, at other similar sites for which the monitored sites can serve as surrogates), and for estimating the frequency and levels of co-occurrences of CAG compounds in finished drinking water derived from raw water from the monitored sites. Finally, Novartis points out the statement in the guidance "information on the use of different pesticides within the same geographic region combined with information on the timing of use and the fate and transport properties of these pesticides can also be used to identify pesticides which are likely to co-occur." This statement is only true if "geographic region" is equivalent to "watershed" and only if co-occurrence is defined in chronic, rather than acute terms, and only if the likely levels of the co-occurring pesticides need not be known. The implication is that if some degree of co-occurrence at a site by any means can be established, the details of the exposure assessment (time of overlap, concentration levels at various times) can be derived from unrelated information on levels of two or more individual pesticide levels and subsequently be combined and treated as if the residues actually co-occurred on a given single data. This is not evidence of co-occurrence, but merely the possibility of co-occurrence

Agency Response: See response to Comments 6.B.1, B.2, and B.3.

6.B.5 Comment: Another commenter (BPFJF-05) believes that EPA must assume that exposure occurs at worst-case tolerance levels because this level encompasses the widest range of people (i.e., if the worst case is protected then we all are protected). There are also important environmental justice issues associated with consideration of a worst-case scenario. To support this "worst-case" exposure argument, the commenter points to several populations that are not represented in risk assessment (e.g., occupational workers, homeless people, homeowners who do not read the label, people exposed through drift). Also, the commenter argues that EPA's assumptions about risk mitigation in occupational exposure assessment and real-world exposure in food exposure assessments may not be realistic, and will result in underestimates of exposure.

Agency Response: The use of "worst case" estimates of exposure (e.g., tolerances) provides a very rough indication of the upper-bound (or above) of potential risk. Combining multiple "worst case" estimates would represent a significant overestimation of potential exposure that would be far from accurate. In addition, OPP notes that its exposure assessments do consider homeowner exposure and exposure to bystanders occurring through pesticide drift. Occupational exposures are excluded from cumulative risk assessments.

6.B.6 Comment: One commenter (ACC-02) urges EPA to take great care in identifying concurrent exposures. Not only must reasonable scenarios be constructed that determine if exposures can overlap in time and place, but the exposure assessment must take into account each chemical's half-life to determine if common mechanisms of toxicity are operative from previous exposures.

Agency Response: OPP agrees. The guidance document discusses the need to use all available sources to determine whether co-occurrence is likely in a given water source. Scenarios that reasonably account for physical/chemical properties, transport properties, as well as the special geographic and temporal aspects of pesticide usage should be constructed. The scenarios should also account for durations of both exposure and the toxic effect being studied.

6.B.7 Comment: CEHN (10) agrees that exposure to pesticides in drinking is a local to regional concern; however, the commenter notes that it is important that EPA recognize the differences in water consumption between adults and children.

Agency Response: OPP agrees. OPP includes differential water consumption between adults and children in all of its risk assessments including any assessment of cumulative risks.

6.B.8 Comment: CEHN (10) is concerned that EPA seems unwilling to use models that incorporate high-end estimates. Children are more likely to be the population with higher exposure levels. The Agency must look from the perspective of the possibly most exposed infant or child, not the average child or adult.

Agency Response: OPP intends to use the most accurate, descriptive data possible in its cumulative risk assessments. OPP intends, to the extent possible, to use the full range of input values in its assessments, incorporating values from the highest to the lowest as indicated by available data. Thus, when "high end" residues or consumption values are indicated in the available data, they will generally be included in estimating cumulative exposures and resulting risks.

6.C Reducing Uncertainty About Exposure Values Derived From Screening Approaches

6.C.1 Comment: One commenter (PMRA-L02) suggests that if probabilistic assessments are used, perhaps the uncertainty could be quantified by performing two-dimensional analyses. In cases where only a few parameters of the analysis are not well defined, an attempt at quantifying the uncertainty around these parameters may result in useful information. For example, such an exercise may demonstrate that those parameters that possess a considerable amount of uncertainty do not significantly affect the outcome.

Agency Response: OPP agrees that two-dimensional probabilistic analyses are desirable. The guidance document discusses the need for characterizing the uncertainties involved with each input parameter used in the cumulative risk assessment as well as performing sensitivity analysis on the results of the cumulative risk assessment.

6.C.2 SAP Comment: The SAP highlighted the problem of very detailed estimates with worst-case or screening level estimates. They suggested that this difficulty could be quantitatively addressed by replacing point estimates derived by traditional procedures with distributions reflecting both: (1) any tendencies for systematic "bias" due to built-in conservatism; and (2) quantitative estimates of uncertainties. The translation from screening level assessments to appropriate uncertainty distributions can be made in part by comparing the results of screening level assessments of exposure with more thorough and detailed measurements for selected chemicals by similar routes. Two approaches offered were: (1) excluding a route of exposure that is suspected to deliver appreciable amounts of the chemical of interest in the cases of some people; or (2) adopting the screening level value as if it were a central tendency estimate applicable to the population studied more extensively via the measurements.

The Panel suggested that OPP put substantial effort into estimating the uncertainties and evaluating their impact on the results. No point estimate should be used if it lacks an associated statement about its uncertainty. The Panel recommended against using screening levels as input values in the cumulative assessment. Actual monitoring data should be used where appropriate.

Agency Response: OPP agrees that a cumulative risk assessment can not be performed by simply combining screening level assessments. The cumulative risk guidance clearly specifies this concept. The variability and uncertainty surrounding each parameter in the assessment should be clearly described as a part of the risk characterization. OPP anticipates adopting a qualitative scheme similar to that described in the SAP comment above (see 6.A.13) wherein a ranking of uncertainty is assigned to each parameter. In addition, each parameter should be included as a distribution to the extent possible. Where necessary, the parameter should be included as a uniform distribution to reflect the range of possible values.

6.D Scenario Building and Methods for Estimating Cumulative Risk Associated with Multipathway Exposure

6.D.1 Comment: The commenter (IWG-06) points out that in identifying residential exposure scenarios, EPA has already given some consideration to simplifying steps. IWG believes that the Agency should go even farther and consider using a tiered, screening approach. Under such an approach the initial assessment would look only at the apparently high-end exposure scenarios. A more extensive analysis would be needed only if the initial screening did not demonstrate clear acceptability of cumulative risk.

Agency Response: OPP generally agrees, and will consider using some screening level estimates in its cumulative risk assessments to identify exposure scenarios which are significant or insignificant contributors. OPP revised its guidance to reflect the value of selective use of screening approaches.

6.D.2 Comment: IWG (06) contends that in aggregate and cumulative risk assessment what constitutes a scenario appears to be totally undefined.

> **Agency Response:** Although the term is not explicitly defined, the concept of an exposure "scenario" is discussed in both OPP's science policy paper setting out its general principles for conducting aggregate risk assessments and in the cumulative risk assessment guidance document. In general, the term means a particular way of using a pesticide (i.e., its use pattern), together with a particular set of human behaviors, that results in exposure of a subpopulation of individuals by a particular route (i.e., oral, dermal, or inhalation).

6.D.3 Comment: IWG (06) points out that the draft document does not discuss how scenario-building should work, except in very general terms. Several different scenario-building software packages for use in aggregate and cumulative assessments are being developed. Until better data are available on human behavior and nondietary exposure parameters, estimates will be crude no matter how good the software is. A great deal of work is underway to gather data that will be usable in these models. Once these new software programs and exposure databases are better understood, and in particular once it becomes understood how the programs use the data and when and how they must still incorporate assumptions, stakeholders will be able to comment more knowledgeably on the Agency's approach to aggregate and cumulative risk assessments and on the extent to which such assessments are likely to be reasonable.

> **Agency Response:** OPP agrees that scenario building is done on a case-by-case basis for most aggregate and cumulative risk assessments. This is necessary both because of the variety of pesticide products that OPP regulates and the early stage of development of software programs to assess their risks. OPP does not agree, however, that the case-by-case character of its exposure scenario building means that the resulting estimates are necessarily either crude or unrealistic.

6.D.4 Comment: CEHN (10) provided specific language to make paragraph 4.2.1 "General Principles" more appropriate for children. Accordingly,

"*Four* key pathways of exposure to pesticides are: food, water, *dermal and respiratory* and other non-occupational exposures....or subpopulations of interest. *For infants and children, this must include their specific eating patterns. It must recognize the consumption of breast milk and or formula in the first year of life. It must recognize their limited repertoire of foods throughout the childhood age span. For infants and children, there must also be recognition of the consumption of chemicals on a mg/kg basis to account for their smaller size.* The likelihood and frequency assumption for residential scenarios would be used to superimpose a pattern of residential exposures that would reasonably be expected to occur throughout the year for an individual in the population. *For infants and children, the residential scenarios must take into account their specific behaviors –hand to mouth activity, more time on or near the floor, greater dermal contact with the flood* [sic]*, carpets, grass, etc.*"

> **Agency Response:** OPP acknowledges that the referenced issues are important considerations in conducting a risk assessment for infants and children. The eating behavior of children is specifically addressed by the use of consumption records for children taken from the CSFII. In addition, exposure scenarios for residential and institutional pesticide uses are currently derived from the Residential Exposure SOPs. The scenarios specify the use of exposure parameters and behavioral factors that are age appropriate for the subpopulations undergoing evaluation. As such, OPP did not deem it necessary to elaborate further on these factors as they have been outlined in a number of previous OPP science policy documents.

6.D.5 Comment: CEHN (10) is pleased to see that the Agency recognizes the importance of age/gender/pathway considerations in cumulative risk assessment. However, the Agency needs to be more explicit in the document with respect to children and the fact that their nondietary ingestion patterns and dermal exposures are different from those of adults.

Agency Response: OPP agrees with the commenter that children may receive different and potentially higher levels of exposure than adults. In recognition of this difference, OPP's Cumulative Risk Assessment Guidance cites the Residential Exposure SOPs. These SOPs describe a number of scenarios which clearly differentiate the exposures experienced by adults and children, including both children's nondietary ingestion and dermal contact with outdoor and indoor surfaces that may have levels of dislodgeable pesticide residues.

6.D.6 Comment: Novartis (04) notes that June 2000 Cumulative Risk Guidance does not discuss the specifics of exposure scenario building except in very general terms; and that there exist, for example, a large number of different possible outdoor and indoor uses of pesticides in and around residences and building a scenario that encompasses the various possible choices could entail large numbers of distributions. Software packages are being developed or have been recently completed by different private organizations which may use different basic approaches, employ different inferences and assumptions and use different databases, and /or use a given set of data in different ways.

Agency Response: See response to 6.D.3.

6.D.7 Comment: Novartis (04) thinks that at the present time there is still no established method for linking information derived from multiple data sources to estimate the total of an individual's exposure and at the same time account for the spatial and temporal congruity of the exposures. IWG and Novartis indicated that their organization was developing a software tool (i.e., CARES) for accumulating exposure across multiple pathways, and thus encourage the Agency to acknowledge this project and to regard CARES as a viable alternative to other software tools. Thus, CARES should be included in a thorough evaluation of all available risk software in identifying the best methods to address the mandate of FQPA.

Agency Response: OPP welcomes the development of additional software models to combine data in aggregate and cumulative risk assessments. OPP has used CALENDEX™, a proprietary program developed by Novigen Sciences Inc., and has encouraged the development of LifeLine™, another software program that is publicly available. Both programs have undergone peer review by the SAP. OPP believes these two models offer effective ways of linking information for multiple data sources to produce realistic estimates of exposure.

6.D.8 Comment: One commenter (PMRA-L02) indicated that the guidance was unclear as to how individual or daily MOEs are to be combined, and that a clearer explanation or reference to the aggregate guidance document was needed.

Agency Response: The reader is referred to the cumulative risk case study presented to the SAP in December, 2000 as well as to the aggregate guidance document in which this question is specifically addressed.

6.E FQPA Interpretation of "Reliable Information"

6.E.1 Comment: IWG raised the issue of data availability and quality, and the basis for combining exposures across multiple pathways in the context of what FQPA says. IWG (06) points out that the law allows EPA to include exposure from any nonfood pathway (such as drinking water or residential pathway) in an aggregate risk assessment only to the extent that the Agency "*for which there is reliable information*"–FFDCA section 408(b)(2)(A)(ii)–on the levels of exposure through that pathway. Thus, when EPA is assessing cumulative exposure, IWG does not think the law allows it to consider information that it cannot consider when assessing aggregate exposure to single compounds. Furthermore, IWG notes that the law does not say that EPA shall "base its assessment of the risk" on information on combined toxic effects; it only says that EPA shall consider available information on such effects, among other factors, when it is deciding whether aggregate exposure meets the statutory criterions. IWG further discusses what kinds of information can be considered "reliable" for particular purposes. A set of information may be "reliable" for screening purposes but not reliable for an estimate of actual exposure. IWG further states, however, that it is inappropriate for EPA to continue to use upper-bound, worst case exposure estimates, combined with refined information on exposure via food in low-tier screens.

Agency Response: OPP has addressed these comments as part of the document containing OPP's responses to comments on the Aggregate Risk Assessment Guidance (USEPA, 2001e). OPP incorporates those responses into this document, by reference.

6.F Extrapolating from Other Data When PDP Data Are Unavailable

6.F.1 Comment: CU (08) supports the use of residue trial data coupled with use data when other data are not available.

Agency Response: The use of residue trial data coupled with use data may be acceptable if these data are used to estimate food exposures for all members of the CAG. The FIFRA Scientific Advisory Panel has advised the Agency that it would not be appropriate to mix data sets such as using both monitoring data and crop field trials because the blending of data sets would not provide credible estimates of cumulative risk. The blending of the data could give disproportionate weight to commodities with little actual contribution to the cumulative risk. In this way the combining of data would obscure the more important contributors making the results of the assessment difficult to interpret. OPP realizes that future data limitations may make it necessary to adapt field trial data for use in cumulative assessments. OPP will continue to seek methods for use of this data in a cumulative setting.

6.G Using Monte Carlo Technique for Children's Exposure

6.G.1 Comment: NRDC (L05) believes that cumulative risk assessments must not be based upon Monte Carlo simulations that incorrectly assume what a child eats on one day is independent of what they eat the next day, or that wrongly assume the residues on an apple or particular food consumed in the morning are independent of the residues on another apple or the same food later in the day.

Agency Response: OPP uses as inputs to its risk assessments the most up-do-date and comprehensive data available. This includes the use of the 1994-96/1998 USDA CSFII data which incorporates reported consumption practices of many thousands of persons as well the USDA's PDP which samples and analyzes thousands of commodities each year.

With respect to the commenter's first point, the commenter is correct in that for any assessments that are done on a rolling time frame there are a limited number of diets to choose from since longitudinal consumption data are not available (the CSFII data only has consumption data available for two, non-consecutive days). Since any biases that this may or may not introduce are very dependent on the *type* of dietary analysis being done (e.g., single day vs. multiple consecutive days), these should be fully discussed in any risk characterization.

With respect to the commenter's second concern regarding an assumption that the residues on particular food consumed in the morning are independent of the residues on the same food later in the day, this is not correct. As explained more fully in the response to comments to "Choosing a Percentile of Acute Dietary Exposure As a Threshold of Regulatory Concern" (USEPA, 200f) each commodity consumed during the day (regardless of the number o times in a day it is consumed) is assumed to contain the same residue. This issue was originally raised during the discussion of the threshold of regulatory concern policy. An excerpt from this response to comments is presented below:

> OPP recognizes this issue [of independence of residues] and notes that there are two basic ways a model can account for this. One way (as is currently done and described above by the commenter) is to assume, for example, that all fresh apples eaten by a given individual in a given day contain the randomly assigned residue concentration. A second method assumes that each fresh apple eaten by a given individual on a given day is randomly picked and is independent of the residue concentration in any other apple consumed by that individual on that day 17. The first method is more consistent with consumed apples being from one source and sharing the same treatment history (i.e., each fresh apple eaten by a given individual in a given day is from the same bag of apples purchased from a grocery store, each baked apple eaten by an individual in a given day comes from the same apple pie, etc.) and is most appropriate when the residue values selected are composite values (an average of many items). The second method is more consistent with each apple consumed in a given day by a given individual being independently acquired from different sources (i.e., no apple consumed necessarily shares the same treatment history). The DEEM™ version currently used by OPP uses the first method, but a recent software update permits the second method (where only items consumed during a given eating occasion are assumed to share the same treatment history) to be used as well. OPP will accept analyses performed with both models. In these cases, OPP will consider the result from both analyses in making a decision and characterize the results. To date, comparison of results using both methods do not suggest that differences are significant.

ISSUE 7. Deferral Criteria

OPP is proposing that deferral criteria be applied to ``negligible" sources of risk in a full cumulative risk assessment (65 FR 40649). OPP believes that this approach will permit a better focus on the more important sources of risk. It will also assist the risk manager in understanding and evaluating sources of risk that may provide the greatest benefit with risk mitigation activities.

Question 7.1: Please comment on whether the deferral criteria discussed in Chapters 4 and 6 appear to be reasonable. Are there other exclusionary criteria that should be considered?

Question 7.2: Should OPP establish more specific criteria, for example, not only the magnitude of the exposure resulting from a particular chemical, use pattern or pathway, but also the size of the exposed population group?

7.A Establishing the Cumulative Assessment Group from the Common Mechanism Group

7.A.1 Comment: IWG (06) suggests rewording the following language, which is found on page 34 of the draft document, to make it clear that overlapping exposure covers the most basic case. The most basic case is that of residues of multiple chemicals from the same source and pathway (e.g., exposure during one meal to a single food that has residues of two CMG pesticides).

EPA will determine whether the combination of exposure scenarios identified present any likelihood of overlapping exposures to multiple chemicals in the CMG. Exposures are considered to overlap if chemicals are likely to be encountered from more than one source or pathway within the time frame in which the common mechanism effect is still operative from previous exposures to other chemicals in the CMG.

Agency Response: OPP agrees with the comment. The guidance document has been revised to clarify that the risk assessment should address exposures which occur sufficiently close in time that the effects of the combined exposures is expected to exceed the effect of any single exposure.

7.A.2 Comment: WWF (03) called for EPA to remove the exclusionary criteria for minor pathways and indicated that the quantitative cumulative risk assessment should strive to be as inclusive as possible. NRDC objects to EPA's proposal that "initial cumulative assessments should not attempt to quantify risk resulting from minor exposure pathways."

Most commenters (PMRA-L02; Novartis-04; IWG-06) were generally supportive of the criteria of defining a CAG from a candidate common mechanism group. Novartis agreed with the draft guidance document that only those chemicals that are significant contributors be included in the cumulative risk assessment. Several commenters, however, did raise issues about further clarification. PMRA indicated that the document needs to clarify that exclusionary criteria should be met for all uses to exclude an entire chemical from the cumulative risk assessment. Novartis and IWG indicated that there needs to be more discussion and examples on the exposure assessment steps (such as the criteria for determining the likelihood of concurrent exposure) to define the CAG. Because the CAG selection process is discussed in various places of the June 2000 Cumulative Risk Guidance, IWG suggested the use of a flow diagram outlining the major steps concerning hazard and exposure characterization, pharmacokinetic/time-course information, and dose-response characterization. They further suggested that the diagram be expanded to explain other critical input steps such as when adjustment/safety/UFs are applied, and when chemicals are deferred, as well as when subpopulations are identified for the risk assessment. The diagram also could show at what points critical feedback is needed, e.g., as stakeholders review or science peer review.

Agency Response: OPP believes that removal of specific chemicals or specific pathways, routes or pesticide uses from the quantification of cumulative risk is an important step in the cumulative risk assessment process because it may significantly simplify the risk assessment to identify and exclude use scenarios that make at most negligible contributions to the overall risk. Instead, cumulative risk assessments should focus on those chemicals and exposure scenarios that are likely to be risk contributors and that may truly require mitigation actions and have an impact on risk reduction. This focus on likely risk contributors is important because the uncertainties and biases for even a small number of chemical components of a mixture can be substantial. When cumulative risk is assessed, a large number of chemicals may increase the complexity and uncertainty with no substantial change in total exposure. Additionally, including a large number of chemicals in the refined quantification of risk also may confound the interpretation and utility of the assessment results for risk management decisions. Although an entire chemical, a route or pathway of exposure, or a particular use may not be included in the final quantitative risk assessment, the guidance document indicates that all chemicals, routes or pathways, and uses

should at least be qualitatively assessed. The guidance document further states that it is critical that all CMG chemicals and their exposure scenarios are accounted for in the cumulative risk assessment. Furthermore, the guidance indicates that the exclusion of negligible contributors may be prudent, caution should be exercised such that excluded chemicals do not constitute a major portion of the total risk. Thus, the guidance is intended to assure that the cumulative risk assessment will be comprehensive

7.A.3 Comment: IWG (06) indicated in their comments, as understood from the July 2000 Technical Cumulative Risk Briefing on Cumulative Risk Assessment, that many CAGs may be identified for a single CMG, and that this would occur because chemicals within a CMG would be assessed for the likelihood of concurrent exposure to any major identifiable subpopulation in terms of: (a) various exposure pathways; (b) various exposure routes; and (c) various exposure durations. Thus, as IWG understand for some kinds of common effects, separate CAGs may be defined for different exposure durations, e.g., acute and chronic, and separately calculated RPFs and group RfDs will be used for each separate exposure duration. The CAG for an acute effect may include CMG compound not included in the CAG for a chronic effect. If some chemicals show common toxicity only via chronic exposure and the exposure information shows that only some of the compounds have use patterns that would result in chronic exposure, the CAG for chronic dermal exposure would exclude all of the compounds. Likewise if all of the compounds in a CMG demonstrate chronic oral toxicity but only three of them have uses that could result in oral exposure, only those three would be in the CAG group for chronic oral exposure. IWG agrees with the Agency's approach.

Agency Response: The commenter's understanding appears to be generally correct. In assessing the potential for cumulative risk from a CAG, the risk assessor must consider the type of effect of concern and the relevant time frame for that effect. Pesticides may elicit more than one type of adverse effect. Each effect may have a different time to effect and/or recovery. To the extent that the different effects warrant separate consideration, they must be considered in light of the exposure scenarios that are most appropriate to the type of effect and time course of events surrounding its onset and recovery. Therefore, as indicated by the commenter, subsets of a CMG might be found in more than one CAG based upon the type of effect under consideration, and each CAG would have its own set of RPFs and POD specific to that effect.

7.A.4 Comment: Regarding the specific exclusionary criteria provided in the draft document, one commenter (ACC-02) discourages the Agency from setting such "bright line" criteria for deferring exposure pathways. EPA should consider

a range of potential minor exposures (for example, pathways that contribute <10%). The decision to include or defer any pathway must be assessed and determined on a case-by-case basis.

> **Agency Response:** OPP agrees that inclusion or removal of a specific chemical, route, pathway or pesticide use requires a careful analysis of each situation on a case by case basis.

7.A.5 Comment: CU (08) questions the wisdom of the CAG from the CMG approach as it may prematurely truncate the scope of the cumulative risk assessment due to shifts in use patterns as the OP and carbamate use profiles change. Until the results of a reasonably complete cumulative risk assessment are available, how will the Agency know whether a given exposure route or chemical adds a trivial increment to CMG/CAG?

Also, CU (08) believes that this approach is inconsistent with the clear intent of the statute. The law requires the Agency to carry out cumulative risk assessments that encompass all pesticides in a cumulative mechanism group and for all routes of exposure. When data are limited or methods are uncertain, FQPA provides a clear remedy–impose an added margin of safety to limit the chances that risks are underestimated.

> **Agency Response:** The guidance document indicates that generally an aggregate risk assessment for each member of a common mechanism grouping should be completed before the cumulative risk assessment is conducted. In that case mitigation actions that change use patterns, use profiles or that remove uses can be considered in the cumulative risk assessment. The statute requires EPA to "consider, among other relevant factors, . . . available information concerning the cumulative effects of [pesticide] residues and other substances that have a common mechanism of toxicity." This language does not mandate that EPA conduct cumulative risk assessments for residues of pesticides in a CMG when exposures to such residues would not be expected to overlap. Further, the guidance is clear that any exposure routes that are excluded from a quantitative assessment must be considered qualitatively.

OPP has not included discussion of the FQPA 10X SF in this document. Instead, a separate document will be issued describing the issues surrounding application of the FQPA 10X SF to a cumulative risk assessment and how this problem differs from application in a single chemical assessment. OPP will request public comment on factors to be considered in developing an FQPA SF decision at that time.

7.A.6 SAP Comment: The SAP (December, 1999) recommended further clarification and definition of exclusionary criteria are needed. The final criteria should serve as deferral arguments that realistically allow the Agency to focus on the real issues of major contributors without being encumbered by detailed analysis of components that have only marginal contributions.

The first criterion is that one may exclude a particular pathway for a specific chemical that "is likely to contribute less than 1.0% of the total exposure." The Panel raised a number of questions about this criterion. What measure of exposure is to be used in calculating the 1%? The calculation of fractional contribution is likely to differ when a short or a long averaging time is in question, so it must be clear whether the pathway's cumulative exposure integrated over the averaging time or a dose rate is intended. The Panel recommended a toxicity weighted exposure be used to account for the difference in potency among the CMG. Otherwise, one may exclude a small exposure (in mg/kg) to a very potent compound and include a larger exposure to a weak agent, even though the first exposure was the larger contributor to cumulative risk. The Panel also suggested clarification as to what population was to be evaluated in using this exclusionary criterion.

In short, a more specific definition of the 1% criterion is needed. In view of the above considerations, the Agency may want to consider a criterion based on a percentage of an allowable toxicity-weighted exposure as the exclusion criterion. For carcinogenic agents, this would amount to a fraction of the acceptable total risk, while for noncancer endpoints it would be a fraction of the "risk cup" (using older terminology). It should probably be expressed as the likely exposure not exceeding X% of the allowable exposure in more than Y% of the exposed population, with both X and Y being fairly small percentages.

The SAP indicated that the other proposed criteria would not be needed if the evaluation of toxicity-weighted exposure was conducted properly. The also noted that the question of exclusion is framed as though the various sources of exposure were fixed. In fact, use patterns may shift and market shares change such that exposures that may have been excludable initially may become relatively greater contributors to total cumulative exposure.

The Panel suggested that it might be helpful to use a priori expectations about the respective sizes of different contributions to allocate modeling resources. The relative magnitudes of the contributions expected from different pathways, routes or chemicals could be used to apportion empirical effort afforded to each. For instance, if prior judgement about a particular pathway is that it contributes very little to the overall cumulative exposure, it would be reasonable to expend little time or empirical effort to get the best possible estimates for the parameters that characterize this pathway. Perhaps even a *relatively* broad interval estimated from the literature would suffice to represent the location and uncertainty about such a parameter. If the value is known to be negligible, then even overestimating the uncertainty would have little consequence for the quantitative results. As the expected magnitude of the contribution through a pathway increases, it would be reasonable to expend more effort to achieve a good estimate of the relevant parameters. It might be decided, for instance, to employ a panel of experts and a formal elicitation procedure to estimate probability distributions to describe the locations and uncertainties about the parameters for pathways expected to have large overall contribution to the cumulative exposure. This kind of structured estimation procedure could be useful in lightening the burden of modeling cumulative exposures.

In addition to better defining the criteria of "exclusion," a comment was made regarding the overall approach to "inclusion," using the case study in exposure as an example. Cumulative risk does not occur just through the co-occurrence of multiple pesticides in a single commodity, but also on the number of pesticides from the CMG that are present in a person's entire diet, which consists of many commodities and foods. Therefore, a better description of inclusion will be helpful for the exposure pathway. It would consist of criteria for commodities and food ingredients based on the variety of foods people eat (i.e., based on the exposure patterns of individuals), rather than the traditional approach for a single pesticide assessment which focuses on pesticide-commodity pairs.

Agency Response: OPP has modified the section on exclusion in the revised cumulative risk guidance, removing the arbitrary value of 1% from the description of the decision-making process. However, the document as currently framed retains the recommendation to work stepwise through the various components of the assessment. Inclusion of these paragraphs are intended as a reminder of the many factors in the assessment that must be considered before a determination is made that a factor can be eliminated from the quantitative risk assessment. In addition, OPP has added a discussion in the risk characterization section of the need to carefully explain the rationale for exclusion and why the decision is appropriate within the confines of a particular CMG and its attendant use patterns.

OPP also agrees with the recommendation to use professional judgement regarding likely magnitude of exposures to determination the level of effort to apply to different pathways/sources. This type of analysis with gain utility as experience is gained in performing cumulative risk assessments. In the meantime, sensitivity analyses will be a valuable tool in addressing this issue.

OPP agrees that the definition of what to include in the assessment is presented in the revised guidance along with discussions of how to combine the various routes and sources of pesticide exposure.

7.A.7 Comment: DPR (09) comments that the criteria appear reasonable. However, some of the criteria "are rather abstract to most readers without extensive experience in pesticide risk assessment. Case studies that present various scenarios would be very helpful."

Agency Response: The guidance document has been revised to better explain the process involved in making a decision to remove a chemical, a pathway, a route or a specific pesticide use from the quantification of cumulative risk. The guidance document provides some general examples of what factors or consideration are involved in such decisions.

7.B Regulatory Status of "Deferred" Chemicals

7.B.1 Comment: IWG (06) comments that in some cases, EPA has taken the position that until the cumulative toxicity evaluation for a chemical within a CMG has been completed, no new tolerances can be granted for the compound. EPA needs to discuss whether that doctrine is still in effect and if so how it would affect the eligibility of a "deferred" compound for tolerances for new uses, etc. To the extent that a"deferral" is in essence a decision that the compound's contribution to cumulative risk is *de minimis* and that resources should not be spent on its regulation, we support the concept.

> **Agency Response:** As explained in the guidance document, OPP intends to use the cumulative risk assessment to identify those uses of a pesticide in a CMG which make, at most, only a negligible contribution to the overall risk. Once such a risk assessment has been completed (and typically following an opportunity for the public to comment on the assessment), OPP takes the position that it may legally declare the tolerances associated with such pesticide uses to be reassessed, notwithstanding that other uses may still be under regulatory consideration.

ISSUE 8. National And Regional Exposures

The potential for people to encounter overlapping exposures to different pesticides will be influenced by many factors. One important consideration is the geographic effects and seasonal uses of pesticides. Thus, a framework is proposed for assessing different pathways of exposure that are essentially driven by these considerations. OPP believes that the food pathway should be approached on both a national and regional scale to account for both national and regional distribution of treated commodities. However, the OPP believes that residential and drinking water pathways are more appropriately dealt with on a regional or multistate basis, since there is no single, national source of drinking water; and residential exposures may be driven by regional use patterns.

Question 8.1: Please comment on whether the concept of developing a series of cumulative assessments on a geographic scale for different pathways is reasonable.

8.A.1 Comment: In general CU (08) sees no reason to conduct a region-specific assessment of exposure as food is distributed on a national basis. However, for hot spots such as water (e.g., atrazine in the Midwest), it may be necessary to conduct regional assessments and incorporate them in the national assessments.

NRDC (L05) points out that each individual's exposure patterns are highly localized. Yet EPA clearly cannot conduct personalized risk assessments on all Americans from conception until death. In deciding how far to proceed toward individual risk assessments, the Agency will have to adopt some basic principles or assumptions and these should be made explicit in the guidance document. While individual exposures may be highly localized, NRDC notes that the tools EPA uses to mitigate dietary risks (e.g., tolerance levels, preharvest intervals, application rates, etc.) are almost all national in scope. Residue data are currently available only on a national basis; thus, dietary assessments have really been done on a national basis. The proposed guidance document needs to clearly describe how EPA intends to improve its tools and risk assessments to address the fact that individuals do vary in their pesticide exposures, including variation due to geographic considerations. Fine tuning of the regional or subnational data and cumulative risk assessments, however, should not serve to delay initial efforts to reduce risks.

Agency Response: OPP agrees. The guidance document indicates that the food component of a cumulative risk assessment should be national but the drinking water and residential/nonoccupational pathways should be assessed regionally. The water and residential/lnonoccupational assessments will then be "superimposed" on or integrated with the food pathway.

8.A.2 SAP Comment: The SAP (December, 1999) indicated to the extent possible, the assessment of residential, nonoccupational, and institutional use patterns should characterize seasonal and geographical variations. These pathway(s) of exposure to pesticides will generally reflect regional use characteristics. In order for cumulative risk assessments to be accurate, the use patterns and practices on a scale sufficient to capture the variability in pesticide use need to be known accurately. However, OPP needs to consider the number of persons exposed for a given scenario, and the overlap of pesticide use areas as they affect the outcome of the assessment.

It seems reasonable to perform national scale assessments for exposures to pesticides in foods. Regional scale assessments for other exposures are worthwhile but are more difficult due to the multiple scales at which data are collected. As has been stated, the sampling frames need to be carefully examined before they are combined. The assessments need well defined and appropriates frames, in order to avoid the problem of combining multiple data sets collected at widely varying scales of aggregation.

The hypothetical scenarios provided for examples A-C (pages 13-14) are helpful in describing possible scenarios that could occur. A case study should exercise the draft guidance by selecting a set of CMG pesticides and performing an exposure assessment with available extant data.

Geography is only one factor in breaking out residential exposure scenarios. Another may be the type of use, for example pet care, that is not geographically driven. OPP should consider the inclusion of user versus nonuser scenarios as a possible break out. The methods used should capture the full variability of cumulative exposures, identify the relative contribution of various pathways, and the relative importance of sources within pathways. This will facilitate the strategic targeting of regulatory practices toward the greatest sources of exposure and risk, within pathways.

Agency Response: As outlined in the revised guidance document, OPP intends to base the use of geographical areas for concentration of risk assessment on pest pressure and climate considerations. Much of the data used to define the use characteristics for the scenarios of interest will be taken from survey data available from a variety of sources that define frequency, rate of application, timing of applications and the myriad other issues that make regional use patterns unique. OPP acknowledges that specific scenarios types may require additional consideration beyond the population-based cumulative risk assessment. OPP will address these types of issues independently to ensure that each type of product use does not present an unreasonable risk when used as directed. This process is already a component of single chemical assessments.

8.A.3 Comment: NRDC (L05) indicates that in nondietary exposure assessment, EPA must move away from the practice of excluding from regional or national assessments extremely localized pesticide use and exposure. FQPA mandates that cumulative risk assessments be performed such that there is a reasonable certainty of no harm to all, including a highly exposed population, and not just a hypothetical average population. It might be appropriate for EPA to restrict the consideration of potential exposures and risks from a nondietary pesticide use under one condition–label restrictions that explicitly limit the use of a pesticide to some specific region and circumstance. The public health implications of even old or seemingly obsolete pesticide labels must be considered under FQPA.

Agency Response: The revised guidance states that for certain routes/pathways of exposure a regional approach to a cumulative assessment should be taken. The assessments are population-based whether exposures are estimated on a national or regional basis.

ISSUE 9. Case Study

Cumulative risk assessment is at an early stage of development. Furthermore, there is very limited experience in conducting such assessments. Thus, the development of case studies using actual data are critical to refining useful and practical guidance, and to identifying future research and testing needs. OPP is taking a stepwise approach to the development of such case studies by starting with simple examples and moving toward more complex situations. Attached is a case study that uses actual food residue data on three pesticides and evaluates only a single pathway/route/duration of exposure. Certain assumptions were made in the case study. In single chemical exposure assessment, for example, nondetects are assumed to be one half the level of detection and composite samples are decomposited. In this case study, for illustrative purposes, nondetects were assumed to be zero, the samples were not decomposited, and surrogate data were not used.

Question 9.1: Given that an important goal of the cumulative assessment is to reliably determine sources of concern from a multichemical exposure, please comment on to what extent is it appropriate to apply standard practices and assumptions used in single chemical assessments.

9.A.1 Comment: Question 9.1 requests comment on to what extent it is appropriate to apply standard practices and assumptions used in single chemical assessments. One commenter (ACC-02) states that the draft document does not indicate which standard practices and assumptions are of concern. Given that cumulative risk assessment is a new risk assessment paradigm, it is essential that all the single chemical assumptions and practices be revisited and not automatically applied in the cumulative risk assessment paradigm. The commenter urges EPA to conduct research on the scientific basis of the assumptions described in draft document. The cumulative risk assessment should be based on solid scientific data, not on assumptions based on poor or no data.

Agency Response: OPP has attempted to clarify in its revised guidance the similarities and differences between aggregate (single chemical) and cumulative (multiple chemicals) risk assessment. OPP agrees that its assessments need to rest on a scientifically sound foundation, but disagrees that it is inappropriate to make assumptions in the absence of data. As discussed in the many science policy documents and accompanying response-to-comment documents, all risk assessment necessarily rely, to some degree, on assumptions, e.g., the assumption that animal toxicity testing predicts human responses or that sampling food for residues for pesticides will represent the distribution of residue levels across the food supply. Therefore the issue is how reasonable an assumption is, not whether to make an assumption in the absence of data.

9.A.2 SAP Comment: Concerns were raised regarding the selection of

pesticides in a CAG. The terms "common mechanism of action" and "common mechanism of toxicity" are used interchangeably without any distinction between them. There is a concern if only the common molecular target of a group of pesticides is considered, without attention to common toxicity symptoms. A common mechanism of action group includes chemicals that share molecular target(s). On the other hand, a common toxicity applies when similar toxicity symptoms are produced by attack on the same or different molecular targets.

Finally, the NOAEL/LOAEL-based modeling of relative potency should be replaced with an assessment of the potency of the variable of interest—inhibition of cholinesterases—as quantitative parameters in their own right. Low dose potency (potencies) should be calculated for inhibition of these enzymes.

At some point in the process, the Agency is encouraged to validate its estimates of the cumulative exposures methodology. This could best be done by conducting the cumulative exposure estimates and then following this with actual human monitoring data.

Agency Response: OPP has outlined its definition of the terms common mechanism of toxicity and common toxicity in the 1999 Common Mechanism Document. In this document, OPP stated that for the purposes of FQPA, common mechanism would require evidence of a common toxic effect by multiple chemicals mediated through the same critical biochemical step in a cascade of events leading to the ultimate effect. The document indicated that this analysis was not targeted at a molecular level target specifically, but could result from other less specific actions such as site-specific irritation or compensatory hyperplasia as seen in hormonally-mediated event.

OPP has indicated in the revised cumulative risk assessment guidance that analysis of dose response data should be done using modeling approaches, and that NOAEL/LOAEL-based evaluation of relative potency should be used only as a last resort.

OPP agrees that the results of risk assessment modeling should be verified. In the interest of developing data for this purpose, OPP participates in a multiagency effort to collect biomonitoring data to permit evaluation of pesticide exposures in the field. Specifically, urine samples are collected during the conduct of the NHANES survey to permit evaluation of pesticide metabolites that can be specifically linked to pesticide exposures. OPP will continue to seek additional sources of data of this type to permit evaluation of the accuracy of the exposure and estimates generated.

9.A.3 Comment: DPR (09) commends the Agency for its effort in developing a reasonable approach to such a complex task such as cumulative risk assessment. The commenter hopes that EPA will develop more case studies in the future so that the principles set forth in the guidance can be illustrated in a more definitive and realistic manner.

Agency Response: OPP does not intend to develop additional case studies but will begin conducting cumulative risk assessments on identified CMGs.

ISSUE 10. Other Comments

10.A General Comments on Guidance, Including Principles and Assumptions Used

10.A.1 Comment: IWG (06) disagrees with the Agency's interpretation of FQPA's statutory language regarding aggregate exposure and cumulative risk. In the draft guidance document, EPA states: "Food Quality Protection Act (FQPA) of 1996 provides that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the pesticide chemical on: aggregate...exposure to the pesticide and available information concerning the combined toxic effects to human health that may result from dietary, residential, or other nonoccupational exposure to other substances that have a common mechanism of toxicity." IWG believes that the law actually says "the FQPA amended the FFDCA to require EPA to decide whether "aggregate exposure" is safe, and defined 'aggregate exposure' to include only: (1) food exposure, plus (2) drinking water and other nonoccupational exposures 'for which there *is reliable information.*'" In assessing cumulative exposure, the commenter believes that the law does not allow the Agency to consider information that it cannot consider when assessing aggregate exposure to single compounds.

> **Agency Response:** OPP has addressed the points made in this comment as part of the document containing OPP's responses to comments on the Aggregate Risk Assessment Guidance (USEPA, 2001e). OPP incorporates those responses into this document, by reference.

10.A.2 Comment: IWG (06) points out that the Agency has not provided any guidance on how it will judge the acceptability of aggregate or cumulative risk.

> **Agency Response:** The purpose of the guidance document is to present a conceptual framework and issues that should be considered in the conduct of a cumulative risk assessment. The guidance intentionally avoids discussing risk management issues. Establishing the acceptability of risk as estimated in an aggregate or cumulative risk assessment is a risk management decision that will be informed by the risk assessment and characterization.

10.A.3 Comment: Most commenters acknowledged EPA's efforts in developing guidance for cumulative risk assessment as called for by FQPA. Several commenters (WWF-03, ADA-07, ACC-02, Novartis-04, IWG-06) agreed with EPA that the draft June 2000 Cumulative Risk Guidance Document is a "work in progress" WWF views EPA's guidance as a major step forward and applauds EPA for the progress made in refining guidance and explaining how it will be applied. ADA (07) notes that, while still quite nonspecific due to the need to develop new methodologies (and it seems to follow the simple philosophy adopted in drafting the aggregate risk policy), the document appears to strive to make realistic estimates and to limit exposure estimates to those chemical combinations likely to be encountered rather than to generate unlikely extreme worst case situations, and thus EPA should be encouraged to continue in this pattern while progressing to completion of this major step.

NRDC (L05) states that EPA should distinguish more sharply between ideals to work towards in a cumulative risk assessment and how to use the methods and data currently accessible to better describe the risks from cumulative exposures and to better protect human health. EPA must clearly state that the criteria and principles describing the ideal risk assessment do not define an implicit "minimum data set" needed to support regulatory actions.

Several commenters (ACC-02, Novartis-04, IWG-L01) note, however, that considerable refinement is needed before the guidance will be usable. These commenters further note that the guidance document is only an overview of principles and concepts and is driven by conservative assumptions, as well as being based on policy documents not yet finalized; and recommend that a demonstration project was needed to illustrate out the guidance will be implemented. IWG indicated that new toxicology data could eliminate the use of assumptions. PMRA (L02) indicated that OPP needed to validate the assumptions used in the cumulative guidance.

> **Agency Response:** In general commenters applaud OPP's progress in advancing guidance, methods and tools for cumulative risk assessment. There is general agreement that this area will continue to evolve, and thus the guidance should be viewed as a work in progress. Commenters also support OPP's efforts to make realistic estimates of cumulative risk rather than relying on worst case situations. EPA appreciates the supportive comments.

Several commenters, however, think considerable refinement is needed before OPP's guidance will be usable. OPP disagrees with this comment. Over the last several years, a number of external reviews have helped shape OPP's cumulative risk assessment guidance. OPP has repeatedly sought scientific review by the SAP on its guidance document itself, and has also taken to the SAP for comment, the various exposure models and tools being developed for assessing aggregate and cumulative risk. For further information, see "Cumulative Risk Assessment: Developing the Methods Available Papers and Where They May be Located;" Online (USEPA, 2001i). OPP has used actual data sets on OPs to illustrate these methods and tools. Furthermore, the SAP has agreed on numerous occasions with the Agency that data and methods exist for conducting cumulative risk assessments.

An important aspect of any risk assessment guidance document is to inform the public of what principles, concepts and assumptions will be used. The assumptions that may be used in cumulative risk assessment are consistent with Agency policy and practice for both single chemical assessment and for the assessments of chemical mixtures. When the draft guidance was published for public comment in June 2000, it did reference other policies that were not yet finalized. These policies have been finalized or will be finalized within approximately the same time frame as the cumulative guidance document. The one exception is the Agency's Guidance for Benchmark Dose, which is anticipated to be finalized by the end of 2001.

OPP agrees that additional data could eliminate the use of assumptions. OPP indicates in its revised guidance that it will depart from defaults if data allow so. Thus, OPP encourages the generation of data to refine cumulative risk estimates. But it is incumbent upon the registrants to take on such studies.

Finally, OPP believes that it has distinguished in the revised Cumulative Guidance between available tools and the ideals to work toward. OPP believes it has data and methods to reasonably pursue cumulative risk assessments. See OPP's December 2001 preliminary cumulative risk assessment on OPs (USEPA, 2001f).

10.A.4 Comment: One commenter (IWG-06) agrees with the principle that it is extremely important to take care to avoid the compounding of individual conservatisms in a manner that would result in serious overestimates of risk. There are several areas to guard against the potential for compounding conservatism. Cumulating worst-case or bounding estimates from the same route of exposure for several common mechanism compounds is one example. The design of the scenario-building integration systems by which food, drinking water and residential exposures are to be linked must also avoid overestimation of high-percentile exposure.

> **Agency Response:** OPP agrees with the commenter and believes its guidance is consistent with this view.

10.A.5 Comment: PMRA (L02) expressed concern regarding the lack of data which would prevent the full implementation of this policy. While the general principles for excluding components of the cumulative assessment have merit, the optics of routinely excluding numerous sources of exposure due to a general lack of data could undermine the public confidence in EPA's ability to address the legislative requirement of FQPA.

> **Agency Response:** OPP's criteria for excluding a known source of pesticide exposure focus on having enough information to conclude that the exposure scenario would make, at most, only a negligible contribution to overall exposure. In view of the extensive information collected about pesticides, OPP expects that it would be able to estimate exposure to essentially all identified pesticide uses. In the unlikely event that OPP cannot estimate potential exposure, OPP could address that limitation through the use of appropriate UFs.

10.A.6 Comment: One commenter (PMRA-L02) finds the definition of CAG confusing. The document indicates on several occasions that "for chronic and cancer effects mediated through reversible precursor events, overlapping exposure should also be considered. For other chronic and cancer endpoints for which long-term exposure is necessary to cause the effect, concurrent exposures are not required for the chemical to act by a common mechanism." This last sentence is confusing; is it the intent of this statement to indicate that concurrent exposures are not required to result in a cumulative effect? Secondly, it is not clear if two chemicals which result in long term effects following short term exposures would be excluded from the CAG on the basis that their exposures do not overlap. It is possible that if more frequent nonconcurrent exposures to these two chemicals are experienced, the cumulative effect could be greater than to either chemical alone. Perhaps this section could benefit from an expanded discussion of when concurrency is a requirement.

Agency Response: The major factor differentiating the treatment of the two occasions of chronic and cancer effects is whether or not the effect itself or the precursor to the effect is reversible. If the effect or its precursor are reversible, then a second exposure occurring after the reversal period will begin at baseline as though no prior exposure had ever occurred. If the second effect occurs before reversal is complete, then the impact of the two exposures may accumulate. In this case, the timing of the exposures is critical to the magnitude of the toxic response elicited. Alternatively, if a toxic effect or its precursor event are irreversible, each subsequent insult may be expected to increase the magnitude of the toxic response elicited. With no possibility for recovery, each exposure may worsen the degree of response even when widely separated in time.

OPP has attempted to clarify this portion of the cumulative risk guidance document.

10.A.7 Comment: Pages 50-59, section 5.1 to 5.5: In the July 20, 2000 technical briefing on this draft guidance document, two definitions were provided, one for POD, defined as a dose causing no effect) and one for POC, defined as a dose causing an equivalent effect; this is stated to be used to establish the RPFs). However, the guidance document itself seems to refer only to the POD and to EDs (e.g., an ED_{10}). On page 52, section 5.2, the document defines POD as either an ED or a NOAEL; the terminology used should be consistent. As well, on page 59, the RPF is calculated by comparing PODs; how can doses which cause no effect be used to compare potency among various chemicals (PMRA-L02)?

> **Agency Response:** OPP's revised guidance document clarifies the different terms used in the hazard evaluation. Essentially, a POD is the dose level which, when compared to organisms in the control group, causes no effect; under EPA's Benchmark Dose Guidance an ED_{10} is equivalent to a POD. The RPF values are developed by comparing the dose of different pesticides necessary to produce the same level of toxic response; the different doses, often described in terms of an EDx, are referred to as POCs.

10.A.8 Comment: CU (08) points out that EPA does not emphasize the likelihood of significant annual shifts in pesticide use and risk patterns that will occur once the Agency starts imposing risk mitigation measures on risk-driver chemicals within a CAG.

> **Agency Response:** The revised guidance states that generally OPP will perform an aggregate risk assessment for each pesticide in a CMG (or CAG) before conducting a cumulative risk assessment. Thus, to the extent that aggregate risk assessments lead to imposition of risk mitigation measures, OPP will be able to take their impacts into account as it conducts the cumulative assessment. OPP agrees that it also needs to anticipate the possibility that risk mitigation measures affecting the members of the CAG will lead to shifts in pesticide use among members of the CAG. OPP recognizes that it will need to take that into account as part of the regulatory decision-making process.

10.A.9 Comment: The proposed guidance could better explain how cumulative risk considerations fit into the reregistration and tolerance reassessment processes; it does not directly address risk or the probability of adverse outcomes (CTRAP-19).

> **Agency Response:** It is not the within the scope of the cumulative risk assessment guidance to discuss risk management. Those policies will be dealt with in a different forum.

10.A.10. Comment: CTRAPS (19) suggests promulgating test guidelines so that registrants can produce data that will show whether or not a pesticide belongs to a common mechanism group, and if so, what potency the pesticide has compared with a reference pesticide.

> **Agency Response:** OPP has recently initiated a number of activities to evaluate the data requirements for pesticides in 40 CFR 158. Part of this re-examination of testing will include consideration of those data needed for cumulative risk assessment.

10.A.11 Comment: NRDC (L05) believes that EPA's proposal for completing steps 5 through 8 of ILSI's eight-step process is not sufficiently detailed to allow evaluation of the Agency's effectiveness in carrying out these tasks.

The same eating day episodes as used in steps 1 through 4 must become the principle focus of the further analysis called for in steps 5 through 7. An approximate answer for step 5 requires a simple calculation. The total number of eating day episodes resulting in an exceedence of risk becomes the numerator in a ratio; the total number of eating days simulated becomes the denominator. The result is an approximation of the percent of the population likely to face excessive exposure on any given day. Other routes of nondietary exposure will also have to be taken into account at this point to determine how many additional eating day episodes result in excessive risks.

For step 6, EPA should identify risk drivers in a straightforward, data-driven way by further analyzing the results of a Monte Carlo simulation that encompasses all chemicals within a CMG. First, all eating day episodes falling in the exceedence group can be isolated and placed in an "excessive risk pool." Within this pool of eating days, the total exposure associated with each unique crop/food combination would be calculated and converted to common toxicity units. Exposure through water would be aggregated and treated just as a given food. Then individual pesticide-individual food risk shares should be ranked, with the largest risk drivers rising to the top of the list. Risk shares by crop/food

combinations can then be aggregated by food or by active ingredient, producing two additional rankings–share of total risks by crop/food and share of total risks by active ingredient. These relative rankings of shares of total cumulative risk will provide the Agency a firm foundation to identify risk-drivers, answering the basic questions inherent in steps 6 and 7.

Regarding step 8: by drawing on the above results, EPA can and should explain in plain language what portion of the most "at risk" subpopulation is likely to face excessive risks, what crops and pesticides contribute most heavily to exposure and risk, and the steps EPA is going to take to reduce exposures to risk drivers.

> **Agency Response:** EPA has considered ILSI's workshop report on aggregate and cumulative. The revised cumulative guidance lays out the cumulative risk assessment process in a series of steps. It should be stressed that the cumulative document is not a "how-to" guide and as such, should not be prescriptive but rather provide guidance that is flexible to address a variety of situations. OPP generally agrees that identification of exposure scenarios that attribute significantly (if there appears to be excessive risk) to overall risk will provide valuable information to decision-makers about risk management.

10.A.12 Comment: The introduction to Chapter 6 states: "The cumulative risk assessment will serve to identify the magnitude of likely exceedence of a cumulative acceptable exposure level, but only in a qualitative sense (i.e., because of uncertainty and lack of precision). The outcome will serve as a focus for returning to the detailed, quantitative single chemical assessments to pursue necessary risk mitigation activities." NRDC (L05) believes that EPA needs to rethink this statement as it implies that a cumulative risk assessment will necessarily entail more uncertainty and lack of precision than will single chemical assessments, and therefore less relevance for risk mitigation and management decisions.

> **Agency Response:** This statement has been revised and emphasis on the outcome of a cumulative risk assessment is placed on the identification of significant contributors.

10.B Overall Breadth of What to Consider in Exposure and Toxicity Assessment

10.B.1 Comment: Sometimes, EPA appears more concerned with narrowing the scope of cumulative assessments than it is with assuring that these requirements provide a "reasonable certainty" of no harm, as FQPA requires. The guidance document prescribes far too narrow a set of circumstances for carrying out a cumulative assessment, given the public health provisions of FQPA. The Agency appears too willing to limit cumulative assessment only to those circumstances where nearly everyone agrees such an assessment is necessary–especially when this sort of consensus could only be achieved with the approval of scientists working directly for manufacturers of products likely to be more strictly regulated based upon results from a cumulative risk assessment. EPA needs to clarify that it will assess cumulative risk in the context of all factors known to influence the susceptibility of people to a given hazard. Specifically, the guidance never adequately explains how nonpesticide chemicals and other substances are to be incorporated into the cumulative risk assessment. In other words, EPA needs to clarify that it will assess cumulative risk in the context of all other factors known to influence the susceptibility of people to a given hazard, or set of hazards posed by pesticides and other substances in a CMG. To comply with the law, EPA ultimately must consider the joint effects of pesticides and viruses, UV radiation, vaccines, and other substances with a potential common endpoint. Second, EPA strives in the guidance to define circumstances when chemicals that fall within a CMG may be dropped from a CAG. NRDC strongly urges against this effort. Third, NRDC is concerned that EPA is being too narrow on the hazard side, limiting cumulative risk assessment to just the hazard endpoint at the cellular level that unites the chemicals within a CMG–not the full suite of hazards known to be posed by the chemicals in the group. The Agency should move forward with cumulative assessments on all substances in a CMG. If the exposure and toxicity is low, they just won't contribute much to risk totals.

Agency Response. EPA is currently preparing a framework for conducting cumulative risk assessments for all stressors. This type of assessment, which would include total risks from all potential stressors, is outside the scope of FQPA. Issues involving total health risk (e.g., environmental justice issues) will need to be addressed by the Agency in the future. Also see comment 10.G.1.

10.C Use of Percentiles and Cumulative Risk Estimates

10.C.1 Comment: IWG (06) wholeheartedly agrees that the output from a cumulative risk analysis should be distributional in nature. They do not think, however, that this principle should be ignored, or limited without a very good reason, and thus objects to the generalized limiting language in the document such as that in section 2.2 which says that "populations and subpopulations distributions of exposures and risk are constructed by probabilistic techniques or a *combination of probabilistic and deterministic methods* (emphasis on italicized)." The italicized phase should be deleted or explained in detail. They also believe that the use of probabilistic methods should extend to determination of toxicological endpoints used in the cumulative risk assessment.

Agency Response: OPP agrees with the commenter in that, ideally, a probabilistic assessment will consist of the most realistic range of potential input values available. Nevertheless, there may be instances in which only high-end point estimates are available and these should not necessarily invalidate any probabilistic assessment, particularly if the associated exposures are small and the results are insensitive to this input. For example, if only a single point estimate were available for a little consumed commodity like celery seed, it would make little sense for OPP to decline to perform or accept a probabilistic assessment due solely to the fact that probabilistic inputs are not available for each and every inputs. If it is found that the results of the probabilistic assessment are very dependent on a (high end) value selected for the point estimate and there is a potential for unacceptable risk, then a refined assessment should be conducted which may require additional data in order to refine the assessment. OPP emphasizes in the revised cumulative guidance document the importance of characterizing the nature of the outputs from the cumulative assessment, and determining whether any high end deterministic inputs were driving the overall risk. This would be pointed out in the assessment and thus the risk manager would be informed.

The Agency has ongoing projects to develop and evaluate probabilistic methods for toxicological endpoints. Although these techniques are not yet ready to apply in a cumulative assessment, OPP agrees that this is an important direction to explore.

10.C.2 Comment: IWG (06) and Novartis (04) raise the issue that the June 2000 Cumulative Risk Guidance Document does not address determining the acceptability of a cumulative risk estimate or how EPA would decide whether a particular distribution of cumulative exposure would be regarded as unacceptable. There is no discussion on application of percentiles; the document only states that cumulative exposure would be measured against an RfD or population adjusted dose (PAD) as done with individual chemicals (IWG). Novartis is supportive of the flexibility in the Aggregate guidance rather than routinely using a fixed percentile. The document does not describe how OPP would decide whether a particular distribution of cumulative exposure is an unacceptable risk (IWG).

Agency Response: Determination of the acceptability of a cumulative risk estimate is a risk management decision which is still under discussion. However, it is important to point out that because of the uncertainty that surrounds assessments on multiple chemicals, there are no bright lines for what is or not acceptable. Therefore, risk characterization tools for describing both uncertainty and variability play a key role in communicating to the risk manager the confidence in the results of cumulative risk assessments. OPP intends to follow the guidance described in its aggregate risk policy of not routinely using a fixed percentile, but rather presenting a range of percentiles for the risk managers.

10.D FQPA Language Regarding Safety Criterion

10.D.1 Comment: IWG (06) notes that the FFDCA section 408(b) safety criterion is that "no harm [is to] result from **aggregate** exposure to the pesticide chemical residue." Cumulative exposure, on the other hand, is merely included in a long list of factors that the Administrator "shall consider, among other relevant factors," when reviewing tolerances. The law does not say anything whatsoever about what, if anything, should be done when the aggregate exposure to residues of a given pesticide meet the "no harm" safety criterion but the cumulative exposure is or may be greater than would be allowed for aggregate exposure. Nor does the sparse legislative history shed light o this issue. At a minimum, therefore, the Agency is not required to regulate cumulative exposure in the same way it chooses to regulate aggregate exposure.

> **Agency Response:** OPP acknowledges that the statute uses different language in specifying the requirements pertaining to aggregate and cumulative exposures. OPP, however, does not believe it would be wise to speculate in the abstract as to how that language should be interpreted.

10.E Need for Clarity About the Cumulative Process

10.E.1 Comment: One commenter (IWG-06) indicated that the next version of the June 2000 Cumulative Risk Guidance should state more clearly the relationship between the various steps in the process, with special attention to differentiating between the steps that define a common mechanism group and those that are taken limited to define or assess the risks associated with members of a CAG. EPA should prepare a flow diagram.

> **Agency Response:** The cumulative risk assessment process involves a series of complex analyses. Thus, OPP appreciates the need to clearly describe the process. OPP has incorporated into the revised guidance a figure that provides an overview of the key steps involved in estimating cumulative risks. Following this figure, the document is organized into sections that describe each step.

10.E.2 Comment: Two commenters (IWG-06, Novartis-04) indicated that the discussion of short and long term exposure situations should be separated in the guidance document, and more clearly noted because of the substantial differences between various exposure scenarios and the issue of simultaneous exposure.

Agency Response: OPP disagrees with the commenter. Cumulative exposure evaluates a continuum of exposure durations as appropriate for the common toxicity endpoint. It would be misleading for the document to separate the discussion of short and long term exposures. An evaluation of concurrent exposure should be done for all the relevant pathways, durations, and routes of exposure that allows one chemical to add to the exposure of another chemical such that the total risk of a group of common mechanism chemicals is an estimate of the sum of the exposures to the individual chemicals. This includes simultaneous exposures as well as any sequential exposures that could contribute to the same joint risk of the common toxic effect, either by overlapping internal doses or by overlapping toxic effects. Simultaneous exposures are necessary for these toxicities that are rapidly reversible, but not for those effects that are persistent.

10.F Populations Covered

10.F.1 Comment: One commenter (PMRA-L02) raised the issue of not including female/fetus workers in assessing cumulative risk.

Agency Response: FFDCA does not regulate workers exposure and, thus, this document does not present guidance for performing occupational, cumulative risk assessments. For the purpose of implementation of the FQPA statutory language as it pertains to tolerance-setting, exposures to the fetus that result from its parent's employment are occupational exposures. To adopt the interpretation that occupational exposure for pregnant women is nonoccupational exposure as to these women's fetuses would essentially read the explicit limitation on considering occupational exposure out of the statute.

10.F.2 Comment: One commenter states (BPFJF-05) that even though FQPA does not require EPA to include occupational scenarios in its cumulative risk assessments, it does not prohibit the Agency from doing do. "In order for a cumulative risk assessment to reflect real world situations EPA must factor in occupational exposures." Also, given that occupational exposure is the most significant type of exposure as reflected in EPA's own risk assessment documents, the Agency cannot justify ignoring occupational exposure in its cumulative risk assessment. In addition, the commenter believes that EPA must consider the homeless population and other segments of society that are particularly susceptible to pesticide exposure.

> **Agency Response:** OPP disagrees with this commenter's interpretation of section 408(b)(2)(D)(vi). To adopt this commenter's interpretation would render the language in section 408(b)(2)(D)(vi) excluding occupational exposure meaningless. See response to Comment 10.D.1. As to segments of society that are particularly susceptible to pesticides, OPP will consider any available information pertaining to aggregate exposure to major identifiable subgroups of consumers.

10.F.3 Comment: WWF (03) believes that cumulative risk assessment should be targeted at the protection of public health through protection of sensitive or susceptible subpopulations, and through protection of biological processes including the development of the human embryo. Another commenter (NRDC-L05) claims that the basis for conducting cumulative risk assessments is to protect the health of children, and others. The guidance should make this public health context explicit, and place it at the center of any cumulative risk assessment to ensure the child protective provisions of FQPA are met. Children's exposure assessment factors (e.g., diets, behaviors) are different than those for adults. It is implausible and unscientific to assume that all this diversity among children can be captured in a Monte Carlo distribution based on data collected on a national level. The only way EPA can generate regulatory decisions that provide a "reasonable certainty of no harm" to all children is to assure that the methods and data supporting cumulative assessment fully reflect the exposure patterns and levels faced by individual children in high exposure scenarios. This would include children and the fetuses of women living in agricultural areas where pesticides are used intensively.

Agency Response: Cumulative risk assessments will play a significant role in the evaluation of risks posed by pesticides, and will enable OPP to make regulatory decisions that more fully protect public health and sensitive subpopulations, including infants and children. OPP has developed a separate guidance document on application of the FQPA SF in cumulative assessments, and is currently taking comments on that guidance. OPP will include the evaluation of special susceptibility in all of its decisions. In addition, consideration of biological processes that may be precursor events to adverse effects will often be the type of mechanistic evaluation needed to identify CMGs.

10.F.4 Comment: CEHN (10) believes that EPA's draft guidance is not considering the special needs of infants and children as directed in FQPA and E.O. 13045 ("Protection of Children from Environmental Health Risks and Safety Risks"). The commenter cites the use of NOAEL and LOAELs instead of no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs), stating that the law is clear that the Agency is to regulate on observed effects, not adverse effects. Also, the guidance is too general and infers too much through reference to other documents. The Guidance document itself needs to explicitly state how it will undertake to protect children; reference to other documents is not sufficient. NRDC (L05) also objects to the use of NOAELs instead of NOELs. FQPA and its legislative history is clear and specific in directing EPA to base its pesticide regulation on NOELs.

Agency Response: OPP disagrees with the comment that the cumulative risk Assessment Guidance must explicitly restate policy positions expressed in other documents in order for those positions to satisfy its obligations under FQPA and applicable Executive Orders. OPP also disagrees that the guidance document fails to articulate OPP's special concerns for protection of sensitive subpopulations, such as children. For example, the current guidance document indicates that, when selecting the effects associated with the common mechanism of toxicity (Chapter 4.1), the risk assessor should assess the available data to determine the pertinent and most sensitive endpoints associated with the common mechanism to protect all populations. If the data are insufficient for dose-response modeling and derivation of a BMD, a NOAEL or a NOEL may be used.

Thus, the endpoint used in estimating cumulative risk may be a precursor or biochemical event that leads to the frank toxicological effect which itself is not considered adverse. Furthermore in Chapter 4.5, the current guidance emphasizes that when characterizing hazard potential, attention should be given to subpopulations that may be more susceptible to the common toxic effect and mechanism.

10.G Scope of Cumulative Guidance and Other Substances

10.G.1 Comment: FQPA calls for EPA to consider the cumulative effects of pesticide residues and "other substances that have a common mechanism of toxicity." CU (08) reminds the Agency about its statutory requirement that chemicals other than pesticides be included in the CMG/CAG, and WWF (03) calls for EPA to increase the scope of its guidance to include sources of exposure to hormonally-active chemicals (i.e., to include industrial, agricultural, and municipal effluents) because FQPA is clear that EPA must consider "other substances." Several commenters raised issues concerning the cumulative policy document's statements on "other substances." One commenter (ACC-02) indicated that the scope of the guidance should be narrowed to pesticides and not include "other substances." Another commenter (PMRA-L02) questioned whether OPP would include drugs in accumulating risk with pesticide chemicals. IWG (06) points out that FQPA did not define the scope of "other substances." The law's legislative history adds no guidance on the term's meaning. However, EPA in the June 2000 Cumulative Risk Guidance asserts that "other substances includes pesticide chemicals, drugs, industrial chemicals, and other substances to which the general population is exposed." IWG in their comments further raises the broad implications and issues regarding this statement to non-FFDCA situations as well as FFDCA situations.

NRDC (L05) points out that EPA does not seem to have a requirement for including chemical-specific pharmacokinetic data regarding important metabolites of OP's (e.g., malaoxon or dimethoxon) in children's risk. Additionally, the Agency has not adequately explained how it will consider the potentially toxic effects of different metabolites in the absence of requirements to collect such data. Finally, at least seven OPs have stereoisomers. EPA collects little or no optical radiation data to indicate the relative proportion of stereoisomers in pesticide products; these need to be included in cumulative risk assessments.

Agency Response: The revised cumulative guidance document is only intended to provide guidance on performing cumulative risk assessments for pesticide chemicals that act by a common mechanism of toxicity. EPA is working on its approach for the consideration of "other substances" that have a common mechanism of toxicity. Until the Agency develops general guidance on this issue, EPA will handle it on a case-by-case basis.

10.G.2 Comment: The commenter (BPFJF-05) believes that EPA must include in its definition of "other substances" the following: the inert ingredients in pesticide formulations; contaminants and metabolites of pesticides; pharmaceuticals that have toxic effects in common with pesticides; and environmental contaminants such as dioxins, PCBs and other byproducts of the chemical industry.

Agency Response: OPP will consider all available, reliable data on "other substances." Inert ingredients in pesticides and contaminants and metabolites of pesticides are pesticide chemicals as defined by FFDCA section 201(q). They are included in current assessments. The inclusion of pharmaceuticals and other toxic substances is currently under discussion.

10.G.3 Comment: WWF(03) also calls for making the definition of cumulative risk more comprehensive. The guidance document defines cumulative risk as the result of concurrent exposure to two or more chemicals (pages 21; 67). This definition excludes the cumulative risk of sequential exposure to two or more chemicals, or the cumulative effects of hormonally-active chemicals on sequential generations or populations which have been exposed.

Agency Response: The revised document clearly defines and interprets concurrent exposure as potential human exposure by all relevant pathways, durations, and routes that allows one chemical to add to the exposure of another chemical such that the total risk is an estimate of the sum of the exposures to the individual chemicals. This includes simultaneous exposures **as well as any sequential exposures** that could contribute to the same joint risk, either by overlapping internal doses or by overlapping toxic effects.

10.H Public and Peer Review

10.H.1 Comment: Several commenters (IWG-06, Novartis-04, ACC-02) indicated that after OPP revises the June guidance document for cumulative risk assessment, there needs to be an opportunity for public comment on that revised document. These commenters indicated that as the databases, methods and tools continue to evolve, and as CMGs and CAGs are identified there should be an opportunity for stakeholder and public comment, and scientific peer review.

> **Agency Response:** OPP has repeatedly sought external review on its cumulative guidance and methods. OPP clearly states in the revised document that it is guidance and not a rule binding on either the EPA or any outside parties. The guidance provides a starting point for OPP's risk assessments, and OPP will depart from its policy where the facts or circumstances warrant. In such cases, the OPP will explain why a different course was taken. Similarly, outside parties remain free to assert that a policy is not appropriate for a specific pesticide or group of pesticides, or that the circumstances surrounding a specific risk assessment demonstrate that a policy should be modified or abandoned. Finally, OPP acknowledges that the cumulative risk assessment process will continue to evolve after this guidance is published. Thus, OPP will update the current guidance or provide supplementary materials as appropriate.

10.H.2 Comment: The commenter (BPFJF-05) believes that EPA should open the meeting process on chemical reviews to the public. No meetings with the chemical industry on risk assessments should be considered confidential unless EPA has determined in advance that the meetings are subject to the confidentiality protections of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), Section 10.

> **Agency Response:** This comment is outside the scope of the cumulative risk assessment guidance. OPP will follow applicable legal standards regarding its obligation to announce the opportunity for the public to attend and participate in meetings on regulatory matters being considered by the organization. In general, OPP does not anticipate changing its current practices and policies.

10.I Cumulative Risk Assessment of Hormonally-Active Chemicals

10.I.1 Comment: The bulk of WWF's (03) comments are directed specifically at issues pertaining to the application of the cumulative risk guidance to hormonally active chemicals, a priority focus of WWF's Global Toxic Chemical Initiative. WWF indicates that EPA needs to be clear that it will assess cumulative risk in the context of mechanisms that concern impacts of hormonally active chemicals. WWF further notes that there needs to be clarification of how hormone disrupting chemicals will be grouped for purposes of cumulative risk assessment, given that the guidance indicates it will group substances that cause multiple toxic effects by a common mechanism from a common site of toxic action (e.g., the multiple effects caused by certain endocrine disruptors).

> **Agency Response:** The cumulative guidance document is written to provide guidance for a variety of different data situations and different types of common mechanism chemicals. There are several pesticides that cause hormonal effects, and OPP plans to make common mechanism of toxicity determinations as the data permit.

10.J. Comments on the Document's Glossary

10.J.1 Comment: IWG (06) offered a number of changes to the definition of terms in the Glossary that begins on page 81 of the June 2000 Cumulative Risk Guidance.

> **Agency Response:** The glossary has been deleted from the cumulative guidance document given that complete and accurate definitions are provided in other OPP guidance documents such as: "Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (EPA, 1999c) and "General Principles For Performing Aggregate Exposure And Risk Assessments" (USEPA, 2001h). Instead the revised cumulative guidance document has included a few key terms that pertain to the cumulative risk assessment process at the beginning of the document.

10K. Petition for Rulemaking

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, if any, comments on this issue. OPP will, however, take this opportunity to respond to a petition from pesticide manufacturer and grower groups requesting, among other things, promulgation of a regulation "specifying how common mechanism of toxicity will be determined, how cumulative risk will be assessed for pesticides demonstrated to have a common mechanism of toxicity, and how the Agency will decide which tolerances to change or revoke if a group of pesticides with a common mechanism of toxicity is determined to pose an unacceptable cumulative effects." Petition for Rulemaking to Develop Policies and Procedures for Implementing the Food Quality Protection Act of 1996 28 (May 22, 1998).

Petition. The pesticide manufacturer/grower petition requested that the Agency undertake rulemaking on a number of topics including implementation of the requirement to consider available information on cumulative effects from pesticides and other substances sharing a common mechanism of toxicity in evaluating the safety of tolerances. Rulemaking on common mechanism/cumulative risk issues is deemed needed by petitioners because these issues are scientifically complex and because determinations whether to modify or revoke tolerance based on a cumulative risk assessment are “likely to have substantial competitive and economic consequences.” Id. at 30.

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; (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

Agency Response. After considering the petition, OPP does not believe that any of the specific reasons relating to common mechanism of toxicity or cumulative risk assessments warrant issuing the cumulative risk assessment policy or common mechanism policy as a rule. First, the fact that the policies address complex science issues does not suggest use of rulemaking procedures is necessary. To the contrary, such science issues counsel against use of rulemaking. The difficult science issues raised by common mechanism/cumulative risk assessment require consideration of numerous factors including rapidly developing scientific concepts, techniques, and methodologies. Such decisions cannot be translated into prescriptive black letter rules without removing the scientific judgment that is critical to producing a sound scientific conclusion.

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*; 51 FR 33992 (September 24, 1986); Guidelines for Reproductive Toxicity Risk Assessment;, 61 FR 56274 (October 31, 1996); *Guidelines for Exposure Assessment*; 57 FR 22888 (May 29, 1992); *Proposed Guidelines for Carcinogen Risk Assessment*; 61 FR 17960 (April 23, 1996). Similarly, EPA's FQPA policy addressing the selection of the population percentile used in calculating the threshold of regulatory concern in acute risk assessments as well as the policy of aggregate exposure were issued as policies not rules. U.S. EPA, *General Principles for Performing Aggregate Exposure and Risk Assessment* (November 28, 2001); U.S. EPA, *Choosing a Percentile of Acute Dietary Exposure as a Threshold of Regulatory Concern* 12 (March 16, 2000). 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).

Finally, that decisions to revoke tolerances based on a cumulative risk assessment might have "substantial competitive and economic effects" does not convince OPP that a rule on these issues would be preferable. Petitioners are concerned about an alleged lack of "certainty and predictability" given the potential for substantial competitive and economic effects. They believe a rule will provide certainty and predictability. Given the dynamic nature of science in this area, however, any rule would have to be very general to allow scientific judgment and thus unlikely to provide the certainty and predictability sought.

EPA found none of the generic arguments set forth in the rulemaking petition to be persuasive. Each of those arguments are 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 EPA followed in developing this policy. EPA published notice of the draft policy in the *Federal Register* (65 FR 40644; June 30, 2000). That notice provided a concise summary of the policy and requested public comment on the policy. Further, EPA 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 EPA's public comment process. As noted, EPA received over 10 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. As to this policy, however, commenters principally made scientific and policy, not legal, comments. Accordingly, this consideration does not appear to 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. OPP would note that SAP review has been repeatedly sought on issues concerning common mechanism and cumulative risk assessment. 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 EPA 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.

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 EPA to establish rules for "general procedures and requirements to implement this section;" it does not mandate such rules.

Accordingly, OPP denies the petition to the extent it sought promulgation of a regulations on common mechanism of toxicity determinations and cumulative risk assessments.

COMMENTS RECEIVED

Commenter		Code Used
Governmental (3)	Arizona Department of Agriculture	ADA-07
	California Department of Pesticide Regulation	DPR-09
	Health Canada Pest Management Regulatory Agency	PMRA-L02
Industry (1)	Novartis	Novartis-04
Trade Associations (2)	American Chemistry Council	ACC-02
	American Crop Protection Association	IWG-06
Advocacy Groups (7)	World Wildlife Federation	WWF-03
	National Coalition Against the Misuse of Pesticides (NCAMP)	BPFJF-05
	Children's Environmental Health Network	CEHN-10
	Consumers Union	CU-08
	Implementation Working Group	IWG-L01
	National Resources Defense Council	NRDC-L05
Consultants (1)	Consultants in Toxicology, Risk Assessment and Product Safety (CTRAPS)	CTRAPS-19

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