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

NOV 4 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Request for a Second Peer Review of Phosmet (Imidan)

FROM: Marion Copley, DVM, Head
Section 4, TB1
HED (7509C)
and
Myron Ottley, PhD
Section 4, TB1
HED (7509C)

Marion Copley 11/3/93

William B. Dixon for 11/3/93

THRU: Karl Baetcke, PhD, Chief
TB1
HED (7509C)

Karl P. Baetcke 11/4/93

TO: Esther Rinde, PhD
Science Analysis Branch
HED (7509C)

Attached is the document supporting this request for a reevaluation of the carcinogenic potential of Phosmet. The previous Peer Review was in 1986. Since that time several new studies and a registrant's response to the previous Peer Review have been received. The Agency is currently proposing to cancel 409 tolerances for this chemical based on the cancer classification as a C carcinogen.

Esther help me?

TABLE OF CONTENTS

coversheet

I EXECUTIVE SUMMARY

The HED Cancer Peer Review Committee (CPRC) is requested to reevaluate the carcinogenic potential of Phosmet taking into consideration new studies and discussion submitted by the Registrant subsequent to the first Cancer Peer Review meeting (June 1986).

The CPRC classified Phosmet as a tentative Category C (possible human) carcinogen since it produced an increased incidence of benign liver tumors only in high dose males (pair-wise) and positive trends for liver adenomas and carcinomas in females, in one strain and species of experimental animal ($B6C3F_1$ mice) in only one experiment. The chemical was questionably mutagenic. They noted that "there was insufficient evidence to consider the B_2 category for carcinogenicity, but agreed to reconsider all information after the results of a repeat two-year rat oncogenicity study and additional mutagenicity studies have been provided."

II BACKGROUND

The Toxicology Branch Peer Review Committee (now called the HED Carcinogenicity Peer Review Committee) met on June 30, 1986 (document dated 10/21/86) to discuss the carcinogenic potential of Phosmet.

The CPRC classified Phosmet as a tentative Category C (possible human) carcinogen. It was concluded that "the data presently available for Phosmet provided only limited evidence for oncogenicity in animals. This conclusion was based primarily on the following: "1) Phosmet produced a significantly elevated incidence of liver tumors (adenomas, and adenomas plus carcinomas combined) in male $B6C3F_1$ mice at the highest dose level tested. These were associated with a decrease in the time to tumor occurrence. 2) The chemical was associated only with positive dose-related trends for liver adenomas and carcinomas in female $B6C3F_1$ mice. 3) Phosmet was not oncogenic in a study conducted in male and female Charles River albino rats, but the study was inadequate in design and needs to be repeated. 4) Mutagenicity testing of Phosmet was conducted in a limited number of tests and the chemical was weakly mutagenic in only one of these. Additional mammalian cell mutagenicity studies are required. 5) Numerous structural analogues of Phosmet were identified for which no oncogenicity data were available. Phosmet is also structurally related to the oncogenic fungicide, Folpet, which causes intestinal tumors in mice. However, the oncogenicity of Folpet is thought to be related to conversion of its side chain to thiophosgene, and this side chain in not present in Phosmet." They noted that "there was insufficient evidence to consider the B_2 category for carcinogenicity, but agreed to reconsider all information after the results of a repeat two-year rat oncogenicity study and additional mutagenicity studies have been provided."

III NEW INFORMATION AND STUDIES (since last Peer Review)

P131

A Chronic/Carcinogenicity Feeding Study - rat (DER and Supplemental DER attached)

Reference: Chang, J.C.F., Morrisey, R.L. and Wynd, S. "2-Year Chronic/Oncogenicity Study with R-1504 in Rats", April 15, 1991. MRID No. 419164-01; Study No. T-13241; Testing Facility: CIBA-GEIGY Corp., Farmington, CT.

1. Experimental Design

Doses 20 -200 ppm for 2yr.

R-1504 Technical (Phosmet) (95.2% a.i.) was administered in the diet to groups of 60 male and 60 female (70/sex in controls) Sprague-Dawley Crl:CD® SD BR rats at dosages of 0, 20, 40 and 200 ppm for 24 months, and to 20 males and 20 females at 400 ppm for 12 months (Equivalent dosages ♂ 0, 1.1, 1.8, 9.4 and 23 mg/kg/d; ♀ 0, 1.1, 2.1, 10.9 and 27 mg/kg/d). The 40 ppm group inadvertently received 100 ppm for the first six weeks, resulting in a time-weighted average of 44.2 ppm (♂ = 10.4 mg/kg/d, ♀ = 12.0 mg/kg/d).

2. Discussion of Tumor Data

P154

Liver (M-161, F172)

Adrenal M157 F169

Pituitary M164 F174

Under the conditions of the study, there was no treatment-related increase in neoplastic lesions. incl liver, adrenal, pituitary

3. Non-neoplastic Lesions and Other Systemic Effects

ChE Brain 40 ppm

BWG - minimal 40 ppm (1 yr?)

An increased incidence of fatty changes in male livers was observed at 20 ppm (1.1 mg/kg/d) and above. At 200 ppm (♂=9.4 mg/kg/d, ♀=10.9 mg/kg/d) and above increases in the incidence of depressed hepatic foci in male and fatty change in female livers were noted; hyperkeratosis of the stomach in males, and mineralization of the thyroid in females were also observed at this dose level.

Other systemic effects included decreased RBC cholinesterase (ChE) levels in males at all dose levels (16% - 74%); in males and females brain ChE was decreased at 40 ppm and above (34% and 43%, resp.); at 400 ppm male and female body weight and body weight gain were decreased (up to 10%, not usually statistically significant), as was female relative and absolute kidney weight (12.6% and 12.2%, resp); also at 400 ppm BUN in females was increased ($p \leq 0.05$).

4. Adequacy of Dosing for Assessment of Oncogenic Potential

The dosing was considered adequate for assessing the carcinogenic potential of R-1504, based on the effects mentioned in the previous section, and especially the decreased RBC and brain ChE levels in males at 40 ppm and above.

B Registrant's Discussion of Mouse Carcinogenicity (attached)

Reference: Codrea Elizabeth. 1993. Phosmet--Discussion Concerning Guideline Series 83-1 and 83-2 Studies. The Gowan Co. Confidential Appendix. August 12.

Summary of Argument: The document argues that the current database does not support EPA's position that Phosmet is a Group C Carcinogen. EPA's basis for this position in 1986 was a $B6C3F_1$ mouse cancer study in which there was an apparent pair-wise increase in benign liver cell tumors in males but not females, with no pair-wise increase in malignant tumors observed in either sex. The document argues that since these findings 1) occurred in one sex only, and 2) were not substantiated by three other chronic studies: two 2-year rat studies and a 2-year dog study, they should not form the basis of our position. The document further argues that the incidence of benign tumors noted in male $B6C3F_1$ mice is within the range of the historical control databases, both in-house, and the NTP data sets.

Data Summary: Below are tables summarizing the incidence of benign and malignant liver tumors in males and females in the critical mouse cancer study, and the background incidence in male and female historical controls.

PHOSMET $B6C3F_1$ Mouse Cancer Study

are statistics correct?

MALE

Liver tumor data [in terms of %] from phosmet study (includes 10/sex/dose from one year interim sacrifice since there were tumors at that time)

Liver tumor	0 ppm	5 ppm	25 ppm	100 ppm
Adenoma	15[T] 9/60	17 19/60	20 12/60	35* 21/60
Carcinoma	23 14/60	18 11/60	18 11/60	23 14/60
Combined	38[T] 23/60	35 21/60	38 23/60	58* 35/60

Comparison historical control data in mean % (range)

Liver tumors	Phosmet HDT	Phosmet Control	Other study Same lab	New NTP '80-'87	Charles River
Adenoma	35*T	15	42	26.4 (4-60)	17.2 (0-41.3)
Carcinoma	~~23~~	23	17	16.4 (3-29)	13.2 (4.2-24.6)
Total	58*T	38	52	35.2 (17-68)	Not avail.

FEMALE

Liver tumor data [%] from phosmet study (does not include interim sacrifice since there were no tumors at that time)

Liver tumors	0 ppm	5 ppm	25 ppm	100 ppm
Adenoma	10T	8	10	18
Carcinoma	10T	8	6	18
Combined	20T	16	16	36

Comparison historical control data in mean % (range)

Liver tumors	Phosmet HDT	Phosmet Control	Other study Same lab[1]	New NTP '80-'87	Charles River
Adenoma	18T	10	18 (15)	12 (2-33)	7.1 (0-17.1)
Carcinoma	18T	10	6 (5)	6 (0-20)	2.4 (0-6.3)
Total	36T	20	21.6 (18)	16 (3-42)	Not avail.

* $p < 0.05$ pair-wise comparison
T $p < 0.05$ trend
[1] Percents do not include interim sacrifice since they are not included in the phosmet data (values in () include the interim data - denominator of 60).

C **Mutagenicity** (DERs available upon request)

Summary of Previously Available Data:

Phosmet was tested in a reversion assay using Escherichia coli strains B/r WP2 hcr$^+$ and WP2 hcr$^-$ and in a rec-assay with Bacillus subtillis strains H17 Rec$^+$ and M45 Rec$^-$ without metabolic activation. Phosmet was negative when tested at levels up to 20 μg dissolved in DMSO. Phosmet was tested at levels up to 5000 μg/plate in an Ames test using Salmonella typhimurium strains TA 100, TA 98, TA 1535, TA 1537 and TA 1538 and in E. coli strains WP hcr with and without metabolic activation. A positive response was obtained only in S. typhimurium strain TA 100 without metabolic activation. A dominal lethal test in the rabbit provided inconclusive results.

New Data:

The following table summarizes the results of six new mutagenicity studies conducted and submitted on Imidan (Phosmet). All tests were graded Acceptable.

- E. Coli & B Subtilis

earlier - except TA 100

Study Title	Results
Salmonella typhimurium (TA100, TA1535) Reverse Mutation Study No. T-12819 Accession No. 265926 March 3, 1986	Positive with and without activation
Mouse Lymphoma Forward Mutation Assay Study No. T12820 Accession No. 265296 May 8, 1987	Positive with and without activation
Mouse Lymphoma Multiple Endpoint Test Cytogenic Assay Study No. T 12821 Accession No. 265926 July 13, 1987	Positive for structural chromosomal aberrations without metabolic activation Positive for SCE with and without metabolic activation
DNA Damage Assay in Human Fibroblast Study No. T 12823 Accession No. 265926 May 21, 1987	Negative with and without metabolic activation

Study Title	Results
Morphological Transformation of BALB/3T3 Cells Study No. T-12822 Accession No. 265926 August 12, 1986	Positive
Micronucleus Assay in Mouse Bone Marrow Study No. T86/756 Accession No. 401994-01 Date: July 31, 1987	No clastogenic effect observed at 17 mg/kg in bone marrow cells 24, 48 or 72 hr after dosing. Dose level adequacy previously determined. Positive control (cyclophosphamide) established adequate sensitivity of test system.

It should be noted that formaldehyde which is released during metabolism of phosmet, is mutagenic ~~only~~ in drosophilia.

D **Other Relevant Information** (concerning liver toxicity)

WHO evaluated this chemical in JNPR 1978, at that time they did not have the **mouse** study. They evaluated several range-finding **rat** studies. In one 16 week study (1963) there were alterations in liver histopathology (hepatic degeneration) at levels above 1120 ppm. This was difficult to evaluate due to the numerous dose level changes during the study. A 24 week study (1962) had no hepatic effects noted up to 500 ppm. In a 20 week **dog** study (1962) there was no evidence of histologic alterations at term. There was no mention of liver alterations in the 2 year dog study (1967). These are consistent with results presented in the tox review in HED DOC. # 1999.

In a recent 2 year rat study liver pathology was limited to fatty change in males at 20 ppm (LDT) and females at 200 ppm and depressed foci in males at 200 ppm and above.

In the recent mouse study at 12 months there was midzonal vacuolation of the liver (females) at 100 ppm and at 2 years males had increased degenerative single cell vacuolation and foci of vacuolated or clear cells in the liver. These changes were described as randomly scattered hepatocytes containing either single large cytoplasmic vacuoles or a cluster of small vacuoles imparting a foamy appearance, and randomly located clusters of foamy hepatocytes, some of which had poorly defined cytoplasmic vacuoles. The 100 ppm females at 2 years had slight changes in the liver including midzonal degenerative vacuolation (5/50 vs. 1/49) and necrotizing inflammation (4/50 vs. 1/49). and necrosis of individual liver cells (4/50 vs. 1/49).

IV SUMMARY/CONCLUSIONS

The incidence of adenomas in male $B6C3F_1$ mice at 100 ppm was clearly higher than concurrent controls (35% vs. 15%). This high-dose occurrence is lower than the control occurrence (42%) in another study in this strain conducted in the same lab at about the same time. However, it is higher than NTP's mean control data (26%) in this strain, but within their range (4 - 60%). Compared with Charles River historical control data in this strain, the 35% incidence in the current study's 100 ppm group was about twice the control mean value (17.2%), but still within their range (0 - 41.3%).

In females, although a statistical pair-wise increase in the incidence of adenomas was not observed, the treatment-related trends were statistically significant. The incidence at the high dose was within the ranges seen in NTP and Charles River historical control data.

WEIGHT-OF-EVIDENCE

It can be concluded that there was a statistically significant ($p < 0.05$) pair-wise increase in benign liver tumors in males and a trend ($p < 0.05$) in females in this study. However, the weight of these findings is moderated by the fact that these tumors are common in the males of this mouse strain, values in the males fall within the historical control ranges, a lack of pair-wise corroboration in females, and there is no apparent neoplastic response in the rat. The dog study, while a chronic study, is not considered a life time study and therefore contributes little to the argument either way.

The mutagenicity data show that Phosmet is positive in ~~both~~ an in vitro ~~and in two~~ systems.

APPENDICES

A Original Peer Review Submission (dated 6/13/86)

B Peer Review Document (dated 10/21/86)

C New Rat Study DER

D Supplemental Rat DER (incl. tumor tables from the study report)

E Spontaneous Neoplastic Lesions on the $B6C3F_1$/CrlBr Mouse (liver)

F New Information Regarding the Phosmet Mouse Cancer Study from Gowan