

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
FENAMIPHOS

Chemical Code # 001857, Tolerance # 349
SB 950 # 222

October 16, 1986

Revised 5/19/87, 5/11/88, 10/17/88, 5/15/90, 4/15/92, 5/19/92, 7/12/96 and 2/8/00

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: t20000208

Revised by C. Aldous, February 8, 2000

This Summary includes all relevant studies indexed as of 1/31/00, including record numbers up to 172627 (Document No. 349-216). Relevant records in the 900,000+ series are also included.

These pages contain summaries only. Individual worksheets may identify additional effects.

COMBINED, RAT

107 045780, "Combined Chronic Toxicity/Oncogenicity Study of Technical Fenamiphos (Nemacur) with Rats", (2/28/86, Mobay). Fenamiphos, 89% (other components are quantitated); fed in the diet for 2 years to 50/sex/group at 0, 2, 10 or 50 ppm with satellite group of 10/sex for control and 20/sex for high dose groups; NOEL < 2 ppm ChE inhibition; 10 ppm for other effects (inflammatory lesions at 50 ppm in nasal, laryngeal and lung tissues) attributed to stress of the severe cholinesterase inhibition, which reached 90% at some intervals for plasma cholinesterase; brain cholinesterase was moderately depressed at 12 month sacrifice but marginal at terminal sacrifice; no evidence of oncogenicity. The suppression of cholinesterase is **not considered an adverse effect in terms of chronic or oncogenic effects but is taken as a measure of adequacy of dose levels in the test as well as in the studies below. **Acceptable**. ChE NOEL = 0.91 ppm effective dose according to a 14 week study included in the same volume. Gee, 10/16/86.

138 069770, Summary data for # 045780.

119 061220, Supplementary data were submitted by Mobay Chemical Corp. for study 45780 in order to add to the data base for fenamiphos. The volumes submitted contain summary mortality, average food consumption, average body weights, individual gross pathology, individual histopathology and the grading system used for histopathology. These data are a more detailed presentation of previously submitted data, however the status of the study remains **acceptable**. M. Silva, 5/11/88.
No EPA one-liner. Last update on fenamiphos was 9/5/84.

CHRONIC TOXICITY, RAT

023 024550, 024551, "Bay 68 138: Chronic Toxicological Studies on Rats (2-year feeding experiment)", (6/20/72, Bayer AG, Report No. 3539). Fenamiphos technical, no purity stated, was fed in the diet to 40/sex/treatment group, 80/sex in control group, for 2 years, at 0, 3, 10 or 30 ppm; unacceptable due to insufficient information with no reported chronic or oncogenic effects; cholinesterase inhibition at high dose with clinical signs of cholinesterase depression; **unacceptable** (no microscopic pathology with individual data handwritten in German, no analysis of diet, no clinical observations, others). Christopher, 8/8/85.

EPA one-liner: Minimum. Systemic NOEL = 10 ppm (increased mortality, increased thyroid gland weights and lung weights); ChE NOEL = 3 ppm (LDT) with slight inhibition at 10 ppm.

138 069769, Summary of 024550, 024551.

CHRONIC TOXICITY, DOG

349-179 112031 Rieth, J. "Chronic Toxicity Study of Technical Grade Fenamiphos (Nemacur®) with Dogs" (Mobay Corporation, Corporate Toxicology Department, Mobay Report No. 101936, 12/20/91). Fenamiphos, purity 88.9%, in the feed at nominal concentrations of 0 (corn oil), 1, 3, or 12 ppm was fed to 4 Beagle dogs/sex/group for one year. Significant plasma cholinesterase inhibition occurred in all fenamiphos-treated dogs (a follow-up study to establish the NOEL for plasma cholinesterase is to be conducted by the sponsor; not necessary to fill data gap for chronic toxicity). NOEL for non-plasma ChE inhibition = 1 ppm. Anemia was reported in high dose males (decreased hemoglobin, hematocrit and erythrocyte counts). Systemic NOEL = 3 ppm (hematology and brain ChE inhibition). **No Adverse effects. Acceptable. (Kishiyama, Kellner and Gee, 5/21/92). NOTE: The following 6-month study (Miles Report No. 101936-1) provides an NOEL of 0.408 ppm for plasma cholinesterase relevant for long-term dog dietary studies. (Aldous, 7/12/96).

349-185 121380 Jones, R. D. and M. L. Loney, "A subchronic feeding toxicity study with technical grade Fenamiphos (Nemacur®) in dogs", Miles Inc., Stilwell, Kansas, 2/19/93. Miles Report No. 101936-1. This is a supplemental study to Miles Report No. 101936 (chronic dog study). The primary purpose was to establish a NOEL for plasma cholinesterase inhibition. Four beagles per sex per group were administered fenamiphos (purity 89.5%) at 0 or nominal 0.5 ppm for 6 months (mean achieved concentration was estimated to be 0.408 ppm). Measured parameters included b.w., diet consumption, clinical observations, plasma and RBC cholinesterase, and ophthalmology. Dogs were not sacrificed as part of this study. There were no positive findings for any of the parameters examined. This study supplies a NOEL for a continuous dosing regimen for plasma cholinesterase, which is applicable to the chronic study (Miles Report No. 101936). This is not a guideline study, but is valid for its intended purpose. Aldous, 7/12/96.

349-192 125696 Supplementary data relating to Record No. 112031 (Mobay Report No. 101936), which data had been requested by the U.S. EPA reviewer. This study had already been accepted by DPR, and the supplemental data do not change acceptability status. Aldous, 7/12/96.

023 024549, 024548, "Bay 68 138: Chronic Toxicological Studies on Dogs", (7/3/72, Bayer AG, Report No. 3561). Fenamiphos, no purity stated; fed in the diet to Beagle dogs, 4/sex/group, at 0, 0.5, 1, 2, 5 or 10 ppm for 2 years; **unacceptable** (no analysis of diet, no description of test article.) Cholinesterase depressed about 50% in high dose so dose level probably adequate. Christopher, 8/8/85.

EPA one-liner: Minimum. Systemic NOEL = 10 ppm (HDT); ChE NOEL = 1 ppm.

138 069765, Summary of 024549, 024548.

049 007788, Summary information.

138 069764-66, Summary tables of results that lead to the conclusion that a dog study will be initiated at dose levels of 0, 1, 3 and 12 ppm. Letter dated 9-6-88.

006 048125; 015 968384; 042 007724, Studies cited in 138 to justify dose selection for new chronic dog study (H. Green and G. Chernoff, 5/15/90).

ONCOGENICITY, RAT

See above, under "combined".

ONCOGENICITY, MOUSE

024 968409, "Technical Fenamiphos (Nemacur) Oncogenicity Study in Mice, Study Number 78CCM02", (2/12/1982, Mobay, Report No. 241). Fenamiphos, 89.2-90.5%; fed to 50/sex/group CD-1 mice at 0, 2, 10 or 50 ppm for 20 months; no oncogenicity reported; initially reviewed by Christopher as unacceptable based on no cholinesterase measurements, excessive mortality (18%) in high dose females in first year of study with no pattern for cause of death, unclear if purity of test compound was considered in preparation of diets, and inadequate presentation of data. Re-review of the study following submission of a rebuttal (in Document 349-111) clarifying the diet preparation and analyses finds the study is **acceptable. Apparent NOEL (systemic) = 10 ppm (nominal) based on body weight decreased gain. No adverse effect identified. Christopher, 8/13/85, Gee and Martz, 5/13/87.

EPA one-liner: Minimum. Oncogenic NOEL > 50 ppm (HDT); systemic NOEL < 2 ppm (decreased absolute brain weights).

008 968410, Invalid IBT study (5/15/72). Christopher, 8/5/85.

EPA one-liner: Invalid.

REPRODUCTION, RAT

** 349-168 097247, "A Two-Generation Dietary Reproduction Study in Rats Using Fenamiphos (Nemacur®)", (D. A. Eigenberg, Mobay Corporation, Corporate Toxicology Department, Mobay Report No. 100692, 4/23/91). Fenamiphos technical, purity 88.6% (mean), was administered at nominal concentrations of 0, 2.5, 10, or 40 ppm in the feed to two generations of 30 Sprague-Dawley rats/sex/group beginning 10 weeks prior to mating. During the lactation period, body weight was less than control for high dose parental F0 and F1 females and for their pups (approximately 17%) and food consumption was reduced for parental females. NOEL (for non-ChE effects) = 10 ppm based on lower body weight and food consumption. Significant plasma ChE (PChE) depression was noted for F0 and F1 adult females at all dose levels. RBC ChE inhibition was significant at 10 and 40 ppm and

brain ChE was only inhibited at 40 ppm. Pup ChE was only effected at high doses (no effect on pup brain ChE). NOEL < 2.5 ppm for plasma ChE inhibition. The NOEL for plasma cholinesterase inhibition was established at 1 ppm in a previous study (Mobay report #90967: U.S. EPA Accession #26729; DPR 107 045779/45780). Reproductive NOEL = 10 ppm (reduced pup weight gain during lactation and lower ovary weights in 40 ppm group). **No Adverse Effects. Acceptable.** Kishiyama, Kellner and Gee, 5/12/92.

349-184 118063 Supplementary data relating to Record No. 097247 (Mobay Report No. 100692), which data had been requested by the U.S. EPA reviewer. This study had already been accepted by DPR, and the supplemental data do not change acceptability status. Aldous, 7/12/96.

022 968414, 968415, "Bay 68 138: Generation Studies on Rats", (5/3/72, Bayer AG, Report No. 3424). Fenamiphos technical, no purity stated; fed in the diet to 10 males and 20 females per group, at 0, 3, 10 or 30 ppm; 3 generations, 2 litters each; **unacceptable** with insufficient information to evaluate for adverse effect (no analysis of diet, test article not characterized, no evidence of toxicity - no cholinesterase analysis - doses judged too low, individual data in German, growth presented graphically only, inadequate histopathology - none on F0 and F1 breeders.) **No adverse reproductive effect** included in report. Christopher, 8/8/85
EPA One-liner: Minimum. Systemic NOEL = 10 ppm (decreased body weight gain at F2b males); reproductive NOEL = 30 ppm (HDT).

138 069767, Summary of #968414, 968415.

138 69767, 69768, 69769, 69770, 69660, Summary tables of results which lead to the conclusion that a rat repro study will be initiated at dose levels of 2.5, 10 and 40 ppm. Letter dated 9-6-88.

107 045779; 015 968376, 968382; 022 048173, Subchronic studies to support the dosing levels for a new rat reproduction study (Green and Chernoff, 5/15/90).

TERATOLOGY, RAT

**153 075610, "Teratology Study in the Rat with Nemacur Technical", (Clemens, G.R., C.M. Troup, and R. E. Hartnagel Jr., Toxicology Department Miles Inc., Mobay Report No. 99650, 8/30/89). Nemacur technical (fenamiphos), Batch 77-297-55, 88.7%, was administered by gavage to groups of 33 or 36 Crl:CDBR female rats on days 6-15 of gestation at dose levels of 0 (2% aqueous Emulphor), 0.25, 0.85 or 3 mg/kg/day. Five females per dose group were killed on day 16 and the remainder on day 20 of gestation. At 3.0 mg/kg/day, all females exhibited tremors, 6 died during the treatment period, body weight and food consumption were reduced, and erythrocyte cholinesterase was significantly decreased on both of days 16 and 20. No treatment related maternal effects were seen at lower doses, and no developmental effects were noted at any of the dose levels tested. Maternal NOEL = 0.85 mg/kg (death, tremors, decreased food consumption and weight gain, RBC ChE

inhibition); Developmental NOEL = 3.0 mg/kg (HDT). The study is **Acceptable**, and no adverse health effects are noted (D. Shimer and G. Chernoff, 5/14/90).

044 007730, (Bayer, 2/5/81). Fenamiphos technical, 92.5%; given by oral gavage to 25 females per group at 0, 0.3, 1.0 or 3.0 mg/kg, days 6-15 of gestation; no adverse developmental toxicity reported; NOEL (maternal) = 1.0 mg/kg (tremors noted at high dose); **unacceptable** (no analysis of dosing solution, no cholinesterase measurements, no data on soft tissue or skeletal abnormalities, no historical data included, no clinical observations). Possibly upgradeable. Christopher, 8/13/85.

TERATOLOGY, RABBIT

024 968412, "Final Report: Teratology Study with Namacur in Rabbits, Study No. 81165", (Hazleton Raltech, Toxicology Report No. 308, 2/3/82). Fenamiphos, 88.8%; given by oral gavage to 20 female New Zealand white rabbits per group at 0, 0.1, 0.3 or 1.0 mg/kg/day, days 6 - 18 of gestation; dosing based on day 6 body weight; no cholinergic signs reported; pilot study data not presented; **unacceptable** (no analysis of dosing solution, doses not justified in report with no evidence high dose was adequate, no cholinesterase determinations to justify doses.) Abortions: 0/14 in controls, 0/16 in low dose, 2/15 in mid dose and 2/16 in high dose groups. The initial review, Christopher, 8/9/85, identified this as a fetotoxic effect. The current review considers this an incidental maternal finding, unrelated to compound administration. Therefore, the maternal NOEL is > 1.0 mg/kg/day. **Adverse effect indicated**. There were 5 fetuses in 3 litters at 1.0 mg/kg/day with "chain fusion of the sternbrae" which is considered to be possibly related to treatment. There were no other changes noted in any fetal parameter measured. Developmental NOEL = 0.3 mg/kg/day. Parker 5/18/87. EPA one-liner: Guideline. Maternal NOEL = 0.1 mg/kg; Fetal toxic NOEL = 0.3 mg/kg (weight and mortality); teratogenic NOEL = 0.3 mg/kg (chain fused sternbrae).

043 007727, Duplicate of 968412.

006 968413, Invalid IBT Study (5/7/71). Christopher, 8/5/85.
EPA one-liner: Invalid.

** 349-120 60683 "Embryotoxicity (Including Teratogenicity) Study With SRA 3886 (Namacur) in the Rabbit," RCC, Research & Consulting Company AG & RCC, Umweltchemie AG, Itingen, Switzerland, 8/22/86. Fenamiphos (SRA 3886, 91%) was administered to mated chinchilla rabbits by oral gavage during days 6-18 post-coitum at 0 (vehicle = 0.5% cremophor EL), 0.1, 0.5 or 2.5 mg/kg (nominal doses). **No adverse effect**. Maternal NOEL = 0.5 mg/kg (nominal) based on increased incidence in salivation, dyspnea, death, as well as reduced body weight gain and reduced food consumption observed at 2.5 mg/kg). However, due to the variability of fenamiphos concentration in dosing solution, the lowest value reported for the dosing material (-53.2% of nominal) will be considered the actual NOEL (46.8% of 0.5 mg/kg = 0.23 mg/kg). The developmental NOEL is \geq 46.8% of 2.5 mg/kg or 1.17 mg/kg (no significant effects observed.) **Acceptable**. M. Silva 5/5/88 & 4/15/92.

Conclusion: Possible adverse effects observed in study 968412 were not confirmed in the more recent study (60683). The two studies are not directly comparable however, for the following reasons:

<u>Points of Comparison</u>	<u>Study# 968412</u>	<u>Study# 60683</u>
Strain of Rabbit	New Zealand white	Chinchilla
Dose of Fenamiphos (mg/kg)	0.1, 0.3, 1.0	0.046, 0.23, 1.17 (actual) 0.1, 0.5, 2.5 (nominal)
Treatment Vehicle	corn oil	cremophor EL
Analysis of Dosing material:	not done	stability, homogeneity and concentration up to 90 min.

At a 2.5 fold higher dose, no adverse effects were observed in study 060683. There may be a species difference between New Zealand white and chinchilla rabbits with regard to spontaneous incidence of variations and the different vehicles used may have influenced bioavailability of fenamiphos. In addition, it is difficult to interpret the data in study 968412, since the stability of fenamiphos after 90 minutes is unknown. Study 060683 assessed stability, concentration and homogeneity of fenamiphos for 90 minutes (the time period for dose administration). Therefore, the overall assessment is that fenamiphos administered in a preferred vehicle (cremophor EL) causes no adverse effects in chinchilla rabbits (M. Silva, 5/5/88)

GENE MUTATION

043 007728, (Bayer, 1979). Fenamiphos, Batch 808817123, no purity stated; Salmonella strains TA1535, TA1537, TA98 and TA100 exposed to 0, 4, 20, 100, 500 or 2500 µg/plate with and without rat liver activation; 4 plates per concentration; no evidence of increased reversion rate; **unacceptable** (no justification for high concentration, inadequate positive controls.) Christopher, 8/13/85.

EPA one-liner: **Unacceptable**.

044 007729, Duplicate of 007728.

101 037332, "Salmonella/microsome Test to Evaluate for Potential Point Mutation", (Bayer AG, Report No. 13365, 3/14/85). Fenamiphos, 92.4%; Salmonella strains TA1535, TA1537, TA98 and TA100 with and without rat liver activation at 0, 20, 100, 500, 2500 or 12500 µg/plate, trial 1 and 125, 250, 500, 1000 or 2000 µg/plate, trials 2 and 3; 4 plates per concentration; no increase in reversion rate. **Acceptable. J. Gee, 2/3/86.

118 061218, Information supplemental to 101 37332 was submitted to describe procedures for standardizing bacterial cell suspensions prior to testing in the Salmonella/microsome mutagenicity assay. The supplemental data did not influence the status of the study. It remains **acceptable**. M. Silva, 5/11/88.

107 045781, "Fenamiphos/ Mutagenicity Test on Bacterial Systems", (Nihon Tokushu Noyaku Seizo, 12/25/85). Fenamiphos, 90.7%, batch Pt. 816396002; Salmonella strains TA1535, TA1537, TA98 and TA100 and E. coli WP hcr-; with and without rat liver activation - liver induced with phenobarbital and benzoflavone; tested at 0, 1, 5, 100, 500, 1000 or 5000 µg, 20 min preincubation in duplicate, one trial; no increase in reversion rate. **Unacceptable** (one trial only). Gee, 10/9/86.

107 045783, Exact duplicate of 037332.

101, 107 037333, 045784, "CHO/HGPRT Mutation Assay in the Presence and Absence of Exogenous Metabolic Activation", (Microbiological Associates, Mobay No. 90100, 3/29/85). Fenamiphos, 85%; CHO/HGPRT with and without activation at 0, 100, 110, 120 or 130 µg/ml, 5 hours without activation and 0, 170, 190, 210 and 230 µg/ml with activation for 5 hours; one trial; no evidence of a mutagenic effect reported; **Unacceptable** (single trial, low purity of test article with no identification of remaining 15%; problems with activation series - contamination of some plates, low plating efficiency in controls, no reason given for inducing with Aroclor for 2 days instead of usual 5.) J. Gee, 2/4/86.

118 061219, Supplementary data for 037333 regarding purity of test article were submitted and found **unacceptable** and not upgradeable since it is unclear that the fenamiphos technical tested in the "compound sample analysis" report is the same as that tested in the CHO/HGPRT assay. M. Silva, 5/11/88.

CHROMOSOME EFFECTS

****135 069937**, "In Vitro Cytogenetic Study With Human Lymphocytes for the Detection of Induced Clastogenic Effects", (Bayer AG, 5/6/88). Fenamiphos technical (purity = 91.9%) was used on human lymphocytes to test for clastogenic effects (2 cultures/sex/dose) with and without activation at 0, 25, 50, 75 and 100 µg/ml (no S-9) or 0, 100, 150, 225 and 350 µg/ml (+S-9). Test substance was incubated with cells for 150 minutes (+S-9) and 21 hours (-S-9). **Possible adverse effect** (The +S-9 group showed an increase in cells with chromosome aberrations at 350 µg/ml). No other effects were observed at any concentration with or without activation. **Acceptable**. M. Silva, 10/12/88.

044 007731, "Nemacur Technical: Micronucleus Test for Mutagenic Effect on Mice", (Bayer AG, 1/7/1980, Study No. SRA 3886/002, Mobay Report No. 68779). Mouse micronucleus test; fenamiphos, 92.5%, batch 808817123; mice were given 0, 0.625, 1.25 or 2.5 mg/kg p. o. twice at 24 hour interval and sacrificed 6 hours after second dosing; 5/sex/group except in high dose with 4/6 deaths; pilot study (no data included) at 2.5 mg/kg caused no overt toxicity; no evidence of increase in micronuclei due to fenamiphos treatment; **unacceptable** (protocol with only one sampling time). Christopher, 8/13/85 and Gee, 10/10/86.

107 045785, Exact duplicate of 07731.

024 968417, "SRA 3886: Dominant Lethal Study on Male Mouse to Test for Mutagenic Effects", (Bayer AG, Study No. SRA 3886/001, Report No. 8838, Mobay No. 69377, 1/16/80). Mouse dominant lethal; Fenamiphos, 92.5%; given in a single dose p.o. to 50 male mice per group at 0 or 5 mg/kg (one dose level); no positive concurrent control; mated for twelve 4-day periods, 1:1; no mortality, no dominant lethal effect reported; **Unacceptable** (no positive control or historical data, no m.t.d. used.) Christopher, 8/5/85 and Gee, 10/10/86.

EPA One-liner: " Acceptable. Insufficient data was provided; inadequate protocol used and chemical composition of test material was given. Negative at 5 mg/kg (HDT). No mortalities or toxic signs."

107 045786, Exact duplicate of 024 968417.

006 968416, Invalid IBT study (1/13/71). Christopher, 8/5/85.

EPA one-liner: Invalid. Appears to be non-mutagenic (males treated with 0.5 mg/kg - hyperactive and ruffled fur.) Doses tested: 0.25 and 0.5 mg/kg.

107 045788, "Sister Chromatid Exchanges in Chinese Hamster Cells Treated with Seventeen Organophosphorus Compounds in the Presence of Metabolic Activation System", (Roswell Park, 5/5/82). Publication by H. H. Chen et. al. in Environmental Mutagenesis 4: 621 - 624 (1982). Sister chromatid exchange in Chinese hamster V79 cells; fenamiphos, 99.2% (not clear if technical or analytical grade); 0, 10, 20, 40 or 80 µg/ml plus rat liver activation, for two doublings; activation and test article in diffusion chamber to reduce cytotoxicity of S9; **no evidence for adverse effect; unacceptable** (with activation only - see 45787; no information on cytotoxicity or mitotic index or cell cycle delay; no justification of concentrations used; insufficient description of methods.) Gee, 10/14/86.

107 045787, "Sister-chromatid Exchanges and Cell-cycle Delay in Chinese Hamster V79 Cells Treated with 9 Organophosphorus Compounds (8 Insecticides and 1 Defoliant)", (Roswell Park, 8/11/81). Publication by H. H. Chen et. al. in Mutation Research 103: 307-313 (1982); sister chromatid exchange in Chinese hamster V79 cells; fenamiphos, 99.2%; 0, 2.5, 5.0, 10.0 or 20.0 µg/ml without activation; SCE/cell were not increased; cell cycle delay reported in a concentration dependent manner; incomplete (protocol but see 045788); **unacceptable** (inadequate description of methods). Possibly could be upgraded along with 045788. Gee, 10/14/86.

****113 055752**, "SRA 3886 (Common Name: Fenamiphos, the Active Ingredient of NEMACUR) Cytogenetic Study of Human Lymphocyte Cultures in vitro to Test for Chromosome Damage", (Bayer AG, 1/12/87, Report No. 15406). Fenamiphos, 91.3%; tested with and without activation at 0, 25, 100 or 400 µg/ml on human lymphocytes of one male and one female subject; incubated with the test article for 2.5 hours with activation, for 24 hours without activation; an **increase** in aberrations was noted at 100 µg/ml for both subjects at 52.4% decrease in mitotic index and in one subject at 400 µg/ml with activation in the presence of great cytotoxicity; **acceptable**. Gee, 5/13/87.

DNA DAMAGE

****133 067629**, "Unscheduled DNA Synthesis in Rat Primary Hepatocytes", (Microbiological Associates, Inc., 3/4/88). Fenamiphos technical (purity = 89.5%) was used with primary rat hepatocytes in an unscheduled DNA synthesis (UDS) assay at 0 (vehicle = DMSO), 1.5, 5.0, 15, 50, 100, 150, and 299 µg/ml. **No adverse effect**. There was no increase in UDS at any concentration of fenamiphos tested. The positive control functioned as expected. **Acceptable**. M. Silva, 10/12/88.

107 045782, "Fenamiphos/Mutagenicity Test on Bacterial Systems", (Nihon Tokushu Noyaku Seizo, 12/25/85). Fenamiphos, 90.7%; Bacillus subtilis NIG 45 (rec-) and NIG 17 (rec+); 20 µg in DMSO onto bacterial streak; no cytotoxicity, **no adverse effect** = no test; **unacceptable** (no activation included, single concentration with no justification.) Gee, 10/10/86.

NEUROTOXICITY

Hen

006 968397, "Bay 68 138: Subchronic Neurotoxicity Studies in Chickens", (Bayer, 1/28/70). Fenamiphos, 50% technical; given in the diet to HNL chickens at 0, 1, 3, 10 or 30 ppm for 30 days only, so not a guideline subchronic (requires 90 days); 8 chickens per group, 15 to 20 months of age; **unacceptable** with insufficient information for assessment (inappropriate route of administration, test

article not adequately described). Up to 60% inhibition of cholinesterase noted but **no delayed neuropathy** described. Christopher, 8/5/85.

EPA One-liner: No grade. Systemic NOEL = 10 ppm (decreased food consumption and body weight); ChE NOEL = 1 ppm (LDT) (blood ChE inhibition. No microscopic neurological lesions were observed.)

007 968372, 968373, "Nemacur P: Acute Neurotoxicity Studies on Hens", (Institut für Toxikologie, 6/14/71). Fenamiphos, no purity stated; given by intubation at 0.5 ml/100 g body weight to 10 White Leghorn hens per group at 1.0, 2.5, 3.75, 5.0, 7.5 or 10.0 mg/ml - calculated LD50 = 5.31 mg/kg; with atropine protection (50 mg i.p. before dosing) LD50 was 12.4 mg/kg (dosed at 3.75, 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, or 25.0); 16 - 18 months of age; **unacceptable** (no histopathology performed, no redosing at 21 days, insufficient number of hens per group, no clinical observations presented, test article not described.) Study needs to be replaced. **No evidence of delayed neuropathy.** Christopher, 8/5/85.

150 074557, "SRA 3886 Technical (Common Name: Fenamiphos), Delayed Neurotoxicity Studies on Hens Following Acute Oral Administration", (Flucke, W. and G. Kaliner, Bayer AG, Institut für Toxikologie Landwirtschaft, Fachbereich Toxikologie, FRG, report # 99166, 11/5/87). SRA 3886 (technical fenamiphos), 91.3% purity, administered by gavage twice (3 week interval) with protection (atropine sulfate at 100 mg/kg 10 minutes prior to dosing and again at 30 or 50 mg/kg 7 hours following treatment) at 25 mg/kg with 30 (1st administration) or 17 (2nd administration) Lohmann Selected Leghorn hens/group. TOCP at 375 mg/kg with 5/group as positive control and 2% Cremophor EL in deionized water at 5 ml/kg with 6/group as vehicle control. # deaths/# with signs/# treated at 25 mg/kg, 1st dose: 13/30/30, 2nd dose: 1/17/17. Signs exhibited included: staggering gait, ruffled feathers, reduced activity, flaccid-drooping wings, etc. The study is **Acceptable and **no acute delayed neuropathy** indicated (H. Green and G. Chernoff, 5/15/90).

015 048172, Summary information.

Rat

**349-214 172625 Dreist, M., "SRA 3886 (Common name: Fenamiphos): Acute oral neurotoxicity screening study in Wistar rats", Bayer AG, Wuppertal, 10/16/95. Study No. T6058166, Bayer Report #107156. Twelve rats/sex/group were dosed once with 0, 0.4, 1.6, or 2.4 mg/kg fenamiphos (95.2%) by gavage in Cremophor® (2% v/v) vehicle. Six additional rats/sex/group were sacrificed 50 minutes after dosing for cholinesterase (ChE) assays. Study was conducted in accordance with FIFRA guidelines for a rat acute oral neurotoxicity study. There was dose-related inhibition in plasma and RBC ChE in both sexes, statistically significant for plasma ChE in females and for RBC ChE in males over the entire dose range. Brain ChE was unaffected. The NOEL for changes other than cholinesterase inhibition was 0.4 mg/kg (0.37 mg/kg after correction for purity), based on clinical signs (primarily muscle fasciculations, most evident in males, which had consistently stronger cholinergic responses than females). These changes were transient, and could no longer be detected by 4 hours after dosing. At "Day 0" FOB, there was a sharp dose-response from 1.6 to 2.4 mg/kg, with piloerection,

incoordination, and constricted pupils primarily or exclusively limited to the high dose. There was a slight (not statistically significant) reduction in motor activity counts in high dose males at day 0, plausibly due to treatment. FOB and motor activity counts were normal at days 7 and 14 after dosing. There were no gross or microscopic changes in rats at day 15, when perfusion-fixed tissues were processed for neuropathologic examinations. Acceptable: no adverse effects. Aldous, 2/7/00.

**349-216 172627 Dreist, M., and A. Popp, "SRA 3886 (Common name: Fenamiphos): subchronic neurotoxicity screening study in Wistar rats (thirteen-week administration in the diet)", Bayer AG, Wuppertal, 03/26/96. Study No. T 9058277, Bayer Report #107434. Twelve rats/sex/group were fed 0, 1, 10, or 50 ppm fenamiphos (purity 95.5-95.7%) in diet for a scheduled duration of 13 weeks. Study was conducted to meet FIFRA guidelines for a rat subchronic dietary neurotoxicity study, with FOB and motor activity measurements on all rats at pretreatment and at weeks 4, 8, and 13, followed at week 14 by sacrifice of 6/sex/group for neuropathology. The other six/sex/group were used for cholinesterase assays at weeks 4 and 15. Cholinesterase inhibition NOEL = 1 ppm (marked and statistically significant reduction in plasma ChE in 10 ppm females at weeks 4 and 15: minor but statistically significant reduction in RBC ChE in 10 ppm males at week 15). The NOEL for cholinergic effects was 10 ppm (muscle fasciculations in all 50 ppm females, limited to the first 3 weeks of exposure). All treatment effects were typical of cholinesterase inhibition. All FOB and motor activity tests were negative, as was neuropathology. There was a significant reduction in brain cholinesterase activity at 15 weeks in the 50 ppm females (12% reduction, $p < 0.01$). Investigators did not consider this to be biologically significant, however this reviewer considers this finding to be treatment-related. The functionally important inhibition was strictly peripheral, based primarily on fasciculations in 50 ppm females, and secondarily on substantial inhibition of plasma and RBC cholinesterase at 50 ppm in both sexes in all assays. The most sensitive cholinesterase finding over the 10 to 50 ppm range was plasma cholinesterase inhibition in females. Acceptable, with no adverse effects. Aldous, Feb. 7, 2000.

349-215 172626 Dreist, M., "Method validation study in rats for the acute and subacute neurotoxicity screening battery", Bayer Report No. 107409, Feb. 6, 1996. Three technicians, names abbreviated as "LE", "KE", and "LI", observed 6 different rats per group in a validation study using 0, 10, or 25 mg/kg carbaryl. There was good concordance between observers in all aspects of a standard FOB, successfully validating the laboratory capability to perform this evaluation. Aldous, 2/7/00.