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

OCT 2

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 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)

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with a Dose-Response Analysis for Ethylene Thiourea (ETU)

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 review of a dose-response risk assessment for the carcinogenic effects of Ethylene Thiourea (ETU) in rats and mice. 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 and Dr. Peter Magee (Dr. Curtis Travis was recused from the proceedings). 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 the EBDC/ETU Task Force: Mr. Edward Ruckert, Dr. Gary Flamm, Dr. Thomas Starr, Dr. Robert Sielken, Jr., and Dr. Kenny Crump.

Written comments were received from the EBDC/ETU Task Force members: Atochem North America, Inc., BASF Corporation, E.I. du Pont de Nemours and Company, and Rohm and Haas Company.

NOTE: Prior to the Panel's discussion and deliberations on ETU, an announcement was made that the ETU Task Force had expressed concern over a possible conflict of interest regarding Dr. Travis. Although discussions between the Designated Federal Official (DFO, FIFRA SAP) and the EPA Office of General Counsel (OGC Ethics Office), prior to the afternoon discussion of ETU, failed to substantiate the alleged conflict of interest, Dr. Travis informed both the DFO and the Chairman of the FIFRA SAP that he recused himself from all proceedings on ETU before the Panel, both public and private discussions of the issues. This does not reflect any real conflict of interest regarding the matter before the Panel, but rather the belief by Dr. Travis that (1) there were several other experts on the Panel who were equally capable of discussing the issues on ETU, (2) at such late notice, it gave the "appearance" of a problem, (3) when there is

no benefit to be gained there should be no risks taken, and (4) the matter deserved more detailed written response by OGC to verify there is no conflict of interest, and to prevent unnecessarily impugning the reputation and scientific integrity of the FIFRA SAP.

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 appropriate use of the (33)100 ppm dose group for risk characterization considering that:

- o this group represents several design flaws,
- o necessitates the exclusion of the highest dose group (1000 ppm) because of the lack of (linearized multistage) model fit,
- o but provides some valid and significant biological data at a lower exposure level and thus may be more relevant for low dose extrapolation than data points with high exposure and nearly saturated tumor response?

Specifically:

The Panel was asked to provide, to the extent possible, the scientific arguments for either inclusion or exclusion of the low dose data point in the dose response assessment.

Panel Response:

The Panel is of the opinion that adequate data should always be included unless there is strong reason to exclude them. In this case, there is a strong reason for the Agency's standard approach which results in the exclusion of the highest dose group since its inclusion was associated with gross distortion of estimates of the probable effects at lower doses when used in the Agency's standard dose-response formula (e.g., linearized multistage model).

The Panel felt strongly that the data from the 33/100 ppm group should be included in the analyses. The arguments for inclusion are:

1. The usual form of the linearized multistage model is probably not statistically appropriate for use in calculating Q_1^* if all data except the control show over 90% rates of cancer.

2. Whole life exposure (the diagonal in the factorial experimental design) is probably most appropriate for utilization for public health purposes.

The principal argument against using the low dose point is potential litter bias, and this appears to have been relatively well addressed in the analyses presented to the Panel.

The Panel noted that the available data would not likely enable the robust detection of an interactive effect between the effects of pre-weaning and post-weaning exposure for the liver cancer endpoint if such an effect were to have been present. Despite the fact that not enough information exists to statistically evaluate the potential for a protective effect of the prenatal exposure, such an effect is not seen in the high dose groups. There is also supporting evidence for this view since no consistent patterns of interaction were observed in other tissues.

The Panel was informed during the meeting that some pharmacokinetic data exist for ETU. The Panel suggested that the analysis could be improved by using (and if necessary gathering) pharmacokinetic data which would allow expression of the results in terms of the internal dose of ETU [e.g. area under a curve (AUC) of concentration vs. time following comparable oral exposures, if possible based on experiments in subchronically dosed animals]. Pharmacodynamic data (e.g., the dynamics of thyroid hormone changes and cell proliferation responses in the thyroid and liver) may also aid in producing an improved estimation of low dose risks.

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)