SAP Report No. 99-02
March 25, 1999

REPORT

FIFRA Scientific Advisory Panel Meeting, February 23-24, 1999, held at the Holiday Inn, Arlington, Virginia

Sets of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

Session I - Sediment Toxicity and Fate of Synthetic Pyrethroids

Session II- Time Sensitive Reversibility of Aldicarb Induced Cholinesterase Inhibition as a Factor in Acute Dietary Risk Assessment

Session III- Consultation on Development of Draft Aggregate Exposure Assessment Guidance Document for Combining Exposure from Multiple Sources and Routes

NOTICE

This report has been written as part of the activities of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP). This report has not been reviewed for approval by the United States Environmental Protection Agency (Agency) and, hence, the contents of this report do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.

The SAP was established under the provisions of FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, to provide advice, information, and recommendations to the EPA Administrator on pesticides and pesticide-related issues regarding the impact of regulatory actions on health and the environment. The Panel serves as the primary scientific peer review mechanism of the EPA, Office of Pesticide Programs (OPP) and is structured to provide balanced expert assessment of pesticide and pesticide-related matters facing the Agency. Food Quality Protection Act Science Review Board members serve the SAP on an ad-hoc basis to assist in reviews conducted by the SAP. Further information about SAP reports and activities can be obtained from its website at http://www.epa.gov/pesticides/SAP/ or the OPP Docket at (703) 305-5805. Interested persons are invited to contact Larry Dorsey, SAP Executive Secretary, via e-mail at dorsey.larry@epamail.epa.gov

SAP Report No. 99-02A, March 25, 1999

REPORT:

FIFRA Scientific Advisory Panel Meeting, February 23, 1999, held at the Holiday Inn Hotel, Arlington, Virginia

Session I - A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

Sediment Toxicity and Fate of Synthetic Pyrethroids

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Mr. Larry C. Dorsey,
Designated Federal Official
FIFRA/Scientific Advisory Panel
Date:_____

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Dr. Ronald J. Kendall,
Chair
FIFRA/Scientific Advisory Panel
Date:_____

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

Session I - A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding Sediment Toxicity and Fate of Synthetic Pyrethroids

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency regarding sediment toxicity and fate of synthetic pyrethroids. Advance public notice of the meeting was published in the Federal Register on January 20, 1999. The review was conducted in an open Panel meeting held in Arlington, VA, on February 23, 1999. The meeting was chaired by Dr. Ronald J. Kendall of The Institute of Environmental and Human Health, Texas Tech University/Texas Tech University Health Sciences Center, Lubbock, Texas. Mr. Larry Dorsey, SAP Executive Secretary, served as the Designated Federal Official.

Participants

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Oral statements were received from the following individuals:
Dr. Steven Maund (Pyrethroid Working Group)

Written statements were received from:
Pyrethroid Working Group

Summary of Agency Presentations

Synthetic pyrethroids are a class of chemicals that are highly lipophilic and tend to strongly partition to sediments. Consequently, assessment of risks from exposure of non-target aquatic organisms to synthetic pyrethroids in the water column do not adequately characterize the risks for this class of chemicals which tend to strongly adsorb to sediments. This SAP session focused on studies performed by the Pyrethroid Working Group (PWG) to evaluate the partitioning, bioavailability, and toxicity of synthetic pyrethroids in sediments. These studies serve as the foundation of an assessment of risks to aquatic organisms exposed to synthetic pyrethroids. Subsequent SAP sessions will focus on the assessment of risks from exposure of non-target aquatic organisms to synthetic pyrethroids in sediments.

Ms. Pat Jennings (EPA/OPP) opened the session by providing information on the history of the use of synthetic pyrethroids as insecticides, their regulatory status, and the scope of this SAP session. Mr. Jose Melendez (EPA/OPP) presented a comparative analysis of physical-chemical properties and environmental fate characteristics of the ten synthetic pyrethroids being examined, with emphasis on results for cypermethrin, the synthetic pyrethroid that PWG examined in developing data on partitioning, toxicity, and bioavailability of synthetic pyrethroids in sediments. Mr. Michael Rexrode (EPA/OPP) presented information on the water column toxicity of the synthetic pyrethroids to aquatic organisms, as well as acute sediment toxicity results that were determined for cypermethrin. Dr. Ron Parker (EPA/OPP) finished the session by presenting a review of studies conducted by PWG on partitioning and bioavailability of cypermethrin in three aquatic sediments.

Panel Response to Agency Presentation and Questions

Agency Questions

The Agency presented the following questions to the FIFRA SAP regarding sediment toxicity and fate of synthetic pyrethroids. The questions are keyed to the Agency background document entitled *Sediment Toxicity and Fate of Synthetic Pyrethroids, January 25, 1999*.

(1) Are the physical-chemical properties, environmental fate characteristics, and water column toxicity of synthetic pyrethroids similar enough that one chemical, cypermethrin, can be used to represent sediment toxicity of synthetic pyrethroids as a class? If not, could any single one of the other synthetic pyrethroids examined be used to represent sediment

toxicity of synthetic pyrethroids as a class? If none of these chemicals individually can be used to represent synthetic pyrethroids as a class, which and how many of these chemicals can be used to represent sediment toxicity of synthetic pyrethroids as a class? Please provide the basis for your conclusions.

The value of using cypermethrin as a surrogate test chemical for the synthetic pyrethroid (SP) class is the relative abundance of laboratory and field data on this chemical. While cypermethrin has some limitations as a surrogate for the entire class of SPs, it appears to be a good choice for the in-depth assessment conducted by the Agency and the Pyrethroid Working Group (PWG). The Panel compliments both the Agency and the PWG for preparing a comprehensive review of this class of chemicals which are known to be difficult to work with due to their extreme binding characteristics.

In general, it is often problematic to extrapolate from a specific compound to a broad class of chemicals when there are significant differences in the physico-chemical properties. The Panel acknowledges that cypermethrin's characteristics do not represent the average condition for any specific feature of the environmental fate of synthetic pyrethroids. SPs contain a cyclopropane ring, either substituted (i.e., methyl or dimethyl, etc.) or unsubstituted, and generally contain halogens (i.e. bromines, chlorines) bound to either alkane or vinyl carbons, and in some cases cyano groups. The chemical structures and hence the reactivity (i.e., photolysis, hydrolysis, sorption etc.) vary considerably. The water solubilities of these chemicals vary by approximately two orders of magnitude, their Henry's law constants range from about 2×10^{-4} to about 2×10^{-11}. In addition, their photolysis, hydrolysis and soil degradation rates vary significantly. The reported log K_{ow}s range from about 5 to 7, with reported adsorption coefficients ranging over several orders of magnitude. Bioconcentration in edible tissue is reported to range by a factor of 100 or more. Reported toxicity values are also very variable and differ by more than an order of magnitude from compound to compound.

On the basis of the SP physico-chemical properties and fate measurements, one would expect different exposure scenarios in surface waters following application and runoff to aquatic systems. Differences in exposure to organisms would be expected *a priori* to be influenced more by chemical property differences (factor of 100) than differences in the application rate (factor of 10).

The argument is made that application rate can normalize for the differences in potency. While one might consider that the pyrethroids used at higher rates are less toxic, this reduced toxicity does not appear to be of the same order of magnitude as the exposure differences that would be predicted from the physico-chemical properties. The Panel recognizes that the relationship between rate of application and toxicity is not consistent across the entire class of compounds. Further, the assumption that underlies this argument is that we are dealing with only one mode of (acute) toxicity. There are at least two types of neurotoxicity involved that are sufficiently different such that lumping all pyrethroids could possibly obscure important differences. Additionally, pyrethroids are known to have sublethal effects, for example, on levels

of enzymes involved in aerobic and anaerobic metabolism.

The Pyrethroid Working Group's written comments provided to the Panel for this meeting attempted to provide support for the use of cypermethrin as a surrogate, as noted in Table 1 and Figures 3 and 4 of their submission. The study approach determining the toxicity and environmental characteristics of the compound as presented in the documents are appropriate to gain insight into the potential hazard of a chemical. While the Panel is not in complete agreement with all the conclusions, the Panel does support the continued use of cypermethrin in conjunction with other members of the class for assessing SPs for several reasons. First, cypermethrin is the best studied pyrethroid with respect to the sediment-water interactions. Second, cypermethrin is a type II pyrethroid and is reasonably stable.

An alternative to the use of cypermethrin by itself should be pursued by selecting representative chemicals to assess the SP class. Testing a minimum of three chemicals, chosen to span the differences in sediment binding/water solubility and organism toxicity, appears appropriate. In addition to cypermethrin, the Panel recommends testing bifenthrin (relatively non-toxic to freshwater aquatic organisms, very insoluble in water, large bioconcentration factor) and possibly trefluthrin (highly toxic to freshwater aquatic organisms, stable in water, intermediate solubility in water to cypermethrin and bifenthrin).

(2) Based on our interpretation of PWG data as well as data submitted to the Agency for individual synthetic pyrethroids, we have determined that the correlation between sediment partition coefficient (K_d) and organic carbon content of sediments is weak. Therefore, OPP thinks the concept of K_{oc} is of little value in explaining the binding behavior of synthetic pyrethroids to sediment. On the other hand, available data indicate that there is a strong correlation between benthic organism body burden per dose and K_d. Given these findings, OPP plans to use K_d rather than K_{oc} to estimate concentrations of synthetic pyrethroids in aquatic sediments. Does the Panel agree or disagree with this interpretation? What is the basis for your conclusion?

The use of K_{ow} rather than K_{oc} to estimate concentrations of synthetic pyrethroids in sediments is counter-intuitive considering the magnitude of their K_{ow}s which is in the range of poly chlorinated benzenes, poly aromatic hydrocarbons, chlorinated pesticides and other highly sorptive non-polar organic chemicals, typically normalized to the organic carbon content of soil/sediments. SPs have a high degree of aromatic character and it is reasonable to expect them to associate with sediment organic carbon (OC). Therefore, before rejecting what has become widely accepted theory for non-ionic organic chemicals in favor of an apparent empirical relationship (K_d), the Panel recommends that the Agency reconsider the use of K_{oc} as a measure of the binding potential of SPs to sediment and soil.

The Panel agrees with the Agency that, for much of the data, carbon normalization (K_{oc}) did not reduce the variability in the partition coefficients (K_d). In these instances, the use of K_d appears to estimate sediment partitioning as well as K_{oc}. However, some of the data presented in

the reports used for this review show a definite relationship between OC and sediment binding. This is further supported by relationships between OC and toxicity/pore water in some of the sediment toxicity studies.

K_d values are obtained under a given set of conditions for a given soil type. The use of K_d in place of K_{oc} limits the Agency to the use of a value which is operationally defined and which cannot be extrapolated beyond the experiment that generated the value. The advantage of using OC as a normalizing basis is that it allows one to estimate partitioning across a wide variety of soil/sediment types. This approach is central to the risk assessment of non-ionic chemicals sorbed to sediments.

The Panel questions the accuracy and reliability of the existing soil partition coefficients for SPs other than cypermethrin. It is extremely difficult to accurately measure the soil partition coefficient for highly sorptive chemicals like SPs. The difficulties associated with these measurements have been well studied (O'Connor and Connolly 1980, Gschwend and Wu 1985, DiToro 1985, and Williams et al. 1995). For these same chemicals, accurate measurements of water solubility are also difficult to obtain due to the formation of colloids, micelles and problems associated with accurate measurements at very low concentrations in water. It is not uncommon to find that both the water solubility and soil partition coefficients are in error for the less soluble members of the class. This may be true for the SPs.

A common technique that has been used to determine whether data are reliable is to measure the K_{ow} for the entire class using the slow-stir shake flask method. EPA (Athens Laboratory, Georgia) has reported this to be the most reliable method for chemicals with a high K_{ow} (DiToro, 1991). K_{ow} measurements should be compared with calculated K_{ow} values based upon molecular structure. Several techniques exist to perform these calculations including the classical Leo and Hansch approach and the SPARK method developed at the EPA Athens, Georgia laboratory. Carefully determining the K_{ow} allows one to predict K_{oc}, water solubility and bioconcentration factor. Likewise, existing water solubility and K_{oc} values can be compared to the measured K_{ow} values. Careful examination of the K_{ow}, K_{oc}, and water solubility relationships should provide the necessary basis to determine whether the physical property data base is acceptable and the potential for using carbon normalization.

On the basis of the Panel's limited review, it appears that the K_d measurements have been performed in systems with high solids to water ratios (1:25). While this ratio may have significance for aquatic toxicity test procedures or outdoor ponds, this is not an appropriate solids level for determining soil-water partition coefficients (i.e., the solids level is much too high for a class of chemicals with large K_d values). This results in values of K_d which are suppressed due to possible sorption to colloids or dissolved organic carbon (DOC) in the water phase when conventional analysis methods are used. The K_d values for the most insoluble SPs are suppressed the most with the result that the differences in sorption potential within the class appears small and normalization to OC appears ineffective (Williams et al, 1995).

In general, carbon normalization accounts for most variability in binding differences between sediment types. However other factors can be important including the type and amount of clay present and the character of the organic matter. Sediment organic carbon is not all the same. For example, there are large differences in the affinity of the same neutral organic chemical for fulvic, as opposed to humic acids. Even in OC that is predominantly of one type or from one source, there can be large differences in aromaticity and affinity of a chemical as a consequence. With non-ionic organic contaminants, the organic matter in Florissant soil (PWG test sediment) has been shown to have a much lower binding potential (bioavailability is greater) than the organic matter from Lake Michigan (Landrum and Faust, 1994). Thus, consideration of the character of the organic carbon can be important for determining the bioavailability of some classes of sediment-associated contaminants.

The PWG has suggested that the less than expected binding of SPs to the Duluth sediment (PWG test sediment) may be a surface area phenomenon. The Panel recognizes that the Duluth sediment contained 13% OC which is very atypical and likely had high DOC associated with it. As a first order approximation, DOC has been shown to have binding constants approximately the same as sediment (DiToro et al, 1991). The presence of DOC could significantly reduce the apparent sediment binding and Kd/Koc measurements (Williams et al. 1995). In addition, the Florissant soils are not sediments, but flood plain soils (Adams et al. 1983). These factors may be confounding the relationships between OC and partitioning. Clays and surface area are also undoubtedly important and can dominate sorption processes when OC is low or the clay fraction is large.

Additional information is needed on SP binding to soils/sediment with varying amounts of clay as well as organic carbon. These data will ensure that the range of sediment characteristics that appear to have substantial influence on binding are appropriately addressed and understood to achieve accurate risk estimates.

The Agency's background document notes that organic carbon was determined indirectly from a measurement of organic matter, specifically by oxidation with $K_2Cr_2O_7$ followed by titration of excess dichromate with $FeSO_4$ (Walkley-Black method). Organic carbon content therein is then derived from the equation: Organic carbon=OM/1.724. Most recent published scientific literature examining aquatic sediment total organic carbon uses a more direct approach toward determination of organic carbon content; typically combustion of the dry sediment, followed by infra-red determination of the evolved CO_2. A number of automated "CHN" instruments are commercially available.

(3) ASTM guidelines suggest testing sediment toxicity using a sediment to water volume ratio of 1 to 1. These guidelines were not finalized at the time the PWG initiated its sediment toxicity testing for cypermethrin. Sediment toxicity tests conducted by the PWG were performed with a sediment to water ratio of 1 to 25. Amphipods such as *Hyalella* can, however, avoid toxicity originating from synthetic pyrethroids in aquatic sediments by swimming away from the sediments toward the overlying water column. Can the Panel help

OPP to weigh the importance of this deviation from the current ASTM guidelines for sediment to water ratio? Would its effect on acute sediment toxicity be expected to significantly affect the overall risk assessment? What is the basis for your conclusion?

The Panel does not believe that water ratios other than the 1:1 ratio recommended by ASTM would significantly alter the results of the toxicity test with *Hyalella azteca*. In static tests, such as those reported for cypermethrin, the water and sediment come to near steady state conditions within approximately 24 hours. One would expect about the same test chemical concentration in the pore water and overlying water of a test system with a 1:25 ratio as in a test system with a 1:1 ratio of sediment to water. The reason being that >98% of the mass of the test chemical is contained in the sediment and the water concentration is determined by the sediment test chemical concentration. Assuming amphipod behavior is the same in both test systems, the amphipods should be exposed to approximately the same concentration in the water in both systems.

The ASTM/EPA guidance states 1:1.75 ratio of sediment to water should be used. However, this value was not selected based on scientific testing, rather it was used because the Duluth EPA laboratory used it. A 1:4 ratio was commonly used prior to the early 1990's. Testing by Stemmer et al. 1990 showed that the sediment to water volume or surface area ratios had to be quite extreme to cause any affect (e.g., 1:149 or 3:1). Landrum (1989) showed when test organisms do not actively avoid the sediment, the ratio of overlying water was found to have no effect on exposure to sediment associated contaminants (the PWG indicated that amphipods did not avoid the sediments during the test). Additionally, the PWG response to the above question, using water column solubility calculations (as a public comment), supports the Panel's belief that this is not a concern.

(4) The authors of the PWG study to evaluate bioavailability of cypermethrin to *Daphnia magna* in sediment-water systems suggest that the concentration of cypermethrin in sediment is a better predictor of concentration of cypermethrin in the organism than is the concentration of cypermethrin in the water column. As a result, these authors propose using a sediment bioconcentration factor (BCF_S), calculated as the concentration in the organism divided by the concentration in the sediment, as an indicator of bioavailability to sediment-dwelling organisms. Is a sediment bioconcentration factor (BCF_S) a useful concept in conducting sediment risk assessments? If so, how should BCF_S be applied in assessing exposure and risk to sediment-dwelling organisms?

Sediment bioaccumulation factors have been found to be useful in assessing the significance of concentrations of non-ionic organic chemicals sorbed to sediments. The Agency (USEPA - ORD, 1993) has previously used this approach in assessing PCBs and Dioxins and other non-ionic organic chemicals. This measurement has been applied to both sediment-dwelling and water column organisms in field assessments. The term BCF_S (bioconcentration factor) is not technically correct. When calculating the relationship between the concentration in the organism and sediment on a bulk basis, the term should be called a bioaccumulation factor (BAFs). Additionally, biota

sediment accumulation factors (BSAFs) have come into wide usage for non-ionic organic chemicals in sediments. BSAFs are equivalent to BAFs normalized to organic carbon in sediment and lipids in the tissues of exposed organisms. The concept has proven very useful and usually accounts for most of the variability in the equilibrium distribution of non-ionic organic chemicals between sediment and biota. BSAFs are used in calculating theoretical bioaccumulation potential (TBP) in site assessments and in regulatory evaluations of dredged sediment before granting permits for open water disposal. The procedure is recommended in the implementation manuals for Section 103 of the Marine Protection, Research, and Sanctuaries Act of 1972 and Section 404 of the Clean Water Act. Considering the number of published reports on the use of BSAFs, the Panel was somewhat surprised this procedure was not investigated for pyrethroids.

BSAFs offer the advantage that they relate tissue concentration to sediment concentration and do so by integrating chemical concentration and bioavailability over time. Contaminants which are difficult to measure in the water phase of aquatic systems (due to large binding coefficients and analytical detection limitation) can usually be measured in the sediment phase. Use of BSAFs provide a way to describe the bioavailability of a contaminant relative to a particular sediment (or site) and to different aquatic species. The utility of BSAFs is that they provide a way to predict organism contaminant concentration from sediment contaminant concentration assuming the sediment OC and organism lipid content are known. In principal, differences in organism accumulation of a contaminant due to differences in bioavailability (i.e., sediment binding properties for a given chemical) are accounted for by this approach. Differences between organisms (behavior, avoidance, feeding habits) can influence the BSAFs among species. Interpretation of BSAFs in terms of predicting toxicity to a given species requires knowledge of the tissue residue effect level in the organism of interest. Overall, this approach provides an opportunity to evaluate the potential for food chain transfer of contaminants based on sediment contaminant measurements.

The organisms used by the PWG for sediment testing (*Daphnia magna, Chironomus* spp., and *Hyalella azeteca*) have been widely used and are acceptable freshwater species. These species are predominantly epibenthic and are filter feeders. Additional testing using a deposit-feeding organism such as a freshwater oligochaete (*Lumbriculus variegatus*) or marine polychaete (*Nereis virens*) may prove useful for assessing bioaccumulation of SPs. Standardized methods exist for these organisms. This approach provides a worst-case scenario for bioaccumulation and food chain risk because 1) these oligochaetes and polychaetes do not readily metabolize most synthetic organics, 2) they ingest sediments, 3) have relatively high lipid content, and 4) are infaunal, burrowing organisms and thereby will be exposed to the highest concentrations of pyrethroids. Thus, while BSAFs may be of use as an empirical indication of bioaccumulation tendencies, *Daphnia* and *Hyalella* data actually showed that BCF from water is sufficient to explain the bioaccumulation data.

The inability to measure SPs in the water phase of toxicity experiments often presents problems in determining effect levels associated with water or pore water. One technique that has been useful for other highly hydrophobic organic chemicals has been the use of semi-permeable

membrane devices (Huckins et al. 1996; Huckins et al. 1990; Lebo et al. 1995) which allow for the chemical of interest to accumulate through a membrane into an organic (lipid) phase. The concentration in the water phase can be back calculated. This methodology also allows for an estimation of organism bioconcentration and may be useful for SPs.

One Panel Member commented that the association of hydrophobic organic contaminants with dissolved organic carbon and colloids affects their availability and thus their potential to accumulate in aquatic organisms. Conventional organic solvent-based extraction methods generally determine the total amount of the contaminant present in the water, not the bioavailable fraction. Thus, BCFs calculated from these "total" dissolved values may be invalid. This issue was raised in respect to problems predicting organism concentrations of pyrethroids from measured water values in the submitted lab studies. The use of alternative analytical approaches may be useful. Solid phase microextraction (SPME) involves the partitioning of the freely dissolved contaminant from the water into a solid phase covering a needle. The needle is then placed into the injector of a gas chromatograph and the analyte thermally desorbed. Scientists have observed this technique to be a rapid and accurate approach for estimating the bioavailable fraction of organic contaminants in water containing humics.

The Panel has also provided a list of references as cited above to support the Panel's conclusions and to assist the Agency in developing its risk assessment. The references are provided below.

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NOTES

SAP Report No. 99-02B, March 25, 1999

REPORT:
FIFRA Scientific Advisory Panel Meeting, February 23, 1999, held at the Holiday Inn, Arlington, Virginia

Session II - A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

Time Sensitive Reversibility of Aldicarb Induced Cholinesterase Inhibition as a Factor in Acute Dietary Risk Assessment

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Mr. Larry C. Dorsey,
Designated Federal Official
FIFRA/Scientific Advisory Panel
Date:_____

_____
Dr. Ronald J. Kendall,
Chair
FIFRA/Scientific Advisory Panel
Date:_____

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

Session II -Time Sensitive Reversibility of Aldicarb Induced Cholinesterase Inhibition as a Factor in Acute Dietary Risk Assessment

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency regarding time sensitive reversibility of aldicarb induced cholinesterase inhibition as a factor in acute dietary risk assessment. Advance public notice of the meeting was published in the *Federal Register* on January 20, 1999. The review was conducted in an open Panel meeting held in Arlington, Virginia, on February 23, 1999. The meeting was chaired by Dr. Mary Anna Thrall, College of Veterinary Medicine & Biomedical Sciences, Colorado State University, Fort Collins, Colorado. Mr. Larry Dorsey, SAP Executive Secretary, served as the Designated Federal Official.

Participants

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Dr. Ernest E. McConnell, Toxpath, Inc., Raleigh, NC
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Dr. Dale Hattis, Research Professor, Center for Technology, Environment and Development, Clark University, Worcester, MA
Dr. Edo Pellizzari, Research Vice President, Research Triangle Institute, Research Triangle Park, NC

Dr. Carey Pope, Professor, Northeast Louisiana University, Monroe, LA
Dr. Lorenz Rhomberg, Assistant Professor, Harvard Center for Risk Analysis, Cambridge, MA

Oral statements were received from the following individuals:
Dr. Joseph P. Rieth (Rhone-Poulenc Ag Company)
Dr. Barbara Petersen (Novigen Sciences, Inc.)

Written statements were received from:
Rhone-Poulenc Ag Company

Summary of Agency Presentation

The Office of Pesticide Programs (OPP) currently evaluates dietary exposure to pesticides in two broad time frames. A chronic exposure is one that occurs for a substantial portion of an individual's life. An acute exposure is one that lasts for approximately one day. The advent of calendar based models for estimating exposure has introduced the potential for using a sliding scale for time of exposure. Calendar based models attempt to model the time course and frequency of exposure events such that exposure and accompanying risk from a pesticide are consistent with likely use patterns. The major limitation for estimating exposure in detail is the scarcity of adequate data, including hazard and exposure data. These data are necessary to support an alternate time frame that attempts to focus the risk assessment process to finer time increments. OPP presented an evaluation of data to determine the acceptability of an alternate exposure time to conduct a dietary risk assessment for the pesticide aldicarb. Dr. William Sette (EPA, Office of Pesticide Programs) highlighted the toxicity of aldicarb while Dr. Elizabeth Doyle (EPA, Office of Pesticide Programs) discussed exposure and risk characterization considerations. The focus of the presentations was not the outcome of the risk assessment, but rather the evaluation process for determining the approach to application of these data.

Panel Response to Agency Presentation and Questions

Agency Questions

The Agency presented the following questions to the SAP regarding reversibility of the adverse effects of aldicarb. The questions are keyed to the draft background document entitled *Evaluation and Incorporation of the Time for Reversibility of the Adverse Effects of Aldicarb, January 22, 1999.*

1. A major assumption underlying the proposed analytical process is that if the behavioral and neurochemical effects are fully recovered, that sensitivity to subsequent exposures to aldicarb has returned to baseline. However, there are no systematic data evaluating multiple within-day exposures and differences in sensitivity. The data used to support the

assumption of return to baseline status is inferred from indirect evidence. Specifically, repeated dose studies in rats show no decrease in effect level with time. Is the assumption that recovery from the effects of aldicarb is directly related to the recovery of cholinesterase inhibition reasonable and valid?

There was general agreement that this assumption was reasonable, but several members of the Panel felt strongly that it should nonetheless be validated directly with a set of experiments. The grounds for concluding that cholinesterase inhibition does track the adverse effects of aldicarb were considered thoroughly by the Panel.

First, both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) recover rapidly from inhibition by aldicarb, with a decarbamylation half-time measured in minutes. Thus, inhibition *in vivo* can be treated as essentially reversible, and binding to ChE can be assumed to be locally in equilibrium with tissue concentration of aldicarb. In this case, recovery time will be dictated by: (1) the level of inhibition created in the first place (related to the peak agent concentration which in turn is related to the size of the initial dose) and (2) terminal half-life of the agent in the body (assuming that clearance is substantially slower than absorption). It must be borne in mind that half-life of the compound itself and that of the ChE inhibition are two separate entities which should not be interchanged in discussion or, especially, in any future physiologically based modeling.

Second, aldicarb has relatively low solubility in fat, so that buildup in depot is not likely. Because this carbamate is a relatively poor inhibitor of carboxylesterases, saturation of those enzymes is an unlikely cause of potentiation from multiple doses of aldicarb. However, it must be recognized that aldicarb has other actions *in vivo*. For example, aldicarb is a relatively potent inhibitor of gamma-aminobutryric acid (GABA) receptor function (Aracava et al., 1998, Soc. Neurosci., Abst. Vol. 24, No. 624.6), which would cause neuronal excitation, adding to the central effects of anticholinesterase action. Because this receptor action is fully reversible, it cannot cause persistent toxicity. However, preliminary data (E. Albuquerque, personal communication) suggest that aldicarb irreversibly blocks sodium channel inactivation. The longer opened sodium channel would result in increased transmitter release, including acetylcholine, which in turn would activate acetylcholine receptors. If these data are confirmed, they would imply a residue of unnoticed adverse effects.

In view of this background, it would be worthwhile to perform the straightforward experiments required to demonstrate that repeated dosing with aldicarb does not produce super-additive effects, at least in rodents. The simplest such experiment, with the fewest animal subjects, would involve repeated blood sampling on one group of rats given two doses of aldicarb (e.g., by gavage) spaced at 6 hr intervals. These samples could be taken at the following times: before treatment, one and six hours after initial dose, one and six hours after second dose. More frequent sampling would permit better definition of the time course and fitting to an appropriate pharmacokinetic model. The results in either case should permit the Agency to decide whether its fundamental pharmacokinetic assumption is sufficiently well grounded to form a solid basis for risk assessment

and policy making.

2. Do the available toxicological data reasonably support the conclusion that the adverse effects of anticipated acute dietary exposure to aldicarb are fully reversible within 8 hours following the last exposure?

The majority of the Panel concluded that the adverse effects, if they are indeed conservatively tracked by cholinesterase inhibition in blood, are fully reversed for many adult subjects within 8 hours of exposure to aldicarb. However, it was noted by several Panel Members that 8 hours may not be long enough for full recovery in a significant fraction of healthy adults, in the very young, or in the very old, based on the Rhone Poulenc data.

Statistical considerations suggest that a shortened time frame for repeated aldicarb exposure is not justified. The entire human data base consists of two controlled studies and case reports. The registrant's study had 38 men and 9 women. When the Panel asked the registrant for a power analysis, none was available. A sample of 47 subjects is inadequate to find a "small" effect and is practically guaranteed to miss effects of magnitude, d=0.2. The power to find an effect is determined by alpha level, effect size, and number of subjects. For a small effect, at an alpha of 0.05, a sample of 48 subjects has a power of 17. The Rhone-Poulenc study has a 17% chance of finding a small effect, if present. Thus, if disturbances in metabolism or behavior persisted beyond 8 hours in a few subjects, the study in question would have missed them. Such effects, though statistically small (i.e. difficult to identify), are not necessarily unimportant.

Good data were presented on recovery of cholinesterases in humans given a single dose of aldicarb (Figures 18.7, 18.8, 18.9 and 18.10; 1992 Rhone-Poulenc Ag Chemical study). However, the Panel received no documentation that any blood or tissue cholinesterase recovers within 8 hours after multiple exposure. In addition, the only outcomes measured in the assessment were obvious clinical symptoms, saliva volumes, and AChE levels. Aldicarb and carbamates in general have other effects on brain chemistry, and one cannot safely assume that an absence of symptoms means an absence of toxic effects.

Infants and children pose additional concerns regarding AChE recovery following aldicarb exposure. Panel Members were concerned about consideration of children in the Agency's analysis. There was no information on the duration of effects of aldicarb on children. Generally speaking, animal studies suggest that while younger rats are more sensitive than adults to acute toxicity from organophosphorus pesticides, their AChE activity recovers much more quickly following sublethal exposures (Chakraborti et al, Pharmacol. Biochem. Behav. 46: 219-224, 1993; Pope et al., Toxicol. 68: 51-61, 1991; Moser and Padilla, Toxicol Appl. Pharmacol 149: 107-119, 1998; Lassiter et al., Toxicol Appl Pharmacol 152: 56-65, 1998). Comparable data regarding age-related differences in acetylcholinesterase recovery following exposures to aldicarb or other carbamates are scarce, however. We should be aware that AChE recovery after aldicarb exposure could be delayed in children, who may also be at higher risk from repeated aldicarb exposures because of more frequent eating.

At least two Panel Members emphasized that "full recovery" should not be construed simply as "the time when a statistically significant effect is no longer present". That would be an inappropriate use of the null hypothesis. Cholinesterase inhibition does not disappear when, in a noisy assay system, one can no longer reliably measure a difference from baseline. Cholinesterase activities are restored continuously, on a molecule-by-molecule basis, as aldicarb adducts detach from the active sites (or, very slowly, as new cholinesterase molecules are produced and delivered). There is no logical relationship between the point at which cholinesterase inhibition loses statistical significance and the point when effects of successive doses of aldicarb are independent enough to be treated separately. Moreover, exclusive reliance on a detectability criterion would create an incentive for statistically weaker experiments in support of pesticide registration. A quantitative criterion of percentage decay from peak inhibition or percentage recovery of initial activity is a better way to isolate judgments of reasonable independence of successive doses from issues of assay detection.

A second issue concerns the use of group mean data rather than individual recovery rates. Group mean effects should not be the primary basis for decisions affecting the public health. We must worry about how the individual pharmacokinetics and pharmacodynamics for inhibition of cholinesterases may place certain people at greater than average risk for persistent adverse effects from carbamates. Individual data are present in a number of the underlying data sets, so there is no excuse not to attempt some analysis of individual variability, at least in the kinetics of cholinesterase inhibition and recovery.

Although there is still room for different opinions regarding the optimal use of existing data on cholinesterase recovery, there was general agreement on the Panel that prudent provisions should be made for outliers. One Panel Member outlined a plausible approach to this problem, starting with the idea that, to define practical "independence" of dose, we need some criterion of the form: X percent decline from peak inhibition for the Yth slowest percentile of the population. A reasonable proposal is to consider a 95 percent decline from peak inhibition for a 99^{th} percentile sensitive individual to be sufficient. Even if a somewhat less stringent criterion is adopted, analysis of the available data on decay of inhibition in human subjects suggests that an 8 hour time frame is too short. Table 1 on the following page shows the results of the Panel Member applying this model to the Union Carbide aldicarb human study data.

The data in Table 9 of the Agency's background document suggest considerable inter-individual variability in the rate at which whole blood cholinesterase activities recover from inhibition by aldicarb. Among the eleven people studied, the range is nearly 3 fold (by no means unusual). Those subjects with the longest half lives for cholinesterase inhibition ($T_{1/2}$ elim) are predicted to have appreciable residual inhibition at 8 hours, in three cases amounting to more than 10% of the initial peak inhibition. It seems, therefore, that 8 hours is too short an interval to afford "complete" independence of different doses for purposes of EPA analysis. The interval probably should be at least 12 hours (possibly a little more, pending an analysis of the individual data specifically measuring red cell and plasma cholinesterase activities). On request, spreadsheet files with the detailed model calculations will be provided to the Agency.

Rhone-Poulenc, in written comments submitted prior to the meeting and in oral remarks, considered the 2-year dietary aldicarb study (HWA 656-151) to be a "systematic evaluation of multiple within-day exposures". Their response also states that "the only findings noted in the study involved ChE inhibition following multiple within-day exposures". However, without knowing exactly when those responses occurred, it is difficult to exclude the possibility that AChE inhibition did increase with repeated dosing.

Table 1. Model Predicted Time Course, Percentage of Peak Total Cholinesterase Inhibition

Case	$T_{½}$ Abs. (hr)	$T_{½}$ Elim (hr)	6 hr	8 hr	10 hr	12 hr
1	Not done-aberrant data					
2	1.06	1.11	21.9	8.0	2.77	0.91
3	1.12	1.34	30.3	13.0	5.25	2.04
4	0.93	0.96	14.1	4.3	1.21	0.33
5	0.22	2.13	20.3	10.6	5.49	2.85
6	0.81	0.84	8.5	2.1	0.47	0.10
7	0.08	0.80	0.8	0.1	0.02	0.00
8	0.84	0.86	9.5	2.4	0.59	0.14
9	0.53	1.56	18.0	7.4	3.01	1.23
10	0.41	2.00	23.3	11.6	5.79	2.89
11	0.38	0.75	1.5	0.2	0.04	0.01
12	0.75	0.76	5.9	1.2	0.24	0.05
Group Mean Fit	0.52	1.32	12.6	4.4	1.54	0.54

Animals have a well known ability to compensate for persistent AChE inhibition (e.g., through modulation of cholinergic receptors), allowing tolerance to develop. An apparent lack of cumulative clinical signs of toxicity with repeated aldicarb exposure could be due to other factors besides target enzyme recovery. Thus, the information provided to the reviewers makes a less than compelling case that AChE, in either humans or rats, recovers completely within 8 hours after aldicarb exposure.

3. The Office of Pesticide Programs (OPP) uses data from the Continuing Survey of Food Intakes by Individuals (CSFII) to provide the consumption data needed to estimate dietary exposure to pesticides. These data are collected in the form of diaries that outline food consumption throughout the course of the day as recalled by individuals interviewed. OPP typically treats the consumption data as a daily aggregate of foods consumed. However, conducting assessments on an 8 hour basis requires a more detailed use of the consumption data, i.e., an hourly breakout of food reported to be consumed. Are the data in the CSFII sufficiently robust to attempt to model behavior below the daily level of exposure? If so, what are the limitations of this extrapolation?

There was a strong consensus that the CSFII data are sufficiently robust for the purpose of modeling behavior on a time scale below the 24 hr level, that is, at 8 hours or even less. One Panel Member has made a special study of this issue and offered a detailed analysis, summarized below.

The Agency should move quickly to acquiring and using the 1994-1996 CSFII database. One possible change from the 1989-1991 to the 1994-1996 database is the eating habits of persons in different age groups of the population and in different regions of the country. For example, changes have been detected in patterns of drinking water consumption. Not only is drinking water consumption across the age range better represented in the newer data, this consumption has shifted significantly from the traditional sources to bottled water, a commodity that is not regulated by the Agency.

Certain cautionary factors should be incorporated into the exposure assessment for aldicarb. Two types of uncertainty will impact the quality of this assessment: parameter uncertainties and model uncertainties. Parameter uncertainty arises from the input to the model, i.e., food consumption and residue data. Model uncertainty is associated with the Dietary Exposure Evaluation Model itself, i.e., intrinsic limitations in the ability to accurately describe the exposure distribution, given perfect input information. Usually sensitivity testing of the model reveals which input parameters are most influential in determining model output, accurate or not. The algorithm (mathematical function) of the model has associated with it some uncertainty in the model's predictive ability.

In its exposure assessments for aldicarb, the Agency should take into account both model and parameter uncertainties. The reasons for doing so are based on the occurrence of different uncertainties with the input parameters (both consumption and residue data) for different exposure assessments contemplated by the Agency. To exemplify such scenarios, it is instructive to examine the features and limitations of the CSFII database.

The 1994-1996 database has 15,000 subjects representing 256 million people. The survey design over-samples children. Thus, as compared with an equal probability sampling of the population, the precision of data from children is increased but the precision of data from the remaining group is decreased. For children < 1 year of age, the CSFII database has 190+ infants representing 2,560,000 infants, assuming that 1% of the population is in this age group

based on Census data. For children between 1 and 2 years of age, there are about 190+ infants representing this group. As one examines the database in one-year increments, it is evident that the sample size varies disproportionately to the Census percentage of the population for each age group. Thus, the confidence intervals for each age subgroup's representation vary and, consequently, exposure assessments for different selected age groups will have differing uncertainties. A similar argument can be made for sub-populations that may have different eating habits.

A second example of differing uncertainties associated with input parameters is in the structures of the 1989-91 and 1994-96 databases. The newer database has 15,000 subjects and two days of diary observations per subject; the older database has 10,000 subjects and 3 days of observations. Hence, the newer database does better in describing the inter-person consumption of food commodities, but does worse on an intra-person basis.

Geography is another factor responsible for varying uncertainty in exposure predictions. The CSFII database was derived from statistical sampling techniques that weight subject data to obtain national estimates of food consumption, and the weighting factors may be quite different from one region of the country to the next. As a result, the confidence intervals will also vary when segmenting the database into regions.

For all the above reasons, and perhaps others, it is recommended that uncertainties be estimated and displayed for all exposure assessments that the Agency conducts for aldicarb. The uncertainty boundaries around the upper tail of the exposure distribution are of greatest importance for decisions about the likelihood of exceeding a toxicity threshold.

4. Aldicarb presents a very extensive data base for evaluating its behavior both toxicologically and with regard to potential concentration in foods. In particular, the information surrounding the pharmacokinetics of aldicarb make it possible to detail the time course of adverse effects to a greater extent than for most other pesticides. Given appropriate data for other carbamate pesticides, particularly pharmacokinetic data, is this decision making process a reasonable approach for increasing the precision of dietary risk assessments for those chemicals?

There was unanimous agreement that taking pharmacokinetic data into account for exposure and risk assessments was a real step forward in applying new science to regulatory decision making. In other words, the Panel concurred with the strategy of using data on time-dependent recovery of AChE to assess risks from repeated exposures to aldicarb. This positive general conclusion contrasts with the Panel's critical response to question 2, which deals with the technical issue of the actual rate of enzyme recovery. As noted in that section, the case that AChE recovers fully within 6-8 hours after aldicarb exposure has not been convincingly demonstrated. Specific refinements are needed to make the best use of the existing aldicarb data, and additional data would be welcome. In addition, more consideration of sensitive individuals should be incorporated into the Agency's proposal. Once these conditions are met, however, the

pharmacokinetic strategy becomes valid and appropriate. Furthermore, this strategy could be applied to other carbamates as similar or better data become available, recognizing that, as some of these compounds are quite lipophilic, their behavior may differ greatly from aldicarb.

SAP Report No. 99-02C, March 25, 1999

REPORT:
FIFRA Scientific Advisory Panel Meeting, February 24, 1998, held at the Holiday Inn Hotel, Arlington, Virginia

Session III -A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

Consultation on Development of Draft Aggregate Exposure Assessment Guidance Document for Combining Exposure from Multiple Sources and Routes

_____
Mr. Paul I. Lewis
Designated Federal Official
FIFRA/Scientific Advisory Panel
Date:_____

_____
Dr. Ronald J. Kendall
Chair
FIFRA/Scientific Advisory Panel
Date:_____

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

Session III - Consultation on Development of Draft Aggregate Exposure Assessment Guidance Document for Combining Exposure from Multiple Sources and Routes

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency regarding a consultation on development of a draft aggregate exposure assessment guidance document for combining exposure from multiple sources and routes. Advance public notice of the meeting was published in the *Federal Register* on January 20, 1999. The review was conducted in an open Panel meeting held in Arlington, Virginia, on February 24, 1999. The meeting was chaired by Dr. Ronald J. Kendall of The Institute of Environmental and Human Health, Texas Tech University/Texas Tech University Health Sciences Center, Lubbock, Texas. Mr. Paul Lewis served as the Designated Federal Official.

Participants

FIFRA Scientific Advisory Panel Members:
Dr. Charles C. Capen, Chair, Department of Veterinary Biosciences, The Ohio State University, Columbus, OH
Dr. Ronald J. Kendall, Professor and Director, The Institute of Environmental and Human Health, Texas Tech University/Texas Tech University Health Sciences Center, Lubbock, TX
Dr. Ernest E. McConnell, Toxpath, Inc., Raleigh, NC
Dr. Fumio Matsumura, Professor, Institute of Toxicology and Environmental Health, University of California at Davis, Davis, CA
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FQPA Science Review Board Members:
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Dr. Natalie C. Freeman, Adjunct Assistant Professor, Robert Wood Johnson School of Medicine, Piscataway, NJ
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Dr. Thomas E. McKone, Adjunct Professor, UC Berkeley School of Public Health and Staff Scientist, Lawrence Berkeley National Laboratory, University of California, Berkeley, CA

Dr. Edo Pellizzari, Research Vice President, Research Triangle Institute, Research Triangle Park, NC
Dr. Nu-may Ruby Reed, Staff Toxicologist, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA
Dr. Lorenz Rhomberg, Professor, Harvard Center for Risk Analysis, Cambridge, MA

Oral statements were received from the following individuals:
Dr. Thomas Starr (American Crop Protection Association)
Dr. David Wallinga (Natural Resources Defense Council)
Dr. Susan Youngren (Novigen Sciences, Inc.)

Written statements were received from:
Dr. Robert Sielken (Sielken, Inc.)

Summary of Agency Presentations

The Agency presented its draft guidance document for the performance of aggregating exposure and conducting risk assessments. The guidance document provided a framework for linking routes and sources of exposure and established criteria and standards to aggregate exposure and risk. Mr. Francis Suhre opened the presentation, highlighting the goals and objectives of the guidance document. Mr. David Miller provided an overview of dietary, residential, and drinking water exposure pathways. Dr. Jonathan Becker closed the Agency's presentation by discussing the steps in performing aggregate exposure and risk assessments. The Agency's meeting with the Panel was a consultation session. The Agency anticipates updating its guidance document, incorporating comments from the Panel and from the public via a Federal Register notice and presenting its revisions to the Panel.

Panel Response to Agency Presentation and Questions

Panel Recommendation

Even though the draft document captures the essence of making aggregate exposure assessments, it remains to be tested as to its utility and level of definition. The Panel strongly recommends that case studies with pesticides be undertaken that implement all the necessary steps outlined in the draft guidance document. The case studies should be a real example, using real data where available, not just hypothetical information. As such, the problematic steps of the process will become more apparent, indicating the lack of information, and revealing unwitting situations not previously anticipated. This approach will identify the strengths and short comings of the process prescribed in the guidance document and the process can be refined accordingly. As each case is undertaken, there no doubt will be circumstances in which the guidance document in

its present form will not address where guidance is, in fact, needed. Because neither the probabilistic nor deterministic approaches will likely be entirely adequate alone in conducting an aggregate exposure, the Agency may need to formulate general principles that permit a combinatorial use of each.

General Comments

The Agency has done a commendable job of formulating a procedure for aggregating exposure to pesticides. The draft guidance document has incorporated contemporary concepts and approaches that reflect the state-of-science and knowledge about how, when, where, and why individuals are potentially exposed to pesticides via dermal, inhalation, and dietary routes. The organization of the document can be improved by presenting the three pathways in the same sequence in all sections. The probabilistic and deterministic approaches, although different, are complementary and necessary depending on the quality and amount of available data. Each of these approaches has strengths and weaknesses.

Nevertheless, in general, the approach taken to aggregate exposure assessment appears appropriate. The emphasis on reconstructing profiles of exposure of individual people is appropriate, and many of the pitfalls and caveats needing to be borne in mind while using this approach are raised in the document. Some of the specifics about how this general approach is to be implemented, however, are not always clear.

At some point, and to the extent possible, it is desirable to unify the terminologies among all the standard operating procedures (SOPs) and guidances, including this guidance for aggregate exposure and risk assessment. For example, the "Potential Dose Rate (PDR)" in the residential SOP is essentially the "exposure" in the aggregate guidance document. More importantly, these packages should cross-reference and/or keep consistent the key methods used. For example, in the residential SOP, the inhalation PDR is calculated as "concentration" x "inhalation rate," while in the inhalation risk characterization and aggregate risk index (ARI) document, the same method was not explicitly used. Instead, the route-specific margin of exposure (MOE) is calculated on a concentration basis.

Specific Issues

Stratification. The point, made repeatedly in the document, that exposure profiles must be specific to demographic, spatial, and temporal considerations is well taken. But it is not evident how these categories should be defined, on how many variables, and with what level of division of each variable into categories. Within a category (e.g., adult females in the northeastern United States), it will be necessary to address the variation occurring within the category, either using carefully constructed scenarios or by some means of simulation using assumed or empirical distributions of the factors that still vary within the category. It is not clear how the division between variables addressed by categorization and variables addressed by analysis of heterogeneity within categories is to be achieved.

It would seem that, loosely speaking, this is a case of stratification and sampling; one stratifies the entire exposed population into groups defined by certain demographic, geographic, and perhaps seasonal variables. Within each such category, one then attempts to estimate the likely profiles of exposure for individuals in that stratum, either probabilistically or deterministically, depending on the data at hand.

Seen in this light, the challenge is to define the strata most usefully. Considerations include: (1) availability of data on the stratifying variables, and data on the numbers of individuals falling in each stratum; (2) defining strata so that they include individuals with similar expected exposure profiles, or at least profiles for which the differences can be characterized as samples from a distribution that characterizes the whole stratum; and (3) availability of data about exposures within the strata.

If the strata are drawn too broadly or include too much heterogeneity, one must face added problems of accounting for dependencies among variables (e.g., correlations between ethnicity and diet, between relevant lifestyle alternatives such as vegetarianism and frequency of residential pesticide use, etc.). Such dependencies cannot be avoided altogether, and the document does a fairly good job outlining some of the major ones to consider, but well drawn strata can help reduce the impact and complexity of assumptions about such dependencies. Ideally, one would be able to treat variations within a stratum as random draws from stratum-specific distributions.

Sources of Variability. Within a stratum, it would seem important to recognize the different effects that lead to variation in exposure. These might include: (1) heterogeneity in habits or lifestyles that lead some people to be exposed in a certain way and others not at all (e.g., prevalence of use of a pesticide-containing product, with some people being non-users); (2) variation in magnitude and duration of exposure among users, owing to variation in how and where they use products; and (3) variation that arises because of different temporal patterns of exposure, with independent events happening to co-occur in some individuals but not in others. In addition, there is the dimension of uncertainty in the characterization of the variability.

It is not altogether clear which variables OPP proposes to handle by stratification and which ones by characterization of variation within groups.

Uncertainty and Variability. Implicit in the document's discussion of probabilistic approaches is the assumption that variability alone is dealt with by probability. Uncertainty is dealt with only in the section on sensitivity analysis. It would be helpful to clarify how the questions of uncertainty and variability will be differently characterized and presented to the risk manager.

Time and Duration. The dimension of time is not well handled by toxicology or risk assessment methodology. It is not surprising that the document's treatment of time and duration is rather awkward, since the state of the art is rather awkward. Nonetheless, the advent of aggregate exposure approaches makes the need to handle time and duration in a better way much more critical; when one is dealing with multiple sources of exposure, the temporal patterns among these becomes critical to the evaluation of the potential impact of each.

The traditional approach of dividing exposures (and toxicity tests) into "acute," "sub-chronic," and "chronic" time frames has several drawbacks. Shorter-term exposures add to the long-term cumulative burden, and so "acute" exposures can be relevant to chronic endpoints. After episodes of higher-than-usual exposure, the body will build up a burden, either of the agent itself or of the damage caused by the agent. Subsequent exposures must be judged not only in terms of the newly encountered agent (and the time pattern of this encounter) but also bearing in mind the lingering effects of previous exposures. In a simple illustration, an acute exposure that might be tolerated without ill effect in a previously unexposed individual could end up causing an effect in another individual with a sub-threshold burden of agent from earlier exposures.

Thus, dividing exposures into duration categories and comparing each only with toxicity endpoints seen for similar durations potentially misses the key element that examining aggregate exposure is meant to address. Yet the document seems to announce the intention to make this kind of division, although the particular implementation is not altogether clear.

Persistence of Residual Effects. Examining exposures only by their duration ignores the potential for residual effects after exposure has ceased. While some effects of this general kind are recognized in the document (e.g., ongoing exposure from persistent residues after a residential spraying), others are not (e.g., body burdens of slowly cleared agents, build-up of concentration in drinking water sources from ongoing contamination). If these effects were examined as processes in which concentrations varied over time, with some characteristic decay of the contribution of each new increment of added agent, then the contribution of persistent aspects of exposure episodes to the health impact expected from future episodes could be more straightforwardly and clearly treated.

Agency Questions

The Agency presented the following questions to the SAP regarding the guidance for performing aggregate exposure and risk assessments. The questions are keyed to the background document entitled *Guidance For Performing Aggregate Exposure and Risk Assessments, February 1, 1999.*

1. The draft guidance document describes methodologies for assessing pesticide risks from single exposure pathways (i.e. dietary, residential and drinking water). Are these methodologies complete and satisfactorily described or does the Panel recommend changes?

General Issues

There are several factors that should be carefully considered to ensure a comprehensive treatment of aggregate exposure. They reside with the estimation of dietary exposure in a residential setting. The draft guidance document properly considers pesticide residues in food as part of the exposure experienced by an individual. However, there are physical mechanisms operative in the residential environment that yield multiple pathways leading to food

contamination, in addition to direct contamination on crops. For example, it is important to consider the contamination of food with pesticides during cooking with contaminated water. The food itself can be a sink by absorbing pesticides from cooking water. There is evidence that other chemicals are concentrated into foods from contaminated water; this possibility exists for pesticides.

Personal hygiene activities may also play a significant role in non-conventional dietary exposures to pesticides. Personal hygiene practices vary with age and education. For example, young children, a highly susceptible subpopulation, often eat in unstructured environments. When a residential environment is contaminated, enhanced potential exposures to contaminants in food can occur. When house dust is laden with pesticides, there are two potential pathways that lead to dietary exposure: surface-to-food and surface-to-hand-to-food contamination.

Given the above factors, consideration must be given to inter-pathway or media cross-over contamination. The Agency's draft guidance document depicts a variety of sources that can initiate a pathway leading to exposure; however, it fails to show actual pathways leading to a route of exposure, and thus the magnitude of exposure by any one route could be significantly underestimated. An example illustrating the important residential pathways leading to a particular exposure route is provided by a Panel Member in Figure 1 on the following page. The solid lines represent direct exposure pathways, i.e., those involving transfer via physical processes not directly governed by human activities, and the dotted lines demonstrate exposure pathways that occur primarily as a consequence of human behaviors that bring together what are normally unconnected environmental media. The figure incorporates a variety of mechanisms including direct and indirect (i.e., those based on personal activity patterns) and cross-media contamination. For example, application of a pesticide outside of a residence leads to contamination inside the home via penetration of pesticides in air (either as a vapor or associated with particulate matter) and by tracking pesticides in dirt. Once inside the home, the settling of the air particulates create surface contamination. Personal activities such as cleaning/vacuuming results in resuspension of the house dust and then resettling throughout the home, including on eating surfaces.

A final important factor that should be considered in aggregate exposure analysis is the environmental half-life of the pesticide. The magnitude of persistence is important in modeling and interpreting the potential for cross-media contamination discussed above. Furthermore, the duration of the exposure, e.g., acute to chronic, will be dependent on the pesticide's half-life. To some extent a long half-life, such as months to years, can temper seasonality considerations. The non-ingestion water routes and associated pathways (i.e. inhalation from showers and other water use and multiple dermal contact with tap water) need to be included and better characterized.

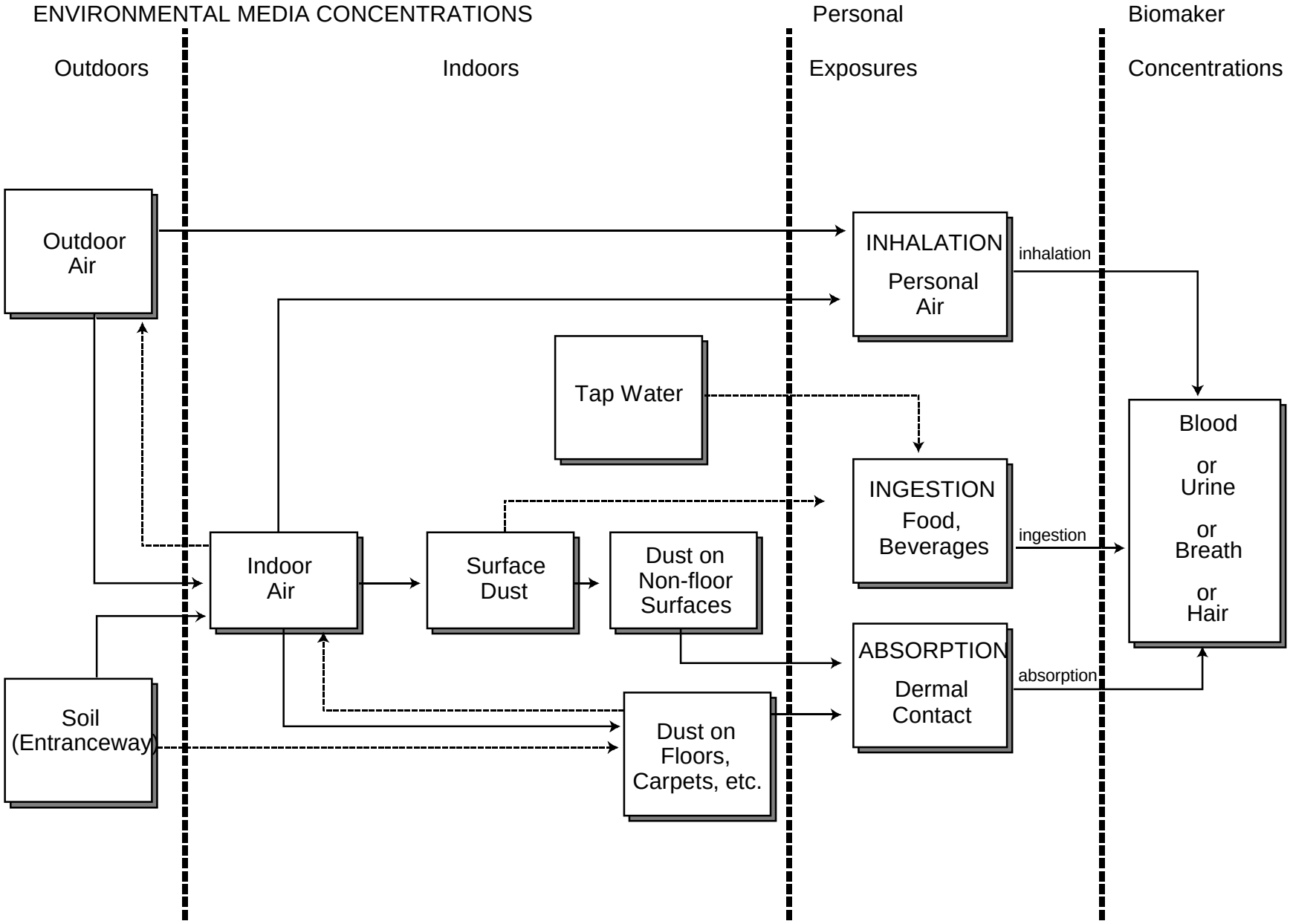

Figure 1. Pathways Leading to Routes of Exposure

Although the guidance document includes these routes, the supporting documents (i.e. Residential Standard Operating Procedures) provide no information on how to deal with these routes and pathways. Indoor environments other than residences need to be included. In particular, schools, especially those schools in agricultural communities and near fields that are treated should be included. The residential exposure guidance does not fully address all pathways by which pesticides are transported from source to contact media. Tracking of pesticides on shoes and clothing, tracking by pets, and drift from agricultural and residential use near but not at a given residence need to be considered.

Each pesticide and pesticide use scenario has a characteristic persistence time and characteristic distance or spatial range of influence. These characteristic times and distances need to be identified in order to define the temporal and spatial scales to be included in the aggregate exposure assessment.

A clear distinction should be made between exposure, dose-response/potency (however expressed), and risk, and these should be consistent throughout the document and through subsequent manipulations of data.

The distinction between variability and uncertainty should be clearly stated and consistently applied throughout the document, for both exposure and dose-response/potency activities.

Specific Comments

Residential Exposure. The methodologies for assessing pesticide risks from single exposure pathways (i.e., dietary, residential, and drinking water) are not complete since they rely on the draft Agency Residential Standard Operating Procedures (SOP). The Panel questioned whether there has been an effort to investigate or to include the residential exposure from agricultural use, especially from aerial applications and resuspension of dust. Using the assumptions in the draft SOP will not provide a reasonable bounding estimate for exposure because some of the assumptions are ill-founded. The SOP still needs to be updated and criteria developed for evaluating the data quality of studies to be incorporated into the various pathway equations. Examples are provided below where changes are recommended.

p.6. paragraph 3. "For most non-dietary exposure estimates, surrogate data and screening level assessments presented in the Residential SOPs (US EPA, 1997a) must be used." The Agency presented this version of the Residential SOPs to the Panel in March, 1998 and the Panel raised concerns regarding the default and surrogate values in the document. The Agency should revise the document, taking into account the suggestions and comments presented at previous SAP meetings.

Two issues arise from this document: the quality of the values used as defaults and the inconsistent use of central tendency and 95th percentile values in the models without logical

justification. Use of the values presented in the SOP produces exposure estimates that are of questionable value. The following four examples address this point.

1. Hand surface area of toddlers (p.21, 88 of SOP) and median surface area of both hands is 350 cm^2.

This is possibly true if the total surface area of the skin of the palm, back of hands, and sides of fingers and hands is taken into account. The area cited in the SOP is appropriate for contact with air, and immersion contact with fluids such as water, and perhaps with sand.

The area is not appropriate for hand contact with dust or surface soil particles. Concentrations of contaminants on children's hands are primarily on the finger tips and pads of the fingers and palm, not on the back or sides. Children do not typically have their knuckles or backs of the hand in contact with surfaces.

A better estimate of hand surface area can be obtained from the Children's Dietary Lead Study (Sheldon, Freeman, Melnyk, Berry, Pellizzari). In this study toddlers (mean age 30 months old) had their hand area traced on graph paper. The average combined surface area of the palms and fingers of both hands was 114 cm^2, approximately 1/3 the value provided in the SOP.

For hand-to-mouth activities of toddlers, even this value of 114 cm^2 is a gross overestimate of the amount of the hand that enters the mouth, typically 1 to 3 fingers. When fingers other than the thumb are placed in the mouth, the finger pads are placed on the tongue in contact with the tongue and saliva, while the top of the fingers are facing the roof of the mouth exposed to the moist air of the buccal cavity. In contrast, when the thumb is placed in the mouth, the back of the thumb and nail are against the tongue and the tongue presses upwards so that the thumb pad is pressed against the roof of the mouth. In this case, the entire finger inside the buccal cavity is bathed in saliva.

2. Rate of hand-to-mouth activity (p.22, 89 of SOP) reported by EPA as 1.56 times per hour.

Based on the independently conducted studies by Zartarian et al (1996, 1997) and Reed et al (1999), this value seriously underestimates the mouthing behavior of children 3-5 years old. As noted at the March, 1998 SAP meeting, a value between 9 and 10 times per hour would be more accurate. The observed value is 6 times the value provided in the SOP. The use of average value point estimates for mouthing behavior, whether the EPA value of 1.56 or the Zartarian/Reed values of 9.5, place limitations on the exposure estimate calculated with the point estimate. Since EPA appears to need to understand high end exposures, the 90th percentile from Reed's data (approximately 20 times per hour) should be used until larger data bases are available.

3. Body weight for toddlers (p.22, 89 of SOP).

The use of this point estimate makes the assumption that the size of the toddler has no important influence on exposure. As with the previous example, the use of an average point estimate places limitations on the value of the exposure calculation. Average body weight of toddlers obtained in the Children's Dietary Lead Study was 13 kg. The 48 children in this study were from an inner city environment. We do not know if the average from this group is simply within normal sampling variation or is indicative of a subpopulation.

Calculated estimated potential dose rate, normalized by body weight (p. 23 of the SOP) increases with smaller body weights. Unless there is good reason to use a point estimate in this calculation, rather than a range of values, a range of values should be used.

4. The estimated incidental ingestion dose for a child assumes that ingestion occurs only during a 2 hour period on the day of application (SOP p.23).

This assumption is based on outdoor play activities and does not address the high end outdoor child. The assumption is that hand-to-mouth activities and contact with surfaces only occurs in the kitchen and bathroom and is limited to 4 hours/day. This is unrealistic. Again, providing better estimates of hand surface area and rate of hand-to-mouth activity doubles the estimated incidental ingestion dose for toddlers from indoor surface residue, even when using the 4 hr/day default value. Since pesticides are used in rooms other than the kitchen and bath, the hours of exposure may be even greater post application exposure.

An additional issue for residential exposure concerns both dermal and non-dietary ingestion exposure that the contact with the surface has been treated. This ignores the semi-volatile character of some pesticides and the fact that the surface from which the exposure is obtained is not the surface that was treated but contains pesticides from secondary redeposition.

Examples of modifying the values discussed above concern foliar residue exposure (p.23). By changing the surface area of the hand in contact with the material from 350 to 114 and increasing mouthing events from 1.56 to 9.5, the PDR (estimated incidental ingestion dose) nearly doubles, increasing from 2.36 to 4.68 mg/day. If the 90^{th} percentile mouthing rate from Reed's data is used, the PDR increases to 10 mg/day.

The estimated potential dose rate, normalized by body weight, doubles from 0.16 mg/kg/day to 0.31 mg/kg/day when the mouthing rate increases from 1.56 to 9.5 times per hour, and quadruples if the high end mouthing rate is used. If the body weight used is lower, i.e. 13 kg, then the estimated potential dose rate, normalized by body weight, increases further to 0.36 mg/kg/day when the 9.5/hr mouthing rate is used.

The second issue is that there is no clear justification for using central tendency point estimates for estimates of incidental ingestion dose (p.23). If a smaller body weight provides a

higher dose rate, how is the model "representative of high-end exposure" if an average body weight is used in the model? The same issue arises with the other exposure scenarios provided in the SOP, such as swimming pool exposure (p. 55), dermal dose from carpets (p. 76, 79), dermal dose from hard surfaces (p. 83), and non dietary ingestion from indoor surfaces (p.88).

Dietary. For the risk presentation of acute exposures, it would be valuable to retain the distinction between the distribution for the entire population subgroup (i.e., consumers and nonconsumers) and consumers only, especially when the difference between the two is substantial. This can easily be done when dietary is the only significant pathway of exposures. Although more complicated for aggregate multiple pathways, maintaining the distinction is still desirable. In terms of tracking an individual throughout the aggregate process, considering "consumer only" is comparable to considering a specific subgroup and exposure scenario under the drinking water or residential exposures.

The Agency should clarify how data from the USDA Pesticide Data Program, total diet studies, and National Pesticide Residue Database will be used. Current monitoring data are mainly based on composite samples and their use are not mentioned in the dietary exposure guidance, unless they are from field trial studies.

The Agency should also explain what exposure (i.e., acute or chronic) would be used for short-term and intermediate-term scenarios. In practice, how would eating locally produced food for 9 months be taken into account? In addition, the Agency should include a citation for calculating the anticipated residue for chronic exposures (the current version of the policy was presented to the SAP in June, 1997).

Drinking Water Exposure. The Panel raised several questions concerning drinking water exposure. Does the drinking water modeling include allowance for accumulation in drinking water source water of contamination from ongoing or repeated episodes of run-off and wash-off (page 9 of the Agency's background document)? How large is the geographic area for drinking water monitoring data and how does this compare to the regions defined in setting up stratification of the exposed population? Will there be heterogeneity within regions, and how is this handled in characterizing the distribution of drinking water exposure in a region's population? Monitoring cannot be applied prospectively. How will potential exposures in drinking water be assessed for agents not yet in the environment?

NOAEL and Uncertainty Factors. Within the framework of the NOAEL/uncertainty factor paradigm, the methodologies described in the Agency's background document appear to be appropriate. There is some apparently unrealized opportunity to test their appropriateness by selecting some representative sample of the cases where Tier 1 and Tier 2 analyses have been done and then doing full Tier 3 or Tier 4 distributional studies. The outcome is that the Agency would have an evaluation of just how conservative the Tier 1 and Tier 2 procedures are in what fraction of representative cases. Recommendations for some adjustment of Tier 1 and Tier 2 assumptions could then be made to achieve a degree of confidence in guarding against false

negatives or false positive findings if these quick evaluations are warranted.

Eventually, the majority of the Panel would like to see the whole NOAEL/uncertainty factor framework replaced by a more quantitative risk assessment approach in which all of the safety factors are replaced by distributions based on the best available data from well studied cases. The results of this would ideally be fully quantitative analyses for non-cancer effects as well as cancer risks with an understanding of both uncertainty and variability. Standards would then need to be set for safety goals.

2. The draft guidance document describes a process for combining pesticide exposures and risk from multiple routes and pathways of exposure. Is the process, as described, logical, scientifically defensible, and complete?

The approach is logical and scientifically defensible. It also appropriately captures temporal, spatial, and demographic factors. However, it is not complete. When combining exposure values, it is important to recognize that we are not just combining numerical values, but combining information with different levels of reliability. For some pathways, the information could be derived from actual data and be relatively accurate while for other pathways exposure information may be derived from models or default assumptions with large uncertainties. When aggregation of exposure occurs across multiple pathways, the relative magnitude of exposure among the different pathways and the dominant contributions to overall uncertainty should be evident. That is, there must be a way to link the value of the aggregate exposure to specific assumptions or to interpretations of specific data sets in a way that makes clear the strengths and limitations of the final quantitative value of aggregate exposure.

However, as discussed previously, there are a few detailed aspects that are not apparently captured in making exposure assessments on an individual basis. It is important to understand the mechanisms of media contamination, inter-pathway cross-over potential, and environmental half-life of pesticides even in cases where a probabilistic estimation approach is employed. As such, the probabilistic method may under estimate the aggregate exposures in some cases and in some sub-populations. Matching an individual's dose against relevant doses in terms of route, duration, and effect, and the use of chemical specific or surrogate data are preferred to using default values.

The process for combining pesticide exposures and risk from multiple routes and pathways of exposure assumes that the chemicals behave the same way in the body independent of the route by which they enter the body. The Agency’s background document stated that "exposures from different routes will be aggregated only if the same toxic effects were seen in studies utilizing different dose routes or when studies are not available." The Panel questioned whether any pesticides meet this criteria.

As the Agency gains more experience in the course of conducting aggregate risk assessment, a periodic revision of the guidance is needed. In addition, the guidance should reflect the up-to-date capability.

3. A basic concept underlying the draft aggregate exposure and risk assessment methodology is that of the individual being exposed through calendar time with all model parameters referring back to that specific individual. Does the Panel agree with using this fundamental principal as the basis for the aggregate exposure and risk methodology?

This approach is preferred since it is to more likely to yield a more realistic exposure distribution of people's exposure to pesticides in a given geographical area. The use of calendar time must consider the rates of transfer of a pesticide to each medium, its rate of mobility within and between pathways, and the environmental half-life of the pesticide. The unit of time selected to represent the peak exposure occurrence can be very important when considering acute and chronic toxicity. The exposure duration may have peak occurrences that are short while the entire exposure duration may be quite long. Time-weighted average pesticide exposure measurements may mask peak exposures if the monitoring or observation interval was sub-optimally chosen for acute toxicity cases.

However, the issue about duration is not just the duration of exposure, but the persistence of the compound in the body as well. Thus, a measure of accumulation of exposure that addresses persistence is really necessary to do what is proposed in this section. An exponential moving average of past exposures could be used, with a half-life set by either the half-life of the agent in the body or the half-life of recovery from damage, whichever is longer. Finally, trying to include all possible scenarios (i.e. temporal, spatial, demographic) could become very time-consuming. In the Agency's experience, how many scenarios have been included in a typical assessment? The logic should be included in the case study presentation as the Panel recommended previously.

The idea of tracking an individual is a good one. However, more guidance is needed on who this individual is. Implicit in the guidance is the concept that this individual is a "statistical" individual, that is an individual who represents a cohort of the population. Unless, the EPA intends to model some 300 million "individuals", there is a need to better define the cohorts to be used and the attributes that will be used to define those individuals. For example, some of the attributes likely to be important are age, gender, geographical region, urban/suburban/rural landscape, income, pet owner, home-gardener, etc. What is needed is to develop a fairly complete set of attributes and then rank them according to which ones account for the largest amount of exposure variation.

Another important issue about the use of an "individual" exposure pattern is how that individual is selected with respect to variability and uncertainty. The guidance document indicates that, at least at the lower tiers, the individual should be selected at the high or very high end with respect to variability. It is not clear that the "individual" is selected at the high or median range with respect to uncertainty. This should be made quite clear.

4. The draft guidance document acknowledges the need to understand how residential exposures co-occur. OPP is developing standards to identify co-dependencies and

inter-relationships between events, and recognizes that product marketing data may be available to aid in this task. Does the Panel have any suggestions on how OPP can best evaluate co-occurrences of exposure events?

There are two basic strategies for developing initial hypotheses about such dependencies or co-occurrences, they are scenario-based hypotheses and correlated-factor-based hypothesis. With scenario-based hypotheses, the analyst makes up a number of stories that logically involve the co-occurrence of different exposures. Then each story is evaluated for its likely relative or absolute frequency in a real population. For example, a Salt Lake City gardener suffers serious losses from a large infestation of locusts inducing more intense than usual uses of insecticides by the gardener's lawn care company and more intense than usual use by the gardener to protect his/her roses.

Concerning correlated-factor-based hypotheses (i.e. age, geographic region, season, temperature and weather), pesticide use may well be strongly associated with age (e.g., because retired people may tend to spend more time gardening than others). Aging could also be associated with systematic changes in dietary habits that can alter the intake of particular residues. This induces age-mediated dependencies in exposure events that can be analyzed.

Seasonal factors and outdoor temperatures can influence the amounts of time people spend indoors and outdoors (leading to greater or lesser indoor or outdoor exposures) and also the frequency of pest infestations that trigger the use of pesticides.

In defining the time period over which exposure events are considered to co-occur, toxicological information (e.g., the time course of pharmokinetic elimination or periods of recovery from effects) from animal studies should be considered. In doing, it is important to consider that animals tend to process materials more quickly than humans. The Panel provided several references to support this conclusion and are provided at the end of this report in Appendix 1. In general, there should be a default assumption that relevant periods for aggregating exposures in humans should be longer than corresponding observations for a given percentage of reversal according to the ratio of human/animal body weights to the 0.25 power. Thus for humans, relevant exposure periods might usually be considered to be about seven times the relevant periods for aggregating exposures in mice $[(70/0.025)^{0.25} = 7.3]$.

Inter-relationships between events need to be understood, in terms of pathways, where the cross-over occurrence leads to additive exposure and/or multiple routes of exposure. This understanding can best be developed on a mechanistic basis. It may be possible to subsequently collapse the analysis and employ probabalistic methods for imputing exposure in the absence of direct measurements or data.

Residential exposure co-occurrences need to be taken into account. The assumption that "use of one product may eliminate the use of another" (page 18 of the Agency's background document) may not be valid. An individual with a roach infestation may use a range of treatments

to assure success. In addition, co-occurrences can take place when multiple problems are being treated (e.g., ants, roaches, and fleas). Whether all the treatments can be included in an aggregate exposure model would depend on the substances used. Survey data may provide information about frequency and type of co-occurrences.

As presented on pages 18 and 19 of the Agency's background document, the Panel agreed with the Agency's evaluation of codependancies and interrelationships for eliminating unlikely combinations. Although the example of flea infestation in pets given here is about the likely combinations, some unlikely examples were given on pages 19 and 20. The Panel also agreed with the Agency taking into account the use pattern, marketing data, and the temporal, spatial, and demographic factors. While longitudinal data are still being collected, it would be prudent to stay with the "elimination of unlikely combination" mode rather than focusing only on the "likely combinations".

5. During an aggregate exposure and risk assessment, some specific exposure scenarios may be identified as having a minimal contribution to the total aggregate risk. Does the Panel agree that it is appropriate to exclude specific exposure scenarios that contribute minimally to the total aggregate risk, and if so, at what risk level should an exposure scenario be dropped from further consideration?

It is reasonable to exclude exposure scenarios that have minimal contribution to the total aggregate risk, if the exposure from such a scenario is believed to be below the upper boundary of uncertainty of the risk from the exposure scenario in question.

The basic criterium is that, in the judgment of the analyst, the likelihood that including the scenario will ultimately change the decision based on the analysis is so remote that the information for real decision-making is likely to be improved by devoting the analytical resources to another topic. When there is a clear certainty that a route or pathway of exposure will not have significant contribution to the total exposure, it should be noted as extant but can be excluded from the quantitative risk assessment. The < 0.1% of the total exposure appears to be a good criterium. The Agency should describe how often this occurs.

There also are other issues to consider. Removing minor contributions to the total aggregate risk when the risk assessment is based on specific individuals exposed through the calendar year should not be done until enough different scenarios have been evaluated with individuals of all age groups to assure that something that appears to be minimal for most is not of special importance to a specific subpopulation.

On page 5 of the Agency's background document, it states that "the potential for dietary exposure can be considered to be relatively constant whereas potential pesticide exposures from residential and drinking water sources may be episodic in nature." The rationale for this statement is unclear other than for removing all exposures other than dietary from consideration. In fact, there are scenarios that show a very different picture. For example, young children during the

summer may spend hours in wading pools. If the water used in wading pools comes from a contaminated well, the dermal and ingestion exposure of the young child may be considerable, since water in wading pools is usually replenished on a daily basis. This would provide opportunities for prolonged "constant" exposure rather than episodic exposure. Indeed, if a well is contaminated with pesticides, the exposure is at least as constant as would occur from food.

Consideration of drinking water exposure was also questioned by the Panel. The Agency's position is that drinking water exposure is not aggregated if it does not contribute to significant dietary exposure. The method by which the adjustment is made should be more clearly explained.

In general, one way to look at ignoring exposures by routes for which an agent has shown no tendency to produce the toxicity endpoint in question is to think of the NOAEL for that route to be very high, so high that toxicity has not been observed. Thus, its MOE will be very large and will not contribute significantly to the total MOE.

The question presents the position that one would want to be sure that the lack of apparent toxicity by a given route is supported by testing that could have shown an effect if it were present. For example, dermal exposures should not be excluded from the aggregation simply because dermal toxicity has never been sufficiently tested. If this is the case, it is not clear how a value of MOE dermal is be calculated. The methodology seems to require that all routes by which exposure exists be tested for toxicity.

Given the Panel's recommendation that the Agency expand the portfolio of exposure pathways, it is essential that there also be a tractable and simple method for excluding exposure pathways that provides only a trivial contribution to total exposure by a given route. It is important that this process address both the relative magnitude and the reliability of the pathway before exclusion. The Panel does not recommend a specific numerical cut-off. This can only be established once a collection of case studies provides more insight. However, the Panel recommends the following process. First, pathways should be excluded based on comparison among pathways that have the same exposure route, but not across different exposure routes. The Agency should select a quantitative cutoff criterion, say, for example any pathway that contributes less than x percent to a given route should be a candidate for exclusion. Next, the Agency must have a quantitative reliability criterion, i.e., a confidence factor, such as a 90 or 95 percent upper bound confidence relative magnitude of a contributing exposure pathway. These two quantitative criteria are applied to any final decision to exclude an exposure pathway. That is, for example, 90 to 95 percent confidence that a given pathway contributes less than x percent to total exposure by that pathway before it can be excluded from the aggregate exposure analysis.

6. The draft guidance document describes three methods for combining risks from the three routes (oral, dermal, and inhalation). The Aggregate Risk Index (ARI) is currently being used by OPP. Does the Panel agree that OPP should continue to use the ARI approach or should OPP consider using one of the other described approaches?

Measures of "Aggregate Risk”

The document talks in several places about "aggregate exposure and risk assessment," but there is little discussion about how aggregating exposure is different from aggregating risk. For a toxicity in which it is presumed that risk is proportional to exposure (for instance, for induced carcinogenicity), aggregating exposure and aggregating risk amount to the same thing, since one is presumed to be a simple multiple of the other. But for noncancer toxicity, and for any endpoint that is presumed to have either a nonlinear or a threshold dose-response pattern, aggregating risk and aggregating exposure (or dose) are quite different.

A clear treatment of this issue is hampered by the traditional lack of attention to dose-response curve shapes in noncancer risk assessment; the dose-response is examined only in order to define a dose level (either a NOAEL or a Benchmark Dose [BMD]) that serves as an index of the doses that begin to show experimentally detectable elevations response. These are used to define a Reference Dose or similar construct that provides a cut-off between exposures deemed "acceptable" and those "of concern."

Presumably, underlying the overt pattern of dose and response is an increasing stress on the system with each added element of exposure, leading to progressive erosion of the organism's reserve capacities or capabilities. Overt toxicity emerges when this underlying capacity is deteriorated sufficiently that it can no longer fulfill its role in maintaining the physiological processes of a healthy, normally functioning body.

The degree of toxic responses resulting from combined exposures will be a function of how they interact with this underlying process of ongoing damage and repair, stress and compensation. These are processes that happen over time, and the temporal patterns with which doses from several sources are encountered will affect the degree to which they add up to create greater physiological impact. We generally have empirical toxicity information only about those dose patterns that were used in specific experiments, and these are usually in previously unexposed animals.

Since current risk assessments rarely have information on underlying biology, it is difficult to use insights into such principles in an all-purpose, practical method for aggregating exposures. In practice, what is proposed is to measure each dose as a fraction of either the NOAEL or BMD (the MOE method), or as a fraction of the RfD (the ARI method), and then adding the fractions over the various dose sources. This should be recognized as a simplified and interim approach that can deal crudely with the time dependencies and the interactions of doses experienced at different dose rates with different degrees of overlap.

“Risk Metric”

The proposed "risk metrics" are not really measures of risk, but rather measures of the fraction of the "critical dose" (i.e., the dose just barely deemed acceptable) posed by the exposure

in question. The MOE method amounts to expressing each exposure as a fraction of the NOAEL or BMD and then adding up the fractions. The ARI method amounts to expressing each exposure as a fraction of the RfD, i.e., of the NOAEL or BMD modified by uncertainty factors, and then adding up these fractions to see if the RfD is exceeded.

In other words, when calling the MOE or RI a "risk metric", the implication is that risk is linearly related to dose, and one adds up the components. The difference from cancer risk assessment is only that one confines the conclusion to whether the aggregated "risks" exceed the acceptable level or not.

This is not really how one would wish to think about noncancer risks, and the "risk metric" terminology, combined with the procedures for combining them, obscure the fact that all one is doing is adding up doses and comparing the total to a critical acceptable dose level. The framework has the danger of being taken more literally than it is intended and hampering the application of these methods to cases where one can investigate the physiological impacts of the individual exposures, e.g., in the examination of degrees of cholinesterase inhibition by a pesticide.

With current risk assessment methodology, with its crude handling of temporal issues and its emphasis solely on exceeding a cut-off dose (rather than estimating the waxing and waning impact on underlying physiology over time), it is hard to see how to improve on a simple adding of fractions of the allowable dose as a means of aggregation. It should be made clear, however, that this is what is being done. The discussion on pages 24-26 of the Agency's background document seems to imply that something about risk rather than dose is being aggregated and that the aggregation is something more complex than simply adding up fractions of the "acceptable" total. Being forthright now, and adding discussion of the shortcomings of the proposed approach, will aid in providing a pathway for evolution of these methods in the future. It will provide insight into how information on time-courses, pharmacokinetics, and modes of toxic action can be applied to provide better methods in the future.

MOE method versus ARI method

The ARI method is not really different from the familiar Hazard Index (HI) approach, it is the same calculation conducted in reciprocals. As a consequence, it has all of the shortcomings of the HI. The essence of the method is to express each dose as a fraction of the RfD (or other index of acceptable total dose that has incorporated Uncertainty Factors [UF]).

The MOE method is really only different from the ARI/HI in that the UFs are left out of the equation. Doses are expressed as fractions of the NOAEL or BMD, and these fractions added up to see if they exceed the NOAEL.

The methods are only different if the UF applied to the applicable NOAELs are different. How the results are interpreted, and whether one should prefer one or the other approach, depends heavily on how one interprets the use of UFs. Unfortunately, the interpretation of what

application of UFs means in noncancer risk assessment is a complicated and controversial area. Agreement was made to use the factors without really agreeing on what they mean or why they are appropriate.

One Panel Member presented three suggestions for the application of uncertainty factors. One idea is that each UF represents a pure allowance for uncertainty in the extrapolation. As an example, we expect humans to have the same NOAEL as the tested animal, but we acknowledge that sometimes humans may be more sensitive (by default, up to 10-times more), although by symmetry, they could be up to 10-times less sensitive as well. That is, the UF is an allowance for a worst-case variation from the norm, and hence its application represents conservatism in the face of uncertainty.

Another idea is that each UF represents an approximate correction for a systematic difference in acceptable dose involved in the extrapolation. For example, some people justify the factor of 10 for animal to human extrapolation as an approximation for the "surface area scaling" of doses often used in cancer risk assessment. Under this view, the factor is needed to lead to the equally toxic dose level in humans compared to the animals, and there is no conservatism added by its use.

A third idea combines the previous two, and most people, at least when forced to think hard about the issue, will say that the UF allows for both some systematic adjustment and for agent-by-agent uncertainty in the appropriate magnitude of that adjustment.

Clearly, some part of some UF applications must be seen as adjustment; the factor for subchronic to chronic or from LOAEL to NOAEL must be partially for adjustment. Acceptable daily exposures for a lifetime must on average be lower than those acceptable for a fraction of lifetime exposure durations, and NOAELs must be lower than LOAELs from the same experiment. Although it has not been well studied for noncancer toxicity, there is evidence that some scaling of mg/kg/day doses may be necessary to give human doses of equivalent toxicity (Travis and White, 1988, Risk Anal.).

On the other hand, some part of the 10-fold UFs clearly is intended to represent allowance for uncertainty in the extrapolations. This means that RfDs are conservative estimates of doses with acceptable effects, but the degree of conservatism is hard to define without settling the unanswered questions about how much of each UF is conservatism and how much is extrapolation.

The ARI method has the disadvantage that the various fractions of the RfD will be conservative to different degrees, depending on which UFs are involved. The calculations tend to be dominated by the components with the largest UF adjustment; that is, the determination of aggregate risk is dominated by the most poorly known values. As a result, the resulting ARI is probably quite conservative, but to an unknown and shifting degree, and its value is more a product of rough attempts to characterize uncertainty than anything about the toxicity.

This would seem to favor the total MOE approach. Especially if the MOEs were figured against BMD (which have better statistical properties and more interpretable toxicological meaning than experimental NOAELs), then no differential conservatism is introduced. However, there are two problems with the Total MOE approach.

The first problem is that it is not clear how to deal with differing levels of uncertainty in the components. Should the total MOE be interpreted against the UFs of the best or worst characterized component or against some composite average (a methodology for which does not yet exist and would be hard to envision as a rigorously justified approach)? Despite the difficulties, OPP would be well advised to begin thinking about how such composite uncertainty could be characterized. Some helpful suggestions were presented during public comments at the meeting.

Second, to the degree that part of each UF is needed for extrapolation adjustment, a calculation without the UF being applied is somewhat anticonservative. The margin of safety implied by a given MOE, and by the total MOE, is less than it appears, because some of the margin needs to be "used up" to allow for the fact that NOAELs really are systematically lower than LOAELs, that lifetime exposures really ought to be somewhat less than subchronic exposures, that humans may truly be more sensitive to a mg/kg/day dose than smaller experimental animals, and that the most sensitive humans in the general population may really be more sensitive than the most sensitive among a small sample of initially healthy, young adult, genetically uniform experimental animals without any relevant co-exposures.

Although the Agency has been reluctant to consider distributional approaches to toxicity (as opposed to exposure), the use of UF is a kind of approximation to doing so. The dilemma above arises because the 10-fold factors are hard to interpret as adjustments for the means of distributed extrapolation factors or as allowances for the worst-case tail of these distributions.

A distributional approach to noncancer risk analysis would resolve the dilemma by specifying the whole distribution of the factors in question. If different components of an aggregation have different uncertainties, the distributional approach easily accommodates calculation of the uncertainty of their sum, with the mean of the output distribution making the necessary extrapolation adjustments without conservatism and its spread providing a measure of the uncertainty, providing a basis for risk managers to apply allowances for uncertainty as they see fit.

In sum, the best method lies somewhere between the total MOE approach and the ARI approach. Settling how this is best done will require working out what the true interpretation of the UF is. In the end, what the truth about UFs is will depend on the actual distribution over agents, and so there is a need for bringing empirical data to bear.

Route Differences

For systemic toxicities, route differences in NOAELs presumably reflect differences in dosimetry. The dosimetry differences can result from route-specific differences in absorption, in metabolic activation or detoxification due to first-pass effects, or in the differing role of nonlinear metabolism steps or toxicity-generating processes when a given amount of agent enters the systematic circulation quickly or gradually.

How exposures by different routes add up to affect toxicity is affected by the agent's pharmacokinetics. Ideally, pharmacokinetic models and data could be applied to help guide how exposures from different routes are combined. It must be acknowledged, however, that such data are often not available.

The current proposal is to add each dose by expressing it as a fraction of the route-specific RfD or NOAEL, and then aggregating these fractions. It should be recognized that, presumably, the reason that different routes have distinct NOAELs in the first place is that exposures by different routes are different in absorption, first-pass effect, and bolus effect. Thus, in an important sense, the proposed method is an approximate means of dealing with underlying pharmacokinetic differences across routes, achieved not by observing the pharmacokinetic differences themselves but by observing their consequences.

To the degree that the relevant thing is absorption fraction or first-pass effect, this should work quite well. However, to the degree that differences in the time course of systemic concentrations is the basis for route-specific NOAEL differences, the proposed aggregation method can lead one astray because the degree to which systemic concentrations linger after an exposure episode are not well expressed by the differences in NOAEL, yet the toxic effect will depend on the total body burden, not its source.

Again, within the context of the NOAEL/uncertainty factor paradigm, the ARI approach seems reasonable. It is, however, desirable in the long run to develop approaches in which the safety factors are replaced by distributions reflecting the real likelihood of different outcomes involving different amounts of real population risk. This was expressed previously in response to question one.

The issue throughout is essentially exposure and not a risk, and that distinction should be clearly stated and applied throughout use. While the ARI method should not be completely abandoned, it needs to be reality tested and sensitivity/specificity analyses examined to see how often odd things happen. This concern was expressed in the public comments presented at the meeting. If this is a frequent event, it is much more important than if it is a rare event; if a rare event, then a method that describes what to do when the calculation is essentially driven by uncertainty needs to be developed.

The more immediate issue is to determine whether the current risk characterization format

should be unified. To some extent, this will facilitate the presentation of aggregate exposures. Currently, both MOE and percent RfD are used. MOE is more often used for the acute exposures while percent RfD is used for chronic exposures. If MOEs continue to be used, the total MOE option should be explored. If percent RfD is to be used, the HQ and HI approach would be the preferred subject to the caveats raised above. It is in keeping with the concept of "total risk cup" that has been used in the FQPA implementation and is a method also used by other programs of the Agency.

Overall, for aggregating the risk from different pathways and routes of exposure, the concept of toxicity equivalence using the benchmark approach would give a better comparative picture of the risks from each route and should be utilized. Whenever possible, the PB/PK models can be used for further refinement.

It should be emphasized that the summing of "risk" should be based on the same types of endpoints when the RfD or toxicity threshold (i.e., NOEL) from one route is used for other routes. The route-to-route equivalence dose, corrected for intake and uptake, should be combined before calculating the HQ. Thus, a clear distinction is made for when route-to-route extrapolation is applied.

When using the MOE approach, consistency in calculating the route-specific MOE is important. For example, the oral MOE is usually calculated on the basis of exposure or dose in mg/kg/day. This dose expression takes into account the concentration in the diet and the intake rate. However, the inhalation MOE appears to be calculated on the basis of concentration in the air. For both MOEs, the same uncertainty factor of 100 appear to be required. A related but very important issue is that, by basing the inhalation MOE on a comparison of concentration alone, without accounting for intake (breathing) rates, the higher exposure of infants and children due to higher intake rates per body weight, is not addressed.

In keeping with the need for risk assessments to be transparent, and for providing useful information for risk management decisions, the uncertainty factors accompanied the determination of RfD and RfC, together with endpoints of toxicity, should be a part of the aggregate risk presentation.

Appendix 1. References on Pharmacokinetic Animal to Human Extrapolation

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