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## **THE AGENCY'S RESPONSES TO PUBLIC COMMENTS ON THE DRAFT FQPA SCIENCE POLICY DOCUMENT:**

*Guidance for Identifying Pesticide Chemicals That Have a Common Mechanism of Toxicity*  
(Announced August 8, 1998; 63 FR 42031, FRL-5797-7.)

( January 29, 1999 )

The Agency reviewed all comments pertaining to this document that were submitted specifically under this docket (OPP-00542) or in relation to the Tolerance Reassessment Advisory Committee (TRAC). A listing of the names and affiliations of the individuals submitting comments is provided at the end of this document. The Agency would like to thank these organizations for critically reviewing the document, and for providing recommendations to improve the document. All comments were extensively reviewed and considered by the Agency. Many of the recommendations made by the commentors were incorporated into the revised document. Most of the comments were similar in content, and pertained to general issues dealing with grouping of chemicals for purposes of cumulative risk assessment, or specific sections within the draft document. To facilitate review and consideration of the comments for purposes of revising the document, the Agency grouped the comments in accordance to nature of the comment, or issue or section of the document with which they addressed. Following is a listing and description of the more significant comments, along with EPA's general responses. The numbers used in the summary below correspond to specific commentors (listed at the end of this document).

### *A. Purpose and Introduction of the Document.*

One commentor [11] stated that the document lacks a clear statement of purpose. Several other commentors [2-6, 9,13] appear to have misunderstood the purpose of the document. These commentors were of the impression that the primary purpose of the document is to describe the approach EPA will use to assess cumulative toxicity and risk from pesticides that have a common mechanism of toxicity. The purpose of the document is stated on page 2: "The primary purpose of the document is to describe the approach that EPA will use for identifying and categorizing pesticide chemical substances that have a common mechanism of toxicity." This statement is retained in the revised version, and has been modified to include other substances (i.e., non-pesticidal substances).

Some commentors [1, 2, 3, 9, 11, 15] stated that the opening paragraphs of the document imply that the issue of considering cumulative effects is new, when in fact it has been a legal requirement under FIFRA and FFDCAs for many years, and promulgation of FQPA has not made cumulative risk assessments a new requirement. The Agency agrees that FIFRA and FFDCAs mandated prior to FQPA that in registering pesticides and setting pesticide tolerances EPA must give appropriate consideration to ways in which consumers may be affected by the same pesticide chemical or by other "related" substances that are "poisonous or deleterious." The Agency has always given, and continues to give, such consideration during its risk assessments of pesticides. The historical statements in the opening paragraphs are correct, however, in that most determinations of safety made to date by the Agency for pesticides have been based largely on the potential for each individual pesticide to cause a particular toxic effect rather than an assessment of cumulative effects of more than one pesticide chemical or other substance. It was the Agency's intention to use the opening paragraphs to inform the reader that, in addition to the pre-existing

statutory mandates, FQPA explicitly mandates the Agency to consider when determining the safety of a pesticide the possibility of cumulative toxicity to human health that may be caused by exposure to other pesticides that have a common mechanism of toxicity. The purpose of the guidance document is to describe the approach that EPA will use for identifying pesticides and other substances that have a common mechanism of toxicity, for purposes of assessing the cumulative toxicity of such pesticides and other substances.

### *B. Exposure Issues.*

EPA received a number of comments concerning exposure. One commentor [1] stated that grouping of chemicals should be based only on causing a common toxic effect by a common mechanism, excluding exposure as a criterion for grouping. Other commentors [9, 11, 15] suggested that to conserve resources and fulfill the FQPA mandates more accordingly, EPA should do an exposure assessment first and use exposure as a basis for grouping. Hence, group only those chemicals which: 1) have overlapping exposures, 2) cause a common toxic effect, and 3) have a common mechanism of toxicity. Some commentors [2, 5, 6] stated that EPA should not restrict cumulative risk assessments to only those pesticides within a common mechanism group for which there is concomitant (i.e., simultaneous) exposure (as stated in the draft version), whereas other commentors [9, 15] stated that the Agency should restrict cumulative risk assessments to only those pesticides within a group for which there is concomitant exposure. The Agency will not use concomitant exposure as a criterion for grouping chemicals that cause a common toxic effect by a common mechanism, because it has no bearing on whether or not substances can cause common toxic effects by common mechanisms. The Agency agrees that cumulative toxicity may result from exposures that are not concomitant, and cumulative risk assessments performed by the Agency on pesticides and other substances within a common mechanism group should not be restricted to only those for which there is concomitant exposure. In revising the guidance document, previous statements that concomitant exposure is a prerequisite for conducting cumulative risk assessments have been removed. The Agency is currently preparing a document (see next paragraph) that will describe the approach EPA will use to conduct cumulative risk assessments on pesticides and other substances that have a common mechanism of toxicity. That document will discuss in more detail all the factors that will be considered by the Agency to assess cumulative toxicity that may be caused by such substances.

Several commentors [1, 8, 9, 11, 15] stated that there is a lack of detail or discussion on how the Agency plans to assess exposure when conducting cumulative risk assessments on chemicals that have been grouped by common mechanism of toxicity. Some commentors [4, 6, 9, 11, 15] stated that the document needs to be expanded to include more detail on how the Agency will conduct cumulative risk assessments on pesticides that have a common mechanism of toxicity. Two commentors [9, 16] suggested that the guidance document should be revised to include examples on how the Agency will apply the common mechanism guidelines, assess cumulative toxicity, and conduct cumulative risk assessments. The Agency's response to these comments is as follows. First, the Agency plans to make available within the next six to twelve months (at public forums such as national conferences, FIFRA Scientific Advisory Panel meetings, etc.) specific examples of how it will apply its guidance for identifying pesticide chemicals that have a common mechanism of toxicity. Secondly, the primary purpose of the draft document is to describe the approach that EPA will use to identify pesticides and other substances that have a common mechanism of toxicity. It is not intended to describe how the Agency will assess exposure to such substances and the cumulative risks that they may pose. The Agency is currently preparing a separate document that will describe the approach it will use to conduct cumulative risk assessments. That document will include at least one example of how the Agency will apply the guidance described in the draft document. The document will also contain discussions on how the Agency will evaluate exposures to pesticides that have a common mechanism of toxicity, and provide examples of how the Agency will assess cumulative risks posed by such pesticides. The document will be made available for public comment in June of 1999.

### *C. Consideration of Substances other than Pesticides.*

One commentor [4] recommended that the guidance document needs to be expanded to include guidance on how the Agency will conduct cumulative risk assessments on pesticides [and other substances] that are not toxic via a common mechanism of toxicity. The Agency did not include such guidance because it is beyond the scope of the document. Some commentors [4, 5, 6] pointed out that the focus of the guidance document is only on identifying *pesticides* that have a common mechanism of toxicity, and not on identifying *other substances* (i.e., non-pesticide chemicals) that have a mechanism of toxicity common with that of a given pesticide or pesticides. These commentors are concerned that forthcoming pesticide cumulative risk assessments performed by the Agency will exclude non-pesticide chemicals that are toxic by a mechanism common with that of a given pesticide or group of pesticides. The Agency agrees that the focus of the draft document is on identifying and grouping pesticide substances that have a common mechanism of toxicity. Although the Agency intends to use the approach described in the document to identify pesticide substances and other substances (e.g., drug products, chemicals used in industry, as well other substances used in commerce) that cause a common toxic effect by a common mechanism, this intent was not made clear in the draft version. The Agency has changed the title of the document and has made other editorial changes throughout the document that broaden its scope to include substances not used as pesticides. The Agency wishes to make clear that it will include other substances that are toxic from a mechanism common with that of a given pesticide or pesticides in a cumulative risk assessment.

### *D. Definitions of Certain Terms.*

A number of commentors questioned the Agency's definitions of certain terms used in the document. Several commentors questioned the Agency's definition of "common mechanism of toxicity." Some commentors [1, 2, 3, 9, 11, 12, 15] believe that the Agency's definition is either too broad, unclear or needs to be made more simple and rigorous. Other commentors [4, 5, 6] believe that the Agency's definition is too narrow in that it encompasses toxic effects that are the same in nature and site, but doesn't encompass toxic effects that are the same but occur at different sites. Commentors 4, 5 and 6 also believe that the Agency's definition departs from a definition proposed by a working group of the International Life Sciences Institute (ILSI). Another commentor [7] believes that the Agency's definition is clear and appropriate, and consistent with the definition proposed by the ILSI working group. One commentor [13] believes the Agency should interpret "common mechanism of toxicity" as used in FQPA to mean "common mechanism of action", because the latter phrase, in the opinion of the commentor, is less descriptive for defining or describing a mechanism of toxicity. Several commentors also questioned the Agency's definition of "mechanism of toxicity." These commentors [2, 9, 11, 15] believe that the Agency's definition of this term is too vague or general, whereas another commentor [7] believes that the Agency's definition is appropriate. The Agency re-evaluated its definitions of these terms. The Agency believes that its definitions of the terms "mechanism of toxicity" and "common mechanism of toxicity" are sufficiently clear, and consistent with that of the ILSI working group and the intent of FQPA. However, the Agency has included additional discussion (Section III of the revised document) that adds further clarification to these terms. It also is important to make clear here that the Agency develops its own science policies; other organizations do not develop Agency policies. While the Agency may utilize the expertise of scientists from sources (e.g., ILSI) outside of the Agency, and consider the recommendations made by such individuals or organizations for purposes of establishing Agency science policies or practices, the Agency does not have to accept or implement any recommendations made from outside sources. Hence, the Agency's definitions of terms used in its policy documents do not have to be consistent with the definitions developed or recommended by individuals or organizations outside of the Agency.

Several commentors [9, 11, 15] questioned the Agency's definitions of "toxic effect" or

“common toxic effect,” and stated that the Agency needs to define these terms more clearly or be more specific. The Agency believes that its definitions of “toxic effect” and “common toxic effect” are sufficiently clear, and consistent with the intent of FQPA. However the Agency has added some additional text to the definition of “common toxic effect”, and has added additional text in Section III of the revised document that adds further clarification to the meaning of these terms, and how they will be applied. One commentor [16] disagreed with the Agency’s definition of “cumulative toxic effect.” This commentor stated that there does not need to be an overall increase in toxicity to be cumulative, and suggested that the Agency remove the part of its definition that states there is an overall increase in toxicity. The Agency agrees that the cumulative toxicity following exposure to two or more chemicals does not necessarily have to result in an overall increase in toxicity relative to exposure to any of the chemicals alone. The Agency has clarified its original definition of “cumulative toxic effect” in the revised version of the document.

#### *E. Assessing Cumulative Toxicity.*

Some of the commentors had comments pertaining to Section IV of the document: *Policies for Assessing the Cumulative Toxic Effects Posed by Two or More Pesticides that are Toxic By a Common Mechanism*. One commentor [9] wants the Agency to clarify this section, by providing more details. The other commentors [11, 12, 15, 16] who commented on this section questioned the example that poses a hypothetical pharmacokinetic interaction between two substances and describes how EPA will consider such an interaction in its evaluation of cumulative toxicity. The primary purpose of the document is to describe the approach that EPA will use to identify the mechanism(s) of toxicity of individual pesticides and other substances and group those pesticides and other substances that have common mechanisms of toxicity. While a description of how the Agency will proceed with assessing the cumulative toxicity of substances within a common mechanism group is beyond the scope of the document, the Agency believed it would be helpful to the reader to mention some of the practices and policies that the Agency intends to use when assessing the cumulative toxicity of pesticides that are toxic by a common mechanism. However, the Agency is currently developing a separate document that will describe in detail the policies, practices and factors the Agency will use or consider in the assessment of cumulative toxicity (risks) of pesticides and other substances that are toxic by a common mechanism, and will be made available for public comment in June of 1999. The Agency no longer believes that discussion of assessing cumulative toxicity is necessary in the present document. Hence, the Agency has made extensive revisions to section IV of the document. The Agency agrees that the hypothetical pharmacokinetic example is inappropriate. Accordingly, the Agency has removed the example and will address the issue of pharmacokinetic interactions in the cumulative risk assessment document.

#### *F. Use of Assumptions or Hypotheses.*

Several commentors [1, 9, 10, 11, 14, 15] expressed concern that the Agency plans to use many assumptions and hypotheses when elucidating or inferring mechanisms of toxicity of individual pesticides, and grouping pesticides, or recommended that the Agency not use default assumptions. Many of these commentors questioned, for example, the Agency’s basis for assuming additivity of a toxic effect when assessing cumulative toxicity, or the use of structure-activity relationships as part of the weight of the evidence approach for determining mechanisms of toxicity.

Historically, the Agency has used and continues to use certain key assumptions and hypotheses during essentially all phases of assessing the risks posed by substances, including substances that are (or intended to be) used as pesticides. It is a necessary aspect of risk assessment for the Agency to make reasonable assumptions and use appropriate hypotheses as a practical means of filling gaps or science questions that may be too difficult, costly, time-consuming or, in some instances, impossible to fill otherwise. The Agency believes that the draft

document does not imply that the Agency will use an unusually large amount of assumptions or hypotheses, or use them inappropriately. Determinations of mechanisms of toxicity will be based largely on a weight of scientific evidence, and not on many assumptions or hypotheses. The Agency anticipates, however, that in the process of identifying pesticides and other substances that have a common mechanism of toxicity, assumptions and hypotheses may need to be made and used on occasion. As alluded to in the draft guidance document, assumptions and hypotheses will be used when they are scientifically defensible. Comments pertaining to the use of structure-activity relationships or the assumption of additivity are addressed separately below.

#### *G. Use of the Phrase “Mechanism of Toxicity.”*

Two commentors [13 and 16] suggested that the EPA should abandon the phrase “mechanism of action [or toxicity],” and replace it with “mode of action [toxicity].” These commentors believe that the latter phrase is more appropriate because it is less descriptive. FQPA specifically mandates that EPA assess the cumulative toxic effects of pesticides that have a common mechanism of toxicity. Therefore, the Agency will continue to use the phrase “mechanism of toxicity”, for purposes of clarity and consistency with FQPA.

#### *H. Use of Genetic Alterations as a Basis for Preliminary Grouping.*

One commentor [16] stated that demonstration of chemically induced, genetic alterations is by itself an inadequate basis for assuming pesticides or other substances are toxic by a common mechanism and grouping chemicals. The Agency agrees with the commentor. However, the Agency believes that this commentor misunderstood the Agency’s intended use of information pertaining to genetic alterations. The Agency stated that it will use data pertaining to genetic alterations for preliminary grouping only (Figure 1, step 1). The Agency did not state it will use chemically induced genetic alterations as a basis for grouping chemicals for purposes of cumulative risk assessment. The Agency will use genetic alterations as a basis for initial grouping only, and not as a basis for conducting a cumulative risk assessment. Chemicals initially grouped by genetic alterations will undergo further evaluation, as with any other chemical, in order to determine their mechanisms of toxicity and which ones, if any, have a common mechanism of toxicity.

#### *I. Use of the Terms “Similar” or “Analogous,” and Distinctions between “Mechanism of Toxicity” and “Toxic Effect.”*

Several commentors [ 3, 9, 11] objected to the Agency’s use of the terms “similar” or “analogous” in the discussions pertaining to comparing toxic effects, toxic mechanisms or grouping of compounds by toxic mechanism. These commentors believed that these terms are not sufficiently clear. Some commentors [9, 11] asked the Agency to distinguish or define the relationship between “mechanism of toxicity” and “toxic effect.” As a result, the Agency has incorporated in Section III of the revised document additional statements and examples that make further distinctions between “mechanism of toxicity” and “toxic effect.” In addition, the Agency has added the terms “site of toxic action” and “site of a toxic effect”, and included definitions of these terms. These terms provide additional clarification on regarding the terms “mechanism of toxicity” and “toxic effect”. The Agency believes that the terms “similar” and “analogous”, as used in the document, are sufficiently clear and appropriate. However, some additional clarification of the meaning of these terms is provided here in the form of a hypothetical example. The mechanism of toxicity of a particular commercial substance that contains a primary alcohol moiety (-CH<sub>2</sub>OH) is known to involve metabolism of the alcohol moiety to a carboxylic acid moiety (-COOH), and that it is the carboxylic acid metabolite that causes a particular toxic effect. Let’s say that the carboxylic acid metabolite is also used commercially as a separate

chemical product. Test data show that it causes the same toxic effect (i.e., concordant in both site and nature) as does its metabolic precursor. Hence, the toxic effect caused by the two substances is common. Strictly speaking, some may feel that the mechanisms of toxicity of each commercial substance are not entirely identical because the first commercial substance requires metabolic oxidation whereas the second does not. However, the Agency believes these mechanisms are “similar” (or “analogous”) in causing the common toxic effect, and that they meet the Agency’s definition of common mechanism of toxicity.

The Agency is using the revised guidance to identify chemicals that cause common toxic effects by common mechanisms. The results from these investigations will be made available, and the Agency believes the results will further demonstrate how the meanings of the terms “similar” and “analogous” will be applied by the Agency when identifying mechanisms of toxicity and grouping (or not grouping) chemicals. These groupings will also demonstrate the relationship between toxic effects and mechanisms of toxicity.

*J. Requests for Specific Examples of Common Toxic Effects and Toxic Effects, and of Substances that Cause Cumulative Toxic Effects.*

Some of the commentors [9, 11] asked the Agency to give specific examples of “common toxic effects” and “toxic effects” that could be used for either initial grouping of pesticides that may have a common mechanism of toxicity or regulatory purposes. The Agency provides such examples in Section II and Section III of the draft guidance document. The revised document contains additional examples in the same sections. Many more examples are available in the Reregistration Eligibility Decision (RED) pesticide documents that are issued by the EPA’s Office of Pesticide Programs.

Some of the commentors [9, 11, 13] requested that the Agency provide specific examples of substances that exhibit cumulative toxic effects through a common mechanism of toxicity. The Agency is currently developing documents that will describe in detail and provide examples of how the Agency will accumulate toxicity and assess the cumulative risks posed by pesticides that are toxic from common mechanisms. The documents will also provide specific examples of substances that exhibit cumulative toxic effects from a common mechanism of toxicity. Some of these documents will be made available by June, 1999. The other documents will become available between June and December of 1999.

*K. The Agency’s Policy of Assuming Additivity.*

Several commentors [9, 11, 13, 15] questioned the Agency’s policy for assuming additivity when accumulating toxicity of chemicals that have a common mechanism of toxicity. As stated in the document, the Agency recognizes that the magnitude of accumulation of a given common toxic effect following exposures to two or more chemicals within a given group of pesticides that cause the effect by a common mechanism may be equal to (i.e. additive), greater than (i.e., synergistic, potentiated), or less than that expected by addition of the toxic effect as caused by each substance individually. The Agency anticipates, however, that in many situations there may not be sufficient experimental data to determine whether the magnitude of the accumulation is equal to, greater than, or less than that expected by addition of the toxic effect. In such instances the Agency will assume that the accumulation is additive. The assumption of additivity in assessing the cumulative toxicity of pesticides that cause a common toxic effect from a common mechanism was presented by the Agency to the FIFRA Scientific Advisory Panel in March of 1997. The Panel concurred with the Agency’s intended use of this assumption. In addition, it is the general practice of the Agency to assume additivity in assessing the health risks posed by two or more chemical substances. For example, the Agency’s document entitled “Guidance for Conducting Health Risk Assessment of Chemical Mixtures” (USEPA/ORD document NCEA-C-0148, June, 1998) states that the Agency will assume additivity unless data to

the contrary are available.

#### *L. Use of Structure-Activity Relationships.*

Several commentors [1, 8, 9, 12, 15, 16] raised concern about the Agency's use of structure-activity relationships for purposes of identifying mechanisms of toxicity. One commentor expressed concern that the Agency will use structure-activity relationships as a tool to deliberately impose unnecessary regulations on certain pesticides. Other commentors believe that the Agency should not use structure-activity relationships at all or, if they must be used, use them with great caution. The Agency is well experienced with using structure-activity relationships. The Agency will use structure-activity relationship data, along with other types of data, as part of the weight of the evidence in determinations of mechanisms of toxicity and judgements regarding whether to group or not to group chemicals. The use of structure-activity relationships for such purposes was presented to the FIFRA Scientific Advisory Panel in March of 1997. The Panel concurred with the Agency's intended use of structure-activity relationships for these purposes. The Agency will not use structure-activity relationships for imposing "unnecessary regulations" on pesticides.

#### *M. Burden of Proof.*

Several commentors raised concern regarding burden of proof. These commentors [4, 5, 6] believe that the document implies that the burden is on EPA to prove that compounds have a common mechanism of toxicity. Under FIFRA and FFDCa, the ultimate burden of proving safety of a given pesticide rests on the proponent of registration (or reregistration) of the pesticide. The FFDCa also requires that EPA consider the possibility of cumulative toxic effects resulting from exposure to the pesticide and other substances that are toxic from a common mechanism when determining the safety of a given pesticide. The science guidance document explains the approach that EPA will use for identifying pesticide chemicals and other substances that are toxic from a common mechanism, for use in assessing the cumulative toxicity posed by such substances. The document is not intended, in any way, to address, much less alter, the burden of proof as established by existing statutes.

#### *N. Criteria that will be Used for Preliminary Grouping of Substances.*

Several commentors [3, 9, 12-16] raised concern regarding EPA's use of structural similarity, mechanism of pesticidal action or common toxic effect as a basis for preliminary grouping of chemicals. These commentors feel that these criteria, alone or in combination, are not scientific and should not be used for grouping chemicals cumulative risk assessment because substances that meet these criteria may not necessarily cause a common toxic effect by a common mechanism of toxicity. The Agency agrees with these commentors. However, the Agency believes that the commentors have misunderstood the Agency's purpose of using either structural similarity, mechanism of pesticidal action, or common toxic effect as described in the draft version of the guidance document. As stated on page 9 (Section III) of the draft document, these criteria, either alone or in combination, will be used for initial grouping only, and **not** final grouping of chemicals for purposes of cumulative risk assessment. The scientific basis for using these criteria for initial grouping is also described in the document. Substances initially grouped using any of these criteria will undergo subsequent rigorous evaluation to determine which substances cause a common toxic effect by a common mechanism of toxicity and which do not. Details of the evaluation are given in the draft document. However, the revised document contains much more text that adds further clarification to how these criteria and other criteria will be applied for initial grouping only, and why they will not be used for final grouping.

## List of Public Commentors and Affiliations

- | <u>I.D. #</u> | <u>Name and Organization</u>                                                                                                            |
|---------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| 1.            | William Patrick Cockrell, Director of Agricultural Policy, <i>Florida Farm Bureau Federation</i> . Gainesville, Florida.                |
| 2.            | Daniel M. Byrd, President, <i>Consultants in Toxicology, Risk Assessment and Product Safety</i> . Washington, D.C.                      |
| 3.            | Louie A. Brown, Jr., Director of Food Safety, <i>California Farm Bureau Federation</i> . Sacramento, California.                        |
| 4.            | Jeannine Kenny, <i>Consumers Union</i> . Washington, D.C.                                                                               |
| 5.            | Shelley Davis, Co-Executive Director, <i>Farmworker Justice Fund, Inc.</i> Washington, D.C.                                             |
| 6.            | David Wallinga, Senior Scientist, <i>Natural Resources Defense Council (NRDC)</i> . Washington, D.C.                                    |
| 7.            | Mark A. Keating, Policy Analyst, <i>Henry A. Wallace Institute for Alternative Agriculture</i> . Greenbelt, Maryland.                   |
| 8.            | Priscilla L. Friedman, <i>DuPont Agricultural Products</i> . Wilmington, Delaware.                                                      |
| 9.            | Louisiana Farm Bureau Federation.                                                                                                       |
| 10.           | Linda M. Johnson, Director of Government Relations, <i>Washington State Farm Bureau</i> . Washington.                                   |
| 11.           | FQPA Implementation Working Group (IWG).                                                                                                |
| 12.           | Charles B. Breckenridge, <i>Novartis Crop Protection, Norvartis</i> . Greensboro, North Carolina.                                       |
| 13.           | Sandra L. Tirey and C.T. (“Kip”) Howlett, Jr. <i>Chemical Manufacturers Association</i> . Arlington, Virginia.                          |
| 14.           | Nancy Erickson, Director of National and Environmental Resources, <i>Illinois Farm Bureau</i> . Illinois.                               |
| 15.           | Andy G. Kurtz, Executive Secretary and Chief Administrative Officer, <i>Arizona Farm Bureau Federation</i> . Phoenix, Arizona.          |
| 16.           | Nancy G. Doerrer, Vice President of Scientific and Policy Programs, <i>American Industrial Health Council (AIHC)</i> . Washington, D.C. |