Comments Before the Scientific Advisory Panel – "Issues Pertaining to Exposure Assessment and Estimating Cumulative Risk"

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Executive Summary

Consumers Union and the Natural Resources Defense Council commend the Environmental Protection Agency (EPA) for moving forward with the development of a method for cumulative risk assessment (CRA) for substances with a common mechanism of toxicity. While much progress has been made, we believe that EPA must also address several key issues in order to assure the protection of infants and children from pesticide risks. EPA must:

Make a Public Health Context Explicit in the Guidance, and in Subsequent CRAs. Protecting the health of children and others is the basis for doing a cumulative risk assessment, as is clear from the Food Quality Protection Act (FQPA), and from the International Life Sciences Institute (ILSI) recommendations on which this document is based. The guidance document should make this public health context explicit, and place it at the center of any CRA to ensure the child protective provisions of the FQPA are met. Instead, EPA offers a proposed guidance that bends over backwards to assuage critics from the pesticide and agriculture industry by delaying regulatory action even in the face of clearly unacceptable cumulative risks until more data are collected, methodologies have been tweaked again and again, and multiple refined analyses of cumulative and individual chemical risks have been completed, reviewed and then rereviewed.

Include OPs and Carbamates in a Single CMG. EPA's decision to place both organophosphates and carbamates in a single assessment grouping is both solidly science-based and important in terms of providing real world protection from chemicals specifically designed to act via the same toxic mechanism.

Assure the Scope of the Cumulative Risk Assessment is Sufficient to Protect Public Health. At times, EPA appears more concerned with narrowing the scope of cumulative assessments than it is with assuring that these assessments provide a "reasonable certainty" of no harm, as the FQPA requires. For example:

- *Limited Range of Substances.* The FQPA is clear that EPA must consider cumulative risks from pesticides *and other substances* with a common mechanism of toxicity. The

title of the proposed guidance belies EPA intention to focus cumulative assessments only on pesticides, evading the full intent of the law.

- *Truncated CMGs.* By proposing to truncate Cumulative Mechanism Groups (CMGs), forming smaller Cumulative Assessment Groups (CAGs), and possibly removing constituents of the latter from the former, EPA threatens to create a process that would narrow the health impact of CRAs, as well as be unnecessarily complex, contentious and resource intensive. EPA should move forward with cumulative assessments based upon on all substances in a CMG. EPA attempts to draw distinctions between CMGs and CAGs are specious, and probably not scientifically defensible.
- *Account for All Metabolites.* Organophosphate and other pesticides have toxicologically significant metabolites, stereoisomers, and metabolites that are stereoisomers. EPA's cumulative risk assessments must account for these compounds, which can contribute significantly to the cumulative impact of their parent and mirror image compounds, even in the absence of requirements to collect the relevant pharmacokinetic and optical radiation data.

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, or set of hazards posed by pesticides and other substances in a CMG.

Take Immediate Action to Reduce Clearly Excessive Risks. To protect public health, as the FQPA mandates, EPA must move ahead with cumulative assessments when information about two or more constituents of a group of substances with a common mechanism indicates excessive risks. EPA must act sooner, not later. It should abandon its proposal to conduct cumulative exposure assessments generally only after completing an aggregate exposure assessment for every member of the group of substances. The major outcome of this proposal will be delay in reaching decisions about cumulative risk that would better protect public health. When a CRA confirms that risks are excessive, EPA should immediately begin targeting regulatory action on pesticide uses known to be "risk drivers."

Dietary Exposures. We commend 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 obviously key pathway.

"Markovicity" in the Context of CRA. CRAs 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.

Geographic Scale and Focus. EPA should abandon its categorical restriction that in evaluating non-dietary exposures in a cumulative risk assessment, extremely localized pesticide use and exposure scenarios should be excluded from regional or

national exposure and risk assessments just because available data shows that a particular product is only used in one area or under narrow circumstances. Similarly, FQPA mandates that cumulative risk assessments be performed such that there is a reasonable certainty of no harm to all, including highly exposed populations, and not just a hypothetical average population.

Chapter 6: Estimation and Characterization of Cumulative Risk. 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 public 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.

The Second Half of the CRA Process Needs More Attention. 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.

Cumulative Assessment Group and Risk Assessment Safety Factors. In this guidance, EPA undermines one of the 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.

Application of the "Incomplete Data Base" Uncertainty Factor. When the database for a specific pesticide is incomplete, the UF_D uncertainty factor 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 tenfold margin of safety. We suggest EPA develop simple guidelines differentiating when the UF_D will be applied to the CMP as a whole, and when it will be applied to one or more active ingredients in the CMG.

A. Introduction

These comments are submitted on behalf of Consumers Union[*] and the Natural Resources Defense Council.[**] Our comments address many of the critical risk assessment and regulatory policies embedded in the approaches to cumulative risk assessment set forth in Chapters 4 and 6 of the Environmental Protection Agency (EPA) document "Proposed Guidance on Cumulative Risk Assessment of Pesticidal Chemicals That Have a Common Mechanism of Toxicity." Chapters 4 and 6 of this document are dated November 10, 1999 and are posted on the SAP website as part of the background materials for this session.

Our comments are extensive on this important and lengthy guidance document. Also attached are copies of slides to be presented by Dr. Charles Benbrook that summarize many of the same points discussed here. The slides also can be viewed on the Internet at http://www.ecologic-ipm.com/SAPcum.ppt.

We commend EPA for moving forward with the development of a method for cumulative risk assessment (CRA). While much progress has been made, we believe EPA must also address several key issues in order to assure the protection of infants and children from cumulative pesticide risks. Some of these issues are general, and have been either insufficiently discussed or ignored by EPA to date. We highlight other issues raised within the current document, focusing on those which we fear will compromise or needlessly delay attainment of the FQPA's basic public health goals. Both our general comments and suggestions and more text-specific issues are summarized below, and are then discussed in greater detail.

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[*] Consumers Union is a nonprofit membership organization chartered in 1936 under the laws of the State of New York to provide consumers with information, education and counsel about goods, services, health, and personal finances and to initiate and cooperate with individual and group efforts to maintain and enhance the quality of life for consumers. Consumers Union's income is solely derived from the sale of *Consumer Reports*, its other publications and from noncommercial contributions, grants and fees. In addition to reports on Consumers Union's own product testing, *Consumer Reports* regularly carries articles on health, product safety, marketplace economics and legislative, judicial and regulatory actions that affect consumer welfare. Consumers Union's publications carry no advertising and receive no commercial support.

[**] The Natural Resources Defense Council (NRDC) is a national, non–profit environmental membership organization with over 400,000 members and contributors nationwide. Many NRDC members, including pregnant women and children, are exposed to pesticides in their diet and through other sources, thereby creating risks to human health. NRDC has no financial or fiduciary interest, either direct or indirect, in entities that manufacture, sell, or use pesticide chemicals.

B. Context for These Comments

The Food Quality Protection Act (FQPA) contained four key provisions designed to better protect infants, children, pregnant women, and other vulnerable people from exposure to pesticides. The FQPA requires EPA to –

- Take account of all routes of exposure in assessing risks (FFDCA Sect. 408 (b)(2)(D)(vi));
- Regulate together pesticide "residues and other substances" that pose risks to people through a common mechanism of toxicity (FFDCA Sect. 408 (b)(2)(C)(i)(III));
- Retain an added tenfold margin of safety to account for the fact that infants and children may be more highly exposed and more vulnerable to toxic effects of a pesticide or group of pesticides in the absence of complete data on toxicity to infants and children, and on their exposures (FFDCA Sect. 408 (b)(2)(C)(ii)); and
- Assure that exposures to a pesticide, or a group of pesticides and other substances found to pose risks through a common mechanism of toxicity do not exceed a level associated with "a reasonable certainty of no harm" to all children in light of the unique risks faced by infants and children and their unique patterns of food consumption and other behaviors (FFDCA Sect. 408 (b)(2)(C)(ii)(I)).

Chapters 4 and 6 of EPA's proposed methodology for cumulative risk assessment are under review today. In September 1999, the SAP reviewed Chapters 3 and 5, which explained how EPA proposes to select the toxic endpoint in a cumulative risk assessment (CRA) and determine what amounts to a Reference Dose for the "Common Assessment Group" (CAG) of active ingredients found to work through a common mechanism.

C. Overview of Needed Revisions

1. Placing the Guidance in a Clear Public Health Context.

In the chapters under review today and indeed in the whole document, EPA fails to place cumulative risk assessment in an appropriate public health context. A diverse group of experts convened by International Life Sciences Institute (ILSI) appropriately states –

> "Traditionally, risk assessments have focused on examining a single chemical. In contrast, cumulative risk assessment shifts the focus to the health endpoint of concern." [1]

At the same time, Administrator Browner has stressed EPA's role as a public health agency. Therefore, guidance documents explaining how to do cumulative risk assessment must place the analysis firmly within a public health context, as is described in the ILSI document. This public health context is absolutely critical for EPA to meet the child-protective provisions of the FQPA.

2. Taking Action to Reduce Clearly Excessive Risks While Advancing Science to Better Understand Remaining Risks.

There is a fundamental tension evident throughout the guidance document. On the one hand, EPA is trying to adhere to the clear mandates and timelines in the statute. The FQPA gives EPA solid direction and important new tools to move ahead with the review and adjustment of tolerances to levels consistent with the FQPA's safety standard, even in the absence of complete data. But to date EPA has failed to fully use these tools, if at all. EPA is already some two years behind schedule in meeting the first major FQPA milestone—reducing pesticide risks facing infants, children, and other vulnerable population groups from List 1 chemicals by August 1999. Without changes in this guidance document and EPA's underlying strategy for use of cumulative risk assessment, the implementation process will render some of the statute's most important new provisions next to meaningless.

On the other hand, EPA bends over backwards to respond to its critics in the pesticide and agricultural industries by promulgating a policy that delays any regulatory action even in the face of clearly unacceptable risks until additional data, novel methodologies, and multiple versions of highly refined analyses of cumulative and individual chemical risk levels have been completed and peer reviewed in great detail.

a. Acting sooner, given outstanding deadlines

Further slippage in meeting FQPA deadlines also seems likely. Given that in December 1999 we are still reviewing and refining science policies and cumulative risk methodology, the agency will be hard-pressed to complete a cumulative OP-carbamate risk assessment until late in the year 2000. Another three to six months will be needed to decide how to divide the necessary degree of risk reduction across some 650 crop uses. More time will be needed for the task of negotiating label changes and tolerance reductions with registrants, some of whom may choose to fight the agency's risk findings through one or more venues. Administrative steps needed to reduce real world pesticide risks will take another half-year to put in place. And so, optimistically, the first major impacts on field use of OP-carbamate insecticides and other List 1 chemicals might occur in crop year 2002.

b. Not waiting for absolute certainty

If the agency's goal is to truly protect people from the cumulative exposures they face in real life, as the statute mandates, EPA must move ahead with cumulative assessments even before all methodological issues are resolved and before complete data sets are compiled for every individual pesticide. Similarly, when a CRA confirms that risks are excessive, the agency without delay should begin to target regulatory actions on the known "risk-driver" uses. The agency should not wait to meet an unrealistic and unattainable standard for risk assessment certainty and data completeness.

To the extent there are toxicological or exposure data gaps and/or methodological uncertainties, the FQPA directs EPA to retain an extra margin in setting tolerances at levels that meet the FQPA's safety standard. The FQPA changed fifty years of lax policy by mandating prudent action to reduce risks to infants and children, while better data and more refined methods are developed. By delaying the initiation of cumulative assessments until all scientific issues are resolved and all data gaps filled, EPA undermines the public health protection provided by this critical new provision of the FQPA.

3. Appropriateness of Conducting a CRA, Selecting Exposures and Endpoints.

The guidance document prescribes far too narrow a set of circumstances for carrying out a cumulative assessment, given the public health provisions of the FQPA. The agency appears too willing to limit cumulative risk 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.

The document also describes circumstances for the removal of a subset of active ingredients from a Cumulative Mechanism Group (CMG). For example, the guidance document discusses the case of the organophosphate (OPs) and carbamate insecticides. The SAP is just the latest scientific group to conclude that these pesticides belong within a CMG because of the cholinesterase inhibition.[2] In addition, though, a subset of these pesticides may also cause developmental and other effects in young animals exposed to doses lower than the no-observed-effect level (NOEL) for cholinesterase inhibition. EPA suggests it might be appropriate to remove the latter subset of chemicals from the larger cholinesterase CMG. It also suggests that the additional FQPA tenfold margin of safety might not be retained for a CMG in cases where some but not all pesticides within the group are more toxic to neonates or children than adult animals. In both cases we present *scientific* reasons why such a decision would be unwarranted. Beyond the scientific reasons, removing active ingredients from a CMG is clearly inconsistent with the statute.

4. Accounting for the Cumulative Toxicity of Metabolites and Chiral Compounds.

Many pesticides, including organophosphate insecticides, have toxicologically significant metabolites. EPA appears to have no requirement for chemical-specific pharmacokinetic studies in developing animals that can help discern the contribution of important metabolites — such as malaoxon or dimethoxon — to children's risk. Nor has the agency adequately explained how it will consider the potentially important toxic effects of different metabolites in cumulative exposure and risk assessments in the absence of requirements to collect such data.

Pesticides, again including at least seven organophosphate insecticides, may also have stereoisomers, mirror-image compounds with different levels of toxicity; or, pesticides may degrade to metabolites that are themselves chiral. EPA apparently collects little or no optical radiation data to indicate the relative proportion of stereoisomers in pesticide products. Since the proportion of these isomers may vary from one production lot to the next, the toxicity of the various lots may vary as well. Similarly, it appears that EPA does not monitor whether pesticide metabolites themselves may have stereoisomers differing in their toxicity. Any risk assessment, including a cumulative risk assessment, that fails to account for the cumulative effects of various stereoisomers, metabolites or stereoisomeric metabolites will not adequately reflect the cumulative risk of pesticide mixtures as people are actually exposed to them.

D. General Issues Related to Cumulative Risk Assessment

In its guidance for cumulative risk assessment, EPA must clearly note that a public health context is the most relevant context for performing CRA, and for meeting the cumulative risk assessment provision of the Food Quality Protection Act. This public health context is set forth by ILSI in its 1999 report *A Framework for Cumulative Risk Assessment* –

> "Risk management by its very nature requires decision making in the face of uncertainty…Risk characterization is the bridge between risk assessment and risk management, and is critical to the development of public policy and the protection of public health. Effective risk characterization should provide an understandable public health context to inform and guide the users of the risk assessment … Traditionally, risk assessments have focused on examining a single chemical. In contrast, cumulative risk assessment shifts the focus to the health endpoint of concern. Cumulative risk assessments may offer several benefits over traditional single chemical, single medium evaluations." [3]

As also described in the ILSI report, the benefits of doing CRA include the following:

- "An evaluation of concurrent exposures and multiple risks is more likely to reflect actual conditions than a single medium, single exposure assessment." [4]
- "Appropriate combination of exposure and toxicity data could mean that uncertainty is reduced." [5]
- "Cumulative risk assessment addresses growing public concerns about multiple exposure and risks, and provides for both industry and regulators to manage cumulative risks." [6]

1. Providing a Reasonable Certainty of No Harm to Infants and Children When Each Child's Experience Varies

As stated, any guidance document for cumulative risk assessment must be firmly placed in a public health context to assure that the child-protective provisions of the FQPA are met. In particular, the strong health-based standard of the FQPA is that tolerance levels must be set so as to provide a "reasonable certainty of no harm" to infants and children. We take it as given that this standard applies to all children in the country, and not just a subset.

The diets of children vary greatly across individuals and over time. They consume beverages from many different sources and can be exposed to pesticides in water through many routes. Children vary greatly in their behavior and geographic proximity to sources of pesticide exposure. Indeed, all these factors conspire to create an extraordinarily variable and broad distribution of exposures across the entire population of children.

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. Such data will necessarily understate the pesticide exposures of children living in areas of greater pesticide use (both agricultural and residential), or who happen to suffer the consequences of illegal or careless pesticide applications. The only way EPA can generate regulatory decisions that provide a "reasonable certainty of no harm" to all children, as the FQPA mandates, 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. These would include children and the fetuses of women living in agricultural areas where pesticides are used intensively. Decisions that adequately protect these children and these women will surely also protect others.

2. Cumulative Impact on Health vs. Common Mechanism

The proposed guidance document sets out when and how EPA will conduct a cumulative exposure and risk assessment for chemicals found to pose risks through a common mechanism of toxicity. At several points in the document, EPA appears more concerned with narrowing the scope of cumulative assessments than it is with assuring that these assessments protect public health, and provide a reasonable certainty of no harm as the FQPA requires.

a. Overly Narrow Focus on Pesticides Alone

First, at the most basic level EPA guidance is entitled, "Proposed Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity," yet the statute clearly indicates that the cumulative assessment must be based upon the cumulative effects on infants and children of pesticide residues "and other substances that have a common mechanism of toxicity." (FFDCA Sect. 408 (b)(2)(C)(i)(III)) The guidance never adequately explains how non-pesticide chemicals and other substances are to be incorporated into the cumulative risk assessment; or if they are not to be

incorporated, then what assumptions must be made to account for this gap.

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. Tolerance decisions should be based on the additional risks posed by pesticide exposures, taking into account risks from other chemicals people are exposed to, as well as other factors impacting sensitivity to a given set of pesticides. 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 toxic endpoint.

b. Artificial distinction between CMG and CAG

Second, EPA strives in the guidance to define circumstances when chemicals that fall within a common mechanism group (CMG) may be dropped from a common assessment group (CAG). We strongly urge against this effort. The agency has struggled for three years to reach closure on how to define a common mechanism of toxicity, yet now seems determined to create another opportunity to debate many of the same technical points.

We see little benefit in establishing first a CMG, and then carrying out another round of assessments to trim it down to a CAG. This added step layers onto an already complex process another unnecessary decision-point that will need final criteria, be subject to disputes, and take up time before bodies like the Scientific Advisory Panel.

Instead, we recommend that EPA carry out its cumulative assessment on all registered uses of chemicals within a CMG. Those chemicals and/or specific registered uses for which there is affirmative evidence indicating a lack of actual use or a lack of exposure will naturally not contribute greatly to estimated risks, and therefore will not be subject to further analysis.

c. Missing hazards

Third, we worry also that EPA is circumscribing cumulative risk assessment too narrowly on the hazard side. The document makes it clear that EPA will limit 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 statute again seems clear on this point. EPA's mission is to protect children from all risks across all exposures from pesticides and other substances in a CMG, not just the single most universally shared risk within a CMG. In its 1998 report ILSI suggests — and we concur — that a mechanism of action or toxicity should never be defined or analyzed at only one level of injury, ignoring the factors at work at higher or other levels of organization and analysis.[7] The ILSI report authors correctly state –

> "An adverse health outcome will probably not be attributable to a single event, but rather to a cascade of many events." [8]

Accordingly, it is important in a cumulative risk assessment to assess factors contributing to hazard at the subcellular, cellular, tissue, organ, and whole body levels. Likewise, the full range of potential adverse mechanisms through which hazards can arise must be taken into account. In the case of the OPs, this range of mechanisms surely include all those affecting development, the functioning and regulation of the immune and reproductive systems, direct effects on neuronal synthesis of DNA as well as other neurotoxic effects, in addition to cholinesterase inhibition.

3. Accounting for the Toxicity of All Metabolites and Stereoisomeric Compounds

a. Metabolites

Many pesticides, including organophosphate insecticides, may have toxicologically significant metabolites. For example, malaoxon — the bioactivated form of malathion — inhibits acetylcholinesterase about 1,000–fold more strongly than does malathion.[9] Similarly, EPA acknowledges that dimethoxon, a significant metabolite of dimethoate, is 75-100 times more potent than dimethoate in inhibiting acetylcholinesterase. Moreover, this metabolite is found under field conditions on food crops. One of the chief metabolites of chlorpyrifos, chlorpyrifos oxon, inhibits cholinesterase more strongly than the parent compound, but appears to be very short-lived. It breaks down to TCP, a metabolite that is much more persistent in blood, and based on a limited sample may be found in the urine of up to 92 percent of children, as was documented in EPA's recently released chlorpyrifos preliminary risk assessment. The impact of these metabolites on developing animals — where even short-lived compounds could conceivably have irreversible effects on the nervous system — is unclear, but heightens the need for prudence in carrying out cumulative assessments.

EPA appears to have no requirement for chemical-specific pharmacokinetic studies in developing animals that would aid in discerning the contribution of important metabolites, such as malaoxon or dimethoxon, to children's risk.

b. Chiral compounds

Chiral compounds are those which have two or more stereoisomers, or enantiomers, identical in their constituent elements, but which are mirror images of one another. Enantiomers can vary greatly in their individual toxicity. At least some organophosphates are chiral or have chiral degradates or contaminants.[10] For example, both malathion and malaoxon have stereoisomers and the toxicity of the latter may vary by up to 22–fold. The most potent malaoxon stereoisomer may be 22,000 times more potent an inhibitor of some types of cholinesterase than is malathion.[11]

In terms of developmental toxicity, the importance of stereoisomeric mixtures is evident from experience with thalidomide. Dr. Chuck Thompson reports that after the teratogenic effects of thalidomide were discovered, analysis showed that thalidomide was in fact a stereoisomeric mixture with one stereoisomer conferring positive effects to prevent morning sickness while the other stereoisomer possessed teratogenic properties.[12]

It has been suggested that at least seven of the thirty seven organophosphates registered by EPA have chiral centers, and therefore the potential for steroisomeric forms with vastly different toxicities. These include malathion, naled (which has a chiral carbon atom), cadusafos (two chiral carbons, four enantiomers), fenamiphos, isofenphos and profenofos (all of which have chiral phosphorus atoms).[13] EPA has stated that it does not know the relative ratios of the specific enantiomers in the technical products of cadusafos, naled, fenamiphos, isofenphos and profenofos, and presumably malathion – for which a preliminary risk assessment has not yet been released.[14]

Chiral OPs therefore are sold as mixtures, with two or more enantiomers of possibly varying toxicity, and EPA has no regulation or optical rotation data to assure that this mixture remains identical from one batch of the pesticide to another.[15] Naturally, the toxicity of the stereoisomeric mixture probably will vary as the mixture itself varies — perhaps widely—from one pesticide lot to another. EPA admits that it as yet has no policy on how to treat chiral OPs. In the interim, it simply assumes that the stereoisomeric mixture that was registered is the one to which any person is exposed.

This assumption is both unscientific and unprotective. Until data are available that are specific to mixtures of stereoisomers or other parent compound/metabolite mixtures for individual pesticides, any cumulative risk assessment involving these chemicals (including that for the organophosphates) will be incomplete. In this case, the most health protective step would be for EPA to retain an additional 10X factor in its risk assessments as mandated by the FQPA for toxicity data gaps.

4. Including OPs and Carbamates in a Single CMG

We applaud the strong message sent by the SAP in its September 22, 1999 Final Report covering Session III –

> "The Panel agreed unanimously with OPP's conclusion that carbamate pesticides that inhibit acetylcholinesterase should be grouped with the organophosphorous pesticides that also cause acetylcholinesterase inhibition."

In the comments that follow we often refer to examples involving the Cumulative Mechanism Group based on cholinesterase inhibition. In light of the SAP's clear guidance, we assume this CMG will include (although not necessarily exclusively) both food use OP insecticides and carbamate insecticides. This decision is both solidly science-based and consequential in terms of impacts on cumulative risk levels. For example, there are 121 OP and carbamate insecticide crop-food combinations for which the U.S. Department of Agriculture's (USDA) Pesticide Data Program (PDP) found residues in 1994-1997 testing (see Appendix Table 1). Carbamates accounted for 31 of these cases.

E. Specific Comments on "Chapter 4: Exposure Assessment and Characterization"

1. CMG vs. CAG

In section 4.2, EPA lays out a series of criteria and principles governing the identification of a Cumulative Mechanism Group (CMG) and a Cumulative Assessment Group (CAG). Ultimately, the agency has determined the CRA will be carried out on the pesticides judged to remain within the CAG. After identifying a CMG, EPA states it will determine whether there are some chemicals and/or exposure pathways for which there is little or no chance of "overlapping exposures." In the absence of overlapping exposures, the chemical, or a route of exposure will be dropped from the CAG.

Two circumstances could lead to a judgment by EPA that a certain chemical or route of exposure does not belong in a CAG. First, EPA might reach such a judgment after consideration of substantial evidence from monitoring studies on various exposure pathways that show little if any exposure. One example might be the absence of residues in food from most applications of pre-emergence herbicides. Another, more common, scenario would be an EPA decision about a particular exposure pathway based upon little actual data indicating whether or not exposures would be "overlapping" or occur at levels posing risks worthy of regulatory attention.

We assert that in the first case scenario – ample data showing essentially no exposure – the routes of exposure and chemicals could and should be included in the CMG , and retained in the cumulative risk assessment. They just won't contribute much to risk totals. In the second case, where there is a lack of monitoring or other exposure data, the FQPA mandates the agency to retain an added safety factor pending the development, submission and review of such data.

a. Unintended consequences, unnecessary complexity

By proposing to truncate a CMG by forming a CAG, EPA is setting up a method that will, as an unintended consequence, circumvent one of the key new provisions of the FQPA. In addition, we fear the process of distinguishing between CAGs and CMGs will prove unnecessarily complex, contentious and resource intensive. Time spent dealing with very low, possibly nil exposure and risk scenarios will divert EPA attention and resources from where the FQPA directs the agency to focus — the upper end of the risk distribution.

Instead, EPA should move forward with cumulative assessments on all substances in a CMG. We assert that in the first scenario described above — where there are ample data showing essentially no exposure — the routes of exposure and chemicals could and should be included in the CMG, and retained in the cumulative risk assessment. They just won't contribute much to risk totals. In other words, any use resulting in low or no exposure will simply drop out of the risk estimate, eliminating the need for the proposed "exclusionary criteria." In the second case described above — where there is a lack of monitoring or other exposure data — the FQPA mandates EPA to retain an added margin of safety pending the development, submission and review of such data. Many pesticides and/or individual uses lacking complete toxicology or exposure data will receive an

additional 10X margin of safety. Even with this additional factor, however, some pesticides or uses will still contribute very marginally to total estimated exposures and risk.

b. Waiting too long

In Section 4.2.1, EPA sets forth principles governing decisions regarding the identification of a CMG. The second principle states –

> "A cumulative exposure assessment generally should not be conducted until an adequate aggregate exposure assessment has been conducted for each member of the CMG."

We urge EPA to drop or significantly amend this principle. Its major outcome will be delays in reaching decisions that better protect public health. Consider the case of the OP insecticides. Under this principle, EPA would delay carrying out a cumulative risk assessment until it had completed individual assessments on all registered OPs within the CMG. Yet EPA might be able to complete individual assessments on most widely used OPs, and still be stymied on a cumulative OP assessment because some registrants had delayed in submitting data on a few older OPs no longer used very widely. Given the many factors outside the agency's control that can influence when it can finish a given set of individual assessments, it is unsound policy to postpone a cumulative assessment until all individual assessments are complete.

Instead, such an approach could provide a perverse incentive to delay completion of individual assessments if the subsequent cumulative assessment (whenever completed) appeared likely to reflect unfavorably on one or more particular chemicals within a CMG.

We urge EPA to move forward with a cumulative risk assessment sooner rather than later. Such assessments should be based on the best data available and initiated whenever individual assessments on the active ingredients within the CMG suggest that there may be inadequate margins of safety when total exposures across the CMG are fully taken into account. In the context of the OPs, EPA should have started the cumulative assessment process after two or three individual OP assessments were found to approach or exceed safe levels of exposure when considered alone. To fully meet the FQPA mandate, EPA should carry out a CRA as soon as the agency defines a CMG. Delay in the face of known risks and exposures — surely the case with the OPs — endangers the public's health needlessly by postponing the initiation of regulatory actions targeting the uses driving the most intractable risks.

c. Not accounting for cumulative effects if individual effects are small

In its third principle for governing CMG decisions, EPA makes it clear that it considers a cumulative assessment to be an iterative process involving stages of refinement. The agency states:

"Initial cumulative assessments should not attempt to quantify risk resulting from minor exposure pathways. Exposures from minor pathways should in the first instance be considered qualitatively."

Examples of exclusionary criteria for use in identifying a "minor exposure pathway" are then offered. These include any chemical-exposure pathway that contributes less than 1 percent of the total exposure. We strongly object to this criterion. The problem is this: there are some 2,100 tolerances covering 800 plus food uses of OP and carbamate insecticides, all or most of which are likely to be included in a CMG for cholinesterase-inhibiting insecticides. Consumers Union has calculated a crude measure of aggregate dietary risk, which Consumers Union calls "residue toxicity load" for all OP and carbamate crop uses resulting in residues detected in Pesticide Data Program (PDP) testing since 1994. For a given pesticide-crop use, its "residue toxicity load" is calculated by the following formula –

Residue Toxicity Load = (% Positives) x (Mean of Residues) x (Inverse Chronic RfD) x (Pounds of Food Consumed)

This measure of the overall contribution of individual pesticide-crop uses takes into account the frequency of detection, mean levels, relative potency as measured by chronic RfDs, and the volume of food consumed. In the data referenced below, we used residue data on domestic samples only in order to focus on uses of pesticides in the U.S.

Using this methodology, the Consumers Union analysis found there are 121 OP plus carbamate insecticide-crop combinations drawing just on PDP data for 1994-1997. *Table 1*, attached, presents the calculation of residue toxicity units for these cases and ranks them from the largest share of risk to the least. Among the insights from *Table 1* is that each of 100 individual OP or carbamate uses accounts for 1 percent or less of the total residue toxicity load, yet cumulatively their impact is enormous. Under EPA's third principle for identifying CMGs, all of these uses might have been considered "minor" and therefore ignored in the CRA. Therefore, we fully support EPA focusing first on the top risk drivers, but the agency must also direct attention further down the list to assure that total OP and carbamate risks are reduced after a first round of high risk reduction measures.

b. Problems of risk trading

Once EPA takes action against the top dozen or so risk drivers — regardless of how risk is ultimately measured — overall risks will surely fall. However, risk trading may erode a significant share of the progress in reducing risks. Risk trading occurs when farmers switch to other pesticides in response to regulatory restrictions. Since there are several lower risk OPs and at least two lower risk carbamate alternatives for virtually all high-risk OP and carbamate uses, the stage is clearly set for possibly significant risk-trading. <u>If EPA initially ignores individual pesticide-crop uses accounting for less than 1 percent of cumulative risk, it will undermine its ability to track and minimize risk-trading.</u>

In addition, once major risk-drivers are dealt with, there may well remain several hundred OP and carbamate uses, each of which initially posed 1 percent or less of baseline cumulative risk. The sum of exposure and risk across so many uses may still exceed the CMG Reference Dose or a minimally acceptable MOE. No one straw will ever break the camel's back. Yet EPA's proposed criterion suggests that the impact of all such "straws" be ignored.

It is also important to note that as EPA takes action on the uses that drive pesticide-specific exposures today, other uses and exposure pathways necessarily will account for a larger share of total exposure and risk. The agency could miss future risk-drivers by excluding them from today's assessments and from efforts to build a stronger exposure database to support decision-making.

c. Including foreseeable exposures

Instead of making a determination up front about which exposures and chemicals to exclude from the CRA, EPA should include in the CRA at a minimum all dietary exposures and *all foreseeable non-dietary 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*.

d. Chemicals with additional, greater toxic mechanisms

EPA proposes an additional exclusionary criterion that must be revised. This criterion states that some subset of the active ingredients within a 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.

Let's consider an example to make the potential impact of this exclusionary criterion more concrete. Suppose six OPs are found to be developmental neurotoxins at dose levels below those noted to cause any cholinesterase inhibition, and therefore lower than cholinesterase inhibition NOELs derived from studies in adult animals. The agency could invoke this exclusionary criterion to exclude these 6 pesticides from a cumulative risk assessment of OPs based upon cholinesterase inhibition, even though the latter is another pathway of toxicity for these chemicals.

Across a major family of pesticides like the OPs or carbamates there may be one common mechanism that unites a large group of pesticides – in the case of the OPs and carbamates, cholinesterase inhibition. However, there may also be another toxic effect and common mechanism associated with a subset of these pesticides. If the second toxic effect results in NOELs below the broader CMG, the agency should proceed with a two-track CMG process. It would be unscientific and less than health protective for the agency to remove the second set of chemicals from the initial cholinesterase inhibition 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.

e. Original toxic mechanism still remains

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. This presumption is scientifically unsound. Moreover, it ignores the possibility that two groups of chemicals may have cumulative effects resulting in the same toxicity endpoint, although via separate mechanisms. Recent studies suggest this may be the case with at least some organophosphates. In a 1999 study, Slotkin points to evidence that chlorpyrifos elicits damage in the developing brain by both cholinergic and noncholinergic mechanisms, the latter including direct inhibition of DNA synthesis.[16] Both mechanisms could lead to irreversible damage in the developing brain.

In addition, since much of EPA's experience with designing and assessing the results from neurotoxicological studies has occurred under the presumption that cholinesterase inhibition is the most sensitive effect, it is logical to question whether the noncholinergic mechanisms described by Slotkin would be detected as sensitively. Brimijoin and Koenigsberger, too, discuss numerous scientific studies supporting the "nonclassical" view that acetycholinesterase and butyrylcholinesterase function in the nervous systems in ways outside the transmission of nerve signals in cholinergic neurons.[17] Unless underlying toxicology studies have assessed these alternative functions, it is scientifically incorrect for EPA to assume that NOELs for OPs based upon cholinesterase inhibition have taken into account all toxic effects of importance to infants and children.

For all these reasons, EPA should drop its scientifically unsupported criteria for distinguishing between CMGs and CAGs. These criteria constitute bad science and poor public health policy.

2. Dietary Exposures

a. Food

Section 4.2.2.1 describes dietary exposures. We commend the agency for acknowledging in this subsection and in several other places in Chapters 4 and 6 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 obviously key pathway.

We also agree 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. Given that many fresh fruits and vegetables and tap water in some parts of the country routinely contain multiple pesticide residues, including two or more pesticides acting through a common mechanism, this refinement in EPA's exposure assessment methods is fully justified.

We also support EPA's proposal generally to not use field trial data in estimating exposures in a cumulative assessment. The agency is correct in noting that no methodology exists to translate field trial data to PDP-like data on food as eaten. Developing such a methodology probably would prove to be more expensive than expanding the PDP to periodically encompass additional pesticide-crop combinations of potential concern.

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, the 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.

b. Drinking water

In discussing drinking water exposure and pesticides "with minimal monitoring data," the agency envisions the use of modeling data "once credible, validated models become available to estimate pesticide concentrations in drinking water." While we can support the use of such models to set priorities for further drinking water monitoring studies, the agency's longer 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, the FQPA requires EPA to retain an added safety margin to account for possible water-based exposures. We note that if EPA merely reserves 20 percent of the CMG Reference Dose for water-based exposures, as proposed, it would amount to a *de facto* lowering of the FQPA's additional 10X margin of safety to a 1.2X margin of safety added to the CMG Reference Dose or MOE.

3. Dealing with "Markovicity" in the Context of CRA

EPA needs to direct further attention to another key challenge in working toward accurate dietary exposure estimates that are fully health protective. EPA's proposed use of Monte Carlo simulations is based on the assumption that what a child eats on one day is independent of what they eat the next day. Plus, Monte Carlo simulations assume that the residues on an apple consumed in the morning are independent of the residues on another apple eaten later in the day. Clearly, neither assumption is correct in all cases, especially those involving fresh fruits and vegetables consumed at home or at a summer camp, for example. Very often consumers purchase a bag of apples, oranges, or potatoes and these are served over several days.

In the final report to its September 22, 1999, review of the LifeLine exposure and risk assessment model, the FIFRA Scientific Advisory Panel states –

> "The world is a complex and highly multivariate place…[another] mistake occurs when a characteristic of an individual exhibits temporal autocorrelation, yet is assumed to be fluctuating independently from one time step to the next. When this

independence assumption (also called 'Markovicity') is inappropriate, it can result in grossly *under*estimating the dispersion of the final exposure." (Italics in original, SAP Final Report, Session II, September 22, 1999.)

In the case of acute dietary exposure assessment, the problem posed by the fact that fresh fruits and vegetables are not purchased in single sized servings arises both on the food consumption side and the residue side of the risk equation. On the consumption side, often a family or person purchasing food will seek out and stock up on whatever fresh fruits and vegetables are in season or offered at a special price. When a family stops at a fruit stand and stocks up on fresh cherries or ripe peaches, children will often consume very significant quantities at two or more times a day and over two or more consecutive days.

On the residue side, the Monte Carlo simulation will choose a random residue profile for each portion of an apple that the child reports as consumed during a given day. It is not uncommon for a child to eat a piece of a fresh apple three times during a day. It is likely that the residue profile for all apples from a bag are similar, and hence this approach is likely to underestimate exposures in many cases.

There is no easy way to solve this problem. Given the importance of a handful of fresh fruits and vegetables as risk drivers, especially in children's diets, EPA should define the upper bound of this problem by running a Monte Carlo that first adds up the quantity of each fresh fruit reported as consumed during a particular day and then selects a residue value. The results will reflect the improbable assumption that each serving of an apple during the day has the same residues. However, insights gained from this exercise may help point to a practical way to at least partially correct for Markovicity.

4. "Urban and Residential" Exposures: Localized pesticide use and exposure scenarios

We question another exclusionary principle discussed by EPA in Section 4.2.2.3, the section on "urban and residential" exposures. The section states that in evaluating the "urban" contribution in a cumulative risk assessment, extremely localized pesticide use and exposure scenarios should be excluded from regional or national assessments. Again, we object to a categorical restriction in an exposure and risk assessment just because available data shows that a particular product is only used in one area or under narrow circumstances. Given the nature of urban and residential pest management problems, use of a particular pesticide can rise dramatically from not-at-all to hundreds of thousands of pounds and millions of people exposed.

The example of temephos use for mosquito control in Florida is illustrative. The encephalitis-triggered mosquito spraying of the New York City area in the fall of 1999 is another case in point. Clearly, the FQPA safety standard — that aggregate pesticide exposures from any individual chemical pose a reasonable certainty of no harm — applies to each person, and not simply those persons living outside New York City, outside

Florida, outside California's Central Valley or outside the Mississippi watershed, to name some relevant examples. In this light, the latter EPA exclusionary principle is at odds with the public health aims of the law itself.

It might be appropriate for EPA to restrict the consideration of potential exposures and risks from an non-dietary pesticide use under one condition — label restrictions which explicitly limit the use of a pesticide to some specific region (or regions) and circumstances. The public health implications of even old or seemingly obsolete pesticide labels must be considered under the FQPA.

5. Assessment of the Exposed Population

a. Geographic considerations

Geographic considerations of exposure are discussed in Section 4.3, where EPA describes ways in which it will strive to customize exposure and risk assessments so as to match specific demographic data to different regions, populations, and times of the year. In this and other sections, EPA describes extremely comprehensive and sophisticated exposure databases that would provide risk assessors with a degree of detail and precision unthinkable just a few years ago.

In this section, EPA states that exposures through food will vary the least as a function of location and time, followed by water based exposures which will generally reflect similar seasonal patterns in certain parts of the country among people drawing their water from the same source. Exposures other than diet are thought by EPA to vary the most dramatically across the country and as a function of a variety of demographic factors, such as economic status, ethnicity, whether a family has a lawn or garden, or whether the family resides in an area where termites are endemic. Further, the draft document states that "highly localized exposures of concern may suggest very different strategies for risk mitigation than exposures that are widely disseminated."

b. Missing exposures in agricultural communities

As noted above, EPA has failed, however, to consider one of the most obvious sources of geographic variations in exposure. As amply demonstrated in NRDC's report *Trouble on the Farm: Growing Up with Pesticides in Agricultural Communities*, millions of people, especially children, who live on or near farms and other areas where pesticides are applied regularly will likely experience substantially elevated levels of exposure.[18] Exposure sources common to agricultural communities (and currently largely ignored by EPA's risk assessments) include, among others: spray drift, especially onto homes and schools located near farms; higher indoor air concentrations of pesticides; contaminated soil blown from treated areas into yards, parks and playgrounds; contaminated soil tracked into homes; pesticide run-off into nearby drinking water sources; and clothing, skin and hair of farmers and farmworkers on return to their homes. EPA must incorporate these exposures into cumulative risk assessments to fully assure the FQPA's safety standard is met.

c. Foodsheds

In general, we agree with EPA that food exposures are likely to vary somewhat less than water or residential exposures. However, it is difficult to generalize. An individual's consumption of locally-grown food in a region where a particular pesticide is heavily used on that food could result in dietary exposures much higher than would be typical elsewhere in the country. In fact, 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.

d. Further refining food consumption data

While individual exposures, including dietary exposures, may be highly localized, we note that the tools EPA commands to mitigate dietary risks are almost all national in scope – tolerance levels, preharvest intervals, and application rates, methods and timing. In the case of imported foods, tolerance levels are the only control variable. Similarly, the National Food Consumption Survey potentially would allow regional dietary assessments to take into account differences in food consumption patterns. Residue data, on the other hand, currently is available only on a national, indeed international, basis. Accordingly, dietary assessments have been done on a national basis.

The USDA's PDP will soon become a source of subnational data on pesticide residues, at least for some key fresh foods like apples, peaches, pears, grapes and tomatoes. These are among the high consumption children's foods that are grown in many different regions with highly variable pests and pesticide use patterns. The PDP survey instrument includes information on where a given sample was grown, packed or processed, distributed, and sold to consumers. Unfortunately, these data have not been collected and reported in the majority of cases.

In a recent letter to the USDA on the PDP, Consumers Union urged the department to assure this information is recorded on a higher percentage of samples so that the efficacy of specific risk mitigation strategies – the extension of preharvest intervals, for example – can be monitored with real-world data.[19] EPA should support the development of these and other subnational databases relevant to pesticide risk assessment.

e. Protecting in the fact of predictable increased localized exposures

While more regional data relevant to dietary and non-dietary pesticide exposures are not yet available, EPA should not let the limited nature of the currently available information dictate how it intends to address more localized pesticide exposures to the individual in the future. The proposed guidance 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.

Drinking water based exposure is clearly regional and should be carried out drawing upon data relevant to a specific segment of the population – for example, people who get their water from a community water system drawing on surface water resources. EPA proposes to couple such regional drinking water estimates with regional dietary assessments. In general, we support the methodology EPA has set forth to do so. And we recognize that the more complete and accurate the database covering pesticide residues in drinking water, the more thoroughly water based exposures will be incorporated into the cumulative assessment.

Fine tuning of the regional or subnational data and cumulative risk assessments, however, should not serve to delay initial efforts to reduce risks. While there are major gaps in data on pesticides in drinking water, EPA and State regulatory agencies know the pesticides found most commonly in drinking water. There are ample data to draw upon in developing preliminary drinking water databases for inclusion in Monte Carlo simulations of cumulative exposure and risks in most of the major farming regions for those pesticides most commonly found in water. The USDA, through its PDP, may also start to include drinking water in its annual testing at some future date. By targeting certain regions and chemicals for more intensive sampling, the PDP program could provide valuable new data on the extent and significance of water based exposures, and provide an independent check for residues in water, as identified in other databases.

F. Specific Comments on "Chapter 6: Estimation and Characterization of Cumulative Risk"

1. Estimation and Characterization as a Tool for Prevention

We concur with the conclusion stated in the section of the ILSI report entitled "Public Health Implications of Population Cumulative Risk Estimates" –

> "The fundamental purpose of a cumulative risk assessment is the evaluation of public health risk. By examining the relationship between multiple exposures and common endpoints, CRA can provide a valuable tool to both the public health and environmental regulatory communities…In essence, CRA can focus prevention efforts by identifying key pollutants and sources, while providing improved refined information on sub-populations at highest risk." [20]

2. Need for an Integrative Public Health Statement

The ILSI report goes on to call for an "integrative public health statement" that places the results of a CRA into perspective, for both the public and for the risk manager. Such an integrative statement places both exposure and toxicity measures into a metric and time frame that allows for people to understand the possible adverse health consequences of projected exposures, who might be affected, and with what probability.

In the case of acute risks, the authors of the ILSI report suggest "total person-days of exceedence" relative to a defined benchmark dose (i.e., a RfD, or the dose leading to a minimally acceptable MOE) as a useful metric to incorporate in a "integrative public health statement." We concur with this suggestion and urge EPA to adopt it as one of the core measures of excessive acute risk.

3. Summary of EPA's Proposed Steps to Achieve CRA

`Table 6A in the ILSI report sets forth a useful eight-step process for cumulative risk assessment.[21] Using ILSI's terminology, these are –

1. Description of the components and rationale for cumulating risk
2. Aggregate multi-pathway measures of environmental concentrations
3. Probabilistic distribution of population exposure levels, including subpopulations
4. Comparison of population exposure to a toxicity based "bright-line" – i.e., cumulative RfD
5. Estimate of the portion of a population potentially exposed in exceedence of toxicity metric
6. Exposure apportionment to identify exposure drivers
7. Quantitative ranking of the contribution of mixture components total risk
8. Integrative Public Health Statement

In the proposed guidance document, EPA offers detailed processes and decision-criteria for steps 1 through 4. The adequacy of a CRA in meeting public health requirements of the FQPA will also depend upon how effectively steps 5 through 8 are carried out. EPA must spell out its thinking and plans in much more detail in the guidance document relative to steps 5 through 8.

4. Goals for Future Levels of Certainty Should Not Impede Action Today

Much of Chapter 6 in the draft guidance document describes the ideal cumulative risk assessment in a world where data are free and complete and there are no limits to the time and resources available to carry out CRA. For example, in a passage in the introductory section to Chapter 6 EPA states that –

> "Each of the individual 'sub-assessments' should be linked back to the same person and the intake should reflect the dietary (food), drinking water, and residential intakes that are for the same individual at the same time, in the same place, and under the same demographic conditions. In other words, the cumulative exposure to the CAG should agree in time, place, and demographic characteristics." (Underlining in original, p. 18).

EPA needs to distinguish more sharply between ideals to work towards in risk assessment, and the methods and data that are currently accessible, and how these can be used to better describe risks from cumulative exposures and to better protect public

health. EPA must state clearly that the criteria and principles describing the ideal risk assessment do not define an implicit "minimum data set" to support regulatory actions.

5. The Second Half of the CRA Process Needs More Attention

The guidance document explains how EPA plans to progress through step 4 in the taxonomy of a CRA as set forth by ILSI. Drawing on data of individual eating days from national food consumption surveys, on PDP residue data augmented with the Food and Drug Administration (FDA) results for additional foods, and on data about pesticides in drinking water, the agency has adequate data on the same person at the same time in a given location to support Monte Carlo distributions of exposure and risk within key population subgroups, like children ages 1 through 5, or non-nursing infants. Then, for all the eating day episodes in a Monte Carlo simulation, the agency can convert the exposure and risk estimate to a ratio of the individual's actual exposure/risk and then compare to the person's acute Reference Dose, which would simply be the individual's weight in kilograms times the acute RfD for the chemical or CMG. All eating days with a ratio value over one are cases where the "bright line" has been exceeded.

a. Step 5—Estimating highly exposed populations

These same eating day episodes must become the principle focus of the further analysis called for in steps 5-7 of ILSI's eight step process. 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 non-dietary exposure will also have to be taken into account at this point to determine how many additional eating day episodes result in excessive risks.

b. Steps 6 & 7—Identifying and ranking risk drivers

Step 6 – identifying risk drivers – is clearly a critical step. 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 pesticide-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 pesticide-crop/food combinations can then be aggregated by food or by active ingredient, producing two additional rankings – share of total risks by crop/food, 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.

c. Step 8—Crafting the Public Health Statement

Crafting an "Integrative Public Health Statement" is step 8. By drawing on the above results, EPA can and should explain in the plainest language possible 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.

d. Assuring sufficient action, measuring results, additional adjustments

The greater the percentage of eating days in the excessive risk pool, and the greater the degree of exceedence, the more aggressive EPA will need to be in imposing risk reduction measures on risk-driver uses and the farther down the risk driver list EPA will need to go in order to achieve an acceptable degree of risk reduction.

One advantage of this 8-step approach is worth mentioning. How will EPA determine that it has imposed an adequate degree of risk reduction? How will it monitor over time whether the risk reduction measures imposed collectively reduce exposure and risks as hoped and projected? At least for the OPs, having proceeded through the eight step process, EPA has the data to demonstrate two conclusions. First, total exposure to OPs is excessive. This much is clear from the fact that several individual OPs appear to exceed or approach their individual acute RfDs in risk assessments to date and so, when evaluated together, they will necessarily result in a sizable "excessive risk pool." Second, EPA has the data to rank the dietary risks associated with specific OP-carbamate insecticide uses. Together, these two pieces of information: a) justify EPA action to reduce risks generally, b) clearly direct the agency where to start in the risk mitigation process, and c) provide useful detail for characterizing and communicating cumulative risks from organophosphate insecticides to the public.

Further, as EPA decides upon risk reduction measures — canceling food uses of methyl parathion, for example — the agency needs to project what will happen as a result to residues in foods. In addition, it must guard against risk trading and to do so, the agency will have to project the alternative pesticides or Integrated Pest Management (IPM) systems that farmers are most likely to switch to. In some cases it will be relatively easy to project the consequences of alternative pest control practices; farmers switching from an OP to mating disruption (and use of an insect growth regulator when needed) to control coddling moths, for example, will vastly reduce risk. In other cases, EPA may have to impose risk reduction measures on most or all retained uses of active ingredients within a CMG — especially uses known to drive risks.

For example, in its attempt to reduce OP risks to children consuming apples and pears, the agency concluded, as many others had, that methyl parathion was a major risk driver. But the agency also knew that many of the apple acres treated in 1999 with methyl parathion would be treated more heavily in year 2000 with azinphos methyl, chlorpyrifos, and phosmet. So when the agency announced the end of methyl parathion food uses, it also announced steps to reduce risks from azinphos methyl on apples and pears. While

we believe the steps the agency took in the case of azinphos methyl on apples and pears will prove inadequate, we commend it for recognizing that to reduce OP risks on apples, pears and other risk-driver crops, the Agency also needs to impose significant risk mitigation measures on other OPs and carbamates that will remain.

As EPA begins to impose risk reduction measures on OPs registered for use on apples and other major children's' foods, it will be necessary to calibrate the scope and aggressiveness of risk reduction to the degree of risk reduction deemed necessary. Doing so will force the agency to make "educated guesses" regarding the impact, for example, of a given change in preharvest intervals on the frequency of the relevant pesticide residues and the level of those residues. EPA can then draw on these expected changes in residue profiles across all OPs (that retain apple registrations, for example) in determining whether the target level of risk reduction has been achieved.

The process of reassessing the distribution of risks across remaining OP food uses, and perhaps imposing additional risk mitigation measures, will need to go on until credible monitoring data and updated CRAs show that cumulative risks have been brought below the "bright line" delineating excessive risk, however EPA ultimately defines and chooses to establish that line.

5. The Critical Outcomes of a Cumulative Risk Assessment

The strategic steps set forth in Section 6.2 by EPA are encouraging and largely consistent with the steps envisioned as necessary by ILSI. Upon completion of a cumulative risk assessment, the agency states its intent to assess the relative contribution to exposure and risk of each chemical and use pattern through each route of exposure. We set forth above one way for the agency to draw upon this sort of analysis to facilitate the identification of risk mitigation priorities and to make the determination of how much risk mitigation is adequate to meet the basic goal of the FQPA.

As discussed earlier, there are three key advantages to carrying out the cumulative risk assessment required by the FQPA –

- CRA can estimate risks in a fashion that better reflects the public health outcomes from chemical mixtures as people are exposed to them in real life, rather than artificially restricting analyses to just one chemical and one medium at a time.

- CRA can determine the extent to which overall exposure and risks must be reduced across all uses of all pesticides in a CMG; and

- CRA can identify and prioritize the crop-chemical, pesticide-use pattern combinations which contribute most significantly toward risk so that a given, necessary degree of risk reduction can be achieved within the CMG.

a. Need for more explicit discussion

In Chapter 6 EPA hints at how cumulative risk assessments will meet the above needs. However, we challenge the agency to discuss these critical questions more explicitly. For example, EPA makes the following statement in the introduction to Chapter 6 --

> "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."

b. Increased, rather than decreased precision

EPA needs to rethink this statement for several reasons. First, and most generally, EPA statement 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. In fact, as pointed out by the recent ILSI panel –

- The combination of exposure and toxicity data in a CRA may mean "uncertainty is reduced and confidence in the risk assessment is increased" relative to single chemical assessments.[22]

- Moreover, a CRA provides the risk manager/mitigator with information about several compounds at once, allowing for a comparative evaluation that can determine relative risk contributions from each compound as well as identify those compounds that drive the cumulative risks;[23] the latter is an especially important factor for risk mitigation.

- Finally, the CRA can help focus the risk manager on coordinated strategies for tackling cumulative risks,[24] whereas a single chemical approach will obscure such opportunities.

c. Cumulative and individual assessments draw on the same datasets

In addition, both individual chemical risk assessments and cumulative risk assessments will draw upon essentially the same food and drinking water consumption database and eating day records, as well as the same residue databases. Thus, Monte Carlo simulations will produce a probabilistic distribution of exposures and risks either to a single chemical or to multiple chemicals within a CMG. Since either individual or cumulative risk assessments may be based upon similar databases and methodologies, they would appear to share many basic sources of uncertainty.

d. Normalizing toxicity

Second, the major additional step that might affect precision in going from a single chemical to a cumulative assessment is the need for a method to normalize toxicity across chemicals within the CMG. Given the great care that EPA is investing in the

establishment of the CMG and identifying "points of departure" (NOELs or lowest-observable-effect levels (LOEL) for specific common toxic endpoints), we think the normalization process proposed by EPA is both straightforward and accurate. Any errors in the normalizing of toxicity across pesticides in a cumulative assessment will arise from imprecision in individual pesticide NOELs and LOELs for the common endpoint. However, this same caveat would apply when comparing results across individual assessments, so there is actually no added source of imprecision as a result of the process of adding risks across all exposures recorded in a given Monte Carlo simulation.

e. NOEL vs. NOAEL

At the same time, though, we must note that the FQPA and its legislative history is clear and specific in directing EPA to base its regulation of pesticides and determination of levels of concern on the no-observed-effect level (NOEL), and not on the no-observed-adverse-effect-level (NOAEL) as is EPA's current practice. So, while EPA's normalization process appears reasonable, we object to the actual points of departure used to date.

f. Managing risk trading

A third reason why EPA must reconsider the limits it places on the usefulness of a cumulative assessment arises from the ultimate purpose of the CRA: understanding and prioritizing individual contributors to real world cumulative risks with the intent of mitigating those risks. The agency cannot evaluate trade-offs between and across multiple chemical risk mitigation options from data in individual chemical assessments. The only way to reliably identify the factors actually driving real world risk is to quantify those individual chemical uses and routes of exposure that contribute most heavily to total exposure among the "excessive exposure" group.

3. Geographic Scale and Focus

In addressing the geographic scale of cumulative assessments in Section 6.3.2, the agency properly notes that a national dietary (food) assessment will be the backbone of any cumulative assessment across all uses within a CMG, though needed refinements to assess and account for regional variations in purchasing, diet and residue consumption should be addressed in forward planning. The need for regional assessments will arise immediately to take account of exposures through drinking water, although by far the best method to do so is direct incorporation of a PDP-like drinking water residue database within a Monte Carlo simulation, as argued earlier.

Incorporating non-dietary exposures in the cumulative assessment poses more complex methodological issues that may need to be resolved outside the context of the results from Monte Carlo simulations. People exposed to pesticides in residential settings or agricultural communities may face higher levels of non-dietary exposure than in their food and drinking water, and their exposures may be brief or chronic. Pregnant women and children in farming areas, especially during seasons with frequent spraying, sometimes face major spikes in acute or intermediate exposures which will need to be factored into

CRAs. EPA must protect highly exposed populations, not just a national average. Collecting regional data and recognizing differences is an important step in assuring a reasonable certainty of no harm.

4. Cumulative Assessment Group and Risk Assessment Safety Factors

The FQPA's provision calling for the retention of an additional 10-fold safety factor serves two basic policy purposes. First, this provision works to shift the burden of proof toward registrants, in this way creating incentives for them to fill data gaps and more carefully study potential developmental effects. The second purpose is to assure, in the interim, that existing tolerances and pesticide uses still meet the Act's basic "reasonable certainty of no harm" safety standard for children. EPA undermines both of these goals by limiting the circumstances when it will retain an added safety factor.

Section 6.4.2 discusses the many critical issues arising from the selection of safety factors in the context of a cumulative risk assessment across all uses within a CMG. We agree with and support EPA's decision to retain the standard 10-fold uncertainty factors, to account for individual variation in susceptibility and for extrapolation between species, for the CMG as a whole.

We also concur with EPA's proposal involving uncertainty factors sometimes applied when there are flaws in the design or conduct of a toxicology study — for example, a study does not demonstrate a NOEL. These uncertainty factors should be applied at the individual chemical level before the cumulative assessment is carried out. The magnitude of the uncertainty factor should be set based on the quality of the data and EPA's best judgment on the NOELs that an adequately designed and conducted study would likely produce.

a. Overly limited use of FQPA margin of safety

We take exception, however, to the limited scope of the circumstances when EPA envisions the need to retain an added, child-protective margin of safety in carrying out a cumulative assessment. The statute states that the Administrator shall retain an added 10X margin of safety "for infants and children to take into account potential pre- and post natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children." The Administrator has some latitude in this strongly presumptive use of an additional margin of safety, in that she "may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Broad application of the 10X safety factor makes complete sense given that the FQPA was written in response to the findings of the 1993 National Academy of Sciences/National Research Council (NAS) report, *Pesticides in the Diets of Infants and Children*. This study concluded –

> "In general, the committee found that the current and past studies conducted by pesticide manufacturers are designed primarily to assess pesticide toxicity in sexually mature animals." [25]

In other words, 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.

b. Discounting relevant information

We object to another circumstance in which EPA is apparently inclined not to retain the additional 10X margin of safety for children. On page 29, the guidance document describes a CMG that fits the toxicological profile of the OPs. This CMG shares a common toxic endpoint, cholinesterase inhibition. But there is a second toxic endpoint associated with exposures to a subset of chemicals in the CMG, developmental neurotoxicity for example. In some cases the second common mechanism of action might suggest or reflect an additional avenue of sensitivity to toxic effects among developing fetuses or immature animals, whereas the first one does not. In deciding whether to retain the 10X for this CMG, the agency offers this caveat --

> "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 toxic mechanism — direct inhibition of DNA synthesis in developing brains, for example — should influence the magnitude of the FQPA margin of safety. We object to EPA's narrow reading of this key provision of the FQPA. In cancer toxicology, it's an accepted fact that exposure to the same chemical carcinogen can cause different cancers in animals than in people, and different tumors in the exposed young as compared to exposed adults. One cannot draw conclusions about the vulnerability or sensitivity of the young by looking at only one endpoint.

There is no scientific or public health reason for EPA to require that ***all*** pesticides within a CMG must display heightened toxicity to young animals before imposing an added safety factor.

5. Application of the "Incomplete Data Base" Uncertainty Factor

EPA proposes to apply the "Incomplete Data Base to Complete Data Base" (UF_D) uncertainty factor to the CMG as a group, after the cumulative exposure estimate is carried out. Incomplete data are likely to be a problem at several stages and levels of a CRA. Common data gaps introducing uncertainty into the assessment include uncertainty about:

- The selection of the common endpoint
- Multiple toxic endpoints, and the risks posed by the pesticides within a CMG

- How to account for multiple possible mechanisms leading to the same or multiple risks
- Individual chemical points of departure
- Lack of exposure data on a specific use or uses for a given chemical
- Lack of exposure data for all or most pesticides within a CMG for one or more routes of exposure.

This critical issue came up during the SAP's September 23,1999 review of Chapter 5 of the guidance document. We note that one panel member in the Final Report raised strong concerns regarding the application of this uncertainty factor solely to the CMG as a whole.[26] We concur with this panel member's reservation and have identified additional pitfalls in this proposal which EPA must consider, should it choose to pursue this approach.

a. UF_D's relation to the FQPA 10X

First and foremost, EPA must not confuse this 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. Second, use of the UF_D must not be construed as somehow preempting the additional use of an extra FQPA margin of safety to assure the protection of children. The NAS report *Pesticides in the Diet of Infants and Children* clearly found that existing EPA pesticide regulations do not adequately protect infants and children from pesticide exposure.[27] The study recognized numerous shortcomings in the ability of EPA's testing protocols to fully address children's exposure to a pesticide and its toxicity to infants and children.[28] NRDC has also published a detailed analysis of the many ways in which EPA's testing guidelines and data requirements fail to assess children's potentially greater susceptibility and special exposures to pesticides.[29] The use of a UF_D does not excuse the Agency from making a determination about the adequacy of the data on any chemical to, as the NAS put it, "adequately address the toxicity and metabolism of pesticides in neonates and adolescent animals or the effects of exposure during early developmental stages and their sequelae in later life."[30]

b. Single chemical and/or entire group, as appropriate

EPA should be clear that it does not have to choose between applying a UF_D to *either* a single chemical *or* the entire CMG. When the incomplete database is pesticide-specific, the UF_D uncertainty factor would apply to the exposure/risk estimates affecting just that chemical. However, use of a UF_D for a specific chemical would not preclude the possible use of another uncertainty factor for gaps in the database for the CMG as a whole.

We suggest that EPA develop simple guidelines differentiating when the UF_D will be applied to a CMG and when it will be applied to one or more active ingredients in the CMG, as well as when it may be used in addition to retaining the FQPA margin of safety for children. This approach is more science-based and will free the agency from making — and defending — a highly visible and unnecessarily contentious decision. Finally, EPA

should keep the safety factor consequences of different data gaps separate to the fullest extent possible. When disputes inevitably arise, this clarity on the underlying issues will lend itself to easier resolution.

G. Conclusion

We appreciate the opportunity to present these comments. We urge the Agency to move quickly to finalize and apply a CRA guidance, and we look forward to further dialogue with the SAP and agency as this key guidance document expeditiously moves through that process.

Endnotes

[1] Mileson B, Faustman E, Olin S, Ryan PB, Ferenc S, and Burke T. "A Framework for Cumulative Risk Assessment," (hereinafter "ILSI Framework"), International Life Sciences Institute, Washington, DC, 1999, p.43. Accessible at <http://www.ilsi.org/rsiframrpt.pdf>.
[2] Scientific Advisory Panel, "FIFRA SAP Meeting, September 21-24, 1999," SAP Report No. 99-05, November 18, 1999. Accessible at <http://www.epa.gov/scipoly/sap/1999/september/finalrpt.pdf>.
[3] ILSI Framework, pp. 42-43.
[4] ILSI Framework, p. 43.
[5] ILSI Framework, p. 43.
[6] ILSI Framework, p.44.
[7] ILSI Framework, p.6.
[8] ILSI Framework, p.6.
[9] Rodriguez OP, Muth GW, Merkman CE, Kim K, Thompson CM, "Inhibition of Various Cholinesterases with the Enantiomers of Malaoxon," *Bull. Environ. Contam. Toxicol.* 58:171-176 (1997).
[10] See Berkman CE, Thompson CM, "Synthesis of Chiral Malathion and Isomalathion," *Tetrahedron Lett.* 33:3313-3320 (1992); Berkman CE, Ryu S, Jackson JA, Quinn DA, Larsen A, Thompson CM, "Stereochemical Aspects of Organophosphate Toxicity," In *Rev. Pestic. Toxicol.* (Roe and Kuhr, Eds.), Toxicology Communications Inc., 2:131-146 (1993); and Berkman CE, Quinn DA, Thompson CM, "Interaction of AChE with the Enantiomers of Isomalathion and Malaoxon," *Chem. Res. Toxicol.*, 6:724-730 (1993).
[11] Ibid.
[12] Personal communication with Chuck Thompson, Ph.D., Chemistry Department, University of Montana.
[13] US EPA Memorandum, Response to Public Comments on the Preliminary Risk Assessment for the Organophosphate Sulfotepp, June 30, 1999, http://www.epa.gov/opssrrd1/op/sulfotepp/response.pdf.
[14] Ibid.
[15] Ibid.
[16] Slotkin TA, "Developmental Cholinotoxicants: Nicotine and Chlorpyrifos," *Environmental Health Perspectives*, vol. 107 (Suppl. 1), February 1999.
[17] Brimijoin S. and Koenigsberger C, "Cholinesterases in Neural Development: New Findings and Toxicological Implications," *Environmental Health Perspectives*, vol. 107 (Suppl. 1), February 1999.
[18] Solomon G, *Trouble on the Farm: Growing Up with Pesticides in Agricultural Communities*, Natural Resources Defense Council: Washington, DC, October 1998.
[19] For more details on the need for this information and other suggested refinements in the PDP, see Consumers Union's October 4, 1999 letter to Kathleen Merrigan, Administrator of the Agricultural Marketing Service, accessible at <http://ecologic-ipm.com/PDP_expansion.html>.
[20] ILSI Framework, p. 53.
[21] ISLI Framework, p. 54.
[22] ILSI Framework, p. 43.
[23] ISLI Framework, p. 43.
[24] ISLI Framework, p. 44.
[25] National Research Council, *Pesticides in the Diet of Infants and Children*, National Academy Press: Washington, DC, 1993.
[26] SAP Report No. 99-05, November 18, 1999.
[27] Ibid.
[28] Ibid, pp. 127-157.
[29] Wallinga D, *Putting Children First: Making Pesticide Levels in Food Safer for Infants and Children*, Natural Resources Defense Council: Washington, DC, April 1998.
[30] NRC, *Pesticides in the Diet of Infants and Children*, 1993, p.4.