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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D C 20460

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: California Department of Food and Agriculture - EPA  
Toxicology Review for Phosmet

TOX Chem No.: 543

FROM: William B. Greear, M.P.H. *William B. Greear*  
Review Section II  
Toxicology Branch I - Insecticide, Rodenticide Support  
Health Effects Division (TS-769C)

TO: William Burnham, Acting Director  
Health Effects Division (TS-769C)

THRU: Marion P. Copley, D.V.M., Acting Section Head *Marion P. Copley*  
Review Section II  
Toxicology Branch I - Insecticide, Rodenticide Support  
Health Effects Division (TS-769C) *4/3/89*

The following responses are provided for each deficiency identified by the Medical Toxicology Branch of the California Department of Food and Agriculture (CDFA).

STUDY TYPE

83-1 - Chronic, Rat - No. 035 1047 ("Imidan Safety Evaluation by Two-Year Feeding Studies in the Rat and the Dog," Woodard Research Corporation, July 21, 1966, MRID No. 00076436).

Deficiency No. 1

The number of animals used in the study, i.e., 25 rats/sex/group, was inadequate.

EPA Response

The EPA Guidelines currently recommend the use of 50 rats/sex/group. At the time the study was conducted, it was

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generally recommended that the study utilize 25 rats/sex/group. However, due to the cholinesterase inhibition and other toxicologic endpoints observed, it is unlikely that this deficiency would alter the conclusion.

Deficiency No. 2

There was no description of the test article.

EPA Response

A detailed description of the test article was not provided. However, the test article was reported to be phosmet technical. Most, if not all of the technicals used for toxicity testing had a purity greater than 90 percent. In the Product Chemistry Chapter of the Phosmet Registration Standard, the typical, "normally-occurring" impurities in a 94 percent phosmet technical have been identified. Identification of the test article as technical phosmet is adequate.

Deficiency No. 3

There was no dietary analysis.

EPA Response

In the past it was not uncommon for the investigator to report only the nominal concentration of the test article in the diet. By today's standards, it is considered to be necessary to analyze the diet in order to determine the analytical concentration of the test material in the diet and to ensure its stability in the diet. In the recent mouse oncogenicity study (No. T-10719, May 1984, Accession Nos. 254608 and 254609), it was determined that at ambient temperature, approximately 35 percent of the test material was lost from the diet (standard rodent chow) over a 28-day period. Thus, this information indicates that the rat chronic feeding study may have been compromised depending on how frequently the fresh test diets were made. Because there were effects on cholinesterase inhibition and because test diets were probably made, at least on a monthly basis, it is reasonable to assume the rats were receiving a high percentage of the nominal concentration of the test material in the diets.

Deficiency No. 4

There were inadequate numbers of animals available for histopathological examination.

EPA Response

The study was examined and it was determined that there were inadequate numbers of animals available for histopathological examination with respect to the oncogenicity study. However, as a chronic feeding study the number of animals available for histopathological examination was marginally adequate.

Conclusion

Nonconcurrency with California. On June 30, 1986, the Toxicology Branch Peer Review Committee assembled to evaluate the data base on phosmet. It was decided that the rat chronic feeding study was adequate as a chronic toxicity study, but was inadequate as an oncogenicity study. The chronic rat study is not a data gap.

Core-Grade

Remains unchanged: Minimum with respect to chronic feeding.

STUDY TYPE

83-2 - Oncogenicity, Rat.

Deficiency No. 1

No study on file.

EPA Response

The chronic rat study reported earlier is deficient as an oncogenicity study because too few animals survived to termination to permit adequate gross and histopathological examination of the tissues.

Conclusion

Concur with California. The data gap is still outstanding.

Core-Grade

Remains unchanged: Supplementary with respect to oncogenicity.

STUDY TYPE

83-4 - Reproduction, Rat - No. 034 1027 ("Imidan Three-Generation Reproduction Study in Rats," Woodard Research Corporation, May 20, 1965, MRID No. 00062649).

Deficiency No. 1

Histopathological examination of only the F3b pups was conducted.

EPA Response

Histopathological examination did not include all the animals recommended for in the Guidelines. However, this is not considered to be a major deficiency and would not be expected to alter the conclusions of the study. The purpose of the study is to determine if the pesticide has a functional adverse effect on reproduction. The histopathological data can be used to further characterize the source of reproductive impairment. In several chronic studies using several species, there were no histopathologic concerns in the urogenital system.

Deficiency No. 2

Only two dose levels were tested and there was no indication that a maximum tolerated dose (MTD) was tested.

EPA Response

Three dose levels should have been tested. The Guidelines recommend that the highest dose level should induce toxicity but not mortality in the parental animals. In the chronic rat study, a dose level of 400 ppm appeared to be well tolerated. The highest dose level in the reproduction study of 80 ppm may have produced a minor toxic effect on the liver of the F3b weanling rats. Based on the effects observed in the chronic feeding study and the apparent lack of effects in the reproduction study, it can be concluded that the levels employed in the reproduction study were too low.

Deficiency No. 3

Only mean litter weights were provided and no cholinesterase measurements were made.

EPA Response

Individual litter weights should have been provided. No cholinesterase measurements were made; however, this is not required. It would have been prudent to incorporate cholinesterase measurements in order to determine if the test compound produced toxic effects (cholinesterase inhibition) in the parental animals.

Conclusion

Concur with California. The reproduction study is a data gap.

Core-Grade

Changed to Supplementary. Note: The Registration Standard on Phosmet should be changed to indicate a data gap exists for a reproduction study.

STUDY TYPE

83-3 - Teratology, Rat - No. 034 1050 - (Multiple citations)

1. "Effect of Imidan Administered to Pregnant Rats,"  
Midwest Research Institute - No. 68-02-2746  
(November 8, 1979, MRID No. 00012555).

Deficiency No. 1

A non-Guideline dosing regimen was used.

EPA Response

The statement is correct; however, strict adherence to the Guidelines is not required.

Deficiency No. 2

There was only minimal toxicity at the high-dose level.

EPA Response

The deficiency is correct. The study's core-classification remains unchanged: Supplementary.

2. No. 037 1051 (NIEHS, 1979, MRID No. 00063192)

Deficiency No. 1

No deficiency stated.

EPA Response

This study was reported as a journal article. Its core-classification remains unchanged: Supplementary.

3. No. 037 1049 "Developmental Toxicity in the Rat After Ingestion or Gavage of Organophosphate Pesticides (Dipterix, Imidan) During Pregnancy" (February 1976, MRID No. 00063192).

Deficiency No. 1

Inadequate dose-range, no analysis of diet or dosing solution, summary data only.

EPA Response

Only summary data were available. Its core-classification remains unchanged: Supplementary.

4. No. 034 1033 (Environ. Health Perspectives 13:133-140 (1976) - Staples et al.)

Deficiency No. 1

Only summary statement is present, no deficiency stated.

EPA Response

Has not been evaluated.

Note: California should be informed that another rat teratology study exists (Department of Biochemistry, St. Mary's Hospital Medical School, MRID No. 00062648).

Conclusion

Concur with California. The above mentioned Core-Supplementary rat teratology studies cannot be used to fill the data gap. However, a study was conducted in Rhesus monkeys (Macaca mulatta) which satisfies the Guidelines, i.e., testing in two species. The status remains the same; there is no data gap.

STUDY TYPE

83-3 - Teratology, Rabbit - No. 034 1028 ("Imidan Oral Compared to Dermal Administration to the Rabbit," Woodard Research Inst., August 26, 1966, MRID No. 00062649).

Deficiency No. 1

The dose levels used were not justified.

EPA Response

Justification of dose levels selected for testing is not required unless there is reason to question the selection, such as lack of toxicity.

Deficiency No. 2

The protocol used was not the Guidelines protocol for teratogenicity testing.

EPA Response

This is correct. The study was conducted 16 years prior to publishing the 1982 Guidelines. Differences are almost certain to be present. In addition, strict adherence to the protocol recommended by the Guidelines is not necessary, provided adequate information is provided. Unlike the Guidelines protocol in which only one route of exposure is tested, this study tested one set of rabbits (3 dose levels) orally and a second set of rabbits (3 dose levels) dermally. There were 10 to 12 female rabbits per group. Although this study deviates from the Guidelines it is clear that the study provides more information in that data are available for two different routes of exposure as opposed to one route of exposure. Another instance in which this study deviates from the Guidelines is the treatment period. The Guidelines recommend treatment from day 6 to 18 of gestation. In this study, treatment began 3 weeks prior to mating and up to 18 days after mating. The importance of this deviation is minor since in both studies the animals were treated during the period of major organogenesis. Some of the other deviations from the Guidelines are: measurement of fetal organs, determination of plasma and erythrocyte cholinesterase, and microscopic pathological examination of several organs. In certain areas, the data this study provides exceeds the requirements of the Guidelines. Therefore, this study provides adequate information on the teratogenic potential of phosmet in rabbits.

Deficiency No. 3

Insufficient numbers of animals per group were tested.

EPA Response

Current Guidelines require 12 pregnant female rabbits per sex per dose. The study incorporated 10 to 12 females per dose. The difference is minor and is not likely to alter the conclusions.

Conclusion

Nonconcurrency with California. The rabbit teratology is not a data gap.

Core-Grade

Remains Unchanged: Minimum.

STUDY TYPE

83-3 - Teratology, Monkey - No. 034 1026 "Teratological Investigation of Captan, Imidan and Thalid mide in Macaca mulatta (Rhesus Monkeys)" (Bionetics April 4, 1968).

Deficiency No. 1

Not a usual species.

EPA Response

The rat and mouse are the species recommended by the Guidelines for teratogenicity testing. Use of the Rhesus monkey is not considered to be a deficiency, because monkeys are more closely related to humans than are rodents. Therefore, the results obtained with the monkeys would be more valid to humans than the results obtained with rats or mice.

Deficiency No. 2

No rationale (sic) presented for dose selection and only marginal effects on cholinesterase.

EPA Response

The dose levels tested could probably have been increased. However, the dose levels selected (HDT = 8 mg/kg) were fairly similar to those used in the rat teratology study (dose levels 10, 30, and 60 mg/kg) and the rat 3-generation reproduction study (2 and 4 mg/kg/day). The marginal effects on cholinesterase noted by CDFA were not deemed to be real effects in our evaluations. Toxicology Branch I (TB I) believes that teratology tests used with monkeys are much more valid to humans than are tests with rodents. Therefore, TB I is willing to accept this study as fulfilling part of the phosmet teratology study requirements (i.e., testing required in two species), even though the highest dose level tested did not induce an effect.

Conclusion

Nonconcurrency with California. The study is acceptable. [It is noted that this study was not designated as a data gap.]



CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PHOSMET (IMIDAN)

SB 950-107, Tolerance = 251

October 28, 1986

Revised February 11, 1987

Revised January 29, 1988

I. DATA GAP STATUS

Chronic rat: Data gap, inadequate study, possible adverse effect indicated

Chronic dog: No data gap, no adverse effect

Onco rat: Data gap, no study on file, study to be initiated in 1988

Onco mouse: No data gap, possible adverse effect

Repro rat: Data gap, inadequate study, no adverse repro effect indicated, possible adverse chronic effect indicated

Terato rat: Data gap, inadequate studies, no adverse effect indicated

Terato rabbit: Data gap, inadequate studies, no adverse effect indicated

Gene mutation: No data gap, possible adverse effect

Chromosoma: No Data gap, possible adverse effect

DNA damage: No data gap, no adverse effect

Neurotox: No data gap, no adverse effect

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Note, Toxicology one-liners are attached

\*\* indicates acceptable study

Bold face indicates possible adverse effect

Original file name SB107PHO.JG1, reviews by J. Gee; Revised name: SB107PHO.JG3, revised by D. Shiner and J. Gee, 1/88.

## II. TOXICOLOGY SUMMARY

### CHRONIC RAT

035 1047 "Imidan Safety Evaluation by Two-Year Feeding Studies in the Rat and the Dog." (Woodard Research Corp., 7/21/66) Phosmet (Imidan), no purity stated, fed to 25/sex/group for 2 years at 0, 20, 40 or 400 ppm; excessive mortality due to respiratory infections; UNACCEPTABLE (number of animals, no test article description, no diet analysis; inadequate numbers for histopathology); ChE NOEL = 20 ppm, systemic NOEL = 40 ppm (marginal effects on the liver (not once) at the high dose.) The significance of the effect cannot be evaluated from this inadequate study. JR(G), 4/19/85.  
EPA 1-liner: Minimum. Sys NOEL = 40 ppm (slight body weight decrease in males and moderate liver cell vacuolation, ChE NOEL = 40 ppm.  
Note: Document 261-062, Record = 050835, Guidance for the Reregistration of Pesticide Products Containing Phosmet, EPA, September 30, 1986, discusses this study and finds "...it is inadequate according to modern standards in terms of the number of surviving animals available for gross and histopathological examination." The limited data make it difficult to determine if the MTD was approached. EPA has requested a repeat oncogenicity test in rats. Apparently EPA has accepted this as a chronic.

### CHRONIC DOG

\*\* 035 1047 "Imidan Safety Evaluation by Two-Year Feeding Studies in the Rat and the Dog." (Woodard Research Corp., 7/21/66). Phosmet, no purity stated, given in the feed at 0, 20, 40 or 400 ppm over two years. 3/sex/group; death of 1 male at high dose, depression of cholinesterases at 400 ppm; ophthalmological exam at term; NOEL = 40 ppm (cholinesterase inhibition); marginally ACCEPTABLE. No other effects reported. JR(G), 4/19/85 and 1/28/88.

Note: If this study were being reviewed in 1988 for the first time by CDFA, it would not have been considered acceptable based on the lack of analyses of the diet for actual content of phosmet and no statement of the purity of the test material. These deficiencies could be addressed in a retrospective study by preparing diets by the identical procedure and analyzing them plus submission of the records for preparation from the study. In view of the findings in other long-term studies at lower NOEL's which will be used for risk evaluation, no change in the status of the dog study is made at this time.  
Gee, 1/28/88.

EPA 1-liner: Minimum. ChE NOEL = 40 ppm, systemic NOEL = 400 ppm.

### ONCOGENICITY, RAT

No study on file. Document 261 - 062 contains a letter dated November 18, 1986, indicating that Stauffer plans to initiate a rat oncogenicity study in 1988, due in December, 1990.

ONCOGENICITY, MOUSE

\*\* 044, 045 026895, 034143 "Two-Year Dietary Oncogenicity Study in Mice with Imidan Technical." (Stauffer, 5/84) Phosmet, technical, 94.7% by weight; fed to 60/sex/group B6C3F1 mice at 0, 5, 25 or 100 ppm for two years; NOEL (cholinesterase) = 5 ppm, NOEL (liver adenoma) = 25 ppm. ACCEPTABLE. The incidence of hepatocellular adenomas in males was 13/60 (22%) in control, 10/60 (17%) in 5 ppm group, 14/60 (23%) in 25 ppm group and 27/60 (45%) in high dose group. In females, overall the incidence of adenomas was 6/60 in controls, 4/60, 5/59 and 11/60 in low-, mid- and high-dose groups. For carcinomas, the incidence in males was 13/60 in controls, 11/60, 11/60 and 14/60 in test groups. In females, incidence was 5/60, 4/60, 3/59 and 9/60. See 47566 for comparison with another control group from a study conducted about the same time at Stauffer.

Note: Document 261-062, Record = 050835, Guidance for the Reregistration of Pesticide Products Containing Phosmet, EPA, September 30, 1986, discusses this study and the incidence of neoplasms compared with controls and with NTP historical control values. Although in incidence of liver adenomas in high dose males was increased, there was no significant increase in carcinomas "...indicating there was no clear trend of progression of benign tumors progressing to malignancy."

JR(G), 9/16/85

057 47566 (Stauffer, 5/22/86) Addendum to 026895 consisting of historical control data with B6C3F1 mice at Stauffer for the incidence of hepatocellular adenoma, carcinoma and either one or the other. The incidence of adenoma in males was 25/60 (42%), carcinoma at 10/60 and adenoma or carcinoma, 31/60 (52%). In females, the incidence of adenomas was 9/60, carcinomas at 3/60 and adenoma or carcinoma, 11/60. Stauffer now uses CD-1 mice so there is a very limited data base on B6C3F1 strain. JG, 10/28/86.

REPRODUCTION, RAT

034 1027 "Imidan Three-Generation Reproduction Study in Rats." (Woodard Research Corp., 5/20/85) Phosmet, 99%, fed in the diet to groups of 20/sex at 0, 40 or 80 ppm, three generations, 2 litters per generation; UNACCEPTABLE (histopathology on F3b litters, dose selection with no evidence for m.t.d. and two doses only, mean litter weights only, no cholinesterase measurements.) NOEL  $\geq$  80 ppm (HDT). In the initial review, an effect on the liver of the F3b animals (only ones for which histopathology was performed) was noted as a possible adverse effect. This is not a reproduction adverse effect and needs to be addressed in an acceptable chronic/oncogenicity study. JR(G), 4/30/85, 10/28/86.

No apparent EPA 1-liner.

034 1037 Summary of 1027. No data.

TERATOGENICITY, RAT

037 1050 "Effect of Imidan Administered to Pregnant Rats." (Midwest

Research Institute, 11/8/79.) Technical phosmet (Imidan), no purity stated; given by oral gavage to 25/group at 0, 0.06, 1.5 or 30 mg/kg, every other day for 9 doses or in a single dose of 30 mg/kg on day 8 or day 12; this dosing schedule is to repeat a study performed in the USSR; UNACCEPTABLE based on non-guideline dosing schedule with minimal toxicity at the high dose. Dev. toxicity NOEL  $\geq$  30 mg/kg (HDT); maternal NOEL = 1.5 mg/kg (body weight gain). JR(G), 4/30/85.  
EPA 1-liner: Supplementary. Terata NOEL  $\geq$  30 mg/kg (HDT), maternal NOEL = 1.5 mg/kg (reduced weight gain), fetotoxic NOEL  $\geq$  30 mg/kg.

037 1051 National Institute for Environ. Health Sciences, 1979. Contains information that phosmet showed a positive effect in the rat in a study conducted in the USSR [see 1050 above] but negative in the US study and negative in the rabbit in the USSR.

037 1049 "Developmental Toxicity in the Rat After Ingestion or Gavage of Organophosphate Pesticides (Dipterax, Imidan) During Pregnancy." Published article, 2/76. Phosmet, 95.8%, fed to rats in the diet of days 6 - 17 of gestation at 0, 10, 22, 27 or 29 mg/kg/day or by oral gavage at 5, 10, 20, 25 or 30 mg/kg; dev. toxicity NOEL  $<$  5 mg/kg by gavage (reduced fetal weight); maternal mortality at 25 and 30 mg/kg by gavage and decreased body weight at 27 and 29 in the diet or 20 and 25 mg/kg by gavage; systemic maternal NOEL = 10 mg/kg by gavage and 22 in the diet. UNACCEPTABLE with inadequate dose range and control of diet (curtailed food intake led to similar intake of agent in the three high groups fed phosmet in the diet), no analysis of diet or dosing solution, summary data only. Insufficient information for an independent assessment. JR(G), 4/30/85.

034 1033 Summary statement for a published paper by Staples, et al., in Environ. Health Perspectives 13: 133-140 (1976) in which no teratogenic effect was noted in CD strain of rats fed up to 30 mg/kg from day 6 through 15. A second publication by Martson and Veronina, Environ. Health Perspectives 13: 121-125 (1976) in Wistar rats conducted in the Soviet Union is abstracted. In this study, a single oral dose of 30 mg/kg was given on day 9 or day 13 of gestation. In the day 9 group, post implantation mortality increased (no data). In the day 13 group, hydrocephaly was noted (no data). The significance of these findings cannot be evaluated due to insufficient information.

Summary: The possible adverse effect indicated in the USSR studies was not substantiated in a repeat trial. The reasons suggested for the difference include test article and diet composition.

#### TERATOGENICITY, RABBIT

034 1028 "Imidan Oral Compared to Dermal Administration to The Rabbit: Effect on Reproduction." Woodard Research Corp., 7/14/66. Imidan technical, 97%, given in the diet or applied to the skin at 0, 10, 30 or 60 mg/kg/day; 10-12 per group; NOEL (ChE inhibition)  $<$  10 mg/kg oral; reproduction NOEL  $\geq$  60 mg/kg oral. No indication of a teratogenic effect. UNACCEPTABLE (doses not justified, protocol not guideline for teratology study or a repro study, insufficient number of animals per group). JR(G), 4/30/85.

EPA 1-liner: Minimum. Rep. NOEL  $\geq$  60 mg/kg (HDT); teratogenic NOEL  $\geq$  60 mg/kg; cholinesterase depression ranged slight to marked in the three oral doses, less marked in the dermally.

034 1025 "Embryotoxic Activity of Some Pesticides and Drugs Related to Phthalimide (Rabbits) (Captan, Phalphan, and Imidan)." St. Marys Hospital Medical School, London, [1965]. Brief report in which dose level(s) and number of New Zealand white rabbits are not given. Contains a statement that Imidan did not cause any signs of embryotoxicity when given days 7 - 12 of gestation. UNACCEPTABLE (insufficient information for assessment.) JR(G), 4/30/85.

034 1035 Summary only, no data.

TERATOGENICITY, MONKEY

034 1026 "Teratological Investigation of Captan, Imidan and Thalidomide in Macaca Mulatta (Phebus Monkeys)." (Bionetics, 4/4/68) Technical phosmet, no purity stated, given by oral gavage to 7 rhesus monkeys at 2, 4 or 8 mg/kg/day (no control) on days 22 to 32 with thalidomide control on days 25 to 27; no evidence for a teratogenic effect with phosmet while thalidomide showed teratogenic effects; UNACCEPTABLE (not a usual species, no rationale presented for dose selection and only marginal effects on cholinesterase). JR(G), 4/30/85.  
EPA 1-liner: Minimum. Terata NOEL  $\geq$  8 mg/kg/day (HDT).

MUTAGENICITY, GERM

Microbial systems

034 1031 Brief reference to a publication by Moriya, et al., Mutation Res. 115: 196-216 (1983) in which phosmet caused an increase in reversions in TA100 but not in TA1535, TA1537, TA1538 or TA98. This finding has now been confirmed - see 050729 below.

\*\* 063 050729 "Mutagenicity Evaluation in Salmonella typhimurium. (Stauffer, 4/2/86, Report T-12819) Salmonella, strains TA1535, TA1537, TA98 and TA100, tested with and without rat and mouse liver activation at 0, 0.156, 0.313, 0.625, 1.25 or 2.50 mg/plate, in triplicate, Imidan, lot WRC 10201-41-1, 95.7% pure; single trial except for TA100; possible adverse effect with increase in reversion rate with TA100 in both trials with rat and mouse activation and less increase without activation; this confirms the finding of Moriya, et al., record = 1031; initially reviewed as unacceptable based on single trial with three of the four strains (JG, 2/10/87); upgraded to ACCEPTABLE status in view of the modified guidelines of May 20, 1987. JG, 2/10/87 and 1/19/88.

## Mammalian systems

\*\* 063 050730 "Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test: Forward Mutation Assay." (Stauffer, 5/8/86, Report No. T-12820) Phosmet, 95.7%, tested for mutagenicity in mouse lymphoma L5178Y TK +/- assay; with and without rat liver activation, tested at 0, 0.02, 0.04, 0.06, 0.07, 0.08 and 0.10 mg/ml, 4 hours, two trials; increased mutation frequency without activation in both trials. ACCEPTABLE. JG, 2/10/87.

## MUTAGENICITY, CHROMOSOME

034 1030 "Phosmet Mutagenicity Data: Chromatid-Type Aberrations Observed in Factory Workers Producing Phosmet." Brief summation of a publication by Kiraly, et al. in Arch. Environ. Contam. Toxicol. 8: 309-319 (1979) in which chromatid-type aberrations were observed in pesticide factory workers compared with non-factory workers. [Review of the publication indicates that the study was conducted on workers in Budapest, Hungary, where Safidon 40 was manufactured. Twenty-five workers were examined, 25 to 58 years of age, all males. The report states they are checking new workers and will conduct a follow-up to determine if the chromosome aberrations increase with time. A total of 20.61% (261 of 1266 mitoses) showed a chromatid-type of aberration including gaps compared with 5.9 in the "normal" control and 10.97 in factory employee control.]

\*\* 063 050731 "Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test: Cytogenetic Assay." (Stauffer, 5/8/86, Report No. T-12821) Phosmet, 95.7%; chromosome aberrations and sister chromatid exchanges determined with and without rat liver activation; 4 hour exposure to 0, 0.008, 0.01, 0.015, 0.02 or 0.04 mg/ml with activation and 0, 0.04, 0.05, 0.06, 0.08 or 0.10 mg/ml without activation; statistically significant increase in sister chromatid exchanges with and without activation but no effect on chromosomal aberrations was reported. Duplicate cultures, scored 50 cells per culture, 500 cells for mitotic index. ACCEPTABLE. JG, 2/10/87.

\*\* 070 57545 "Phosmet Report of a Micronucleus Test in the Mouse." (Beecham Pharmaceuticals Research Division, Genetic Toxicology Unit, report no. T86/756/phosmet, 12-86) Phosmet, 95.5%, was tested in a preliminary study with COBS CD1 (ICR) BR mice at 15.0, 20.0 and 30.0 mg/kg with all animals dying at 30 mg/kg, 1/3 females at 20 mg/kg. The main test used 17.0 mg/kg as the treatment level; 5/sex sacrificed at each of 24, 48 and 72 hours. Cyclophosphamide was the positive control, 5/sex, sampled at 24 hours. Negative controls were 1% methyl cellulose, 5/sex. Scored 1000 cells/animal. No increase in micronucleated polychromatic erythrocytes at any of the sampling times. ACCEPTABLE. Shiner, 1-5-88 and Gee, 1/14/88.

## MUTAGENICITY, DNA/OTHER

\*\* 063 050733 "Morphological Transformation of Balb/3T3 Cells." (Stauffer, 8/12/85, Report No. T-12922) Phosmet, 95.7%; Balb/3T3 cells without activation only, tested at 0, 0.004, 0.006, 0.008, 0.010, 0.012 or

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Rev. January 29, 1988

0.014 mg/ml, 3 days; no increase in foci reported; 15 flasks per concentration, two trials with the cloning efficiency in the first trial at 9% - below acceptable level so repeated; ACCEPTABLE. JG, 2/10/87.

063 050732 "Effects of Imidan on Human Fibroblast DNA." (Stauffer, 5/30/86, Report No. T-12823) Phosmet, 95.7%; human foreskin fibroblasts incubated for 1 hour with and without rat liver activation at 0, 0.25, 0.5 or 1.0 (limit of solubility) mg/ml; sedimentation of nucleoids in 15 - 30% neutral sucrose gradients; rate of sedimentation compared with control: no change in rate of sedimentation; supplemental information - not an acceptable assay. JG, 2/10/87

#### NEUROTOXICITY

\*\* 036 1048 "Acute Delayed Neurotoxicity Study With Imidan Technical in Adult Hens." (Stauffer, Richmond, 8/9/82) Phosmet technical, 94.7%, given by oral capsule to 10 hens/group at 0, 0.02, 0.2 or 2.05 g/kg followed by another dose after 21 days; TOCP as positive control; atropine and 2-PAM to protect; ACCEPTABLE with no evidence for acute delayed neuropathy. NOEL for other effects (cholinesterase inhibition, neurological signs) - 0.02 g/kg. JR(G), 5/1/85  
EPA 1-linear: Acceptable. Not a delayed neurotoxic agent.

035 1044 "Demyelination Study in the Chicken (Imidan)." (Woodard Research Corp., 2/27/63.) JR(G), 4/30/85. Phosmet, no purity stated, fed in the diet for 6-7 weeks to hens at 0, 100, 316 or 1000 ppm, 10 per group; TOCP as positive control; histopathology on 5/group only; UNACCEPTABLE (dose selection - no toxicity at high dose, cannot determine neurotoxicity from the study.)