codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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DISCUSSION PAPER ON THE METHODOLOGY OF CUMULATIVE CUMULATIVE RISK ASSESSMENT

Prepared by the United States of America

INTRODUCTION

At the April 2001 meeting, the CCPR "agreed that the development of cumulative risk assessment required further consideration, especially regarding the development of common understanding of methodology. Therefore, it requested the Delegation of the United States to prepare a paper on this matter for consideration by the next session of the committee."

This brief paper describes the methodology that the United States (EPA) has developed to conduct cumulative risk assessments on pesticide chemicals that share a common mechanism of toxicity. It is an abstract from the recently issued policy document on cumulative risk assessment (USEPA, 2002): "Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity;" available on the internet at:

http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf

While this brief summary concentrates on the cumulative exposures from food sources, please keep in mind that there may be other sources of exposure to pesticide chemicals e.g., residential uses or drinking water.

The first section of this paper provides background information on why the U.S. developed this methodology while the second section explains the steps involved with conducting cumulative risk assessment.

BACKGROUND

In the United States, to establish a pesticide tolerance (maximum residue limit, MRL) or exemption from a tolerance, EPA must determine with reasonable certainty that consumption of raw agricultural commodities and processed foods containing residues of that pesticide will not cause harm to humans, especially infants and children.

Historically, EPA has generally evaluated the safety of pesticides on the basis of **single-chemical** and single-exposure pathway scenarios. This would be analogous to the current situation in Codex. However, an individual may be exposed by multiple pathways to multiple chemicals, some of which may have the same mechanism of toxicity. Therefore, The Food Quality Protection Act provides that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the pesticide chemical on *aggregate* (i.e., total food, drinking water, residential, and other nonoccupational) exposure to the pesticide. EPA is also required to consider available information concerning the ***combined*** **toxic effects (i.e., cumulative effects)** to human health that may result from exposure to chemicals that share a common mechanism of toxicity.

GUIDANCE ON CUMULATIVE RISK ASSESSMENT

On January 16, 2002, EPA published its final guidance on cumulative risk assessment (USEPA, 2002). Among other things, this document describes in a stepwise manner how to go about assessing the cumulative risk for a group of pesticide chemicals that share a common mechanism of toxicity. In applying the steps, it is important for a risk assessor to keep in mind the complexity of the task and the fact that assessing the combined risk for a group of chemicals via multiple pathways is quite different from the traditional single-chemical, single-pathway risk assessment.

Step 1. Identify Common Mechanism Group (CMG). A cumulative risk assessment begins with the identification of a group of chemicals, a Common Mechanism Group or CMG. Such a group consists of chemicals for which scientifically reliable data demonstrate that the same toxic effect occurs in or at the same organ or tissue by essentially the same sequence of major biological events. For example, organophosphorus pesticides affect the nervous system by reducing the ability of cholinesterase to control acetylcholine, and can be considered a CMG.

Step 2. Identify Potential Exposures. Once a Common Mechanism Group is identified, the risk assessor must evaluate, for each Common Mechanism Group member, the potential exposure pathways (i.e., food, drinking water, residential) and exposure routes (oral, inhalation, dermal). This step is an information-intensive analysis, relying on detailed risk assessments for individual CMG member pesticides as well as detailed knowledge of their GAP and actual usage. In addition, the risk assessors' judgment on how an individual might be exposed to multiple CMG member pesticides is critical. For pesticides used on food, the food and drinking water pathways along with the oral exposure route should be considered. The exposure and use data from individual chemical assessments should be evaluated to identify pesticides that are likely to result in significant exposures and to determine where the use of a pesticide overlaps with uses of other pesticides in the CMG. Similarly, those pesticides should be identified that are unlikely to result in cumulative risk because the uses are limited or the expected exposures or effects will not overlap. Some pesticide-pathway/pesticide-route combinations may be left out of the final assessment due to "common sense" considerations. For example, even though the label indicates that pesticide X is used on crop Y resulting in food exposure through the oral route, it may be dropped from the cumulative assessment if pesticide monitoring data show no detectable levels.

The exposure information from individual risk assessments that would be used in making the judgment on the inclusion of a particular pesticide/use combination in the cumulative risk assessment would include: registered uses, tolerances (maximum residue limits), % Acceptable Daily Intake (ADI), significant sources of exposure, average field trial values, monitoring data, %crop treated use patterns, and similar information.

The discussion under Step 7 provides specifics on evaluating exposure, particularly for food.

Step 3: Characterize and Select Common Mechanism Endpoint(s). In Step 1 a Common Mechanism Group was identified. In Step 3, the risk assessor further evaluates the individual pesticides' hazard potential to characterize and to select the common toxic effects that should be considered in the cumulative risk assessment. An important aspect of this hazard assessment is to identify the common effects associated with the common mechanism, the test species/sex that provides the most extensive data on the common effects,

and the exposure routes and durations by which the common toxic effects are manifested. An initial qualitative evaluation of the data will help guide the final selection of common toxic endpoints and choice of dose/response methodology for determining the relative toxic potency among chemical members for quantifying risk.

For example for the organophosphorus pesticides the common toxic effect for which the most appropriate data are available is brain cholinesterase inhibition in the rat. The available data were used to develop relative potency rankings for members of the organophosphorus group.

Step 4: Determine the Need for a Comprehensive Cumulative Risk Assessment. At Step 2 the risk assessor began to consider logical pathways and routes of exposure. During Step 4, the risk assessor carries this further by looking at the necessary scope and depth of the cumulative risk assessment–not every cumulative risk assessment needs to have the same scope or depth. There may be certain Common Mechanism Groups that will require only screening-level assessments to decide whether to invest resources in collecting and analyzing data for a more extensive cumulative risk assessment. Screening-level assessments are more likely to apply to Common Mechanism Groups that comprise only a few chemicals and have low exposure potential given the use patterns of the pesticides.

A screening-level assessment for exposures to food, for example, might assume treatment of 100% of crops with each Common Mechanism Group chemical registered for use on a crop, and assume tolerance-level (maximum residue limit) residues for the exposure component rather than a more refined estimate of actual residue levels from monitoring data. If the evaluation indicates no risk of concern, then no further detailed assessment is necessary.

Step 5: Determine Candidate Cumulative Assessment Group (CAG). At this point in the assessment the risk assessor decides which pesticides within the CMG and exposure-route combinations will be included in the quantitative cumulative risk assessment; this subset is referred to as a Cumulative Assessment Group or CAG. When assessing cumulative risk, a large number of chemicals may increase the complexity and uncertainty of the assessment with no substantial change in total exposure. Additionally, including a large number of chemicals in the refined quantification of risk also may confound the interpretation and utility of the assessment results for risk management decisions.

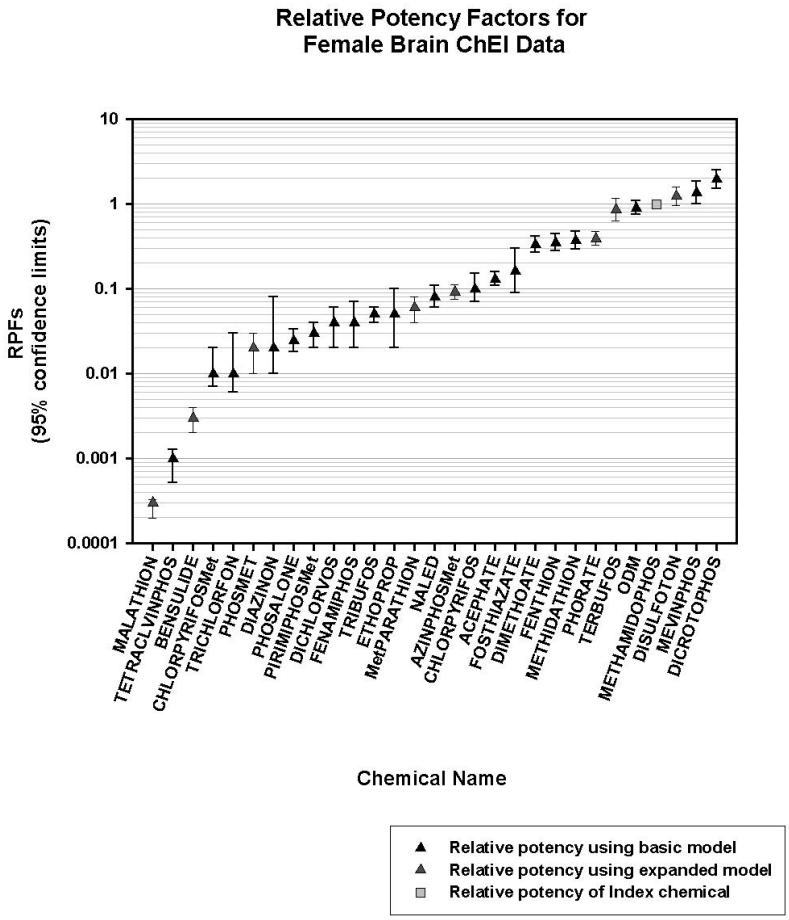
Although a particular chemical, a route or pathway of exposure, or a particular segment of the GAP use may not be included in the final quantitative risk assessment, all chemicals, routes or pathways, and uses should at least be qualitatively assessed. It is critical that all Common Mechanism Group chemicals and their exposure scenarios are accounted for in the cumulative risk assessment with documented reasoning for not focusing on certain subsets within the entire universe of CMG-exposure mechanisms.

A chemical may be excluded from the CAG if its contribution to toxic potency for the common toxic effect is negligible when compared to the other Common Mechanism Group members. Further, a specific pesticide-pathway combination may be removed if it makes negligible contribution to the exposure assessment because of limited use (e.g. dormant spray) or low consumption of a treated commodity.

Step 6: Conduct Dose-response Analyses and Determine Relative Potencies and Points-of-Departure. At Step 6 the risk assessor selects and applies an appropriate dose-response method to evaluate the common mechanism effects and determines the relative toxic potencies of the Common Assessment Group by each exposure route and duration of interest. The point-of -departure is also determined for extrapolating the risk of the Common Assessment Group. A point-of-departure is a dose that can be considered to be in the range of observed responses, without significant extrapolation. A point-of-departure is used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. In other words, it is the dose against which the estimated exposures are compared when conducting the risk assessment.

This is the step where the pesticides in the Common Assessment Group are ranked against an index chemical and relative potency factors are calculated. In the case of the organophosphate pesticides cumulative risk

assessment, methamidophos was used as the index chemical against which the potencies of other members of the CAG group were compared. The relative potency factors are based on a ratio of the point of departure for a given chemical versus that for the index chemical. Please see figure below showing the relative potency factors of the organophosphorus CAG. Members of the CMG with relatively small relative potency factors produced less of the common toxic effect at a given dose level than members with greater potency factors.



Step 7: Develop Detailed Exposure Scenarios for All Routes and Durations. After the members of the Common Assessment Group have been identified, the next step in developing a cumulative risk assessment is to evaluate the exposure scenarios resulting from the uses for each member compound. Single-chemical aggregate assessments should be used to inform the risk assessor in designing the cumulative risk assessment. However, a refined, quantitative, multipesticide cumulative risk assessment should not be

performed by summing single-pesticide aggregate assessments. The cumulative risk assessment should reflect linkages and co-occurrences of use between complementary and competing pesticides.

The questions that need to be addressed in Step 7 include:

- Who is exposed?
- To which chemicals and in what amounts?
- What is the timing of the exposures and do they overlap?
- Do the exposures occur in the same location such that they will be experienced together?
- What are the pathways, routes, and duration by which the exposures will occur?

Step 8: Establish Exposure Input Parameters. In Step 8 the risk assessor, using the exposure scenarios developed in Step 7, determines the magnitude, frequency, and duration for all pertinent exposure pathway/route combinations. Sources of data for food exposure in the U.S. include: USDA's Continuing Survey of Food Intakes by Individuals (CSFII) (1994-1996, 1998); field trial data submitted to EPA from the registrants; monitoring data from USDA's Pesticide Data Program (PDP); the United States Food and Drug Administration's Surveillance Monitoring Data; and Market Basket Monitoring Data.

Step 9: Conduct Final Cumulative Risk Assessment. **During Step 9 the risk assessor combines the exposure data, exposure scenarios, and dose-response characteristics to provide a coherent, realistic picture of the range of potential risks likely to be encountered by exposed populations and their associated probabilities.**

In order to derive cumulative residue (for the dietary food pathway) chemical-specific residue on a food sample is converted to a residue expressed in equivalents of the index compound. Any processing factors for foods are factored in: $\mathbf{Residue_{IE} = Residue_{compound} \times PF \times RPF}$

Where: $Residue_{IE}$ is the compound-specific residue concentration expressed as equivalents of the index compound,

$Residue_{compound}$ is the compound-specific residue concentration,

PF is a compound specific processing factor, and

RPF is the relative potency factor used to normalize the compound-specific residues to the toxicity of the index compound. This factor converts the compound–specific concentration to an index – compound-equivalent basis.

Once all of the residues for a given food or water sample are converted to index compound equivalents, they are summed to give a total cumulative residue value for each sample:

$$\mathbf{Residue\ Cumulative} = \sum_{CAG} \mathbf{Residue}$$

The residue data, normalized to index equivalents and accumulated for each sample, are ready for introduction into a probabilistic risk assessment. Please see the Figure below.

FIGURE 1. CALCULATING THE CUMULATIVE RESIDUE

In this example there are three chemicals in the common mechanism group: A, B, and C. Chemical A has a potency of 5 , Chemical B has a potency of 10 , and Chemical C has a potency of 1. Each chemical has an exposure of 10 ppm; the processing factor is 1. What is the cumulative residue?

To calculate the cumulative residue the first thing you need to know is the "relative potency" that each chemical contributes to the cumulative residue. This is done by choosing an "index chemical" and normalizing its potencies to it. Using our simple example and allowing Chemical A to be the index, the RPFs of A, B, and C would be:

Chemical	Potency	Relative Potency (RPF)*
A (the index chemical)	*5 (index)*	*1*
B	10	0.5
C	1	5

*RPF=Index/Potency

Next, the individual chemical residues ($Residue_{IE}$) are calculated by multiplying the RPFs for each chemical by the residue measured:

Chemical	RPF	Residues Measured	$Residue_{IE}$ Corrected for Potency
A	1	10	10
B	0.5	10	5

The normalized residue values are then combined with consumption data to obtain a measure of exposure which is expressed in the common index chemical units.

The Margin of Exposure, a measure of risk (MOE) for the CAG, can then be calculated by comparing exposure to the point-of-departure (POD) e.g., a BMD_{10} (benchmark dose 10; or dosage at which the level of cholinesterase inhibition is 10%):

$$\mathbf{MOE = POD_{Index} : \sum_{CAG} Exposure}$$

Step 10: Conduct Characterization of Cumulative Risk. Risk characterization is the interpretation phase of the assessment process. It is an integrative process that brings together the assessments of hazard, dose-response, and exposure to characterize risk estimates for the exposure scenarios of interest, and presents the major results and conclusions of the risk assessment as well as the associated uncertainties. A risk characterization provides a discussion for a diverse audience that minimizes the use of technical terms. It is an appraisal of the science that supports the risk manager in making public health decisions.

FURTHER CONSIDERATION

The United States is aware that the international community is interested in examining the feasibility of conducting cumulative risk assessment. The United States is willing to participate in the preparation of a paper on approaches to cumulative risk assessment at the international level for consideration at the next session of the CCPR.

REFERENCE

U.S. Environmental Protection Agency. 2002. "Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity;" January 14, 2002. 67 FR 2210. Office of Pesticide Programs, Office of Prevention, Pesticides, and Toxic Substances. Washington, DC. Available:

http://www.epa.gov/fedrgstr/EPA-PEST/2002/January/Day-16/p959.htm