AGENDA

FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
OPEN MEETING
June 16 – 18, 2009

FIFRA SAP WEB SITE http://www.epa.gov/scipoly/sap/
OPP Docket Telephone: (703) 305-5805
Docket Number: EPA-HQ-OPP-2008-0489

U.S. Environmental Protection Agency
Conference Center - Lobby Level
One Potomac Yard (South Bldg.)
2777 S. Crystal Drive, Arlington, VA 22202

Evaluation of the Common Mechanism of Action of Pyrethroid Pesticides

Please note that all times are approximate (see note at end of Agenda).

Tuesday, June 16, 2009

8:30 A.M. **Opening of Meeting and Administrative Procedures** – Joseph Bailey, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:40 A.M. **Introduction and Identification of Panel Members** – John Bucher, Ph.D., Session Chair, FIFRA Scientific Advisory Panel

8:50 A.M. **Welcome and Opening Remarks** – Steven Bradbury, Ph.D., Deputy Director, Office of Pesticide Programs, EPA

8:55 A.M. **Goals and Objectives** – Tina Levine, Ph.D., Director, Health Effects Division, Office of Pesticide Programs, EPA

9:00 A.M. **Summary of Proposed Common Mechanism Grouping for the Pyrethrins and Synthetic Pyrethroids** – Anna Lowit, Ph.D., Health Effects Division, Office of Pesticide Programs, EPA; Timothy Shafer, Ph.D., Integrated Systems Toxicology Division, National Health Effects and Environmental Research Laboratory, Office of Research and Development, EPA; Edward Scollon, Ph.D., Health Effects Division, Office of Pesticide Programs, EPA

10:30 A.M. **Break**

10:45 A.M. **Summary of Proposed Common Mechanism Grouping for the Pyrethrins and Synthetic Pyrethroids (continued)**

11:30 A.M. **Public Comment**

12:00 noon **Lunch**

1:15 P.M. **Public Comment (continued)**

2:45 P.M. **Break**

3:00 P.M. **Panel Discussion of Charge**

Pyrethroids are a class of synthetic insecticides which are structurally based on the pyrethrins, botanical insecticides extracted from *Chrysanthemum cinerariaefolium*. Pyrethroid exposure can occur from food, water, or non-occupational settings. Potential exposure of the general public to pyrethroid pesticides has increased over the past

decade, due in part to a shift in usage away from the organophosphate and *N*-methyl carbamate pesticides.

Pyrethroids are scheduled for re-evaluation under the Office of Pesticide Program's registration review program as required under the Federal Insecticide, Fungicide, Rodenticide Act (FIFRA). Background information on the program is provided at: http://www.epa.gov/ oppsrrd1/registration review/. The current schedule is available at: http://www.epa.gov/oppsrrd1/registration_review/schedule.htm. An explanation of the schedule is at: http://www.epa.gov/oppsrrd1/registration_review/explanation.htm.

With the passage of the FQPA (1996), EPA was required to consider available information concerning the cumulative effects on human health resulting from aggregate exposure to multiple chemicals that have a common mechanism of toxicity. At this time, although some uncertainties still exist, the Office of Pesticide Programs (OPP) believes that there is sufficient scientific evidence to demonstrate that the pyrethrins and synthetic pyrethroids share a common mechanism of action. The Agency's analysis and preliminary conclusions are provided in the document titled: "Draft Science Policy Paper: Common Mechanism Grouping for the Pyrethrins and Synthetic Pyrethroid Pesticides." This draft issue paper was developed by the Health Effects Division (HED) of OPP with support from EPA's Office of Research and Development (ORD). Specifically, OPP is proposing that the naturally occurring pyrethrins and synthetic pyrethroids form a common mechanism grouping based on 1) shared structural characteristics; and 2) shared ability to interact with voltage-gated sodium channels (VGSC), resulting in disruption of membrane excitability in the nervous system, and ultimately neurotoxicity characterized by two different toxicity syndromes. As described in more detail below, OPP is further proposing to subgroup the pyrethroid CMG into two subgroups representing Type I and II pyrethroids based on differences in structure, sodium channel perturbations, and neurobehavioral effects.

The Agency is soliciting comments from the Panel on science issues related to the common toxicity pathway for pyrethroids, remaining uncertainties, and the proposal to separate the pyrethroids into two subgroups (Type I and II) [1]. Pending the outcome of the June, 2009 peer review, the pyrethroid pesticides are expected to be subject to cumulative risk assessment during the forthcoming registration review.

1. *Common pathway to neurotoxicity:*

a. OPP is proposing that the naturally occurring and synthetic pyrethroids share the ability to interact with voltage-gated sodium channels (VGSC) resulting in disruption of membrane excitability in the nervous system, and ultimately neurotoxicity. The shared ability provides the initial and common key event in the pathway to pyrethroid neurotoxicity and thus provides a basis for forming a common mechanism group. As

[1] The Agency acknowledges that at least two pyrethroids (esfenvalerate and fenpropathrin) appear to exhibit characteristics of both Type I and Type II. In the coming months and as the Agency moves into developing the preliminary cumulative hazard and exposure assessments, the Agency will make a determination as to how to handle these two pyrethroids in the actual cumulative risk assessment. The public will have opportunities to comment on this issue in the future.

described in Section 4.0 of the draft paper, the Agency has determined that interaction with the VGSC is an initial and common key event in the pathway to pyrethroid neurotoxicity.

Unlike the cholinesterase inhibiting organophosphorous and *N*-methyl carbamate pesticides, pyrethroids lack a readily measurable *in vivo* biomarker for the initial key event (i.e., sodium channel interaction). Despite this, the scientific evidence correlating pyrethroid-induced changes in VGSC function with neurotoxicity for purposes of forming a common mechanism grouping is substantial. Given the availability of extensive studies on the mechanism of toxicity and toxic effects of pyrethroids, the lack of an *in vivo* biomarker does not preclude grouping via a common mechanism.

Please comment on the evidence which does and does not support the Agency's proposal that sodium channel interaction provides the initial and common toxic event in the pathway to neurotoxicity for the synthetic pyrethroids and pyrethrins. As part of your response, please comment on the uncertainty associated with lack of a readily measurable in vivo biomarker for sodium channel interaction.

b. The Agency is aware of studies which show that pyrethroids can bind to other sites such as the calcium, chloride channels and ligand-gated chloride channels currents. The Agency acknowledges that interaction between the pyrethroids and these sites may mediate their potency. However, the data which support interactions with the calcium, chloride, and ligand-gated chloride channels are not sufficiently robust for purposes of common mechanism grouping under the FQPA. Therefore, these pathways do not provide the basis for establishing their binding as a common key event leading to neurotoxicity. The Agency has concluded that the evidence on pyrethroid interaction with the calcium and chloride channels and ligand-gated chloride channels currents is limited and inconsistent. The Agency has therefore concluded that the evidence does not support characterizing these interactions as a common key event in the pathway to neurotoxicity by the pyrethrins and synthetic pyrethroids (Section 4.2.5). **Please comment on the evidence which does and does not support this determination.**

5:00 P.M. ADJOURN

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Wednesday, June 17, 2009

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8:40 A.M. **Introduction and Identification of Panel Members** – John Bucher, Ph.D., Session Chair, FIFRA Scientific Advisory Panel

8:50 A.M. **Follow-up from Previous Day's Discussion**
Health Effects Division, Office of Pesticide Programs, EPA

9:15 A.M. **Panel Discussion of Charge continued**

2. *Sodium channel structural heterogeneity:*

Briefly, mammalian sodium channels are comprised of α and β subunits that exist in multiple isoforms, giving rise to tissue, regional and lifestage heterogeneity in sodium channel expression (Goldin 2001; Plummer and Meisler 1999). Mammalian neurons typically express multiple isoforms of both α and β subunits, making it difficult to determine the composition of subunits comprising sodium channel currents in native neurons. Evaluation of specific alpha- and beta-subunits (either alone or in combination) may be interesting for purposes of evaluating species differences, potential population pharmacodynamic variability, and lifestage differences. With respect to the proposal to form a CMG, however, incomplete knowledge of the role of the α and β subunits in pyrethroid toxicity does not discount the role of sodium channel interaction as a key event in pyrethroid toxicity. As described in Sections 4.2 and 5.0, the Agency has concluded that although there is heterogeneity among the subunit combinations, the pathway of toxicity remains the same---namely that sodium channel interaction as a critical and initial key event in toxicity of pyrethroids.

Please comment on the scientific support for and against the Agency's conclusions with respect to the sodium channel structural heterogeneity information.

10:15 A.M. Break
10:30 A.M. Panel Discussion of Charge continued

3. Sub-grouping the Type I and II pyrethroids:

a. The Agency has proposed to separate the pyrethrins and synthetic pyrethroids into Type I and Type II subgroups as discussed in detail in Section 5.0 of the Draft Science Policy Paper. Briefly, this proposal is based on the structural difference in Type I and Type II pyrethroids, i.e, the absence or presence of an α-cyano group, respectively[1]. This structural difference is correlated with length of time the sodium channel is inactivated (-CN=shorter; +CN=longer) which in turn corresponds with the 2 distinct toxicity syndromes (-CN=T syndrome; +CN=CS syndrome). This separation is based on a weight of the evidence evaluation that considered both historical and newer studies from in vitro (i.e., intact and transected sodium channels and microelectrode array) and in vivo studies (i.e., motor activity and functional observational battery).

Please comment on the evidence which does and does not support this determination.

b. With respect to assigning the pyrethroids to sub-groups;

- The Agency's preliminary designation for 11 pyrethroids and pyrethrin is based on a weight of the evidence assessment utilizing three key lines of evidence: presence/absence of the alpha-cyano group, effects on sodium channel kinetics, and in vivo toxicity syndromes.
- Five additional pyrethroids are being characterized in a special FOB study. For these five the structure is also known. Thus for tetramethrin, cyphenothrin, imiprothrin, phenothrin, and prallethrin, information from two lines of evidence will be available (structure, toxicity syndrome) for assigning these.
- Tralomethrin is metabolized to deltamethrin in vivo and is also converted in the environment to deltamethrin. As such, given the presence of the alpha-cyano group and its relationship to deltamethrin, the Agency expects tralomethrin to be assigned a designation of Type II.
- Cinerin and jasmolin are naturally occurring pyrethrins and do not have the alpha-cyano group on their structure. Thus, the Agency expects cinerin and jasmolin to be assigned a designation of Type I.
- Two other pyrethroids, metofluthrin (non-cyano) and fluvalinate (cyano) have scant databases. With respect to their toxicity, the Agency is unaware of detailed characterization of their profiles which would allow designation. Moreover, the Agency is unaware of studies describing their interactions with sodium channels. The Agency expects metofluthrin and fluvalinate to be designated as Type I and Type II compounds, respectively, based on structure.

Please comment on the Agency's approach to assigning the pyrethroids to the Type I and Type II sub-groups. Please include in your comments consideration

for those without special FOB information and for which structure will be the major determinant in their designation.

c. Two pyrethroids, fenpropathrin and esfenvalerate, exhibit characteristics of Type I and Type II compounds (i.e., "mixed" Type). In the anticipated cumulative risk assessment, the Agency must determine the appropriate approach for these two. In performing exposure assessment and ultimately in estimating human risk, several options have been identified—include fenpropathrin and esfenvalerate in the Type I sub-group, in the Type II subgroup, or in both subgroups.

Please comment on these possible options and any others identified by the Panel.

12:00 noon Lunch
1:15 P.M. Panel Discussion of Charge continued

4. Evaluation of Dose-Addition of pyrethroids

As discussed in Section 4.4, there are a limited number of mixture studies on pyrethroids. Electrophysiological studies have evaluated mixtures of two pyrethroids but used excessive doses and/or lack robust study designs and statistical analyses. As such, these studies preclude thorough evaluation of dose or effect addition. More recent studies include Wolansky et al (2009) and Shafer et al (in prep) which evaluate motor activity *in vivo* and micro electrode arrays, a newer assay for mammalian neural networks, *in vitro.* The Wolansky et al (2009) and Shafer et al (in prep) studies were specifically designed to test dose additivity but endpoints measured in both studies lack in their ability to establish dose additivity specifically at the level of the sodium channel.

Please comment on additional research which could be undertaken to evaluate the assumption of dose-addition as it relates to the proposed common mechanism pathway.

3:00 P.M. Break
3:15 P.M. Panel Discussion of Charge continued
5:00 P.M. ADJOURN

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8:40 A.M. **Introduction and Identification of Panel Members** – John Bucher, Ph.D., Session Chair, FIFRA Scientific Advisory Panel
8:50 A.M. **Follow-up from Previous Day's Discussion**
Health Effects Division, Office of Pesticide Programs, EPA
9:15 A.M. **Panel Discussion of Charge (continued as needed)**
10:15 A.M. **Break**
10:30 A.M. **Panel Discussion of Charge (continued as needed)**
12:00 noon **Lunch**
1:15 P.M. **Panel Discussion of Charge (continued as needed)**
3:00 P.M. **Break**
3:15 P.M. **Panel Discussion of Charge (continued as needed)**
5:00 P.M. **ADJOURN**

Please be advised that agenda times are approximate; when the discussion for one topic is completed, discussions for the next topic will begin. For further information, please contact the Designated Federal Official for this meeting, Joseph Bailey, via telephone: (202) 564-2045; fax: (202) 564-8382; or email: bailey.joseph@epa.gov