3/11/86

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

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MAR 11 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Benomyl Risk Assessment Assumption for $Q_1^* = 3.9 \times 10^{-3}$ for Carcinogenicity Potency

FROM: Bertram Litt, Leader, Statistical Team
for Mission Support Staff
Toxicology Branch/HED (TS-769)

TO: Marion Copley
Section VI
Toxicology Branch/HED (TS-769)

THRU: Reto Engler, Chief
Mission Support Staff
Toxicology Branch/HED (TS-769)

Based on the suggestions of the HED/TOX Peer Review Committee the liver tumor data for all females studied in the MBC mouse 2-year feeding study (CD-1 strain) were used as the source for estimating cancer potency of Benomyl.

The data were fitted to a polynormial of the 3rd degree by Crump's Global82 program using Abbott's correction.

The data fitted were:

Dose mg/kg/day	0	75	257	1125
Tumor Bearing Animals	1/	9/	21/	15/
No. Examined	/79	/78	/80	/78

and a Q_1^* of 3.1×10^{-4} was estimated for mice $(mg/kg/day)^{-1}$.

The mouse estimate was then extrapolated to man by the surface area adjustment of $\left(\frac{60{,}000 \text{ g. human body wt.}}{30 \text{ g mouse wt.}}\right)^{1/3} = 12.6$

i.e. $3.1 \times 10^{-4} \times 12.6 = 3.9 \times 10^{-3}$ $(mg/kg/day)^{-1}$ = human Q_1^*.

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2/14/86

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

FEB 14 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Interim Revised Estimate of Benomyl Cancer Potency.

FROM: Bertram Litt, Leader
Biostatistics Team/MSS
Toxicology Branch/HED (TS-769)

Herbert Lacayo for Bertram Litt

TO: Peer Review Committee
Toxicology Branch

THRU: Reto Engler, Chief
Mission Support Staff
Toxicology Branch/HED (TS-769)

R.G. Engler

Following the recent peer review of Benomyl carcinogenicity it was agreed that two estimates of cancer potency were indicated. The first was a best estimate based on the Q_1^* for MBC female liver data and the geometric mean of the Q_1^* for female liver tumors in Benomyl MBC. Secondly an alternative was to be developed which would save as an example of how to estimate risk for class C oncogens. The following Q_1^* estimates fulfill the first request, a subsequent report will be prepared fro the alternative approach.

	Animal Risk	Human Risk
MBC	3.1×10^{-4}	3.9×10^{-3}
Benomyl	4.7×10^{-4}	5.9×10^{-3}
Geometric Mean	3.8×10^{-4}	4.8×10^{-3}

#8

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3/26/86

MEMORANDUM

SUBJECT: Definition and Use of the Term "MTD" (Maximum Tolerated Dose)

FROM: R. Bruce Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769) RBJ 3/26/86

My signature acknowledges concurrence with the peer review on Benomyl/MBC providing the use of the term "MTD" in this document is consistent with the definition and use as given in: (1) HED SEP: Oncogenicity Potential (Guidance for Analysis and Evaluation of Long Term Rodent Studies) (EPA-540/9-85-019, June 1985); (2) Report of the NTP Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation, DHHS (August 17, 1984); and (3) Chemical Carcinogens; A review of the Science and its Associated Principles, February 1985, Office of Science and Technology Policy (FR/Vol. 50, No. 50/March 14, 1985).

4-22-86

INFORMATION CONCERNING THIOPHANATE METHYL

FOR THE

SCIENTIFIC ADVISORY PANEL

April 22, 1986

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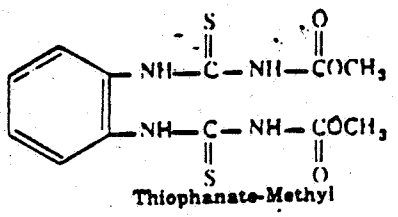
A Set of Scientific Issues Being Considered by the Agency in Connection with the Registration Standard for Thiophanate Methyl

A Set of Scientific Issues Being Considered by the Agency
in Connection with the Registration Standard for Thiophanate Methyl

Introduction

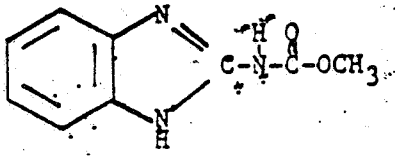
The Agency asks the Panel to consider the analysis of the weight-of-the-evidence in classifying thiophanate methyl as a Group C oncogen, or possible human oncogen, and what weight the Agency should place on a quantitative risk assessment for thiophanate methyl as a class C oncogen based on results with the metabolite MBC. In addition, the Agency requests the Panel to consider the need for a quantitative risk analysis for applicators who are expected to be exposed primarily to thiophanate methyl, and as part of such an assessment, the need for a dermal absorption study.

Thiophanate methyl is a broad spectrum systemic fungicide which is available in the form of wettable powders, a flowable, a liquid, dusts, or granulars. It is used on fruits, nuts, beans, peanuts, celery, soybeans, sugar beets, potato and sugar cane seed pieces, turf, and greenhouse ornamentals. The fungicide's chemical name is dimethyl 4,4'-o-phenylene bis(3-thioallophanate), and its structure is as follows:



Thiophanate-Methyl

The fungicidal activity of thiophanate methyl depends on its conversion to methyl benzimidazole carbamate (MBC). The chemical structure of the active form is as follows:



MBC

MBC has been shown to interfere with cell division and DNA biosynthesis in fungi and is potentially associated with genetic toxicity as an inhibitor of the spindle apparatus in cell division.

Relevant data on thiophanate methyl include a chronic feeding study in rats (Taniguchi et al., 1972) and an oncogenicity study in mice (Nishibe et al., 1973). In the first study, groups of rats were given diets containing 0, 10, 40, 160, or 640 ppm for two years. Body weight decreases were noted in female rats given the 640 ppm diet (10 to 18% below that for control group females); decreased spermatogenesis and decreased follicular colloidal content and hypertrophy of follicular epithelium in the thyroid were observed in the high dose group males. There were no compound-related effects on

tumor incidence.

In the second study. there were no compound-related effects or increases in tumor incidence in mice after two years on diets containing 0, 40, 160, or 640 ppm of the fungicide (Nishibe et al., 1973). However, the highest dose tested was not a maximum tolerated dose (MTD) in mice.

Relevant data on MBC consist of one chronic rat and three long-term mouse feeding studies. The rat study is negative with respect to oncogenic effects, and two of the MBC mouse studies (using genetically related CD-1 and Swiss strains) showed oncogenic effects in the liver of male and female mice. However, MBC showed no oncogenic effect in the NMRKf mouse (a genetically different strain from the others used).

On December 7, 1977, the Agency initiated a Special Review (previously referred to as the Rebuttable Presumption Against Registration [RPAR] process) for thiophanate methyl (42 Fed. Reg. 61970) because its metabolite methyl 2-benzimidazole carbamate (MBC) had the potential to cause mutagenic effects. This Special Review was supported by a Position Document (PD 1).

In the Preliminary Determination concluding the Special Review, the Agency stated that the available evidence did not clearly demonstrate a risk to humans on uses registered at that time (44 Fed. Reg. 58798, Oct. 3, 1979). The support document for this preliminary determination was Position Document 2.

Prior to the publication of EPA's final regulatory decision, new data were received by the Agency indicating that MBC is carcinogenic. The Agency issued its final regulatory decision on thiophanate methyl on October 20, 1982 (47 Fed. Reg. 46747). In this notice and position document supporting the decision, the Agency determined that the potential oncogenic and mutagenic risks of thiophanate methyl were exceeded by the benefits associated with their use.

Weight of the Evidence

A. Data on Thiophanate Methyl

1. Oncogenicity Study in Mice (Nishibe et al., 1973)

Five groups containing 50 male and 50 female ICR SLC strain mice were given diets containing 0, 10, 40, 160, or 640 ppm thiophanate methyl for two years. The results did not indicate the occurrence of effects that could be attributed to administration of the test substance. In addition, results of a 6-month feeding study in mice showed no effects in those given dietary levels as high as 1600 ppm (Hashimoto et al., 1970). (The highest dose tested was 8000 ppm which cuased body weight decreases in females and increased liver and liver-to-body-weight ratios in both sexes.) These results indicate that an MTD was not tested in the mouse study.

2. Chronic rat feeding study (Taniguchi et al., 1972)

Four groups containing 35 male and 35 female rats were given diets containing 10, 40, 160, or 640 ppm test substance and one group containing 50 animals of each sex was given the diet without test substance for 24 months. (There were interim sacrifices of 5 animals per sex at 3 and 12 months in the study.) There were no significant differences noted between the treated and control groups with respect to food consumption. The highest dosed group of females exhibited a 10 to 18% decrease in group mean body weight below that for the control group females during the feeding period, but all other treated groups (males and females) had group mean body weights comparable to those for the control groups. Decreased spermatogenesis was noted in 6 males given the 640 ppm diet. Five of those cases were observed in animals after 103 weeks on the test diet.

Thyroid effects including decreased colloidal content and epithelial hypertrophy in the follicles were observed in 6 of the 640 ppm group males (4 were observed after 103 weeks of the study). These effects are considered to be associated with thiophanate methyl administration because they were observed in male rats given a diet containing 8000 ppm for 6 months (Noguchi et al., 1970), and a metabolism study in rats showed that radiolabel was more slowly released from thyroid tissue than other tissues in rats given ^{14}C-thiophanate methyl (repeated doses of 2.25 mg/kg administered by gavage; see Noguchi et al., 1971). These results indicate that an MTD was approached.

The incidence of tumors was not increased in rats given dietary levels of thiophanate methyl as high as 640 ppm for two years.

3. Mutagenicity Studies of Thiophanate Methyl

Microbial assays showed that thiophanate methyl did not cause reverse mutations of the frame shift or base pair substitution type in Salmonella typhimurium with or without liver microsomal activation, and the fungicide did not show differential toxicity to repair deficient and proficient strains of Bacillus subtilis (Shirasu et al., 1976).

Thiophanate methyl also failed to induce mitotic gene conversion in Saccharomyces cereviciae (yeast) (Guerzoni et al., 1976). The study was a 8

screen for a large number of chemicals which were tested at only one dose and without a positive control substance. The study is therefore considered to be incomplete.

Thiophanate methyl at intraperitoneal doses ranging from 8 to 500 mg/kg/day (5 consecutive doses) did not affect fertility in surviving mice or induce dominant lethal mutations in mice (Makita et al., 1971). The 400 and 500 mg/kg doses increased mortality. No positive control substance was included in this study.

The dominant lethal and yeast assays are considered to be unacceptable since they are incomplete.

4. Metabolism Studies of Thiophanate Methyl

Eighty to ninety percent of the dose is recovered in the excreta of rats within 24 hours after administration regardless of the amount given (Noguchi et al., 1971a).

Major metabolites in the excreta of rats include MBC and 5-hydroxy-MBC (approximately 1/3 of the repeated 2.25 mg/kg/day dose). Minor metabolites include dimethyl-4,4'-phenylene-bis (allophanate) and its 4-hydroxy derivative as well as 5-hydroxy-thiophanate methyl (approximately 1/6 of the dose in excreta). The remainder of the radioactivity in the urine and feces was associated with other unidentified metabolites (Noguchi et al., 1971b). All of the metabolites mentioned above are also formed in vitro by rat liver microsomal enzymes (Noguchi et al., 1971b).

Although treated rats cleared thiophanate methyl or its metabolites rapidly, radioactivity in the thyroid remained high relative to that in blood and organs associated with absorption and excretion. The thyroid levels declined more slowly than levels in other organs during the 8 days after the last of 20 consecutive 2.25 mg/kg/day doses was administered (Noguchi et al., 1971a).

In mice the majority of administered radioactivity was recovered from the urine (70 to 90%) 24 hours after single gavage doses ranging from 50 to 150 mg/kg (Noguchi et al., 1971a). The pattern of distribution in the organs of the mice was similar to that reported in rats, and the metabolites identified in the urine, feces, and tissues were similar to those found in rats, but the amount of each was not reported.

B. Data on MBC

1. Mouse Oncogenicity Study

Haskell Laboratory administered MBC in the diet to groups of 80 male and 80 female CD-1 mice at concentrations of 0, 500, 1500, 7500 (females) or 7500/3750 (males) ppm for 2 years. The high dose of 7500 ppm was reduced to 3750 ppm at 66 weeks in males due to increased mortality, and all males were ultimately sacrificed at 73 weeks. The following incidence pattern of liver tumors was observed.

Liver Tumor Type	Sex	Dose (ppm) 0	500	1500	7500/#
Adenoma	M	11/80(14%)	15/80(19%)	14/80(17%)	3/80(4%)
Carcinoma	M	2/80(2%)	5/80(6%)	9/80(11%)*	0/80(0%)
Combined	M	13/80(16%)	20/80(25%)	23/80(28%)*	3/80(4%)
Adenoma	F	0/79(0%)	5/78(6%)*	5/80(6%)*	3/78(4%)
Carcinoma	F	1/79(1%)	4/78(5%)	15/80(18%)*	12/78(15%)*
Hepatoblastoma	F	0/79(0%)	0/78(0%)	1/80(1%)	0/79(0%)
Total	F	1/79(1%)	9/78(11%)*	21/80(26%)*	15/78(19%)*

* = $p < 0.05$ compared to controls
# = Reduced to 3750 ppm in males at 66 weeks.

The lack of oncogenic response in high dose males may be attributed to the early deaths (possibly due to hepatotoxicity) and sacrifice at 73 weeks. No increased incidence of liver hyperplasia occurred in treated mice. A comparison of the MBC liver tumor data with historical control data from two other studies conducted at Haskell Laboratory (see Copley /Harris memorandum of 12/19/85, page 10) indicated that only the carcinomas (mid and high dose levels) and the adenomas/carcinomas combined (all 3 dose levels tested) in female mice exceeded the control response rates in the other studies.

The high dose level of MBC tested in male mice clearly exceeded an MTD level because of excessive mortality. The mid dose level appeared to approximate an MTD level. Both of these doses in males caused reduced weight gain, hepatocellular toxicity (e.g., pigmented macrophages, hypertrophy, and centrilobular necrosis), renal tubular pigmentation, thymic lymphoid depletion, and sperm stasis. The changes however were more severe at the high dose level.

The highest dose of MBC tested in females appeared to approach but did not exceed the MTD level. This dose caused increased liver weight and foci of eosinophilic hepatocellular alteration, renal tubular pigmentation, and thymic lymphoid depletion.

2. Mouse Oncogenicity Study of Carbendazim (99% MBC):

In a study performed by the Central Institute for Nutrition and Food Research (TNO), and reviewed in summary form by the World Health Organization (WHO)(see Copley/Harris memorandum of 12/19/85, page 7), MBC was administered in the diet to groups of 100 male and 100 female SPF Swiss mice at concentrations of 0, 150, 300 or 1000/5000 ppm for 80 weeks. The 1000 ppm concentration was increased to 5000 ppm in males and females at week 8. Data were presented in summary form only. The following incidence pattern of liver tumors was observed.

Liver Tumor Type	Sex	Dose (ppm) 0	150	300	1000/5000
Neoplastic Nodule	M	9/100(9%)	7/98(7%)	14/100(14%)	16/100(16%)
Carcinoma	M	1/100(1%)	1/98(1%)	9/100(2%)	3/100(3%)
Hepatoblastoma	M	0/100(0%)	1/98(1%)	1/100(1%)	7/100(7%)*
Total	M	10/100(10%)	8/98(8%)	16/100(16%)	17/100(17%)
Neoplastic Nodule	F	0/97(0%)	1/99(1%)	1/98(1%)	9/97(9%)*
Carcinoma	F	1/97(1%)	0/99(0%)	0/98(0%)	0/97(0%)
Hepatoblastoma	F	0/97(0%)	0/99(0%)	0/98(0%)	0/97(0%)
Total	F	1/97(1%)	1/99(1%)	1/98(1%)	9/97(9%)

*= P<0.01 compared to controls, Exact test.

Hepatoblastomas (a less common and more malignant liver tumor than hepatocellular carcinoma) were significantly elevated in male mice (high dose level); neoplastic nodules (i.e., adenomas) were significantly elevated in female mice (high dose level). The Toxicology Branch Peer Review Committee noted that the SPF Swiss strain of mouse used in this study is genetically similar to the CD-1 strain of mouse in which MBC was tested. The CD-1 strain is an outbred strain of the SPF Swiss mouse. Both strains tend to exibit a high background incidence of liver adenomas in male mice.

Based on the summary information available for this study, the highest dose level of MBC tested did not appear to exceed a MTD level. The highest dose tested caused increased relative liver weights and clear cell and/or mixed hepatic cell foci in males and females.

3. Mouse Oncogenicity Study of Carbendazim (99.3% MBC):

In another study reviewed by the WHO (see Copley/Harris memorandum of 12/19/85, page 8 and Copley/Harris review), MBC was administered in the diet to groups of 100 male and 100 female HOE-NMRKf (SPF 71) mice at concentrations of 0, 50, 150, 300 or 1000/5000 ppm for 22 months. The 1000 ppm concentration was increased to 5000 ppm at week eight. No evidence of an oncogenic response in the liver or at any other site was observed. The Toxicology Branch Peer Review Committee noted that the NMRKf strain of mouse, in contrast to CD-1 and SPF Swiss mice, normally exhibits a low background incidence of liver tumors.

The highest dose of MBC tested in this study appeared to be close to a MTD level as indicated by findings of liver toxicity in both male and female mice (e.g., liver cell hypertrophy, clear cell foci, liver cells in mitosis, pigmented Kupffer cells, enlarged cell nuclei, and multiple cell necrosis).

4. Rat Oncogenicity Study of MBC

MBC was studied in a 2 year dietary study (0, 100, 500, 2500/10,000, 5000 ppm) in ChR CD rats; no oncogenic effects occurred. The 2500 ppm dose was increased to 10,000 ppm (HDT) during week 20 of the study. The MTD was established at the highest dose demonstrated by weight loss in males and females (10%-20% less than controls) and hepatic pericholangitis. The study was performed by Haskell Laboratory.

5. Mutagenicity of MBC

Data provided in the Position Document 4 on benomyl indicated that MBC is a spindle poisons in cell division. Effects associated with this mechanism were observed in A. nidulans (nondisjunction). MBC also produced positive effects in tests to assess structural chromosome aberrations which were consistent with a spindle effect; e.g., MBC caused increased incidences of micronuclei in polychromatic erythrocytes in mice bone marrow.

In other studies performed to assess gene mutations, MBC was weakly positive in one mouse lymphoma test (L5178Y $TK^{+}/-$) but was negative in a second test. MBC produced both positive and negative results in different Ames tests, and it produced negative results in Chinese hamster ovary cells (HGPRT).

Finally, negative results were obtained for DNA damage repair with MBC in studies with primary mouse and rat hepatocyte cultures.

The Toxicology Branch Peer Review Committee concluded that these results indicated MBC has weak genetic toxicity that is primarily attributable to adverse effects on the cellular spindle apparatus.

Oncogenicity Risk Assessment

1. Classification of MBC

The Agency has reviewed oncogenicity studies for thiophanate methyl and its metabolite, MBC, and concluded that these data provide limited evidence of oncogenicity for MBC in male and female mice. According to EPA Proposed Guidelines for Carcinogen Risk Assessment (November 23, 1984, 49 FR 46294), MBC has been classified as a Group C oncogen, that is, possibly a human oncogen.

The Toxicology Branch Peer Review Committee (TPRC) chose to classify MBC as a Group C carcinogen (limited evidence of carcinogenicity) for the following reasons:

a) The oncogenic responses observed with MBC were confined solely to the mouse liver, even with repeated experiments,

b) MBC was not oncogenic in ChR-CD rats.

c) Although oncogenic responses were seen in more than one study, each study had similar dosing ranges and the test chemical was administered in the feed. Furthermore, the liver tumors produced by MBC were observed in two genetically related strains of mice (CD-1 and SPF-Swiss), whereas no liver tumors were produced by MBC in a genetically unrelated strain of mouse [HOE NMRKf (SPF-71)].

d) MBC produced weak mutagenic effects consistent with spindle poison activity rather than gene mutation or DNA repair activity. The Toxicology Branch Peer Review Committee noted that this pattern of mutagenic activity correlates well with teratogenic and spermatoxic effects. Correlation, or lack thereof, with oncogenicity has not been demonstrated.

The Peer Review Committee concluded that the data available for MBC provide limited evidence of oncogenicity in male and female mice. Criteria contained in the proposed EPA Guidlines (CFR, November 23, 1984) for classifying a carcinogen in either Category B_2 or C were considered. MBC met some of the criteria specified for the B_2 classification. That is, MBC produced an increased incidence of malignant or combined malignant and benign tumors in genetically related strains on mice (CD-1 and SPF Swiss) and in multiple experiments. Furthermore, MBC did produce an unusual type of liver tumor (heptablastoma) but only in male SPF Swiss mice.

Despite these considerations, the Peer Review Committee decreased the classification to Category C (limited evidence of carcinogenicity) for the following reasons: (1) MBC did not produce tumors in the rat. (2) The oncogenic responses observed with MBC werre confined solely to the mouse liver in 2 genetically related strains of mice (SPF Swiss and CD-1). (3) No liver tumors were produced by MBC in a genetically different strain of mouse [HOE NMRKf (SPF-71)]. (4) The genetic toxicity of MBC is nominal, that is, it produced weak mutagenic effects consistent with spindle poison activity rather than gene mutation or DNA repair activity. Because of these factors the Committee determined that there was insufficient evidence for the B_2 category and therefore, in conformity with the EPA Guidelines noted above, classified MBC as Group C (possible human) carcinogen.

2. Dietary Risk:

In the PD 4, the Agency performed a quantitative oncogenic risk assessment for benomyl. Though not estimated directly, the oncogenic risk from thiophanate methyl was assumed to be about the same as that from benomyl. This assumption was based upon their similar use patterns and data showing that both benomyl and thiophanate methyl degrade to MBC in aqueous solution, in the soil, and in plants which are ingested by humans or domestic animals. That assessment was based on a body weight to body weight species conversion. Present Agency guidelines call for a surface weight species correction unless a biological reason for using a different conversion exists. Therefore, an updated risk assessment was performed.

The 95% upper confidence level potency estimator, Q*, for oncogencity of MBC based on the increased incidence of liver tumors in the mouse study is 3.9×10^{-3} $(mg/kg/day)^{-1}$. The Agency is unable to determine the exposure to MBC resulting from the use of thiophanate methyl. The exposure to thiophanate methyl resulting from the Theoretical Maximum Residue Contribution (TMRC) is 0.0183 mg/kg/day of which only a portion is MBC. Assuming a complete conversion of thiophanate methyl (mol. wt. = 342) to MBC (mol. wt. = 191) in the plant, the TMRC is 0.0102 mg/kg/day (calculated as MBC: 0.0183 X (191/342) = 0.0102). It should also be noted that the TMRC is based on tolerance levels and provides a conservative estimate. Calculations based on these assumptions suggest a risk between 10^{-4} to 10^{-5} (C). Correction for percent of crop treated should lower the risk by at least an order of magnitude.

3. Applicator Risks

The oncogenic risk to applicators exposed to thiophanate methyl would be based on the rate and extent of conversion of the fungicide to MBC in the body and the dermal absorption rate of thiophanate methyl. To date, studies in the rat and mouse showed no oncogenic activity although the MTD was not tested in the mouse study. Therefore, to evaluate more adequately the oncogenic risk of the thiophanate methyl to the applicator, a new oncogenicity study in the mouse would be required as well as a dermal absorption study.

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