SAP Report No. 99-01C, January 22, 1999

REPORT:
FIFRA Scientific Advisory Panel Meeting, December 9, 1998, held at the Sheraton Crystal Hotel, Arlington, VA

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

FQPA 10x Safety Factor Update

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Larry C. Dorsey	Dr. Ernest E. McConnell
Designated Federal Official	Chair
FIFRA/Scientific Advisory Panel	FIFRA/Scientific Advisory Panel
Date:_____	Date:_____

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL MEETING

III - FQPA 10x Safety Factor Update

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 an update of the FQPA 10x safety factor. Advance public notice of the meeting was published in the *Federal Register* on November 13, 1998. The review was conducted in an open Panel meeting held in Arlington, VA, on December 9, 1998. The meeting was chaired by **Dr. Ernest E. McConnell** of Toxpath, Inc. **Mr. Larry Dorsey,** SAP Executive Secretary, served as the Designated Federal Official.

Participants

FIFRA Scientific Advisory Panel Members:
Dr. Ernest E. McConnell, Toxpath, Inc. Raleigh, NC
Dr. Ronald J. Kendall, Director and Professor, The Institute of Environmental and Human Health/ Texas Tech University Health Sciences Center, Lubbock, TX
Dr. Fumio Matsumura, Professor, Institute of Toxicology and Environmental Health, University of California at Davis, Davis, CA
Herb Needleman, M.D. , Professor of Psychiatry and Pediatrics, School of Medicine, University of Pittsburgh, Pittsburgh, PA
Dr. Mary Anna Thrall, Professor, College of Veterinary Medicine & Biomedical Sciences, Colorado State University, Fort Collins, CO

FQPA Science Review Board Members:
Dr. Janice Chambers, Professor, College of Veterinary Medicine, Mississippi State University, Mississippi State, MS
Dr. Luz Claudio, Professor, Division of Environmental and Occupational Medicine, Mount Sinai Medical Center, New York, NY
Dr. Richard Fenske, Professor and Director, Pacific Northwest Agricultural Safety and Health Center, Department of Environmental Health, University of Washington, Seattle, WA
George Lambert, M.D., Associate Professor of Pediatrics, Environmental and Occupational Health Sciences Institute, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway, NJ
John O' Donoghue, V.M.D., Ph.D, Director, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY
Dr. William Slikker, Director, Division of Neurotoxicology, National Center for Toxicological Research, Food and Drug Administration, Jefferson, AK

Dr. John Wargo, Professor, School of Forestry and Environmental Studies, Yale University, New Haven, CN

Oral statements were received from the following individuals:
Dr. Gary Burin, Dr. Susan Hurt, and Mr. Rick Tinsworth, American Crop Protection Association
Mr. Ed Gray, Cheminova, Agro A/S
Mr. Dan Byrd, CTRAPS
Ms. Jeannine Kenney, Consumers Union
Dr. Laura Plunkett, Plunkett & Associates
Ms. Carol Stroebel, Children's Environmental Health Network
Mr. James Tozzi, Mulinational Business Services, Inc.
David Wallinga, M.D., Natural Resources Defense Council

Written statements were received from:
American Crop Protection Association
Cheminova Agro A/S
Multinational Business Services, Inc.
Natural Resources Defense Council
Plunkett and Associates

Summary of Agency Presentations

The Agency updated the Panel on its decision-making processes and to encourage public comment and input on this developing process concerning the FQPA 10x safety factor. Ms. Susan Makris (EPA/Office of Pesticide Programs) discussed the background and history of events leading to this presentation and a summary of the basic principles and interim policy on FQPA 10X recommendations, as detailed in a March, 1998 Health Effects Division interim policy paper. Information was provided on other concurrent Agency efforts that are directly related to the resolution of issues regarding the FQPA 10X safety factor, prime among these being the activities of the interoffice 10X Task Force. Mr. Ed Zager (EPA/Office of Pesticide Programs) described the current approach used by the Office of Pesticide Programs, Health Effects Division (HED) FQPA Safety Factor Committee in recommending the retention, removal, or reducing of the 10-fold safety factor for risk assessment prepared in support of tolerance decisions. Mr. Bill Burnam (EPA/Office of Pesticide Programs) completed the Agency's presentation by providing six example recommendations of the HED FQPA Safety Factor Committee.

Panel Response to Agency Presentation and Questions

<u>General Comments</u>

The Panel was reminded by the Chair to consider only the scientific aspects of the issue, and indicated that the Panel defers to the Agency on policy matters. The Panel complimented the Agency on responding to an earlier SAP recommendation by developing criteria from which to make the 10x recommendations. The Panel also urged the Agency to continue to work for transparency in its assessments and recommendations. The Panel finds the efforts of the Agency to implement the FQPA to be commendable. In general, the presentations by the Agency were helpful to understand the quality of data and criteria the Agency is using to make judgments regarding application of the additional tenfold safety factor. The Panel would like the Agency to make its decision logic and standard operating procedures more explicit and transparent, perhaps through additional case studies. The Agency commonly faces either unreliable data or no data at all, demanding the use of models and the choice of modeling assumptions. The Panel would like to review these assumptions and models in the future in relation to safety factor decision making.

Pharmacokinetic Differences with Respect to Age

The Panel pointed out that, with respect to pharmacokinetics, there are very large differences between neonates and adults, as is well illustrated with pharmaceuticals. There are different levels and forms of xenobiotic metabolizing enzymes in the infant compared to the adult, leading to differences in rates and patterns of xenobiotic metabolism between infants and adults. The rate of xenobiotic metabolism does not accurately predict the ultimate toxicity of a compound. In addition, end organ responsiveness differs with age, and the newborn has some unique differences in response, that may not even be possible in adults. There are also differences between males and females during puberty, and pregnancy leads to differences in drug metabolism. Also, it is necessary to know differential effects and differences in pharmacokinetic modeling between animals and humans in order to assess the sensitivity of the animal models. It is possible to use human tissues to obtain human data which would be more relevant to the risk assessment process. Therefore, the Agency is urged to be cognizant of these differences in physiology and biochemistry in its risk characterizations.

Dose-Response Relationships

The Panel urged the Agency to carefully evaluate dose-response relationships, and to be aware that responses seen at high doses may not occur at low doses. Much of the existing data is from high dose experiments, and these may be of limited value in predicting toxic responses at low doses because of such factors as the saturation of detoxication enzymes. The majority of the Panel agreed with the Agency's position of considering each pesticide on a case-by-case basis, because the toxicity profile elicited by each chemical may be distinct from others. The Panel agreed that a common mechanism of action of all chemicals possessing a similar chemistry may not be accurate. In addition, the time frame of the toxic response must be kept in mind, with the time to peak effects and the time of recovery likely to vary among compounds within the same chemical class because of distinct differences in the disposition and metabolism of compounds. These concepts will be particularly important as cumulative risk assessments are performed.

Concern was expressed regarding the use of NOELs. The method assumes a theoretical threshold dose. Not only is the determination of a threshold dose influenced by the sensitivity of

the analytical methods employed, but also the theoretical bases of a threshold dose may be questioned. Unfortunately, less sensitive experiments can result in higher NOELs. In addition, the NOEL approach relies on a single experimental observation instead of using complete dose-response curve data in the calculation of risk estimates. Because chemical interactions with biological systems are often specific, stereoselective, and/or saturable, a chemical's dose-response curve may not be linear. The Panel asked whether the Agency might consider in the future newer, more quantitative methods such as the Benchmark Dose or other quantitative approaches to evaluate data under the FQPA process.

Agency Evaluations on Retaining, Reducing or Removing FQPA 10x Safety Factor

The Panel was interested in how many evaluations have been conducted by the Agency and the outcomes to date. The Agency presenters responded that 92 chemicals had been evaluated and 18 retained the 10x factor, 24 had the factor reduced to 3x and 50 had it reduced to 1x (removed). Later, Agency comments indicated that of 105 decisions, 12 chemicals retained the safety factor, 15 reduced the factor to 3x, and 78 removed the factor. The Agency should be particularly transparent in its decision(s) of removing the FQPA safety factor.

The Panel felt that it is important for the Agency not revert to the practice of allowing product registrations and uses to continue as usual until such time as new data provide clear evidence of risks for infants and children. This is a reactive rather than a proactive approach, and can only lead to instances in which it is discovered too late for some children that Agency policies were not adequately protective. The 10-fold safety factor provides a means of protecting infants and children until such time as it is shown that such protection is unwarranted. Alternatively, the Agency can adopt health-protective methods of hazard and exposure evaluation which ensure that risks for infants and children are not being underestimated. In this case, the need for the 10X safety factor would be obviated.

Use of data

The issue of using non-guideline, literature data was considered. It was suggested that there needed to be some decision process developed to use with literature data as well as in cases of lack of data. While one Panel member indicated that it would be useful to have criteria for acceptance of literature data, another Panel member indicated that such criteria may not be manageable and that the best approach might be consideration of literature data on a case-by-case basis. Another Panel member indicated that, while criteria exist for GLP studies and such detailed criteria would probably be counter-productive for literature data considerations, an extension of some of these criteria to literature data might be useful. Therefore, the Agency is urged to further consider how it will use literature data.

The Panel finds that the Agency should more carefully define what constitutes "reliable" toxicity and exposure data. The diversity of types of data used to judge toxicity and exposure makes this a complex task. The central question the Agency should confront is: Are data of sufficient quality to fully capture the range of probable human susceptibility and the range of

probable human exposure? If the Agency is reasonably certain that it has defined these ranges accurately, and it chooses to employ highest bound estimates of toxicity and exposure when calculating risk, then it may consider the use of safety factors less than tenfold. The Agency may also conclude that while the registrant has fully complied with its requests for data, that it is still not possible to characterize variability in exposure and toxicity with the accuracy needed to relieve the additional tenfold safety factor.

Agency Questions

The Agency presented the following questions to the SAP regarding the FQPA 10x Safety Factor update. The questions are keyed to the background document entitled *Presentation for FIFRA Scientific Advisory Panel By The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) on Standard Operating Procedures (SOP) of the HED FQPA Safety Factor Committee*.

1) Are the members of the Panel in agreement with the two criteria used (Section IV of the Agency background document) in making the recommendation to retain, reduce, or remove the FQPA 10-fold safety factor?

If not, what modifications to these criteria would the Panel recommend?

In general, the Panel felt that the criteria were quite complete. Specific comments are provided below.

Criterion 1: The data on the pre-and/or post-natal effects are complete and reliable. A weight-of-evidence approach is used in evaluation of the toxicology data base for the chemical and the potential risks for the developing fetus, infant, and child as well as other populations.

The answer to the question depends on the meaning of "complete and reliable," and on what is meant by "weight of evidence." If the methods used can only detect changes at higher doses, they cannot be considered "complete" and cannot be relied upon to protect infants and children because of the lack of sensitivity.

The Panel heard testimony from several sources suggesting the need for studies on the developing immune and endocrine systems. Additional concerns were raised over the adequacy of simple morphometry of developing kidneys and liver as an indication of functional health. Possible testing suggested includes: pharmacokinetics, direct dosing of neonates, specialized developmental neurotoxicity studies, developmental immunotoxicity studies, developmental carcinogenesis studies, and endocrine disruptor testing and screening.

The differential response of developing organisms to many stimuli, including toxicants, is well known and widely accepted. It is axiomatic that the level at which the effects of a toxicant will be seen varies inversely with the sensitivity of the methods used to identify them. The history of our

knowledge of lead toxicity shows this beyond dispute. Studies of large numbers of children who had no signs of illness, using sensitive measures of cognition, attention, and perception showed deficits in children with low levels of lead in their bodies. The same principle probably applies to setting acceptable levels of pesticide exposure for children, and can be expected to be observed as new measures are introduced.

The critical issues then, are as follows:
a) Is the Agency obliged to show this increased sensitivity in infants and children for each pesticide in order to apply the 10x factor?

b) In the cases where the Agency chooses a smaller margin of safety than 10x, are the data reliable? Are they sensitive enough to detect important but difficult to identify deficits?

c) Are the testing protocols designed in recognition of the developmental trajectory of infants and children? Does EPA have protocols and test instruments in place that will discover developmental effects that have latencies?

Criterion 2: The assessments of all exposure scenarios associated with the use of the chemical are based on reliable data, either directly or through the appropriate use of conservative assumptions, which themselves are based on reliable data.

Categorizing Types of Exposure

The Agency relies on three categories of exposure: food, water, and residential. These nonoccupational exposures together constitute the total exposure that an infant or child can receive. Dietary exposure estimates are based on tolerances and food consumption data initially. These estimates can be modified by factoring in the percent of a crop treated with the chemical, and exposure estimates can be developed for subpopulations based on age, ethnicity, and gender.

The residential category is confusing, in that the Agency defines it to include all non-dietary exposures, while others wonder how the Agency considers exposure in schools, day care centers, and other settings. The Agency should distinguish these additional potential locations from the term “residential”. In addition, the criterion for residential exposure states that the Agency shall assess all exposure scenarios associated with the use of the chemical, and shall ensure that these assessments are based on reliable data. The Agency proposes that reliable data can take the form of actual data, or the appropriate use of conservative assumptions which themselves are based on reliable data. A more careful definition of reliable data in the context of residential exposure would be helpful, particularly a clarification as to what reliable data underlay conservative assumptions.

Drinking Water Exposure

Drinking water exposure estimates are highly dependent on models, with monitoring data used to verify that models do not underestimate exposures. The monitoring data come from a variety of sources, and have not been collected systematically for the purpose of evaluating exposure in the

context of FQPA. The monitoring data that do exist may not be representative of general population exposures, but may be important in defining identifiable subpopulations for whom such exposures are significant contributors to aggregate exposure.

Total Exposure and Aggregation

The Agency is well-aware that it faces an enormous task when attempting to aggregate exposure across diverse environments. The Agency must aggregate exposures from all sources for a particular compound. This concern is addressed very well in the Standard Operating Procedures for the HED FQPA Safety Factor Committee. In this document, the Agency has identified the major exposure categories and has given them appropriate weight in the risk estimation procedure. The Panel views this document as very responsive to the Panel's earlier-voiced concerns that exposure was being ignored in the Agency's 10X safety factor deliberations (July, 1998 SAP Final Report). The general approach outlined by the Agency is supported by the recent ILSI report on aggregate exposure assessment. The Panel encourages the Agency to continue its efforts to apply probabilistic methods in exposure analysis, where appropriate and useful.

The Agency should attempt to capture the range of potential exposure using available data and probabilistic modeling techniques. A separate probability distribution of exposure should be developed for each environment. To do so, the Agency must use its best judgment regarding the shape and bounds of the distribution. These choices will normally be driven by complex assumptions regarding pesticide application, transport, fate and degradation, and human behavior by those potentially exposed. Given considerable complexity, variability, and uncertainty, the Agency faces a serious burden if it suggests that existing data and models accurately portray the range and bounds of exposure.

Data Reliability and Default Assumptions

To estimate aggregate exposure, the Agency should rely upon credible and scientifically defensible data and models that have been validated to accurately reflect exposure. In the absence of credible data and models, the Agency should rely upon conservative "default" assumptions to produce these probability distributions. As discussed previously, the Panel hopes that it may in the near future review the Agency's progress in defining the concept of "complete and reliable" data. The Panel would also like to review the Agency's progress in defining "conservative default assumptions" to be used when data are of insufficient quality, or models have not been validated.

Variability

The Panel is concerned that the Agency needs to more carefully identify the variability in human exposure that exists in the real world. Exposure may vary systematically across space, time, demographic characteristics of the population, or as a function of other patterns in human behavior. Release of pesticides, their movement, and environmental fate have obvious spatial dimensions. The Agency should develop a more scientific and convincing method to understand how well its data and methods capture the real-world variability in exposure that occurs in the population at any point in time. Misunderstanding variability forces the Agency to rely upon

statistical summaries of contamination, exposure, and risk such as averages or 95th percentile values, that may leave significant populations unprotected.

Uncertainty

The Agency must understand uncertainty in chemical release to the environment, movement and fate, human exposure, risk, and health effects to determine the need for an additional safety factor. Thus, the Panel encourages the Agency to more carefully characterize uncertainty. Specifically, the Agency should:

a) systematically and formally describe uncertainty in its estimates of exposure and risk for each decision
b) identify the sources of uncertainty
c) characterize uncertainty in both a quantitative and qualitative manner
d) estimate its ability to bound uncertainty using models and assumptions
e) identify the relative contribution of each source to estimates of exposure and risk
f) identify opportunities to reduce uncertainty quickly.

Case Studies

The case studies presented in the Agency background document entitled "Example Recommendations of the HED FQPA Safety Factor Committee" included useful summaries of data on chemical hazards and exposure. They did not, however, include the Agency's judgment regarding uncertainty in the data or any summary of estimated variability in anticipated exposure.

Identifying Highly Exposed Groups

For each regulatory decision, the Agency should attempt to identify populations that may be highly exposed to the chemical in question. Another approach raised during the public comment period proposed that the Agency exclude exposures from such sources as drinking water and residential use in its aggregate exposure analysis until reliable monitoring data are available. That approach also advocated no regulatory action (e.g., no application of the FQPA 10X safety factor to chemicals which currently have a tolerance) until such data gaps are filled. This approach relies on the Agency's ability to issue data call-ins to gather needed data. While this approach might be feasible for existing data that a registrant could provide quickly to the Agency, the Panel does not believe it is practical for the generation of new data, and begs the question of what action the Agency is to take in the interim. Data call ins which require environmental residue or personal monitoring typically have a time frame of years rather than months, since they involve registrant generation and Agency review of study protocols, conduct of field studies, sample, and data analysis, and subsequent review and evaluation by the Agency. In cases where data call-ins are addressed by formation of industry task forces, the time frame is likely to be even longer.

Impact of Cumulative Risk on Chemical-by-Chemical Regulation

The Agency recognized the importance of cumulative risk estimation for chemicals with a common mechanism of action in its FQPA Implementation Plan. The Agency has also applied cumulative risk analysis recently to an evaluation of three triazine herbicides. Yet, in reviewing the FQPA Safety Factor Committee's SOPs and current criteria for retention, reduction, or removal of the FQPA 10X safety factor, the cumulative risk concept is notably absent. The Committee's proposed approach is restricted to analysis of risks associated with a single chemical. The Panel must raise the question: how can a margin be assumed "safe" for any particular chemical, if the contribution to cumulative risk from other chemicals with a common mechanism of action is unknown? At the Panel's March and July, 1998 meetings, it supported the Agency's view that the FQPA safety factor should be considered after all of the other risk assessment calculations have been performed. In the case of chemicals which belong to a group with a common mechanism of toxicity, it is the Panel's view that the risk assessment process is not complete until cumulative risk has been estimated. This is so because it is not possible to evaluate the true health risks to infants and children until the outcome of the cumulative risk analysis is known. Thus, a decision regarding the FQPA safety factor cannot rest solely on the evaluation of toxicology and exposure data for a single compound when that compound shares a common mechanism of action with other pesticides. The Panel understands that the Agency is actively developing a method for cumulative risk and will share its progress with the Panel in the near future.

Use of Proprietary Information in Risk Assessment

Most of the toxicological and exposure data generated by registrants in support of product registration is considered proprietary; i.e., data are provided to the Agency but are not available to the public. In the case of toxicological data, studies are normally conducted under well-defined guidelines established by the Agency that have been peer reviewed by the Panel and perhaps others. In the case of exposure data, however, such guidelines are still being formulated, and, for some types of data, no guidelines exist. Furthermore, some of the data used in exposure analyses are drawn from sources unrelated to health risk estimation. The Panel encourages the Agency to develop standard operating procedures for evaluating data that have not been generated under well-defined Agency guidelines and to indicate how analyses based on such data can be made transparent to interested members of the public.

A particular case in point is the use of percent crop treated data in its refinement of dietary exposure estimates. The Draft OPP Policy for the Use of Anticipated Residues indicates that percent crop treated data (usage data) are available from many sources, including proprietary data from marketing research firms. The methods used to collect these data are not well known within the environmental health sciences community, and seem to use such subjective techniques as panels and expert opinion. Although expert opinion is often valuable in guiding public policy and has been used in retrospective epidemiology to place individuals into exposure categories, it is rarely used in quantitative exposure assessments. The Panel urges the Agency to give special attention to such data sources, and to ensure that the use of these data is made transparent in the Agency's exposure analysis procedures.

2) Considering the questions within each of the categories (hazard, dietary food exposure, dietary drinking water exposure, and residential exposure considerations) included in the current draft of the FQPA Safety Factor Committee Standard Operating Procedure, what additional hazard and/or exposure characterization is required for improving the FQPA safety factor recommendation process?

Quality of Drinking Water Monitoring Data

The Panel urges that the Agency refine its SOPs for drinking water exposure to include more detailed guidance for evaluation of model input parameters, and of monitoring data that are used to confirm the model estimates. In particular, Agency evaluators should be asked to determine when data were collected, and how relevant they are to what would be found if the measurements were taken today. They should also be asked to characterize the representativeness of the data for the general population and for specific subpopulations. The Panel also urges improved definition of subpopulations by geographic regions that would be relevant to drinking water exposure.

Residential Exposure

The current draft of the residential SOPs (November, 1997) attempts to outline procedures for estimating exposures in and around the home. The approach is organized by pesticide use patterns rather than by viewing exposure from the perspective of infants and children, and their everyday interaction with the world. This source-based approach is logical in light of the need to develop regulations for specific registrations and uses. A receptor-based approach is less tractable in this regard, but it may be helpful in identifying the most important exposure pathways. The Panel was encouraged by responses of Agency scientists to this concern, and look forward to reviewing the revised residential SOPs, with inclusions of scenarios which portray childhood exposure patterns.

The Panel also notes that the residential SOP document does not address exposures from non-residential uses. Chemicals not registered for residential use can nonetheless become a part of a child's environment, and the child may receive exposure to such chemicals. The Panel supports the Agency's plan to address inadvertent residential exposure from agricultural uses, track in, and redistribution of pesticides into homes in the revision of the residential SOPs.

One Panel member commented that in the case where residential exposure was explored by the SAP (July, 1998) concerning dichlorvos, household exposure was underestimated. When the dichlorvos registrant was asked if any data on levels of the toxicant in rugs, furniture and drapes was available, none were present. Children spend a great amount of time playing on rugs and furniture. The omission of this obvious source of exposure is a serious error, and strengthens the validity of the 10x safety factor on the basis of inadequate exposure data for children. Yet the SOP states "The DRAFT SOP's for residential exposure assessment are thought to be conservative in all cases."

Other Considerations

- The necessity for a more complete neurobehavioral assessment battery has been mentioned.

- To model pesticide exposure to children, household exposure must take into account levels of toxicants in rugs, furniture, and drapes.

- The cumulative exposure from multiple pesticides must be considered including drinking water, lawn pesticides, and household exposure.

Panel Comments on the Agency Document “Toxicology Data Requirements for Assessing Risks of Pesticides Exposure to Children's Health”

The Panel was disappointed that the Agency had not provided the report, "Toxicology Data Requirements for Assessing Risks of Pesticides Exposure to Children's Health", to SAP members prior to the meeting for review. It was apparent from the November 30, 1998 date on the document that there was sufficient time to distribute the report to the SAP members. The way in which the report was provided to the SAP made it seem as if the review conducted by the SAP of the developmental neurotoxicity studies was of questionable value, as the Agency had already decided that the SAP would accept its assessment of these studies without any possibility of debate. This is very unfortunate, as it was clear from the SAP's discussion that the Agency's review of the developmental neurotoxicity studies does not support its policy decision to require developmental neurotoxicity testing for all pesticides. The SAP should expect the data requirements report be returned to it in the future for an adequate review.

The Panel ended with an expression of appreciation to Dr. Lynn Goldman, EPA Assistant Administrator for Prevention, Pesticides and Toxic Substances, for her impressive efforts over the last several years.