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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Third Peer Review of Benomyl/MBC

FROM: John A. Quest, Ph.D., Head JAQ 2/14/89
Science Support Staff
Science Analysis and Coordination Branch
Health Effects Division (TS-769C)

TO: Jane Mitchell, PM Team 21
Fungicide-Herbicide Branch
Registration Division (TS-767C)

The Health Effects Division Peer Review Committee met on January 25, 1989 to discuss whether or not the tumor data on Benomyl/MBC necessitated a quantification of oncogenic risk.

A. Individuals in Attendance

1. Peer Review Committee: (Signature indicates concurrence with peer review unless otherwise stated.)

Robert Beliles: Robert Beliles

William Burnam: William L. Burnam

Marion P. Copley: Marion P. Copley

Bernice Fisher: Bernice Fisher

Marcia van Gemert: Marcia van Gemert

Judith W. Hauswirth: Judith W. Hauswirth

John A. Quest: John A. Quest

William Sette: [illegible]

2. Peer Review Committee Members in Absentia:
(Committee members who were not able to attend the discussion; signature indicates concurrence with the overall conclusions of the committee).

Reto Engler: _____

Richard N. Hill: _____

Diane Beal: _____

Kerry Dearfield: _____

Lynnard Slaughter: _____

Esther Rinde: _____

Richard Levy: _____

3. Interested Observers:

Albin Kocialski: _____

Phil Hundemann: _____

B. Material Reviewed:

This material available for review by the Committee was a package prepared by Dr. Copley containing information on most of the major scientific and regulatory activities conducted by the OPP over the past several years.

C. Background

Background information on Benomyl/MBC is comprehensively provided in Dr. Copley's memorandum of January 20, 1989 (attached). In brief, at the Peer Review Committee meeting of January 7, 1986, it was determined that Benomyl/MBC met some of the criteria for both the B2 and C categories of carcinogen classification. In support of a B2 category classification, both Benomyl and MBC produced an increased incidence of malignant or combined malignant and benign tumors of the liver. In the case of MBC, tumors were produced in multiple strains of mice (closely related CD-1 and Swiss SPF strains) and in multiple experiments. Furthermore, MBC produced an unusual type of hepatocellular tumor (hepatoblastoma) in male Swiss SPF mice. In support of a C category classification, it was noted that: 1) the oncogenic responses observed with Benomyl and MBC were confined solely to the mouse liver, even with repeated experiments; 2) the liver tumors produced by Benomyl and MBC were observed in two related strains of mice (CD-1 and Swiss

SPF) known to have high background incidence rates of liver tumors whereas no liver tumors were produced by MBC in another strain of mice [HOE NMRKf (SPF 71)] known to have a low background incidence rate of liver tumors; and 3) Benomyl and MBC produced weak mutagenic effects consistent with spindle poison activity rather than gene mutation or DNA repair activity.

Based on the above information, the Peer Review Committee decided that there was insufficient evidence for the B2 category and classified Benomyl/MBC as a Category C oncogen. Although there was some discussion by the Committee of possible quantification of risk, a formal decision about whether or not to quantify was not made. A similar situation prevailed at an SAP meeting on Benomyl/MBC held May 21, 1986. It should be noted that at that time, HED had calculated interim estimates of cancer potency for both Benomyl ($Q1^* = 5.9 \times 10^{-3}$;human risk) and MBC ($Q1^* = 3.9 \times 10^{-3}$;human risk) using tumor information from the female mouse portion of an MBC study where the incidence of liver tumor bearing animals (adenomas, carcinomas, and hepatoblastomas was 1/79 at 0 ppm, 9/78 at 500 ppm, 21/80 at 1500 ppm, and 15/78 at 7500 ppm. To resolve the outstanding issue of whether the group C categorization of Benomyl/MBC is appropriate for quantification of risk using the Q1*, the Registration Division requested that the present Peer Review Committee be convened.

D. <u>Conclusion of the Peer Review Committee on Risk Quantification</u>

The Committee determined that quantification of risk was warranted for Benomyl/MBC in view of the above described biological data supportive of the category B2 classification. In particular, this data included the occurrence of a mostly malignant hepatocellular tumor response with MBC in two strains of mice (and with Benomyl in one strain of mouse), the fact that the malignant response was generally seen in both sexes of mice, and the presence of the unusually occurring and malignant hepatoblastomas with MBC in male SPF Swiss mice. In addition, mutagenicity information was provided by Dr. Dearfield indicating that the aneuploidy (i.e., loss of chromosome material) known to be produced by Benomyl could theoretically result in a loss of tumor suppressor genes and a potential oncogenic effect (see Cancer Research 48:1623-1632, 1988).

The assignment of a Q1* value for human risk to Benomyl/MBC was temporarily deferred until a brief review of the incidence data for MBC-induced liver tumors in female mice is conducted to check for numerical accuracy of numerator and denominator values. In all probability, the

Q1* value cited above in this document for MBC will be employed for MBC and Benomyl.

Other Deliberations of the Committee

The Committee also briefly considered whether a quantitative risk assessment should be performed on Thiophanate Methyl, another pesticide that, like Benomyl, is metabolized to MBC in both animals and plants. It was decided that the Q1* value derived for MBC from Benomyl metabolism could now be used to characterize the Q1* for MBC derived from Thiophanate-Methyl metabolism, provided that the latter agent results in MBC residues on plants. This issue can be considered further in the future when Thiophanate Methyl per se is peer reviewed. At present, a chronic mouse study on Thiophanate methyl is outstanding and the Committee could not comment further on this parent compound.

In view of the Agency's issue paper on mouse liver tumors and the recent workshop held in Virginia Beach, Virginia, both of which discussed the relevance of these tumors to humans, the Committee considered that the need for quantitative risk assessment on Benomyl/MBC could be modified. Further information on Benomyl/MBC that could influence this decision would include data on comparative metabolism, peroxisome proliferation, hepatic microsomal drug metabolism, and hepatocytotoxicity in mice. The Committee will schedule a separate meeting to discuss these generic issues.

Attachment

TOXICOLOGY SUMMARY FOR THE THIRD PEER REVIEW OF BENOMYL AND MBC

Data Evaluation Report for the
Third Meeting of the
Peer Review Committee for Benomyl and MBC

Submitted by Marion P. Copley, D.V.M., Sect.2, Tox. Br.1, HED
Through Judith Hauswirth, Ph.D., Branch Chief
Toxicology Branch 1 (IRS), Hazard Evaluation Division

completed January 19, 1989

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Data Evaluation Report for the Third Meeting of the Peer Review Committee for Benomyl and MBC

Submitted by Marion P. Copley, D.V.M., Sect.2, Tox. Br.1, HED
Through Judith Hauswirth, Ph.D., Branch Chief
Toxicology Branch 1 (IRS), Hazard Evaluation Division

1. Issues

The Hazard Evaluation Division (HED) Peer Review Committee (formerly the Toxicology Branch (TB) Peer Review Committee) is requested to:

a) reevaluate whether Benomyl and MBC should be evaluated using the multistage model of risk quantification. This should take into consideration that this Committee already classified Benomyl and MBC as C oncogens based on liver tumors.

b) If a Q_1* is deemed appropriate, to determine whether the previous calculations are adequate or whether they should be redone.

2. Background

a) Benomyl produces liver tumors, both hepatocellular adenomas and hepatocellular carcinomas in two closely related strains of mice (males and females) but not in an unrelated strain of mice or in rats.

Benomyl and MBC were discussed by the Peer Review Committee first on 10/3/85. At that time additional information was requested from the reviewer. No Peer Review Document resulted from that preliminary meeting. On 12/19/85 the Committee reconvened and following review of tumor data, metabolism and structure-activity information, historical control information, mutagenicity data and a listing of one-liner material, classified both fungicides as Category C (possible human) carcinogens.

Although it was discussed at some length, the Committee did not establish whether this compound was suitable for risk quantification by the standard procedures.

b) Benomyl has undergone a complete Special Review cycle. The result of the PD4 (10/1/82) was to regulate exposure by requiring dust masks.

A risk quantification was conducted for the PD4 with the Q1* of 2.065×10^{-3} $(mg/kg/day)^{-1}$. This was based on a benomyl chronic/oncogenicity study that has since been core-graded as supplementary for oncogenicity. Since that time a new value for the human Q1* was calculated : 3.9×10^{-3} $(mg/kg/day)^{-1}$ (see appendix 4 for statistical memos). This used data from

an MBC study which was core-graded minimum for oncogenicity.

NOTE: As stated in the PD4, benomyl rapidly hydrolyses to MBC in an aqueous environment. MBC also appears to be the initial metabolite in mammalian systems. It has similar or increased toxicity, both acute and chronic, to benomyl. For these reasons MBC data has been used to confirm and supplement benomyl data where applicable.

c) Benomyl was presented to the Scientific Advisory Panel in 5/21/86. They agreed with the classification of Benomyl and MBC as class C (possible human) carcinogens. No comment was given to the question of when to quantify using the multistage model. However the panel stated that,

> "... Benomyl and its major metabolite ... MBC produce tumors in livers of two genetically related strains of mice. It does not produce tumors in a genetically unrelated mouse strain nor does it produce tumors in a two-year rat study. Both benomyl and MBC produce weak mutagenic effects consistent with spindle poison activity rather than gene damage and DNA repair activity. In view of these species differences in oncogenic activity and lack of evidence of any direct action on DNA, there are reasonable grounds for doubt that benomyl and its major metabolite MBC are human oncogens. The Panel believes that the classification C seems appropriate."

d) There have been two MBC studies reviewed since the previous peer review. They were discussed and World Health Organization summaries of these studies were included with the previous peer review. Attached in Appendix 5 are completed DERs for:

1) Repeated-dose (24-month) feeding study for determination of the cancerogenic effect of HOE 17411 O F AT204 (carbendazim) in mice. (NMRKf(SPF71) strain)

and

2) Carcinogenicity study with Carbendazim in mice. (Swiss random strain)

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3. Summary Weight-of-the-Evidence

Category C oncogen (possible human oncogen) for Benomyl and MBC

1. Tumors in one specie (mouse)

2. Tumors in two strains of mouse (CD-1 and Swiss random)

   a. Tumors in two sexes (of above studies)

   b. Both benign and malignant hepatocellular tumors

   c. Genetically related - both are outbred derivitaves of the Swiss strain

   d. Both strains have high historical control values for liver tumors in male mice

   e. Tumors limited to one organ (liver)

   f. Tumors only at end of study

   g. Tumors primarily only at high doses

   h. No evidence for metastases or invasion

   i. No evidence for decreased time to occurrance of tumors.

3. Tumors not in one (genetically unrelated) strain

   a. NMRKf strain;

   b. Low historical control values for liver tumors.

   c. Evidence for hepatotoxicity is present

4. Mutagenicity - weak

   a. Genotoxicity - equivocal: DNA repair, gene mutation

   b. Cytotoxicity - Spindle inhibition

5. Teratogenic (microphthalmia in mice)