CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

MEVINPHOS

DPN #: 00157, SB950 #: 079
Chemical Code #: 000480

Revised: 5/28/87; 3/5/90; 5/25/90; 3/2/92

I. DATA GAP STATUS

Chronic rat :	Data gap, inadequate study, no adverse effect indicated
Chronic dog :	Data gap, inadequate study, no adverse effect indicated
Onco rat :	Data gap, no study submitted
Onco mouse :	No data gap, no adverse effect
Repro rat :	No data gap, no adverse effect
Terato rat :	No data gap, no adverse effect
Terato rabbit :	Data gap, inadequate study, possible adverse effect indicated
Gene mutation :	No data gap, possible adverse effect
Chromosome :	No data gap, possible adverse effect
DNA damage :	No data gap, possible adverse effect
Neurotox :	No data gap, no adverse effect

Note, Toxicology one-liners are attached

** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File Name: T920302
Revised by M. Silva, 5/25/90; J. Kishiyama & M. Silva, 3/2/92.

Rectified through volume #: 050 and record #: 111291

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These pages contain summaries only. Each individual worksheet may contain additional effect.

II. TOXICOLOGY SUMMARY

CHRONIC, RAT

009 034546, "Toxicity Studies on the Organophosphorous Insecticide Phosdrin: 2 Year Oral Experiment with Rats", (Tunstall Laboratory, Shell Research LTD, London, #TLRG.0043.71, October 1971). Phosdrin technical, 60.2% cis-isomer, 39/sex, fed in the diet at 0, 0.5, 1.5, 5.0, and 15.0 ppm; negative control had 78/sex; mean dietary concentrations were calculated to be 74.25% of nominal; interim sacrifices at 6, 12, and 18 months; males 42-58% mortality and females 54-71% - not dose related; no adverse effect noted; UNACCEPTABLE, incomplete, data presented in summary form only; inadequacies exist in individual animal data, dose justification, ophthalmology, hematology, urinalysis and histopathology, not upgradable. (Shimer, Apostolou 9/23/85, Martz 11/30/86)

006 020019. Summary of 034546 in 009

010 and 013 048723, rebuttal/response to CDFA review of 034546 in 009, (no status change). (Martz 11/30/86)

CHRONIC, DOG

AMVAC requests a waiver for the chronic toxicity testing on dogs. The request is based on the possible inability to administer mevinphos doses high enough to obtain useful toxicity data. Two preliminary subchronic studies (DPR record # 092716 and # 092717) are submitted with the letter (4/26/91) of request for waiver. Emesis appears to be a problem for dogs treated with 0.5 and 1.0 mg/kg mevinphos <u>in capsule form.</u> Mevinphos dose of at least 0.5 mg/kg to 1.0 mg/kg appears to be the required high dose and if lowered, would not provide meaningful data for a definitive study. An attempt was made to test the effect of split dosing and reduce/eliminate emesis in preliminary test #2. The letter for waiver request interprets the results on page 2, first paragraph as follows; "The results of this preliminary study show that split dosing does slightly reduce emesis although the problem does not disappear." However, preliminary study #2 does not discriminate the effect of split dosing on the reduction/elimination of emesis. Vomiting was observed for dogs treated with only one 0.5 mg/kg dose/day, therefore, it would not be expected that the same dose twice/day would reduce the effect. A waiver based on the results presented is not acceptable. Alternative dosing methods should be considered. M. Silva, 2/20/92.

045 092717, "Range-Finding Study of Mevinphos Administered Orally to Beagle Dogs (Preliminary Study #1)," (V. Reddy, D.W. Arneson, B.W. Maidment, Midwest Research Institute, MRI Project No. 9497-F, 3/26/91). Mevinphos technical (purity = 89.57%) was administered orally in capsules at concentrations of 0 (corn oil), 0.025, 0.05, 0.25 (elevated to 1.0 mg/kg on day 14 of dosing), or 0.50 mg/kg to 2 Beagle dogs/sex/group for three weeks. NOEL = 0.025 (Decreased plasma cholinesterase values of $\geq$ 45% in both sexes at $\geq$ 0.25 mg/kg. Vomiting occurred in both sexes at $\geq$ 0.05 mg/kg. Motor activity decreased at $>$ 0.5 mg/kg). These data are supplemental. (Kishiyama & Silva, 1/31/92).

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045 092716, "Range-Finding Study of Mevinphos Administered Orally to Beagle Dogs (Preliminary Study #2)," (V. Reddy, D.W. Arneson, B.W. Maidment, Midwest Research Institute, MRI Project No. 9497-F, 3/26/91). This study was initiated to test a split dosing system to reduce emesis and to test specific areas of the brain for cholinesterase activity. Mevinphos technical (89.57% pure) was administered orally in capsules at concentrations of 0 (corn oil) or 0.5 mg/kg/day to 1 Beagle dog/sex/group once daily and to another like set but dosed twice daily (0 and 1.0 mg/kg total/animal/day) for 5 days. Vomiting seemed to be somewhat related to the amount of treatments. Appetite (food consumption) and weight were affected in the twice treated group. Cholinesterase was not significantly affected by mevinphos. (Kishiyama & Silva, 2/5/92).

009 034547, "Toxicology Studies on the Organophosphorous Insecticide Phosdrin, Two Year Oral Dosing Experiment with Dogs", (Tunstall Laboratory, Shell Research LTD, London, #TLGR.0052.71, December 1971). Phosdrin technical, 60.2% cis-isomer, at 0, 0.025, 0.075, 0.25, and 0.75 mg/kg in gelatin capsules in olive oil, 4/sex/group, no consistent dose related effects observed; no adverse effect noted; apparent NOEL 0.025 mg/kg/day (CHE inhibition); UNACCEPTABLE, incomplete; deficiencies include dose level justification, hematology, urinalysis, ophthalmology, individual animal data, and histopathology; not upgradable. (Shimer, Apostolou 9/23/85, Martz 11/30/86).

006 020018. Summary of 034547 in 009

010 and 013 048724, rebuttal/response to DPR review of 34547 in 009, (no status change). (Martz 11/30/86).

ONCOGENICITY, RAT

No studies currently available.

ONCOGENICITY, MOUSE

** 028 073163, "An Eighteen Month Oncogenicity Feeding Study in Mice with Mevinphos", (Bio/dynamics Inc., Project no. 86-3006, 2/23/89). Mevinphos technical (purity = 100%) mixed in the feed at concentrations of 0 (diet only), 1, 10, or 25 ppm were fed to 50 CD-1 mice/sex/group for approximately 18 months. No adverse effect. NOEL = 10 ppm (transient decrease in body weights for both sexes). NOAEL $\geq$ 25 ppm. Cholinesterase inhibition was not measured. Dose selection was based on a 3 month study. ACCEPTABLE. (Kishiyama & Silva, 3/1/90).

REPRODUCTION, RAT

** 050 111291 "Multi-Generation Rat Reproduction Study MRD-88-331: Mevinphos," (Beyer, B.K., Exxon Biomedical Sciences, Inc., ID#: 233135, 11/26/91). Mevinphos technical was administered via oral intubation (7 days/week) to Crl:CD BR VAF/Plus Sprague-Dawley rats (35/sex/group) at 0 (reverse osmosis water), 0.05, 0.1 and 0.5 mg/kg for 2 generations (1 litter/generation). Reproduction NOEL = 0.1 mg/kg (There were decreased numbers of corpora lutea in P2 dams at 0.5 mg/kg.) Chronic NOEL = 0.1 mg/kg (P1 females at 0.5 mg/kg showed ataxia, coarse and fine tremors, oral discharge and pinpoint pupils. There was a significant decrease in

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ovaries/body weight at 0.5 mg/kg.) Pup NOEL = 0.1 mg/kg (There was a significant decrease in mean pup weights on day 21, survival indices for days 1, 4 and 14 and the lactation index in the P1 generation. There was a significant decrease in male pup weights on day 21 and in day 4 survival index in the P2 generation.) Cholinesterase NOEL = 0.1 mg/kg (Plasma (44-60%) and brain (41-51%) cholinesterase were inhibited at 0.5 mg/kg in both sexes for both generations.)
No adverse effect. The study is acceptable. M. Silva, 2/20/92.

NOTE: A disclosure statement for possible adverse effects was submitted by the registrant (January 18, 1991) in reference to results observed in a rangefinding study (no record #, ID # SBC-126884-E). In light of the results of the definitive rat reproduction study (no adverse effects), this document does not need to be further addressed (no worksheet). M. Silva, 2/20/92.

009 034549, "3-Generation Reproduction Study of Phosdrin Insecticide in Rats", (Hill Top Research, Inc., Miamiville, Ohio, #P-5, 10/24/67). Phosdrin Insecticide, 60% alpha isomer and 40% related compounds; at 0, 1.2, and 24 ppm in Purina Lab Chow to 10 males/group and 2 females/group for 3-generations, 2 litters/generation; no adverse reproductive effect reported; NOEL $\geq$ 24 ppm (nominal), UNACCEPTABLE, incomplete; lack of toxicity at high dose, poor pup survival in F2b control and treated groups; does not include analysis of diet, dose level justification, and complete histopathology data; not upgradable. (Shimer, Parker 9/24/85, Martz 11/30/86).

006 955232. Summary of 034549 in 009.

010 and 013 048726, rebuttal/response to DPR review of 034549 in 009 (no status change). (Martz 11/30/86).

TERATOLOGY, RAT

**016 055833, "Mevinphos - A Teratology Study in Rats with Mevinphos", (Bio/dynamics Inc., 85-3009, March 2, 1987). Mevinphos technical, lot 50826, 12/18/85, administered by gavage in distilled water to groups of 24 mated Sprague-Dawley rats at levels of 0, 0.2, 0.75, and 1.00 mg/kg on days 6 - 15 of gestation. The initial high dose group, 1.25 mg/kg/day was terminated due to excessive maternal toxicity (tremors and salivation) was observed at 0.75 and 1.00 mg/kg/day, Maternal NOEL = 0.2 mg/kg/day. There was no evidence of developmental toxicity at any dose level, Developmental NOEL > 1.00 mg/kg/day. ACCEPTABLE, no adverse effect. (J. Parker, 4-28-87)

015 055832. Range finding study for 055833.

TERATOLOGY, RABBIT

042 096991, "Teratology Study in Rabbits (MRD-88-331: Mevinphos)", (B. K. Beyer, Exxon Biomedical Sciences Inc., Laboratory Project I.D. 233134RB, 2/22/91). Mevinphos (89.57% pure), administered by oral gavage at concentrations of 0, 0.05, 0.5 and 1.5 mg/kg/day to artificially inseminated New Zealand White rabbits (20/group) on days 7 through 19 of gestation. **Maternal NOEL** = 0.5 mg/kg (There was a significant decrease in body weight gain at 1.5 mg/kg.) **ChE NOEL** = 0.5 mg/kg (There was a decrease of 47% plasma ChE at 1.5 mg/kg.) **Developmental NOEL** = 0.5 mg/kg (A few fetal variations, such as accessory vessels, hypoplastic hyoid and unossified forepaw were observed.) Maternal body weight gains were decreased, but no other toxic

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effects were observed. A slight decrease in plasma cholinesterase was measured without cholinergic signs. Although there was little evidence of maternal toxicity, the dose selection for this study was justified, based upon the pilot. Currently, this study is unacceptable but possibly upgradeable upon submission and review of stability data, recomputed data from Table 3, historical control data for fetal malformations and variations and information on pregnancy status of animal HEB054. (Kishiyama & Silva, 2/6/92).

009 034548, "Toxicity Studies with Phosdrin: Teratological Studies in Rabbits Given Phosdrin Orally", (Tunstall Laboratory, Shell Research LTD, London, #TLGR.0016.74, April 1974). Technical Phosdrin, batch #ACD/73/5, in gelatin capsules in corn oil at 0, 0.3, and 1.0 mg/kg/day to 20 females/group, day 6 through 18 of gestation; no teratogenicity noted; increased maternal toxicity at high dose; no adverse effect noted; apparent NOEL = 1.0 mg/kg/day (general health and body wt. gain); UNACCEPTABLE, incomplete; deficiencies include no analysis of dosing material, no justification of dosage levels and selection, and incomplete litter data; not upgradeable, possible status change: study may be acceptable/upgradeable if more information is supplied. (Shimer, Apostolou 9/23/85, Martz 11/30/86).

006 020017. Summary of 034548 in 009.

010 and 013 048725, rebuttal/response to CDFA review of 034548 in 009; possible status change, study may be acceptable/upgradable if more information is supplied. (Martz, 11/86).

MUTAGENICITY, GNMU

** **034 085454**, "CHO/HGPRT Mutation Assay with Confirmation with Mevinphos", (Microbiological Associates Inc., Laboratory Study No. T8858.332001, 11/9/89). Mevinphos (purity = 74.48% alpha isomer and 15.09% beta isomer) was tested with Chinese Hamster ovary cells (CHO-K_1-BH_4) at concentrations of 0.1, 0.4, 0.6, 0.8, 1.0 µl/ml without S-9 activation and at 0.1, 0.6, 1.2, 1.8, or 2.4 with Arochlor-induced rat liver S-9 (exposure = 5 hours) in an initial study. In another study the cells were tested with mevinphos at 0.5, 0.6, 0.7, 0.8, 0.9, or 1.1 without S-9 and 0.6, 0.9, 1.2, 1.4, 1.6, or 1.8 µl/ml with S-9 in a repeat assay. **Adverse effect** (the number of mutant/10^6 clonable cells, without S-9 increased at 1.0 µl/ml in the initial test and at 0.9 µl/ml in the repeat test). Relative cloning efficiency averaged 16-20% and 42% for mevinphos doses at 1.0 and 0.9 µl/ml, respectively. ACCEPTABLE. (Kishiyama & Silva, 2/26/90).

** **030 087669**, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with A Confirmatory Assay with Mevinphos", (Microbiological Associates, Inc., Laboratory study No. T8858.501014, 10/23/89). Mevinphos (purity = 74.48% alpha isomer, 15.09% beta isomer) was used at concentrations of 0 (deionized water), 100, 1000, 3333, 6667 or 10000 µg/plate exposures to *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation (S-9 Mix) for 48 hours. **Adverse effect.** An increase in TA100 revertant colonies was observed at > 3333 mg/plate both with and without S-9. ACCEPTABLE. (Kishiyama & Silva, 2/28/90).

009 034551, "The Mutagenic Effect of Organophosphate Insecticides on Escherichia coli", (Tunstall Laboratory, Shell Research LTD, London, #TLGR.0034.71, August, 1971). Phosdrin, 67.3% W cis-isomer, plate incorporation assay with E. coli B/r WP2 in triplicate seeded at $9x10^8$/plate;

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no reverse mutation reported; UNACCEPTABLE, incomplete, summary information only; no data - results as "-" only, lacks dose level selection and justification and control information. (Green, Parker 5/13/87).

006 035764. Summary of 034551 in 009.

MUTAGENICITY, CHROMOSOME

** **035, 036 090374, 086427** "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells With Mevinphos," (Microbiological Associates, Inc., 1/18/90). Mevinphos technical (purity = 76% alpha isomer; 13.5% beta isomer) was used in a chromosome aberration assay using Chinese hamster ovary cells at 0 (vehicle = culture medium or water), 0.04, 0.08, 0.15, 0.3 and 0.6 ul/ml (without S-9; 18 hour treatment in duplicate) and 0.13, 0.5, 1.0 and 2.0 ul/ml (with S-9; 2 hour treatment in duplicate). A repeat assay was performed without S-9 at 0.15, 0.21, 0.30 and 0.42 ul/ml Mevinphos. **Possible adverse effect.** The percentage of Mevinphos treated cells (no S-9) with chromosome aberrations was significantly increased over the controls at $\geq$ 0.15 ul/ml. This worksheet was revised with the addition of CDFA volume/record #: 036/086427 which contains an analysis of technical Mevinphos (no separate worksheet). ACCEPTABLE. M. Silva, 5/18/90.

009 034550, "Toxicity Studies with Phosdrin: Dominant Lethal Assay in Male Mice after a Single Oral Dose of Phosdrin", (Tunstall Laboratory, Shell Research LTD, London #TLGR.0031.74, July, 1974). Phosdrin, methyl 3-(dimethoxy phosphinyloxy) crotonate, E-isomer 70.0%, batch no. ACD 73/69; single oral dose in water at 0, 1.5, 3.0, and 6.0 mg/kg to males 12/group, mated 1 male/3 females/week for 8 weeks; females sacrificed 13 days after mating; no dominant lethal effects reported; no adverse effect noted; UNACCEPTABLE, not upgradable; deficiencies include no MTD, no concurrent historical or positive control, and no individual data. (Shimer, Remsen 9/25/85).

006 035763. Summary, insufficient information for evaluation.

006 955233. Summary of 034550 in 009.

010 and 013 048727, rebuttal/response to CDFA review of 034550 in 009, (no status change). (Martz 11/30/86).

009 034555, "Toxicity Studies with Phosdrin: Chromosome Studies on Bone Marrow Cells of Mice after Two Daily Oral Doses of Phosdrin", (Tunstall Laboratory, Shell Research LTD, London, #TLGR.0008.74, February 1974). Phosdrin E-isomer 70.0%, batch no. ACD 73/69 dosed twice orally on 2 consecutive days in water 8/sex/group at 0, 1.5, and 3.0 mg/kg, positive control of 100 mg/kg cyclophosphamide; colcemid 90 minutes prior to sacrifice, sacrificed at 8 and 24 hours after dosing 100 cells/animal; no bone marrow chromosomal aberration reported; UNACCEPTABLE, not upgradeable. (Shimer, Remsen 9/25/85).

010 and 013 048728, rebuttal/response to CDFA review of 034555 in 009, (no status change). (Martz 11/30/86).

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MUTAGENICITY, DNA

** 035, 036 090373, 086427 "Unscheduled DNA Synthesis in Rat Primary Hepatocytes With Mevinphos," (Microbiological Associates, Inc., 1/25/90; Study #: T8858.380). Mevinphos technical (purity = 76.34% alpha isomer; 13.5% beta isomer) was used in a UDS assay on primary rat (Fischer 344 or Sprague-Dawley) hepatocytes at 0 (vehicle = William's Medium E), 0.0003, 0.001, 0.003, 0.01, 0.03, 0.06, 0.1, and 0.3 ul/ml for 18-20 hours (3 plates/dose + [3-H]Thymidine at 10 uCi/ml/plate). A parallel cytotoxicity test was also performed (3 plates/dose). After treatment, cells were placed on coverslips and slides were prepared (50 cells/slide were scored; 3 slides/dose). No adverse effect. No increase in UDS was observed at any dose. This worksheet was revised with the addition of CDFA volume/record #: 036/086427 which contains an analysis of technical Mevinphos (no separate worksheet). ACCEPTABLE. Volume 036/086427 contains an analysis of Mevinphos technical. M. Silva, 5/18/90.

009 034552, "Toxicity Studies with Phosdrin: Effect of Phosdrin on Micro-Organisms in the Host-Mediated Assay and in vitro", (Tunstall Laboratory, Shell Research LTD London, #TLGR.0067.74, November 1974). Technical Phosdrin, 81.9% E-isomer of methyl 3-(dimethoxyphosphinoxy) crotonate; spot test on plates with Serratia marcescens; NTG as postive control; no reversion reported; no data, summary only; UNACCEPTABLE, not upgradeable. (Shimer, Remsen 9/25/85).

009 034553, "Toxicity Studies with Phosdrin: Effect of Phosdrin on Micro-Organisms in the Host-Mediated Assay and in vitro", (Tunstall Laboratory, Shell Research LTD, London, #TLGR.0067.74, November 1974). Technical Phosdrin, 81.9% E-isomer of methyl 3-(dimethoxyphosphinoxy) crotonate, in vitro study in triplicate with Saccharomyces cerevisiae at 0, 0.2, 1, 2, and 4 mg/ml NTG positive control; at 1 mg/ml increase in conversion rate at adenine locus after 24 hour incubation; summary data only; possible adverse effect (genotoxicity); UNACCEPTABLE, not upgradeable. (Shimer, Remsen 9/25/85).

009 034554, "Toxicity Studies with Phosdrin: Effect of Phosdrin on Micro-Organisms in the Host-Mediated Assay and in vitro", (Tunstall Laboratory, Shell Research LTD, London, #TLGR0067.74, November 1974). Technical Phosdrin 81.9% E-isomer of methyl 3-(dimethoxyphosphinoxy) crotonate, host-mediated assay in triplicate, male CF-1 dosed orally at 0, 1.5, and 3.0 mg/kg, EMS positive control; Saccharomyces cerevisiae D4 injected; sacrificed at 5 hours; tryptophan and adenine plate assay, no positive effects reported; no adverse effect noted; summary data only, UNACCEPTABLE, not upgradeable. (Shimer, Remsen 9/25/85).

006 035762. Summary of 034552, 034553, and 034554 in 009.

NEUROTOXICITY, HEN

010 048729. Rebuttal to 034556, in 009, status change: report acceptable with major deficiencies.

**009 034556, "Toxicity Studies on the Organophosphorus Insecticide Phosdrin: An Investigation of the Potential Neurotoxicity of Technical Phosdrin", (Tunstall Laboratory, Shell Research LTD, London, #TLGR.0047.72, November, 1972). Technical Phosdrin (purity 60.2% cis-isomer), 0 or 7.5 mg/kg (D50) by oral gavage once on day 1 and 23 with sacrifice on day 43, TOCP positive control, atropine and protopam protection; no clinical signs of delayed neurotoxicity in phosdrin group; 3/6 phosdrin hens died after second dose; 1

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dead and 3 survivors examined histologically no evidence of delayed neurotoxicity found. Previously reviewed (AA, 9/23/85) unacceptable and not upgradable. Rebuttal accepted, repeat of study would not provide additional information. Report ACCEPTABLE with major deficiencies. (F. Martz, 12/2/86).

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