6/20/86

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

JUN 20 1986

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review on Imidam (Phosmet) for Oncogenic Effects.

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

TO: Addressees

A meeting has been scheduled in Dr. Farber's office on June 30, 1986 at 10:30 AM to discuss the weight-of-the-evidence concerning oncogenic effects of Imidam.

Attached for your review is a package prepared by William Greear.

Attachment

Addressees:

Theodore Farber
William Burnam
Jack Quest
Judy Hauswirth
Esther Rinde
Albin Kocialski
Bertram Litt/Bernice Fisher
Louis Kasza
Anne Barton
Stephen Johnson
Robert Beliles
Richard Hill/Don Barnes
Diane Beal

#13 6/20/86 sb

Imidam

Reviewer's Peer Review Package for 1st Meeting

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: The Weight of the Evidence Evaluation for the Oncogenic Potential of Phosmet (Imidan)

TOX Chem. No. 543

FROM: William B. Greear, M.P.H. William B. Greear 6/13/86
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: The Peer Review Committee for Phosmet
Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Albin B. Kocialski, Ph.D. ABK 6/13/86
Supervisory Pharmacologist
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Attached is a report prepared for the Peer Review Committee on Phosmet. Data is provided so that a "Weight of the Evidence" determination may be made regarding the oncogenic potential of phosmet.

Attachment

Contents

F. Data Evaluation Reports

1. Mouse Oncogenicity Study

2. Lifetime Rat Feeding Study

3. Metabolism Studies

G. Toxicology Branch "One-Liners"

H. World Health Organization Report on Phosmet

REPORT FOR THE PEER REVIEW COMMITTEE
FOR ASSESSING THE ONCOGENICITY OF PHOSMET

I. Background

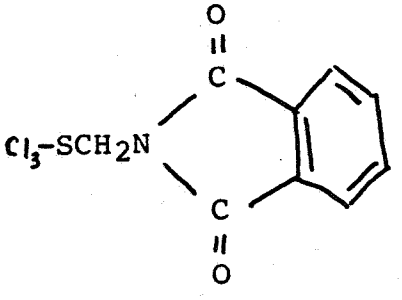
Phosmet [N-(mercaptomethyl) phthalimide S-(O,O-dimethyl phosphorodithioate] is a systemic, broad spectrum insecticide and acaricide. It is currently available under the trade names Appa, Imidan, Prolate, and R-1504. It is registered for use on domestic animals and on a variety of crops.

II. Metabolism

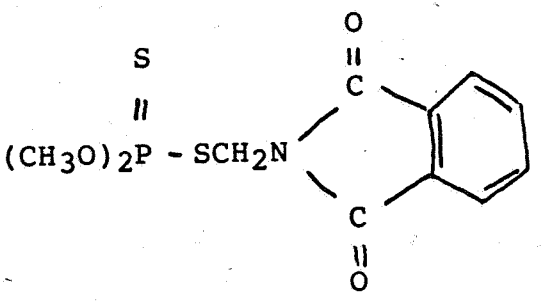
The results of three metabolism studies (MRID#'s 00056864, 00056865, and 00093487) indicate that phosmet is rapidly eliminated with 78 percent being eliminated in the urine and 19 percent in the feces within 72 hours after administration of a single oral dose to rats. The major water soluble urinary metabolites have been "tentatively" identified as a phthalamic acid (51-54%), phthalic acid (16-21%) and a derivative of phthalic acid (7-9%). The major water soluble metabolite "tentatively" identified in the feces was phthalmic acid. (See Appendix A for a diagram of the metabolic pathway.)

III. Structure Activity Relationships

A search was conducted on the Chemical Information System (CIS) to determine those chemicals containing the mercaptomethylphthalimide moiety which is contained in phosmet (see below).

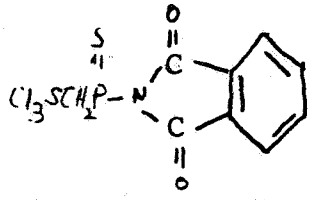


metcaptomethylphthalimide moiety



phosmet

A list was generated containing 16 chemicals, including phosmet (see Appendix B for identification). A literature search was then conducted over several of the National Library of Medicine databases including: Registry of Toxic Effects of Chemical Substances, Toxline, Toxback 76 and Toxback 65. With the exception of phosmet, no information was available online which would indicate that any of the chemicals were oncogenic or mutagenic. One additional chemical which contains a phthalimide moiety, similar to phosmet, and is of concern to the Agency is folpet (structure shown below). Folpet produces intestinal tumors in mice and is mutagenic in in vitro systems. However, folpet, unlike phosmet, contains a side chain which is thought to convert to thiophosgene, a highly reactive compound which may be responsible for producing the oncogenic effects observed in the mouse (Copley, 1985).



folpet

IV. Subchronic Studies with Preneoplastic Effects

Two subchronic studies have been conducted in rats; a 19- to 24-week feeding study (MRID#'s 00081456 and 00080566) and a 16-week feeding study (MRID# 00081429). The studies were conducted in albino rats obtained from Charles River Breeding Laboratories. In both studies there were no indications that administration of phosmet to rats produced preneoplastic lesions.

V. Summary of Lifetime Studies

a. Two-Year Dietary Oncogenicity Study in Mice with Phosmet

Species/Strain:	Mouse/$B_6C_3F_1$
Testing Facility:	Stauffer Chemical Company Environmental Health Center
Number of Animals:	60 mice/sex/group (interim sacrifice of 10 mice/sex/group at 12 months)

Mice were administered phosmet technical in the diet at levels of 0, 5, 25, 100 ppm for a period of two years. The number of animals surviving until termination was 56, 53, 50 and 52 males and 46, 45, 49 and 48 females in the 0, 5, 25

and 100 ppm groups, respectively. There was an increased incidence of convulsions in males in the 25 and 100 ppm groups. Plasma cholinesterase was inhibited in males and females in the 100 ppm group. Brain cholinesterase was inhibited in all treatment groups at 12 months and in females in the 100 ppm group at termination. The absolute and relative weight of the liver was increased in females in the 25 and 100 ppm groups. The absolute weight of the liver was increased in males in the 100 ppm group. There was an increased incidence of degenerative vacuolation of individual liver cells and foci of vacuolated or clear cells in the liver of males in the 100 ppm group. Males in the 100 group also exhibited perivasculitis of muscle, hyperplasia of stomach mucosa and testicular atrophy. Females in the 100 ppm group exhibited midzonal degenerative vacuolation, necrotizing inflammation and individual cell necrosis of the liver, inflammation of the stomach and duodenum and myometrial atrophy of the uterus. The incidence of neoplasms observed in the study can be found in Appendix C. Neoplastic findings included an increased incidence of hepatocellular adenomas and carcinomas in males and females in the 100 ppm group. The incidence of hepatocellular tumors is provided in the table on the following page.

The results of the Toxicology Branch's statistical analysis of the data using the Cochran-Armitage Dose-Adjusted Trend test for Summary results, and Peto's Prevalence Method for time of death adjusted dose-response, indicates that there is a significant dose-response trend ($p < .01$), for tumors associated with increasing doses of Imidan, in both males and females. In the statistical comparisons of tumors in the controls versus the high dose group of phosmet, (by means of Fisher's Exact test) there is only borderline associations in both males and females, $p = .05$ and .06 respectively (see Appendix D for the statistical analysis).*

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*The statistical analysis was performed on data obtained from a preliminary analysis of the study. The numerator and the denominator are somewhat different in the final analysis. This would tend to produce a lower p value in males when comparing the control and high-dose groups.

Incidence of Hepatocellular Tumors in $B_6C_3F_1$ Mice

Males

Interim Sacrifice	Control	Low (5 ppm)	Mid (25 ppm)	High (100 ppm)
Hepatocellular adenoma	0/11 (0%)	1/10 (10%)	2/10 (20%)	2/10 (20%)
Hepatocellular carcinoma	0/11 (0%)	0/10 (0%)	1/10 (10%)	1/10 (10%)
Hepatocellular adenoma or carcinoma	0/11 (0%)	1/10 (10%)	2/10 (20%)	3/10 (30%)

Final and Interim Sacrifices	Control	Low (5 ppm)	Mid (25 ppm)	High (100 ppm)
Hepatocellular adenoma	13/60 (22%)	10/60 (17%)	14/60 (23%)	27/60 (45%)
Hepatocellular carcinoma	13/60 (22%)	11/60 (18%)	11/60 (18%)	14/60 (23%)
Hepatocellular adenoma or carcinoma	23/60 (38%)	21/60 (35%)	23/60 (38%)	35/60 (58%)

Females

Interim Sacrifice

No hepatocellular tumors were observed.

Final and Interim Sacrifice	Control	Low (5 ppm)	Mid (25 ppm)	High (100 ppm)
Hepatocellular adenoma	6/60 (10%)	4/60 (7%)	5/58 (9%)	11/60 (18%)
Hepatocellular carcinoma	5/60 (8%)	4/60 (7%)	3/58 (5%)	9/60 (15%)
Hepatocellular adenoma or carcinoma	10/60 (17%)	8/60 (13%)	8/58 (14%)	18/60 (30%)

The time-to-tumor appearance was 545, 659, 651 and 617 days for females and 610, 364, 365, and 364 for males in the 0, 5, 25 and 100 ppm groups, respectively. Pulmonary metastasis of hepatocellular carcinoma occurred in 2, 4, 2 and 3 males in the 0, 5, 25 and 100 ppm groups. The number of mice dying prior to termination that had hepatocellular tumors (excluding mice with hepatocellular tumors at the interim sacrifice) was 3, 4, 4 and 7 for males and 3, 2, 1 and 3 for females in the control-to-high-dose groups, respectively.

Historical control data on the incidence of hepatocellular tumors in $B_6C_3F_1$ mice at the laboratory that conducted the study can be found in Appendix E. Historical control data from studies conducted by NCI/NTP obtained from an article by Goodman (1985) and an article by Tarone (1981) can be found in Appendix E.

The study was conducted with at least one dose level being tested at the maximum tolerated dose (MTD) as indicated by depression of cholinesterase activity in plasma and brain of males and females in the 100 ppm group, convulsions in males in the 25 and 100 ppm groups, microscopic pathological changes in the liver of males and females in the 100 ppm group, and histopathological changes in miscellaneous organs/tissues in animals in the 100 ppm group.

b. Two-Year Lifetime Feeding Study in Rats with Phosmet

Species/Strain: Rat/Charles River
Testing Facility: Stauffer
Number of Animals: 25 rats/sex/group

Charles River rats were administered technical phosmet in the diet at levels of 20, 40 and 400 ppm for a period of 2 years. Body weight gain was slightly decreased in males in the 400 ppm group. Plasma, erythrocyte and brain cholinesterase activity was decreased in rats in the 400 ppm group. Minimal liver cell alteration was observed in rats in the 400 ppm group. Neoplasms found and diagnosed were judged to be unrelated to treatment. The NOEL was determined to be 40 ppm.

VI. Summary of Short-term Tests

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 subtilis* strains H17 Rec^+ and M45 Rec^- without metabolic activation. Phosmet was negative when tested at levels up to 20 ug dissolved in DMSO (Shirasu, 1975; Shirasu *et al.*, 1976). Phosmet was tested at levels up to 5000 ug/plate in an Ames test using *Salmonella typhimurium* strains TA 100, TA 98, TA 1535, TA 1537 and TA 1538 and in *E. coli* strain WP2 hcr with and without metabolic activation. A positive response was obtained in *S. typhimurium* strain TA 100 without metabolic activation (Moriya *et al.*, 1983).

VII. Summary

Phosmet is structurally related to 16 chemicals containing the mercaptomethyl phthalimide moiety. No data are available which would indicate that these chemicals are carcinogenic. Phosmet is similar in structure to folpet which contains the phthalimide moiety. Folpet produces intestinal tumors in mice. However, the oncogenicity of folpet is thought to be associated with its metabolic conversion to thiophosgene. The side chain in folpet which converts to thiophosgene is not, however, present in phosmet. Several subchronic studies have been conducted in rats with phosmet, but no preneoplastic lesions were observed. Phosmet has been tested in a reversion assay with E. coli strains B/r WP2 hcr^+ and WP2 hcr^- and in a rec-assay with Bacillus subtilis H17 Rec^+ and M45 Rec^- without metabolic activation. Negative results were obtained. When tested in E. coli strain WP2 hcr and Salmonella typhimuruim strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 with and without metabolic activation, postive results were obtained in strain TA 100 without metabolic activation.

In the lifetime feeding study in Charles River Rats, there was no indication that phosmet produced an oncogenic effect when fed at levels up to 400 ppm in the diet for 2 years. Neoplasms found and diagnosed were judged to be unrelated to treatment. In the 2 year mouse study, there were increases in the incidences of hepatocellular tumors in mice (primarily in males) in the high-dose group (100 ppm) when compared to controls. However, there were no increases in hepatocellular tumors in mice in the low (5 ppm)- and mid (25 ppm)-dose groups when compared to controls.

References

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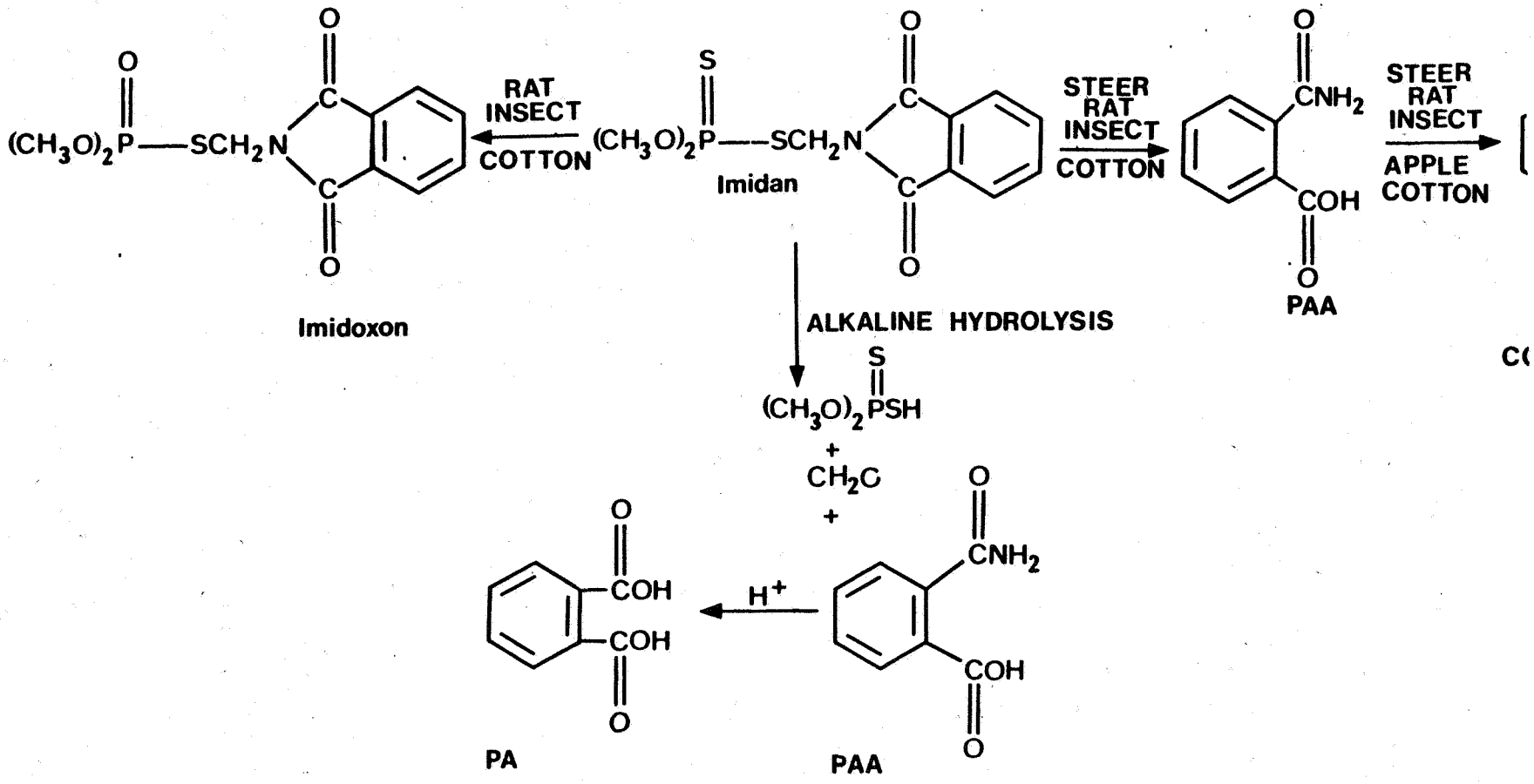
APPENDIX A

Diagram of Metabolic Pathway for Phosmet

APPENDIX A

PATHWAY OF IMIDAN METABOLISM IN COTTON, INSECTS AND RATS AND HYDROLYSIS IN WATE



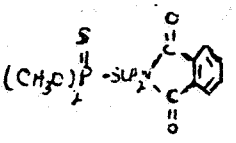
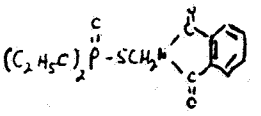
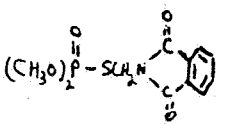
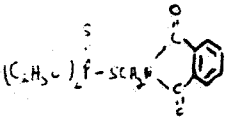
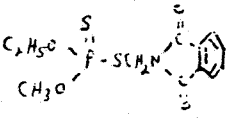
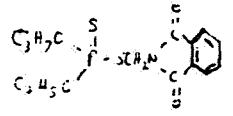
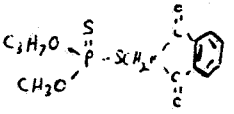
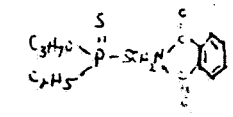
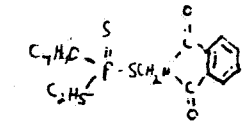
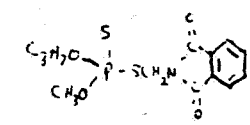
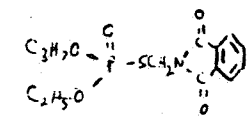
PA - Phthalic Acid
PAA - Phthalamic Acid

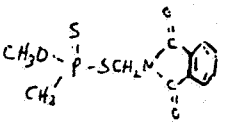
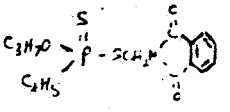
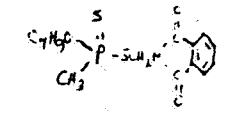
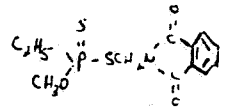
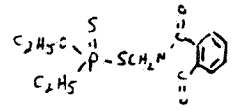
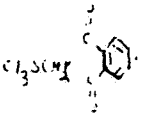
APPENDIX B

Structure Activity Relationships
Indetification of Similar Chemicals

APPENDIX B

Structure Activity Relationship
Identification of Similar Chemicals

Chemical Name (Synonym)	CAS No	Structure
Phosphorodithioic acid, S-[(1,3-dihydro-1,3 dioxo-2H-isoindol-2-yl)methyl]0,0-dimethyl ester (phosmet)	732-11-6	
Phosphorothioic acid, S-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]0,0-diethyl ester (ENT 25,706)	3734-92-7	
Phosphorothioic acid, S-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]0,0-dimethyl ester (imidoxon)	3735-33-9	
Phosphorodithioic acid, S-[(1,3-dihydro-1,3-dioxo-2H-isiondol-2-yl)methyl]0,0-diethyl ester (ENT 25,532)	6119-96-6	
Phosphorodithioic acid, S-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]0-ethyl 0-methyl ester (ENT-25,865)	13104-29-5	
Phosphorodithioic acid, O-ethyl 0-isopropyl ester, S-ester with N-(mercaptomethyl) phthalimide (ENT 25,866)	14813-38-8	
Phosphorodithioic acid, S-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]0-(1-methylethyl) ester (ENT 25,867)	15863-65-7	
Phosphonodithioic acid, ethyl-,S-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]0-(1-methylethyl) ester (N 4539)	16537-51-2	
Phosphonodithioic acid, ethyl-,S-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]0-(2-methylpropyl ester (casil)	16537-52-3	
Phosphorodithioic acid, S-[1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]0-methyl 0-propyl ester (ENT 25,863)	19133-14-3	
Phosphorodithioic acid, 0-ethyl 0-propyl ester,S-ester with N-(mercaptomethyl) phthalimide (ENT 25,864)	19133-16-5	

Phosphonodithioic acid, methyl-S-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl] O-methyl ester	22243-91-0	
Phosphonodithioic acid, ethyl-o-propyl ester, S-ester with N-(mercaptomethyl) phthalimide	24017-17-2	
Phosphonodithioic acid, methyl-,0-isobutyl ester, S-ester with N-(mercaptomethyl) phthalimide	24017-18-3	
Phosphonodithioic acid, ethyl-,0-methyl ester, S-ester with N-(mercaptomethyl) phthalimide	24017-20-7	
Phosphonodithioic acid, ethyl-,0-ethyl ester with N-(mercaptomethyl)phthalimide	24017-24-1	
N-(Mercaptomethyl)phthalimide S-(0,0-dimethyl phosphorodithioate), 0-analog	NA	
1H-Isoindole-1,3(2H)-dione, 2-((trichloromethyl)thio) (folpet)	133-07-3	

APPENDIX C

Summary Tables on the Incidence of Tumors in Mice

APPENDIX C

18 pages of Stauffer data (stamped confidential) is not included.

APPENDIX D

Toxicology Branch Statistical Analysis of Mouse Study

APPENDIX D

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

FEB 26 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Imidan Technical (T-10719) - Qualitative Analysis of Mouse Oncogenicity Study

FROM: Bernice Fisher
Statistician, Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: David G. Van Ormer, Ph.D.
Toxicologist, Section II
Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Bertram D. Litt, Leader, Statistical Staff
Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Summary:

Survival is not significantly affected by increasing doses of Imidan in either male or female mice. However, some early deaths with tumors are noted.

The liver tumor rates for combined number of adenomas and carcinomas, are significantly ($p < .01$) associated with increasing doses of Imidan for both sexes. The comparisons of control's liver tumor rates with the highest dosed Imidan groups support these findings with borderline results in both males ($p = .05$) and females ($p = .06$).

Background:

A 2-year dietary oncogenicity study in mice was conducted by Stauffer Chemical Company (April 1981 to May 1983). The mice, B6C3F$_1$-CRL-Br strain, were given concentrations of 0, 5, 25, and 100 ppm of Imidan Technical, respectively, for 24 months.

APPENDIX D

Sixty mice per sex were assigned by block randomization based upon weight distributions to each of the four treatment groups. At the end of 52 weeks, 10 animals were sacrificed in each of the groups.

Qualitative Analysis:

Survival analysis (see table 1A and B) indicated that mortality was not affected by increasing doses of Imidan. In females, the actual mortality trend was so obviously not dose related that further statistical analyses were not needed; while in males some additional statistical analysis was required. The Cochran-Armitage Trend test was applied first to male mortality for 81 to 104 weeks and then to the cumulative deaths that were tallied at the end of the study. No significant trends were found in either time period. In addition, the use of Fisher's Exact Test to compare all deaths in the control group with those in the highest dosed group in males for the two time periods mentioned above, did not show significant differences.

This Imidan study indicated that liver tumors alone were numerous enough to suggest statistical evidence of an effect with increasing doses . These occurrences in both males and females began only after 52 weeks of the study period and they were more or less equally distributed for adenomas and carcinomas (see table 2A and B for details). Most of the tumors were detected in the Final Kill data.

In males, adenomas were more prevalent with increasing doses of Imidan in comparison to the number of carcinomas. In females, both the adenomas and the carcinomas increased substantially with the increasing doses of Imidan during the time of the study. The liver tumor findings are shown in table 2A and B. Statistical tests were performed on the combined rates of adenomas and/or carcinomas.

The results of the Statistical Analysis By the Cochran-Armitage Dose-Adjusted Trend test for Summary results, and Peto's Prevalence Method for time of death adjusted dose-response, indicated that there is a significant dose-response trend ($p < .01$), for tumors associated with increasing doses of Imidan, in both males and females.

In the statistical comparisons of tumors in the controls versus the high dose group of Imidan, (by means of Fisher's Exact test) there is only borderline associations in both males and females,

p=.05 and .06, respectively. However in the evaluation of the Final Kill data, where most of the liver tumors were found, the females showed a significant (p = .027) increase in the comparison of the controls and the highest dose of Imidan by Fisher's Exact test. In addition, statistically significant (p = .036) differences were found in the number of liver tumors between the combined group of 0, 5, and 25 ppm of Imidan versus the highest dose of 100 ppm in the male mice and a borderline (p = .06) difference in the females.

APPENDIX D

4

Table 1. Imidan, Survival

A. Mortality,* Mice - Males

Time interval (weeks)	Dose (ppm) 0	5	25	100
0-28	1/60	0/60	0/60	0/60
29-52[a]	10/59	10/60	10/60	10/60
53-80	0/49	1/50	0/50	0/50
81-104	3/49	6/49	10/50	8/50
Total Deaths	4	7	10	8
104th week survivors	46	43	40	42

B. Mortality,* Mice - Females

Time interval (weeks)	Dose (ppm) 0	5	25	100
0-28	1/60	0/60	1/60	0/60
29-52[a]	11/59	10/60	11/59	10/60
53-80	1/48	1/50	1/48	0/50
81-104	11/47	14/49	8/47	12/50
Total Deaths	14	15	11	12
104th week survivors	36	35	39	38

* Deaths/Animals at Risk
[a] Includes 10 animals sacrificed at week 52

APPENDIX D

Table 2. Imidan - Liver Tumors

A. Number of Mice - Males with Tumors

Diagnosis	Dose (ppm) 0	(%)	5	(%)	25	(%)	100	(%)
Adenoma	10	(17)	11	(18)	12	(20)	21	(35)
Adenoma and Carcinoma	3	(5)	-	(0)	2	(3)	6	(10)
Carcinoma	12	(20)	11	(18)	9	(15)	8	(13)
All Tumor-Bearing Animals	25	(42)	22	(37)	23	(38)	35	(58)
Animals Examined	59	(100)	60	(100)	60	(100)	60	(100)

B. Number of Mice - Females with Tumors

Diagnosis	Dose (ppm) 0	(%)	5	(%)	25	(%)	100	(%)
Adenoma	5	(10)	4	(8)	4	(8)	9	(18)
Adenoma and Carcinoma	1	(2)	-	(0)	-		2	(4)
Carcinoma	4	(8)	4	(8)	3	(6)	7	(14)
All Tumor-Bearing Animals	10	(21)	8	(16)	7	(15)	18	(36)
Animals Examined	48	(100)	50	(100)	48	(100)	50	(100)

Table 3. Imidan - Incidence* of Liver Tumors

A. Mice - Males

Dose (ppm)	Weeks	52[a]	53-104	FK	Total**
0		0/10	2/3	23/46	25/59
5		1/10	5/7	16/43	22/60
25		2/10	3/10	18/40	23/60
100		2/10	5/8	28/42	35/60
T		92.5	18.75	638.333	749.583
V		7207.53	11447.5	69051.4	87706.43
Z		1.090	0.175	2.429	2.531
p		0.14	0.43	7.60×10^{-3}	5.70×10^{-3}

B. Mice - Females

Dose (ppm)	Weeks	52[a]	53-104	FK	Total***
0		-	4/12	6/36	10/48
5		-	2/15	6/35	8/50
25		-	1/9	6/39	7/48
100		-	3/12	15/38	18/50
T			22.5	576.284	598.784
V			13327.8	41810.7	55138.50
Z			0.195	2.818	2.550
p			0.42	2.40×10^{-3}	5.39×10^{-3}

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[a] Sacrifice deaths only
* Deaths of Tumor-Bearing Animals/All Deaths
** Liver tumors did not appear in males previous to 52 weeks
*** liver tumors did not appear in females previous to 53 weeks

APPENDIX E

Historical Control Data on the Incidence of Neoplastic Lesions in Mice

APPENDIX E

1. Neoplastic Lesions in B6C3F1 Mice-Stauffer

Liver Tumors in Historical Controls

The incidences of adenomas, carcinomas or either tumor were tabulated for male and female $B6C3F_1$ mice from the historical control group. As indicated in section 2, Dr. Doyle W. Frank was the study pathologist who examined tissues from both male and female historical animals. Liver tumors for males and females were not combined because of the obvious sex difference in incidences. Combination would have resulted in misleading data that underestimated tumor incidence in males and overestimated it in females. Data for all historical control mice, including those sacrificed at 12 months, are included in the following table.

Tumor type	Incidence	
	Male	Female
Hepatocellular adenoma (single or multiple)	25/60 (42%)	9/60 (15%)
Hepatocellular carcinoma (single or multiple)	10/60 (17%)	3/60 (5%)
Either hepatocellular adenoma or carcinoma	31/60 (52%)	11/60 (18%)

APPENDIX E

2. Neoplastic Lesions in B6C3F1 Mice-Goodman et al.(1985)

Table 4: Common Primary Neoplasms in B6C3F1 Mice[a,b]

	Male			Female		
	Number of Tumors (%)	Standard Deviation, %	Range, %	Number of Tumors (%)	Standard Deviation, %	Range, %
Circulatory system	2343[d]			2486[d]		
Hemangioma	34 (1.5)	3.3	0-16	39 (1.6)	1.9	0-6
Hemangiosarcoma	64 (2.7)	2.6	0-10	48 (1.9)	2.3	0-8
Digestive system						
Liver	2334[c]			2469[c]		
Hepatocellular adenoma	240 (10.3)	5.5	0-24	98 (4.0)	3.9	0-18
Hepatocellular carcinoma	498 (21.3)	6.9	8-36	101 (4.1)	3.0	0-15
Total	725 (31.1)	7.5	16-58	196 (7.9)	4.6	0-20
Endocrine system						
Anterior pituitary	1903[c]			2051[c]		
Adenoma	11 (0.6)	1.6	0-6	163 (7.9)	8.5	0-32
Carcinoma	1 (0.1)	0.3	0-2	8 (0.4)	0.9	0-5
Adrenal	2240[c]			2306[c]		
Cortical adenoma	53 (2.4)	3.0	0-15	7 (0.3)	1.1	0-4
Cortical carcinoma	3 (0.1)	0.6	0-4	1 (<0.1)	0.3	0-2
Pheochromocytoma	28 (1.2)	1.9	0-6	16 (0.7)	1.2	0-4
Pheochromocytoma, malignant	2 (0.1)	0.4	0-2	0	-	-
Thyroid	2178[c]			2203[c]		
Follicular cell adenoma	22 (1.0)	1.6	0-6	40 (1.8)	2.1	0-9
Follicular cell carcinoma	5 (0.2)	0.6	0-2	6 (0.3)	1.5	0-10
Hematopoietic system	2343[d]			2486[d]		
Lymphoma/leukemia	29 (1.2)	7.3	2-32	677 (27.2)	9.9	8-62

(continued)

APPENDIX E

2. Neoplastic Lesions in B6C3F1 Mice-Goodman et al.(1985)-cont'd

Table 4: (continued)

	Male			Female		
	Number of Tumors (%)	Standard Deviation, %	Range, %	Number of Tumors (%)	Standard Deviation, %	Range, %
Integumentary system	2343[d]			2486[d]		
Fibroma/neurofibroma	28 (1.2)	2.7	0-12	1 (<0.1)	0.6	0-4
Sarcoma (all types)	106	-	0-19	38	-	0-10
Reproductive system						
Mammary gland	2343[d]			2486[d]		
Adenoma	0	-	-	8 (0.3)	1.1	0-6
Carcinoma	0	-	-	40 (1.6)	2.3	0-12
Respiratory system						
Lung	2328[c]			2388[c]		
Alveolar/bronchiolar adenoma	282 (12.1)	6.7	0-28	131 (5.5)	3.6	0-14
Alveolar/bronchiolar carcinoma	119 (5.1)	4.3	0-18	47 (2.0)	2.3	0-8
Special sense organs						
Harderian gland	2343[d]			2486[d]		
Adenoma	50 (2.1)	2.8	0-12	32 (1.3)	1.7	0-6
Carcinoma	1 (0.1)	0.4	0-2	1 (<0.1)	0.3	0-2

[a]Tumors with an incidence of 1% or greater in one or both sexes
[b]Taken from Reference 17
[c]Number of tissues examined histopathologically
[d]Number of animals necropsied

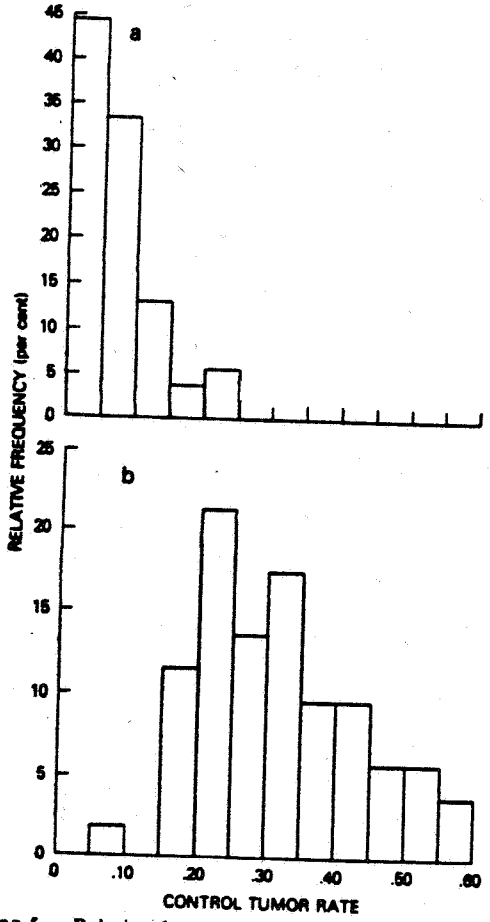
TABLE 2.—*Percentage of B6C3F$_1$ mice with naturally occurring tumors at the specified sites for five laboratories*

Tumor site or type	Sex	Percentage of tumors in mice at laboratory No.:[a]					All laboratories
		1, $n=7$	2, $n=7$	3, $n=7$	4, $n=22$	5, $n=11$	
Lung	♂	18.7(10–26)	10.6(2–13)	10.8(4–17)	21.9(0–45)	19.9(13–35)	17.0[b]
	♀	7.1(0–12)	5.2(2–12)	3.6(0–12)	6.8(0–16)	6.0(0–20)	6.0
Lymphoma-leukemia	♂	11.7(2–33)[b]	12.2(8–14)	7.2(0–14)	11.8(0–28)	12.0(0–20)	11.2[c]
	♀	25.4(8–42)[b]	30.4(22–41)	17.0(12–25)	23.0(5–45)[c]	22.7(10–42)	24.4[b]
Liver	♂	40.1(24–58)[b]	31.3(17–39)	25.0(16–39)	32.2(15–55)	27.4(7–45)	32.1[b]
	♀	9.7(2–21)[c]	4.6(2–10)	7.3(0–13)	5.1(0–21)	4.8(0–17)	6.2[b]

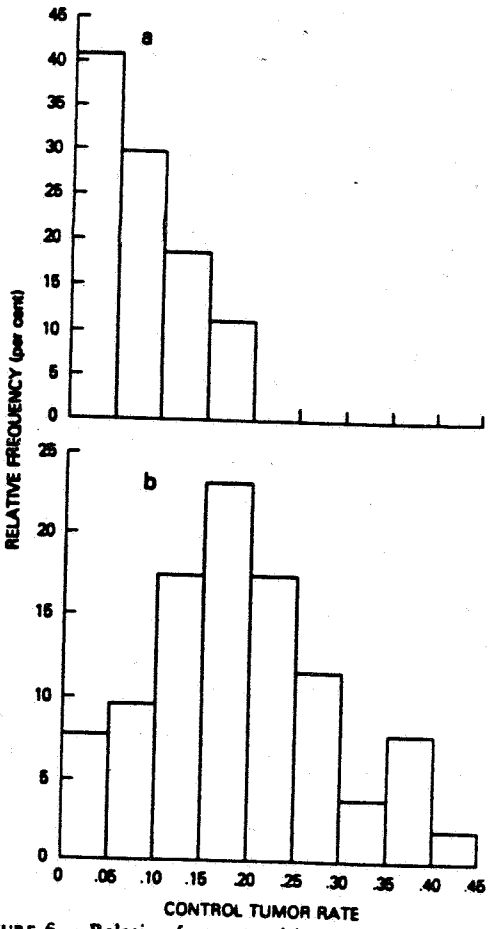
[a] n=No. of control groups in each laboratory. *Values in parentheses* are the range of control tumor rates observed in the separate experiments.
[b] Significant heterogeneity, $P<0.01$.
[c] Significant heterogeneity, $P<0.05$.

pheochromocytomas was extremely variable. This assessment was made prior to the accumulation of the data presented in this paper.

The dose-related increase in lung tumors observed in female F344 rats administered NTA (*see* table 4) was also suggestive of a compound induced effect. The lung tumor rates in both treated groups exceeded the summary mean control rates in all six laboratories (table 1). In addition, the high-dose tumor rate of 15% is greater than the highest control rate observed in the 72 experiments reported in table 1. These findings, in conjunction with the significance of the dose-related increase in lung tumors, support the conclusion that NTA induced the lung tumors in female F344 rats. The finding of a significant dose-related lung tumor increase was not emphasized in the bioassay report (*10*), and the alveolar-bronchiolar carcinoma was described as "a frequently encountered neoplasm in the



TEXT-FIGURE 5.—Relative frequency histograms for control rates of liver tumors in female (a) and male (b) B6C3F$_1$ mice.



TEXT-FIGURE 6.—Relative frequency histograms for control rates of lung tumors in female (a) and male (b) B6C3F$_1$ mice.

APPENDIX F

Data Evaluation Reports

APPENDIX F
1. Mouse Oncogenicity Study

Reviewed by: William B. Greear, M.P.H.
Section VII: Toxicology Branch (TS-769C)
Assisted by: David G. Van Ormer, Ph.D.
Section II: Toxicology Branch (TS-769C)
Secondary Reviewer: Albin B. Kocialski, Ph.D.
Section VII: Toxicology branch (TS-769C)

DATA EVALUATION RECORD

Study Type: Oncogenicity - Mouse TOX CHEM No. 543

Accession Numbers: 254608, 254609 MRID No: Not available

Test Material: Imidan® Technical

Synonyms: Decemethion, ENT 25,705, Phthalophos, Prolate, R 1504, Imidan, Stauffer R 1504.

Study Number: Stauffer Report No. T-10719.

Sponsor: Stauffer Chemical Company
Richmond, CA 94804

Testing Facility: Stauffer Chemical Company
Environmental Health Center
Farmington, CT 06032

Title or Report: T-10719 Two-Year Dietary Oncogenicity Study in Mice with Imidan Technical-Final Report.

Authors: A.C. Katz, G.L. Sprague, D.W. Frank, J.C. Turnier, G.M. Zwicker and R.I. Freundenthal.

Report Issued: May 1984.

Conclusions:

NOEL (ChE) < 5 ppm
LEL (ChE) = 5 ppm (inhibition of brain ChE in males and females)
NOEL (systemic) = 5 ppm
LEL (systemic) = 25 ppm (convulsions in males)

Oncogenicity: negative

Core Classification: Guideline

A. Materials:

1. Test compound - Imidan Technical Lot No. EHC-0139-37/WRC-4921-3131; 94.7%, described as a greyish-white crystalline material.

2. Test animals - Species: mouse; Strain: $B_6C_3F_1$-Crl-BR; Age: 6 weeks when dosing commenced; Mean weight: 22 to 23 g (males), 18 g (females); Source: Charles River Breeding Laboratories, Inc., Portage, Michigan.

B. Study Design:

1. Animal assignment - During a 3-week acclimatization period the animals were examined by a veterinarian. Then, the mice were assigned to treatment groups (60 mice/sex/group) so that group mean body weights would be similar at the time of assignment. Animal identification was by ear tag and by color coded labels affixed to each cage. The animals were assigned to the following test groups:

Test Group	Dose in Diet (ppm)	Main Study-2 Years Male	Female
1 control	0	60	60
2 Low (LDT)	5	60	60
3 Mid (MDT)	25	60	60
4 High (HDT)	100	60	60

2. Animal maintenance - The animals were housed individually in wire mesh stainless steel cages in one room. Ventilation provided at least 15 air changes per hour. The temperature was maintained at 21 ± 3 °C and the relative humidity ranged from 40 to 60 percent. Twelve-hour per day illumination was provided by fluorescent lighting.

3. Diet preparation - Test diets were prepared by first dissolving the test material in Mazola® corn oil which was then premixed with basal feed (Purina Certified Rodent Chow #5002) using a 20-quart Hobart mixer. Each premix was blended with basal feed in a 3 ft^3 Patterson-Kelley twin shell blender. All blended diets contained 1 percent (wt/wt) added corn oil. Diets were stored at 4 °C for up to 3 weeks. Food jars in the animal room were replaced on a weekly basis. Stability of the 5 ppm test diet was determined at 7, 14, 21, and 28 days when stored at 4 and 60 °C and at ambient temperature. The concentration and homogeneity of the test material in the test diets were determined at approximately 3- to 6-week intervals throughout the study.

   Results - At 4 °C, no more than 2 percent of the test material was lost from the diet over a 28-day period. At ambient temperature, approximately 35 percent of the test material was lost from the diet over a 28-day period. At 60 °C, 87 percent of the test material was lost by day 7. During the experiment batches of the diets varied from 26 to 28 percent of the desired concentrations. The relative standard deviation for homogeneity ranged from 2.8 to 9.2 percent.

4. Statistics - Quantitative continuous variables such as body weights, food consumption, clinical laboratory values, and absolute and relative organ weights were analyzed by one-way analysis of variance and Dunnett's t-test. The critical level of significance was $p < 0.05$. The Fisher's Exact test was used to analyze incidence data on gross and microscopic findings. A level of significance of $p < 0.01$ was used to analyze the incidence of hepatic tumors. Tumor incidence was analyzed by specific site, individual tumor type, organ system and according to whether the tumor was benign or malignant.

5. Quality assurance was conducted with inspections dates ranging from April 28, 1981 to November 10, 1983. The Quality Assurance Statement was signed by Patricia D. Royal.

C. Methods and Results:

1. Observations - Animals were inspected twice daily for general appearance, behavior, mortality, and other signs of toxicity. The animals were also palpated once each week for the presence of tissue masses.

   Results - Clinical observations in males show a dose-related trend in the incidence of convulsions, with incidence of 8, 11, 17, and 20 in the control-to-high dose groups, respectively. In females, the incidence of convulsions was 3, 10, 3, and 0 for the control-to-high dose groups, respectively. The authors state that the convulsions were observed in conjunction with handling during the second year of the study, and that a tendency to convulse is characteristic of mature male mice of the certain strains. The report also states that, "Although unestablished by the present study, Imidan treatment may lower the relative convulsive threshold or potentiate predisposing genetic and/or environmental factors" [leading to convulsions].

   Survival was not affected by compound administration. Unscheduled deaths in males occurred at levels of 4, 7, 10, and 8 in the control-to-high dose groups, respectively. In females, unscheduled deaths occurred at levels of 14, 15, 11, and 12 in the control-to-high dose groups, respectively.

2. Body weight - The mice were weighed once a week for the first 12 weeks and then once every 2 weeks for the remainder of the study.

   Results - Administration of the test material had no significant effect on body weight. After the first 3 months, body weights of mice in the high-dose group (particularly males) tended to be slightly greater than those of control mice. At termination, males in the high-dose group weighed approximately 8 percent more than controls and females in the high-dose group weighed 2 percent less than controls. The slight increase in body weight was not dose-related.

3. Food consumption and compound intake - Food consumption data were provided weekly for the first 12 weeks and once every 2 weeks for the remainder of the study.

   Results - Mean weekly food consumption was reduced in all males in the treated groups and in females in the mid- and high-dose groups. The decrease in food consumption in females appeared to be dose-related. In the absence of concomitant weight reductions, this may be interpreted as an increase in food efficiency and/or reduced food wastage.

   Mean compound intake was estimated to be 1.2, 5, and 18 mg/kg/day for females and 1.0, 4, and 14 mg/kg/day for males in the low-, mid-, and high-dose groups, respectively.

4. Blood was collected from 10 mice/sex/group at the interim sacrifice (12 months) and at terminal sacrifice via severed cervical vessels while the mice were under sodium pentobarbital anesthesia. The CHECKED (X) parameters were examined.

   a. Hematology

X	Hematocrit (HCT)		Total plasma protein (TP)
X	Hemoglobin (HGB)	X	Leukocyte differental count
X	Leukocyte count (WBC)	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)	X	Mean corpuscular HGB conc. (MCHC)
X	Platelet count	X	Mean corpuscular volume (MCV)

   Results - At 12 months, there were no biologically significant effects on the hematological parameters measured that could be related to treatment. At termination, there was a decrease in the leukocyte count in mice in all female treated groups when compared to controls. However, a dose-response relationship was not apparent.

   b. Clinical chemistry

X	Cholinesterase - erythrocyte
X	Cholinesterase - plasma
X	Cholinesterase - brain

Results - At 12 months, plasma cholinesterase depressions of 11, 13, and 54 percent were observed in males in the low-, mid-, and high-dose groups, respectively, when compared to controls. In females, plasma cholinesterase was depressed 13 and 56 percent in the mid- and high-dose groups, respectively. Due to a problem with reagents, erythrocyte cholinesterase levels could not be determined in the treated animals. Brain cholinesterase was depressed 29, 22 and 31 percent in males in the low-, mid- and high-dose groups, respectively. In females, brain cholinesterase was depressed 28, 31 and 34% in the low- mid- and high-dose groups, respectively. At termination, plasma cholinesterase depression of 4, 10, and 47 percent was observed in males in the low-, mid- and high-dose groups, respectively. In females, plasma cholinesterase was depressed 7 and 52 percent in the mid- and high-dose groups, respectively. Erythocyte cholinesterase activity was comparable among the treatment and control groups in males and females. Brain cholinesterase activity in males was not affected by compound administration. In females, brain cholinesterase was depressed 14 and 22 percent in the mid- and high-dose groups when compared to controls.

5. Sacrifice and Pathology - At 12 months, 10 mice/sex/group were selected for sacrifice. All animals that died and that were sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. In addition, the followed (XX) organs were weighed in mice that were sacrified.

X	Digestive system	X	Cardiovasc./Hemat.	X	Neurologic
X	Tongue	X	Aorta (thoracic)	XX	Brain
X	Salivary gland (parotid)	XX	Heart	X	Peripheral nerve (sciatic)
X	Salivary gland (submaxillary)	X	Bone marrow (sternal)	X	Spinal cord (cervical and lumbar)
X	Esophagus	X	Lymph node (mesenteric)		
X	Stomach	X	Spleen	X	Pituitary
X	Duodenum		Thymus		Eyes and Harderian glands
X	Jejunum		Urogenital		Glandular
X	Ileum	XX	Kidneys	X	Adrenals
X	Cecum	X	Urinary bladder		Lacrimal gland
X	Colon	XX	Testes with epididymides	X	Mammary gland (inguinal)
	Rectum	X	Prostate	X	Thyroids
X	Liver	X	Seminal vesicle and coagulating gland		Other
X	Gall bladder				Bone
X	Pancreas	X	Ovaries		Skeletal muscle
	Respiratory	X	Uterus	X	Skin
X	Trachea	X	Vagina	X	All gross lesions and masses
X	Lung			X	Tibiofemoral joint and attached muscle

Results

a. Organ weight - At 12 months, there was an increase in body weight and in the absolute weight of the kidneys and liver in females in the high-dose group. The relative weight of the brain, heart, and kidneys were decreased in females in the high-dose group. The relative weight of the liver was increased in males in the high-dose group. At termination, the absolute weight of the liver was increased in males in the high-dose group and in females in the mid- and high-dose groups. The relative weight of the liver was increased in females in the mid- and high-dose groups.

b. Gross pathology - In high-dose males, there was a slightly increased incidence of masses, nodules or cysts, and areas of focal discoloration/depression in the liver. There was an increase in the incidence of enlarged lymph nodes and spleens in males in the low- and mid-dose group.

c. Microscopic pathology

d. Non-neoplastic - At 12 months, there was a slight increase in the incidence of regenerative epithelial hyperplasia of the kidneys in males in the high-dose group. In females, there was an increase in the incidence of midzonal degenerative vacuolation of the liver, dilation of the uterus and "inflammation" of the kidneys in females in the high-dose group. At termination, there was an increased incidence of perivasculitis of the muscle in males in the high-dose group (7/50 vs. 0/49 in controls). Testicular atrophy was slightly increased in high-dose males (19/50 vs. 11/49 in control). The incidence of hyperplasia of the stomach mucosa was slightly increased in high-dose males (10/48 vs. 5/49 in controls) and females (9/49 vs. 3/49 in controls). In high-dose males, there was an increased incidence of degenerative vacuolation of individual liver cells (16/50 vs. 3/49 in controls) and foci of vacuolated or clear liver cells (13/50 vs. 4/49 in controls). The liver 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. High-dose females had slight changes in the liver including midzonal degenerative vacuolation (5/50 vs. 1/49 in controls), necrotizing inflammation (4/50 vs. 1/49 in controls) and necrosis of individual liver cells (4/50 vs. 1/49 in controls). High-dose females also exhibited slight increases in myometrial atrophy of the uterus (8/50 vs. 2/49 in controls) and meningitis of the spinal cord (18/50 vs. 12/49 in controls).

Neoplastic - The incidence of hepatocellular adenomas and hepatocellular carcinomas are tabulated on the following page for both the interim sacrifice (study days 0 to 365) and the terminal sacrifice (study days 366 to 736). Hepatocellular adenomas were described as "autonomous hepatocytic proliferation, lack of normal lobular architecture, and

Incidence of Hepatocellular Tumors

Males

Interim Sacrifice	Control	Low (5 ppm)	Mid (25 ppm)	High (100 ppm)
Hepatocellular adenoma	0/11(0%)	1/10(10%)	2/10(20%)	2/10(20%)
Hepatocellular carcinoma	0/11(0%)	0/10(0%)	1/10(10%)	1/10(10%)
Hepatocellular adenoma or carcinoma	0/11(0%)	1/10(10%)	2/10(20%)	3/10(30%)
Final and Interim Sacrifice	**Control**	**Low (5 ppm)**	**Mid (25 ppm)**	**High (100 ppm)**
Hepatocellular adenoma	13/60(22%)	10/60(17%)	14/60(23%)	27/60(45%)
Hepatocellular carcinoma	13/60(22%)	11/60(18%)	11/60(18%)	14/60(23%)
Hepatocellular adenoma or carcinoma	23/60(38%)	21/60(35%)	23/60(38%)	35/60(58%)

Females

Interim Sacrifice

No hepatocellular tumors were observed.

Final and Interim Sacrifice	Control	Low (5 ppm)	Mid (25 ppm)	High (100 ppm)
Hepatocellular adenoma	6/60(10%)	4/60(7%)	5/58(9%)	11/60(18%)
Hepatocellular carcinoma	5/60(8%)	4/60(7%)	3/58(5%)	9/60(15%)
Hepatocellular adenoma or carcinoma	10/60(17%)	8/60(13%)	8/58(14%)	18/60(30%)

compression of adjacent liver cells." Liver tumor malignancy was characterized by "anaplasia, vascular invasion and trabecular formation." Liver tumors were not observed in females or control males that died or were sacrificed during the first year. During the first year, hepatocellular adenomas were found in one male in the low-dose group, two males in the mid-dose group and two males in the high-dose group. Hepatocellular carcinomas were found in one male in each of the mid- and high-dose groups. The time-to-tumor appearance was 545, 659, 651, and 617 days for females in the control-to-high-dose groups, respectively, and 610, 364, 364, and 364 days for males in the control-to-high-dose groups, respectively. Pulmonary metastasis of hepatocellular carcinoma occurred in 2, 4, 2, and 3 males in the control-to-high-dose groups, respectively. The number of early deaths that occurred in mice with hepatocellular tumors (excluding mice with hepatocellular tumors at the interim sacrifice) was 3, 4, 4 and 7 for males and 3, 2, 1 and 3 for females in the control-to-high-dose groups, respectively. In summary, the incidence of hepatocellular tumors was 23/60, 21/60, 23/60, and 35/60 in males in the control-to-high-dose groups, respectively. Hepatocellular tumors were observed in 10/60, 8/60, 8/58, and 18/60 females in the control-to-high-dose groups, respectively. Harderian gland adenomas occurred in 3/60(5%), 7/50 (14%), 4/52(8%), and 9/60(15%) males in the control-to-high-dose groups. Harderian gland adenocarcinomas occurred in 2/60 males in the low-dose group. The distribution of Harderian gland tumors did not appear to be related to treatment. The incidence of Harderian gland adenoma and carcinomas in historical control male $B_6C_3F_1$ mice has been reported to range from 0 to 12 percent and 0 to 2 percent, respectively (Goodman et al., 1985).

D. Discussion/Summary:

Survival and body weight gain were not significantly affected by administration of the test material. Clinical examination of the animals revealed an increased incidence of convulsions in males that exhibited a dose-response relationship. (Males in the mid- and high-dose groups were

significantly affected). Mean weekly food consumption was slightly decreased in males in all treatment groups and in females in the mid- and high-dose groups. The hematologic parameters measured were not affected by administration of the test material. At 12 months, plasma cholinesterase was inhibited in males (54%) and females (56%) in the high-dose group. Brain cholinesterase was depressed 22 to 31 percent in treated males and 28 to 34 percent in treated females. At termination, plasma cholinesterase was inhibited in males (47%) and in females (52%) in the high-dose group. Brain cholinesterase was depressed in females (22%) in the high-dose group. At the 12-month sacrifice, the relative weight of the liver was increased in males in the high-dose group. At necropsy, there was an increase in the incidence of "masses, nodules or cysts" and areas of "focal discoloration/ depression" of the liver in males in the high-dose group. At terminal sacrifice, the absolute and relative weight of the liver was increased in females in the mid- and high-dose groups. The absolute weight of the liver was increased in males in the high-dose group. There was an increased incidence of degenerative vacuolation of individual liver cells and foci of vacuolated or clear cells in the liver of males in the high-dose group. Other findings in high-dose males included perivasculitis of muscle, hyperplasia of stomach mucosa and testicular atrophy. In high-dose females, there were also slight increases in the incidence of inflammation of the stomach and duodenum, myometrial atrophy of the uterus and midzonal degenerative vacuolation, necrotizing inflammation and individual cell necrosis of the liver.

Neoplastic findings show an increased incidence of hepatocellular adenomas and carcinomas in male and female mice in the high-dose group. There was no increase in the incidence of hepatocellular tumors in the low- and mid-dose groups when compared to controls. Statistical analysis of the data on the incidence of hepatocellular

tumors in male and female mice administered the test material indicated borderline associations in both males and females of p = .05 and .06, respectively, using the Fisher's Exact test. It should be noted that the incidences used for analyzing liver tumor incidence were: 25/59, 22/60, 23/60, and 35/60 in the male control-to high-dose groups, respectively, and 10/48, 8/50, 7/48, and 18/50 in the female control-to-high dose groups, respectively (see attached memorandum of B. Fisher dated February 28, 1986). These incidences are not identical to the incidences reported in the study. Analysis of the data reported in the study would produce a lower p value when comparing the high-dose male group to controls.

A paper cited by the authors (Tarone, 1981) indicates that in 54 chronic studies conducted with the $B_6C_3F_1$ mouse at five different laboratories, the mean incidence of liver tumors was 32.1 percent for control males with a range of 7 to 58 percent. For females the range was 0 to 21 percent with a mean of 6.2 percent. The incidence of liver tumors in the $B_6C_3F_1$ mouse from the five laboratories are provided below:

Liver Tumor Incidence $B_6C_3F_1$ Mice at Five Laboratories

	Lab 1 N*=7	Lab 2 N*=7	Lab 3 N*=7	Lab 4 N*=22	Lab 5 N*=11
Male	40.1(24-58)	31.3(17-39)	25.0(16-39)	32.2(15-55)	2.4(7-45)
Female	9.7(2-21)	4.6(2-10)	7.3(0-13)	5.1(0-21)	4.8(0-17)

*N = Number of studies

The sponsor recently submitted data on the incidence of hepatocellular tumors in $B_6C_3F_1$ mice from one additional study that was conducted prior to switching to CD-1 strain mice. The cumulative mortality for male and female mice at 106 weeks was 34 and 40 percent, respectively. The data on the incidence of hepatocellular tumors in historical $B_6C_3F_1$ mice are provided below:

Incidence of Hepatocellular Tumors in $B_6C_3F_1$ Mice at Stauffer Chemical Co. Environmental Health Center

Tumor Type	Male	Female
Hepatocellular adenoma	25/60(42%)	9/60(15%)
Hepatocellular carcinoma	10/60(17%)	3/60(5%)
Hepatocellular adenoma or carcinoma	31/60(52%)	11/60(18%)

From the data compiled by Tarone, it is apparent that hepatocellular tumors occur with a high incidence in male control mice (mean of 32.1%). It is also apparent that the incidence is quite variable ranging from 7 percent to 58 percent. The incidence of hepatocellular tumors observed in high-dose males falls within the range observed for control males at Laboratory #1. When the incidence of hepatocellular tumors in high-dose males is compared to the incidence observed in 60 historical control male mice from the laboratory that conducted the study with phosmet, no significant difference is present. The incidence of hepatocellular tumors in high-dose males is only 6 percent greater than the incidence observed in the historical control mice.

In examining the data on the incidence of hepatocellular tumors in males and females, it is noted that there is not a good dose-response relationship for males or females. In addition, as the dose increases there is no significant increase in the incidence of malignant liver tumors occurring in the treatment groups. Pulmonary metastases occurred in 2, 4, 2, and 3 males in the control-to high-dose groups, respectively. This lack of a dose-response relationship would indicate that the degree of malignancy of the hepatocellur tumors failed to be increased by administration of the material. The time to first liver tumor is 545, 659, 651, and 617 days for females in the control-to-high-dose groups, respectively. The time to first liver tumor is 610, 364, 364, and 364 days for males in the control-to-high-dose groups, respectively. In females, there appears to be no decrease in the latency period. In males, there were 0, 1, 2, and 3 males observed with liver tumors at interim sacrifice (364 days), which indicates a decrease in the latency period. In light of the discussion presented above, the increase in incidence of hepatocellular tumors in high-dose males and the marginal increase in hepatocellular tumors in high-dose females are considered to be within biological variation.

The study was conducted with at least one dose level being tested at the maximum tolerated dose (MTD) as indicated by depression in cholinesterase activity in plasma and brain of high-dose males and females, an increase in microscopic pathological changes in the liver of high-dose males and females, and convulsions in males in the mid- and high-dose groups. (It was stated in a letter from R. L. Riggs dated August 30, 1984, that a 4-week range-finding study had been conducted. Males in the 150 ppm group exhibited decreases in mean food consumption and mean body weights. In addition, the absolute liver and kidney weights of males in the 150 ppm group were significantly lower than controls while the relative liver weights were increased.)

The no-observable effect levels (NOEL's) are set as follows:

NOEL (ChE) <5 ppm
LEL (ChE) = 5 ppm (inhibition of brain ChE in males and females)
NOEL (systemic) = 5 ppm
LEL (systemic) = 25 ppm (convulsions in males)

Oncogenicity: negative for hepatocellular tumors in male mice

Core Classification: Guideline

References

1. Goodman, D.G.; Boorman, G.A.; Strandberg, J.D. (1985) Selection and use of the $B_6C_3F_1$ mouse and F344 rat in long-term bioassays for carcinogenicity. In: Handbook of Carcinogen Testing.

2. Tarone, R; Chu, K.; Ward, J. (1981) Variability in the rates of some common naturally occurring tumors in Fisher 344 rats and (C57BL/6N X C3H/HeN)F_1($B_6C_3F_1$) mice. J.NCI 66(6):1175-1181.

Memorandum

APPENDIX F FOOD AND DRUG ADMINISTRATION

2. Lifetime Rat Feeding Study - see page 2

TO : Mr. William Stokes
Petitions Control Branch

DATE: January 11, 1967

FROM : Dr. G[redacted] Whitmore
Divis[redacted] of Toxicological Evaluation
Petiti[redacted] Review Branch

SUBJECT: Imidan-40 ppm on alfalfa; 10 ppm on apples, apricots, nectarines, peaches, and pears; 5 ppm on cherries, plums and prunes; and 0.1 ppm in the meat and fat of cattle, goats, swine and sheep.

PESTICIDE PETITION NO. 7FO 523

Stauffer Chemical Company
Richmond, California
(AF 17-839)

Imidan (Prolate) toxicity data supporting the safety of a no residue registration was evaluated in the 21 Feb. 1966 memorandum.

This data was summarized thus:

ChE inhibition no effect levels

Rat - 13 week study, 20 ppm
Dog - 13 week study, 75 ppm

Rat reproduction study

No effect - 3 generations at a diet level of 40 ppm

80 ppm for 2nd and 3rd generation following the 1st generation at 40 ppm.

Potentiation - Negative except for questionable results with Ronnel.

Rabbit embryo toxicity test - negative at 35 ppm intake.

Demyelination hen study - negative at 1000 ppm diet level.

Additional data provided for this petition included a 2 year dog feeding study and a 2 year rat feeding study.

Imidan 2 year dog feeding study: Groups of purebred beagles, 3 of each sex were fed 0, 20, 40 and 400 ppm Imidan diets for 2 years.

Observations for effects included:

1. Weekly examination - weight, body temperature, respiration and heart rates.

PCB

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2. Lifetime Rat Feeding Study(cont'd)

2. Hemograms including hemoglobin, hematocrit, sedimentation rate, total and differential leucocyte counts were done initially and at 14, 26, 40, 52, 78 and 104 weeks.

3. Clinical chemistry done at the same intervals as the hemograms included BUN, SAP, GPT, erythrocyte and plasma cholinesterase activity. Brain cholinesterase was measured at the termination of the experiment.

4. Urine analysis including pH, specific gravity, albumin, sugar and sediment was done at 0, 13, 26, 40, 53, 72 and 104 weeks.

5. Neurologic, opthalmologic and electrocardiogram examination of subjects was done at 104 weeks.

6. Organ weights obtained at termination of experiment included heart, liver, kidney, spleen, lung, brain, gonads, adrenal, pituitary, thyroid and prostate or uterus.

7. Microscopic examination of suitably prepared specimens of heart, liver, kidney, thyroid, bone marrow, brain, pheripheral nerve and spinal cord from all dogs was done. Additional tissue and organs examined microscopically from the control and 400 ppm dogs included spleen, lung, gonads, adrenal, pituitary, trachae, thymus, stomach, large and small intestine, mammary gland, gall bladder, esophagus, lymph node, urinary bladder, skin, aorta, salivary gland, pancreas, skeletal muscle, eye and uterus or prostate.

Results:

Observations did not reveal compound influences except for erythrocyte and brain ChE inhibition in the dogs consuming 400 ppm diets. Twenty and 40 ppm diets were demonstrated as no effect intakes.

Imidan 2 year rat feeding study: Groups of Charles River strain albino rats, 25 of each sex, were fed 0, 20, 40 and 400 ppm Imidan diets for 2 years.

Observations for effects included:

1. Weekly examinations for body weights, food intake, and physical condition.

2. Hemograms of 5 of each sex in each group including hemoglobin, microhematocrit, total and differential leucocyte counts were done at 14, 26, 39, 52, 78 and 104 weeks.

3. Cholinesterase activity

   a. Plasma and erythrocyte ChE activity at the same intervals as the hemograms.

2. Lifetime Rat Feeding Study(cont'd)

3. Cholinesterase activity

   b. Brain ChE at termination of experiment.

4. Necropsy of rats dying during experiment and of all subjects at termination of experiment.

5. Organ weights determined at termination of experiment included liver, kidney, heart, spleen, lung, adrenal, thyroid, pituitary, gonads and prostate or uterus.

6. Mortality during test period.

7. Microscopic examination of suitably prepared specimens from succumbing and surviving rats included liver, kidney heart, spleen, lung, adrenal, thyroid, pituitary, lymph node, gonads, prostate or uterus, stomach, small intestine, pancreas, colon, urinary bladder, brain, bone marrow, skeletal muscle, eye, trachae, seminal vesicle and skin.

Results:

Body weights of males consuming 400 ppm diets were slightly influenced as recorded as lessened gains until termination of experiment when the few survivors produced erractic results.

Weights of females consuming 400 ppm diets were not influenced. Effects were absent as determined by mortality, hemograms, organ weights, food intake and necropsy.

Cholinesterase inhibition of erythrocytes and plasma was recorded at every test interval in the rat consuming 400 ppm diets. Inhibition was absent in the 40 and 20 ppm diet rats. Brain cholinesterase was inhibited in the 400 ppm diet rats at termination of the experiment but not in the lower diet groups.

Microscopic changes possibly related to compound ingestion were confined to minimal liver cell alterations in the rats consuming 400 ppm diets. The lesion possibly related was described as moderate liver cell vacuolation.

Neoplasms found and diagnosed were judged to be unrelated to compound feeding both in type found and number occurring in the different rat groups.

Conclusion:

The data demonstrate that rats can consume 20 and 40 ppm Imidan diets for two years without effects. Four hundred ppm diets produced brain, erythrocyte and plasma ChE inhibition, slightly lowered weight gains of male rats,

2. Lifetime Rat Feeding Study(cont'd)

and possible liver cell alterations described as moderate liver cell vacuolation.

SUMMARY:

The petition toxicity data and previously reviewed toxicity data have demonstrated 40 ppm diets are ChE no effect levels in dogs and rats and 40 ppm fed for three generations in a rat reproduction study was without effects.

Four hundred ppm fed to dogs for two years was without effects except for lowered erythrocyte and brain ChE.

Effects other than ChE inhibition in rats fed 400 ppm diets were confined to moderate liver cell vacuolation and slightly lower weight gains of male rats.

CONCLUSION:

Toxicity data provided support the safety of the requested residue tolerances.

INIT:HBlumenthal 1/12/67

cc:
FSA
TE
PP Nos. 7F0523 & 6G0455

GEWhitmore:mmt 1/11/67

APPENDIX F
3. Metabolism Study # 1

Study Type: Metabolism-Rat

MRID No: 00056864

Sponsor: Stauffer Chemical Co.

Testing Facility: Stauffer Biological Research Center

Report No./Date: 481/February 10, 1964

Test Material: ^{14}C-Imidian, purity 92%

Protocol:

The dosing mixture was prepared by dissolving ^{14}C-Imidan with a specific activity of 4.8 uc/g in 1 ml of pure ethanol and diluting with 2 ml of polyethylene glycol E200. A single male Long Evans strain rat weighing 73 g was housed in an all glass and stainless steel metabolism cage. Air coming into the system was dried with Drierite and rendered CO_2 free with Ascararite. Air flow was maintained at 0.4 to 0.6 L/min and the temperature was maintained at 25 ± 1 °C. Food and water were available ad libitum. Exhaled CO_2 was trapped in a scrubber containing 20% w/v carbonate-free sodium hydroxide. A trap containing silica gel prevented moisture from entering the vacuum system. The rat was acclimated to the system for 4 days afterwhich the dosing mixture was administered by gavage. Samples of urine, CO_2 and feces were collected at the following times: 0 (at time of dosing), 6, 12, 24, 36, 48, 60, and 72 hours. A blood sample was taken from the retroorbital venous plexus 11 hours after dosing. After 3 days postdosing, the rat was sacrificed and samples of blood liver, heart, kidney, abdominal fat, skeletal muscle, lung, spleen, brain, intestine, skin and gonads were collected for radioanalysis.

Results:

The rat exhibited normal behavior throughout the experiment. Weight gain, feed consumption, and urinary and fecal excretion were reported to be normal. Radioanalysis of the dosing mixture revealed a specific activity at 10.50 uc/gm. Urine counting efficiencies ranged from 40.9 to 54.8 percent. Feces counting efficiencies ranged from 48.2 to 54.8 percent. Counting efficiencies from 50 mg samples of various tissues ranged from 18.0 percent for blood to 52.8 percent for muscle. Excretion of ^{14}C in the urine and feces accounted for 45.72 percent of the recovered radioactivity at the end of 12 hours, 64.07 percent in 24 hours, 89.55 percent in 48 hours and 96.51 percent in 72 hours. The remaining 3.48 percent of the radioactivity was detected in the tissues. Tissue residues ranged from 0.18 ppm in the gonads to 1.92 ppm in the blood. The 11-hour blood sample was 2.62 ppm. The average counting efficiency for expired CO_2 was 50.7 percent. No significant activity

APPENDIX F
3. Metabolism Studv # 1(cont'd)

Conclusions: Approximately 78 percent of the recover radioactivity was excreted in urine and 19 percent in the feces at the end of 72 hours. Tissue residues ranged from 0.18 ppm in the gonads to 1.92 ppm in the blood.

Classification: Inadequate. This study together with other metabolism studies on phosmet (MRID#'s 00093487 and 00056865) do not adequately assess the fate of phosmet in the rat. Specifically, more vigorous methods should have been used to identify the metabolites in study MRID# 00093487. All three studies lacked sufficient detail to adequately verify the results of the studies.

APPENDIX F
3. Metabolism Study # 2

Study Type: Metabolism-Rat

MRID No: 00093487

Sponsor: Stauffer Chemical Company

Testing Facility: Agricultural Research Center
Stauffer Chemical Company

Report No./Date: Report No.?/1966

Test Material: Imidan, purity ?

Protocol:

The protocol used to dose the rats is identical to the one used in the rat metabolism (balance) study (MRID No. 00056865). Samples of urine and feces were obtained for analysis from rats in the balance study. Samples of urine and feces were extracted with benzene. Both the benzene extract and aqueous phase were used in the analysis. The urinary and fecal metabolites were tentatively identified by cochromatography by fortifying control rat urine samples with standards believed to be comparable with the metabolites. The following standards were used: imidoxon, N-hydroxymethlphthalimide (HMPI), phthalimide (PI), phthalamic acid (PAA), and phthalic acid (PA). In addition to these standards, ^{14}C-carbonyl labels were available for Imidan, PA, and HMPI. Liquid scintillation counting was used to quantitate the amounts of the metabolites in samples of urine and feces from rats administered ^{14}C-Imidan.

Results:

Seventy-nine percent of the radioactivity administered to rats was recovered in urine with approximately 1.8 percent appearing in the benzene extract. Nineteen percent of the radioactivity was recovered in the feces of which 4.4 percent appeared in the benzene extract. The metabolites that were tentatively identified in the aqueous phase of urine were reported to be PAA (51%-male, 54%-female), PA (21%-male, 16%-female) and a derivative of phthalic acid (7%-male, 9%-female). Imidan, imidoxon, PI and HMPI were not present in the benzene extracts of urine samples. 3- and 4-hydroxy-phthalic acids were not found in samples of urine, thus indicating that Imidan is eliminated primarly via hydrolytic cleavage. The major water soluble metabolite identified in fecal samples was PAA.

Conclusions: The major water soluble urinary metabolites found after orally dosing rats with ^{14}C-Imidan were tentatively identified as PAA, PA, and a derivative of phthalic acid. The major water soluble metabolite tentatively identified in fecal samples was PAA. Imidan, imidoxon, PI, and HMPI were not identified in the benzene extract of urine samples.

Classification: Inadequate (refer to MRID# 00056864).

APPENDIX F
3. Metabolism Study # 3

Study Type: Metabolism-Rat (Balance Study)

MRID No: 00056865

Sponsor: Stauffer Chemical Company

Testing Facility: Stauffer Chemical Company
Biological Reseach Center

Report No./Date: Report No.?/1965

Test Material: ^{14}C-Imidan, purity ?

Protocol:

Three male and two female Long Evans rats, weighing 73 to 111 g, were housed in all glass and stainless steel metabolism cages. Air flow into the system was maintained at a rate of 0.4 to 0.7 L/min. For 1 male rat, the air entering was cleared of moisture and CO_2. Exhaled CO_2 was trapped in a scrubber containing either a solution of sodium hydroxide (2 males, 1 female) or a solution of ethanolamine in 2-ethoxy-ethanol (1 male, 1 female). The rats were acclimated to the metabolism cages for 4 to 5 days prior to dosing. During the acclimatization period samples of urine, feces and CO_2 (1 sample) were collected from each animal to act as control samples. Feces were collected separately from urine by the use of tail cups. A small amount of ^{14}C-Imidan, labeled at one of the carbaryl groups of the phthalimide moiety, was dissolved in ethanol and diluted with polyethyleneglycol E-200 so that each mole contained approximately 2.5 mg (12 uc) of the radioactive material. About 1 ml of this mixture was given orally to each rat. The radioactive dose ranged from 12.06 to 12.33 uc/rat. The dose of active ingredient ranged from 19 to 31 mg/kg. Urine, feces, and CO_2 were collected at "regular" intervals from 72 or 120 hours. A sample of blood was taken from the retrooribital venous plexus of 1 male rat 11 hours after treatment. At termination (3 or 5 days postdosing), the following tissues were taken for radioanalysis: fat, gonads, intestine, brain, spleen, heart, liver, carcass (minus hide), hide, lungs, muscle, kidneys, and blood.

Results:

All rats exhibited normal appearance and behavior. Weight gain was "satisfactory" except for 1 female rat that appeared to gain less weight than the others. Feed consumption and urinary and fecal output were reported to be normal. No observable gross pathology was noted at sacrifice. Approximately 98.3 percent of the calculated radioactivity was recovered. Seventy-eight percent was excreted in urine and 18.5 percent was excreted in the feces by the time of sacrifice, either 72

or 120 hours after treatment. Less than 0.04 percent of the radioactivity was eliminated as CO_2. Tissues residues accounted for 2.6 percent of the radioactivity. There appeared to be no selective storage of radioactivity in any tissue.

Conclusions: Imidan was rapidly excreted from rats with approximately 98.3 percent of the calculated radioactivity being excreted within 72 or 120 hours. Seventy-eight percent and 18.5 percent of the dose was excreted in urine and feces, respectively, by the time of sacrifice.

Classification: Inadequate (refer to study MRID# 00056864).

APPENDIX G

Toxicology Branch "One-Liners"

Tox Chem No. 543-Imidan | File Last Updated 7/6/84 | Current Date 4/11/86

APPENDIX G

Study/Lab/Study #Date	Material	EPA Accession No.	Results:	TOX Category	CORE Grade/Doc I
One-generation/teratology-rabbit; Woodard Research Lab.; August 26, 1966	Technical	MRID# 00062649	Reprod. NOEL $\geq$ 60 mg/kg (HDT) Teratogenic NOEL > 60 mg/kg (HDT) Dosage = 10, 30, 60 mg/kg given either orally or dermally. Cholinesterase depression ranged slight to marked in the three oral doses, less marked dermally.		Minimum 001999
3-Generation reproduction-rat; July 8, 1968	Technical	MRID# 00081432	Reprod. NOEL $\geq$ 80 ppm (HDT)		Minimum 001999
2-Year feeding/oncogenic-rat; Stauffer; January 11, 1967	Technical	PP No. 7FO-523 MRID# 00076436	Sys NOEL = 40 ppm ChE NOEL = 40 ppm Sys LEL = 400 ppm (Slight body weight decrease in males and moderate liver cell vacuolation). ChE LEL = 400 ppm Dosage levels = 20, 40, and 400 ppm		Minimum 001999

Tox Chem No. 543-Imidan | File Last Updated 7/6/84 | Current Date 4/11/86

APPENDIX G

Study/Lab/Study #Date	Material	EPA Accession No.	Results:	TOX Category	CORE Grade/Doc No.
Teratology - rabbit; IBT: #J4529; November 14, 1966	Imidan	Unknown	IBT - Invalid Clement Associates/EPL Accepted by EPA: October 14, 1981		003192
Teratology - rabbit; St. Mary's Hospital Medical School; Report?; 1965?	Imidan	MRID# 00062648	Administration of Imidan to pregnant females at a rate of 35 mg/kg during days 7-12 of pregnancy failed to produce a teratogenic effect.		Supplementa
Teratology - monkey; Stauffer Chem. Co.; April 23, 1968	Technical	PP Nos. 8FO-699 and 8GO-705 MRID# 00053821	Terata NOEL $\geq$ 8 mg/kg/day (HDT) Dosage levels = 2, 4, and 8 mg/kg		Minimum 01999
Teratology - rat; Midwest Res. Inst.; (HERL contract); contract #68-02-2746; November 8, 1979	Technical	MRID# 00031555	Terata NOEL $\geq$ 30 mg/kg (HDT) Maternal toxic NOEL = 1.5 mg/kg Maternal toxic LEL = 30 mg/kg (reduced weight gain) Fetotoxic NOEL $\geq$ 30 mg/kg (HDT) Dosage levels = 39 mg/kg (single dose) 0.06, 1.5, and 30 mg/kg (multiple dosing)		Supplementa 001999
Teratology - rat; NIEHS; Report #?; February 1976	Technical 95.8%	MRID# 00063192	Terata NOEL (gavage) = 25 mg/kg Terata NOEL (diet) = 29 mg/kg Levels tested (gavage) 5, 10, 20, 25, and 30 mg/kg. Levels tested (diet) 0, 10, 22, 27, and 29 mg/kg. (Literature Article-summary data only).		Supplementa

Tox Chem No. 543-Imidan | File Last Updated 7/6/84 | Current Date 4/11/86

APPENDIX G

Study/Lab/Study #Date	Material	EPA Accession No.	Results:	TOX Category	CORE Grade/Doc N
2-Year feeding - dog; Stauffer; January 11, 1967	Technical	PP No. 7FO-523 MRID# 00076436	ChE NOEL = 40 ppm ChE LEL = 400 ppm (RBC and brain ChE inhibition). NOEL (systemic) = 400 ppm Dosage levels = 20, 40, and 400 ppm		Minimum 001999
Neurotoxicity - hen; Biodynamics, Inc.; #4725-77; April 26, 1979 (revised)	Imidan/Prolate, Technical, 96.1% pure	242478 MRID# 00046187	Questionably positive - neurotoxicity (delayed neuropathy) exhibited by 10/12 of birds surviving double treatment. Axon and neuron degeneration; body weight decrease; tremors; prostration, locomoter impairment.		Minimum 000820 001999 Cannot supp regulatory actions.
Neurotoxic esterase assay - hen; Stauffer Chem. Co.; #T-6840; February 25, 1980	Imidan Technical, 93.1% ai	242478 MRID# 00046186	Brain: acetylcholinesterase (ChE) neurotoxic esterase (NTE) and pseudocholinesterase (PChE). Enzyme — Inhibition (%) ChE — 65.6 PChE — 47.3 NTE — 20.2* Dose: 892 mg/kg NTE depression of less than 70% has been correlated with absence of delayed neurotoxicity for a limited number of organophosphates, using a 21-day observation period after a single dosing.		Acceptable 000820

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Study/Lab/Study #Date	Material	EPA Accession No.	Results:	TOX Category	CORE Grade/Doc No.
Neurotoxicity - hen; Stauffer; #T-10910; August 9, 1982	Technical 94.7%	071044 MRID# 00109652	Not a delayed neurotoxic agent. However, body weight, food consumption, and egg production significantly depressed at 2050 mg/kg. Dosage levels = 20, 200, and 2050 mg/kg. LD_{50} = 2020 mg/kg 30% inhibition in plasma and brain ChE at 32 mg/kg. 55% inhibition in brain ChE at 1050 mg/kg. 85% inhibition in plasma ChE at 1050 mg/kg. Atropine and 2 PAM are effective antidotes.		Guideline 002245 002601

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Study/Lab/Study #Date	Material	EPA Accession No.	Results:	TOX Category	CORE Grade/Doc No.
Neurotoxicity - hen; Cooper Technical Bureau; #180-66; December 29, 1966	Imidan 20-30% in PEG 200	MRID# 00043469	Not neurotoxic when administered at 1,413 mg/kg (2 doses, 3 weeks apart).		Supplementary
Neurotoxicity - hen; Woodard Research Corp; Report #?; February 27, 1963	Imidan	MRID# 00081431	Administration of up to 1000 ppm in the diet for 6 weeks failed to elicit signs indicative of neurotoxicity in hens.		Supplementary
Antidotal - rat; Cooper Technical Bureau; #180-66; December 29, 1966	Imidan 20-30% in PEG 200	MRID# 00043469	Pralidoxime methane sulphonate and atropine when given together confer protection against the acute toxic effects of phosmet.		Adequate
Metabolism, - rat; Stauffer; #481; February 10, 1964	^{14}C-Imidan 92%	MRID# 00056864	Approximately 78% of the recovered activity was excreted in urine and 19% in the feces at the end of 72 hours. Tissue residues ranged from 0.18 ppm in the gonads to 1.92 in the blood.		Inadequate
Metabolism - rat; Stauffer; Report #? 1966	^{14}C-Imidan	MRID# 00093487	The major urinary metabolites found after orally dosing rats with ^{14}C-Imidan were "tentatively" identified as phthalmic acid (52%) phthalic acid (18%). The major water soluble metabolite tentatively identified in feces was phthalmic acid.		Inadequate

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Study/Lab/Study #Date	Material	EPA Accession No.	Results:	TOX Category	CORE Grade/Doc No.
Metabolism - rat; Stauffer; Report?; 1965	^{14}C-Imidan	MRID# 00056865	After admistration of ^{14}C-Imidan to rats, 98.3% of the "calculated radioactivity" was excreted within 72 or 120 hours. Seventy-eight percent and 18.5% of the dose was excreted in feces and urine, respectively, by the time of sacrifice.		Inadequate
Mutagenic dominant lethal - rabbit; November 9, 1970		Unknown			Information incomplete 001999
Potentiation - rat; Stauffer; Report No.?; June 4, 1963	Technical LWF XXIII	MRID# 00075432	At 1/4 of the respective LD_{50}'s Ronnel potentiated. At 1/2 of the respective LD_{50}'s 5/17 OP's were potentiating.		Adequate 001999
Acute oral LD_{50} - rat; Stauffer; Report# 153-051; November 7, 1977	Technical 92.5%	MRID# 00063196	LD_{50} (males) = 121.3 (90.6 to 162.5) mg/kg LD_{50} (females) = 121.3 (96.7 to 152.1) mg/kg Levels tested 50.42, 80.05, 127.1, 201.7 and 320.2 mg/kg (gavage).	II	Minimum
Acute oral LD_{50} - rat; Stauffer; T-6304; August 18 to 19, 1978	Technical 96.1%	MRID# 00046189	LD_{50} (males) = 113 (101-127) mg/kg LD_{50} (females) = 113 (98 to 130) mg/kg Levels tested 60, 75, 100, 115, 130, 150, 170, and 175 mg/kg (gavage).	II	Minimum

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Study/Lab/Study #Date	Material	EPA Accession No.	Results:	TOX Category	CORE Grade/Doc No.
Acute oral LD_{50} - rat; Hazleton Nuclear Science Corp.; #20-0240-32; April 30, 1962	Technical PP-62 98%	MRID# 00075426	LD_{50} (males) = 140 (76-255) mg/kg Levels tested 50, 75, 100, 150, 200, and 250 mg/kg (gavage).	II	Unclassified*
Acute oral LD_{50} - rat; Hazleton Labs.; Report No. - ? May 16, 1960	Technical R-1504 100% (?)	MRID# 00075425	LD_{50} (males) = 147 mg/kg Levels tested 46.4, 100, 215, and 464 mg/kg (gavage).	II	Unclassified*
Acute oral LD_{50} - rat; Stauffer; #345 September 19, 1963	Technical 323-B 89.7%	MRID# 00075427	LD_{50} (males) = 220 (180-268) mg/kg Levels tested 50, 100, 150, 200, 250, 300, and 400 mg/kg (gavage)	II	Unclassified*
Acute oral LD_{50} - rat; Stauffer; #307; July 18, 1963	Technical LWF XXIII	MRID# 00075429	LD_{50} (males) = 245 (161-367) mg/kg Levels tested 100, 200, 300, and 400 mg/kg (gavage).	II	Unclassified*
	Technical		LD_{50} (males) = 242 (192-305) mg/kg Levels tested 100, 150, 300, 350, 400, and 500 mg/kg (gavage).	II	Unclassified
	Technical AC-140 57C		LD_{50} (males) = 304 (261-356) mg/kg Levels tested 100, 200, 250, 300, 400, and 500 mg/kg (gavage).	II	Unclassified
Acute oral LD_{50} - rat; Richmond Research Center; #65-2; January 26, 1965	Technical LWF XXIII	MRID# 00075433	LD_{50} (males) = 245 (161-367) mg/kg Levels tested 100, 200, 300, 400, and 500 mg/kg (gavage).	II	Unclassified*
Acute oral LD_{50} - rat; Stauffer; #507 February 18, 1964	Technical RP4-RCT-116	MRID# 00112288	LD_{50} (males) = 310 (267-360) mg/kg Levels tested 100, 200, 250, 300, 350, 400, and 500 mg/kg (gavage).	II	Unclassified*

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Study/Lab/Study #Date	Material	EPA Accession No.	Results:	TOX Category	CORE Grade/Doc No.
Acute oral LD_{50} - mouse Richmond Research Center; #65-2; January 26, 1965	Technical LWF XXIII	MRID# 00075433	LD_{50} (males) = 50.1 (34.4-73.0) Levels tested 10.0, 21.5, 46.4, and 100 mg/kg (gavage).	II	Unclassified*
Acute oral LD_{50} - mouse; Woodard Research Corp.; #T-2047; November 25, 1966	Technical LWF XXIII in corn oil	MRID# 00043470	LD_{50} = 38 mg/kg Levels tested 20, 25.1, 31.6, 39.8, 50.1, 63.1, and 79.4 mg/kg (gavage).	I	Minimum
	Technical LWF XXIII 20% in polyethylene glycol		LD_{50} = 49 mg/kg Levels tested 20, 25.1, 31.6, 39.8 50.1, 63.1, and 79.4 mg/kg (gavage).	I	Minimum
Acute dermal LD_{50} - rabbit; IRDC: #153-051; August 3, 1977	Technical 92.5%	MRID# 00063196	LD_{50} > 5000 mg/kg Level tested 5000 mg/kg	III	Minimum**
Acute dermal LD_{50} - rabbit; Hazleton Nuclear Science Corp.; Report No.?; December 14, 1960	Technical R-1504	MRID# 00075439	LD_{50} > 3160 mg/kg Levels tested 100, 316, 1000 and 3160 mg/kg	III	Minimum**
Acute dermal LD_{50} - rabbit; Stauffer; T-6304;	Technical 96.1%	MRID# 00046190	LD_{50} > 5000 mg/kg Level tested 5000 mg/kg	III	Minimum**

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Study/Lab/Study #Date	Material	EPA Accession No.	Results:	TOX Category	CORE Grade/Doc No.
Acute inhalation LCt_{50} t = 4 hrs - rat; IRDC; #153-051; November 8, 1977	Technical 92.5%	MRID# 00063197	LCt_{50} > 0.152 mg/L t = 4 hrs Highest level tested = 0.152 mg/L. No deaths.	I	Supplementary
Acute intraperitoneal - rat; Richmond Research Center; #65-2; January 26, 1965	Technical LWP XXIII	MRID# 00075433	LD_{50} (males) approximately 100 mg/kg Levels tested 50, 75, 100, 150, 200, and 400 mg/kg		Unclassified
Acute intraperitoneal - mouse; Richmond Research Center; #65-2; January 26, 1985	Technical LWP XXIII	MRID# 00075433	LD_{50} (males) 40-50 mg/kg Levels tested 5, 15, 30, 40, 50, and 60 mg/kg		Unclassified
Acute subcutaneous - rat; Richmond Research Center; #65-2; January 26, 1985	Technical LWF XXIII	MRID# 00075433	LD_{50} (males) > 1200 mg/kg Levels tested 50, 100, 150, 200, 400, 800, and 1200 mg/kg		Unclassified
Acute subutaneous - mouse; Richmond Research Center; #65-2; January 26, 1985	Technical LWF XXIII	MRID# 00075433	LD_{50} (males) = 300 mg/kg Levels tested 5, 15, 30, 60, 120, 180, 240, 360, 480, and 600 mg/kg		Unclassified
Primary eye irritation - rabbit; Stauffer; #T-6123; November 11, 1977	Technical 92.5%	MRID# 00063195	Unwashed eyes: mild redness at (3 rabbits) 24 hrs; mild discharge and chemosis after 24 hours. Eyes normal at 7 days. Washed eyes: no irritation (6 rabbits).	III	Minimum***

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Study/Lab/Study #Date	Material	EPA Accession No.	Results:	TOX Category	CORE Grade/Doc No.
Primary eye irritation - rabbit; Stauffer; T-6304; August 18,1978	Technical 96.1%	MRID# 00046192	Unwashed eyes: corneal opacity, redness, chemosis and discharge reversible within 7 days. Washed eyes: No irritation.	III	Minimum***
Primary eye irritation - rabbit; Hazleton Nuclear Science; Report #?; December 14, 1966	Technical R-1504	MRID# 00075439	Mild transient irritation when 3.0 mg/kg instilled in eye. Eyes normal within 2 hours.	III	Unclassified
Primary dermal irritation - rabbit; Stauffer; #T-6304; August 18, 1978	Technical 96.1%	MRID# 00046191	No irritation was produced.	IV	Minimum
21-Day dermal - rabbit; Richmond Research Center; #65-74; June 1965	Imidan 50-W and Imidan 3E	MRID# 00080554	NOEL (systemic) < 0.08 ml/kg (Imidan 3E) NOEL (systemic) < 120 mg/kg (Imidan 50-W) Levels tested 0.08, 0.16 and 0.80 ml/kg (Imidan 3E) 120 mg/kg (Imidan 50-W). Focal seminiferous tubular cell degeneration and/or reduction in mature spermatoza were observed in all treated groups. Deaths occurred with typical signs of cholinesterase inhibition in animals in the 0.80 ml/kg group. Irritation of the skin was caused by both test substances. Irrition was also observed in animals in the inert control group.		Inadequate

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Study/Lab/Study #Date	Material	EPA Accession No.	Results:	TOX Category	CORE Grade/Doc No.
21-Day dermal - rabbit; Diablo Laboratories; #2H7275; May 14, 1963	Imidan 3E and Imidan 50-W	MRID# 00080552	NOEL (systemic) cannot be determined. NOEL (ChE) cannot be determined. Levels tested 0.08, 0.16, 0.80, and 1.6 ml/kg (Imidan 3-E) and 0.1, 0.5, and 1.0 g/kg (Imidan 50-W). The study is extremely poor. Deaths occured in the 0.80 and 1.6 ml/kg (Imidan 3-E) and 1.0 g/kg (Imidan 50-W) groups. Body weight gain was decreased in the 0.16, 0.80, and 1.6 ml/kg Imidan 3-E and in all Imidan 50-W groups. Cholinesterase inhibition data were uninterpretable.		Inadequate

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*In the development of the Registration Standard the reviewer determined that these studies were not useful in determining the LD_{50}.

**Studies MRID# 00046190, 00063196 and 00075439 would individually be classified Supplementary but together are considered to be Minimum.

***Studies MRID# 00046192 and 00075439 would individually be classified as Supplementary but together are considered to be Minimum.

APPENDIX H

World Health Organization Report on Phosmet

PHOSMET

Explanation

This compound was evaluated by the 1976 Meeting (FAO/WHO, 1977b) but no acceptable daily intake could be allocated in the absence of the required full toxicological data. Although available residue data were sufficient to allow some guideline levels to be recorded, more detailed data from supervised trials on fruit and forage crops were requested. The data received in response to these requests are reviewed in this monograph addendum.

EVALUATION FOR ACCEPTABLE DAILY INTAKE

BIOCHEMICAL ASPECTS

Absorption, distribution and excretion

Phosmet is rapidly absorbed, translocated and excreted in mammals. Following a single oral administration of ^{14}C (Carbonyl-labelled) phosmet to rats at doses ranging from 23 to 35 mg/kg body weight, phosmet was eliminated rapidly (within 48 hours) via the urine, (greater than 75%) and feces (Ca 16%). Tissue residues accounted for a very small portion (less than 3%) of the phosmet administered. The radiolabelled residue was fairly uniformly distributed among many tissues. The gonads and fat contained exceptionally low levels. Essentially no cleavage of the carbonyl carbon of the phthalimide, group occurred as no $^{14}CO_2$ was observed. These data suggested the rapid absorption, distribution and elimination of phosmet in mammals (Ford et al., 1966).

Phosmet was adminsitered orally or by direct intra-ammionic injection to rats in the final stages of pregnancy. Phosmet was detected in fetuses following oral administration and in fetuses in the uterine horn opposite of the site of intra-ammionic injection. These studies readily demonstrated the rapid absorption as well as the placental passage of phosmet (Ackermann et al., 1976).

Biotransformation

Following oral administration of phosmet to pregnant rats and following injection directly into the fetus, metabolic (primarily hydrolytic) products were rapidly noted. These products, small amounts of the oxygen analog and the hydrolytic derivatives were observed and were further degraded. Phosmet was also rapidly metabolized in the fetus following direct injection into the fetus. Thus, fetal tissues have the capacity to rapidly metabolize phosmet which may pass the placental barrier during latter stages of pregnancy (Ackermann et al., 1976). In further characterization of the metabolites, the presence of phthalimide was noted which was further observed to breakdown to phthalic acid. All of these metabolites were proposed for fetal tissue metabolism (Ackermann et al., 1978).

Examination of urine and feces of rats treated with phosmet (oral administration, 27 mg/kg body weight) suggested that metabolic breakdown *in vivo* occurred primarily via hydrolytic pathways and is believed to resemble degradation products from many other organophosphorus pesticides. The major phosmet metabolite, identified in urine of both sexes, was phthalamic acid. Phthalic acid and a small number of unidentified minor metabolites. Oxidative conversion, *in vitro*, of phosmet to its oxygen analog was shown to occur in the presence of an active microsomal oxidation system (McBain et al., 1968). In cotton plants, following surface application to leaves, the major metabolites of phosmet were found again to be phthalic and/or phthalamic acid, benzoic acid and possibly some benzoic acid derivatives. It was suggested that oxidation in the plant to the active

oxygen analog was bypassed in favor of hydrolysis as the oxygen was not found in plant extracts (Menn and McBain, 1964).

Acute Toxicity

Following acute intoxication with phosmet the typical parasympathomimetic signs of poisoning, generally seen with other anticholinesterase agents, were observed. The onset of signs of poisoning was rapid, generally within the first one-half hour after treatment and included: tremors, salivation, lacrimation, mastication, exophthalmia, bloody exudate from eyes, nose and mouth, dyspnea, diarrhea, convulsions and death. The sings of poisoning were transient, generally disappearing rapidly within 24 to 72 hours. On gross examination of animals acutely poisoned by gavage treatment, congested lungs and adrenals, discoloration of liver, spleen and kidney and distention and irritation of the GI tract were observed.

Phosmet (3 mg technical) active ingredient or 0.1 ml of a 3EV emulsifiable concentrate formulation instilled into the conjuctival sac of rabbits was found to be irritating. The rabbits displayed erythema of the eyelid, vacularization of the sclera and nictitating membrane and lacrimation. The crystalline phosmet did not dissolve readily. The signs of irritation induced by the technical phosmet were transient, disappearing within 24 hours after treatment. The irritation induced by the formulation lasted longer than 7 days (Meyding, 1960; Meyding and Fogleman, 1962).

Acute one hour inhalation exposure of male rats to an aqueous emulsion of phosmet at concentrations ranging from 50 to 800 ml/L air resulted in changes in behavior and signs of poisoning ranging from mild tremors and face washing to extreme tremors and distress. Mortality was not noted. Gross examination after a 14 day rest and recovery interval revealed lung, adrenal and pancreatic changes. The lungs were brightly colored (orange red) and the adrenals and pancreas were engorged or hemorrhagic (Hill, 1963).

The results of acute toxicity studies are summarized in Table 1.

Special studies

Hen - Delayed Neurotoxicity

Groups of white leghorn hens (10 hens per treatment group, 3 hens were used as a negative control) were fed dietary levels of phosmet at dose levels of 0, 100, 316 and 1000 ppm over a six week period. A positive control group was fed tri-o-cresyl phosphate (TOCP) at a dietary level of 1000 ppm over the same time interval. At the conclusion of the study surviving hens were sacrificed and histological examinations of the spinal cord, brain and sciatic nerve were performed following H&E staining of these tissues. A delayed neurotoxic response was not observed either clinically of histologically over the course of the study as a result of the presence of phosmet in the diet. The presence of TOCP in the diet resulted in ataxia and paralysis. Both clinical and histological examinations confirmed this event. Based upon this dietary study it was concluded that there was no delayed neurotoxic potential for phosmet (Johnston, 1963b).

Potentiation

Technical phosmet was tested alone and in combination with seventeen anticholinesterase insecticides (one carbamate and sixteen organophosphate esters) in an effort to evaluate its additive or potentiating effect. Groups of rats (5 females rats/group) were used to evaluate the potentiation. Mortality ratios were calculated from the toxicity of phosmet administered alone or in combination with another anticholinesterase agent at one-half or one-fourth of the respective LD_{50} value. Greater than additive mortality was observed with several other compounds when dose levels of one-half of the acute LD_{50} level were employed. However, when the dose level was reduced to one quarter of the LD_{50} potentiation was observed only with one organophosphate, fenchlorphos (Ronnel). The potentiation effect with fenchlorfos was, however, questionalbe because of possible interference from solvent effects (Johnston, 1963a).

TOXICOLOGICAL STUDIES

Acute Toxicity

Species	Sex	Route	Solvent[1]	LD_{50} (mg/kg)	95% C.L.	References
Rat	M	Oral	Me Cell	147		Fogleman, 1960
		Oral	CO	140	76-235	Ford & Fogleman, 1962
		Oral	Me Cell	220	180-268	Ford & Fogleman, 1962
		Oral	Me Cell	245	161-367	Meyding, 1963
		Oral	Me Cell	242	192-305	Meyding, 1963
		Oral	Me Cell	304	261-356	Meyding, 1963
		Oral	Me Cell	310	267-360	Ray, 1064
	F	Oral	PEG	271	200-369	Johnston, 1963a
		Oral	PEG	369	271-501	Johnston, 1963a
		Oral	PEG	316		Johnston, 1963a
		Oral	PEG	224	176-286	Johnston, 1963a
	M	IP	Me Cell	100		Meyding, 1965a
		SC	Me Cell	1200		Meyding, 1965a
Mouse	M	Oral	Me Cell	50.1	34.4-73.0	Meyding, 1965a
	M	Oral	Polysorbate 80	25.2	22.9-27.7	Haley et al., 1975
	F	Oral	Polysorbate 80	23.1	22.2-24.0	Haley et al., 1975
	M	IP	Me Cell	40-50		Meyding, 1965a
	M	SC	Me Cell	300		Meyding, 1965a
Rabbit	M&F	Dermal (intact skin)	CO	3160		Meyding, 1960

Emulsifiable Concentrate

Rat	M	Oral	Socal #2	623		Ray, 1963a
	M	Oral	Water	501	344-730	Ray, 1963b
			Water	316		Meyding, 1965b
			Water	596	409-868	Meyding, 1965b
Mice	M	Oral	Water	96	79-116	Ray, 1963b
Rabbit	M&F	Dermal	None	1560	633-2220	Meyding & Fogleman, 1962

Wettable Powder

Rat	M	Oral	Water	223	143-378	Anonymous, 1963
Mice	M	Oral	Water	108	74-157	Anonymous, 1963
Rat	M	Oral	Water	275	245-303	Bullock & Kamionski, 1972
Rat	F	Oral	Water	258	239-289	Bullock & Kamionski, 1972
Rabbit	-	Dermal	Neat	4640		

[1] Me Cell = Aqueous Methyl Cellulose CO = Corn Oil PEG = Polyethylene Glycol 300

APPENDIX H

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Mutagenesis

Phosmet was tested for mutagenicity using a series of in vitro microbial assays. At levels up to 20 micrograms dissolved in DMSO, without metabolic activation, phosmet was inactive when tested against B. subtillis (H17 - Rec$^+$ and M45 - Rec$^-$): E. coli B/r WP2hr$^+$ and WP2hcr$^-$, 2 tryptophan$^-$ requiring mutants and S. typhimurium (TA 1535, TA 1536, TA 1537, and TA 1538) (Shirasu, 1975; Shirasu et al., 1976).

Teratology

Rats

Groups of CD rats (group size varied from 9 to 32 individuals/group) were either administered phosmet in the diet at concentrations yielding daily doses of 0, 10, 22, 27 and 29 mg/kg body weight or by gavage at doses of 0, 5, 10, 20, 25 and 30 mg/kg body weight from day 6-15 of gestation. Day 1 of gestation was the day semen was detected. The unusual dosage levels of the dietary treatment were a result of food rejection and correspond to actual intake of phosmet calculated from diet consumption data. On day 21 of gestation, the rats were sacrificed and fetuses examined for external and internal malformations. Maternal toxicity was evident in the two highest dietary levels. Food consumption was decreased and no weight gain was recorded at these two levels. There was no indication of fetal toxicity as measured by mortality, fetal weight or an overall incidence of malformation. Maternal mortality was evident at the two upper dose levels administered by gavage. Again, the incidence of fetal mortality and malformation was not significantly increased even in the presence of severely adverse maternal effects. There was no evidence of somatic or skeletal abnormalities in the pups attributable to the administration of phosmet (Staples et al., 1976).

Groups of wistar rats (group size varied from 9 to 13 pregnant females/group) were admistered phosmet orally by gavage at a single dose of 30 mg/kg (9 females) on day 9 of gestation; at a single dose of 30 mg/kg (8 females per dose) on day 13 of gestation; at doses of 0.06 or 1.5 mg/kg body weight (10 females/group) every other day throughout pregnancy. Day 1 of gestation was the day semen was detected. Suitable groups of controls varying from 10 to 13 animals per group were used to compare results (it was not indicated whether controls were administered solvent (not specified) or were not treated). Administration of phosmet on day 9 of pregnancy resulted in an insignificant increase in post implantation mortality of embryos and malformations described as hypognathia, edema and dislocation of extremities. Administration on day 13 of pregnancy did not affect mortality but did induce hydrocephaly in 33 of 55 embryos examined. Administration of phosmet (1.5 mg/kg bw every other day throughout pregnancy) resulted in a reduction in the number of live fetuses and the occurrence of hydrocephaly and subcutaneous hemmorhages. Embryo toxicity was a dose-dependent occurrence as it was not noted at the lowest concentration (0.06 mg/kg body weight) examined (Martson and Voronina, 1976).

Monkey

Groups of rhesus monkeys (Macaca mulatta, 7 pregnant females per group; were administered phosmet by gavage from days 22 through 32 of gestation at dose levels of 2, 4 and 8 mg/kg/day. The females had previously borne normal young and served as their own controls in the study. A positive control was included utilizing various dose levels of thalidomide (5 or 10 mg/kg/day) administered on days 22 through 32 of gestation or (10 mg/kg/day) administered on days 25, 26 and 27.

Malformations were observed in all fetuses delivered to females administered 10 mg thalidomide kg/day during days 25-27 of gestation. Administration of thalidomide from days 22-32 of gestation resulted in abortion of all parents with an exception being noted at the high dosage level (10 mg/kg/day) where 2 of 4 fetuses conceived were delivered. These fetuses were malformed. Over the entire course of this study all fetuses delivered

all fetuses delivered to females treated with phosmet showed no abnormalities. Two females at the low doses and one female at the high dose group aborted during the course of this study. All other females delivered live viable fetuses which were anatomically normal. There was no indication of a teratogenic event as a result of administration of phosmet during the sensitive period of organogenesis in the rhesus monkey (Courtney and Finkelstein, 1968).

Rabbit

Groups of pregnant rabbits (5 rabbits/group) were orally administered phosmet by gavage at levels of 0 or 35 mg/kg/day from day 7-12 of gestation. The day of mating was considered as day zero for calculation of gestation. There were no differences observed in the reproductive parameters (implantation, resorption, litter size, litter weight) and abnormalities were not observed over the course of the study. In contrast, a positive control using thalidomide administered orally at a dose of 150 mg/kg during the same period of gestation resulted in a significant number of malformed fetuses (Fabro et al., 1965).

Reproduction

Rabbit

Groups of rabbits (10-12 males and 10-13 females/group) were administered phosmet either in the diet or by dermal application for three weeks prior to mating and thereafter for 18 consecutive days of gestation. Rabbits subjected to dietary administration were fed dosage levels of 0, 10, 30 and 60 mg/kg/day, 7 days per week. Rabbits subjected to dermal application received a dose of 0, 10, 30 and 60 mg/kg/day 5 days per week for the same treatment interval. At the conclusion of the study, day 29 of gestation, pups were delivered by Caesarian section. Gross and microscopic examinations of tissues and organs of parental animals and gross and skeletal examinations of pups were performed. Cholinesterase activity of females, performed during the course of the study, was depressed confirming that exposure to phosmet had occurred. Depression of cholinesterase was evident at all dose levels in animals administered phosmet by both the dermal and dietary route.

There was no mortality observed in the study attributable to phosmet. A slight reduction in growth was observed at the highest dose level in animals of both the oral and dermal treatments. Gross and microscopic examination of tissues and organs of the parents showed no effects of the administration of phosmet. Reproductive parameters were not affected by phosmet and teratogenic events were not observed over the course of this study. Dietary and dermal administration of phosmet at dose levels of 60 mg/kg/body weight per day prior to and during mating and over the entire period of gestation, did not affect reproductive parameters in rabbits and induced no teratogenic event in offspring (Kidwell et al., 1966).

Rat

Groups of rats (20 males and 20 females/group) were fed dietary concentrations of phosmet and utilized in a standard three-generation, two-litter generation, reproduction study. Two groups of rats were used in the first generation and three groups were used for the second and third generations. The first generation, consisting of two complete litters, were fed dietary concentrations of 0 and 40 ppm. Immediately after weaning the test material was withdrawn for 3-4 weeks. The second and third generations were fed dietary concentrations of 0, 40 and 80 ppm, the latter group being derived from offspring of parents previously fed 40 ppm in the diet. The first litters of each generation were sacrificed at weaning and the second litter was used as the parental group of the following generation. At weaning of the second litter the parental animals were discarded. A 2-9 day withdrawal period from the phosmet diet occurred immediately after weaning. At the conclusion of the F_{3b} offspring, representatives of the second litter were grossly examined at necropsy and histological examination of selected tissues and organs was made.

There were no differences in any of the test and control groups with respect to mortality, survival, general condition, growth and reproductive performance. Malformations were not observed over the course of the study. Gross and microscopic examinations of tissues and organs at the conclusion of the study showed some slight degenerative hepatic changes in both groups fed phosmet in the diet. These changes were believed to be minor and included slight hepatic cell vaculation and reduced glycogen content. Based upon comparison of data from corresponding phosmet-treated and control litters in the three generation reproduction study, the administration of phosmet at 80 ppm in the diet for two generations and 40 ppm in the diet over a single generation (all generations producing two litters) resulted in no effect or any reproductive parameter (Hollingsworth et al., 1965).

Short Term Studies

Rabbit

Groups of rabbits (2 males and 2 females per group) were administered phosmet (an emulsifiable concentrate or wettable powder formulation) dermally five days/week for three weeks. Phosmet was administered to both normal and abraded skin at daily doses of 0, 0.08, 0.16, 0.8 and 1.6 mg/kg/body weight (this dosage of the emulsifiable concentrate corresponds to a concentration of 0, 30, 60, 300 and 600 mg/kg/body weight) and 0, 0.1, 0.5 and 1.0 gms/kg body weight (this dosage of the 50% wettable powder formulation corresponds to a concentration of 0, 50, 250 and 500 mg/kg body weight).

Mortality was evident with the emulsifiable concentrate as all animals dosed at 600 mg/kg died and three out of four animals treated with 300 mg/kg also died within the first week. Animals dosed at the two intermediate dose levels lost weight. No effects were seen at the lowest dose level. Repeated application of the emulsifiable concentrate produced thickening of the skin in the treated area followed by a dry, scaly condition. Cholinesterase depression was observed at all dosage levels and did not appear to be affected by skin abrasion. Cholinesterase depression was noted at 60 mg/kg body weight with the emulsifiable concentrate. Cholinesterase was not depressed at 50 mg/kg body weight when the wettable powder formulation was used. These data suggested differences in dermal absorption or penetration patterns with the two formulated materials. Brain cholinesterase evaluated at the conclusion of the study showed significant depression only at 300 mg/kg with the emulsifiable concentrate and at 50 mg/kg with the wettable powder formulation. Gross and microscopic examination of tissues and organs, with the exception of dermal thickening, showed no changes attributable to phosmet administration (Hill and Moulten, 1963).

Rabbit

Groups of rabbits (10 males and 10 females/group, 5 of each sex were used as the controls) were dermally administered phosmet (emulsifiable concentrate formulation, 3-E) at dose levels of 0, 30 and 60 mg/kg/day, 5 days a week for 3 consecutive weeks. Phosmet was again administered to either intact or abraded skin.

Mortality was observed in the high dose group with all animals dying within one week having been treated with from 2-4 applications. In the surviving animals no overt signs of poisoning were observed at the low dosage level. Food consumption and body weight was reduced. Dermal irritation was evident with no differences noted in the intact and abraded skin with respect to evaluating the degree of irritation. Hematology and urinalysis determinations at the end of the study were normal. Cholinesterase depression was observed, particularly with red blood cell and again no differences were observed in animals with intact or abraded skin. Gross and microscopic examination of selected tissues and organs showed no somatic response to the dermal treatment (Meyding, et al., 1965).

In a repeat experiment, groups of male and female rabbits were administered the

a week for 3 weeks. Again, mortality was observed at the high dose level and overall results of this experiment confirmed that reported previously. One additional group was used to evaluate the inert ingredients of the emulsifiable concentrate formulation. Irritation of the intact and abraded dermal surface was noted with this formulation suggesting that skin irritation was a property of the formulation rather than of the active ingredient (Meyding and Horton, 1965).

Cattle

Groups of steers (15 hereford steers/group) were fed phosmet (Prolate^{R}, as a 50% wettable powder) in the diet at concentrations of 0 and 1 mg/kg for 8 weeks and thereafter at levels of 0 and 2 mg/kg for an additional 8-week period. There were no adverse effects on behavior, growth and hematological parameters. Whole blood cholinesterase depression was observed at the 2 mg/kg group after 6 weeks of dietary administration. Regeneration of cholinesterase was slow over a 4-week control diet treatment after the 16 week trial (Meyding, 1965c).

Rat

Two groups of rats (10 males and 10 females per group) were fed varying dietary levels of phosmet over a sixteen week range-finding study. A third group of rats consisting of 10 males and 10 females were designated as controls and fed diets containing no phosmet for the same sixteen week interval. A high level group was fed 800 ppm for three weeks, 1600 ppm for weeks 4-9, 2000 ppm during the tenth week, 3000 ppm during the eleventh week and 6000 ppm from the 12-16 weeks. The low level group was fed 450 ppm for the first three weeks, 900 ppm for weeks 4-9 and 1120 ppm the tenth week and thereafter until the conclusion of the study. Mortality was observed in the high dietary level group where two females died at the sixteenth week. Abnormalities in behavior were observed after the third week where all treated animals appeared to develop a degree of hyper-excitability. By the fourth week, tremors were noted which continued throughout the remainder of the study. Persistent low grade diarrhea occurred in all test animals after the 5th or 6th week. Growth was slightly depressed at fifteen weeks in the low group and was more significantly depressed in the high dose group. Growth depression was associated with decreased food intake, after the eight week. Hematological values were normal in all groups. Cholinesterase depression was observed in red blood cell and brain in both groups while plasma cholinesterase was only partially depressed. Gross and microscopic pathological changes were observed. Mean organ weights were increased in the high level. This occurred in liver, kidney, spleen and adrenal gland. In addition, testes weight was increased in both treatment groups. There were some additional gross events noted in the low level group. Histologically, hepatic degenerative changes were noted particularly in the high level. To a lesser degree these changes were observed in the low level animals. Adrenal hypertrophy was also reported. In this range finding study it was observed that high levels of phosmet in the diet resulted in significant toxicological effects (Johnston, 1963c).

Rat

Groups of rats (30 males and 30 females per group) were fed phosmet in the diet at concentrations of 0, 20, 100 and 500 ppm for periods varying from 19-24 weeks. The animals were fed a constant dietary preparation over the course of this study. There was no mortality attributable to the presence of phosmet in the diet. Growth, as evidenced by weight gain, was reduced in males at 500 ppm. Females were not affected. General appearance and behavior of all animals over the course of the study was unaffected by the presence of phosmet. Hematological evaluations made periodically over the course of the study were within normal limits. Cholinesterase activity was depressed at the dietary levels of 100 ppm and above. Red blood cell cholinesterase was significantly more depressed than was plasma. Brain cholinesterase, examined in a selected group of animals at thirteen weeks, was found to be depressed in a manner similar to that observed with cholinesterase from red blood cells. Gross and microscopic examination of tissues and organs, performed on a small group of animals sacrificed at fourteen weeks, showed no outstanding abnormalitie

attributable to the presence of phosmet in the diet. Based upon cholinesterase depression observed at 100 ppm, 20 ppm phosmet in the diet was considered to be a no-effect level (Johnston, 1962).

Dog

Groups of beagle dogs (4 males and 4 females per group) were fed dietary concentrations of phosmet at dosage levels of 0, 10, 75 and 563 ppm. Growth and behavior over the course of the study were unaffected by the presence of phosmet in the diet. Hematological and blood chemistry determinations were made periodically during the course of the 20 week study. With the exception of blood cholinesterase activity, all values were normal. Plasma and red blood cholinesterase (and brain cholinesterase at the conclusion of the study) were significantly inhibited by 563 ppm phosmet in the diet. At 75 ppm in the diet the red blood cell was slightly depressed in females. Plasma cholinesterase activity was not depressed at this dose level. Gross examination of tissues and organs performed at the fourteen week interval showed a slightly increased kidney and adrenal organ weight at the high dose level. Microscopic examination of sections of tissues and organs suggested no cellular changes attributable to the presence of phosmet in the diet (Johnston, 1962).

Dog - Two Year Study

Groups of purebred beagles (3 males and 3 females/group) were fed dietary concentrations of phosmet for two years. Phosmet was mixed with a dry diet at concentrations yielding 0, 20, 40 and 400 ppm. With the exception of one dog, which was sacrificed in extremis at one year of age, there was no mortality observed over the course of the study. Growth, as evidenced by body weight changes, was unaffected. Hematological values, clinical chemistry values, urinalysis values and physical and physiological measurements taken at periodic intervals and at the conclusion of the study showed no effects due to the presence of phosmet in the diet. Transient physiological evidence of the presence of an anti-cholinesterase agent in the diet was sporadically reported as lacrimation and diarrhea noted in the treated groups. Red blood cell, plasma and brain cholinesterase activity (brain cholinesterase activity was recorded only at the conclusion of the study) showed a distinct effect of phosmet at 400 ppm in the diet. Depression of red blood cell and brain cholinesterase activity was observed. Cholinesterase activity at 40 ppm in the diet was normal. Neurological and ophthamological examinations performed at the conclusion of the study were normal. Based upon cholinesterase depression at 400 ppm in the diet, a no-effect level of 40 ppm was observed in the study (Lobdell and Johnston, 1966).

Long Term Studies

Rat

Groups of Charles River rats (25 males and 25 females/group) were fed dietary levels of phosmet for two years at dosage levels of 0, 20, 40 and 400 ppm (the animals were originally fed dietary levels of 0, 10, 20 and 200 ppm for three weeks after which time the dietary levels was increased to compensate for differences in food intake). There was no mortality nor behavioral differences in these animals that were attributable to the presence of phosmet in the diet. Growth was depressed at the dietary level of 400 ppm and was more readily apparent in males. Food consumption was normal in all groups. Hematological parameters, examined at various intervals over the course of the study, were unaffected by phosmet in the diet. Plasma and red blood cell cholinesterase activity, evaluated at various time intervals and brain cholinesterase, evaluated at the conclusion of the study, were depressed at the highest dose level. At dietary levels of 40 ppm and below there were no effects on cholinesterase activity. In addition, cholinesterase activity, measured initially at 14 weeks, was constant over the course of the study in each of the dietary groups.

Gross and microscopic examination of tissues and organs at the conclusion of the study showed no consistent dose-related effects. Histopathological changes noted were common in

normal aging rats although a degree of liver cell vaculation, observed at 400 ppm, may have been attributable to the presence of phosmet in the diet. There were no differences with respect to neoplasms in the study although a larger proportion of rats sacrificed at the conclusion of the study having been fed 40 ppm phosmet and above showed the presence of pituitary neoplasms. As the frequency of this event was significantly small, no conclusions could be reached. In addition, thyroid adenomas were observed at the 400 ppm group in greater frequency than were noted in other dose groups. Again, the number of animals sacrificed at the conclusion of the study was too small to fully evaluate this parameter.

Based upon cholinesterase depression at 400 ppm, a proposed no-effect level would be 40 ppm equivalent to 2 mg/kg/bw/day (Lobdell and Johnston, 1966).

Observations in Man

No specific studies available. Limited observations of occupationally exposed workers show no adverse effects although depressed peripheral cholinesterase activity suggested that exposure had occurred in some instances.

COMMENTS

The lipophilic nature of the phosmet molecule allows rapid gastrointestinal absorption and dermal penetration but is not of such a nature to suggest bioaccumulation in adipose tissue. Phosmet is rapidly translocated in the body, metabolised and excreted. The metabolic products in mammals and plants appear to be similar and are well defined.

The acute toxicity of phosmet has been evaluated and data have been presented to demonstrate its anticholinesterase activity and parasympathomimetic properties. It is moderately toxic on an acute basis.

Short term studies, in vitro bioassays for potential mutagenic hazard and delayed neurotoxicity have been negative. Teratology bioassays using a variety of species and protocols have, with one exception, been negative. A teratological response in rat for phosmet using a protocol not generally followed by other investigators, has shown effects at exceptionally low levels. A no-effect level of 0.06 mg/kg noted in this teratology bioassay was of significant concern to the Meeting. These teratology results served as a basis for applying an unusually large safety margin to the allocated temporary ADI. In another study in rat using high dose levels and a longer treatment interval, data showed no teratological response. Negative results obtained in the rat study and in a primate teratology bioassay did not fully reduce the concern raised above with respect to the teratogenic potential of phosmet.

Short term and long term bioassay programmes in dogs and rats have shown no significant effects on a variety of physiological, biochemical and pathological parameters. As expected, a sensitive indicator of effect, cholinesterase depression, was observed at high dietary levels in all tests. Growth depression and cholinesterase activity depression in two species served as the basis for estimating the no-effect level.

TOXICOLOGICAL EVALUATION

Level causing no significant toxicological effect in animals

Rat: 40 ppm in the diet equivalent to 2.0 mg/kg bw

Dog: 75 ppm in the diet equivalent to 1.9 mg/kg bw

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Estimate of temporary acceptable daily intake for man

0 - 0.005 mg/kg body weight

RESIDUES IN FOOD AND THEIR EVALUATION

RESIDUES RESULTING FROM SUPERVISED TRIALS

Potatoes

Supervised trials of spray applications of phosmet to potatoes at six sites in the USA and five sites in Canada in 1970 yielded only one result (at 0.04 mg/kg) above the detection limit of 0.02 mg/kg for either the parent compound or its oxygen analogue (Stauffer, 1970).

Sweet potatoes

Supervised trials of dust and dip treatments of stored sweet potatoes yielded residues of phosmet which ranged up to 203 mg/kg. Most results on unwashed tubers were in the range 50 to 100 mg/kg; washing the tubers reduced the residue to between 2 and 10 mg/kg. The bulk of the residue remains in the peel, levels in the edible pulp being generally below 1 mg/kg (Stauffer, 1972).

Apples and pears

Additional data on residues in apples grown in Czechoslovakia (Batora, 1978) have confirmed those reported by the 1976 Meeting, observed levels ranging from 0.80 mg/kg just after treatment to 0.10 mg/kg 18 days later. Similar residues (0.85 to 0.11 mg/kg) were observed on pears.

Apricots and nectarines

Data on residues of phosmet on apricots and nectarines (Stauffer, 1968) showed that levels were similar to those reported in 1976 for residues on peaches; they were below 5 mg/kg 7 days after treatment and below 1 mg/kg after 21 days.

Grapes

Grapes treated with phosmet showed residues up to 15 mg/kg, most results lying in the range 1 to 8 mg/kg and showing limited diminution with time up to 28 days after treatment (Stauffer, 1969).

Kiwifruit

Kiwifruit (*Actinidia chinensis*) is a major horticultural product exported from New Zealand. Because of the hairy nature of its skin, pesticide spray residues are retained to an appreciable extent. Data reported by the 1976 Meeting showed that residues of phosmet ranged up to 25 mg/kg, though most results were below 10 mg/kg. Further recent information has shown that most of this residue (ca 90%) is associated with the inedible skin, levels in the fruit pulp being in the range 0.3 to 2.5 mg/kg with a mean of 1 mg/kg (Love et al., 1978). These data have been supported by monitoring studies; results from 57 samples examined in 1975, 1977 and 1978 ranged up to 23 mg/kg with a mean value of 4 mg/kg (New Zealand, 1978).

Citrus fruit

Residues of phosmet on grapefruits, lemons and oranges, ranged from 0.6 to 4 mg/kg at a pre-harvest interval of 7 or 8 days, most being between 1 and 3 mg/kg. Studies on oranges and grapefruits showed that nearly all of the residues in the peel, very little appearing

in the flesh or the juice. The proportion of the total residue occurring as the oxygen analogue varied widely, from 1 to over 50% (Stauffer, 1974).

Maize (field corn)

On maize ears (i.e. kernels plus cob with husks removed) phosmet residues were generally below 0.05 mg/kg but ranged up to 0.2 mg/kg; residues in the stalks were appreciably higher, reaching 12 mg/kg (Stauffer, 1974).

Nuts

Data were available on phosmet residues in almonds, filberts, pecans and walnuts (Stauffer, 1974). Residues in the nut meat were all below 0.08 mg/kg, most being in the range 0.01 to 0.05 mg/kg. Residues in almond hulls ranged up to 5.6 mg/kg.

Blueberries and cranberries

Phosmet residues on blueberries and cranberries showed a similar pattern, ranging from 1 to 7 mg/kg at a 3-day pre-harvest interval (Stauffer, 1974).

Peas

On peas plus pods, phosmet residues ranged from 0.07 to 0.34 mg/kg at a 7-day pre-harvest interval. Residues in dry peas were not greater than 0.02 mg/kg (Stauffer, 1974).

NATIONAL MAXIMUM RESIDUE LIMITS

National MRLs reported to the Meeting are given in Table 2.

TABLE 2. National MRLs reported to the Meeting

Country	Commodity	MRL, mg/kg
Australia	Fat of meat of cattle, pome fruit, stone fruit	1
	Milk and milk products (fat basis)	0.2
Canada	Apples, grapes, peaches, pears	10
	Cherries	7
	Plums	5
Netherlands	Apples, pears	1
	Potatoes	0.02
New Zealand	Fruit	10
Switzerland	Peas	0.1
	Pome fruit	1
	Potatoes	0.05
USA	Alfalfa	40
	Almond hulls, apples, blueberries, cherries, corn forage and fodder (including sweet corn, field corn	

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TABLE 2. (continued)

Country	Commodity	MRL, mg/kg
USA	Apricots, citrus fruits, nectarines, plums.	5
	Fresh corn including sweet corn (kernels plus cobs with husk removed), corn grain (including popcorn), peas	0.5
	Meat, fat and meat by-products of cattle, goats, hogs, horses and sheep	0.2
	Potatoes	0.1
	Nuts	0.1 (negligible residues)

APPRAISAL

Some additional data have become available concerning residues of phosmet in several crops. As the Meeting allocated a temporary ADI, the previously recorded guideline levels were converted to temporary maximum residue limits and some additional and amended limits were also recommended.

RECOMMENDATIONS

The previously recorded guideline levels are replaced by the following temporary maximum residue limits, which now refer to the sum of phosmet and its oxygen analogue.

Commodity	Temporary MRL, mg/kg	Pre-harvest intervals on which limits are based, days
Sweet potatoes (washed before analysis)	10	-
Kiwifruit	10	10
Blueberries	10	3
Grapes	5	21
Forage crops (dry)	5	14
Citrus fruit	5	7
Cranberries	5	7
Apples	1	21
Apricots	1	21
Nectarines	1	21
Peaches	1	21
Pears	1	21
Fat of meat of cattle	1	-

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Commodity	Temporary MRL, mg/kg	Pre-harvest interval on which limits are based, days
Maize (kernels & cobs, husks removed)	0.2	14
Milk products (fat basis)	0.2	-
Tree nuts (shelled)	0.1	-
Peas (fresh or dried)	0.1	7
Potatoes	0.05	20
Milk (whole)	0.01	-

FURTHER WORK OR INFORMATION

Required (on or before June 30, 1979)

1. Additional teratogenic studies in rodents.

APPENDIX H

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