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

MAY 20 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review of Phosmet (2nd)

FROM: Marion P. Copley, D.V.M., Section Head
Review Section IV
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Health Effects Division (7509C)
Marion Copley 5/24/94
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TO: George LaRocca, PM #15
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Registration Division (7505C)
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Re-Registration Division (7508W)

THROUGH: Penelope A. Fenner-Crisp 5/24/94
Penelope Fenner-Crisp, Ph.D.
Director, Health Effects Division (7509C)

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on November 17, 1993 and January 26, 1994, to discuss and evaluate the weight-of-the-evidence on Phosmet with particular reference to its carcinogenic potential. The CPRC agreed that Phosmet should be classified as Group C - possible human carcinogen and recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk.

This decision was based on an increased incidence of liver tumors in male B6C3F1 mice at the high dose, that was statistically significant by pair-wise comparison, with a statistically significant trend and which also had an apparent early onset. Female mice had a significant dose-related trend for liver tumors, and for mammary gland adenocarcinomas, as well. There was no evidence for carcinogenicity in an acceptable study in rats. Phosmet was determined by the CPRC to be a potent, direct-acting mutagen.

A. Individuals in Attendance at one or both meetings:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Penelope Fenner-Crisp

Reto Engler

William L. Burnam

Marcia Van Gemert

Karl Baetcke

Kerry Dearfield

Hugh Pettigrew

Esther Rinde

Elizabeth Doyle

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Marion Copley[1]

Bernice Fisher

Lucas Brennecke[2]
(PAI/Clement)

3. Other Attendees:

Diane Mandell (Clement)

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[1]Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

[2]Signature indicates concurrence with pathology report.

B. Material Reviewed:

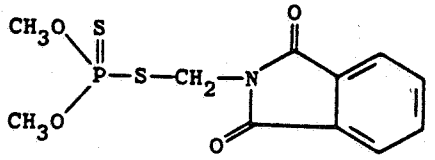
The material available for review consisted of DERs and other data summaries prepared by Marion Copley and statistical analyses prepared by Bernice Fisher. The material reviewed is attached to the file copy of this report.

C. Background Information

Phosmet [N-(mercaptomethyl) phthalimide S-(O,O-dimethyl phosphorodithioate] is a systematic, broad spectrum organophosphate insecticide and acaricide that is registered for use on a variety of crops and on domestic animals.

The Caswell (or Tox Chem) Number of Phosmet is 543.
The Chemical Abstract Registry Number (CAS No.) is 732-11-6.
The PC Code is 059201.

The structure of Phosmet is presented below:



The CPRC first met on June 30, 1986 to review the evidence for the carcinogenicity classification of Phosmet. The Committee concluded that the "data available for Phosmet provided only limited evidence for oncogenicity in animals," and classified Phosmet as a "tentative Category C (possible human) carcinogen." This was based on (1) the increased incidence of liver tumors (adenomas, and adenomas plus carcinomas combined) in male B6C3F1 mice at the highest dose tested (HDT); (2) the positive dose-related trends for liver adenomas and carcinomas in female B6C3F1 mice; (3) no oncogenic effects in an inadequate study conducted in male and female Charles River albino rats; (4) weakly positive results in one mutagenicity test; and (5) structural similarity to analogs with limited carcinogenicity data. 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." The CPRC agreed to reconsider all available information after the two-year rat study is repeated, and additional mutagenicity studies are provided.

The Gowan Co. submitted new information regarding the Phosmet mouse cancer study to the Agency in a document entitled "Phosmet--Discussion Concerning Guideline Series 83-1 and 83-2 Studies" (dated August 12, 1993). This document presents the argument against the Agency's position that Phosmet is a Group C Carcinogen. The Agency's basis for this position in 1986 was a B6C3F1 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 Gowan 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 B6C3F1 mice is within the range of historical control data, both in-house, and the NTP data sets.

The present meeting of the CPRC was held to discuss and evaluate the following data: (1) the new rat oncogenicity study completed in 1991 by Ciba-Geigy Corporation (MRID No. 419164-01, Study No. T-13241), (2) the mouse study and newly submitted information as discussed by Gowan, and (3) six new genotoxicity studies conducted by the registrant. The first rat oncogenicity study, which was previously considered unacceptable by the CPRC on June 30, 1986, was not re-considered at this meeting.

D. Evaluation of Carcinogenicity Data

1. Rat Oncogenicity Study

Reference: RH-7592 Technical: 2-Year Chronic/Oncogenicity Study with R-1504 in Rats. MRID No. 419164-01, Study No. T-13241. Ciba-Geigy Corporation, Farmington, CT. Report issued April 15, 1991.

a. Experimental Design

Groups of Sprague-Dawley rats (Crl:CD(SD)BR) (60/sex/group, except 70/sex in controls) were fed diets containing Phosmet (95.2% purity) at doses of 0, 20, 40, and 200 ppm (equivalent dosages, males: 0, 1.1, 1.8 and 9.4 mg/kg/day, female: 0, 1.1, 2.1 and 10.9 mg/kg/day) for two years, and to 20/sex/group at 400 ppm (equivalent dosages, males: 23 mg/kg/day, female: 27 mg/kg/day) for 1 year. An interim sacrifice of 20/sex/group was conducted at 12 months; survivors were sacrificed at the termination of the study. The 40 ppm group inadvertently received 100 ppm for the first 6 weeks resulting in a time weighted average of 44.2 ppm in this group.

b. Discussion of Tumor Data

There were no significant compound-related tumors observed.

c. Non-neoplastic Lesions and Other Findings

The statistical evaluation of mortality did not indicate significant incremental changes with increasing doses of Phosmet in male or female rats. At 400 ppm in both sexes, body weight and body weight gain were decreased, though these decreases were not, for the most part, statistically significant.

An increased incidence of fatty change in male livers was observed at the 20 ppm dose and above. At 200 ppm and above, increases in the incidence of depressed hepatic foci (in males) and fatty liver change (in females) 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 red blood cell (RBC) cholinesterase (ChE) levels in males at the mid and high dose levels (> 15 %) and borderline decreases in the low dose males; in males and females brain ChE activity was decreased (> 34 %) at 40 ppm and above; and at 400 ppm BUN in females was increased.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The 200 ppm dose was considered adequate for assessing the carcinogenic potential of Phosmet, based on decreased brain ChE activity in both sexes. Adequacy of dosing was supported by the non-neoplastic liver effects at doses ≥200 ppm.

2. Mouse Oncogenicity Study

Reference: T-10919: Two-Year Dietary Oncogenicity Study in Mice with Imidan Technical-Final Report. Stauffer Chemical Company. Accession No. 254608, 245609. Report issued May, 1984.

a. Experimental Design

Groups of B6C3F1 mice (50/sex/group) were fed diets containing Phosmet at doses of 0, 5, 25, or 100 ppm (male - 0, 1.0, 4 and 14 mg/kg/day; females - 0, 1.2, 5 and 18 mg/kg/day) for 2 years. An additional 10 animals/sex/group were treated and sacrificed at week 52; survivors were sacrificed at the termination of the study.

b. Discussion of Tumor Data

Male mice had increases in hepatocellular adenomas and combined adenoma/carcinoma that were statistically significant by pair-wise comparison of the HDT with controls, and a statistically significant increasing trend. Female mice had a significantly increasing trend in carcinoma, and combined adenoma/carcinoma (Tables 1 and 2).

At interim sacrifice, there was an increasing trend in the incidence of combined hepatocellular adenoma/carcinoma in male mice (Table 3). Females did not have liver tumors at this time.

Female mice also had a statistically significant increasing trend in the incidence of mammary gland adenocarcinomas (Table 4). This tumor was considered to be uncommon.

Table 1. Phosmet(Imidan) - B6C3F1 Male Mice, Liver Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (ppm)			
	0	5	25	100
Liver Tumors				
Adenomas (%)	10/59 (17)	10[a]/60 (17)	12/60 (20)	21/60 (35)
p=	0.002**	0.437	0.245	0.008**
Carcinomas (%)	13/59 (22)	11/60 (18)	11[b]/60 (18)	14/60 (23)
p=	0.364	0.815(n)	0.843(n)	0.599
Both (%)	23/59 (39)	21/60 (35)	23/60 (38)	35/60 (58)
p=	0.002**	0.727(n)	0.585(n)	0.019*

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

a First adenoma observed at week 52, dose 5 ppm.
b First carcinoma observed at week 52, dose 25 ppm.

n Negative change from control.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 2. Phosmet(Imidan) - B6C3F1 Female Mice, Liver Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	5	25	100
Liver Tumors				
Adenomas	5/49	4/50	5[a]/48	9/50
(%)	(10)	(8)	(10)	(18)
p=	0.061	0.487(n)	0.617	0.205
Carcinomas	5[b]/49	4/50	3/48	9/50
(%)	(10)	(8)	(6)	(18)
p=	0.046*	0.487(n)	0.369(n)	0.205
Both	10/49	8/50	8/48	18/50
(%)	(20)	(16)	(17)	(36)
p=	0.007**	0.379(n)	0.416(n)	0.066

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53 or were sacrificed at week 52.

a First adenoma observed at week 93, dose 25 ppm.
b First carcinoma observed at week 78, dose 0.

n Negative change from control.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 3. Phosmet(Imidan) - *Interim Sacrifice*
B6C3F1 Male Mice, Liver Tumor Rates[+]
and Exact Trend Test and Fisher's Exact
Test Results (p values)

	Dose (ppm)			
	0	5	25	100
Liver Tumors				
Adenomas (%)	0/10	1/10 (10)	1/10 (10)	2/10 (20)
p=	0.0925	0.5000	0.5000	0.2368
Carcinomas (%)	0/10	0/10	1/10 (10)	1/10 (10)
p=	0.1306	1.000	0.5000	0.5000
Both (%)	0/10	1/10 (10)	2/10 (20)	3/10 (30)
p=	0.0436*	0.5000	0.2368	0.1053

[+] Number of tumor bearing animals/Number of animals examined.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with
control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 4. Phosmet(Imidan) -B6C3F1 Female Mice, Mammary Gland Adenocarcinoma Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	5	25	100
Mammary Gland Adenocarcinomas	1/49	0/50	1/48	5[a]/50
(%)	(2)	(0)	(2)	(10)
p=	0.007**	0.495(n)	0.747	0.107

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53 or were sacrificed at week 52.

a First tumor observed at week 92, dose 100 ppm.

n Negative change from control.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then p<.05 and if ** then p<.01.

The CPRC had historical control data available from a single study in B6C3F1 mice conducted at Stauffer Chemical Company. Historical control data were also obtained from the National Toxicology Program (NTP) database. The NTP historical control data used in the last peer review document were obtained in 1986 and have since been updated. A summary of the tumor incidence and historical controls is tabulated in Table 5. Charles River data were also presented to demonstrate the highly variable nature of this tumor type in male mice.

Table 5. Historical Controls: Incidence of Hepatocellular Adenomas and Carcinomas in Male B6C3F1 Mice[a]

	Present Study		Historical Control Studies		
Liver Tumors	Phosmet HDT(%)	Phosmet Control(%)	Other study Stauffer Chem. Co.(%)[b]	New NTP Data(%)[c]	Charles River(%)
			Males		
Adenoma	35**, T**	17	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 Available
			Females		
Adenomas	18	10	18	12 (2-33)	7.1 (0-17.1)
Carcinomas	18 T*	10	6	6 (0-20)	2.4 (0-6.3)
Total	36 T**	20	22	16 (3-42)	Not Available

a Comparison historical control data in mean % (range).
b This data was obtained in 1985 and consisted of only one incomplete summary of control data.
c This data was obtained from the Gowan Co. (Document dated Aug. 12, 1993) and included all studies conducted from 1980-1987.

* $p < 0.05$ pair-wise comparison T = trend significance
** $p < 0.01$ " "

In male mice, the liver tumor incidences (adenomas, carcinomas and combined adenoma/carcinoma) exceeded the means but were all within the upper range of the NTP historical control data. The same was true for the adenoma and carcinomas relative to the Charles River historical control data (although carcinomas were near the top end reported in the latter). The incidence of combined adenoma/carcinoma in male mice (58%)[3], although within the range of 10 - 68% reported by NTP for 30 studies, exceeded the average of 36.2% and only 3 of the 30 NTP studies conducted from 1981-1984 had incidences $\geq$ 58%. The incidences of carcinoma and combined adenoma/carcinoma also exceeded the corresponding incidences in the other Stauffer study. In female mice, the liver tumor incidences (adenomas, carcinomas and combined adenoma/carcinoma) exceeded the means of the NTP data, and the incidence of carcinomas was near the top end of the range. The incidences of adenomas and carcinomas were also outside of the range of Charles River historical control data and the incidences of carcinomas and combined adenoma/carcinoma exceeded the corresponding incidences in the other Stauffer study.

It was further noted that the incidences of liver tumors in concurrent control mice of both sexes were near or slightly above the average of the ranges reported for historical controls. The increases found in treated animals could thus not be attributed to unusually low incidences in the concurrent controls.

In considering the incidences of liver tumors at the interim 1-year sacrifice in the male mice, the CPRC referred to interim data from 7 NTP studies[3] started between 1978 and 1979 in which the combined liver tumor incidence rates at 40-62 weeks were 0-6%. The combined liver tumor incidences at 52 weeks in the Phosmet study exceeded this range in all dose groups (10, 20, 30% at 5, 25, and 100 ppm, respectively), and there was a statistically significant positive trend.

The incidence of mammary tumors (10%) in female mice, while within the range 0-10% for 30 studies in the NTP database, exceeded the average of 1.5%; furthermore, only 1 out of these 30 studies had an incidence of 10%[3].

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[3]J.Haseman (personal communication to Kerry Dearfield).

c. Non-neoplastic lesions and other findings

The statistical evaluation of mortality and body weight gain indicated no significant incremental changes with increasing doses of Phosmet in male or female mice. The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Clinical examination of the animals revealed a dose-response increase in the incidence of convulsions in males. At both the interim and terminal sacrifices, plasma ChE activity was inhibited about 50 % in males and females at the HDT. Additionally, brain ChE was depressed greater than 20 % in females at the HDT.

Treatment-related non-neoplastic lesions at the 12-month sacrifice included increased incidence of regenerative epithelial hyperplasia of the kidneys in HDT males and midzonal degenerative vacuolation of the liver, dilation of the uterus, and inflammation of the kidneys in HDT females.

At terminal sacrifice, there was an increased incidence of perivasculitis of the muscle, testicular atrophy, hyperplasia of the stomach mucosa, and degenerative vacuolation of individual liver cells in HDT males. Slight increases in midzonal degenerative vacuolation, necrotizing inflammation and necrosis of individual liver cells, myometrial atrophy of the uterus, and meningitis of the spinal cord in HDT females.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

Dosing in this study was adequate for carcinogenicity testing, based on decreased plasma and brain ChE activity in both sexes, testicular changes in males, and liver changes in both sexes at the HDT.

e. New Information Regarding the Study

As described in Section C. (Background), a report dated August 12, 1993 was submitted to the Agency by the registrant, Gowan Company, arguing that the EPA failed to consider critical information in its evaluation of Phosmet. The report introduces new historical control data from NTP for liver tumors in B6C3F1 mice. These data include additional NTP studies conducted during the same time period as the studies given in the original NTP report. Gowan Company believes that these new NTP data are essential in evaluating the test material because they "confirm that the liver tumors observed in the Phosmet mouse study are

toxicologically meaningless in light of the unpredictable and nearly universal incidence of spontaneous liver tumors in control B6C3F1 mice."

The CPRC considered these new data and noted that while the incidences of liver tumors (adenomas, carcinomas and combined adenoma/carcinoma) in the mouse study were within the new NTP historical control range, they exceeded the corresponding means, in both sexes. In female mice, the incidence of carcinomas was near the top end of the NTP range. The CPRC also took into account the incidence of combined adenoma/carcinoma in male mice at the interim sacrifice.

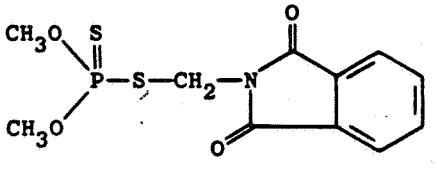
E. Additional Toxicological Data on Phosmet.

1. Structure-Activity Relationships

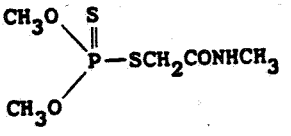
Phosmet contains the mercaptomethylphthalimide moiety as its primary structural configuration. A computer based search on the Chemical Information system (CIS) generated a list of 16 additional chemicals that also contained this moiety. Of these 16 chemicals only one, Folpet, is known to be carcinogenic or mutagenic, however it was not considered to be an appropriate structural analog for Phosmet. It was suggested (after the meeting) that a good structural analog for Phosmet would be Dimethoate, another organophosphate, which has been shown to be both carcinogenic and mutagenic. Dimethoate was associated with lymphatic tumors in male B6C3F1 mice and tumors of the skin and lymphatics in male Wistar rats.

Figure 1. Structures of Phosmet and Dimethoate

Phosmet



Dimethoate



2. Genotoxicity

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 dominant lethal test in the rabbit proved inconclusive.

Summary of New Data:

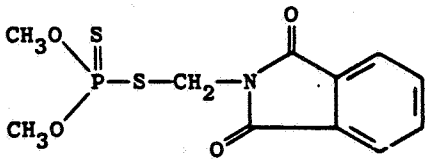
The following table summarizes the results of six new mutagenicity studies conducted and submitted on Imidan (Phosmet). All tests were graded Acceptable.

Study Title	Results
Salmonella typhimurium (TA100, TA1535) Reverse Mutation Study No. T-12819; MRID No. 00164884 March 3, 1986	Positive with and without activation
Mouse Lymphoma Forward Mutation Assay Study No. T12820; MRID No. 00164885 May 8, 1987	Positive with and without activation
Mouse Lymphoma Multiple Endpoint Test Cytogenetic Assay Study No. T 12821; MRID No. 00164886 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; MRID No. 00164887 May 21, 1987	Negative with and without metabolic activation
Morphological Transformation of BALB/3T3 Cells Study No. T-12822; MRID No. 00164888 August 12, 1986	Positive
Micronucleus Assay in Mouse Bone Marrow Study No. T86/756; MRID No. 401994-01 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.

Published literature also demonstrate the mutagenic activity of Phosmet in the Salmonella assay, gene mutation in mammalian cells and transformation in the SHE (Syrian hamster embryo) cells.

It should be noted that Formaldehyde, which is a probable metabolite of Phosmet, has been reported to be mutagenic in many systems (IARC Monographs on Evaluation of Carcinogenic Risks to Humans, Supplement 6, 1987). These include gene mutations in Salmonella, E.coli, yeast, Drosophila and in cultured mammalian cells without exogenous metabolic systems. Formaldehyde induces chromosome breaks, sister chromatid exchanges (SCE), structural aberrations, unscheduled DNA synthesis (UDS) and cell transformation in cultured mammalian cells without exogenous metabolic systems. In in vivo mouse micronucleus, structural aberration, mouse dominant lethal and SCE tests, results have been mainly negative (although there is an occasional positive report for aberrations and SCE).

The CPRC concluded that Phosmet is a very potent, direct-acting mutagen. This very potent in vitro activity may be attributed to the fact that Phosmet is expected to be a methylating agent, since it is a methyl ester of thiophosphoric acid. The poor correlation between carcinogenicity and mutagenicity of organophosphates may be due to rapid detoxification before they can reach their target sites[4]. Once an organophosphate loses one of its three ester groups, it is no longer an alkylating agent. The side chain in Phosmet is expected to undergo hydrolysis in acidic media (to formaldehyde and dimethyl thiophosphate) due to the presence of the methylene group between 2 heteroatoms (N & S); this may explain Phosmet's very weak carcinogenic activity despite its potent in vitro activity.



Phosmet.

[4]Woo, YT and Arcos, JC. Role of Structure-Activity Relationship Analysis in Evaluation of Pesticides for Potential Carcinogenicity. In: Carcinogenicity and Pesticides, NN Ragsdale, RE Menze, Eds. ACS Symposium Series 414. American Chemical Society, Wash. D.C. (1989).

F. Weight of the Evidence Considerations

The Committee considered the following observations regarding the toxicology of Phosmet for a weight-of-the-evidence determination of its carcinogenic potential:

1. Sprague-Dawley rats had no compound-related tumors in a study determined to have adequate dosing.

2. Phosmet produced a statistically significant elevated incidence of hepatocellular adenomas and combined adenomas/carcinomas in male B6C3F1 mice by pair-wise comparison between the HDT (100 ppm) and controls. The incidence of these tumors also occurred with a statistically significant increased trend.

   In female B6C3F1 mice there was a statistically significant increased trend for carcinomas and adenoma/carcinoma.

   At interim sacrifice, there was a statistically significant increasing trend in the incidence of combined hepatocellular adenoma/carcinoma in male mice. Females did not have liver tumors at this time.

   Female mice also had a statistically significant increasing trend in the incidence of mammary gland adenocarcinomas, a tumor type considered to be uncommon.

3. The NTP historical control database which was used in 1986 to evaluate Phosmet has since been updated. The CPRC noted that while the incidences of liver tumors (adenomas, carcinomas and combined adenoma/carcinoma) in the mouse study were within the new NTP historical control range, they exceeded the corresponding means, in both sexes. In female mice, the incidence of carcinomas was near the top end of the NTP range.

   The incidences of liver tumors in concurrent control mice of both sexes were near or slightly above the average of the ranges reported for historical controls. The increases found in treated animals could thus not be attributed to unusually low incidences in the concurrent controls.

   The incidence of mammary tumors (10%) in female mice, while within the range 0-10% in 30 studies, exceeded the average of 1.5%; furthermore, only 1 out of these 30 studies had an incidence of 10%.

4. Phosmet was demonstrated to be a very potent, direct-acting mutagenic agent in in vitro genotoxicity tests. Formaldehyde, a probable metabolite of Phosmet, also had direct-acting in vitro activity. The poor correlation between the strength of the response of Phosmet in in vitro mutagenicity tests, compared to that obtained in the carcinogenicity studies, may be due to its rapid detoxification in vivo.

5. Phosmet is structurally related to Dimethoate, another organophosphate pesticide which has been shown to be both carcinogenic and mutagenic.

6. Carcinogenicity in animals -- Phosmet

After a full evaluation of all of the data and supporting information regarding animal carcinogenicity based on the criteria used by the NTP[5], the Committee concludes that exposure to Phosmet resulted in a statistically significant increase in the incidence of hepatocellular adenomas and combined hepatocellular adenoma/carcinoma in male mice. There was also a statistically significant trend for these tumors in males and for hepatocellular carcinoma and combined adenoma/carcinoma and mammary adenocarcinoma in females, as well. Phosmet has been shown to be a direct-acting mutagen in many in vitro mutagenicity assays. There was no evidence for carcinogenicity of Phosmet in a rat study. The relevance of the tumor data to an evaluation of Phosmet's potential for human carcinogenicity is discussed elsewhere.

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[5]Arguments were presented for both "equivocal" and "some" evidence for the mouse, based on the NTP criteria for carcinogenicity:

> ***Some evidence*** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence. (***Clear evidence*** *of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such lesions to progress to malignancy.)*
>
> ***Equivocal evidence*** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical-related.

The majority opinion of the CPRC was that the animal evidence, using the NTP criteria as stated above, is "equivocal" for carcinogenic activity of Phosmet with studies showing a marginal increase in neoplasms in the mouse that may be chemically related. The overall consensus of the CPRC, based on the criteria contained in the EPA Guidelines in a weight-of-the-evidence determination, was that the evidence for Phosmet was "limited" and met the criteria for a Group C - possible human carcinogen. A discussion of this determination is provided elsewhere in this document (Section G).

G. Classification of Carcinogenic Potential:

The CPRC considered the criteria contained in the EPA's "Guidelines for Carcinogenic Risk Assessment" (FR51: 33992-34003, 1986) for classifying the weight of evidence for carcinogenicity.

There was much discussion on whether Phosmet should be given the classification of Group C or Group D. Arguments presented for a Group D classification were that liver tumors have a high background rate in the male B6C3F1 mice, the increases in males were considered to be marginal and occurred only at the high dose. The female liver tumor response had a statistically significant trend, but was not statistically significant by pair-wise comparison, and the response occurred only at high dose. The increases in both sexes were within the NTP historical control range. The increase in mammary gland adenocarcinomas in the females was also considered to be marginal.

The arguments for Group C were: increased incidence of liver tumors in male B6C3F1 mice at the high dose, which were statistically significant by pair-wise comparison, with a statistically significant trend and which also had an apparent early onset. Female mice had a significant dose-related trend for liver tumors. Although the incidences of these tumors were within the range of the NTP data base, they all were well above the means reported for these data. Also concurrent control incidences for liver tumors in both sexes were near or slightly above average (the increases found in treated animals could thus not be attributed to unusually low incidences in the concurrent controls). Further support for the Group C was that the incidences of tumors in male mice at the interim sacrifice exceeded the range of the NTP *interim* data base. Female mice also had a very significant trend ($p=0.007$) for mammary gland adenocarcinomas, as well. This tumor type is considered to be uncommon (10% incidence in the HDT vs 2% in concurrent controls); while the NTP data communicated to the CPRC indicated a range for this tumor of 0-10%, the average was 1.5%, and only one out of 30 studies had an incidence of 10%. Furthermore, Phosmet was determined by the CPRC to be a potent, direct-acting mutagen.

There was no evidence for carcinogenicity in an acceptable study in rats.

The consensus of the CPRC was that Phosmet should be classified as Group C - possible human carcinogen and recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk.