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April 28, 1997

MEMORANDUM

SUBJECT: Transmittal of the Final Report of the FIFRA Scientific Advisory Panel Meeting for March 19 and 20, 1997.

FROM: Larry C. Dorsey
Designated Federal Official
FIFRA Scientific Advisory Panel

TO: Daniel M. Barolo, Director
Office of Pesticide Programs

Please find attached the final report of the FIFRA Scientific Advisory Panel(SAP) open meeting held in Arlington, Virginia on March 19 - 20, 1997. This report includes SAP findings on scientific issues discussed at the meeting concerning Toxicology Endpoint Selection Process, Inhalation Risk Assessments and the Combining of Margin of Exposures, Aggregate Exposure Methodology Issues, Common Mechanism of Action, Visual System Toxicity Testing of Organophosphates, and Standard Operating Procedures for Peer Reviews.

Attachment

cc: Lynn Goldman
Penny Fenner-Crisp
Stephen Johnson
Joseph Cara
Freedom of Information Office
Al Heier
Don Barnes
Vicki Ellis
Margaret Stasikowski
Stephanie Irene
Lois Rossi
Angela Auletta
Vanessa Vu

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FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

MEETING

A Set of Scientific Issues Being Considered by the Agency to Discuss and Evaluate the Selection of Toxicology Endpoints for Which a Risk Assessment is Required.

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of the selection of Toxicology Endpoints for which a Risk Assessment is required. The review was conducted in an open meeting held in Arlington, Virginia, on March 19, 1997. The meeting was chaired by Dr. Ernest E. McConnell. Other panel members present were: Dr. Leo Abood (University of Rochester); Dr. Charles C. Capen (Ohio State University); Dr. Michael L. Dourson (Toxicology Excellence for Risk Assessment); Dr. Richard Fenske (University of Washington); Dr. Charles H. Hobbs (Inhalation Toxicology Research Institute); Dr. Ronald J. Kendall (Clemson University); Dr. Harihara M. Mehendale (Northeast Louisiana University); Dr. Michele A. Medinsky (Chemical Industry Institute of Toxicology); Dr. Robert L. Peiffer, Jr., (University of North Carolina); Dr. James Render (Michigan State University); Dr. Lorenz Rhomberg (Harvard Center for Risk Analysis); Dr. James A. Swenberg (University of North Carolina); Dr. Mary Anna Thrall (Colorado State University).

Public Notice of the meeting was published in the Federal Register on January 29, 1997.

Oral statements were received from:
Dr. William L. Chen, American Crop Protection Association
Ms. Shelley Davis, Farmworker Justice Fund, Inc.
Dr. John A. Todhunter, SRS International Corporation
Dr. David Wallinga, Natural Resources Defense Council

Written statements were received from:
American Crop Protection Association

QUESTIONS AND PANEL RESPONSES FOR TOXICOLOGY ENDPOINT SELECTION PROCESS

QUESTION 1:

Is the overall Toxicology Endpoint Selection process used for identifying dose and endpoints for risk assessments for the various exposure scenarios appropriate? If not what modifications are necessary?

SAP RECOMMENDATION

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In general, the Scientific Advisory Panel viewed the Toxicology Endpoint Process Document as clear and well presented, although several specific suggestions to improve clarity are noted below. The overall process is considered to be appropriate, logical in presentation, and transparent in the various steps progressing from acute to chronic risk assessments. It is very apparent where additional information is needed to reduce uncertainties from both the document and the EPA presentation. Data gaps are easily identifiable and the Agency is encouraged to consider additional information that will help to close these gaps. A number of specific examples of the application of the TES process toward specific chemical data sets were presented to the Panel by the Agency during the meeting. The Panel strongly encourages the incorporation of these examples, along with explanatory text, into the final guidance document. These examples serve as very useful illustrations of the various steps and default assumptions involved in using the weight-of-evidence approach for toxicity endpoint selection. The Agency was also encouraged to begin the process of harmonization of the TES process with the European regulatory agencies, to consider comments by the registrants and when appropriate, to incorporate the comments into the final guidance document.

Specific Suggestions to Improve Clarity:

1. EPA's scheme for health advisories used by the Office of Water (OW), should be reviewed as a possible way to distinguish among exposure durations. At the very least the OW scheme could be cited in the TES document. Similar (identical) schemes between OPP and OW might be desirable.

2. EPA should state that the use of a 21-day dermal study as the basis for a short-term exposure will likely be conservative for Toxicology Endpoint Selection (all other things being equal); however, use of the 21-day dermal study may not be conservative for Toxicology Endpoint Selection for an exposure of intermediate-term duration (page 6 of the TES document).

3. It appears that the use of a 90-day dermal study with a UF for subchronic to chronic exposure is a less uncertain extrapolation than a chronic oral NOAEL to a chronic dermal NOAEL. If so, then the text on page 8 (items 3B & 3C) needed to be reworked.

4. The use of Uncertainty Factors (UF) in sections D4 & D5 (page 10 of TES document) needs to be clarified. Is EPA suggesting the use of UF other than for subchronic to chronic extrapolation?

5. The use of the terms NOEL and LOEL are inconsistent with other Offices in EPA (Office of Water, Office of Solid Waste and Emergency Response, Office of Research and Development, Office of Air and Radiation) where NOAEL and LOAEL are used. Although, the underlying definitions may be similar, OPP may wish to harmonize with other EPA groups for clarity and in its decisions to other groups outside of EPA (page 12).

6. The margin of exposure text (page 16) needs to be made consistent with the draft document "Inhalation Risk Assessments and the Combining of Margins of Exposure".

QUESTION 2:

Is the assumption appropriate that developmental effects can occur after a single dose?

_____

_____a. If yes, do you concur with the rationale for using this study for acute dietary hazard identification?

_____b. If no, what would be the scientific basis for their opinion?

SAP RECOMMENDATION

The panel was in agreement that developmental effects can occur after a single dose. This assumption of a single dose leading to developmental toxicity provides a rationale for using a developmental toxicity study involving multiple doses to identify acute dietary hazards. However, the Agency is encouraged to expand on the section of the document addressing this assumption. Contemporary references from the toxicology literature substantiating this assumption should be incorporated into the document. For instance, the example that decreased fetal birth weights could be the result of a single dose was raised during the Agency presentation. A literature citation supporting the observation of a reduction in birth weight due to a single dose would be useful in the document. As a general comment, contemporary citations from the scientific literature incorporated into the text where appropriate will serve to strengthen the scientific basis of the final guidance document.

QUESTION 3:

Is it appropriate to use oral studies for hazard identification for dermal risk assessments, taking into consideration the dermal absorption factor? If no, what would be an acceptable alternate approach?

SAP RECOMMENDATION

It is the Panel's view that, in the absence of dermal toxicity data, and with the need to develop a risk assessment for the dermal route of exposure, that the only possible approach is to use data from oral toxicity studies and conduct a route-to-route extrapolation. The extensive discussion of the most appropriate strategy for taking into account a dermal absorption factor that occurred during the meeting highlights the need for the Agency to consider additional data in this area. In the absence of data to assess differences in absorption between dermal and oral routes, one suggestion by the Panel was to assume absorption equivalency between the dermal and oral routes. However, it is also important to acknowledge that absorption equivalency between these two routes probably does not exist, or exists only rarely. Numerous potential differences in absorption between the oral and dermal routes were raised by the panel including: low oral and high dermal absorption, very low dermal absorption compared with extensive oral absorption, and high oral absorption but extensive first pass metabolism by the liver. First-pass metabolism could reduce the systemic concentrations of the agent compared with direct absorption from the skin into blood. The Panel's strong recommendation in this area is that the Agency seriously consider various alternate methodologies currently in use for directly assessing dermal absorption in rodents and for assessing in vitro absorption by human and rodent skin for interspecies extrapolations. It was the general consensus of the Panel that the state of the science in this area has progressed such that alternative methodologies exist that are well accepted by European regulatory agencies and pharmaceutical groups. The Agency should seriously consider the dermal absorption protocols currently accepted by the OECD, UK, State of California, and FDA.

Discussion of delayed effects from a single exposure should be included in the TES document (possibly at the bottom of page 4 of the draft document). Although toxicity studies are seldom conducted to determine such effects, their occasional occurrence should be noted.

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As a final suggestion to improve the document, the caveats on the use of route-to-route extrapolation offered in the text of the "Inhalation Risk Assessment and the Combining of Margins of Exposure" document should be referenced in the TES document.

QUESTION 4:

When the dose identified for dermal exposure risk assessment is from an oral study and dermal absorption data are not available, the TES Committee assumes a default value of 100% for dermal absorption which is equivalent to the default value of 100% assumed for oral absorption.

a. Is this appropriate ?

b. If not, what would be more appropriate ?

SAP RECOMMENDATION

In general, the Panel was not comfortable with the TES Committee assumption of "a default value of 100% dermal absorption which is equivalent to the default value of 100% assumed for oral absorption." As noted above in response to Question 2, rather than assuming 100% absorption, it would be preferable to state that the default assumption was absorption equivalency between the oral and dermal routes. Thus, there would not be the explicit assumption that absorption by either route was 100%. The panel viewed the most appropriate approach in this area to be consideration of additional data on the extent of dermal absorption for the specific chemicals under review. The Panel noted some reluctance by the Agency toward accepting new methods for measuring dermal absorption rather than relying on default assumptions. This reluctance was quite different from the Agency's willingness to use new data for determining common mechanisms of action. The Panel encourages the Agency to be flexible and accept reliable data, i.e., peer-reviewed publications on dermal absorption.

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FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

MEETING

A Set of Scientific Issues Being Considered by the Agency to Discuss and Evaluate the Inhalation Risk Assessments and the Combining of Margins of Exposure.

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of the Inhalation Risk Assessments and the Combining of Margins of Exposure. The review was conducted in an open meeting held in Arlington, Virginia, on March 19, 1997. The meeting was chaired by Dr. Ernest E. McConnell. Other panel members present were: Dr. Leo Abood (University of Rochester); Dr. Charles C. Capen (Ohio State University); Dr. Michael L. Dourson (Toxicology Excellence for Risk Assessment); Dr. Charles H. Hobbs (Inhalation Toxicology Research Institute); Dr. Ronald J. Kendall (Clemson University); Dr. Harihara M. Mehendale (Northeast Louisiana University); Dr. Michele A. Medinsky (Chemical Industry Institute of Toxicology); Dr. Robert L. Peiffer, Jr., (University of North Carolina); Dr. James Render (Michigan State University); Dr. James A. Swenberg (University of North Carolina); Dr. Mary Anna Thrall (Colorado State University).

Public Notice of the meeting was published in the Federal Register on January 29, 1997.

Oral statements were received from:
Dr. Douglas G. Baugher, Orius Associates
Dr. Donald R. Saunders, American Crop Protection Association
Mr. James D. Wilson, Center for Risk Management

Written statements were received from:
American Crop Protection Association

_QUESTIONS AND PANEL RESPONSES FOR INHALATION RISK ASSESSMENTS AND MARGINS OF EXPOSURE SESSION

The Agency's efforts to develop methods for calculating a route-specific margin of exposure (MOE) as a preferred approach over the route-to-route extrapolations is commendable. The document was well written and covered several difficult issues. The following comments

are offered as ways to improve the text.

QUESTION 1:

Is the route-specific method for deriving an MOE (Equation 4) an improvement over the route-to-route method? Is there anything you would change?

SAP RECOMMENDATION

The panel endorses the use of the route-specific method described in the text. However, the panel recommends that the dosimetric adjustments used currently by the EPA (1994) in its determination of RfC, specifically in the use of RDDR (regional deposited dose ratio) in its adjustments of inhaled experimental concentration, should be used in preference to the exposure data as proposed. Dosimetry is now recognized by the scientific community to be a superior approach to interspecies extrapolation rather than the use of a default value of 10 when such data are available. Although EPA's (1994) methods for determining RfCs could be improved, it represents the inclusion of additional data in the extrapolation process and thus is to be highly valued.

The panel also recommends that EPA clearly document that different MOEs may be appropriate with different data bases. For example, for human data a MOE less than 100-fold might be appropriate, perhaps 10-fold. The use of an RDDR from a chronic animal study may result in a MOE of less than 100-fold, perhaps 30-fold.

QUESTION 2:

Do you concur with the rationale and equations (Equations 6 and 10) for combining MOEs for:

a) single chemicals with multiple routes of exposure, which may or may not have the same target organs and mechanisms of toxicity;

SAP RECOMMENDATION

The panel endorses the combination of route-specific MOEs for single chemicals with common mechanisms of toxicity, target organs

and critical effect. This is clearly an improvement over the present approach which combines routes after a calculation of common dose metrics. However, this combination of MOE is more difficult to justify when mechanisms of toxicity, target organs or critical effects differ. We encourage EPA to seek data to address different mechanisms, target organs, or critical effects, and support a full description of uncertainties inherent in any combination of MOE that must be done in the absence of such data.

b) multiple chemicals (with or without multiple routes of exposure)?

SAP RECOMMENDATION

The panel applauds the initiative demonstrated by EPA in tackling this problem. This

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effort to use equations 6 and 10 would be enhanced by further use of EPA guidelines on chemical mixtures risk assessment of 1986, the technical support document to these guidelines prompted by the SAB review which endorses the use of additivity, and the ongoing revisions to these guidelines by EPA. The Mixtox database of EPA also could be consulted to determine whether the toxicity of existing chemicals can be expected to be additive, antagonistic or synergistic. The suggested uncertainty factors for use with additivity, antagonism or synergism are appropriate first cuts at addressing the uncertainties with the chemical interactions. Ongoing research efforts of EPA and those of ATSDR should be reviewed as well. In general, this entire section would benefit from the use of additional citations.

(c) What Would You Change?

SAP RECOMMENDATION

Equations 6 and 10 as one approach for combinations of routes or chemicals should be compared and contrasted with that proposed by public comments, roughly described as the summation of percent of the RfDs or RfCs used.

QUESTION 3:

When is it appropriate to substitute toxicity or exposure data from one route for another route in our MOE calculations, e.g. when is it appropriate to use oral or dermal toxicity data to calculate an inhalation MOE?

SAP RECOMMENDATION

The caveats listed on the use of route-to-route extrapolation offered throughout the text are excellent and should offer adequate guidance in this area. When they are consistently applied, the number of times a route-to-route extrapolation will be justified is not expected to be great. Therefore, it is recommended that EPA request appropriate route-specific data from the registrants. This approach will minimize or eliminate the need for route-to-route extrapolations fraught with many uncertainties.

QUESTION 4:

What percentage should be used as a default for absorption by the inhalation route? Since the default is used during route-to-route extrapolations with mixed route data, would it be more appropriate to use a default of 100% since we are actually comparing absorption by inhalation to equivalent absorption by another route?

SAP RECOMMENDATION

The SAP finds insufficient data to enable EPA to recommend a default value for absorption by the inhalation route. This illustrates why it will not usually be possible to conduct route to route extrapolations. It is unlikely that absorption of a compound following inhalation will be equivalent to absorption of that compound following ingestion or dermal application. In fact, absorption following inhalation may be much greater than absorption following ingestion or dermal application. If this is the case, assumption of a 100% default value for each route will underestimate the effect following inhalation. There is no substitute for requiring sufficient data. If adequate data on the pharmacokinetics and pharmacodynamics are available for two routes of exposure, then PBPK modeling may be reasonably used to extrapolate for systemic effects. However, possible local effects following inhalation cannot be ignored.

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GENERAL RESPONSE OF PANEL MEMBERS

1. On page 7, depositions and in some cases retention of inhaled materials will also influence route-to-route extrapolations.

2. On page 6, a statement attributed to Dr. Mauderly is made. The wording of the section should be verified with Dr. Mauderly. Dead space does not equate with residual volume as implied.

3. The working of the paragraph starting on the bottom of page 8 and continuing on page 9 needs improvement. What does blood becomes toxic mean? Why were only liver, kidney or marrow selected for combining MOEs? Wouldn't lung also apply? Additional rationale and an appropriate reference are needed.

4. For equation 12, it needs to be noted that this is for 25C and 760 mg Hg pressure. Many pesticides will be used under warmer conditions and the increased temperatures will affect this calculation.

5. Although the statement on the top of page 12 on LC50s following whole body and nose only exposures appears logical, it should be backed by an appropriate reference and/or examples.

6. On page 9, the statement is made, "If concern is for the whole organism". Isn't the concern always for the whole organism?

7. On page 9, Absorption (A) is defined as "the ratio of inhaled material absorbed into circulation, expressed as a decimal; default is 0.75 (i.e., 75%)". This is an unusual way of defining absorption from the respiratory tract. For inhaled materials, the usual practice is to first determine the fraction of inhaled material deposited in the respiratory tract and then to determine the fraction deposited that is absorbed into the systemic circulation. The SAP recommends using this more conventional definition of absorption from the respiratory tract. Both deposition and retention of inhaled materials are important parameters when MOE's are calculated and route to route extrapolations are considered.

8) Page 2 (attached) contains a number of suggested word changes that would serve to improve the text.

9) Equation 6 is well justified when critical effects are the same (page 8).

10) How is negligible human exposure defined? 10%? (page 8).

11) Text at the top of page 9 is very confusing and appears to be at odds with the published mixtures risk assessment guidelines of EPA.

12) Cite the use of the Mixtox data base of EPA (page 9) for additivity, synergism and antagonism data.

13) Cite research in EPA's ORD and ATSDR on different approaches to the use of UF for additivity, synergism or antagonism (page 9).

14) Check the precision of values listed in table 2. Values

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in table 3 are calculated from table 2 and cannot have greater precision than their components (see hamster subchronic values in table 3; these cannot have 4 digits of precision because body weights in table 2 only have 2 digits of precision).

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

MEETING

A Set of Scientific Issues Being Considered by the Agency to Discuss and Evaluate the Aggregate Exposure Assessment.

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of the Aggregate Exposure Assessment in Agency Decision-Making Process. The review was conducted in an open meeting held in Arlington, Virginia, on March 19, 1997. The meeting was chaired by Dr. Ernest E. McConnell. Other panel members present were: Dr. Leo Abood (University of Rochester); Dr. Charles C. Capen (Ohio State University); Dr. Michael L. Dourson (Toxicology Excellence for Risk Assessment); Dr. Richard Fenske (University of Washington); Dr. Charles H. Hobbs (Inhalation Toxicology Research Institute); Dr. Ronald J. Kendall (Clemson University); Dr. Harihara M. Mehendale (Northeast Louisiana University); Dr. Michele A. Medinsky (Chemical Industry Institute of Toxicology); Dr. Robert L. Peiffer, Jr., (University of North Carolina); Dr. James Render (Michigan State University); Dr. Lorenz Rhomberg (Harvard Center for Risk Analysis); Dr. James A. Swenberg (University of North Carolina); and Dr. Mary Anna Thrall (Colorado State University).

Public Notice of the meeting was published in the Federal Register on January 29, 1997.

Oral statements were received from:
Dr. Charles B. Breckenridge, American Crop Protection Association
Ms. Carolyn Brickey, National Campaign for Pesticide Policy Reform
Dr. Robert E. Sielken, Jr., NOVARTIS
Dr. John H. Sullivan, American Water Works Association

Written statements were received from:
American Crop Protection Association

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GENERAL RESPONSE OF PANEL MEMBERS FOR AGGREGATE EXPOSURE SESSION

The Food Quality Protection Act of 1996 has charged the U.S. Environmental Protection Agency with setting pesticide residue tolerances by considering ".. . available information concerning the aggregate exposure levels of consumers (and major identifiable subgroups and consumers) to the pesticide chemical residue and to other related substances, including dietary exposures under the tolerance and all other tolerances in effect for the pesticide chemical residue, and exposures from other non-occupational sources." [Section 408(b)(2)(D)(vi)]

This charge greatly increases the scope of data needed to set tolerances, as the Agency must now consider exposure data related to water consumption and residential pesticide use, and integrate these data into the overall tolerance setting process. This requires the Agency to develop new methods for calculating exposures, doses, and risks for the general U.S. population and for specific subpopulations. As such it places the Agency on the leading edge of scientific thinking in these areas, challenging the Agency to participate in the creation of new scientific procedures while applying these procedures to public policy in a timely fashion.

The Panel commends the Agency for putting together an interim methodology within a very short time span, despite the several new and difficult issues encountered and the lack of data to support a definitive approach. The Panel agrees that the issue of aggregate exposure estimation is one of the most challenging yet most important that the Agency faces at present. It is recognized that it is difficult to be pioneers, trying to forge approaches to problems previously deemed too difficult to tackle successfully.

In general, the Panel finds that several aspects of the interim methodology--and the report documenting it--**could profit from more thought and wider discussion within the Agency and with outside parties.** It will be an important Agency product and hence ought to be tightly argued, carefully explained, and documented to the extent possible. **The Panel strongly recommends that the Office of Pesticide Programs coordinate efforts with Agency's Office of Research and Development to develop an aggressive research program that addresses the key data gaps and methodology development issues discussed at this meeting.**

The Panel's discussion of these issues included general comments related to aggregate exposure, specific comments regarding documents provided by the Agency, and responses to specific questions posed by the Agency to the Panel.

GENERAL COMMENTS

Relative Importance of Exposure Pathways as Contributors to Total Dose

The Agency perspective on aggregate exposures has naturally emerged from its work on dietary exposures, since the FQPA focuses on the revision of pesticide residue tolerance levels. This perspective has led the Agency to develop its current exposure analysis methodologies

within the framework of dietary exposure analysis, adding exposures from other sources or pathways to this analysis. Exposure analyses of these other pathways have until now been conducted independent of dietary exposures. While this approach is logical and probably efficient, it is likely to result in the importation of certain nomenclature, assumptions, and standard scientific procedures from dietary exposure to aggregate exposure analysis. The Panel would caution that this sort of importation is likely to confound the aggregate exposure analysis in unexpected ways. For example, the Agency enters this new area of analysis with the presupposition that "by far, the largest continual exposure for an individual is via the food and water that is consumed each day." While this assertion may seem self-evident from within a dietary exposure framework, and may prove to be a reasonable generalization for the general U.S. population, it may prove less applicable to specific subpopulations.

The Panel believes there is value in taking a fresh view of the exposure issue within the Agency, viewing aggregate exposures from the perspective that all pathways are potentially important contributors to total dose. Such an approach would place exposures from food, drinking water, and residential activities on an equal footing, and allow development of a conceptual framework and methods compatible with all exposure pathways. For all of these pathways it is important to recognize that exposure has three primary components: an environmental concentration component, a behavioral component, and a duration component. The accuracy of exposure estimates will be affected by the variability and uncertainty in each of these components.

The Panel urges the Office of Pesticide Programs to develop a precise language for dealing with exposure assessments that is consistent with the language used in other parts of the Agency, and in the broader scientific community. For example, the use of the terms "acute" and "chronic" as descriptors of certain types of exposures may prove confusing, since these terms are normally reserved for health effects or toxicological endpoints. Also, the

Agency's decision to employ the term "margin of exposure" in place of "margin of safety" leads to some confusion related to the distinction between exposure and dose. The toxicological benchmark used for the MOE -- the NOEL -- is a dose. The direct comparison of an exposure and a dose inherent in the MOE equation assumes that exposure and dose can be equated. This assumption is not valid in many exposure scenarios, and will become particularly problematic when summing across different routes of exposure (e.g., respiratory and dermal). The Panel encourages the Agency to use the terms exposure and dose more precisely in its documents and communications.

Distributional Analysis of Exposure Data

It is noteworthy that, during the public comment period and subsequent discussion, there was general approval of the idea that a distributional approach to exposure characterization provides a means to consider the potential for multiple pathways to affect total exposure but still to avoid the difficulty of compounding conservatism by using "worst case" representations of each element of the exposure analysis. While few cases may currently present enough knowledge of the distributions of contributory factors to do a full distributional analysis with confidence, the Agency already has underway development of approaches that it can utilize as such data become available. The Panel felt that it would be helpful for the Agency to regard its interim methodology in the light of the goals of distributional analyses--to examine the effect of

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variation in the magnitudes of exposures by multiple pathways, but to find realistic estimates of the frequencies with which exposure elements of different magnitude will co-occur. That is, one could look at the interim methodology as an attempt to characterize where the "high end" (and not necessarily the "worst case") of the joint distribution of exposure contributions (as might be assessed with a full distributional analysis) would be expected to lie. This characterization of the high end should be gauged so that it fulfills the mandate of "reasonable certainty of no harm," i.e., that the real high end of the joint distribution is identified in at least a reasonable and approximate way, but that attempts be made to avoid an overly conservative compounding of worst-case assumptions.

Making this connection explicit in designing the interim methods would smooth the transition to more fully data-rich cases as they can be developed, and would keep analyses adhering to a common philosophy. Just as a full distributional approach balances the existence of occasional large exposures with consideration of the unlikelihood that several such large contributors are experienced together, the interim methodology could be thought out from the point of view of the rarity of each of its individual pathway scenarios (such as high values of acute exposure to

residues in diet, high levels in drinking water, episodes of residential exposure), and hence the degree to which such high-end exposures would or would not be experienced together.

In general, the documentation of the interim methodology employed a rather loose distinction between the concepts of exposure and dose--and even of the connection between these and possible ensuing risk. There is clearly a tie among these concepts, but the connection involves assumptions that are left unarticulated when exposure, dose, and risk are presumed to be almost interchangeable in the description of methods. More rigor would clarify the description and rationale for the methodology.

Similarly, as noted elsewhere, the concepts of "acute" and "chronic" (and other time-scale descriptors) are used rather loosely in terms of whether they refer to time-scale of exposure episodes, to the time-scale over which elevated doses can cause specific kinds of health effects, or to the time-scale over which health effects of concern have been observed experimentally. As a consequence, it is often unclear whether the methodology might be overlooking the possibility of short-term health effects (for instance) as a consequence of coincidence of exposures defined as occurring on different time-scales.

From this point of view, it should be clear that long-term health effects depend on dose levels averaged over the long-term, and not simply on those exposures designated as "chronic." That is, it is important that the cumulative effect of "chronic" and episodic exposures be considered as they together contribute to long-term average exposures. It is not clear from the present documentation how this issue is handled by the interim methodology.

The mandate of "reasonable certainty of no harm" would seem to imply that, to omit from consideration the coincidence of episodic exposures from different sources, one should be confident (to some appropriate degree) that the coincidence is sufficiently improbable as to be rare in practice. A low-probability co-occurrence of events that is too rare to be likely to happen within a small population or within a small timespan, however, may become appreciably likely to occur within a large population or a large time-span. Thus, the size of the population at risk and/or the timespan of consideration may be a relevant variable that the Agency may want to

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think about in judging how to combine episodic sources of exposure.

SPECIFIC COMMENTS ON AGENCY DOCUMENTS

The Agency provided two documents related to aggregate exposure for the Panel's review: Document 3A is an issue paper on

the Agency's interim approach to aggregate exposure assessment; Document 3B is an example of the interim approach for a screening-level assessment. The Agency also produced a series of questions for the Scientific Advisory Panel's consideration.

Current Exposure Assessment Practices

The Agency's section on current exposure assessment practices states that several risk assessments have already been performed which have integrated multiple exposure pathways, and identifies a Special Review of three triazine compounds as an example. However, no details of the methods used in these assessments are provided. The Panel encourages the Agency to include a detailed methodological example as part of its revised concept document. While Document 3B could be considered such an example, it is limited to the screening level.

Scenario Descriptors based on Duration of Exposure

The Agency's section on scenario descriptors could benefit from revision and a more systematic organization. The definition of "chronic exposure" should be clarified. It is not clear whether exposure needs to be continuous to be chronic, or at what point an exposure is of sufficient magnitude to move from the chronic exposure to the acute exposure category. Chronic exposure appears to mean exposures that are relatively low; i.e., are not likely to produce an acute toxic response. It should be noted, however, that there is almost certainly great variability in such exposures, and that in a distribution of such exposures there might be episodes of relatively high exposure.

The Agency states that only "occasionally" will a pesticide used around the home (i.e., residential) contribute to chronic exposure. This assertion is not supported by current scientific evidence. Studies by EPA/ORD have shown that many homes have measurable concentrations of pesticides in indoor air, and that many of these same chemicals can be found in housedust. In the case of termiticide treatments, it is well documented that airborne pesticide residues can be measured in indoor air months and years following treatment.

There are many residences, such as public housing and apartment buildings, in which pesticides are applied routinely (e.g., on a monthly schedule) to prevent infestations. The assumption that residential exposure is unlikely to contribute to chronic exposure again reflects an analysis that has developed within a dietary exposure framework.

The Agency states that an acute exposure is estimated using worst-case assumptions for pesticide residues in foods. These assumptions are not provided, nor is there reference to an

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appropriate document that would provide the details of this methodology. The Panel recommends that the Agency include the assumptions and methods used to produce an estimate of acute food exposure in its revised document. It is not clear, for instance, whether high-end food-use rates of some kind are used in determining acute food-based exposure, as would seem appropriate.

The Agency states that the co-occurrence of an acute food and acute water exposure is unlikely, but no estimate of probability is provided. The Panel understands from the public discussion of this document that the Agency's conclusion is based on the fact that the worst-case assumptions for food exposure are very conservative. However, the Panel believes that even some approximate estimate of probability would be preferable to strict reliance on scientific judgment in this case.

The Panel strongly endorses the Agency's plans to develop a statistical approach for reviewing drinking water concentrations, and the adoption of Monte Carlo methodologies. These efforts will allow the Agency to estimate the probability of very high end exposures within the U.S. population and identified subpopulations. Such methods should also account for the distribution of drinking water consumption. Care should be taken to incorporate appropriately the contribution of temporal patterns and durations of exposure episodes, so that probabilities of co-occurrence and overlap are well represented.

There was some concern expressed about the means for assessing an acute drinking water exposure. The matter is not clear in the document, but in the discussion it became apparent that a single high drinking water sample value is used. For the population taking its daily drinking water from this highest-concentration source, however, that high level constitutes its chronic level in drinking water. That is, it is not clear that such a value represents an excursion in the degree of daily exposure. The Panel felt that the notion of acute exposure in drinking water needed to be further clarified and carefully defined.

The Agency characterizes the remaining exposure duration categories as "short-term" and "intermediate-term". The distinction in these categories appears to be based on potential health effects, as determined by the Toxicology Endpoint Selection Committee (TESC). It is not clear how these categories accommodate short-term exposures which may be repeated; e.g., periodic treatments in the home or garden. The example provided for intermediate-term exposure -- rodenticides -- does not seem
appropriate. The most common concern with rodenticides is accidental ingestion, which would probably be classified as an acute exposure. The Panel suggests that the distinction between these two categories be further clarified, and that the most common scenarios for each category be identified. Also, it is not clear that sufficient attention has been paid to the possibility that short-term or intermediate-term health effects might be risked by the coincidence of exposures consigned to other time-scales. For example, a series of several "acute" exposures closely following one another (perhaps of insufficient magnitude to risk acute toxicity) could risk a "short-term" toxic effect, even though no "short-term" exposure scenarios are thought likely for the agent.

Exposure Pathways/Scenarios Necessary to Perform Risk Assessments

This section of the document begins with a description of the current tiered approach used by the Agency for chronic dietary exposures. This material would fit more logically in the first section, which reviewed current exposure assessment practices. The same would be true for the next topics, acute dietary exposures and occupational exposures, since such exposures are

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routinely conducted and no changes are proposed in these methods.

The Panel recognizes the need for the Agency to conduct tiered analyses to conserve resources. The tiered approach allows the Agency to review a larger number of tolerances, and serves to identify chemicals and scenarios which need greater scrutiny.

In regard to the Tier 1 chronic dietary exposure methods, the Panel had a general concern with the quality of data employed for these analyses. The food consumption data appears to be 20 years old. It is well known that eating habits have changed dramatically over the last twenty years and that many more meals are consumed outside of the home. The utility of these data for estimating exposures among various subpopulations is not described. The quality of data related to percent of crop treated and percent of crop imported is also not described. What are the accuracy and precision of such estimates?

The Panel supports the use of residue levels measured in field trials for the Tier 2 analysis of chronic dietary exposures. The Agency should clarify what estimate it uses from such data (e.g., maximum, 95th percentile, median) and explain why.

In regard to acute dietary exposures the tiered approach described by the Agency seems reasonable, although it is described very briefly. The Panel supports the use of Monte Carlo techniques in Tier 3 to determine the distribution of exposures. The Panel encourages a more detailed description of tiers 3 and 4 in the revised document.

In regard to occupational exposures, the Agency cites the Pesticide Handler's Exposure Database (PHED) as the primary source for exposure estimation. While this database is an important resource, the Panel notes that this database does not address "most" occupational exposures. A very large component of occupational pesticide exposures in the U.S. occurs during agricultural reentry, and these worker activities fall outside the scope of the database. PHED can serve to estimate exposures for pesticide handlers when appropriate qualifications on the database are kept in mind; namely, many of these data were collected under idealized working conditions, many observations in the database are not independent in a statistical sense, and many well-conducted studies published in the scientific literature were not entered into the database. One European scientist reviewing this database recommended that use of the 90th percentile exposure values would be most appropriate, in light of these limitations.

This document's discussion of current knowledge in the area of residential exposures is very brief. The Agency notes that information is limited in this area, but provides no detailed discussion of these limitations. The Panel recognizes the importance of such initiatives as the Outdoor Residential Exposure Task Force, and encourages such efforts. However, the Agency should clearly define its policies regarding peer review of such activities, and the criteria which will be used to include or exclude studies from this database. The Agency notes that five residue sampling methods are currently under study. The Agency should clearly define the criteria and the peer review process which will be used to determine which of these methods will become the standard method for such studies. The Agency provides no information regarding efforts to improve understanding of residential behaviors relevant to exposure (e.g., activity pattern analysis). Research and development efforts should be placed both on sampling of environmental concentrations and on characterization of exposure-related behaviors in residential environments.

The final topic in this section of the document is drinking water exposures. Drinking water exposures were also discussed in an earlier section. The Panel suggests reorganizing the

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document such that the drinking water topic is discussed in a single section. The Panel agrees that development of national drinking water exposure estimates is not appropriate, and that a regional approach is most appropriate. The Agency will need to take great care in defining these regions, both geographically, and according to particular subpopulations. The Agency proposes to use drinking water concentration data from high use areas as estimates for general population exposures. This approach appears reasonable, since these concentrations are in fact the normal concentrations that the local population consumes. It is not clear how the Agency would use these data, however. Would they be used as part of a tiered analysis, in estimates of acute and chronic exposure? It also is not clear what happens if these data yield a risk of concern. What would be the next step?

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Current Activities

The Agency has developed interim default assumptions regarding the relative importance of exposure pathways, partitioning risk as follows: 80% food, 10% drinking water, 5% indoor residential, and 5% outdoor residential. The Panel does not object to this formula as an interim approach, but notes, that there is no clear scientific rationale for these percentages, and that this partitioning needs to be documented and amended where appropriate, particularly for subpopulations.

Next Steps

The Panel encourages the work outlined in this section, and reemphasizes the importance of the Agency to take advantage of expertise both within EPA and in the broader scientific community. Use of probabilistic techniques will require substantial training of Agency staff, as noted. The Panel encourages the Agency to think creatively in this regard, and to invest considerable resources in this effort.

Example of the Interim Approach for Aggregate Exposure Assessment (Document 3B)

This document provides an example of the decision logic and calculations used by the Agency in a screening level assessment for chronic and acute exposures in response to a Section 18 Emergency Exemption. The Agency notes that the turnaround time for such decisions is very short, and that an expedited process is therefore appropriate.

The Panel encourages the Agency to provide examples of this kind. In regard to the addition of a drinking water assessment to a traditional dietary assessment the example was very clear. The use of a default value for chronic assessment due to an absence of data seems justified; the use of the GENEEC program for acute assessment seems reasonable, although the caveats associated with use of this program are not reassuring (e.g., "preliminary indications", "not used in repeat applications"). Hopefully, the tools and data available to the Agency for such assessments will continue to be improved.

The aspects of this example which were not clear involved overall parameters of the assessment and calculation of food exposures. In regard to overall parameters, mention is made in passing of "22 subpopulation groups examined". Nowhere in the material provided to the Panel are these subpopulations discussed or enumerated. In regard to carcinogenicity classification, the example states simply that "it was determined that estimation of a Q1* would be inappropriate". This is a very important part of the assessment, since it

determines the appropriate toxicological benchmark used to estimate risk. What was the basis for this determination? In regard to the selection of the reproductive toxicity endpoint for acute exposures seems reasonable, but what about the previously identified subpopulation of children 1-6 years? The data from the chronic exposure assessment indicated that this subpopulation was about 2.5 times more exposed than the general U.S. population. What is the NOEL for this subpopulation? Should there be a separate evaluation for children?

In regard to calculation of food exposures, the example does not provide sufficient detail regarding inputs and assumptions. It was clearly the Agency's intent in this example to focus on the addition of drinking water to traditional dietary assessments, but this approach underscores the Panel's earlier comments regarding a rethinking of multi-pathway exposure assessments. It is clear, for instance, that the environmental concentrations used were tolerances, but it is not clear what food consumption rates were used within the DRES system. It also can be inferred that a 100% absorption factor was used for ingested residues, but no information was provided related to absorption.

It appears that the limitations of the example in regard to chronic and acute dietary exposures have their origin in a presupposition that the reader has great familiarity with the Agency's internal processes. Since this document will be read widely, it is important that inputs be identified and explained, assumptions be justified, and calculations be transparent. This example serves as a good first step towards that goal.

The portion of the example related to short-term exposure highlights the ambiguity associated with this category. Short-term exposures can potentially result in acute health effects, but they also contribute to cumulative exposure. In this example, however, short-term exposure is reviewed only within the context of acute exposures.

The reproductive health endpoint has been carried forward from the acute exposure analysis, again raising the question of risks for the child subpopulation.

In the final calculation of exposure, exposures from food (chronic), drinking water (chronic), indoor residential, and outdoor residential were added together. This sum was then compared with the NOEL with the "margin of exposure" approach. The drinking water exposure has been translated for a 10% default to an estimated dose, but the indoor residential value has been left as a 5% default. The Panel noted that final equation cannot be solved without a numerical value for indoor residential exposure. The Agency's explanation which follows in the risk characterization section is not wholly satisfactory. The Agency does not believe that an estimate of indoor residential exposure can be determined, so this value has been omitted from the final exposure value. The Agency notes that food exposure would likely be much less than estimated, but fails to note that the food exposure represents only 2% of the final exposure value.

In summary, the Panel found the methodology proposed by the Agency in this example to be sensible, noting that it suffers primarily from inadequate data. The Panel encourages the Agency to be more thorough, precise, and transparent in the presentations of such examples.

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QUESTIONS AND PANEL RESPONSES FOR OPERATING PROCEDURES FOR AGGREGATE EXPOSURE SESSION

QUESTION 1:

Is the tiered approach for estimating total acute dietary exposure reasonable until the Agency develops statistical approaches for reviewing a distribution of drinking water concentrations, and implements Monte Carlo methodologies for drinking water?

SAP RECOMMENDATION

We understand that "acute" exposure means an exposure of sufficient magnitude to produce an acute health effect, normally within one day or one event. An answer to this question raises a number of fundamental issues about the quality of data sources and their proper use.

We have concerns regarding the quality of data used in calculations of food exposures. The inputs for food consumption patterns are unclear. Consumption data appear to be approximately 20 years old. No information is provided regarding the frequency of pesticide residue data from field trials or surveys. Will average consumption patterns or high end consumption patterns be used? We believe it is reasonable to assume a coincidence of high food concentrations and high food consumption. While we cannot estimate the probability of such occurrences, they cannot be considered improbable without some further analysis.

We understand a high end estimate for food concentrations will be drawn from either tolerances or from maximum measured concentrations. Will maximum concentrations be used when available in lieu of tolerances? We believe this would provide a better high end estimate of residue levels, assuming the concentration data are representative of the food supply.

QUESTION 2:

Considering that pesticides have specific agricultural-use areas, is the use of regional drinking water exposures appropriate to assess subpopulation risk in specific regional areas?

SAP RECOMMENDATION

The Agency wants to use drinking water concentrations from geographical areas of high use and/or areas with geological vulnerability. It assumes that these will serve as high end estimates for the U.S. population.

This appears to be a reasonable interim approach, but should eventually be replaced by distributional data.

For the subpopulation exposed to this concentration, it constitutes the daily exposure; i.e., the average for this group, even though it may be considered high end for other areas. What is the high end of varying day-to-day exposure for this sub-population? Within the geographic region with high exposure potential there will be daily fluctuations in drinking water concentrations. Will the data EPA uses from the region reflect the average concentration or will

it also capture the high end of exposure for the local population?

How rare does the coincidence of high end food exposure and high end water exposure have to be to exclude it from concern? We believe it is plausible for populations in regions with high drinking water concentrations to have high food concentration events. It may be reasonable to assume in this interim period that maximum food and water concentrations will not coincide for any given day, but this population is always exposed to a relatively high water concentration.

In the Panel's discussion of this question, there was some concern expressed about the definition of subpopulations; relevant demographic populations should be considered as well as geographic ones, and the definitions may need to be tied to the nature of the exposures in question.

QUESTION 3:

Is the addition of a residential short-term exposure to the chronic background dietary exposure a reasonable interim methodology for aggregating residential exposures?

SAP RECOMMENDATION

Yes, with some caveats. First, in the calculation of a time-integrated estimate of dose (e.g., annual average daily dose) resulting from chronic exposure, residential short-term exposures should be included as a part of cumulative exposure, together with exposures from food and drinking water. This approach can be inferred from the figure provided by the Agency, but the mathematical relationship between dietary and residential exposures should be clarified. If the residential exposure episodes are infrequent, then this inclusion will have but minor effect on the long-term average dose rate.

Second, the Panel noted that such residential exposure events may occur periodically. The frequency of occurrence of these events should be considered in such an analysis. If residential exposures occur periodically (e.g., an apartment being sprayed monthly), then the episodes may significantly affect chronic exposure levels, even though the episodes do not overlap.

Third, the appropriateness of adding these residential exposure events to chronic dietary exposure may also depend on the frequency with which residential exposures are repeated. If they are infrequent, then several residential exposures are unlikely to coincide with one another. As they become more frequent, however, it becomes more likely that two episodes will overlap (leading to higher short-term exposure and possibly an acute event). If there are several types of residential exposures that are conceivable, then it becomes more likely that two may coincide. A more detailed analysis of such exposures will require an understanding of the metabolism, distribution and excretion of the study compound.

A general issue raised by the integration of different types of exposures is the potential for undue conservatism by combining events elevating exposure that will rarely coincide in practice. While undue conservatism should be avoided, it is also true that if the individual events are not so rare, and if each one lasts over some period of time, then the probability of coincidence begins to climb. The key is that the overarching concept of "reasonable certainty of no harm" needs to be interpreted as to how rare exposure excursions must be in order to escape coverage by a standard. Too strict an interpretation leads to protecting against the mere possibility of

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coincidence of rare events that rarely happen in reality, but too lax an interpretation leads to failure to protect against those perhaps infrequent but nonetheless reasonably probable occasions when events do indeed coincide.

Especially for interim methodology, it is unreasonable to expect the Agency to have precise numerical standards for event frequency and the probability of co-occurrence. But it is important that the interim methods be explicit in their reasoning about why, in the professional judgment of those setting up the methods, it is reasonable to suppose that exposure events do or do not coincide at a rate worthy of being considered as being in the range of situations to be protected.

QUESTION 4:

Is the Agency's interim approach a reasonable way to aggregate exposure? Are there other considerations that should be added to this approach?

SAP RECOMMENDATION

In view of the need for an immediate interim solution to what is a very difficult and complex problem, the Agency's proposed approach is a reasonable start, given the limited data available at present for most cases. The Panel nonetheless felt that the interim methodology--and the report documenting it--could profit from more thought and wider discussion. Specifically, clarifications to the tiered approach to dietary exposure should be provided. The role of acute drinking water exposures needs further exploration. The effect of the frequency of residential exposures on the likelihood of co-occurrence of such exposures should more explicitly be examined. The ability of temporal fluctuations in the daily level of ongoing "chronic" exposure sources, combined with episodes of residential exposure, to engender concern for health effects appearing at different time-scales needs to be more explicitly considered. A clearer and more thorough documentation of methods is also needed. Further recommendations appear in the above report on the Panel's discussions.

QUESTION 5:

Do you have any specific suggestions for future improvement of our tools and databases for aggregate exposure assessment?

SAP RECOMMENDATION

In addition to the specific points raised earlier, the Panel has the following recommendations. As noted above, the Panel encourages the development of distributional approaches to address the combined effects of multiple sources of exposure without compounding conservatism in estimation of the magnitudes of individual exposure elements. Even the interim methodology could profitably take as the target for its analysis the estimation of the practically realized upper end of the distribution of aggregate exposures in view of our knowledge (or reasonable estimates) of the likelihood that higher-level exposures from multiple sources will combine in some meaningful fraction of an exposed population. The implementation of distributional methods such as Monte Carlo simulation should take care appropriately to account for temporal patterns and fluctuations of exposure episodes.

Methods can only be as reliable as the data that go into them. The Panel recognizes that data are few for many key questions in the estimation of aggregate exposures, and the

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development of databases to address these gaps is strongly encouraged. In particular, the means to estimate residential exposures--indoor and outdoor--appears limited, and current efforts to improve this situation should be encouraged. Dietary data in current use are rather old, and would profit from updating. Since exposure through drinking water is a newly prominent concern of OPP analysis, methods for doing so (and the data on which to base them) need to be improved. Discussion and harmonization with procedures in other EPA program offices is to be encouraged.

Again the Office of Pesticide Programs must engage the Agency's research apparatus in developing improved bases for estimation of multi-pathway pesticide exposures, an effort that will benefit risk assessments in all parts of the Agency.

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FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT
SCIENTIFIC ADVISORY PANEL
MEETING

A Set of Scientific Issues Being Considered by the Agency to Discuss and Evaluate the Common Mechanism of Toxicity.

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of a Common Mechanism of Toxicity for use in Combined Risk Assessment. The review was conducted in an open meeting held in Arlington, Virginia, on March 20, 1997. The meeting was chaired by Dr. Ernest E. McConnell. Other panel members present were: Dr. Leo Abood (University of Rochester); Dr. Charles C. Capen (Ohio State University); Dr. Michael L. Dourson (Toxicology Excellence for Risk Assessment); Dr. Richard Fenske (University of Washington); Dr. Charles H. Hobbs (Inhalation Toxicology Research Institute); Dr. Ronald J. Kendall (Clemson University); Dr. Harihara M. Mehendale (Northeast Louisiana University); Dr. Michele A. Medinsky (Chemical Industry Institute of Toxicology); Dr. Robert L. Peiffer, Jr., (University of North Carolina); Dr. James Render (Michigan State University); Dr. James A. Swenberg (University of North Carolina); Dr. Mary Anna Thrall (Colorado State University).

Public Notice of the meeting was published in the Federal Register on January 29, 1997.

Oral statements were received from:
Dr. Michael J. L. Clapp, ZENECA
Dr. Donald R. Saunders, American Crop Protection Association
Dr. John A. Todhunter, SRS International Corporation
Dr. David Wallinga, Natural Resources Defense Council
Dr. Alan G. E. Wilson, Monsanto

Written comments were received from:
American Crop Protection Association
Monsanto

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GENERAL RESPONSE OF PANEL MEMBERS

QUESTIONS AND PANEL RESPONSES FOR COMMON MECHANISM OF TOXICITY SESSION

For the purposes of FQPA, mechanism of toxicity has been defined as the major steps leading to an adverse health effect following interaction of a pesticide with biological targets. All steps leading to an effect do not need to be specifically understood. Rather, it is the identification of the crucial events following chemical interaction that are required in being able to describe a mechanism of toxicity. Common mechanism of toxicity has been defined as cases where two or more chemicals produce or may be expected to produce adverse effects by the same crucial step(s). The Agency recognizes that fully developed molecular understanding of mechanisms by which pesticide chemicals exert adverse effects will not be available **in most cases.**

QUESTION 1:

For the purposes of FQPA, are the Agency's proposed definitions of mechanism of toxicity and common mechanism of toxicity consistent with current toxicological concepts?

SAP RECOMMENDATION

The Scientific Advisory Panel finds that the proposed definitions are useful and agrees with the overall approach for identifying common mechanisms of action; however, the Panel is of the opinion that the document could be improved in several ways. For example, the document should include a discussion or summary of the definition for mechanism of toxicity taken from the current published literature such as the most recent edition of Cassarett and Doull's Toxicology (page 35). As a general comment, the Panel recommends incorporation of references into the document where appropriate. The section of the document describing common mechanisms should also be expanded to include a discussion of the different levels of evidence for common mechanisms, and definitions of terms such as toxic endpoint, biological plausibility (least amount of data), mode of action (moderate amount of data), and ultimate mechanism of toxicity (most amount of data). Clarification of what the agency considers the biological target would also be useful. For example, is the target considered to be a specific molecule, cell or tissue, or does target refer to the whole organism? Biological interaction with a specific receptor or enzyme should be used as the starting point for grouping chemicals into a common mechanism.

Some concerns were raised regarding the use of the phrase "may be expected to produce." It would be most useful if the Agency could expand on the concept and include examples how

this phase could be applied. The Agency should leave some flexibility in the guidelines to allow for situations where the toxic endpoint effect has not been demonstrated, but the established causative toxic metabolite intermediate has been. In such a case, there would be sufficient rationale to anticipate expected toxic effect and therefore not exclude such a chemical from the common mechanism grouping.

QUESTION 2:

The Agency plans to use a number of different elements of evidence in making decisions about mechanism of toxicity and whether a common mechanism applies to members of a group of pesticide chemicals. Usually included will be considerations of chemical structure, metabolism, types of toxicological effects and other data as appropriate.

Determinations of whether a common mechanism of toxicity is operating will be based on all available information evaluated by a weight of evidence approach as demonstrated by the case study. How might this process be improved to make it more scientifically sound?

SAP RECOMMENDATION

The Panel strongly endorses the weight of evidence approach for determining presence or absence of common mechanism of action. The Panel encourages the Agency to incorporate peer reviewed scientific publications into the weight of evidence. Additional scientific evidence can be incorporated provided it is reliable and reproducible. Anecdotal information should not be used.

QUESTION 3:

Two basic strategies will be employed to determine whether a common mechanism of toxicity is operating.

a. STRUCTURE BASED: Begin with a group of pesticide chemicals that have one or more structural similarities. Proceed with an investigation of metabolism of the compounds. Determine whether there is a common biological effect. Ascertain the mechanism by which the effect is produced if information is available to do so. Judge whether the mechanism is common to chemicals in the group. Combine risks for those with a common mechanism.

b. **Mechanism based:** Determine the mechanism of individual pesticide chemicals that are or are not structurally related. Combine risks for those that have a common mechanism.

Comment on the merits of these two strategies to identify pesticide chemicals for inclusion in combined risk assessment.

SAP RECOMMENDATION

Chemicals with similar structures may not have the same mechanism of action. However,

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grouping chemicals with structural similarities can serve as a starting point or a convenient way to triage chemicals for examining the basis for common mechanisms. The important point is that whether the Agency begins by examining a group of chemicals with similar structures or a group of chemicals with a common mechanism, the weight of evidence approach must be applied for grouping chemicals with regard to a common mechanism of toxicity. Starting with a group of chemicals with similarities in structure and toxic endpoint would appear to be superior as an initial strategy to starting with a given mechanism. The Panel encourages the Agency to develop and use Structure Activity Relationship (SAR) information technology to enhance their effort to develop the common mechanisms approach.

Although, for a class of structurally homologous agents, it is appropriate to relate a toxic end point to a common mechanism of action, there are instances where some or all members of the class may have alternate mechanisms resulting in the same or different toxic end points. For example, in addition to their ability to form DNA adducts after bioactivation and formation of reactive electrophiles, xenobiotic carcinogens can also cause neoplastic growth promotion, cytotoxicity, inhibition of tissue growth regulation, peroxisome proliferation, endocrine modification, immunosuppression and/or sustained tissue ischemia.

The Scientific Advisory Panel finds that the use of SAR and QSAR (quantitative SAR) methodology is an important component for predicting common mechanisms in the absence of mechanistic data and for determining potential mechanisms by analyzing diverse model parameters. In recent years, a number of computerized structure-activity programs have been developed to model and analyze multiple or overlapping mechanisms with a single toxic end point. Such methodology can provide confidence levels on predictions in the absence of mechanistic data, as well as determine the potential mechanistic significance of diverse model parameters. A combination of comparative molecular field analysis (coMFA) and QSAR has been used to relate ecotoxicological data with the steric and electrostatic fields of chlorophenola for 16 different biological systems. The technique also allows prediction of values

in the absence of missing ecotoxicological data. The Panel recommends that the Agency take necessary action to develop and acquire such technology to facilitate evaluation of pesticides through structure activity relationships as an initial approach.

QUESTION 4:

The case study for chloroacetanilides groups pesticide chemicals according to three grouping scenarios based upon varying degrees and quality of evidence.

a) For the nasal tumors, a well-developed understanding of the underlying mechanism is available for one member of the class and appears to be applicable to others. For these pesticide chemicals, precursors to the putative, critical metabolite quinone imine have been identified for each chemical.

b) For the thyroid tumors, a hypothetical mechanism has been developed for one chemical, linking the response to concurrent changes in microsomal enzymes that metabolize thyroid hormone. Effects on the liver for other members of the group are consistent with an influence on microsomal enzymes, suggesting a common mechanism of toxicity.

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c) For pesticide chemicals inducing liver tumors, there is no specific knowledge of a mechanism of action. However, the pesticide chemicals are linked by structural similarity and common toxic endpoints.

The Agency believes that there is sufficient evidence to support groupings a and b, but insufficient evidence for paragraph c above. Are these groupings consistent with the Agency's proposed methodologies and definitions?

SAP RECOMMENDATION

The case study provided by the Agency on an approach for determining common mechanism of action was excellent, well-presented, and very appropriate. The Panel suggests that the Agency develop an equally illustrative example for determining a common mechanism of action for a group of chemicals with a non-cancer endpoint.

The Scientific Advisory Panel agrees with the Agency's conclusion that there is sufficient evidence to support the proposed groupings for the nasal tumors. Regarding the thyroid tumors, even though the case study illustrated a common mechanism

could be used to group certain chemicals for the development of thyroid tumors, the Panel recommends that this endpoint not be used in combining margins of exposure because the toxic effects were noted at doses above the Maximum Tolerated Dose (MTD). While the full range of doses employed can be used to determine common mechanisms, endpoints occurring solely at doses above the MTD should not be used in risk assessments.

QUESTION 5:

The Agency recognizes that scientific judgment is critical to the determination of whether a mechanism of toxicity has been identified and whether a mechanism is common across chemicals. To ensure that Agency decisions are based on good scientific principles, at least initially, individual assessments on chemical classes will be subjected to external peer review. Comment on the adequacy of this plan in ensuring high scientific standards.

SAP RECOMMENDATION

The Panel strongly endorses the use of peer review to support or reject the Agency's position regarding a common mechanism of action for selected groupings of chemicals. Peer review will be especially important initially when methodologies to combine chemicals into common groupings are being developed. The panel recognizes that while some groupings such as that provided in the case study for nasal tumors will be relatively straightforward, many more groupings will be in “grey zones” that are less well defined. It will also be important for the Agency to interact with a wide range of other groups to develop paradigms to move forward with the grouping of chemicals with the same mechanism of toxicity. The Panel supports the draft guidelines that the Agency has outlined so far for determining common mechanism of toxicity.

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FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

MEETING

A Set of Scientific Issues Being Considered by the Agency to Discuss and Evaluate the Visual System Toxicity Testing of Organophosphates.

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of the Visual System Toxicity Testing of Organophosphates. The review was conducted in an open meeting held in Arlington, Virginia, on March 20, 1997. The meeting was chaired by Dr. Ernest E. McConnell. Other panel members present were: Dr. Leo Abood (University of Rochester); Dr. Charles C. Capen (Ohio State University); Dr. Michael L. Dourson (Toxicology Excellence for Risk Assessment); Dr. Charles H. Hobbs (Inhalation Toxicology Research Institute); Dr. Ronald J. Kendall (Clemson University); Dr. Harihara M. Mehendale (Northeast Louisiana University); Dr. Robert L. Peiffer, Jr., (University of North Carolina); Dr. James Render (Michigan State University); Dr. James A. Swenberg (University of North Carolina); Dr. Mary Anna Thrall (Colorado State University).

Public Notice of the meeting was published in the Federal Register on January 29, 1997.

Oral statements were received from:
Dr. R. D. Jones, American Crop Protection Association

Written statements were received from:
American Crop Protection Association

GENERAL RESPONSE OF PANEL MEMBERS

Demonstrated or strongly suspected ocular effects of organophosphate compounds (OPs) in humans and/or animals include: (a) abnormal extraocular muscle function since high levels of cholinesterase (ChE) may make these muscles more sensitive than other striated muscles; (b)

astigmatism; (c) altered regulation of eye growth and emmetropization that appear to be age and species dependent, but are likely to be more pronounced in the developing eye; (d) cataract; (e) optic neuropathy; and (f) retinal atrophy. Species and age susceptibility differences and differences in the ability of individual or groups of OPs to induce these changes likely exist. The mechanisms, pathogenesis, and relationship of retinal and optic nerve changes to each other, to biochemical and electrophysiological parameters and to other OP induced toxic effects, i.e., neuropathy, are currently not well understood. Therefore, definitive resolution of current topics of controversy is challenging.

The need for prospective, long-term studies, involving a number of species and a variety of compounds that addresses these issues is obvious. Serial testing involving electroretinography (ERG); visual evoked responses (VER); retinal, ciliary and extraocular muscular ChE levels; markers including neuropathy target esterase (NTE) and glial fibrillary acidic protein (GFAP); and morphologic evaluation for decreased axonal counts in the optic nerve and abnormal ultrastructural retinal morphology would help in the determination of adverse effects and their relationships. Until these data are forthcoming, less than optimal recommendations for safety testing will be unavoidable.

In general, we found the October 1994 ILSI Report ("Evaluation of Organophosphorus Compounds for Potential Toxicity of the Visual System") an excellent review of the science but somewhat limited in its recommendations likely related to limited input due to the size and areas of specialization of the working group.

From a practical perspective, we acknowledge rat and dog as appropriate species to study ocular and visual effects of OPs but do not know if they are the most appropriate. Species differences in sensitivity exist and testing two species maximizes chances of uncovering adverse effects. Because of the delayed nature of the ocular lesions, studies should be a minimum of one year and should commence with animals as young as possible in order to detect myopia. At one month, refraction by retinoscopy and biometry (measuring axial length, anterior chamber depth, lens thickness, and vitreous length) should be routinely performed. Kertatometry (automated technology is expensive, but can be adapted to small rodent eyes) would allow detection of astigmatism.

QUESTIONS AND PANEL RESPONSES FOR VISUAL SYSTEM TOXICITY OF OPS SESSION

With regard to the draft protocols for assessing the visual system toxicity potential of organophosphorus pesticides in the rodent and non-rodent prepared by Agency and reviewed at a Workshop held at the ILSI Risk Science Institute (RSI) in 1994:

QUESTION 1: The panel is asked to **comment on the recommendations and address the unresolved issues** presented in the 1994 ILSI RSI Workshop report. These recommendations and unresolved issues have been highlighted and summarized in the Background document prepared for this meeting. A copy of the full ILSI Workshop report and the unmodified draft protocols have been provided to the panel. In particular, the panel is asked for specific recommendations on the following three areas:

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A. Issues Left Unresolved by the ILSI Workgroup:

ISSUE: Whether or not to recommend inclusion of retinal cholinesterase activity assessment as a protocol element?

PANEL RESPONSE: Until an association can be made between ocular tissue (retinal, ciliary muscular and extraocular muscular) ChE levels and toxicity, these data have questionable value. As such, we would exclude them as required data from the draft protocol. Studies relating brain ChE levels and retinal ChE levels would be useful and perhaps obviate the need for assaying both tissues. Measurement of retinal cholinesterase activity should not be a required element of a protocol, but may be optional.

ISSUE: Appropriate test strain of animal e.g. the albino vs. pigmented rat.

PANEL RESPONSE: We find the rat, and in particular the albino rat, a less than optimal model for evaluating ocular toxicity. Since the eye is small, in vivo testing is generally technically more difficult than species with larger eyes. The retina of rats is composed of almost all rod photoreceptors, and is thus different than human and canine retinas, which are composed of both rods and cones. Retinal changes due to aging, inherited disease, and phototoxicity are common and can confound interpretation of the electrophysiologic and morphologic data.

Strain and sex differences in OP sensitivity have been documented. The albino rat is a mutant far removed from the target species and the lack of pigment adds to the limitations of in vivo diagnostic testing (i.e., ophthalmoscopy) and makes albino strains more susceptible to light induced degeneration. Therefore, we encourage research on the use of pigmented strains of rats to determine if they are more similar to humans than are albino rats.

B. Issues commented on by the ILSI Workgroup for which the Agency would like additional comment and edification by the panel:

ISSUE: Whether or not to recommend the inclusion of ERG and/or VEP assessments as protocol elements?

PANEL RESPONSE: In general, functional assessment of toxicity is of greater sensitivity than morphologic methodologies. The visual pathways are complex and difficult to evaluate in their entirety using morphological techniques. For these reasons, we feel that the ERG and VEP are valuable tools in assessing the effects of OPs on visual function. However, these techniques are time and labor intensive and susceptible to technical variables. Strict adherence to standardized techniques is essential in obtaining valid data. Results of these techniques should be considered when evaluating morphologic findings.

ISSUE: The appropriate technique(s) for performing an adequate histopathological exam of the optic nerve (e.g. the need for special staining, such as the PPD stain, and qualitative or quantitative analysis to assess nerve injury);

PANEL RESPONSE: Histopathologic study of retina and cross sections of optic nerve by light microscopy should be performed routinely, but we raise the question of where best to examine the optic nerve. If the pathogenesis of the optic nerve lesions involve a distal neuropathy, the further one gets from the ganglion cells in the retina the more likely one is to see lesions and examination of the optic tract or geniculate body would be more sensitive.

Morphologic evaluations in addition to light microscopic examination which may include

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thin sectioning of retina and optic nerve embedded in epon or glycol methacrylate, staining with toluidine blue or PPD, respectively; quantitative morphometry on cross sections of optic nerves; and/or other ultrastructural evaluations, should be considered only if ophthalmoscopic, light microscopic or electrophysiologic observations, or the presence of other findings, i.e.,peripheral neuropathy or inhibition of brain ChE, suggest OP toxicity. Sections of the retina, optic nerve, and possibly selected areas of the brain may be available from neurotoxicity studies.

ISSUE: What is the appropriate test species?

PANEL RESPONSE: From a practical perspective, dogs and rats are used. Without data to define species-sensitive sensitivity, their selection is arbitrary.

ISSUE: The importance of assessing ocular refraction if doing so involved using two test species to perform a study i.e rat and dog?

PANEL RESPONSE: Ocular refraction and keratometry in at least one species should be requisite; techniques must be standardized and validated.

ISSUE: The appropriate study duration?

PANEL RESPONSE: Given the current information, it appears that adverse effects should be detected after one year in the dog and in the rat. Results of studies involving two year old rats may be complicated by spontaneous and age-related lesions.

C.Remaining topics for which recommendations were made by the ILSI Workgroup (see Workshop report and Background document).

ISSUE: Does the SAP concur with the remaining ILSI Workgroup recommendations?

PANEL RESPONSE: The Panel agrees with the recommendations of the ILSI workgroup report listed on pages 5-8 of the background document with the following minor exception; in section 1.c.ii. high resolution light microscopic examination of plastic embedded sections stained with paraphenylene diamine (PPD) or toluidine blue would be indicated only when electrophysiologic findings or other findings indicate possible OP toxicity and there are no light microscopic findings as a second tier of evaluation.

QUESTION 2: From the panel's perspective, are any of the draft protocol parameters unnecessary or have any pertinent parameters been excluded? If so, what would be the rationale for their exclusion or inclusion in the draft protocols?

PANEL RESPONSE: In response to the Agency's prototypic study protocol, the panel would make the following recommendations:

A. That dog studies be initiated in animals three months of age in order to allow optimal detection of induction of myopia, and that studies in this species be a minimum of one year, as many of the potential toxic effects presumably require long-term exposure to develop.

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B. The panel feels that the determination of plasma erythrocyte and brain cholinesterase levels should be routinely performed. The determination of cholinesterase activity in specific ocular tissue (extraocular muscles, ciliary muscle, and/or retina) would be desirable as optional tests, but should not be required until direct association between cholinesterase levels and toxicity can be established.

C. Regarding ocular assessment, we feel that greater emphasis should be placed on detection of the possible effects of the test compounds on ocular growth, and would recommend that biometry be required in both dod and rat, and that keratometry and refraction (retinoscopy) be required in dog, and encouraged as an optional test in rat. We feel that routine fundus photography is not essential, but should be required to document significant lesions in both species. The panel feels that electrophysiology should be emphasized in the initial tier of compound evaluation; we would recommend electroretinography and VEPs be required in the dog, with electroretinography required and VEPs optional in the rat. Techniques of keratometry, biometry, refraction, and electrophysiology should be standardized and validated.

QUESTION 3: Finally, are the draft protocols for the non-rodent and rodent **adequate and useful** for assessing the visual system toxicity potential of organophosphorus pesticides. Could an adequate assessment be made using less detailed measures and, if so, what would they be?

PANEL RESPONSE:

A self-contained visual system toxicity study has the potential of being composed of excessive and redundant measures. The most adequate useful and focused protocol is one that is based on results of other studies. Therefore, we wish to emphasize or add comment to the following statements in the draft proposal.

A. Encourage the incorporation of the visual system toxicity testing components in other types of studies (i.e., acute study, chronic, and especially neurotoxicity studies) and if necessary, design self-contained studies based on the findings of these other studies.

B. If whole animal perfusion with fixative is used, especially as a part of a neurotoxicity study, globes with
extraocular muscles and optic nerves should be collected to have available for ancillary examination if desired.

In summary, it is obvious that additional research is needed by EPA to address issues such as: 1) pathogenesis of OP-induced ocular changes in different species and their relationship to human risk, 2) use of albino versus pigmented strains of rats, and 3) standardizing and validating methods of ocular refraction and electrophysiology. The use of a tier system for evaluation should also be considered.

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FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

MEETING

A Set of Scientific Issues Being Considered by the Agency to Discuss and Evaluate the Standard Operating Procedures for Peer Reviews.

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of the Standard Operating Procedures for Peer Reviews of Major Scientific and Technical Documents. The review was conducted in an open meeting held in Arlington, Virginia, on March 20, 1997. The meeting was chaired by Dr. Ernest E. McConnell. Other panel members present were: Dr. Leo Abood (University of Rochester); Dr. Charles C. Capen (Ohio State University); Dr. Michael L. Dourson (Toxicology Excellence for Risk Assessment); Dr. Charles H. Hobbs (Inhalation Toxicology Research Institute); Dr. Ronald J. Kendall (Clemson University); Dr. Harihara M. Mehendale (Northeast Louisiana University); Dr. Michele A. Medinsky (Chemical Industry Institute of Toxicology); Dr. James A. Swenberg (University of North Carolina); Dr. Mary Anna Thrall (Colorado State University).

Public Notice of the meeting was published in the Federal Register on January 29, 1997.

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GENERAL RESPONSE OF PANEL MEMBERS

QUESTIONS AND PANEL RESPONSES FOR OPERATING PROCEDURES FOR PEER REVIEW SESSION

QUESTION 1:

What OPP work product categories (e.g., special reviews, test guidelines, etc.) should receive SAP peer review, other forms of external peer review or internal review?

Is there a need to use external peer review in those routine cases where the underlying scientific principles/guidelines/models have already been peer reviewed?

SAP RECOMMENDATION

The Standard Operating Procedure (SOP) for peer review provided to the Science Advisory Panel (SAP) was thorough as related to principles and procedures for implementing peer review within the Agency. Implementation of peer review should continue to provide the best scientific input available to assist the Agency in making science-based policy decisions. The use of peer review should be quantitated, so that new knowledge can be contributed in an accelerated manner to assist the Agency in decision-making. For instance, use of peer review can reduce Environmental Protection Agency (EPA) person hours, thereby saving the Agency money and time, as well as facilitating the development of new review technologies that can improve risk assessment and registration review.

Peer review training within the Agency should continue and be enhanced wherever possible. For instance, line managers should be trained so that peer review is widely applied throughout the Agency in a way to identify the best scientific input that may be acquired. Since EPA has been challenged by a recent GAO audit related to the implementation of a consistent peer review process within the Agency, every effort possible should be made to better quantitate the financial and scientific advantages of peer review.

Peer review to ensure sound scientific basis for EPA policy is particularly important with the passage of the Food Quality and Protection Act, the Federal Insecticide, Fungicide and Rodenticide Control Act, and other complicated environmental legislation. Most importantly, research knowledge related to human and environmental toxicology is exponentially increasing, and peer review is an efficient method for EPA to assess this information.

QUESTION 2:

Given the rapid rate of SAP member turnover as well as the often large number of consultants, should OPP systematically provide such feedback to the SAP?

SAP RECOMMENDATION

The unanimous response from the Science Advisory Panel (SAP) was that feedback should be provided, particularly as it relates to the ultimate decision making process that was implemented by the Agency. Scientific credibility of the SAP can be enhanced by providing feedback as to how SAP input influenced the overall quality and/or quantity of the work product.

QUESTION 3:

How effective is OPP's use of the SAP? Are there actions that OPP could take to strengthen its use of the SAP?

SAP RECOMMENDATION

The SAP responded to the Agency with an awareness that the SAP appeared to be more widely used currently than it was even last year or several years ago. Since the passage of the Food Quality Protection Act will generate many new scientific issues, it appears that the SAP may be more widely needed and used in the future. The Agency, particularly in the OPP, is often faced with applied research questions that need to be addressed through the Office of Research and Development (ORD) or other research operations either within or outside the Agency. SAP input, particularly in the early stages of new programmatic development, could be quite valuable. In the past, SAP input has often come at the latter stages of the planning process. SAP input would usually be of more value if it were utilized at an earlier stage of planning. The Agency appears to be utilizing the SAP at earlier stages, and we encourage a continued evolution of up-front planning in addition to continued review of progress of programs when appropriate and economically feasible. In summary, the impact of the SAP on Agency decisions can be better assessed if feedback is provided to the SAP. Ultimate implementation of higher quality-based policy will further justify the value of the peer review process.

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