4-27-89

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

APR 27 1989

MEMORANDUM

Subject: Follow up to the Third Peer Review of Atrazine

From: Marion P. Copley, D.V.M.
Section Head, Section 2
Toxicology Branch I (IRS), HED (TS-769C)

To: Robert Taylor (PM 25)
Registration Division (TS-767C)

and

Jude Andreasen (TS-767C)
Special Review Branch
Special Review and Reregistration Division

The Health Effects Division Peer Review Committee reevaluated their decision of 11/22/88 with respect to the classification of the carcinogenicity of Atrazine.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated)

William Burnam
Reto Engler
Judith Hauswirth
Marcia van Gemert
Marion Copley
Kerry Dearfield
Esther Rinde

V/17

John Quest

Lynnard Slaughter

Robert Beliles

Richard Hill

Richard Levy

Diane Beal

B. Material Reviewed:

Previous Peer Review documents

C. Conclusions:

Upon further review of the hormonal data (or lack thereof), the Health Effects Division Peer Review Committee feels that there is not sufficient justification for varying from the otherwise supported position of using a Q_1*. Therefore, they concluded that the oncogenic risks due to Atrazine should be evaluated using a linearized low dose extrapolation method, Weibull model (due to survival disparity).. This method of quantification is justified due to (1) the induction of malignant mammary gland tumors and possible decreased latency for their appearance and (2) positive SAR data for mammary gland tumors.

In summary:

1) Atrazine should be classified as a category C oncogen.

2) Risks should be characterized using the Weibull model.

This applies until additional data (see previous peer review document) are submitted to elucidate the most appropriate method of risk characterization.

The Committee strongly recommends that the registrant continue to generate data supporting a hormonal mechanism and submit it to the Agency in a timely manner. The Committee also looks favorably upon the Registrant's decision to conduct an oncogenicity study in the Fischer rat. This information is required for the Committee to determine the most appropriate alternate method of risk determination.

COPLEY\PC6\ATRAZINE\PR3_1.RSP, 3/16//20/89

Marion Copley

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

September 14, 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Transmittal of the Final FIFRA Scientific Advisory Panel Reports on the September 7, 1988 Meeting

TO: Douglas D. Campt, Director
Office of Pesticide Programs (TS-766C)

The above mentioned meeting of the FIFRA Scientific Advisory Panel (SAP) was an open meeting held in Arlington, Virginia to review the following topics:

A Set of Scientific Issues Being Considered by the Agency in Connection with the Special Review of Aldicarb;

A Set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review of Atrazine as a Class C Oncogen;

A Set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review of Isoxaben as a Class C Oncogen;

A Set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review of Prochloraz as a Class C Oncogen; and

A Set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review of Rotenone as a Class D Oncogen.

Please find attached the Panel's final reports on the agenda items discussed at the meeting.

Stephen L. Johnson
Executive Secretary
FIFRA Scientific Advisory Panel

Attachments

cc: Panel Members
John A. Moore
Vic Kimm
Jim Roelofs
Susan H. Wayland
Ted Farber
Al Heir
Mary Beatty, CMO
EPA Participants

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FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review Classification of Atrazine as a Class C Oncogen

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of a set of scientific issues being considered by the Environmental Protection Agency's peer review classification of atrazine as a Class C oncogen. The review was conducted in an open meeting held in Arlington, Virginia, on September 7, 1988. All Panel members, except Dr. Thomas W. Clarkson, were present for the review.

Public notice of the meeting was published in the Federal Register on Monday, July 25, 1988.

Oral statements were received from staff of the Environmental Protection Agency and from Dr. James Stephens of Ciba-Geigy and Dr. Robert Squire of Johns Hopkins University representing Ciba-Geigy.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF PANEL RECOMMENDATIONS

Atrazine

The Agency requested the Panel to focus its attention upon a scientific issue relating to the Peer Review of atrazine. There follows the issues and the Panel's response to the issues:

Issue:

Atrazine was classified by the Toxicology Branch Peer Review Committee as C (Possible Human Carcinogen), based on: 1) increased incidence of tumors in one sex (primarily malignant tumors in females); 2) a possible mutagenicity concern and 3) a structure activity relationship with agents demonstrated to produce mammary tumors. The tumors associated with atrazine included mammary fibroadenoma/adenocarcinomas and adenocarcinoma in female rats.

1. The Agency requests any comments the Panel may wish to make regarding the biological significance of the mammary tumors in Sprague-Dawley rat.

Panel Response:

The Panel believes that mammary tumors in Sprague-Dawley rats should be considered as a biologically significant endpoint. As such, one relies not only on statistics to determine whether or not an effect is compound related, but also biological plausibility. The variability of this endpoint and its potential for secondary hormonal influence make this an important issue.

ISSUE:

2. Does the Panel have any specific comments regarding our overall assessment of the weight of evidence and classification of this chemical in accordance with the Agency's Guidelines for Carcinogen Risk Assessment.

Panel Response:

The Panel agrees with the Agency's classification of atrazine as a category C oncogen. We are, however, concerned about performing quantitative risk assessment (QRA) on the mammary tumor data. The Sprague-Dawley rat is clearly different from humans in sensitivity, contrary to an inherent assumption in QRA. The issue is further complicated by the influence of secondary factors such as endocrine imbalance at high, but not low doses. Therefore, the Panel recommends that QRA not be done on atrazine.

FOR THE CHAIRMAN:

Certified as an accurate report of Findings:

Stephen L. Johnson
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 9-14-88

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Special Review of Aldicarb

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of the data base supporting the Environmental Protection Agency's (EPA) preliminary decision to cancel registrations of aldicarb unless certain modifications to the terms and conditions of registration are made by the registrant. The review was conducted in an open meeting held in Arlington, Virginia, on September 7, 1988. All Panel members, except Dr. Thomas W. Clarkson, were present for the review. In addition, Drs. Jack Fischer, U. S. Geological Survey, and George Hallberg, Iowa Department of Natural Resources, served as ad hoc members of the Panel.

Public notice of the meeting was published in the Federal Register on Monday, July 25, 1988.

Oral statements were received from staff of the Environmental Protection Agency and from Mr. Stephen A. Schmotzer of Rhone-Poulenc AG Company, Dr. Andrew J. Klein of Monsanto Company, and Dr. Olivier Banton of the University of Quebec, Canada.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF PANEL RECOMMENDATIONS

Aldicarb

The Agency requested the Panel to focus its attention upon a set of scientific issues relating to the Special Review of aldicarb. There follows some general comments by the Panel, the issues and the Panel's responses to the issues:

GENERAL COMMENTS

The Panel supports the concept of a State Management Plan for protecting groundwater. The process developed for aldicarb appears to adequately protect human health and the groundwater environment, and it should lead to a more scientifically sound program. It can be individualized to the soil, geologic, climate and use conditions of local areas. Furthermore, the process should provide incentive for the registrant to generate appropriate data for proper environmental management and to work with states to develop acceptable management plans.

Given the environmental fate and toxicological data for aldicarb, the Panel recommends the Agency consider cancellation of aldicarb in states, with identified vulnerable groundwater regions, that decline to submit a State Management Plan.

ISSUE:

The Agency requests any comments the Panel wishes to make on the methodology the Agency used in its ground water assessment. Specifically, the Panel is asked to comment on the use of Heath Regions, DRASTIC, crop use practices, and county level analyses for a ground water risk assessment. Are the parameters used in the Heath Region and county approaches scientifically justifiable for determining the vulnerability of ground water to leaching by a pesticide?

Panel Response:

METHODS USED FOR GROUNDWATER VULNERABILITY ASSESSMENT

The methods employed have been discussed, in part, by other panels and advisory groups, such as the National Pesticide Survey and Ag-chemicals and Groundwater Strategy, so elaborate comments do not seem necessary. All of these approaches are subject to criticism, and none are entirely satisfactory for an area, or for a compound about which a great deal is known. However, some of the methods are valid and reasonable for a data base that provides a nation-wide overview that is consistent among regions of the country. The two "methods," the "Heath Region" and county-based analyses, as they were used by the Agency, are not wholly different, and both employ a matrix of input data, some of which are common to both. The fundamental difference in the methods is the scale of geographic region used to define areas (states) that indicate the need to develop a local Aldicarb Management Plan.

We recommend that: 1. the Heath regions not be utilized because these regions are far too generalized to be used for this purpose; 2. the Agency continue to use a county-based approach, and also continue to utilize other pertinent available information, or require registrants, or states in their management plans, to provide more detailed information where needed. The county-based method should include a rating matrix consisting of:

A. County DRASTIC scores. While this "index model" has its shortcomings, it has been agreed that it will provide a consistent framework, nationally, as developed for the National Pesticide Survey;

B. Groundwater monitoring data;

C. Cropping data and pesticide usage data;

D. Pertinent climatic data (see comments on parameters);

E. If available, other detailed modeling (e.g., PRZM) of field data, or soil distribution information as compiled or developed by the Agency, Registrant, or other involved/ interested parties.

For aldicarb, the Agency's composite county-based assessment of vulnerability indicated that an estimated 15-24 states would require a Management Plan. The Agency should review the data provided by Rhone-Poulenc, which indicated "vulnerable" areas of aldicarb use in 37 states, based on sub-county evaluation of soil-types. These added data may necessitate that additional states develop a Management Plan. This also illustrates the shortcomings of the county-based assessment; important, but small vulnerable areas may not be apparent in county averages. Hence, the Agency should review ways to overcome this shortcoming for future reviews of other compounds. For aldicarb, the Agency's review, coupled with information supplied by the registrant, is sufficient.

The results of county-based assessment should not be used to indicate that <u>only</u> the counties identified require Management Plans. Rather the process should be used to identify states requiring State Management Plans, the general vulnerable areas within states, and environmental factors that states should address in their Management Plan.

The suggestion was made that PRZM be used, in addition to, or possibly in lieu of DRASTIC, because a "mechanistic" model may be more exact than Index models. This, in our opinion, is not a viable option for the Agency for nation-wide overviews, for the following reasons: 1. the data and time requirements of such models are too great; 2. PRZM is a point/soil-specific model, and cannot readily provide the overview sought because of the many analyses needed to cover the range of national conditions;

3. PRZM only models one facet of water/solute transport and is inadequate for preferential flow; 4. PRZM or DRASTIC, or any model has simplifying assumptions and requires that arbitrary judgements be made regarding poorly quantified variables.

PRZM and other models can be useful to provide a sensitivity analysis to identify parameters for consideration in the Management Plans or evaluation of alternative management schemes. Clearly, these can be used as a supplemental part of the process.

ARE THE PARAMETERS USED IN THE AGENCY'S GROUNDWATER VULNERABILITY ASSESSMENTS SCIENTIFICALLY JUSTIFIABLE?

We believe that the parameters themselves are scientifically justifiable. However, the Agency should not lose sight of the fact that the parameters used in DRASTIC vary substantially within single fields, let alone across counties and states. Therefore, assigning a single vulnerability rating to a county based on DRASTIC will lead to inappropriate assessments for many areas within counties. Because of this situation, the Agency should not rely wholly on DRASTIC rankings, but should make use of additional data (as discussed earlier), and should allow state governments flexibility in developing Management Plans. Moreover, the Agency should consider supporting programs within the Agency or in other Agencies that will lead to improvement in the hydrogeologic data base in order to provide a more defensible foundation for the application of DRASTIC.

We note that temperature, an important parameter in aldicarb degradation, is incorporated in ground water vulnerability for Heath regions but not in the assessment based on counties. We do not endorse the use of Heath regions, but we do suggest that temperature be incorporated in any scheme for determining groundwater vulnerability for aldicarb.

The vulnerability analyses do not appear to consider chemical reactions in the subsurface. We suppose this relates to the lack of data on this subject. There is little doubt, however, that chemical reactions play important roles in the fate and transport of aldicarb. Therefore, we anticipate that State Management Plans will move toward determining the nature of these reactions and incorporate that information in vulnerability assessments. The Agency should be receptive to these initiatives.

In making assessments of vulnerability, the Agency compared DRASTIC index scores to a simple system using only leachability of topsoil and depth to groundwater. The scores from the two approaches were very similar, which is a little disconcerting in itself, but we question the emphasis on topsoil. Although this is the soil layer in which most reactions can be expected to

occur, it is in many cases rather thin--on the order of a foot or two. The unsaturated soil below the topsoil is usually much thicker and this zone has not received the attention it deserves in evaluating the fate and transport of aldicarb. For example, in the material provided to us, we found little evidence of unsaturated zone monitoring. We believe that such sampling would be an appropriate element in additional monitoring and State Management Plans. It should not be assumed that because saturated zone monitoring does not reveal detectable levels of aldicarb that the constituent is not moving downward in the soil profile.

ISSUE:

The Agency also requests any comments the Panel wishes to make on the assumptions the Agency used in determining the risks to the population from consuming contaminated ground water. These assumptions are: 1) the daily intake of water is composed of two separate doses, and 2) the estimated NOEL of 0.01 mg/kg for cholinesterase inhibition is accurate.

Panel Response:

The Panel believes that calculations of water intake as two daily doses is an acceptable (although conservative) first approximation on the basis of currently available information.

Regarding the NOEL for cholinesterase inhibition, the Panel urges the Agency to review all available data (e.g., the new data from NCI regarding water intake, the differential toxicity of specific breakdown products present in water samples, etc.) prior to reaching a final conclusion.

ADDITIONAL COMMENTS

We believe that a provision to prohibit the handling and application of aldicarb within a certain distance of a well is justified. We are not convinced, however, that it is appropriate to specify that distance, e.g., 300 feet, on a national basis. It would appear to be more consistent to provide the same flexibility to states and counties that the overall strategy allows, i.e., development of state-generated, EPA-approved setback based on ground water vulnerability.

The Agency should encourage an increase in monitoring, both in the saturated and unsaturated zones, the collection and accumulation of hydrogeologic data that will eventually permit assessment of vulnerability on smaller scales, e.g., sections and quarter sections.

The Agency should consider the potential hazards of aldicarb to nontarget soil organisms and to wild animals from secondary poisoning or direct consumption of the granulated compound.

FOR THE CHAIRMAN:

Certified as an accurate report of Findings:

Stephen L. Johnson
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 9-14-88

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review Classification of Isoxaben as a Class C Oncogen

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of a set of scientific issues being considered by the Environmental Protection Agency's peer review classification of Isoxaben as a Class C oncogen. The review was conducted in an open meeting held in Arlington, Virginia, on September 7, 1988. All Panel members, except Dr. Thomas W. Clarkson, were present for the review.

Public notice of the meeting was published in the Federal Register on Monday, July 25, 1988.

Oral statements were received from staff of the Environmental Protection Agency and from Dr. J. L. Emmerson of Elanco Products Company and Dr. Joseph V. Rodricks of ENVIRON Corporation representing Elanco Products Company.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF PANEL RECOMMENDATIONS

Isoxaben

The Agency requested the Panel to focus its attention upon a scientific issue relating to the Peer Review of isoxaben. There follows the issues and the Panel's response to the issues:

Issue:

1. The Agency requests any comments the panel wishes to make regarding the assessment of the weight of evidence and classification of Isoxaben, with respect to Agency Guidelines for Carcinogen Risk Assessment.

Panel Response:

The Scientific Advisory Panel recognizes that the data base for evaluation of Isoxaben is unusual, i.e., the dose range used in the tumorigenesis studies was broad but the lack of a dose between 1,000 and 12,500 parts per million made assessment of the oncogenic classification difficult. Since significant hepatocarcinogenesis was observed only at the highest dose of Isoxaben, a level at which hepatotoxicity (elevated serum enzymes, nodular hyperplasia , fatty degeneration) occurred, the Scientific Advisory Panel believes that the proper classification of this agent should be D.

ISSUE:

2. The Agency requests any specific comments the Panel may have on the conclusion that the data on oncogenicity of Isoxaben does not warrant a conventional quantification of human risk? Alternatively, what methods can the Panel suggest to establish exposure levels which represent acceptable/minimal risks to humans?

Panel Response:

The Scientific Advisory Panel recommends the use of the RfD (reference dose) approach for the setting of human exposure levels.

FOR THE CHAIRMAN:

Certified as an accurate report of Findings:

Stephen L. Johnson
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 9-14-88

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review Classification of Prochloraz as a Class C Oncogen

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of a set of scientific issues being considered by the Environmental Protection Agency's peer review classification of prochloraz as a Class C oncogen. The review was conducted in an open meeting held in Arlington, Virginia, on September 7, 1988. All Panel members, except Dr. Thomas W. Clarkson, were present for the review.

Public notice of the meeting was published in the Federal Register on Monday, July 25, 1988.

Oral statements were received from staff of the Environmental Protection Agency.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF PANEL RECOMMENDATIONS

Prochloraz

The Agency requested the Panel to focus its attention upon a scientific issue relating to the Peer Review of prochloraz There follows the issue and the Panel's response to the issue:

Issue:

Prochloraz was classified by the Toxicology Branch Peer Review Committee as a group C carcinogen (possible human carcinogen), based on significant and dose-related increases in liver adenomas and carcinomas in both sexes of CD-1 mice.

Does the Panel have any specific comments regarding our overall assessment of the weight of evidence and classification of this chemical in accordance with the Agency's Guidelines for Carcinogen Risk Assessment?

Panel Response:

The Scientific Advisory Panel is in agreement with the assessment of evidence and classification of prochloraz as a Group C carcinogen.

FOR THE CHAIRMAN:

Certified as an accurate report of Findings:

Stephen L. Johnson
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 9-14-88

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review Classification of Rotenone as a Class D Oncogen

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of a set of scientific issues being considered by the Environmental Protection Agency's peer review classification of rotenone as a Class D oncogen. The review was conducted in an open meeting held in Arlington, Virginia, on September 7, 1988. All Panel members, except Dr. Thomas W. Clarkson, were present for the review.

Public notice of the meeting was published in the Federal Register on Monday, July 25, 1988.

Oral statements were received from staff of the Environmental Protection Agency and Dr. Dieter Riedel of the Health and Welfare of Canada and Ms. Rosalie Schnick of the U.S. Fish and Wildlife Service.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF PANEL RECOMMENDATIONS

Rotenone

The Agency requested the Panel to focus its attention upon a scientific issue relating to the Peer Review of rotenone. There follows the issue and the Panel's response to the issue:

Issue:

Rotenone was classified by the Toxicology Branch Peer Review Committee as a group D carcinogen. The Agency requests any specific comments the Panel may have on the assessment of the weight of evidence and classification of rotenone with respect to Agency Guidelines for Carcinogen Risk Assessment.

Panel Response:

The Scientific Advisory Panel believes that the data on oncogenicity of rotenone does not warrant its classification as a Group D oncogen. The Panel endorses the classification of rotenone in Group E because of lack of evidence of carcinogenicity in life-time studies in rats and mice.

Although not pertinent to classification as to oncogenicity, the SAP is aware of the potential effects of the use of rotenone on sensitive or threatened and endangered species of wildlife that depend on "unwanted" fish populations for major portions of their dietary intake. The Agency should consider these effects in the upcoming Registration Standard Process for rotenone.

FOR THE CHAIRMAN:

Certified as an accurate report of Findings:

Stephen L. Johnson
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 9-14-88