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MEMORANDUM

SUBJECT: Acephate - Updating the Oneliner by Inclusion of the Recently Prepared Executive Summaries and New DERs

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Most of the studies listed in the Acephate Oneliner were reviewed several years ago and, therefore, did not have the currently required executive summaries. The executive summaries listed below have been written for the recently completed Toxicology Chapter for the Acephate RED, but are not in the Oneliner. Also, three studies (two 4-Week Inhalation, MRID Nos. 40504818 and 40645903, and a Rat Developmental, MRID No. 41081602), were obtained from the Document Room and reviewed for the RED Chapter. These studies are also not yet in the Oneliner. In order to facilitate connecting these executive summaries with appropriate studies, a hard copy of the (corrected) Oneliner, printed on October 30, 1997 is being submitted with this memorandum.

2

ACEPHATE: STUDIES REQUIRING EXECUTIVE SUMMARIES AND DERs NOT YET IN THE ONELINER

Guideline No.	MRID No.	Type of Study	Page in Attached Oneliner (10/30/97)
81-7	00154884	Acute delayed neurotoxicity (hen)	10
83-1a	00084017	Rat feeding/onco.	16
83-1b	41812001	1-Year dog feeding	14
83-2b	00105197	Mouse onco.	15
83-3b	00069684	Rabbit developmental	15
83-4	00129508	Rat reproduction	16
	40323401	Rat reproduction	16
84-2	**Mutagenic - Gene Mutations**		
	00119080	Ames	17
	00132948	Ames	21
	00132947	Ames	22
	00132949	Sacch. cerevisiae	20
	00132950	Mouse lymphoma TK locus	19
	00137738	Mouse lymphoma TK locus	20
	40209101	Somatic cell mutation	20
84-2	**Mutagenic - Chromosome Aberrations**		
	00132953	Micronucleus assay	18
	00119081	Dominant lethal (mouse)	18
84-2	**Mutagenic - Other Genotoxic Effects**		
	00132955	DNA Damage in S. typh.	18
	00132949	Gene conversion	19
	00132954	Sister chromatid exchange	18

Guideline No.	MRID No.	Type of Study	Page in Attached Oneliner (10/30/97)
84-2	00028625	Unsch. DNA synth.	20
85-2	00154886	Dermal absorption	25
	Nonguideline Studies		
	40504820	Cholinesterase (ChE) inhibition after acute dermal exposure (rat)	1
	00015160	Subchronic ChE study with humans ■	13
	40504819	3-Month feeding (ChE) study (rat) ■■	11
	00014219	Metabolism (rat) ●	23
	00014994	Metabolism (rat) ●	24
	Not Yet Recorded in a Oneliner		
82-4	40504818	Subchronic inhalation toxicity (4-week) in the rat #	
	40645903	Subchronic inhalation toxicity (4-week) in the rat #	
83-3a	41081602	Developmental (teratology) in the rat ##	

■ This study is listed in the attached Oneliner as the 82-1(b) study. Actually, it is a nonguideline study.

■■ This study is also listed in the Oneliner as the 82-1(b) study. However, it is really a special (cholinesterase inhibition) and nonguideline study.

● These two studies, listed in the Oneliner as 85-1 studies, provide information on the metabolism of Acephate by the rat, but do not satisfy, even partially, the guideline requirements for the metabolism studies (85-1). These studies were, therefore, classified as nonguideline studies in the recent Tox. Chapter for the Acephate RED.

These two inhalation toxicity studies, found in the bibliography for Acephate RED, were obtained from the

4

Document Room and were then reviewed by an HED scientist. However, because there were problems with the reviews, the Tox. Branch II senior staff concluded that a very detailed Executive Summary for each study would replace the "regular" review. These Summaries were accepted in lieu of the reviews by the SAC and SARC Committees and are now being submitted for inclusion in the Oneliner.

This study was also obtained from the Document Room during the preparation of the Tox. Chapter for the Acephate RED and was reviewed within the Tox. Branch II in September, 1997. Therefore, this study is not yet in the Oneliner.

EXECUTIVE SUMMARIES AND DERs NOT YET IN ONELINER

In this acute delayed neurotoxicity study (81-7; MRID 00154884), 53-week old white leghorn hens were intubated with single doses of the following test substances: water (negative control), Acephate Technical, 785 mg/kg and TOPC (tri-o-tolyl phosphate; positive control), 600 mg/kg. Acephate (purity: 99%) was administered in water and TOPC (purity:95%) in corn oil. After the initial dosing, the hens were observed for 21 days and then the negative control group and the Acephate-treated group were redosed with water and Acephate (785 mg/kg), respectively. Both groups were sacrificed 21 days later (on study day 43), whereas the TOPC-treated group was sacrificed after study day 21. All Acephate-treated hens received also an intramuscular injection of atropine sulfate at dosing and at 4, 8, 12 and 21 hours after dosing. The dose of 785 mg/kg (LD_{50}) was selected by the sponsor and was based on the results of two acute oral LD_{50} studies conducted in February and March, 1985 and included in the main report).

Toxic signs observed in the Acephate-treated group were: (1) Mortality (9/16 or 56% hens died, due to cholinergic effects, during days 3-7 after dosing); (2) Weight losses after initial dosing and redosing; (3) Diarrhea, lethargy, weakness in lower limbs, loss of coordination, wing droop and reduced reaction to sound and movement - each sign occurring at about 3 hours after dosing and redosing, and persisting through day 10); (4) Ataxia (during the first 7 days after each dosing and decreasing in severity thereafter); and (5) Swelling (minimal) of axis cylinder of the sciatic nerve in one hen only.

In the TOPC-treated group, toxic signs (loss of coordination, weakness in lower limbs, ataxia and staggering gait) were observed during days 14-21 after dosing and increased in severity with time after exposure. Lesions (minimal to moderate) were observed mostly in the sciatic nerve and in all hens. These lesions included lymphocytic foci, swollen and fragmented axons, nerve fiber and myelin degeneration, and Schwann cell

hyperplasia.

Based on the cholinergic and neurotoxic effects occurring shortly after dosing and disappearing within some 10 days and on the absence of lesions in the sciatic nerve (except for a slight swelling in one hen), Acephate Technical was negative for acute delayed neurotoxicity at 785 mg/kg (only dose tested). Based on the cholinergic and neurotoxic effects observed 14-21 days after dosing and increasing in severity with time, and on the prominent lesions in the sciatic nerve, in all hens, Tri-o-tolyl phosphate (TOPC; 600 mg/kg; positive control), caused acute delayed neurotoxicity.
This study is ACCEPTABLE-guideline and satisfies the guideline requirement for an acute delayed neurotoxicity study in the hen (81-7)

In a chronic feeding/carcinogenicity study **(MRIDs 00084017 [main study] and 00101623 [additional data]**, Sprague-Dawley rats, 45 days old at study initiation, 75 males and 75 females/group, received Technical RE-12420 (Acephate; purity: 92.5%) in the diet for 28 months at the following nominal doses: 0, 5, 50 and 700 ppm. Using the FDA/HED conversion factor (1.0 ppm in food = 0.05 mg/kg/day, for the older rat; Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, 1959), these doses were equivalent to 0, 0.25, 2.5 and 35.0 mg/kg/day, respectively. No justification was presented for the selection of doses. Parameters examined for all rats in the study included daily observations, body weights, food consumption, food efficiency (during the first 8 weeks) ophthalmological examination, hematology, clinical chemistry (including cholinesterase [ChE] activities in plasma, erythrocytes [RBC] and brain), urinalysis, necropsy, histopathology of some 40 ograns/tissues (including brain, eyes, spinal cord and sciatic nerve), organ weights and organ/body weight ratios (for adrenals, brain, heart, kidneys, liver, lungs, spleen, testes/ovaries and thyroid gland - for all scheduled sacrifices). Plasma and RBC ChE activities were determined during weeks 6, 7, 19 and 28, and months 12, 18, 22, 24 and 28, using randomly selected 4, 5 or 10 rats/sex/group. Brain ChE activity was determined during weeks 7 and 19, and months 12, 22 and 28.

The following treatment-related findings were observed in the high-dose (700 ppm) male rats: **(1)** Hyperactivity in some (8%) of the males during the initial 5 months of the study; **(2)** Increased incidence of aggressive behavior (31% vs 5% in the controls), also during the initial 5 months of the study; **(3)** Decreased body weight gain (6-18%; $p \leq 0.01$) during study weeks 8-106, when compared with the controls; and **(4)** Significantly ($p \leq 0.01$) decreased food efficiency during the entire testing interval (weeks 1-8). Aggressive behavior was also observed in 13% of the low-dose and 13% of the mid-dose male rats.

6

Relative to the control values, plasma ChE activity was inhibited at all sampling times in the high-dose males (10-50%) and females (50-72%; $p \leq 0.01$). In the mid-dose group, the inhibitions were 0-29% for the males and 0-38% for the females. Plasma ChE activity was not inhibited in the low-dose males and slightly inhibited (0-19%) in the females. Erythrocyte ChE activity was decreased ($p \leq 0.01$) at all sampling times in the high-dose males (21-67%) and females (21-61%). In the mid-dose groups, ChE inhibitions in RBC were 0-31% and 0-42% for males and females, respectively. In the low-dose group, RBC CHE activity was decreased 0-13% (males) and 0-29% (females). Relative to the control values, the inhibitions of brain ChE activity in the low-dose, mid-dose and high-dose males were 0-13%, 34-43% and 69-77%, respectively. The corresponding values for the female rats were 1-13%, 33-45% and 66-83%, respectively. Most of these inhibitions were statistically significant ($p \leq 0.01$).

There was a higher incidence of adrenal medullary tumors (pheochromocytomas) in the treated male rats than in the concurrent control males. However, the reported incidences for the 5, 50 and 700 ppm groups (9.7, 15.5 and 12.2%, respectively) were within the historical control range. The historical incidence of medullary tumors was 0-20.3% and the cocurrent incidence, 2.7%. All of the tumors, but two, in the current study were benign.

Based on the above findings, the systemic LOEL and NOEL for the male rats are 700 ppm (35 mg/kg/day) and 50 ppm (2.5 mg/kg/day), respectively. The systemic NOEL for the female rats is > 700 ppm. The LOEL and NOEL for the inhibition of plasma, RBC and brain ChE activities in males and females are 50 ppm (2.5 mg/kg/day) and 5 ppm (0.25 mg/kg/day; borderline value), respecvively. Technical RE-12420 (Acephate) was not carcinogenic in this study.

This study is ACCEPTABLE and satisfies the guideline requirement for the chronic feeding study (83-1a) and carcinogenicity study (83-2a) in the rat.

In a chronic feeding study **(MRID 41812001)**, beagle dogs (4.0-4.5 months old), 5/sex/group, received Acephate Technical (purity: 99.9%) in the diet for one year at the following (nominal) doses: 0, 10, 120 and 800 ppm (analytical values: 0, 0.27, 3.11 and 20.16 mg/kg/day, respectively). Doses used in this study were based on the results of a 4-week preliminary study (No. HWA 2107-164) in which 8, 20, 250 500 ppm doses of Acephate Technical were tested. Parameters examined for all dogs in the current study included daily observations, physical and ophthalmological examinations, body weight gains, food consumption and utilization, hematology, clinical chemistry (including cholinesterase [ChE] levels in plasma, erythrocytes [RBC] and brain), urinalysis, necropsy, histopathology of some 40 organs/tissues (including brain, eyes, spinal cord and sciatic

nerve), and absolute and relative (organ/terminal body weight and organ/brain weight ratios) weights for 12 organs. Plasma and RBC ChE levels were determined for all dogs during the study weeks -3, -2, -1, 4, 13, 26 and 52, whereas brain ChE levels were assayed only at study termination. Substrates used for ChE determinations were acetylthiocholine (RBC and brain) and butyrylthiocholine (plasma).

The primary treatment-related effect observed in this study was the inhibition of ChE levels in brain and RBC. Relative to the control values, brain ChE levels (uMol/g) were significantly ($p<0.05$) inhibited in all male groups (17, 53 and 66%, respectively) and in the mid-dose and high-dose female groups (49 and 66%, respectively). Erythrocyte ChE levels (uMol/mL) were significantly ($p<0.05$) inhibited in the mid-dose (42-55%) and high-dose (76-87%) groups of both sexes. Plasma ChE levels (uMol/mL) were inhibited in the mid-dose (13-18%) and high-dose (6-10%) male groups and in all female groups (6-30%), but the inhibitions were dose-unrelated and statistically insignificant. Despite severe brain ChE inhibition in the mid-dose and high-dose groups of both sexes, symptoms usually associated with ChE inhibition (tremors, ataxia) were not observed.

Other treatment-related statistically significant ($p<0.05$) effects were: **(1)** Decrease in RBC count (13-26%), hemoglobin concentration (14-21%) and hematocrit (6-9%), all in the high-dose males); **(2)** Increase in activated partial thromboplastin time (34-96%), in the high-dose males; **(3)** Increase in the absolute weight of liver, in the high-dose males (29%) and females (17%); and **(4)** Perivascular infiltration and pigment in the livers (reticuloendothelial cells) of one mid-dose male and most high-dose males and females.

Based on decreases in hematological parameters (RBC, hemoglobin and hematocrit), increase in thromboplastin time, increase in absolute liver weight and histological changes in the liver (perivascular infiltration and pigment in reticuloendothelial cells), the LOEL and NOEL for systemic effects are 20.16 mg/kg/day (800 ppm; HDT) and 3.11 mg/kg/day (120 ppm), respectively (both sexes). The LOELs for cholinesterase (ChE) inhibition are as follows: Brain: 0.27 mg/kg/day (10 ppm), LDT, (males) and 3.11 mg/kg/day (females); RBC: 3.11 mg/kg/day (both sexes); and Plasma: >20.16 mg/kg/day (both sexes). The NOELs for ChE inhibition are as follows: Brain: <0.27 mg/kg/day (males) and 0.27 mg/kg/day (females); RBC: 0.27 mg/kg/day (both sexes); and Plasma: 20.16 mg/kg/day (both sexes).

This study is ACCEPTABLE-guideline and satisfies the guideline requirements for the chronic feeding study in the dog (83-1b).

8

In a carcinogenicity study **(MRIDs: 00105197 [main study]; and 00077209, 00105198 and 00129156 [additional data])**, Charles River CD1 mice, 75/sex/group, were fed diets containing Orthene Technical (RE-12420; Acephate; purity: 92.6%) at nominal doses of 0, 50, 250 and 1000 ppm. The analytical doses were 0, 7, 36 and 146 mg/kg/day, respectively, for males and 0, 8, 42 and 167 mg/kg /day, respectively, for females. No explanation was given for the selection of dose levels. Ten mice/sex/group were sacrificed after 12 months of feeding the test material and the remaining mice, after 24 months. Parameters examined for all mice in the study included daily observations, body weight gains, food consumption, hematology (for 10 mice/sex/group at study termination), necropsy, histopathology of some 40 organs/tissues (including brain, eyes, spinal cord and sciatic nerve) at study termination, and absolute and relative (% of body weight) weights of brain with stem, heart, liver, gonads and kidneys (at study termination). Tissues from mice which died during the study or were sacrificed moribund were also examined microscopically.

Female mice, fed 1000 ppm (167 mg/kg/day) of Orthene Technical, had higher incidence of hapatocellular carcinomas (HC) and hyperplastic nodules (HN) than did the concurrent controls. The incidence of HC in the control, 50, 250 and 1000 ppm female groups was 1.3, 1.3, 0 and 15.8%, respectively. The corresponding values for the male groups were 5.3, 2.7, 4.0 and 4.0%, respectively. All of these HC were observed at the terminal sacrifice. The incidence of HN in the control, 50, 250 and 1000 ppm groups was 2.7, 1.3, 0 and 19.7%, respectively. The corresponding values for the male groups were 13.3, 9.3, 5.3 and 17.3%, respectively. Most of the nodules (14.5 and 12.0% in the 1000 ppm females and males, respectively) were observed at the terminal sacrifice. The incidence of HC in the historical controls (22 studies; 1630 CD1 mice) ranged from 0 to 6%.

Other treatment-related findings were: **(1)** Liver lesions (hypertrophy of hepatocytes, karyomegaly and intracellular inclusion bodies) in the mid-dose (250 ppm) and high-dose (1000 ppm) males and females; **(2)** Lung lesions (dark pigmented alveolar macrophages, eosinophilic foreign bodies and alveolar hyalinosis) and lesions in nasal cavity (acute rhinitis) in the mid-dose and high-dose males and females; **(3)** Significantly ($p \leq 0.01$) decreased body weight gains in the mid-dose males (8-11%) and females (6-14%) during the study weeks 52-104, and in the high-dose males (15-30%) and females (14-29%) during the study weeks 13-104, when compared with the controls; and **(4)** Significant ($p \leq 0.01$) changes in organ weights at the high-dose level in the males (smaller livers and kidneys) and the females (larger livers and smaller kidneys, brains and ovaries), when compared with the controls.

Based on decreased body weight gains, decreased (in males) or increased (in females) weights of livers, decreased weights of kidneys, and non-neoplastic lesions in liver and lungs, the

systemic LOEL is 250 ppm (mg/kg/day: 36 ♂ and 42 ♀) and the systemic NOEL is 50 ppm (mg/kg/day: 7 ♂ and 8 ♀). Based on the increased incidence of hepatocellular carcinomas in the 1000 ppm (167 mg/kg/day; HDT) females, Orthene Technical (Acephate) was carcinogenic to female mice in this study.

This study is ACCEPTABLE-guideline and satisfies the guideline requirements for the carcinogenicity study in the mouse (83-2b).

In this developmental toxicity study **(83-3b; MRIDs: 00069684 [main study] and 00069683 [pilot study])**, artificially inseminated and then chorionic gonadotropin-injected (to induce ovulation) Dutch Belted rabbits, 16/group, received by gavage 0, 1, 3 and 10 mg/kg/day of Technical RE-12420 (Acephate; purity: 92.8%) from gestation day (g.d.) 6 through 27. The test material was administered as an aqueous solution at a constant volume of 1 mL/kg of body weight. Doses selected for this study were based on the results of the pilot study in which doses of 3, 10, 30 and 100 mg/kg/day of Technical RE-12420 (purity: 92.8%) were tested; (40% deaths and 10% weight loss were observed on g.d. 24 in the 30 mg/kg group). In the current study, the rabbits were observed daily and weighed every 6 days, and also on day 28 before they were sacrificed. The following parameters were examined at study termination: **(1)** Gross necropsy on the dams; **(2)** Determination of the uterine weights, number of implantations, postimplantation losses, resorptions, corpora lutea/dam, living and dead fetuses, and sex and body weights of fetuses; and **(3)** Examination of fetuses for malformations, variations and skeletal defects.

Two rabbits in the 10 mg/kg group aborted and were sacrificed and discarded without examination, one on gd 25 and another on gd 27. A slight increase in nasal discharge, possibly treatment-related, was observed in the 3 and 10 mg/kg groups, when compared with the controls. With the exception of these two findings, Technical RE-12420 had no effect on the maternal and developmental (teratogenic, fetotoxic) parameters examined.

Based on 2/16 (12.5%) abortions in the high-dose group and none in the controls, the LOEL and NOEL for maternal toxicity are 10 mg/kg/day (HDT) and 3 mg/kg/day, respectively. The NOEL for developmental toxicity is > 10 mg/kg/day.

This study is ACCEPTABLE - guideline and satisfies the guideline requirement for the developmental (teratology) toxicity study in the rabbit (83-3b).

In this 2-generation reproduction study **(83-4; MRID 00129508)**, four-week old Charles River rats, 12 males and 23-24 females/ group, were fed diets containing Technical RE-12420 (Acephate; purity: 93%) for 15-17 weeks before they were mated to produce

the F_1 and F_2 generations. The F_2 offsprings were not fed RE-12424 and were not bred. The nominal doses used (based on preliminary studies) were 0, 50, 150 and 500 ppm. The actual intake of RE-12420 (calculated by the testing facility from the analytical content of RE-12420 in diets, food consumption and body weight) was 0/0, 3.30/3.43, 9.80/10.21 and 34.53/36.82 mg/kg/day for the F_0/F_1 control, low-dose, mid-dose and high-dose males, respectively. The corresponding values for the F_0/F_1 females were 0/0, 4.04/4.12, 12.13/12.35 and 41.82/45.12 mg/kg/day, respectively. Parameters examined were those routinely examined in a multigeneration rat reproduction study.

Various effects on reproduction (low pregnancy rate, high loss of total litters, high fetal losses, decreased size and weight of total litters, and decreased number of young born alive) were observed in rats fed 50 ppm (LDT) of the test material. Systemic effects noted in the 50 ppm group included decreased body weight gain in the females and decreased food utilization in males and females.

Based on the above findings, the reproductive NOEL is < 50 ppm (4.08 mg/kg/day; LDT) and the systemic NOEL is also < 50 ppm.

This study is ACCEPTABLE but does not satisfy the guideline requirement for the rat reproduction study (83-4) because the reproductive NOEL was not definitively determined.

In this 3-generation reproduction study **(83-4; MRIDs: 40323401 [main study] and 40605701 [corrections])**, Charles River rats, 30 males and 30 females/group, were fed diets containing Acephate Technical (purity: 98.7%) for 75 days before they were bred to produce F_{1a}, F_{1b}, F_{2a} and F_{2b} litters. Because of low fertility in all groups, including the controls, for the F_{1b} and F_{2b} litters, a third generation (F_{3a}) was produced from the F_{2b} litters. All rats were continuously exposed to the test material or the control diets either directly in their feed or through the mothers' milk during lactation. The nominal doses used were 0, 25, 50 and 500 ppm, and were based on the results of an earlier (1983) rat reproduction study (MRID 00129508) in which a reproductive NOEL was not determined. Using the FDA/HEW conversion factor (1 ppm in food = 0.05 mg/kg/day, for the older rat; Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, 1959), these doses were equivalent to 0, 1.25, 2.5 and 25 mg/kg/day, respectively. Parameters examined were those routinely examined in a multigeneration rat reproduction study.

Treatment-related effects were observed only in the 500 ppm group and included: **(1)** Decreased body weights and/or weight gains for adult males (in each generation) and females (in some generations) and for pups in the F_{2a} and F_{3a} generations; **(2)** Increases in food consumption for males and females during the.

11

premating period and decreases in food consumption for females during the gestation and lactation periods; (3) Clinical signs in males (increased incidence of alopecia in the first generation and increased incidence of soft or liquid stools in the second and third generations); (4) Decreases in mating performance for the F_{2b} generation; (5) Decreases in mean litter size (25-30%, $p<0.01$) for the F_{1b}, F_{2a}, F_{2b} and F_{3a} generations; and (6) Significant ($p<0.01$) decreases in pup survival to day 4 for the F_{1a} (3.2%) and the F_{2a} (6.3%) generations.

Based on decreased body weights and/or weight gains for adult males (each generation), and for adult females and pups (some generations), decreased food consumption during gestation and lactation periods, and decreases in litter size (some generations), the parental LOEL and NOEL are 500 ppm (25 mg/kg/day) and 50 ppm (2.5 mg/kg/day), respectively. Based on decreases in viability index (two generations) and in mating performance (one generation), the reproductive LOEL and NOEL are also 500 ppm (25 mg/kg/day) and 50 ppm (2.5 mg/kg/day), respectively.

This study is ACCEPTABLE-guideline and satisfies the guideline requirement for a reproduction study in the rat (83-4).

Gene Mutations

Salmonella typhimurium reverse gene mutation assay **(MRID 00119080):** Independent tests with both the Technical (purity: 92.9%) and Analytical (purity: 99.3%) grade Acephate were positive in S. typhimurium strain TA100 in both the presence and absence of S9 activation at high levels (10000-50000 ug/plate). There was no mutagenic response in TA1537 or TA98 up to the highest dose tested (HDT) of the technical product (10000 ug/plate +/-S9).

Salmonella typhimurium reverse gene mutation assay **(MRID 00132948):** Six samples of Technical Acephate with varying purity (92.6 to >99%) were positive in this partial Ames test using only S. typhimurium strain TA100 in the absence of S9 activation at 50000 ug/plate. The >99% pure test substance was cytotoxic at concentrations >500 ug/plate and positive at 500 ug/plate. There was no trend of decreased genotoxicity with increased purity.

Salmonella typhimurium reverse gene mutation assay **(MRID 00132947):** Seven of eight samples of Technical Acephate with varying purity (85-99.6%) were positive in this partial Ames test in S. typhimurium strain TA100 in the absence of S9 activation at 50000 ug/plate. The eighth sample (purity: 100%) was negative in strain TA100 and all samples were negative in strains TA1537 and

TA98 up to the HDT (50000 ug/plate). S9 activation was not used in this study.

Saccharomyces cerevisiae reverse mutation assay **(MRID 00132949):** Independent tests were positive for the induction of gene mutations in S. cerevisiae D7. Dose-related increases in the mutation frequency (MF) were seem at test levels of 2-5% in the presence of S9 activation. The test material used in this study was Technical Acephate (purity: 93.5).

Mouse lymphoma L5178Y TK+/- forward gene mutation assay **(MRID 00132950):** The test was positive with Technical Acephate (purity: 93.5%). Generally dose-related increases in the MF were seen at ≥2000 ug/mL - S9 or ≥3000 ug/mL + S9. Cytotoxicity occurred at the HDT (5000 ug/mL +/- S9).

Mouse lymphoma L5178Y TK+/- forward gene mutation assay **(MRID 00137738):** The test was positive with Technical Acephate (purity: 93.5%); dose-related increases in the MF were calculated at all assayed concentrations (2429-5000 ug/mL +/- S9).

In vivo mouse somatic cell mutation assay **(MRID 40209101):** The test was negative for the induction of somatic cell mutations in the offspring of pregnant C57B1/B6 female mice administered dietary concentrations of 200, 600 or 800 ppm of Technical Acephate (purity: 98%) during gestation days 8.5-12.5. Mortality occurred in 23% of the high-dose dams; other signs of maternal toxicity (tremors, hunched back and labored breathing) were seen in the 600 ppm and 800 ppm dams. Decreases in the percentage of pregnant females (36-37%) and percentage of pups surviving to day 28 (25-26%) were also observed at 600 and 800 ppm.

Chromosome Aberrations

In vivo micronucleus assay **(MRID 00132953):** The test was negative in Swiss male mice receiving oral gavage doses of 75, 150 or 300 mg/kg of Technical Acephate (purity: 93.5%) once daily for two days. No deaths were observed and clinical signs, if any, were not reported. The highest dose used in this study was based on a published oral LD_{50} value for Acephate in mice (361 mg /kg).

Mouse dominant lethal assay **(MRID 00119081):** The test was negative in male CD-1 mice receiving dietary concentrations of Technical Acephate (purity: 98.4%) of 50, 500 or 1000 ppm for 5 days (equivalent to 5.8, 60 or 71 mg/kg/day). Toxicity was

manifested as decreased body weight (18% lower than control) and decreased food consumption (52% of control) in the high-dose group. A 22% reduction in the pregnancy index was also seen at the HDT, but it was statistically insignificant.

Other Genotoxic Effects

DNA damage/repair in Salmonella typhimurium assay **(MRID 00132955):** The test was negative in DNA repair deficient strains up to the HDT (5000 ug/plate; spot test). S9 activation was not used in this study. The test material was Technical Acephate (purity: 93.5%).

Saccharomyces cerevisiae recombination and gene conversion assay **(MRID 00132949):** Independent tests were positive in S. cerevisiae D7 at both endpoints. Dose-related increases in mitotic recombination and gene conversion were seen at Acephate concentrations of 1-5% in the presence of S9 activation. Dose-related increases in recombination and gene conversion were also seen at nonactivated levels of 3-5%. The test material was Technical Acephate (purity: 93.5%).

In vitro sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cell assay **(MRID 00132954):** The test was positive with significant increase in the frequency of SCEs at the highest levels of Technical Acephate (purity not reported) tested (2000 ug/mL - S9; 5000 ug/mL + S9).

Unscheduled DNA synthesis (UDS) in cultured WI-38 human fibroblasts assay **(MRID 00028625):** The test was positive at high concentrations of Technical Acephate (≥1000 ug/ml) but only in the absence of S9 activation. The purity of the test material was 93.5%.

Dermal Absorption Study **(MRID 00154886):** In this study, male Sprague-Dawley rats (age: 144-151 days; weight: 498-618 g), 4/dose/exposure period, received single applications of a mixture of Acephate Technical and radioactive (^{14}C) Acephate, and were sacrificed after 0 (immediately after dosing), 2, 8 and 24 hours of exposure. The purity of Acephate Technical was 98.7% and the radiochemical purity of ^{14}C-Acephate was 99.1%. The concentrations of Acephate applied in 0.05 mL of a dosing solution (distilled H_2O + 0.1% w/w Tween 80) were 0.5 mg (4421000 dpm) and 5.0 mg (4435000 dpm) per rat or 0.899 mg/kg and 9.333 mg/kg (actual mean values), respectively. Acephate was labeled in the carbon atom of the $*CH_3S$- group of the molecule. After the applications on the intact (shaved) dorsal trank, the rats

were housed singly in metabolic cages and had unlimited access to food and water.

Acephate Technical was absorbed slowly through the intact skin of the male rats. At 24 hours after dosing, the recovery of applied radioactivity (expressed as ^{14}C-Acephate) was 78.3% and 90.6% in the 0.5 mg/rat and 5.0 mg/rat groups, respectively. Most of this radioactivity was recovered from the surface of the skin (application site). Systemic absorption was defined as the percentage of the recovered dose in the carcass, blood, urine, feces, CO_2 trap and cage wash. In the 0.5 mg/rat group, 2.1, 3.0 and 10.5% of the recovered dose (radioactivity) was absorbed in 2, 8 and 24 hours, respectively. The corresponding values for the 5.0 mg/rat group were 1.6, 3.6 and 7.6%, respectively. Most of the absorbed radioactivity was found in urine (6.0% in the low-dose group and 4.4% in the high-dose group at 24 hours after exposure). Systemic absorption was not examined immediately after dosing (0 time).

This study is ACCEPTABLE-guideline and satisfies the guideline requirement for a dermal absorption study in the rat (85-2).

Nonguideline Studies

In this special cholinesterase (ChE) inhibition study **(MRID 40504820)**, Sprague-Dawley rats, 5 52-day old males and 5 59-day old females per group, were treated dermally with the following single doses of Acephate Technical (purity: 98.2%): 0, 2, 10, 30 and 60 mg/rat. These doses were equivalent to 0, 7.9, 36.7, 107.0 and 201.0 mg/kg, respectively, for males and 0, 9.4, 51.7, 153.9 and 305.5 mg/kg, respectively, for females. The test material, dissolved in 0.1% (w/v) aqueous Tween 80, was applied (0.2 mL) on the shaved backs and the rats were then fitted with Queen Anne's collars until sacrifice (3 days later). Parameters examined included daily observations for toxic signs and (at study termination), body weights, gross pathology, histopathology, hematocrit, brain protein, and ChE activities in plasma, erythrocytes (RBC) and brain. The substrates used in ChE assays were acetylthiocholine (RBC and brain) and butyrylthiocholine (plasma).

With the exception of ChE activities in plasma, RBC and brain, Acephate Technical had no effect on all of the remaining parameters examined. Relative to the control values, ChE activities were statistically significantly inhibited at the following dose levels and above: **Plasma:** 34% in the 10 mg/rat male group and 41% in the 30 mg/rat female group ($p<0.05$; both groups); **RBC:** 59% ($p<0.05$) in the 60 mg/rat female group only; and **Brain:** 30% ($p<0.05$) and 38% ($p<0.01$) in the 30 mg/rat male and female group, respectively.

Based on the statistically significant inhibitions of ChE activities, the NOELs for male and female rats are as follows: Plasma, 2 mg/rat (7.9 mg/kg ♂) and 10 mg/rat (51.7 mg/kg ♀); RBC, >60 mg/ rat (>201 mg/kg, HDT, ♂) and 30 mg/rat (153.9 mg/kg ♀); and Brain, 10 mg/rat (36.7 mg/kg ♂ and 51.7 mg/kg ♀).

Based on the statistically significant inhibitions of ChE activities, the LOELs for male and female rats are as follows: Plasma, 10 mg/rat (36.7 mg/kg ♂) and 30 mg/rat (153.9 mg/kg ♀); RBC, 60 mg/rat (305.5 mg/kg ♀); and Brain, 30 mg/rat (107.0 mg/kg ♂ and 153.9 mg/kg ♀).

This study is ACCEPTABLE as a special acute dermal (ChE inhibition) study.

In this special cholinesterase (ChE) inhibition study **(MRID 00015160)**, 7 male and 7 female volunteers (age: 21-48; weight: 54-122 kg) were given orally (gelatin capsules) mixtures of RE-9006 (Methamidophos; Monitor) and RE-12420 (Acephate; Orthene) in two ratios, 1:4 or 1:9 (Monitor:Orthene). The group receiving the 1:9 ratio (3 males and 3 females) was given the following doses of the mixture (mg/kg/day): 0.1, 0.2, 0.3 and 0.4. The group receiving the 1:4 ratio (2 males and 2 females) was given only the 0.1 and 0.2 mg/kg/day doses. Each group was given increasing levels of the test materials until a significant inhibition of ChE activity occurred, at which time treatment was discontinued. The subjects did not know whether they were receiving test materials or corn oil (vehicle, given to 2 males and 2 females). Parameters examined included ChE activities in plasma and erythrocytes, hematology, clinical chemistry and observation for toxic signs.

Relative to the pretreatment values, plasma ChE activity was inhibited in both groups. In the 1:4 (Monitor:Orthene) group, the inhibition (22-26%) was first noted at the 0.2 mg/kg/day level after 16 days of dosing and occurred in all subjects. In the 1:9 group, the inhibition (16-22%) was first observed at the 0.3 mg /kg/day level after 21 days of dosing and occurred only in the male subjects. All inhibited ChE activities returned to the pretreatment values during the 7-day recovery period. Dosing human subjects with graded levels of the Monitor:Orthene mixtures for 37 to 73 days had no effect on the remaining parameters examined. Erythrocyte ChE activity was not inhibited and general health of the subjects was not affected. Unsupervised weekend dosing, no record of food intake and too few subjects per test group constitute week points in this study.

Based on the inhibition of plasma ChE activities, the NOELs and LOELs are as follows:

Monitor:Orthene Combination	Sex	NOEL (mg/kg/day)	LOEL (mg/kg/day)
1:4	M+F	0.1	0.2
1:9	M	0.2	0.3
1:9	F	0.3	0.4

This study is ACCEPTABLE as a special subchronic (ChE inhibition) study.

In this special cholinesterase (ChE) inhibition study **(MRID 40504819)**, Sprague-Dawley rats (about 45 days old at the start of dosing), 30 males and 30 females/group, received Acephate Technical (purity: 98.2%) in the diet for 13 weeks at the nominal doses of 0, 2, 5, 10 and 150 ppm. The actual intake of the test material was 0, 0.12, 0.21, 0.58 and 8.90 mg/kg/day, respectively, for males and 0, 0.15, 0.36, 0.76 and 11.48 mg/kg/day, respectively, for females. Cholinesterase activities in brain, erythrocytes (RBC) and plasma were determined on 10 rats/sex during weeks 4, 9 and 13. Other parameters examined for all rats studied were signs of toxicity, body weights (weekly) and necropsy.

Relative to the control values, Acephate Technical had no effect on body weights and no toxic signs were observed in this study. Tissue abnormalities were not observed at necropsy and there was no mortality.

Brain ChE activity was significantly ($p<0.01$) inhibited in the 2 ppm group, during week 13 in the males (7%) and during weeks 9 and 13 in the females (9% each). In the remaining groups, brain ChE activity was significantly ($p<0.01$) inhibited at all times as follows: 5-10%, 10-16% and 44-53% in the 5 ppm, 10 ppm and 150 ppm groups, respectively. The inhibitions were similar in males and females. Erythrocyte ChE activity was significantly inhibited (32-48%; $p<0.01$) only in the 150 ppm group, in males during weeks 4 and 9, and in females during weeks 9 and 13. Plasma ChE activity was significantly inhibted (43%; $p<0.01$) only in the 150 ppm females and only during week 13.

Based on the inhibitions of ChE activities, the NOELs and LOELs for male and female rats are as follows: Brain, < 2 ppm (mg/kg/day: 0.12 ♂ and 0.15 ♀) and 2 ppm (LDT), respectively; RBC, 10 ppm (mg/kg/day: 0.58 ♂ and 0.76 ♀) and 150 ppm (mg/kg/day: 8.90 ♂ and 11.48 ♀), respectively; and Plasma, 10 ppm and 150 ppm, respectively.

This study is classified as ACCEPTABLE-nonguideline (a special subchronic ChE inhibition study).

The purpose of this metabolism study **(MRID 00014219)** was to investigate whether Methamidophos (ORTHO 9006) was formed from Orthene (Acephate) in rats. Six-week old male and female Sprague-Dawley rats were dosed (gavage) with nonradioactive Acephate (purity: 99.94%) at 100 mg/kg for 4 days. Two rats were sacrificed 3 hours after each dose (except the third) and the whole carcasses were quickly frozen and then analyzed (by GLC) for Acephate and Methamidophos. In addition, 3 male and 3 female rats were sacrificed 3 hours after the fourth dose for Acephate and Methamidophos analyses in tissues. Excreta were collected for analyses (by GLC) during the 24 hours following the third dose. The rats were sacrificed at 3 hours after being dosed because it was estimated that Methamidophos would be at or near maximum concentration at that time.

Acephate was rapidly absorbed and rapidly eliminated by the rats. The carcasses contained only 12-48% and the gastrointestinal tracts 3-14% of the final dose at 3 hours after dosing. The excreta (chiefly urine) contained 54-56% of the final dose at 6 hours after dosing. There was no tendency for Acephate to concentrate in blood, liver, muscle, fat, heart and brain.

Rats converted a portion of Acephate to Methamidophos. Evidence was presented that the conversion took place in the small intestine and, to a lesser extent, in the stomach, and was apparently effected by the microorganisms. Methamidophos was then absorbed from the stomach and intestines, and distributed throughout the body. At 3 hours after the last dose, the carcass contained 0.6-1.6% and the excreta (chiefly urine) 1.1-1.5% of the final dose of Acephate as Methamidophos. There was no tendency for Methamidophos to accumulate in blood, liver, muscle, fat and heart. Concentrations of Methamidophos in these tissues varied from 0.2 to 1.1 ppm. Highest concentrations of Methamidophos were found in kindeys (4.1-11.5 ppm), testes (2.4-3.9 ppm) and brain (2.1-2.5 ppm).

This study is classified as ACCEPTABLE-nonguideline. It provides information on the metabolism of Acephate by the rat, but does not satisfy (even partially) the guideline requirement for the metabolism studies (85-1).

In this metabolism study **(MRID 00014994)**, male and female Sprague-Dawley rats were intubated daily with nonradioactive Orthene (Acephate; analytical grade; 25 mg/kg) for 7 consecutive days. On day 8, the animals were dosed with radioactive Acephate (S-methyl-^{14}C-Orthene; purity: >99.5%; 25 mg/kg) and were sacrificed 3 days later.

Acephate was rapidly and completely absorbed from the stomach and was rapidly excreted in urine. About 87% and 95% of the administered radioactivity (^{14}C) was excreted, respectively,

during the first 6 and 12 hours after dosing. Most of the remaining ^{14}C was found in the exhaled air (probably CO_2; 1-4.5%), feces (1%) and tissues (0.4%). The ^{14}C found in urine was unchanged Acephate (O,S-dimethyl acetylphosphoramidothioate; 73-77%), DMPT (O,S-dimethyl phosphorothioate; 3-6%) and S-Methyl acetylphosphoramidothioate; 3-4%). Methamidophos (O,S-dimethyl phosphoramidothioate; ORTHO 9006) was not detected in urine, and the author concluded that Methamidophos was only a plant and soil metabolite of Acephate. Of the 0.4% ^{14}C recovered in tissues, most (0.13-0.26%) was in the liver and least (0.001-0.004%) in the brain. Male and female rats had the same excretion pattern.

This study is classified as ACCEPTABLE-nonguideline. It provides information on the metabolism of Acephate by the rat, but does not satisfy (even partially) the guideline requirement for the metabolism studies (85-1).

Not Yet Recorded in a Oneliner

In this 4-week inhalation toxicity study **(MRID 40504818)**, Acephate Technical (purity assumed to be 100%) was administered (whole body exposure) at 0 (house air only), 1.05, 10.8, and 93.6 mg/m^3 (MMAD: 1.57-2.25, 2.65-3.60 and 1.98-3.22 um, respectively; GSD: 1.79-3.28, 1.77-2.21 and 1.80-2.78, respectively) to Fischer 344 [CDF(F-344)/CrlBR] rats (25/sex/group for controls, 15/sex/group for low-dose, 10/sex/group for mid-dose, and 20/sex/group for high-dose). The main exposure period consisted of 21 six-hour exposures over a 30-day period (10 animals/sex/group). All animals were rinsed in tepid tap water after exposure, to reduce topical exposure to Acephate. Five animals/sex from control and low-dose groups received 12 exposures over a 16-day period, at which time they were sacrificed for determination of plasma, erythrocyte, and brain cholinesterase (ChE) activities. In addition, 10 animals/sex from control and high-dose groups were retained for 4 additional weeks after cessation of exposure (recovery group).

Rats were observed twice daily for mortality and moribundity. Modified physical examinations (for toxic and pharmacologic effects) were performed after removal from exposure chamber following each exposure. Animals were weighed and detailed physical examinations were performed weekly. Food consumption was determined twice weekly for the first two weeks and weekly thereafter. Ophthalmic examinations were preformed pre-test, during week 4 for all main study animals, and during week 8 for recovery animals. Plasma and erythrocyte ChE activities were determined pre-test and at day 16 (control and low-dose rats), day 17 (all groups from main study), at termination of main study, at test day 44 and at termination of recovery phase. Brain ChE activity was determined at day 16 (control and low-dose groups), at termination of main study, and at termination of

recovery phase (control and high-dose groups). Hematological and clinical chemistry parameters were measured at termination of the main study and at termination of recovery phase (control and high dose groups). All animals received gross necropsy at study termination. All main study animals from control and high-dose groups were examined histopathologically. In addition, gross lesions, nasal turbinates, trachea, lungs and eyes from low-dose and mid-dose groups (main study), and recovery phase animals were examined histopathologically.

At post-exposure observations, high-dose males and females exhibited tremors and increased secretory responses (data not provided). In addition, 2 high-dose females exhibited tremors, and 6 exhibited polypnea during clinical observations (no other groups demonstrated these findings). On ophthalmic examination, 7/10 high-dose females exhibited miosis at week 4, and 2/10 females in the recovery phase exhibited miosis at week 8. Although no males exhibited miosis at week 4, 2/10 had this response at week 8.

Body weights were significantly less for high-dose females than control females at several time points during the study; body weights for mid-dose females were significantly decreased at week 4 only. Body weight gains were significantly decreased for high-dose males and females during weeks 0-4. There were no significant differences in food consumption among groups. There were scattered significant changes in hematological and clinical chemistry parameters.

Brain ChE activity was significantly decreased in all treated animals at all time points, except for low-dose males at days 29-30 (range: 29-36% of controls for high-dose, 62-68% of controls for mid-dose, and 62-93% for low-dose during treatment; 83-84% of controls for high dose after 4 week recovery period). Plasma and erythrocyte ChE activities were significantly inhibited for mid- and high-dose groups for males and females during the treatment phase (62-90% of controls for mid-dose plasma, 29-68% of controls for high-dose plasma; 80-85% of controls for mid-dose erythrocyte, 27-33% of controls for high dose erythrocyte). Erythrocyte ChE activity was inhibited in low-dose males and females on day 16 only (88-89% of control levels). During the recovery phase, plasma ChE activity was significantly inhibited in high-dose males only at day 44 (89% of control levels); erythrocyte ChE activity was inhibited in high-dose males and females (82-84% of control levels) at day 44; neither plasma nor erythrocyte ChE activities remained inhibited at day 59 for either sex.

There were no treatment-related gross pathological findings. Histopathological examination demonstrated increased incidence of "induced exudate in the lumen, suppurative inflammation, individual cell necrosis, and regenerative epithelium of the

middle and posterior sections of nasal turbinate (nasal passages)" of high-dose males and females. After 4-week recovery period, histopathological findings included "reduced cellularity and intraepithelial cysts of the middle and posterior sections of nasal turbinates". No similar lesions were found in the mid-dose group.

Based on the results of this study (tremors, miosis, decreased body weight and weight gain, and histopathological findings), the systemic LOEL is 93.6 mg/m^3 (0.0936 mg/L) and the systemic NOEL is 10.8 mg/m^3 (0.0108 mg/L). The LOEL for the inhibition of plasma cholinesterase (ChE) activity is 10.8 mg/m^3 (0.0108 mg/L), with a NOEL of 1.05 mg/m^3 (0.00105 mg/L). The LOEL for the inhibition of erythrocyte and brain ChE activities was 1.05 mg/m^3 (0.00105 mg/L), with a NOEL less than 1.05 mg/m^3.

This study is classified as ACCEPTABLE-guideline when combined with range-finding (MRID 40504817) and satellite (MRID 40645903) studies and satisfies guideline requirements for a subchronic inhalation study in rat (82-4).

In this 4-week inhalation toxicity study **(MRID 40645903)**, Acephate (purity >99%) was administered (whole body exposure) at 0 (house air only), 0.187 and 0.507 mg/m^3 (MMAD: 2.84-3.59 and 2.43-3.14 um, respectively; GSD: 1.60-1.80 and 1.61-1.83, respectively) to Fischer 344 [CDF(F-344)/CrlBR] rats (10/sex/group). The main exposure period consisted of 21 six-hour exposures over a 30-day period (10 animals/sex/group). All animals were rinsed in tepid tap water after exposure, to reduce topical exposure to Acephate. Five animals/sex from control and low dose groups received 12 exposures over a 16-day period, at which time they were sacrificed for determination of plasma, erythrocyte, and brain cholinesterase (ChE) activities. In addition, 10 animals/sex from control and high dose groups were retained for 4 additional weeks after cessation of exposure (recovery group).

Rats were observed twice daily for mortality and moribundity. Animals were weighed and detailed physical examinations were performed weekly. Food consumption was determined weekly. Ophthalmic examinations were performed pre-test and during study week 4. Cholinesterase activities in brain, plasma and erythrocytes, and hematological and clinical chemistry parameters were determined at study termination (10 animals/sex/group). All animals received gross necropsy at termination. In addition, gross lesions, nasal turbinates, and lungs were examined histopathologically.

There was a slight, dose-related, increase in urine staining of the fur in treated females when compared to controls (maximum incidence was 2 animals in each of groups 2 and 3 during week 4).

In addition, two females in Group 3 demonstrated dyspnea during study week 2. The toxicological significance of these findings is questionable. There were no treatment-related changes in body weight, food consumption, clinical chemistry or hematology parameters, plasma, erythrocyte or brain ChE activities, or histopathology findings.

Based on the results of this study (lack of treatment-related effects), the systemic LOEL is >0.507 mg/m^3 (0.0005 mg/L; HDT) and the systemic NOEL is 0.507 mg/m^3. The LOEL for the inhibition cholinesterase activities in plasma, erythrocytes and brain is also >0.507 mg/m^3, with a NOEL of 0.507 mg/m^3.

This study is classified as ACCEPTABLE-guideline when combined with range-finding (MRID 40504817) and main (40504818) studies and satisfies guideline requirements for a subchronic inhalation study in rat (82-4).

In a developmental (teratology) study **(MRID 41081602)**, virgin female rats (Crl:CD®(SD)BR strain) received, by gavage, Acephate Technical (Purity: 99.7% a.i.; Lot No.: SX-1725) in deionized water from gestation days (g.d.) 6 through 15 and were sacrificed on g.d. 20. The doses used were 0, 5, 20 or 75 mg/kg/day.

The following findings were observed in the high-dose and mid-dose groups: **(1)** Decreased body weights and body weight gains (% of control for body weight gain): 47-84 during g.d. 6-16; 80-90 [uncorrected for gravid uterine weight] and 37-71 [corrected for gravid uterine weight] during g.d. 6-20; and 86-92 [uncorrected for gravid uterine weight] and 71-84 [corrected for gravid uterine weight] during g.d. 0-20; and **(2)** Decreased food consumption and food efficiency (% of control for food consumption): 73-92 during dosing; 81-93 during g.d. 6-20; and 87-96 during g.d. 0-20. Decreases in body weights, body weight gains and food consumption were statistically significant ($p \leq 0.01$); decreases in food efficiency were not analyzed statistically. There was also a statistically significant (≤ 0.01) increase in the number of rats with tremors and decreased motor activity in the high-dose group.

Developmental toxicity was noted in the high-dose group as slight decreases in the mean number of ossified caudal vertebrae, sternal centers, metacarpals, and the forelimb and hindlimb phalanges (with the hindlimb phalanges significantly reduced [$p<0.05$).

Based on reduced body weights, body weight gains, food consumption and food efficiency, the maternal toxicity LOEL is 20 mg/kg/day and the NOEL is 5 mg/kg/day. Based on decreases in mean numbers of ossification centers per litter, the developmental toxicity LOEL is 75 mg/kg/day and the NOEL is 20 mg

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/kg/day.

This study is classified as ACCEPTABLE-guideline and satisfies the guideline requirements for a developmental (teratology) study in the rat (83-3a).

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Chemical:	**Acephate**
PC Code:	**103301**
HED File Code	**13000 Tox Reviews**
Memo Date:	**03/24/1998**
File ID:	**TX012544**
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