

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA  
PHOSMET (IMIDAN)

Chemical Code # 000335, Tolerance # 00261  
SB 950 # 107

October 28, 1986  
Revised 2/11/87, 1/29/88, 6/21/91, 8/6/92

I. DATA GAP STATUS

Combined (chronic & onco): No data gap, no adverse effect

Chronic dog: No data gap, no adverse effect

Oncogenicity mouse: No data gap, possible adverse effect

Reproduction, rat: No data gap, possible adverse effect

Teratogenicity, rat: No data gap, no adverse effect

Teratogenicity, rabbit: No data gap, no adverse effect

Gene mutation: No data gap, possible adverse effect

Chromosome: No data gap, possible adverse effect

DNA damage: No data gap, no adverse effect

Neurotoxicity: No data gap, no adverse effect

-----1 - There is also  
an unacceptable teratology study in a third species: monkey. This study showed no adverse  
effects.

Toxicology one-liners are attached.

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: T920806

Revised by M. Silva, 6/21/91; Kishiyama & Silva, 8/6/92.

Volumes through 092 and record numbers through 089613 were examined.

The one-liners in this document are summary statements only. It is necessary to obtain a  
worksheet for a thorough review of each study.

## II. TOXICOLOGY SUMMARY

### COMBINED RAT

\*\* 089 089424, "2-Year Chronic Toxicity/Oncogenicity Study with R-1504 in Rats", (J.C.F. Chang, Morrissey, R.L., and Wyand, S., Ciba-Geigy Corp., Agricultural Division, Environmental Health Center, T-13241, 4/15/91). R-1504 (Imidan\*, purity = 94.3%) was administered at concentrations of 20, 40, 200, or 400 ppm/day in the feed for Sprague-Dawley Crl:CD\* SD BR rats (70/sex for control, 60/sex/dose at 20, 40 and 200 ppm and 20/sex at 400 ppm). A 12 month interim kill was scheduled for 10 rats/sex at 20, 40 and 200 ppm and 20 rats/sex for control and 400 ppm. Chronic NOEL = 40 ppm (Fatty change in livers of both sexes at  $\geq$  200 ppm was observed.) ChE NOEL = 40 ppm (Serum, RBC and brain ChE activity was significantly decreased in both sexes at  $\geq$  200 ppm). Oncogenicity NOEL: No treatment related oncogenic effects were observed at any level. There was no evidence of oncogenicity. ACCEPTABLE. (Kishiyama & Silva, 6/12/91).

NOTE: Although there were possible adverse effects indicated in a previous chronic rat study (035 001047, 038454) based upon high mortality, this effect was not demonstrated in the most recent combined study (see above: 089 089424). The high incidence of mortality was apparently due to respiratory infections, rather than phosmet. Therefore, phosmet is considered not to induce adverse chronic or oncogenicity effects.

### CHRONIC RAT

035 001047, 038454 "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 (Insufficient numbers 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 at the high dose.) No treatment effect on neoplasia. The significance of the effect cannot be evaluated from this inadequate study. J. Remsen (Gee), 4/29/85.

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. EPA has accepted this as a chronic study (see memo, EPA to DPR (now DPR), 2/15/89).

CHRONIC DOG

\*\* 035 001047, 038454 "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. J. Remsen (Gee), 4/29/85 and 1/28/88.

Note: If this study were being reviewed in 1988 for the first time by DPR, 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.

002, 006, 020, 034 934454, 046328, 046329, 001038, 034500, Summary of record # 001047, 038454.

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."  
J. Remsen (Gee), 9/16/85

057 047566 (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. J. Gee, 10/28/86.

#### REPRODUCTION, RAT

034 001027 "Imidan Three-Generation Reproduction Study in Rats." (Woodard Research Corp., 5/20/65). Phosmet, 99%, fed in the diet to groups of 20/sex at 0, 40 or 80 ppm, three generations, 2 litters per generation. UNACCEPTABLE (dosage range not justified, and appeared to be much too low, histopathology was limited to F3b litters, only mean litter weights given, no cholinesterase measurements.) NOEL  $\geq$  80 ppm (HDT). In the initial review, an effect on the liver of the F3b animals (the only group for which any histopathology was performed) was noted as a possible adverse effect. This is considered by DPR as a "chronic" effect, rather

than as a "reproductive" effect. J. Remsen (Gee), 4/30/85 and 10/28/86; Aldous (one-liner update only), 1/17/90.

NOTE: The memo from EPA to DPR addressing differences in data gap status for this chemical (dated 2/15/89) notes EPA classification as "Core Supplementary" (changed since most recent Registration Standard).

002, 006, 020, 034, 035 934456, 046327, 001037, 001042, Summary of 001027. No data.

006, 008, 020 934455, 046326, Summary information.

**\*\* 086 091000**, "A Two-Generation Reproduction Study in Rats with R-1504", (L. S. Meyer and J. A. Walberg, Ciba-Geigy Corporation, Environmental Health Center, 400 Farmington Avenue, Farmington, CT., Study # T-13260, 5/18/90). R-1504 (Imidan) analytical (95.2% pure) was fed in the diet through 2 generations (2 litters/generation) at nominal concentrations of 0, 20, 80, and 300 ppm to 25 Cr1: CD\* (SD) BRVAF/Plus<sup>TM</sup> rats/sex/group. Systemic (Parental) NOEL = 80 ppm (An increase in chromorhinorrhea was reported in P1 females at 300 ppm as well as decreased absolute ovary and testes weights in P0 animals at 300 ppm and in testes weights in P1 males at 300 ppm. Hepatocellular vacuolation was observed in P1 males at 300 ppm.) ChE NOEL = 20 ppm (A significant decrease in RBC ChE was reported at  $\geq$  80 ppm in both sexes of P0. A significant decrease in Serum ChE was noted in both sexes of P1 at 300 ppm). **Adverse effect:** Reproductive NOEL = 20 ppm (Significantly reduced fertility in both sexes of P0 at  $\geq$  80 ppm and in both sexes of P1 at 300 ppm was reported. Decreased spermatogenesis was observed in P1 males at 300 ppm. Reduced litter size and pup survival were observed in all litter groups in both generations at 300 ppm.) ACCEPTABLE. (H. Green & M. Silva, 5/7/91).

#### TERATOGENICITY, RAT

**\*\* 092 089613**, "Phosmet: Teratogenicity Study in the Rat", (M. C. E. Hodge, ICI Central Toxicology Laboratory, Cheshire, UK, Study No: RR0544, 6/17/91). Phosmet (purity = 96.4%

w/w) was administered by gavage to mated Wistar rats (24/dose) at concentrations of 0 (corn oil), 5, 10, or 15 mg/kg on days 7 through 16 of gestation. **Maternal NOAEL = 5 mg/kg/day** (Body weight gain and food consumption were decreased at 15 mg/kg. Staining around the mouth and piloerection were observed at 15 mg/kg. Increased urinary incontinence was observed at  $\geq$  5 mg/kg.) **Developmental NOEL = 10 mg/kg/day** based on reduced fetal weight at 15 mg/kg. There was no evidence of developmental toxicity. **ACCEPTABLE. No adverse effect.** (Kishiyama & Silva, 7/29/92).

037 001050 "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. Developmental toxicity NOEL  $\geq$  30 mg/kg (HDT); maternal NOEL = 1.5 mg/kg (body weight gain). J. Remsen (Gee), 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 001051, 038455, 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 001050 above], but negative in the rat in the US study and negative in the rabbit in the USSR.

NOTE: The memo from EPA to DPR addressing differences in data gap status for this chemical (dated 2/15/89) notes EPA classification as "Core Supplementary".

037 001049 "Developmental Toxicity in the Rat After Ingestion or Gavage of Organophosphate Pesticides (Dipterex, Imidan) During Pregnancy." Published article, 2/76. Phosmet, 95.8%, fed to rats in the diet during 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. Developmental 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 mg/kg/day in the diet or 20 and 25 mg/kg/day by gavage. Systemic maternal NOEL = 10 mg/kg by gavage and 22 mg/kg/day 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. J. Remsen (Gee), 4/30/85.

NOTE: The memo from EPA to DPR addressing differences in data gap status for this chemical (dated 2/15/89) notes EPA classification as "Core Supplementary".

034 001033 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 Voronina, 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. One liner presumably by J. Gee, presumably 4/ /85.

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. At this time, DPR has not determined that a "possible adverse effect" is indicated (Gee, 1988; Aldous, 1/17/90).

#### TERATOGENICITY, RABBIT

\*\* 092 089611, "Phosmet: Teratogenicity Study in the Rabbit", (M. E. Moxon, ICI Central Toxicology Laboratory, Cheshire, UK, Study No: RB0545, 6/20/91). Phosmet (purity = 96.4% w/w) was administered to artificially inseminated New Zealand White rabbits (20/dose) by gavage at concentrations of 0 (corn oil), 2, 5, or 15 mg/kg on days 7 through 19 of gestation. Maternal NOEL = 5 mg/kg (Clinical signs and decreased body weight gain (reduced less than 3%) was observed at 15 mg/kg. Developmental NOEL = 5 mg/kg (Fetal skeletal ossification

(odontoid, sacral vertebrae, sternebrae, and transverse process) was delayed at 15 mg/kg.)  
ACCEPTABLE. No developmental toxicity. (Kishiyama & Silva, 7/30/92).

034 001028 "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. ChE inhibition NOEL << 10  
mg/kg in the oral treatment study; ChE inhibition was marginal at 10 mg/kg, and was modest but  
dose-related at higher dosages. Otherwise, no definitive signs of parental toxicity.  
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 reproduction study,  
insufficient numbers of animals per group). Remsen (Gee), 4/30/85; Aldous (in response to EPA  
memorandum of 2/15/89), 1/17/90.

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 dermal treatment groups.

034 001025 "Embryotoxic Activity of Some Pesticides and Drugs Related to Phthalimide  
(Rabbits) (Captan, Phaltan, and Imidan)." St. Mary's Hospital Medical School, London,  
[1965]. Brief report in which dose level(s) and number(s) 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.)  
J. Remsen (Gee), 4/30/85.

020, 034 046325, 001035 Summary only, no data.

#### TERATOGENICITY, MONKEY

034 001026 "Teratological Investigation of Captan, Imidan and Thalidomide in Macaca Mulatta  
(Rhesus 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 (dose levels and timing of administration were not justified, no negative control group, no QA, other deficiencies typical of older studies). J. Remsen (Gee), 4/30/85; C. Aldous (as part of response to 2/15/89 EPA memorandum) 1/17/90.

EPA 1-liner: Minimum. Terata NOEL  $\geq$  8 mg/kg/day (HDT).

#### MUTAGENICITY, GENE MUTATION

##### Microbial systems

**034 001031** Brief reference to a publication by Moriya, et al., Mutation Res. 116: 186-216 (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, 4/3/86, 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 # 001031; initially reviewed as unacceptable based on single trial with three of the four strains (J. Gee, 2/10/87); upgraded to ACCEPTABLE status in view of the modified guidelines of May 20, 1987. (J. Gee, 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. J. Gee, 2/10/87.

MUTAGENICITY, CHROMOSOME EFFECTS

034 001030 "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. J. Gee, 2/10/87.

\*\* 070 057545 "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. Shimer, 1-5-88 and Gee, 1/14/88.

MUTAGENICITY, DNA/OTHER

\*\* 063 050733 "Morphological Transformation of Balb/3T3 Cells." (Stauffer, 8/12/86, Report No. T-12822). Phosmet, 95.7%; Balb/3T3 cells without activation only, tested at 0, 0.004, 0.006, 0.008, 0.010, 0.012 or 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. (J. Gee, 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. (J. Gee, 2/10/87).

NEUROTOXICITY

\*\* 036 001048 "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. J. Remsen (Gee), 5/1/85.

EPA 1-liner: Acceptable. Not a delayed neurotoxic agent.

035 001044 "Demyelination Study in the Chicken (Imidan)." (Woodard Research Corp., 2/27/63.) 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.) J. Remsen (Gee), 4/30/85.

035 001041, Summary of record # 001044.