Federal Insecticide, Fungicide, and Rodenticide Act

Scientific Advisory Panel Meeting

I. A Set of Scientific Issues Being Considered by the Agency to Discuss Office of Pesticide Programs (OPP) Policy for Determination of Anticipated Residues of Pesticides in Foods for Use in Chronic Dietary Exposure Assessments

II. A Set of Scientific Issues Being Considered by the Agency to Determine Data Requirements for Tolerance Petitions in the Absence of a U.S. Registration, also known as Import Tolerances

III. A Set of Scientific Issues Being Considered by the Agency to Determine Antimicrobial Issues

IV. A Set of Scientific Issues Being Considered by the Agency Concerning the Office of Pesticide Programs (OPP) Cholinesterase Inhibition Policy

V. A Set of Scientific Issues Being Considered by the Agency Concerning the Office of Pesticide Programs (OPP) Hazard Characterization of N,N-diethyl-meta-toluamide (DEET) and the Decision Not to Establish Toxicity Endpoints for Risk Assessment Use

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL MEETING

A Set of Scientific Issues Being Considered by the Agency to Discuss Office of Pesticide Programs (OPP) Policy for Determination of Anticipated Residues of Pesticides in Foods for Use in Chronic Dietary Exposure Assessments

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of the Office of Pesticide Programs (OPP) policy for determination of anticipated residues of pesticides in foods for use in chronic dietary exposure assessments. The review was conducted in an open meeting held in Arlington, Virginia, on June 3, 1997. The meeting was chaired by Dr. Ernest E. McConnell. Other Panel Members present were: Dr. Janice E. Chambers (Mississippi State University); Dr. Richard Fenske (University of Washington); Dr. Robert Herrick (Harvard University); Dr. Paul Kuznesof (U S Food and Drug Administration; Dr. Harihara M. Mehendale (Northeast Louisiana University); Dr. Richard Parry, Jr. (U S Department of Agriculture); Dr. Stephen Saunders (Frito-Lay Corporation); Dr. Edward Stein (U.S. Department of Labor); Dr. Donald Wauchope (U.S. Department of Agriculture); Dr. Willis Wheeler (Wheeler Associates).

Public Notice of the meeting was published in the Federal Register on April 22, 1997.

Oral statements were received from:
Dr. Douglas Baugher, Orius Associates, Inc.
Dr. Leslie Bray, Novartis Crop Protection, Inc.
Dr. Edward Day, Jr., Dow Elanco
Dr. Michele Loftus, TAS, Inc.
Dr. Janet Ollinger, American Crop Protection Association

Written statements were received from:
American Crop Protection Association

<u>QUESTIONS FOR THE PANEL ON ANTICIPATED RESIDUES METHODOLOGY</u>

1. Please comment on the overall reasonableness of the tiered approach for determining anticipated residues for use in chronic dietary exposure analysis for pesticides in foods.

The Panel finds that the tiered approach for determining anticipated residues for use in chronic dietary exposure analysis for pesticides in foods is both reasonable and scientifically valid.

The Panel suggests in one instance the inclusion of another tier in which simple calculations show that no residues above the LOQ can be present. The Agency has such a policy to be used on a case-by-case basis, but the Panel suggests that it be developed and explained in this document.

The Panel recommends that one of the existing tiers be folded into another. Tier 2 and Tier 3 individually are based upon data that are available or have been submitted by the registrants. Tier 2 has a correction for the percentage of crop treated. Tier 3 uses data provided by the registrant in support of a registration. Since all the information is available, it is suggested, perhaps, that the Agency consider combining these tiers.

The Panel urges EPA to utilize the best possible and most current food consumption data available. The Agency indicated that it primarily uses data collected in 1977-78 as the basis for food consumption calculations today. The Panel pointed out that the food consumption patterns today are, in all likelihood, dramatically different than they were in 1978.

In the Tier 3 calculation of anticipated residues, the Agency uses mean values to represent several data sets: the mean residue level from each field trial (e.g., from triplicate measurements in an Arizona field trial); the mean of the mean values from all field trials; and, the mean value from multiple concentration/reduction factors. These mean values are used as point estimates and multiplied to produce an estimate of the anticipated residue. The Panel recognizes that the use of means simplifies the calculations, and that in many cases the quality of existing data does not allow distributional analysis. Thus, this approach may be the most efficient use of Agency resources at present. The Agency should strongly consider, however, that such an approach does not capture the variability inherent in these data sets, and the final anticipated residue value has no estimate of variance. As the Agency moves towards the use of distributional analyses in lieu of such point estimates, it will be important to more fully evaluate these procedures and their application in risk assessment.

The Panel supports the use of an adjustment factor for percent of crop treated in Tier 2 and in subsequent tiers, but notes that in some cases compounds with common toxic mechanisms may be used across a crop type. Thus, in the consumption of a particular crop the consumer may be exposed to more than one compound of concern. In the case where some percent of a crop has been treated with the compound under review, and some percent has been treated with a compound with a common mechanism of toxicity, how will the Agency combine these exposures? The Panel recognizes that this issue is newly emerging, and encourages the Agency continue to develop a strategy to address this and similar issues of common mechanisms and exposure aggregation.

2. Does the Panel see any areas where the Policy needs further development, considering availability of data?

The Panel suggests two areas for further development: 1) Use of models to predict residues present on crops. For example IR-4 has done many field trials and residue analyses for malathion on many crops in response to FIFRA re-registration requirements. Some efforts should go to developing a modeling approach to predict residues with time and storage conditions. The industry, IR-4, USDA, and the Agency could work together to develop such a modeling concept. 2) Use of all available data sources to predict residues. The Panel encourages EPA to utilize all possible sources of information on residues on raw agricultural crops, processed products, etc. Sources of information could include state and federal enforcement data, data submitted in support of registration, the food industry (crop producers and food processors), etc.

The Agency is encouraged to continue efforts for international harmonization of methodologies in the development of these policies and data requirements.

3. What types of data should the Agency be looking for in the future to augment the available databases?

The Panel strongly recommends collaboration between relevant federal agencies, affected industry and other stakeholders to develop anticipated residues of pesticides in foods which addresses the limitations of current methodology. Moving in the direction of computer simulation modeling of food consumption would expose weaknesses and gaps in these data. The results of such an exercise could allow for the design of a food consumption survey which would enhance the Agency's risk assessment capabilities.

FOR THE CHAIRPERSON:
Certified as an accurate report of findings:

Larry C. Dorsey
Designated Federal Official
FIFRA/Scientific Advisory Panel
DATE:_____

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL MEETING

A Set of Scientific Issues Being Considered by the Agency to Determine Data Requirements for Tolerance Petitions in the Absence of a U.S. Registration, also known as Import Tolerances

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of the Office of Pesticide Programs (OPP) policy for determination of data requirements for tolerance positions. The review was conducted in an open meeting held in Arlington, Virginia, on June 3, 1997. The meeting was chaired by Dr. Ernest E. McConnell. Other panel members present were: Dr. Janice E. Chambers (Mississippi State University); Dr. Richard Fenske (University of Washington); Dr. Robert Herrick (Harvard University); Dr. Paul Kuznesof (U.S. Food and Drug Administration); Dr. Harihara M. Mehendale (Northeast Louisiana University); Dr. Richard M. Parry, Jr. (U.S. Department of Agriculture); Dr. Stephen Saunders (Frito-Lay Corporation); Dr. Edward Stein (U.S. Department of Labor); Dr. Donald Wauchope (U.S. Department of Agriculture); Dr. Willis Wheeler (Wheeler Associates).

Public Notice of the meeting was published in the Federal Register on April 22, 1997.

Oral statements were received from:
Dr. Richard Costlow, Rohm and Haas Company
Dr. Barbara Petersen, Novigen Sciences Inc.

Written statements were received from:
American Crop Protection Association

QUESTIONS FOR THE PANEL ON IMPORT TOLERANCE GUIDANCE

1. Please comment on the methodology used to determine the number and location of crop field trials required for estimating appropriate tolerance levels.

The Panel finds the methodologies reasonable and agrees that the import guidance document will be a very useful step toward harmonization of standards used in international trade. The Panel believes that the guidance should be shared with the U.S. Delegation to the Codex Committee on Pesticide Residues, the North American Free Trade Agreement effort and the Organization for Economic Cooperation and Development for their comments. The development of a standardized guidance, when harmonizing internationally, promotes the exchange and use of data generated among the various countries.

A raw agricultural commodity (RAC) is a low consumption commodity if it is less than or equal to 0.05% of the diet. The commodities which cover this definition were identified in the DRES based on 1977-78 food consumption survey. Information was presented by EPA on the commodities forming a percentage of the diet. It is recommended that these data be updated as soon as possible to reflect current food consumption patterns of the U.S. population.

The Panel would like to see the wording on adherence to GLP's (or their international equivalents) made stronger to indicate that compliance to those standards is required.

2. Please comment on the criteria for limited review of residue chemistry studies when a Codex Maximum Residue Limit (MRL) has been established.

The Panel recognizes that increasing globalization of world trade and consequent international movement of agricultural

commodities makes important the issue of Codex MRL's. The criteria elaborated by the Agency for a limited review of Codex MRL's seem overly conservative. The Panel suggests the Agency consider modifying this approach to recognize the extent of US participation in the establishment of MRLs. In particular there is little scientific rationale provided for using the 0.05% consumption limitations.

The Panel suggests that the Agency consider elimination of this restriction and instead develop a case-by-case policy which would accept Codex MRLs as a default position, but reserving the right to conduct a full review of the data based on the scientific merits of each case. Under such a scheme, the Agency could require any level of review necessary. If, based on the experience of the US in the development of the Codex (JMPR) MRL, there were significant scientific issues which were not adequately addressed by the JMPR then additional review would be justified. On the other hand, if the Agency believed that the Codex MRL was an accurate reflection of the underlying data and no other issues pertained, then acceptance of the MRL for limited review without restrictions based on consumption would seem more scientifically justifiable. Such a policy would give the Agency the flexibility to use available resources for maximum efficiency.

FOR THE CHAIRPERSON:
Certified as an accurate report of findings:

Larry C. Dorsey
Designated Federal Official
FIFRA/Scientific Advisory Panel
DATE:_____

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL MEETING

A Set of Scientific Issues Being Considered by the Agency to Determine Antimicrobial Issues

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of the Office of Pesticide Programs (OPP) policy for determination of antimicrobial issues. The review was conducted in an open meeting held in Arlington, Virginia, on June 3, 1997. The meeting was chaired by Dr. Ernest E. McConnell. Other panel members present were: Dr. Janice E. Chambers (Mississippi State University); James Fairchild (Midwest Science Center); Dr. Richard Fenske (University of Washington); Dr. Robert Herrick (Harvard University); Dr. Paul Kuznesof (U.S. Food and Drug Administration); Dr. Ronald J. Kendall (Texas Tech University/Texas Tech University Health Sciences Center); Dr. Harihara M. Mehendale (Northeast Louisiana University); Dr. Richard M. Parry, Jr. (U.S. Department of Agriculture); Dr. Stephen Saunders (Frito-Lay Corporation); Dr. Lynne Sehulster (Center for Disease Control); Dr. Edward Stein (OSHA-U.S. Department of Labor);Dr. Mary Anna Thrall (Colorado State University); Dr. Donald Wauchope (U.S. Department of Agriculture); Dr. Willis Wheeler (Wheeler Associates).

Public Notice of the meeting was published in the Federal Register on April 22, 1997.

Oral statements were received from:
Dr. Sally Hayes, Chemical Specialties Manufacturers Association
Dr. J. Michael Kelly, Great Lakes Chemical Company
Mr. R. Bruce Jaeger, Stewart Pesticide Registration Associates
Dr. Don Grant, Pesticide Management Regulatory Agency, Health Canada

Written statements were received from:
Chemical Manufacturers Association

QUESTIONS FOR THE PANEL ON ANTIMICROBIAL ISSUES

A. Toxicology

Question: Traditionally, EPA has required a full battery of toxicity testing for agricultural pesticides which result in residues on raw agricultural commodities. For non-food and sanitizing uses of antimicrobial pesticides, the toxicology data requirements are proposed as a tiered testing scheme. This approach is similar, but not equivalent, to the FDA's approach. For certain use categories where significant human exposure is expected to occur (swimming pools, aquatic outdoor, human drinking water, animal drinking water), a full food use toxicology data set is required. Is the tiered approach an acceptable approach and does it provide for pertinent scientific data for each tier?

The Agency's efforts to streamline toxicology testing of antimicrobials and sanitizing agents through a Tiered approach is commendable. Based on use pattern, antimicrobial pesticides are grouped into 12 categories. This should facilitate management of regulatory issues in close alignment with their uses and anticipated human exposures. The Tiered approach developed by the Agency is a reasonable approach and the Panel supports the Agency in this regard. The limited testing used to support registration of sanitizers and related products with minimal potential for human exposure can be scientifically supported and will be discussed in more detail later in this section. The Guidance Document is long and difficult to follow but with additional refinement the document can be improved particularly as regards to scientific citations of current literature. Clarity of presentation and unambiguous trigger points indicating next Tier level of toxicity testing (reproductive and developmental testing, postnatal development, chronic/carcinogenicity, etc.) would substantially improve the present document. The Panel also encourages the Agency to continue dialogue with Canadian counterparts to harmonize, clearly define trigger points, and improve the guidelines. Use of the ‘threshold of regulation’ concept used by FDA and levels of human exposure to trigger Tier I and II toxicity testing is highly encouraged to minimize unnecessary testing in cases of minimal human exposure.

Tier I testing lists a battery of toxicological studies that would be required for all antimicrobials, which now include components of sanitizer formulations used on food-contact surfaces and sanitizers which may be embedded in food-contact plastics and rubber articles. Progression to a higher Tier (additional testing) would occur if estimated dietary exposure to the sanitizer exceeded 200 ppb. FDA also has used a Tiered Approach. For exposures less than 10 ppb, only an acute oral study (rodent) and literature search for potential carcinogenicity issues has been required. Exposures between 10 ppb and 200 ppb have required a 90 day rodent study, a 90 day non-rodent study, and possibly a multi-generation feeding study with a teratology phase in a rodent, and short term tests for genotoxic potential which inform the need for concern about the carcinogenic potential.

For the specific cases of sanitizers, dietary exposure as determined by FDA has often been lower than 10 ppb. For these cases, The Agency's requirements will significantly increase the data demand and the costs of toxicological testing for sanitizer applications that, according to FDA, lead to insignificant exposure. For dietary exposures below 0.5 ppb (which are sometimes estimated in the case of repeat-use rubber or plastic articles), the FDA, at the request of the applicant, may apply its "Threshold of Regulation Policy" which can result in a letter stating that the food additive is exempt from the need for a regulation. No new toxicological data need be generated for this approach, although a literature update on the substance of interest is required. If FDA is not satisfied with the applicant's package, the applicant is informed of the need for a formal petition and the necessary toxicity studies. This flexible policy has been highly successful in freeing up scarce resources in FDA's technical review groups, has benefitted industry by not requiring a food additive petition with its attendant costs and time delays, and has not compromised public health because of the extremely low exposures and resultant low risk. The Agency should reassess its proposal for toxicology studies specifically with respect to sanitizers to avoid excessive requirements for applications that will result in exposures substantially below 200 ppb based on the current state of knowledge.

Examples of clarification needed in the Guidelines include: the exemptions for oral, dermal, and eye irritation testing where the test compound undergoes phase change from liquid to vapor. This Guideline assumes that exposure to liquid will not occur. However, unless a defined measure of liquid to vapor phase transition is used to make the decision, ambiguity will remain in exempting tests. Similarly, clear and defined measurable criteria should be developed as trigger points to require higher Tier level

of testing in each category of toxicology testing.

B. Residues

Question: Is the science approach presented for the four major use categories reasonable for obtaining data pertinent to determining human dietary exposure? More specifically, is the decision logic for indirect food contact sanitizers reasonable and does it provide pertinent scientific data for dietary exposure testing?

The Panel finds that the scientific approach presented for the four major antimicrobial use categories (i.e. industrial processes, antifoulant coatings, wood preservatives, aquatic outdoor uses) appears reasonable for obtaining data pertinent to determining human dietary exposure. The Panel offers several comments for Agency consideration.

Specifically, the data requirements for exposure and toxicity data for sanitizers (i.e, pesticides embedded in plastic food-contact articles and those applied to food-contact surfaces, egg washes and vegetable rinses) proposed in Subpart W of 158 are similar to those that have been used by FDA for their regulation as food additives. There are certain instances, however, where the Agency is proposing more stringent requirements. Some of these requirements could provide additional data useful for assessing dietary exposure. But, they bear further consideration in light of any additional benefits to the public health, balanced with wise use of government and industry resources.

For evaluation of chronic toxicity hazards due to exposure to these substances, the Agency assumes that complete migration into food occurs over the useful lifetime of the plastic product. Estimates of the amount of food contacting the product over its service life will permit an estimate of chronic exposure without the need for costly experimental migration studies by the petitioner (However, in certain instances, migration studies may be needed). FDA has used this approach. In addition to plastics, the Agency will need to apply the same approach for sanitizers embedded in food-contact rubber articles, such as conveyor belts and gloves. EPA should revise its proposal to include references to rubber articles.

If concerns of an acute toxic hazard arise from use of a sanitizer embedded in food-contact plastic, the Agency is requiring migration studies to determine the transfer rate into the plastic. The migration studies presumably would be used to determine exposure for assessing the gravity of the concern. For a migration

study, the Agency (or the petitioner or registrant) would need to design a study protocol that mimics the time/temperature food/article contact scenario. FDA has recognized, however, that significant migration is not likely to occur for food/article contact at room temperature or below for short periods of time (minutes to a few hours). A low level of migration and, therefore insignificant dietary exposure, under anticipated conditions of use should not be expected to raise concerns of acute toxicity. It would be helpful, therefore, if the Agency were to define the time frame that defines a hazard as acute and explain the basis for triggering such concerns (e.g., known neurotoxicity) for sanitizers embedded in food-contact plastics. The need for acute toxicity studies might be made a Tier I Conditional Requirement.

The Agency's new approach to regulating sanitizer formulations requires that a petitioner propose a numerical tolerance in food for the active ingredient component of the sanitizer formulation or, based on reasonable grounds, request an exemption to a tolerance. The imposition of a tolerance presents a significant burden on the Agency and the petitioner, requiring residue analysis in all foods that may contact a given sanitizer formulation and means of enforcement. Given that FDA has never required a tolerance to be established for any of the about 40 antimicrobial formulations it has regulated, it appears unlikely that the Agency will need to establish tolerances during its stewardship of sanitizer formulations. As the Agency observes, the chemicals cleared for use as sanitizers include “soaps, surfactants, chlorine or other halogen precursors, and high molecular weight polymeric materials with surfactant properties....designed to be highly water soluble .... are generally characterized by low intrinsic toxicity or toxicity which is rapidly dissipated once they come in contact with microorganisms.” The Agency should consider eliminating the requirement that the petitioner address the need for a tolerance. However, the Agency should also retain its authority to require a tolerance in the unlikely event that a concern arises for the need for one.

Note (6) of Section C Table 1 of § 158.1109 states that an analytical method capable of measuring residues of sanitizer formulations in foods/feeds is required for any food use. The Table indicates that this is a Conditional Requirement, so that there may be mitigating circumstances that result in a conclusion that a method is not needed. It is well-known, nonetheless, that the development of analytical chemistry methods for analysis of compounds, particularly antimicrobials, present at extremely low concentrations in a highly complex food matrix is difficult, if not impossible, and costly. Added to this concern is the possibility that a particular formulation may be used in contact with any

number of foods and food types in settings ranging from agricultural premises to public food service establishments and the proposal seems untenable. Therefore, alternative approaches to assessing the residues of sanitizer formulations transferred to food in order to evaluate safety should be considered (e.g modeling, etc.).

In this light, § 158.1108 (a) (2) (ii) of Subpart W notes that the calculation of the amount of any component of a sanitizer formulation that will transfer to food is based on Directions for Use of the formulation (i.e., the at-use concentration of the specific component) combined with "historical residue data concerning the amount of sanitizing solution remaining on food-contact surfaces." This reference to "historical" data derives from the approach that FDA has used to clear sanitizers. The 1986 FDA guidance for sanitizers (revised in 1993 with no substantive changes) stated, based on substantial experimental data, that a worst-case assumption for residual sanitizer solution on an "adequately drained" surface is 1 mg/cm^2. FDA concluded that this value could be used, in the absence of residue data from the petitioner, as the basis for a conservative dietary exposure assessment by assuming all of the residual sanitizer is transferred to food. The Agency might wish to explicitly incorporate this 1 mg/cm^2 into Section C Table 1 of § 158.1109, as a default surface residue for estimating sanitizer residues in food.

C. Ecological Effects/Environmental Fate

Question: The Agency believes there are eight use scenarios for which ecological risk assessments are not necessary: agricultural premises and equipment; food handling/storage establishments premises and equipment; commercial, institutional and industrial premises and equipment; residential and public access premises; medical premises and equipment; human drinking water systems; materials preservatives; and swimming pools. For these use scenarios the Agency will require only a minimal set of ecological effects and environmental fate data for use in labeling manufacturing and certain end-use products. These data are: avian acute oral LD_{50}, acute freshwater fish LC_{50}, acute freshwater invertebrates EC_{50}, and hydrolysis study. Does this approach seem reasonable?

The Panel believes that the reduced data set requested for these specified uses (i.e. agricultural premises and equipment; food handling/storage establishments premises and equipment;

commercial, institutional and industrial premises and equipment; residential and public access premises; medical premises and equipment; human drinking water systems; materials preservatives; and swimming pools) appears justified only if data available from other programs both within and outside the Agency are adequate to assess risk. This must be verified because as the proposed rule indicates there are some industrial uses which may result in significant, frequent releases. The use of antimicrobials may likely increase due to widespread concern over direct and indirect contamination of food, waters, and equipment in many processing activities. The assumption of minimal exposure should be verified by examining existing data sets of environmental residues of frequently monitored chemicals in addition to data from NPDES permitting/testing activities to determine the frequency of detection, concentrations, and effects of chemicals likely to be used in antimicrobial use-patterns. For some uses, these data could be used to conduct basic risk assessments based on recommended efficacious concentrations and potential loading levels based on facility size, production rates, use rates, etc.

The Panel also is concerned over the lack of chemical fate data requested. Hydrolysis will be an important fate pathway for only a subset of chemicals. Biodegradation data under both anoxic and aerobic conditions are needed to perform risk assessments. Again, the Agency indicates that these data will be available from other places both within and outside the Agency. These data sources should be provided in a tabular format which provides the test reference number used by the responsible office or agency with primacy for the data. It is recommended that data access from other Agency Offices (e.g. Office of Water) should be "seamless", or preferably, that these fate and effects data are merged with existing on-line databases within OPP. This will facilitate data access for site-specific risk assessments.

The Panel is further concerned about the lack of inclusion of any microbial testing. The proposed rule indicates that efficacy testing will be conducted for a selected group of chemicals such as sanitizers. However, additional non-target microbial data should be provided for all chemicals. These tests are needed not only to ensure the safety of environmental discharge but also for protection of POTWs and other treatment systems which often rely on microbial treatment processes. These data should be considered in addition to the basic fish and invertebrate toxicity tests.

Finally, the Panel is interested in what appropriate precautionary labeling might be used to protect fish and wildlife from improper use of antimicrobials. For traditional pesticides this may consist of a buffer zone or precautions about disposal in

aquatic systems to minimize exposure. However, for many of the proposed indoor-use categories the majority of antimicrobial chemicals would enter a POTW or private sewage system through normal use patterns. It is unclear how a precautionary label would be constructed to minimize exposure to ecological resources.

Question: The Agency believes that for the remaining four use scenarios (industrial processes and water systems; antifouling coatings; wood preservatives; and aquatic areas) we will perform ecological risk assessments (primarily, aquatic risk characterizations). Therefore, The Agency will require a tiered set of ecological effects and environmental fate data for these use scenarios (with an emphasis on water column and benthic studies addressing effects on aquatic organisms and environmental fate in these compartments). Does this decision logic seem reasonable? Further, since the data required are designed to address aquatic risks, does the Agency need to gather more information to address other risks?

The Panel finds that full ecological risk assessments are necessary for the four major-use categories (i.e. industrial processes and water systems, antifoulant coatings, wood preservatives, aquatic outdoor uses).

The Agency presentation indicated that there is concern about possible redundancy of testing requirements across Agency Program Offices. If redundancy of requirements is a concern then this should be addressed through harmonization among other Agency Program Offices of fate and effects testing where possible. Experience should indicate those cases where testing from one Agency Office may be substituted for the requirements of the Office of Pesticide Programs.

The Agency indicated that exposure data may be difficult to obtain. Exposure assessments must be generated either from modeling (e..g. based on efficacious concentrations and potential loading levels based on facility size, production rates, etc.) or actual data sets (e.g. existing data from NPDES or other monitoring activities). The number of facilities should not be a deterrent. Rather, the diversity of type and use should be examined to further categorize use patterns and exposure scenarios. This is reasonable and should be pursued for representative industries, chemicals, and uses.

Aquatic exposures should be the greatest concern. However, there are terrestrial situations where some chemicals such as wood preservatives (e.g. animal feeders, bird houses, places where high exposure could occur due to intimate skin contact, licking,

chewing, etc) or anti-fouling coatings (e.g. boat yards or painting facilities where paint chipping, dust, and subsequent exposure) could present terrestrial wildlife risks. These specific cases need to be reviewed carefully by the Agency.

In terms of the conduct of ecological risk assessments which the Agency alluded to that would be primarily aquatic risk characterizations, it is unclear as to the focus or endpoints considered in this risk characterization process. This process needs to be focused and refined considering the increasing amount of data available in this area and improvements in ecological risk assessment methodologies.

A final concern, which is not unique to antimicrobials, concerns the toxicological testing of metabolites identified from degradation experiments. Full testing under the 835 Guidelines of Part 158 requires biodegradation testing under aerobic and anaerobic conditions in which primary metabolites are identified. The Agency should ensure that some mechanism exists for toxicity testing of these metabolites. Some metals and metalloids (e.g. mercury and selenium) with antimicrobial activity can be microbially methylated to more toxic by-products. Similar changes can also occur with organic materials. It may not be necessary to explicitly test every metabolite. However, it is possible to sequentially test chemicals subjected to degradation processes using designs similar to a microcosm or sediment toxicity test. Replicate series of chemical/water or sediment/water mixes could be sequentially tested over the degradation life of the chemical to determine if toxicity decreases according to anticipated loss of the parent compound. Departure from the expected decline may indicate the presence of a toxic metabolite.

D. Human Exposure

Question: Are the approaches presented reasonable for obtaining data pertinent to determining application and post-application exposure? Has the Agency adequately covered all use/exposure scenarios? For multiple exposure scenarios for one pesticide product, should the Agency require data for all exposure scenarios or for a subset of scenarios?

QUESTION 1: Are the approaches presented reasonable for obtaining data pertinent to determining application and post-application exposure?

The Agency has proposed twelve antimicrobial use categories to assist in the explication of human exposure data requirements. These categories, or general use patterns, provide the framework

for subsequent data requirement tables. The Panel found that these categories provide a sensible and reasonable approach to organizing data requirements, considering the wide range of individual chemicals, possible use scenarios, and environmental and health-related endpoints. While the classification into twelve categories is complex, it should be recognized that it is a starting point for information collection; as time passes, it will probably be possible to merge and collapse categories and data elements, resulting in a simplified system. The Pest Management Regulatory agency of Health Canada has reviewed the Agency approach and found it to be generally consistent with their own approach. They note in their comments that the use of common categories will facilitate comparison of data across agencies, and opens the possibility of joint or shared reviews. During public comment the Agency indicated that a similar relationship exists with the California Environmental Protection Agency, and that the use of common categories has proven helpful in the sharing of information and in risk assessment activities. Comments submitted by the Chemical Manufacturers' Association expressed the view that the Agency categories were too broad to be useful. In public comment, the Agency indicated its awareness that these categories are broad, and that they may need to be subdivided to provide more specific guidance. The Panel believes that this greater level of detail would be appropriate for a guidance document, but not for a data requirement such as Subpart W. Therefore, the Panel endorses the use of the categories as presented by the Agency, and encourages further refinement as new information becomes available.

One additional concern is that the Agency's definition of "post-application exposures" may be too restrictive in light of the actual exposure situations. "Post-application exposures" were described as exposures to bystanders, or people who enter an area treated with pesticide. This definition would not necessarily include exposures which result from handling, or otherwise coming into contact with treated material. For example, people handling preserved wood, textiles, and leather have been demonstrated to have significant exposure to preservatives (e.g., chlorophenols).

QUESTION 2: Has the Agency adequately covered all use/exposure scenarios?

It is impossible to identify all use/exposure scenarios, but the Agency appears to have identified the most significant use/exposure scenarios.

In the discussion of Use Categories on page 6 of the Proposed Rule document, the Agency enumerates the twelve general use patterns which provide the framework for subsequent data

requirement tables. The Agency then describes the use categories on pages 7-10. This description is very helpful, and should be retained. It would also be helpful for the Agency to add succinct language which would explain the Agency's rationale for each of these categories.

QUESTION 3: For multiple exposure scenarios for one pesticide product, should the Agency require data for all exposure scenarios or for a subset of scenarios?

The Agency should work initially with the full set of possible exposure scenarios for a particular product, then allow submission of data which would support combining specific scenarios, or which would allow the elimination of some scenarios where there is no documented exposure.

ADDITIONAL COMMENTS

The proposed rule states that the EPA will determine whether industrial standards for OSHA-regulated industries provide adequate protection for antimicrobial pesticides. If these standards were determined to be adequate, monitoring for uses in those industries would not be required. This provision would put EPA into the position of evaluating the adequacy of OSHA standards, which would not seem to be a wise strategy. Furthermore, even in cases where the OSHA standard is protective, it is possible (for example in a business with fewer than 10 employees) that the enforcement of the OSHA standard is so limited that the standard is not, in fact, protective. Finally, it should be kept in mind that the OSHA standards are intended to protect healthy working people who are exposed 8 hrs/day, 40 hours/week -- not the sort of long-term exposures to a range of populations which EPA must address.

The role of biomonitoring in the exposure assessment should be described more fully. While more biological monitoring has the advantage described in the proposed rule, it is most effective when used as part of a comprehensive exposure assessment strategy, which includes measurement of inhalation and dermal exposure. From an exposure prevention point of view, biological monitoring used alone has the significant limitation that it does not reveal anything about the route of exposure. This information is essential to direct preventive measures to reduce exposure. Finally, many biological markers of exposure are subject to wide inter-person variability, which makes them difficult to use and interpret in population studies.

One point which was raised but not fully explored in the

discussion is the difference between children and adults when evaluating indoor residential exposures. For example, a child's exposure to antimicrobials in carpet could be very significantly different from the exposure an adult would experience in the same residential environment.

E. Efficacy

Question: Should the Agency begin using a new efficacy standard method, Hard Surface Carrier Test, when only one part of the method has been validated (i.e.,distilled water)? The remaining portions of the method (organic soil, hard water) are under collaborative study and are expected to be completed by the end of 1997.

The Panel acknowledges these are draft documents, subject to revisions as new information becomes available or better methods and procedures are developed. Concerning the use of the "Hard Surface Carrier Test" (HSCT) in full, knowing that the only component of the test to be validated to date is that of distilled water, the Panel finds that it is prudent to continue using the Use Dilution Test Method, despite its shortcomings, as the Agency awaits completion of the validation trials for the other two components of the HSCT, namely that for hard water and organic soil. These appears to be support for the development of a fully validated test with a phase-in period to allow for a smooth transition to the new method. If there is concern about drafting language into the proposed Subpart W which would allow the Agency to adopt the HSCT in the future, it could be noted that the Agency will replace the Use Dilution Test with the HSCT, pending satisfactory completion of the validation trials for hard water and organic soil.

FOR THE CHAIRPERSON:
Certified as an accurate report of findings:

Larry C. Dorsey
Designated Federal Official
FIFRA/Scientific Advisory Panel
DATE:_____

A Set of Scientific Issues Being Considered by the Agency Concerning the Office of Pesticide Programs (OPP) Cholinesterase Inhibition Policy

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of the Office of Pesticide Programs (OPP) review of Cholinesterase. The review was conducted in an open meeting held in Arlington, Virginia, on June 4, 1997. The meeting was chaired by Dr. Ernest E. McConnell. Other panel members present were: Dr. William S. Brimijoin (Mayo Clinic); Dr. Janice E. Chambers (Mississippi State University); Dr. Amira T. Eldefrawi (University of Maryland); Dr. Richard Fenske (University of Washington); Dr. Ernest Hodgson (North Carolina State University); Dr. Ronald J. Kendall (Texas Tech University/Texas Tech University Health Sciences Center); Dr. Harihara M. Mehendale (Northeast Louisiana University); Dr. Genevieve M. Matanoski (Johns Hopkins University); Dr. Carey Pope (Northeast Louisiana University); Dr. Stephen Saunders (Frito-Lay Corporation); Dr. Edward Stein (U.S. Department of Labor); Dr. Mary Anna Thrall (Colorado State University).

Public Notice of the meeting was published in the Federal Register on April 22, 1997.

Oral statements were received from:

Dr. Barry Astroff, Bayer Corporation
Dr. Sir Colin Berry, Royal London Hospital
Dr. William Chen, Dow Elanco
Dr. David Clegg, American Crop Protection Association
Dr. Donald Grant, Pest Management Regulatory Agency, Health Canada
Dr. Carolyn Lewis, State of California EPA
Dr. Marcello Lotti, University of Padua, Italy
Dr. Larry Sheets, Bayer Corporation
Mr. R. Thomas Van Arsdall, National Council of Farmer Cooperatives
Ms. Carolyn Van Pelt, DuPont Agricultural Products
Dr. David Wallinga, Natural Resources Defense Council
Dr. Chris Wilkinson, Technology Sciences Group, Inc.

Written statements were received from:
American Crop Protection Association
Acute Cholinesterase Risk Assessment Work Group
Ricerca, Inc.
Dr. Brian Dementi, Environmental Protection Agency

QUESTIONS FOR CONSIDERATION BY THE PANEL:

Literature Review

1. Does the review include the major concepts and citations from the literature and present an overall objective analysis consistent with the proposed policy?

The Panel gave a strongly positive answer. A question was raised about the relation between part A and part B. It was noted that part A did not reflect a broad consensus within the Agency. Another Panel Member commented on the discussion of the epidemiologic data and offered the opinion that present studies do not allow a conclusion as to whether long term effects in pesticide workers might represent a persistent effect of acute overexposure or chronic low dose exposure. Additional information on a number of points was presented by the Panel, including the likelihood that some organophosphate pesticides bind with nanomolar affinity to muscarinic or nicotinic receptors. Overall, however, the review was judged to comprise an excellent survey of the relevant data, and the Panel was quite satisfied by the review. The weight of evidence approach seems like an especially rational approach for a group of compounds which display so much inter-compound variability in response (qualitative, quantitative and time course). The complexities of metabolism and the differences in acetylcholinesterase potencies for inhibition among compounds results in great differences in both time course and magnitude of effect among various anti-cholinesterases. All of these diverse factors would be expected to yield different responses, qualitatively and quantitatively, among different compounds. Therefore a very rigid approach to risk assessment of all anticholinesterases might lead to the missing of important, critical biological responses.

2. ChE methodology. ?Does the paper accurately lay out the state of the science and the limitations regarding the measurement of cholinesterase inhibition?"

Again the answer was very positive. It was pointed out that the section does not describe a standard operating procedure and attention was focused on factors that promote variability in assays of red blood cell AChE, especially when there has been exposure to

carbamates. However, it was recognized that many of these issues were treated in depth in earlier EPA documents and workshops and are receiving continued attention inside EPA.

3. Case studies. ?Do the case studies help to illustrate an adequate variety of data sets and how in the recent past the EPA has been using the ?Weight of Evidence" (WOE) approach to assess ChE inhibiting chemicals in accordance with the proposed science policy?"

The Panel agreed that these case studies did illustrate fairly how EPA has used and might use the WOE approach in this area with a few possible exceptions. One Panel Member offered the opinion that the case studies also point out the difficulties that would likely be encountered in trying to apply a more rigid, algorithmic approach to the same problem. It was noted that none of the presented cases demonstrated how an assessment might use blood cholinesterase data when there was a large difference in dose required to inhibit that activity relative to other endpoints such as brain AChE inhibition.

4. Science Policy. ?Is a weight of evidence approach a reasonable means of evaluating the overall significance of: clinical signs and overall behavioral or functional effects in humans and animals; symptoms in humans, central or peripheral nervous tissue measures of ChE inhibition; and blood measures of ChE inhibition?"

This question was deemed by the Panel to be of major importance. There was a consensus that the weight of evidence approach is indeed reasonable and justified on the basis of the available scientific data so long as these data are derived from rigorous experiments with standardized methods and proper controls. In particular, this approach allows flexibility to weight heavily inhibition in non-target tissues when the overall toxicologic context suggests that other approaches pose danger of serious risk from overexposure.

Careful study of the ?counterproposal" in the Acute Cholinesterase Risk Assessment Work Group (ACRA) document reveals that the industry work group also favors a weight of evidence approach in most respects. Thus, ACRA proposes to discount data that are ?out of context" in the sense of representing effects that do not appear to be clearly dose-related or occur sporadically rather than consistently across time. Other examples of industry consensus with WOE include the recommendation to give priority to human over animal data (where of equivalent quality) and to emphasize effects on target vs non-target tissues (where data are available). The major difference between the ACRA position and the

EPA position with regard to WOE is that ACRA would not use data on effects falling below an arbitrarily designated level of 20%. This cutoff value seems reasonable on the surface but, when dose-response curves are steep, it could lead to RfDs uncomfortably close to those that actually cause toxicity.

5. ?Recognizing that people disagree as to the significance of blood cholinesterase values, is it supportable to use them as a matter of science policy in certain cases where;

a. there is a steep dose-effect curve for ChEI toxicity and blood ChE is the most sensitive endpoint?

b. the NOELs and LOELs for various effects are essentially the same?

c. the pesticide poorly penetrates the blood brain barrier, and blood ChE is the only indicator of adverse effect for the peripheral nervous system other than clinical signs?

d. human data indicate that blood ChE is the most sensitive endpoint?"

There was unanimous support for the notion that, under SOME circumstances, measurements of SOME blood-borne cholinesterases would be appropriate to consider in establishing RfDs for anticholinesterases. Several panel members pointed out that generic measurements of total ChE activity in whole blood were unsuitable from this point of view. With human blood samples, where plasma contains almost exclusively BChE, it would be acceptable to measure separately red cell ChE (entirely AChE) and plasma ChE. With animal samples, where plasma contains a variable proportion of BChE and AChE (about 1:1 in rat), it would be better to divide plasma activity into specific types by using selective enzyme inhibitors in the assay (eg., iso-OMPA or ethopropazine to block BChE, BW284C51 to block AChE).

It was recognized that measured inhibition of cholinesterase activities in any of the blood fractions is best regarded as an imperfect mirror of enzyme inhibition in the true target tissues: brain, neuromuscular junctions, autonomic ganglia, and autonomic synapses. When, or if, direct measurements at the probable target sites become available, data from the blood might be under-weighted or even ignored. The best course would be to use ?blood cholinesterase values" as a matter of science policy in cases a) and c) above. This course of action is readily justified if the discrepancy between blood ChE and functional endpoints is not too great. One Panel Member pointed out that such use simply introduces a safety factor. It becomes more difficult to justify <u>permanent</u> reliance on blood ChE as the relevant endpoint when the discrepancy is very wide (e.g., 100 fold or more). This situation, however, is the subject of the next question, number 6.

6. ?There is uncertainty and disagreement in interpreting cases where blood ChE is perturbed at doses far below those showing concern from other effects. As a means of prompting the development of further information to resolve the issue (as described below), OPP is proposing to use the blood ChE measurements on an interim basis for RfD determination, awaiting further data. Is this proposed science policy a reasonable way of helping to resolve these cases?"

As implied above, the Panel felt it reasonable to use blood cholinesterase measurements on an interim basis, awaiting further information pertaining to cholinesterase inhibition in the peripheral tissues (e.g., heart, diaphragm). Another way of stating this view is to say that the registrant who wishes to see an agent regulated on some basis other than cholinesterase inhibition 2n the blood faces a burden of proof. This burden would be difficult to meet without generating data on cholinesterases in the presumed target tissues.

7. ?Following the selection of critical endpoint, the program will generally apply the traditional uncertainty factors of 10X for inter-species variations and 10X for intra-species variations. Is this approach reasonable?"

The committee generally felt that the common 10X factors for intra- and inter-species extrapolation were appropriate following the selection of the critical effect. It was argued that, even though we understand at a molecular level the structural basis for AChE inhibition in red cells, for example, this is no reason to use a smaller safety factor when extrapolating from animal species to humans. For one thing, experiments with purified enzymes from rat and human tissue show that inhibitory potency of some anticholinesterases is species dependent. For another, it is well known that some species, as compared with humans, have different concentrations of blood-borne or hepatic enzymes that represent "sinks" or different levels of metabolic pathways which bioactivate or degrade certain pesticides.

In considering intra-species safety factors, it was emphasized that, not only must one take into account genetic differences in enzyme and receptor levels, and developmental changes from infancy to adulthood, but also variations that might stem from drug interactions in patients treated with cholinergic drugs (e.g., for neurologic disease, ulcerative colitis, glaucoma) as well as smokers whose blood has high concentrations of nicotine. After discussion, the Panel concluded that a 10X intra-species safety factor remains appropriate.

In the current testing paradigm, effects of cholinesterase inhibitors on the peripheral nervous system (PNS) have not been systematically examined. Generally, the only measures available are clinical signs and other neurobehavioral endpoints, which are often rather gross and insensitive measures of adverse effects. The Panel believes that it is important that joint efforts be mounted to evaluate ChEI in the PNS per se and in the neuroeffector junctions.

8. ?Is the collection of data from peripheral nervous tissues and/or neuroeffector organs technically feasible?"

There was some discussion of the difficulties in obtaining homogeneous, consistent tissue preparations (e.g., skeletal muscle, diaphragm) for measuring cholinesterase activity. Several members of the Panel did consider it technically feasible to routinely conduct cholinesterase assays in such tissues, however. This information would be extremely important in establishing the value of blood cholinesterase information in predicting peripheral effects of anticholinesterases or replacing that information, at least in animal tests.

9. ?What factors are important to the conduct of that testing"

The most important factors identified by the Panel were a) standardized and reproducible dissection and homogenization of the tissue; b) use of assays that can be conducted with minimal tissue dilution (critical in dealing with carbamate inhibitors), c) selection of tissues representing the most toxicologically relevant targets; d) t2me elapsing between collection and assay; e) standardization of tissue storage conditions. It is important that the Agency move to develop a required or recommended standard testing protocol.

10. ?Which nerves or tissues should be measured?"

Several suggestions were offered by the Panel. Skeletal muscles, heart, lung, salivary glands, diaphragm and autonomic ganglia (e.g., superior cervical ganglia) are particularly appropriate. Consistent dissection of any of these tissues would be necessary. Perhaps at least two or more of these tissues could be agreed upon to pursue as peripheral targets of anticholinesterases. One tissue not believed to be particularly useful in this sense was the ma2n trunk of peripheral nerve itself. Sciatic nerve, for example, is easy to dissect and assay. However, it is protected by an efficient blood nerve barrier (unlike the autonomic ganglia which are fairly open to circulating compounds). Thus, nerve trunks are expected to behave more like brain than like the tissues that represent true peripheral targets of pesticides.

11. ?Along with the PNS ChE measures, what other endpoints should be included?"

Two Panel members felt strongly that cholinergic receptor binding assays should be incorporated into long-term exposure studies, and the rest of the Panel concurred. The development of tolerance during long-term exposures can ?mask" neurochemical changes induced by the anticholinesterases. Changes in receptor populations may therefore be able to explain discrepancies in studies wherein cholinesterase inhibition in target tissues does not appear to correlate with signs of toxicity, in particular when the target tissue assays are only performed at the end of the study. The ultimate regulatory significance and use of this information is speculative at present.

12 ?Should elements of this proposal become a research priority?"

This idea was endorsed enthusiastically and it was agreed that both acute and chronic studies on PNS ChEI are needed. Several Panel members noted that the importance of blood cholinesterase values in the regulation of organophosphate and carbamate pesticides has been a point of debate for decades. This conflict might be resolved by comparing the relative sensitivity of acetylcholinesterase inhibition in peripheral tissues to that noted in plasma and erythrocytes. Support for such research could be an excellent investment, since we may need to continue relying on blood cholinesterase values as the only biomarker of exposure/effect in humans. Therefore, more definitive knowledge on the utility of these markers will be essential to provide a sound scientific basis for hazard assessment and regulation.

One Panel Member suggested that research on the direct action of organophosphates on muscarinic and nicotinic receptor subtypes in vitro might have some value. Such action could exacerbate or ameliorate organophosphate toxicity depending on the organophosphate, the receptor subtype and its location (presynaptic or postsynaptic). Anticholinesterases may produce excessive receptor activation in acute exposure, but change receptor numbers in chronic exposure to produce tolerance.

Related research priorities would address the developing brain (prenatal and postnatal), which undergoes many changes, including cell migration and consolidation and elimination of synapses. Therefore, it is potentially more sensitive than an adult brain to disruptions caused by a toxicant. If an anticholinesterase did affect brain development, there would be potential for permanent

deficits.

Additional Comments related to Medical Surveillance by Cholinesterase Monitoring

As the Agency considers policies associated with cholinesterase inhibition, it is important to keep in mind the role of cholinesterase monitoring in medical surveillance programs in the United States and throughout the world. There are literally thousands of farm operators who are collecting periodic measurements of plasma or erythrocyte activity cholinesterase levels from exposed workers with the belief that such monitoring is an effective means of preventing pesticide-related illness. They have come to this belief through an effective campaign mounted by public health scientists. This campaign, in turn, was based on clinical evidence that workers with significantly depressed cholinesterase were at greater risk for acute intoxications than were workers without notable depression.

The State of California requires removal of workers from pesticide handling activities on the basis of plasma and erythrocyte activity cholinesterase monitoring. The regulation states specifically: "If plasma cholinesterase falls to 60 percent or less of the baseline, or if red blood cell cholinesterase falls to 70 percent or less of baseline, the employee shall be removed from further exposure until cholinesterase values return to 80 percent or more of their respective baseline values."

In a recent review of the California program, researchers found that plasma cholinesterase inhibition was predictive of pesticide-related illness. They state this point as follows: "The relative risk of pesticide poisoning was increased in workers whose initial baseline plasma levels were low, or if their levels had already dropped to 60-80 percent of their baseline previously in the season. (Fillmore C., Lessinger J.E. A cholinesterase testing program for pesticide applicators. Journal of Occupational Medicine, Volume 35, January 1993)

FOR THE CHAIRPERSON:
Certified as an accurate report of findings:

Larry C. Dorsey
Designated Federal Official
FIFRA/Scientific Advisory Panel

DATE:_____

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL MEETING

A Set of Scientific Issues Being Considered by the Agency Concerning the Office of Pesticide Programs (OPP) Hazard Characterization of N,N-diethyl-meta-toluamide (DEET) and the Decision Not to Establish Toxicity Endpoints for Risk Assessment Use.

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of the Office of Pesticide Programs (OPP) hazard characterization of N,N-diethyl-meta-toluamide (DEET) and the decision not to establish toxicity endpoints for risk assessment use. The review was conducted in an open meeting held in Arlington, Virginia, on June 4, 1997. The meeting was chaired by Dr. Ernest E. McConnell. Other panel members present were: Dr. Janice E. Chambers (Mississippi State University); Dr. Amira T. Eldefrawi (University of Maryland); Dr. Ernest Hodgson (North Carolina State University); Dr. Harihara M. Mehendale (Northeast Louisiana University); Dr. Genevieve M. Matanoski (Johns Hopkins University); Dr. Stephen Saunders (Frito-Lay Corporation); Dr. Mary Anna Thrall (Colorado State University).

Public Notice of the meeting was published in the Federal Register on April 22, 1997.

Oral statements were received from:
Dr. Gerald Schoenig, Toxicology Regulatory Services

Written statements were received from:
Chemical Specialties Manufacturers Association

QUESTIONS FOR THE PANEL ON HAZARD CHARACTERIZATION OF DEET

1. Based on the currently available data on DEET, OPP requests that the members of the SAP comment on the OPP's hazard characterization of this chemical and the decision for not establishing the toxicity endpoints for risk assessment.

The Panel agrees with the Agency's hazard characterization and decision not to establish toxicity endpoints to be used for risk assessment, as exposure to DEET does not result in clearly characterized specific toxicological responses; to rationally choose toxicity endpoints that reflect a consistent response to DEET would be impossible. However, hazard characterization could be improved by the Agency's consideration of factors such as impact of multiple applications, inhalation or ingestion of DEET, site of dermal application, and amount of dermal absorption in children. Because of the potential exposure to aerosol-sprayed DEET via breathing, it was recommended that limited animal studies be conducted to compare data from exposure via inhalation to those available from ingestion and dermal exposure.

Panel Members were supplied as background reading the peer review reports from CAL-EPA and Health Canada and several Panel Members noted differences in these data and methodologies used by these two groups but the Agency did not elaborate on these differences at the meeting. For example, a spokesperson for Health Canada noted that they used an endpoint from a one year dog study for a chronic risk assessment. Several Panel Members recommended that the current Agency risk assessment be expanded to include much better exposure scenarios, chronic exposure being one of the recommended scenarios for which use of the one year dog study endpoint might be appropriate for a risk assessment.

2. What do you think about our approach to and methodology for the risk assessment and characterization?

In general, the Panel agrees with the Agency's approach to and methodology for risk assessment and characterization. While the assessment appears to be thorough, the Panel suggests that the Agency consider using several more realistic human exposure scenarios for risk assessment and characterization. Factors in these scenarios should include repeated applications, particularly around the face, smaller body weight of children (20 to 25 lb., rather than 55), and ranges of exposure situations including possible chronic exposure. Additionally chronic exposure studies of over one year may be warranted based on the number of people who

are exposed occupationally.

3. What is your opinion of our interpretation of the incident information? (EPA believes that the reported incidences are inconclusive.)

The Panel agrees with the Agency's interpretation of the incident information (that the reported incidences are inconclusive). There is no compelling information that exposure to DEET is causing an appreciable number of seizures, and data from animal studies do not support or predict symptoms experienced by children exposed to DEET. However, a more complete description of the reports of children and adults who have had symptoms associated with DEET exposure should be included in the document, including serum concentration of DEET when that information is available. Animal experiments do suggest some synergism when DEET is used in conjunction with other toxicants, and such synergism may precipitate clinical signs in sensitive individuals. Moreover, physicians may not be recognizing seizures related to DEET exposure, since the product is considered to be safe. While several members of the Panel believed that appropriate warning labels should be adopted, it was recognized that seizures not actually related to DEET exposure might then be attributed to DEET. In summary, the panel recommends that the Agency continue to accumulate data from cases of suspicious DEET intoxications from pediatric neurologists, poison control centers, and the manufacturer. The continued maintenance and analyses of accurate incidence records is very important for DEET.

FOR THE CHAIRPERSON:
Certified as an accurate report of findings:

Larry C. Dorsey
Designated Federal Official
FIFRA/Scientific Advisory Panel
DATE:_____