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

OCT 2 1991

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Transmittal of the Final FIFRA Scientific Advisory Panel Report on the September 18, 1991, Meeting

FROM: Robert B. Jaeger RBJ 10/2/91
Designated Federal Official
FIFRA Scientific Advisory Panel

TO: Douglas D. Campt
Director
Office of Pesticide Programs

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

1. A set of Scientific Issues Regarding the Agency Peer Review Committee's Classification of Prodiamine as a Group C Carcinogen.

2. A set of Scientific Issues Regarding the Agency Peer Review Committee's Classification of Metolachlor as a Group C Carcinogen.

3. A set of Scientific Issues Regarding the Agency Peer Review Committee's Classification of Triphenyltin Hydroxide (TPTH) as a Group B_2, Probable Human Carcinogen.

4. A set of Scientific Issues Regarding the Agency Peer Review Committee's Review of a Dose-Response Risk Assessment for the Carcinogenic Effects of Ethylene Thiourea (ETU) in Rats and MIce.

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

Attachment

cc: Panel Members
Linda J. Fisher
Victor J. Kimm
Susan Wayland
Penny Fenner-Crisp
Mike Ioannou
Steve Dapson
John Doherty
Reto Engler
Don Barnes
Al Heier
Mary Beatty

Freedom of Information (Susan Lawrence)

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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 Metolachlor as a Group C Carcinogen

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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 regarding the Environmental Protection Agency Peer Review Committee's classification of Metolachlor as a Group C Carcinogen. The review was conducted in an open meeting held in Arlington, Virginia, on September 18, 1991. Panel members present for the review were Dr. Edward Bresnick (Chairman), Dr. Mont Juchau, Dr. Peter Magee, Dr. Curtis Travis, and Dr. John Wilson. In addition, Dr. Edmund Crouch of Cambridge Environmental, Inc, Dr. Richard Griesemer and Dr. Christopher Portier of the National Institute of Environmental Health Sciences, served as Agency representatives; and Dr. Dale Hattis of Clark University, and Dr. Ernest McConnell of Raleigh, NC served as Special Government Employees on the Panel.

Public notice of the meeting was published in two Federal Registers on Friday, August 23, and Friday, September 13, 1991.

Oral presentations were made by Dr. James Swenberg of the University of North Carolina; Dr. James Stevens, Dr. Darrell Sumner, and Dr. Charles Breckenridge of CIBA-GEIGY Corporation; and Dr. Eugene Logusch and Dr. Dennis Ward of Monsanto Agricultural Company.

Written comments were received from Dr. James Swenberg of the University of North Carolina; CIBA-GEIGY Corporation; and Monsanto Agricultural 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

The Agency requested comments from the Panel relative to the Peer Review Committee's recommendations for the carcinogenicity evaluation of metolachlor.

Specifically:

Does the Panel have any comments regarding the weight given to Structure-Activity Relationships (SAR), particularly when the same effects are evident in the same species?

Panel Response:

The Panel considered two issues to be central to the question posed by the Agency:

1. Is the effect of METOLACHLOR ("MET") well established in animals with regard to liver or nasal turbinate tumors?; and

2. Are SAR and metabolism findings important for interpretation of adverse effects from MET?

#1 The Panel considered the tumor incidence in female rats that had been treated with high doses of MET to be adequate in assessing its carcinogenic effect in that species. A positive dose-dependent trend was also evident in the treated male rats. In both, the tumors were benign and hyperplasia was evident.

The incidence of nasal turbinate tumors in rats was low and not statistically significant. Although no evidence for nasal turbinate tumorigenicity of MET existed, other structurally related herbicides do cause nasal turbinate tumors. This raised some concern of the Panel as to the biological significance of the small but statistically insignificant number of nasal tumors found in the metolachlor-treated animals.

#2 The similarity of chemical structure in these herbicides may not result in a similarity in metabolism, either in a qualitative or quantitative sense, or in biologic effect. Evidence exists that metabolites of metolachlor are in fact different from those of either of the other dialkyl-benzylamino herbicides, for example, the lack of formation of quinone imine from metolachlor. To further distinguish MET from other compounds, the pharmacokinetics were stated as dose dependent. However, this was based upon the amount of total 14C in urine (the individual metabolites were not identified in this study). The assertion that MET went from a 2 to a 1 compartment open model at high doses is highly presumptuous and may have little to do with the SAR issue.

The Panel considered the evidence to be minimal but sufficient for the classification of MET as a Group C carcinogen.

FOR THE CHAIRMAN:

Certified as an accurate report of Findings:

Robert B. Jaeger _____ 10/2/91 _____

Robert B. Jaeger
Designated Federal Official
FIFRA Scientific Advisory Panel

(date)