1-24-89
2A

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

Excellent response

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: California Department of Food and Agriculture - EPA Toxicology Review for Acephate (Tox. Chem. No. 2A)

FROM: Krystyna K. Locke, Toxicologist Krystyna K. Locke 1/24/89
Section I, Toxicology Branch I (IRS)
Health Effects Division (TS-769C)

THRU: Edwin R. Budd, Section Head
Section I, Toxicology Branch I (IRS)
Health Effects Division (TS-769C)

Budd 1/24/89

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

The following responses are provided for each specific deficiency identified by the Medical Toxicology Branch of the California Department of Food and Agriculture:

STUDY TYPE: Chronic feeding/dog; (Two-Year Chronic Oral Toxicity Study with RE 12420 in Beagle Dogs; IBT; No. C-8732; (12/28/72))

Deficiency #1: Inadequate dose justification.

EPA Response: True. It is clear, however, from this and other subchronic and chronic studies on other species with acephate that cholinesterase inhibition is the most sensitive end-point for toxicity and furthermore that the rat is far more sensitive than the dog in this respect. In situations such as this where the dog is clearly of lesser sensitivity to the effect of concern, EPA does not require demonstration of pronounced toxicity in chronic studies on dogs provided that the dosage levels tested are considerably higher than for the rat. In EPA's judgement, the lack of dose

justification in this particular instance is insufficient reason to reject the study.

Deficiency #2: Diets not analyzed for actual content (of acephate).

EPA Response: True, but this was not generally done or required, or performed as easily and reliably 16 years ago as it is now. Furthermore, based on our considerable experience with numerous new and old studies on acephate, the theoretical and analytical concentrations of acephate in diets used in these studies rarely varied by more than 10%, which we regard as fully acceptable. Also, stability data for acephate in many diets in many studies has also been fully acceptable. In our judgement, the lack of these data in this particular study does not warrant rejecting the study.

Deficiency #3: No ophthalmological exam.

EPA Response: True, but we did not regard the lack of this eye examination in this study to be so serious that it necessitated rejecting the study. Based on a consideration of all available subchronic and chronic studies on acephate, many of which did contain eye examinations, there is no reason to suspect that acephate may induce damage to the eye. Furthermore, a one-year dog feeding study with a closely structurally related pesticide (methamidophos) is available and in that study ophthalmological examination was performed and adverse effects were not observed.

Deficiency #4: Inadequate presentation of histopathology.

EPA Response: We disagree. Gross and histopathological findings were reported in tabular form (8 pages) showing dose level, individual animal number, sex, findings and degree of severity (grade) for each finding. Gross and pathological observations were

correlated. In the case of nonsurvivors, time of death (such as "37 weeks on the test") for each dog was reported. A comment was also made that all tissues and organs not listed in the table were normal. The above report was signed by two veterinary pathologists, Craig A. Fischer, D.M.V. and Donovan E. Gordon, D.V.M., Ph.D., Diplomate, American College of Veterinary Pathology. In our judgement, although an elaborate format currently used in pathology reports is missing, the essential information is present and is fully adequate.

CONCLUSION: Concur with some of California deficiencies (#1, 2 and 3), but do not regard them as serious enough to reject this study. Do not concur with Deficiency #4. It should also be noted that this study was audited in 1978, 1981 and 1982 by both EPA and Canadian authorities, and found to be valid in that the raw data compared favorably with the study report.

CORE-GRADE: Remains unchanged (Minimum)

Acephate

CHRONIC TOXICITY, DOG

015 973189 "Two Year Chronic Oral Toxicity Study with [illegible] 2420 in Beagle Dogs." (IBT, No. C-8732, 12/28/72) Acephate (87 to 94 %, 0.5 % metnamidophos content), lots SX-257, 1st six months and SX-357, final 18 months; fed in the diet at 0, 10, 30 or 100 ppm for two years; 4/sex/group; decrease in rbc cholinesterase in both sexes at the high dose level; no adverse effects reported; Unacceptable /(dose selection not adequately justified 2. high dose may not be sufficient, 3 no analysis of diet for actual content // no ophthalmological exam, 5 inadequate presentation of histopathology). Document 108-169, Record 61136, contains two validation reports including many variations between the raw data and the report and also, identifies data not recorded. Not upgradeable. Wong, 5/13/85 and Gee, 1/5/88.

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MEMORANDUM

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FROM: Krystyna K. Locke, Toxicologist Krystyna K. Locke 1/24/89
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Health Effects Division (TS-769C)

THRU: Edwin R. Budd, Section Head
Section I, Toxicology Branch I (IRS)
Health Effects Division (TS-769C)
Budd 1/24/89

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

The following responses are provided for each specific deficiency identified by the Medical Toxicology Branch of the California Department of Food and Agriculture:

STUDY TYPE: Teratogenicity/rat (Teratogenic Study with Orthene Technical in Albino Rats; IBT; No. B-190; 9/17/71)

Deficiency #1: Individual data not submitted.

EPA Response: True, but this was not required 17 years ago when this study was performed. In addition, this study was audited in 1978 and 1982 by both EPA and Canadian authorities, and found to be valid in that the raw data compared favorably with the study report. Therefore, although individual data were not included in the study report, the individual data nevertheless have been located, checked and found to be fully consistent with the summary data provided in the study report. The lack of individual data in the study report,

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then, is not sufficient reason in this particular case for rejecting the study.

Deficiency #2: Dose levels not justified.

EPA Response: We disagree. Although a preliminary dose-range finding study may not have been performed in this case, the maternal toxicity noted in this study at the high dosage level clearly indicates that a sufficiently high dosage level was used in this study. At sacrifice, the high-dose females weighed 29% less and had twice as many resorptions as did the controls (1.3 vs. 0.5). In our judgement, decreased body weight gain and increased resorptions satisfy the Guidelines criterion of "--some overt maternal toxicity." Furthermore, cholinesterase from the other rat studies on acephate indicate that the dosage level of 200 mg/kg/day, the highest dosage level used in this study, would induce considerable and substantial inhibition of cholinesterase activity in the dams in this study. In our judgement, this dosage level is high enough to assess the teratogenic potential of acephate in rats.

Deficiency #3: Dosing solutions not analyzed.

EPA Response:

True. The maternal toxicity observed in this study at the highest dosage level tested, however, clearly indicated that these animals did receive sufficient test material to induce toxicity. The precise dosage level at which this occurs is not of great importance in a teratology study, provided that the level is considerably higher than levels used in other studies for the purpose of establishing ADIs and that adequate MOSs do exist for maternal and fetal toxicity. In this case, a nominal dosage level of 200 mg/kg/day, although not analyzed precisely, was considered by EPA to be sufficiently high for these purposes. We regarded the absence of these data as a weakness in the study

but
~~and~~ not a sufficient reason for rejection.

Deficiency #4: Statistical analysis not provided.

EPA Response: True, but a careful visual scrutiny of the data in this study was sufficient to determine effects, when they occurred, and a statistical analysis of the same data would have been superfluous and unnecessary in this particular case. The lack of statistical analysis was regarded as a weakness in the study, but not ~~as~~ a sufficient reason for rejection.

CONCLUSION: Concur with some of California deficiencies (#1, 3 and 4), but do not regard them as serious enough to reject this study. Do not concur with Deficiency #2. The following statement was included in our evaluation of this study for the Registration Standard: "Toxicology Branch considers this study as weak but valid, and adequate to indicate that Orthene is not a potential teratogen in rats." This statement is still valid.

CORE-GRADE: Remains unchanged (Minimum)

TERATOLOGY, RAT

C12 973200 "Teratogenic Study With Orthene Technical in Albino Rats." (IBT No. B190, 9/17/71). Acephate (approximately 90%, lot SX-284) given by oral gavage at 0, 25, 100 or 200 mg/Kg/day on days 6-15 of gestation; 17-21 pregnant females/group; slight increase in resorption rate at the high dose, dose related decreases in maternal body weight gain, maternal toxicity considered contributory to resorption rate at 200 mg/Kg; no developmental toxicity directly attributable to test article: Unacceptable (1 no individual animal data presented, 2 dose level not justified, 3 no analysis of dosing solutions, 4 statistical analysis not provided), Not upgradeable... Purity of test article from 165, 063368, which contains the results of a 1978 audit of the raw data compared with the report. The audit found that the control data were from another study and no data were sent to the sponsor of the acephate study. Note: Initial review by J. Wong, 5-13-85 indicated a possible adverse effect. Review by D. McGee, 5-6-86, and J. Parker found no effect without maternal toxicity. Gee, 1/7/88.

EPA one-liner: teratogenic NOEL > 200 mg/Kg, slightly more resorption sites per female at 200 mg/Kg than in controls, less wt. gain at 100 mg/Kg level and 200 mg/Kg by females during gestation; core grade--minimum.

161 Rebuttal of 11/20/86 to CDFA review of 973200.

Letter of 5/5/88. Chevron has committed to perform a new Rat Teratology Study to be submitted to CDFA before 7/31/89.

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ACEPHATE

SB 950-125, Tolerance #108

October 1, 1986
Revised February 5, 1987
Revised January 25, 1988
Revised June 2, 1988
Revised November 7, 1988

I. DATA GAP STATUS

Combined, rat:	No data gap, no adverse effect
Chronic toxicity, rat:	See Combined, rat
Chronic toxicity, dog:	Data gap, inadequate study, no adverse effect indicated
Oncogenicity, rat:	See Combined, rat
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	Data gap, inadequate study, no adverse effect indicated
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome mutation:	No data gap, possible adverse effect
DNA damage:	No data gap, possible 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.
FILE NAME: T881107
Revised by M. Silva, 11/88.

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II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

** 139, 144 037723, 037728 "Lifetime Oral Toxicity/Carcinogenicity Study with Technical RE-12420 (Orthene) in Rats." (Bio/dynamics, 6/30/81). Acephate (92.4%, lot SX-992) fed in the diet at 0, 5, 50 or 700 ppm (0.24/0.31, 2.44/3.06 or 38.2/47.2 mg/Kg, M/F), 80/sex/group; significantly lower body weight in males at high dose; consistent cholinesterase inhibition at high dose and to a lesser extent at low and mid dose levels; systemic NOEL = 5.0 ppm (based on brain cholinesterase); McGee evaluation (4/28/86) was unacceptable but upgradeable; Davis evaluation (1/5/87) of supplemental data and Chevron response was complete and acceptable.

No EPA one-liner available.

067 973192 Interim report for record 037723.

067 973187 Supplement to record 037723--photomicrographs.

136 026943 Supplement to 037723--discussion of amendments to report.

146 037732 Supplement to 037723--rationale for amendments to report.

067 971388 Less complete version of study identified as record 037723 (Reviewed by J.Wong, 5/22/85, with insufficient information for evaluation).

160 050280 (Bio/Dynamics 3/20/78) Supplement to 108-139 to 144 and 108-146, 037723-8 --Diet analysis data. Samples from cage hoppers after 3-4 days were 93.1% of nominal for the 5 ppm level, 1.8% for the 50 ppm level, and 80.7% for the 700 ppm level. Problems in the diet analysis included acephate found in the negative control samples between 5/5/78 and 7/3/78, corrections needed in the calculations on most pages, and missing chromatograms. With this addendum and the information from the Chevron response of 11/24/86, the study is complete and acceptable. Davis 1/5/87.

161 Rebuttal of 11/20/86 to CDFA review of 037723-8.

CHRONIC TOXICITY, RAT

015 973190 Invalid IBT study, 1/29/73.

CHRONIC TOXICITY, DOG

015 973189 "Two Year Chronic Oral Toxicity Study with RE-12420 in Beagle Dogs." (IBT, No. C-8732, 12/28/72) Acephate (87 to 94 %, 0.5 % methamidophos content), lots SX-257, 1st six months and SX-357, final 18 months; fed in the diet at 0, 10, 30 or 100 ppm for two years, 4/sex/group; decrease in rbc cholinesterase in both sexes at the high dose level; no adverse effects reported; Unacceptable (dose selection not adequately justified - high dose may not be sufficient, no analysis of diet for actual content, no ophthalmological exam, inadequate presentation of histopathology). Document 108-169, Record 61136, contains two validation reports including many variations between the raw data and the report and also, identifies data not recorded. Not upgradeable. Wong, 5/13/85 and Gee, 1/5/88.

EPA one-liner: NOEL ≥ 100 ppm (HDT) for systemic toxicity; cholinesterase activity NOEL = 30 ppm; core grade--minimum.

161 Rebuttal of 11/20/86 to CDFA review of 973189.

169 061136 Supplemental to 973189, two validation reports including variations between raw data and the report. Also, stability in dog diet over 7 days at room temperature. Gee, 1/5/88.

012 046560 One year interim report for study identified as record #973189.

170 061137 "90-Day Subacute Oral Toxicity Study with Orthene In Beagle Dogs." (IBT, no. C9527, 8-24-71) Range finding study for record number 973189, volume 108-015. Orthene, SX-284, was administered to beagles at dietary levels of 0, 10, 30 or 100 ppm, 4/sex/group for 90 days. No abnormalities were noted in body weight, food consumption, behavior, clinical studies, necropsy or histopathology except for up to 60% RBC ChE inhibition at the high dose. Dogs were housed 4/kennel, sac 2/sex/group at 90 days, the other 2 were allowed to recover for a 40 day period. EPA has determined the study is "invalid". Shimer, 11/10/87 and Gee, 12/30/87.

165 057929 Validation report of 061137 prepared by F. X. Kamienski of Chevron. A number of discrepancies between the raw data and the report are pointed including the fact that the hematology, clinical chemistry and urinalysis data are from the two-year study, not the range-finding study. Stability, chemical analyses and corrections are contained in the appendices. Gee, 12/30/87.

Letter of 5/5/88. Chevron has committed to perform a new Non-Rodent Chronic Feeding Study to be submitted to CDFA before 3/31/91.

ONCOGENICITY, RAT

085 973195 "Oral Toxicity/Carcinogenicity Study in Technical RE 12420 in Rats." (Bio/dynamics, 5/14/79, 77-1870). Acephate, lot 016-SFO-8847-8600, SX941; fed to 70/sex/group at 0, 10, 50 or 250/350 ppm; Sprague-Dawley rats; the two year study was terminated after 190 days due to discovery of impurity in the test article - the impurity was not identified; ophthalmoscopic exam at three months was negative; **Unacceptable, not upgradeable.** Wong, 5-16-85.

ONCOGENICITY, MOUSE

** **145, 204 037729, 069074** "Orthene Technical (RE-12420) Lifetime Oral Carcinogenicity Study in Mice," (IRDC, 2/24/82). Acephate (purity = 92.7, 92.1%; lot no. SX-1032) was fed in diet to CD1 mice for 104 weeks at 0 (vehicle = chow), 50, 250 or 1000 ppm (7, 36 or 146 mg/kg/day) for males; 8, 42, or 167 mg/kg/day for females (75/sex/group). **Possible adverse effect.** Nominal NOEL = 50 ppm (decreased body weight at mid- and high doses; hepatocellular carcinoma, adenoma and hyperplasia were observed in females at the high dose; other dose-related non-neoplastic changes in males and females were observed primarily at mid- and high-doses; microscopic lung changes were observed at all dose levels in both sexes but were not well defined ("pigmented alveolar macrophages," "eosinophilic foreign bodies"). Originally reviewed as unacceptable by McGee, 4/29/86 (no individual data on food consumption; no individual clinical observations; no statistical analysis of

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tumor data) and not upgradeable, based on lung findings at all treatment levels. In view of the uncertain nature of the lesions and the consideration of this study as an oncogenicity study, it may be upgradeable with submission of the missing data. CDFA has received and reviewed the requested information (204 069674), and the study is upgraded to acceptable. M. Silva, 10/28/88.

EPA one-liner (Partial excerpt): (NOEL not indicated), Increased incidence of hepatocellular carcinomas and hyperplastic nodules in females at high dose level, dose-related non-neoplastic liver and lung injuries in male and females, decreased weight gain at the high dose level in male and female; core grade--minimum.

172 061139 Addendum to 37729 - Diet analysis data - duplicate of Reference 2 of 145 037729. A letter at the beginning of the document, dated August 20, 1987, indicated that the data on food consumption and individual clinical observations would be submitted to CDFA in September, 1987. Gee, 1/6/88.

085 973194 Interim report of record 037729. (Reviewed by J. Wong, 5/16/85, as unacceptable with a possible adverse oncogenic and/or chronic effect.)

067 973193 Interim report for record 037729.

128 016928 Supplement to record 037729 -- discussion of hepatocarcinomas in female mice.

128 016929 Historical histopathology data for record 037729.

161 Rebuttal of 11/20/86 to CDFA review of 037729.

161 50991 Homogeneity of diet mixing for 037729.

Letter of 5/5/88. Chevron has committed to supply individual data as requested.

015 973191 Invalid IBT study, 3/7/73.

REPRODUCTION, RAT

148 037738 "Effect of Technical Re-12420 (Orthene) on Reproductive Function of Multiple Generations in the Rat." (Huntingdon, 4/18/83). Acephate technical (92.8%, SX-1032) fed in the diet at 0, 50, 150 or 500 ppm for a three generation, two litter/generation study; CrL:cobs CD(SD)BR rats; 12 males and 24 females per group; reduced fertility especially in males, reduced pup viability; parental (maternal) MTD = 500 ppm; fertility and viability NOEL not determined due to fact that noted effects had a similar frequency at low and high doses but not at mid dose; Unacceptable (inadequate number of gravid animals per group, incomplete histopathology, other studies conducted in same animal rooms, no standardization of litter size, no historical control data presented), Not upgradeable. A repeat study following guidelines is recommended. McGee, 8-1-86.

No EPA one-liner.

110 973202 Supplement to record 037738--Statistical analysis report.

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110 973204 Less complete version of record 037738 (Reviewed by J. Wong, 5/22/85, as unacceptable due to insufficient but with a possible adverse effect identified in the report as submitted by registrant).

** 182 060979 "Two-Generation (Two Litter) Reproduction Study in Rats with Chevron Acephate Technical." (Argus Research Laboratories: 303005, 4-3-87) Chevron acephate technical, 98.5%, was fed in the diet to Crl:COBS CD (SD) BR rats, 30/sex/group, at 0, 25, 50 or 500 ppm for two generations, 2 litters/generation, and one litter in the third generation. Parental NOEL = 50 ppm (soft/liquid feces), Reproductive NOEL = 50 ppm (reduced litter size and postnatal survival). This study was conducted primarily to address the effects reported in an earlier study (CDFA # 37738) in which a NOEL was not established. This present study does demonstrate a NOEL for both viability and fertility. **Acceptable.** Shimer, 11-24-87, J. Gee, 12/30/87.
No EPA one-liner.

014 973205 Invalid IBT study, 1/10/73.

Summary: The study conducted at Huntingdon, CDFA Record #037738, identified a possible adverse reproductive effect on fertility, especially in males, and decreased pup viability at 50 and 500 ppm. These effects were not confirmed in the later study (CDFA Record #060979) at 50 ppm with reproductive effects seen only at 500 ppm in the presence of parental effects. The collective data are adequate to fulfill the requirement with the reproductive NOEL at 50 ppm and no effect seen without some parental effects. The overall conclusion is that acephate does not cause adverse reproductive effects. Gee, 1/5/88.

REPRODUCTION, CHICKEN

014 973207 Invalid IBT study on chicken; not a SB950 test species.
111 973081 Reference to record #973207.

TERATOLOGY, RAT

012 973200 "Teratogenic Study With Orthene Technical in Albino Rats." (IBT No. B190, 9/17/71). Acephate (approximately 90%, lot SX-284) given by oral gavage at 0, 25, 100 or 200 mg/Kg/day on days 6-15 of gestation; 17-21 pregnant females/group; slight increase in resorption rate at the high dose, dose related decreases in maternal body weight gain, maternal toxicity considered contributory to resorption rate at 200 mg/Kg; no developmental toxicity directly attributable to test article; **Unacceptable** (no individual animal data presented, dose level not justified, no analysis of dosing solutions, statistical analysis not provided), **Not upgradeable**. Purity of test article from 165, 063368, which contains the results of a 1978 audit of the raw data compared with the report. The audit found that the control data were from another study and no data were sent to the sponsor of the acephate study. Note: Initial review by J. Wong, 5-13-85 indicated a possible adverse effect. Review by D. McGee, 5-6-86, and J. Parker found no effect without maternal toxicity. Gee, 1/7/88.
EPA one-liner: teratogenic NOEL > 200 mg/Kg, slightly more resorption sites per female at 200 mg/Kg than in controls, less wt. gain at 100 mg/Kg level and 200 mg/Kg by females during gestation; core grade--minimum.

161 Rebuttal of 11/20/86 to CDFA review of 973200.

Letter of 5/5/88. Chevron has committed to perform a new Rat Teratology Study to be submitted to CDFA before 7/31/89.

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TERATOLOGY, RABBIT

146 037733 "Teratology Study in Rabbits (Technical RE 12420, Orthene)." (IRDC, 11/13/80). Acephate (92.8%, SX-1032) given by oral gavage at 0, 1, 3 or 10 mg/kg/day on days 6-27 of gestation, not adjusted for purity; 16 per group; no significant developmental effects, slight maternal toxicity at high dose; developmental NOEL = >10 mg/kg, maternal NOEL = 3 mg/kg; initially reviewed as unacceptable (McGee, 5/2/86) based on incomplete necropsy data, no analysis of dosing solutions and fetuses aborted days 25 and 27 were not examined for malformations but **study possibly upgradeable. Submission of record #061138 provides copies of records for preparation of the daily dosing solutions and 058219 - 058222 address stability in neutral aqueous solutions. ACCEPTABLE (see Medical Toxicology Response of 6/2/88). J. Gee, 12/31/87; Davis 6/2/88.

EPA one-liner: Teratogenic NOEL => 10 mg/Kg, fetotoxic NOEL => 10 mg/Kg, maternal toxic NOEL = 3 mg/Kg; core grade--guideline.

146 037734 Positive control data for 037733 with 6-aminonicotinamide.

171 061138, 058219-058222 Stability data for 037733.

067 973196 Less complete version of record 037733. (Reviewed by J. Wong, 5/22/85, with insufficient information for evaluation.)

067 973197 Pilot study for record 037733.

161 050990 Supplement to 37733. Individual data for does #4511 and 4518.

161 Rebuttal of 11/20/86 to CDFA review of 037733.

Rebuttal letter of 5/5/88. Reconsideration of all information provided led to upgrading the study to acceptable. Because acephate is quite stable under the conditions of the study, because dosing solutions were prepared daily, and because IRDC notebook pages on dosing solution preparation were provided, the lack of dosing solution analysis was not considered to invalidate the study. Davis 6/2/88.

014 973198 Invalid IBT study, 4/14/72.

GENE MUTATION

Bacterial Systems

101 973209 "Potential of Technical and Analytical Grade Orthene to Mutate Histidine Deficient Strains of Salmonella typhimurium (S-1202)." (Chevron, 11/28/77). Acephate (92.41%, SX-941) tested at 0.001 to 10 mg/plate on Salmonella strain TA100 and at 1, 2 and 10 mg/plate on strains TA 98 and 1537; +/- rat liver S9; 2 plates/dose level; weak mutagenic activity noted in TA 100 with and without activation; **Acceptable by J. Wong. Comments by J. Gee, 9/30/86: This study included only 3 of the 4 strains listed in the guidelines. It did, however, include high amounts of acephate and repeat

trials to confirm the weak effect with TA100 with the mutants per plate increasing in a concentration dependent manner but not reaching twice the spontaneous rate even at 10 mg/plate. Alone, this effect in one strain, especially TA100, would not be conclusive as to the genotoxic effect of acephate. Taken together, however, with other studies listed below, the positive effect needs evaluation. Wong, 5-20-85; Gee, 9-30-86.

EPA one-liner: Weakly positive with S. typhimurium strain TA 100 and negative with TA 98 and TA1537 strains, with or without metabolic activation; core grade--acceptable.

113 028970 "In vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides: Excerpt for Acephate on Reverse Mutation with Salmonella typhimurium and Escherichia coli." (SRI, 10/79). Acephate (93.5%, Lot SX-7562) tested at 0, 1, 10, 50, 100, 500, and 1000 ug/plate (Exp. 1), 10 to 5000 ug/plate (Exp. 2), 1000 to 10,000 ug/plate (Exp. 3) and 2500 to 10,000 ug/plate (Exp. 4); +/- rat liver S9 on Salmonella strains TA98, TA100, TA1535, TA1537, and TA1538; weakly mutagenic in TA 100; also weakly positive with E. coli WP2; **Unacceptable** (only a single plating/dose level, statistical treatment of data not evident), **Probably not upgradeable.** Wong, 5-17-85.

EPA one-liner: Positive results on TA 98 and 100 at 5000 ug/plate and above; core grade--acceptable.

149 039417 More complete version of record 028970. Some of the objections of the initial review by J. Wong still stand [J. Gee, 9/30/86]. The data gap is filled by other studies.

113 973217 "Further Mutagenicity Studies on Pesticides (Bacterial Reversion Assay - S. typhimurium and E. coli." (Inst. Environ. Tox.-Japan, 5/18/82). Publ. in Mutation Res. 116: 185-216 (1983) -- survey of 228 pesticides in Ames test on Salmonella strains TA 98, 100, 1537 and 1538; Acephate (no purity stated) tested at 0 to 50 mg/plate; no data - results given as "+" for TA100 and E. coli; increase in reversion frequency above 5 mg/plate with TA100; **Unacceptable.** Wong, 5-20-85.

147 973214 "Salmonella/Mammalian Microsome Mutagenicity Test (Ames Test) with six Samples of Chevron Acephate Technical and Purified (SX-911, SX-941, SX-978, SX-984, SX-986, SX-988) S. typhimurium." (Chevron, 12/82). Acephate (6 lots, SX-911, -941, -978, -984, -988 and -986) tested at 0 - 50 mg/plate on Salmonella strain TA100; one trial, no activation; all lots were weakly mutagenic in TA100; **Incomplete, unacceptable** (no metabolic activation, no repeat trials, missing data, no individual plate counts, number of platings not clear), **Not upgradeable.** Wong, 5-16-85, Gee, 5-12-86.

EPA one-liner: All six batches of acephate tested positive on strain TA100; core grade--supplementary.

147 16927 "Salmonella/Mammalian Microsome Mutagenicity Test (Ames Test) with Seven Samples of Chevron Acephate Technical (SX-257, SX-284, SX-357, SX-941, SX-978, SX-979 and Acetamide SX-976)." (Chevron, 12/82). Acephate (8 lots--85 to 100%, SX-257, -284, -357, -911, -941, -976, -978, -979) tested at 0 - 50 mg/plate on Salmonella strains TA98, 100 and 1537 without activation; one trial, no individual plate counts; 7 of 8 lots weakly positive in TA 100; **Unacceptable** (should TA100 read TA1537 in Table 2(?), no repeat trial, number of platings not clear, no individual plate counts, no activation included), **Not upgradeable.** Gee, 5-12-86.

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EPA one-liner: 7 of 8 batches of acephate tested positive on strain TA 100; core grade--supplementary.

128 016927 Duplicate of 147 016927 without the analytical pages.

113 973213 Unrevised version of study identified as record 016927.

113 028970 "In vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides: Excerpt for Acephate on Reverse Mutation with Salmonella typhimurium and Escherichia coli." (SRI, 10/79). Acephate (93.5%, SX-7562) tested at variable dose levels on E. coli strain WP2 +/- S9; no adverse effect indicated; **Unacceptable** (no description of statistical treatment of data, no individual plate counts) **Possibly upgradeable.** Wong, 5-17-85.

EPA one-liner: Weakly mutagenic with (5000 mg/plate) and without (6000 mg/plate) metabolic activation; core grade--acceptable.

149 039417 More complete version of record 028970. (J. Gee, 9/30/86: Some of the objections of the initial review still stand.)

Insect Systems

113 973218 "Mutagenesis Screening of Pesticides Using Drosophila Sex Linked Recessive Lethal: Chromosome Loss, Rearrangement and Nondisjunction." (WARF, 2/81). Acephate (purity not stated, no lot number) tested at 10 ppm with 14 other pesticides in sex-linked recessive lethal assay on Drosophila melanogaster; no adverse effect reported; **Unacceptable** (report missing pages-including tables with acephate results). Wong, 5-17-85.

EPA one-liner: negative at 10 ppm; core grade--inadequate.

Mammalian Systems

113 973216 "Evaluation of Mutagenic Potential of Acephate Employing the L5178 TK +/- Mouse Lymphoma Assay (Forward Mutation)." (SRI, 9/80). Acephate (purity not indicated, lot SX-734 -- 93.5% in 113 973225) tested at 10 levels between 1000-5000 ug/ml +/- rat liver S9 on mouse lymphoma cells (L5178Y); 2 platings/dose level with 4 hour exposure, 2-day expression time with a repeat trial; increased mutation frequency at TK locus without S9 at 1000-5000 ug/ml and increased mutation frequency with S9 at 2000-5000 ug/ml; **Unacceptable** (need positive characterization of test article), **Upgradeable.** Wong, 5-17-85, Gee, 10-2-86.

EPA one-liner: Positive effects at 2000 ug/ml and above +S9 and positive effects at 1000 ug/ml and above -S9; core grade--acceptable.

****101 973210** "L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay with Chevron Acephate Technical (SX-1102)." (Microbiological Associates, 8/2/82). Acephate (technical, lot SX-1102, 98.7%) tested at 2429, 3071, 3714, 4357 and 5000 ug/plate +/- rat liver S9 on mouse lymphoma cells (L5178Y); 6 platings/dose level, 4 hour exposure, 48 hr expression time; dose-dependent increase in mutation frequency over entire dose range +/- S9; Acceptable. Wong, 5-21-85.

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EPA one-liner: Moderately positive, with and without S9, core grade--acceptable.

101 973211 "Mouse Lymphoma Mutagenesis Assay with Chevron Acephate Technical (SX-762)." (Microbiological Associates, 8/2/82). Acephate (93.5%, lot SX-762) tested at 2429, 3071, 3714, 4357 and 5000 ug/plate +/- rat liver S9 on mouse lymphoma cells (L5178Y); 6 platings/dose level, 4 hour exposure and 48 hr expression time; identical to study identified as record #97310 except a different lot of test article used; dose-dependent increase in mutation frequency at TK locus over entire dose range +/- S9; **Acceptable. Wong, 5-21-85.

EPA one-liner: Moderately positive, with and without S9, core grade--acceptable.

167 058112, 058113 "Evaluation of Chevron Acephate Technical in the Mouse Somatic Cell Mutation Assay." (Hazleton, Project No. 2107-141, 10-86) Acephate technical, batch SX-1102, 98.7%, was tested in the mouse somatic cell spot test. 854 females were tested by feeding 0, 50, 200, 600 or 800 ppm acephate in the diet on days 8.5 to 12.5 of gestation, ethylnitrosourea was the positive control given at day 10.5, ip. On days 14 and 28 of lactation pups were examined for recessive coat spots. Toxic effects observed in females at 600 and 800 ppm include lacrimation, tremors, and staggered gait. The positive control was functional, no increase in recessive coat spots in acephate treated litters. **Unacceptable** (route of administration, no good evidence fetuses were exposed to test material) Shimer, 11-18-87 and J. Gee, 1/4/88.

Summary: Multiple reports on file with CDFA contain evidence that acephate is weakly mutagenic/genotoxic in both bacterial and mammalian tests in vitro. A number of lots of acephate have been tested with Salmonella typhimurium strains with positive effects especially in strain TA100 with and without metabolic activation at high concentrations (in the mg/plate range). With mammalian cells, three reports are on file showing positive mutagenic effects in mouse lymphoma (L5178Y) in two acceptable studies and one which is upgradeable. Three different lots were used in the mg/ml range with and without S9 activation. It should be noted that TA100 is often considered the most sensitive strain of Salmonella and L5178Y has been shown to give a higher percent of "false positives" for chemicals than, for instance, Chinese hamster cells. Some of the animal data, however, on which the evaluation of a chemical as a carcinogen/noncarcinogen is based, are not adequate, putting the "false positive" rating in some question. The fact that other test types are also positive (see below) and the reproducibility of the two tests under discussion above lend weight to the weak genotoxic effect. The in vivo mouse somatic cell mutation assay was not acceptable largely because there was no evidence presented to verify that the test article had crossed the placenta. Gee, 10/3/86 and 1/5/88.

CHROMOSOME MUTATION

112 028968, 028969 "Orthene Technical: Cholinesterase Inhibition and Cytogenetics in the Monkey, Final Report." (LSR, 1/21/83). Acephate (98.7%, lot SX-1102) tested for SCE (028968) and chromosome aberrations (028969) at 0 and 2.5 mg/Kg only by gavage for 20 days; peripheral lymphocytes of monkey (Macaca fascicularis) stimulated with phytohemagglutinin; cells arrested in mitosis after 45 hours incubation for 3 hours, then harvested; 1/sex/group for SCE and 1/sex/group for chromosome aberrations - lymphocytes

for SCE from same animals were incubated as for aberrations but with BUDR added and incubation extended to 72 hours total; cholinesterase inhibition demonstrated, but no mutagenic effects noted; **Unacceptable** (no data included in the report), **Not upgradeable.** Wong, 5-21-85.

EPA one-liner: Negative at 2.5 mg/kg or body weight (only level tested) after 20 days of dosing by gavage; core grade--acceptable as supplementary.

113 973221 "Micronucleus Test on Acephate-Mice." (SRI, 3/10/80). Acephate (purity not reported but written notation of 96.6% for lot SX-734) given by gavage twice over 24 hrs at 0, 75, 150 and 300 mg/Kg to mice for micronucleus assay; justification of dose based on an oral LD50 in mice of 361 mg/kg; 24 males/group, 8 in positive control group; sampling from 8 males at 48, 72 and 96 hrs post-treatment; 500 PCE's/animal; no fatalities; no genotoxic effect reported; **Unacceptable** (only males tested with no justification, too few PCE's/animal, husbandry problem suggested with weight loss in controls due to "unreachable water" -- only evidence of toxicity at high dose is based on weight loss), **Possibly upgradeable.** Wong, 5-20-85.

EPA one-liner: Not mutagenic according to this test; core grade--minimum.

101 973220 "Dominant Lethal Study of Acephate Technical (SX-1102)" (Chevron, 6/11/82). Acephate (99%, lot SX-1102) given in the diet for five days at 0, 50, 500 and 1000 ppm to CD-1 mice for a dominant-lethal assay; 12 males and 190 females/group, 2 females:male for 8 weeks of mating, positive control included; no adverse effect noted; **Acceptable. Wong, 5/21/85.

EPA one-liner: Negative, when fed to CD-1 male mice; core grade--acceptable.

012 973219 Invalid IBT study.

101 973212 "Cytogenetics Study in Mice Acephate Technical (SX-1102)." (E G & G Mason Res. Inst., 8-27-82) Acephate (98.7%, lot SX-1102) given by oral gavage in a single dose at 0, 11.2, 37.3 and 112 mg/Kg to Swiss white mice for a bone marrow cytogenetic assay; 4/sex/group, positive control included; clinical signs of toxicity reported; dose selection based on acute toxicity studies included with the report; no adverse effect indicated; **Acceptable. Wong, 5-21-85.

EPA one-liner: Negative at 112 mg/Kg; core grade--acceptable.

** 113 **973224** "Evaluation of the Effect of Acephate on Sister Chromatid Exchange Frequencies in Cultured Chinese Hamster Ovary Cells." (SRI, 6/80). Acephate (purity not indicated, lot SX-734 with purity given as 93.5% in report 113 973225) tested at 0, 125, 250, 500, 1000 or 2000 ug/ml for 21.5 hours without S9 and at 0, 312.5, 625, 1250, 2500 or 5000 ug/ml for 2 hours with rat liver S9 activation; CHO cells in culture for SCE assay; 2 platings/dose level, positive controls included; increase frequency of SCE at 500 ug/ml without S9 and at 5000 +S9; **unacceptable** (test article not characterized) was the initial review by Wong. In view of the fact that the purity of this lot is contained in another report submitted at the same time, the deficiency is not considered grounds for rejecting an otherwise adequate study -- Gee. Wong, 5-20-85, Gee, 10-1-86.

EPA one-liner: Positive results without metabolic activation above 1000 ug/ml, positive results with metabolic activation at 5000 ug/ml; core grade--acceptable.

112 973222 "Mutagenicity Evaluation of Chevron Acephate Technical SX-1102 in the Sister Chromatid Exchange Assay in vivo in Mouse Bone Marrow." (Litton, 1/83). Acephate (technical, purity not stated, lot SX-1102 [purity of this lot from other reports is 99%]) given by oral gavage in a single dose at 0, 29 or 96 mg/Kg to CD-1 mice for SCE assay; 5/sex/group, positive controls included; no adverse effect indicated; **Unacceptable** (test article not positively characterized, inadequate number of dosing levels, report incomplete--missing appendices and tables, number of animals not indicated), **Not upgradeable.** Wong, 5-21-85.

EPA one-liner: Negative at 96 mg/kg; core grade--acceptable as supplementary.

158 045233 More complete version of record #973222. JG, 9/29/86. Study is still unacceptable based on inadequate dose selection justification and lack of toxicity, no individual values and no spindle inhibitor given so inadequate number of mitotic cells were available in some groups. The reason for not evaluating slides from the 289 mg/kg group used in the preliminary study and also in the main study from dosing error is not adequate in view of the lack of m.t.d. at 96 mg/kg.

Summary: In vivo chromosome studies for dominant lethal and bone marrow chromosomal aberration formation in CD-1 and Swiss mice respectively, were both acceptable and negative for observable effects. A study for micronuclei formation in polychromatic erythrocytes, in male mice only, also showed no response to acephate but this was not an acceptable report as submitted. Another study with PHA-stimulated peripheral lymphocytes from monkeys exposed for 20 days in vivo showed no observable effect for sister chromatid exchange or chromosomal aberrations. An in vitro study with Chinese hamster ovary cells did show an increase in SCE's. This was an acceptable test. Another study on in vivo sister chromatid exchange in CD-1 mice was negative but the high dose was questionable as adequate for the test. None of the in vivo reports included good evidence that the bone marrow was exposed to a meaningful dose unlike in vitro tests where exposures of the target cells are more readily controlled. Clinical toxicity other than that to bone marrow precluded higher doses in some studies in mice (e.g., #973212). The conclusion is that there is evidence in vitro for a possible genotoxic effect. Gee, 10/3/86 and 1/5/88.

DNA DAMAGE/REPAIR

113 973225 "Differential Toxicity Assays of Nineteen Pesticides Using Salmonella typhimurium strains (DNA Damage/Repair)." (SRI, 2/81). Acephate (93.5%, SX-734) tested at 0, 1 and 5 mg/disk on Salmonella strains SL 4525 (rec+), SL 4700 (rec-), TA1978 (uvrB+) and TA1538 (uvrB-) in a spot test for differential toxicity without metabolic activation; 2 platings/dose level, positive controls included; two trials; no adverse effects reported in first trial but differential growth reported with SL (rec) strains in second trial: rec+ with 9 mm and rec- with 12 mm zone of inhibition (6mm disk); **Unacceptable** (no activation included). Review by Gee identifies a possible adverse effect. Wong, 5-20-85, Gee, 10-1-86.

EPA one-liner: Negative up to 5 mg; core grade--acceptable.

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113 028972 "In vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides: Excerpt for Acephate on Differential Toxicology in Escherichia coli and Bacillus subtilis." (SRI, 10-79) Acephate (93.5%,, lot SC-7562) tested at 0.01, 0.10, 1.0 and 5.0 mg/disc/plate on E. coli strain W3110/p3478 and B. subtilis strains H17/M45 in a spot test (damage/repair); 1 plate/dose level, no repeat trial; no adverse effect indicated; **Unacceptable** (single plating and no repeat trial, no activation.) Reason why B. subtilis H17/M45 (rec +/-) did not show differential effect as did Salmonella (#973225) is not clear. Wong, 5-17-85.
EPA one-liner: negative; core grade -- unacceptable.

149 039419 More complete version of record 028972. Gee, 10/1/86. The objections in the initial review stand.

113 028971 "In vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides: Excerpt for Acephate on Mitotic Recombination with Saccharomyces cerevisiae." (SRI, 10/79). Acephate (93.5%, lot SX-7562) tested at 0, 0.1, 0.5, 1.0 and 5.0 % (trial 1) and at 1, 2, 4 or 5% (trial 2) +/-S9 on S. cerevisiae strain D3 in a mitotic recombination assay; incubated for 4 hours on a roller drum, then diluted serially and plated on 5 plates for 10^{-5} and 3 plates for 10^{-3}; positive effects at 1% and above with and without metabolic activation; **Unacceptable** (dose selection not justified with marginal cytotoxicity demonstrated, no individual plate counts and no statistical analysis reported, use of DMSO as solvent is not recommended.)

EPA one-liner: Positive at 1% and above; core grade--acceptable. Wong, 5-17-85.

149 039418 More complete version of record 028971. Gee, 10/1/86. Evaluation stands.

113 973215 "Orthene Technical: Cholinesterase Inhibition and Mitotic Gene Mutation, and Reverse Mutation with S. cerevisiae D7 for 7 Pesticides - Orthene." (SRI, 6/80). Acephate (93.5%, lot SX-734) tested at 0, 1, 2, 3, 4 and 5% +/- rat liver S9 on S. cerevisiae strain D7 (diploid) in mitotic crossing over and gene conversion assays; repeat test using 3, 3.5, 4, 4.5 and 5%; incubated for 4 hours, then diluted and plated; with S9, an increase in mitotic crossing over and reverse mutation at 2% and above-- increased frequency of gene conversion at 1% and above; without S9, an increase in frequency of crossing over, reverse mutation and gene conversion at 1% and above; **Unacceptable** (number of plates/group not clear, no rationale for dosing levels, individual plate data not included, methods of statistical treatment not clear), **Possibly upgradeable.** Wong, 5-16-85.

EPA one-liner: Positive for crossing over , gene conversion and reverse mutation at 1% and above without metabolic activation, positive for gene conversion at 1% and above, positive for crossing over and reverse mutation at 2% and above with metabolic activation; core grade--acceptable.

** 113 028973 "In vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides: Excerpt for Acephate on Unscheduled DNA Synthesis." (SRI, 10/79). Acephate (93.5%, lot SX-734) tested at 0.1 to 72 ug/ml without S9 (Exp. #1), 125 to 2000 ug/ml without S9 (Exp. #2), 0.1 to 1000 ug/ml with rat liver S9 (Exp. #3) and 250 to 4000 ug/ml (Exp. #4) with contact-inhibited WI-38 human fibroblasts in UDS assay; 3 hour exposure without activation and 1 hour with activation; hydroxyurea to block

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semiconservative DNA synthesis; DNA was extracted, DNA determined by diphenylamine reaction and tritium quantitated by liquid scintillation counting; slight increase in UDS at and above 1000 ug/ml. Initial review by Wong indicated an incomplete report with no protocol submitted. 149 039428 contains the full document making the study acceptable with an adverse, genotoxic effect (Gee, 10/1/86). Wong, 5-17-85,

EPA one-liner: Positive response without metabolic activation at 1000 ug/ml and above; core grade--acceptable.

149 039420 More complete version of record 028973. Gee, 10/1/86. See above.

Summary: Comparison of differential toxicity in repair proficient versus repair deficient strains of Salmonella suggest an adverse effect on viability of cells with a defective recombinant repair pathway (rec-), while the UV-repair deficient strain (uvrB-) grew approximately the same as the uvrB+ strain. Bacillus subtilis rec+/- strains, however, did not show any difference in growth for reasons that are not known. On the other hand, Saccharomyces cerevisiae D3 and D7 both showed increased mitotic recombination, mitotic crossing-over and gene conversion with exposure to acephate, lending support to the data with Salmonella. In these tests, DNA damage occurs of a type which is repaired by DNA recombination. When a cell cannot perform this function, it is killed reproductively. In proficient strains, repair occurs, allowing for survival or, in Saccharomyces, enhancing mitotic crossing over, which is essentially a test of repair. In addition, there was a slight increase in unscheduled DNA synthesis in mammalian cells, substantiating the results in microbial systems. Gee, 10/3/86 and 1/5/88.

SUMMARY OF GENOTOXICITY STUDIES: Taken altogether, the studies in the three areas indicate the in vitro tests reported to CDFA were more sensitive than the in vivo genotoxicity studies submitted or acephate is nonmutagenic in vivo. The possibility of in vivo effects should not, however, be dismissed 1) because correlation of in vitro to in vivo effects is not well well understood and 2) in vivo tests in other areas on file suggest adverse oncogenic effects. Full assessment of these effects cannot be made unless adequate in vivo studies in the area of genotoxicity are available. The data requirements are fulfilled by the in vitro studies. Gee, 10/3/86 and 1/5/88.

NEUROTOXICITY

** 151 039603, 039602 "Acute Delayed Neurotoxic Study in Chickens with Chevron Acephate Technical Final Report and Addendum. (Wildlife International, 10/18/85). Acephate (98%) at 785 mg/Kg, redosed after 21 days, 5 mg/kg atropine to protect at dosing with additional atropine given over 21 hours; 6 hens in control groups and 12 in treatment group; TOPC positive control; no delayed neurotoxicity noted; Acceptable. McGee, 4/21/86.

** 067 973171 "Studies on Acute Delayed Neurotoxicity of Orthene (Chickens)." (Bozo Research Center-Japan, 11/79). Acephate (98.9%) at 375 mg/Kg by gavage, one dosing, 5 mg/kg atropine to protect; 12 hens in control groups and 24 in treatment group; TOPC positive control; no delayed neurotoxicity noted; Acceptable. Wong, 5/22/85.

EPA one-liner: Negative, but insufficient; core grade-supplementary.

015 973172 Invalid IBT study, 1/20/72.

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MISCELLANEOUS

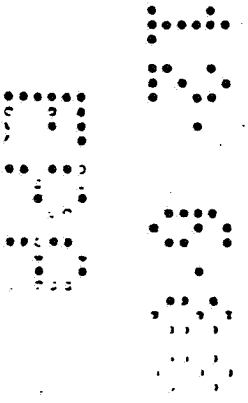
Guidance for the Reregistration of Pesticide Products Containing Acephate as the Active Ingredient, EPA, September, 1987, gives the following data gaps for acephate: Twenty-one day inhalation study in rats, chronic toxicity in the rat to determine the NOEL for brain cholinesterase inhibition and rat reproduction study to establish the NOEL - this has been satisfied with CDFA Record #060979, not included in the EPA review. Acephate has been classified as a class C carcinogen or "possible" human carcinogen based on the increase in liver adenomas/carcinomas and hyperplastic nodules in female mice only at the high dose at term plus the positive findings in in vitro mutagenicity tests. In vivo studies were negative for genotoxicity.

Methamidophos: Technical acephate contains [redacted]methamidophos*, a cholinesterase inhibitor and a metabolite of acephate as well as a contaminant. By acute studies, it is highly toxic, being category I. Methamidophos was not oncogenic at 25 ppm in rats and not teratogenic in rabbits (2.5 mg/kg) or in rats (3.0 mg/kg). In a 1-year dog study and a 2-year rat study, inhibition of brain cholinesterase was observed at 2 ppm (0.05 mg/kg/day) (LDT). The EPA reregistration document identifies a rat reproduction study and mutagenicity studies as remaining data gaps.

Methylthioacetate: This is an impurity* in the currently registered product. According to EPA, additional studies (acutes and 90-day dermal in rabbits) are required. Also, they indicate that a battery of mutagenicity tests in addition to the positive mouse lymphoma test are needed.

*Chevron's rebuttal letter of 5/5/88 states that current manufacturing processes produce > 99.9% pure acephate.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED



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