FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL MEETING

A Set of Scientific Issues Being Considered by the Agency in Connection with Linear Low Dose Extrapolation for Cancer Risk Decisions: Sources of Uncertainty and How They Affect the Precision of Risk Estimates

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency in connection with Linear Low Dose Extrapolation for Cancer Risk Decisions: Sources of Uncertainty and How They Affect the Precision of Risk Estimates. The review was conducted in an open meeting held in Arlington, Virginia, on July 29, 1998. The meeting was chaired by Dr. Ernest E. McConnell (ToxPath, Inc.). Other Panel Members present were: Dr. Janice Chambers (Mississippi State University); Dr. Rory Conolly (Chemical Industry Institute of Toxicology-CIIT); Dr. Michael Cunningham (National Institute of Environmental Health Sciences-NIEHS); Dr. Amira Eldefrawi (University of Maryland School of Medicine); Dr. David Gaylor (National Center for Toxicological Research); Dr. Gordon Hard (American Health Foundation); Dr. Fumio Matsumura (University of California); Dr. Christopher Portier (National Institute of Environmental Health Sciences-NIEHS); Dr. Jay Schreider (California Department of Pesticide Regulation); Dr. Mary Anna Thrall (Colorado State University); and Dr. John Wargo (Yale University).

Public Notice of the meeting was published in the Federal Register on June 19, 1998.

Oral statements were received from the following:

Dr. Christine Chaisson (TAS-Environ)

Dr. Elliot Gordon (Makhteshim-Agan of North American, Inc.)

Dr. David Wallinga (Natural Resources Defense Council)

Written statements were received from the following:

Natural Resources Defense Council

Questions to the Scientific Advisory Panel

The Agency posed the following questions to the SAP regarding Linear Low Dose Extrapolation for Cancer Risk Decisions: Sources of Uncertainty and How They Affect the Precision of Risk Estimates.

The cancer risk assessment using the upper-bound estimates contains inherent uncertainties due to the limitations of scientific knowledge, available data, or choice of models. As discussed in the book, *Science and Judgment in Risk Assessment* (National Research Council, 1994), some claim EPA's risk assessments reflect "cascading conservatism," layering an overly conservative assumption upon another. However, the Council also cautions against

underestimating the true risk by stating,

"[T]his mathematical truism that the more uncertainty, the greater the level of conservatism required not to underestimate the mean,... If each of a series of uncertain quantities is distributed in such a way that a reasonable conservative estimator (say, the 95th percentile) approximates or even falls below the mean of that quantity, then the more steps in the cascade the less conservative the output becomes with respect to the correct risk-neutral estimator" (p. 608 in *Science and Judgment in Risk Assessment*).

1) Does the presentation of data in the *Examples* in this paper adequately define the potential impact of uncertainties on the risk? Given that the uncertainties may be qualitatively defined with respect to the direction and magnitude of the risk estimate, but may be unquantifiable, is the presentation of the uncertainties in the example risk characterizations adequate?

The SAP agrees that a brief summary for each cancer risk assessment could be useful. Presumably, the abbreviated summary is not intended to replace a detailed summary of the risk characterization section of a risk assessment. Apparently, an abbreviated summary is intended primarily for risk managers and also should be useful for individuals who may or may not be familiar with cancer risk assessment techniques. The SAP recognizes that the level of detail for an abbreviated summary is difficult to ascertain. The abbreviated summary should discuss each of the major sources of uncertainty in at least a qualitative sense. The full risk characterization section of a risk assessment will present more detail regarding the various sources of uncertainty and their impact on the risk estimate; therefore, it would seem that the risk manager would have to use this latter document to make an informed decision. The abbreviated description may be of limited use to the risk manager other than as an executive summary. On the other hand, it may be useful for the public and others who also will use the information.

The SAP cannot give more detailed suggestions for constructing an abbreviated cancer risk assessment summary. This should be an iterative process that is revised based on feedback from risk managers.

2) Could the Panel comment of the appropriateness of presenting the rounded numeric cancer risk estimate (e.g. 10^{-6}) as a tool to the risk manager as part of the risk characterization?

The SAP recognizes that the uncertainty and variability in cancer risk estimates is so large that estimates expressed only with one significant figure are justified. That is, estimates should be expressed as a single integer times 10-x, where x also is an integer.

3) Could the Panel give guidance on how uncertainty should be handled in the risk assessment?

Point (best) estimates of risk along with a range denoting the extent of uncertainty and variability are most desirable. This may only be possible when adequate mechanistic information, pharmacokinetic data, and human exposure data are available. Mechanistic models can improve

risk assessments by removing assumptions and utilizing a broader spectrum of data. In this way, they truly reduce uncertainty. In general, there is a direct relationship between the amount of mechanistic data used to develop a risk assessment and the level of precision with which a risk estimate can be expressed. However, one should be cautious in attributing a reduction in conservatism to the use of any alternative modeling approach. It is difficult to characterize conservatism without data for humans.

As noted by the Agency, some uncertainty may not be quantifiable. The risk characterization section of the risk assessment should contain a detailed description of the various sources of uncertainty and their impact on the risk estimates. In some cases, when uncertainty is due to a choice between different values, assumptions, data sets, tumor sites, etc., it may be appropriate to indicate the impact of alternatives. This can be accomplished descriptively or by presenting a range of risk estimates resulting from the different values or assumptions. If uncertainty is quantifiable, it should be presented. These issues are discussed in the EPA documents on Policy and Guidance on Risk Characterization.

The SAP recognizes that, in general, it may only be possible to provide some type of upper bound estimates of cancer risk that reflect the uncertainty and variability of existing data. Even so, a range should accompany this upper bound to indicate the likely direction (higher, lower, or both) and the confidence (not in a statistical sense) of this risk estimate, possibly indicating the magnitude of the uncertainty and variation.

Uncertainty of cancer risk estimates, without ancillary mechanistic and/or pharmacokinetic data, is likely to be at least an order of magnitude and may be illustrated by calculating risk estimates with various assumptions for affected organs/tissues from all species/sex combinations tested along with various plausible exposure scenarios. The SAP suggests that a better approach than using the results from a single bioassay may be to consider all of the upper bound slope estimates derived from the available cancer data and report a value in the central range along with an upper bound cancer risk estimate.

It is important to separate variability from uncertainty. Variability among measurements can be addressed by usual statistical methods, whereas uncertainty can only be addressed through use of assumptions that influence the estimate of the cancer risk slope.

4) Could the Panel give guidance on alternative methods of expressing cancer risk estimates (e.g. rounding to half orders of magnitude; 10^{-6}, $10^{-6.5}$, 10^{-7}).

The Panel addressed this question in response to question #2.

FOR THE CHAIRPERSON:

Certified as an accurate report of findings:

Paul I. Lewis

Designated Federal Official

FIFRA/Scientific Advisory Panel

DATE:_____