ACEPHATE

RISK CHARACTERIZATION DOCUMENT

Medical Toxicology Branch

California Department of Pesticide Regulation

California Environmental Protection Agency

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List of Abbreviations

AADD	Annual Average Daily Dosage
AChE	Acetylcholine esterase
ADD	Absorbed Daily Dosage
ADI	Acceptable Daily Intake
BMD	Benchmark Dose
CDFA	California Department of Food and Agriculture
ChE	Cholinesterase
DPR	California Department of Pesticide Regulation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FOB	Functional Observational Battery
FQPA	Food Quality Protection Act
HDT	Highest Dose Tested
IL-1	Interleukin 1
IRED	Interim Reregistration Eligibility Decision
LDT	Lowest Dose Tested
LDH	Lactate Dehydrogenase
LOD	Limit of Detection
LOEL	Lowest Observed Effect Level
M/L/A	Mixer/Loader/Applicator
MOE	Margin of Exposure
MOS	Margin of Safety
MTD	Maximum Tolerated Dose
NOEL	No Observed Effect Level
PCO	Pest Control Operative
PMZ	Pesticide Management Zone
ppm	part per million
ppb	part per billion
RAC	Raw Agricultural Commodity
RBC	Red blood cell
RfD	Reference Dose
RT-PCR	Reverse transcriptase polymerase chain reaction
SADD	Seasonal Average Daily Dosage
SCE	Sister Chromatid Exchange
SD	Sprague-Dawley
TAS	Technical Assessment Systems, Inc.
TLC	Thin Layer Chromatography
TSCA	Toxic Substances Control Act.
UCL	Upper Confidence Limit
UDS	Unscheduled DNA Synthesis
UF	Uncertainty Factor
USDA	United States Department of Agriculture
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

I. SUMMARY

Introduction

Acephate (*O,S*-dimethyl acetylphosphoramidothioate) is a systemic insecticide with residual activity lasting *ca.* 10-15 days. It is effective against a wide range of insects and is not phytotoxic. As of May, 2007, there are 61 formulations registered in California. In addition to its uses on crops, principally lettuce, celery, peppers, cotton and beans, it has been used for residential purposes. Most of the latter uses were canceled by the registrants in 2001.

The environmental fate of acephate and degradation products have been extensively studied. The principal degradate of interest is methamidophos, a compound possessing high mammalian toxicity, which is used as an insecticide/acaricide in its own right. Because of acephate's rapid degradation in the field, it has little tendency to leach into groundwater.

The current Risk Characterization Document addresses potential human exposures from the California use of acephate as an active ingredient in insecticide formulations for treatment of a variety of crops. The potential dietary risk from the consumption of foods containing the highest legal residues of acephate is also assessed.

The Risk Assessment Process

The risk assessment process consists of four aspects: hazard identification, dose response assessment, exposure evaluation, and risk characterization.

Hazard identification entails an evaluation of the toxicological properties of each pesticide. The dose-response assessment then considers the chemical's toxicological properties and estimates the amount that could potentially cause an adverse effect. The largest amount that will not result in an observable or measured effect is called the No-Observed-Effect-Level, NOEL. A basic principle of toxicology is that at a high enough dose, virtually all substances will cause some type of toxic manifestation, although chemicals are often referred to as "dangerous" or "safe", as though these concepts were absolutes. In reality, these terms describe chemicals that require low or high doses, respectively, to cause toxic effects. Toxicological activity is determined in a battery of experimental studies which define the kinds of toxic effects that can be caused, and the exposure levels (doses) at which the toxic effect is first seen. State and federal testing requirements mandate that chemicals be tested at doses high enough to produce toxic effects, even if that testing requires dose levels many times higher than those to which people might be exposed.

In addition to the intrinsic toxicological activity of the pesticide, the other parameters critical to determining risk are the level, frequency and duration of exposure. The exposure assessment includes an estimation of the potential exposure through occupational and dietary routes on an acute (one-time) and chronic (long-term) basis. For potential occupational exposure, the levels of exposure are determined by measurement of acephate in air and skin absorption by people working with the pesticide. For potential dietary exposure, the levels of exposure are determined by the

amount of pesticide residue on specific commodities and processed food, and the consumption rate.

The risk characterization then relates the toxic effects observed in the laboratory studies, which are generally conducted with relatively high dosages of pesticides, to potential human exposures to low dosages of pesticides in the diet or work place. The potential for possible non-tumor adverse health effects in human populations is expressed as the margin of safety or exposure (MOE), which is the ratio of the dosage that produces no effect in laboratory studies to the estimated human dosage. For genotoxic carcinogens, the probability of risk is calculated as the product of the cancer potency of the pesticide and the estimated human dosage.

Toxic Effects in Animal Studies

In chronic toxicity studies conducted according to FIFRA guidelines, oncogenicity was assessed in the rat and mouse. In the former a significant increase in adrenal medullary adenomas/ carcinomas (combined) was observed at the top two dose levels (50 and 700 ppm) in males but not females. The vast majority were adenomas *i.e.* benign; there was no treatment-related increase in carcinoma incidence. It is possible that the MTD was exceeded at the HDT for male though not for female rats because the body weight was reduced by 18% ($p<0.01$) and 0.7% (n.s.) for males and females, respectively, compared with controls. In the mouse, females but not males at the HDT had a significantly increased incidence of hepatocellular carcinomas, without a significant effect on survival. There was evidence of toxicity to the liver in both sexes. In particular, there was a significant elevation of hyperplastic nodules in females ($p<0.001$), but not in males, at the HDT of 1000 ppm. It is possible that tumors in both species were secondary to excessive toxicity, based on body weight deficits, compared with controls, at the HDT of 18% (male rat) and 29% (female mouse), both $p<0.01$.

Based on the currently available data, DPR has concluded that the principal toxicological effect of acephate is an inhibition of ChE (plasma, RBC, brain). The lowest acute NOEL from an animal study is 0.5 mg/kg/d, for inhibition of brain AChE at the LOEL (2.5 mg/kg/d) in a rat neurotoxicity single oral gavage study. Plasma and RBC ChE inhibition had LOEL/NOEL values of 5 and 2.5 mg/kg/d, respectively. However, for the purposes of risk assessment, a human, oral capsule study is available. The NOEL for inhibition of plasma and RBC ChE in this study was 1.0 mg/kg/d. This NOEL was used for calculating acute MOE values. Following longer duration exposure, NOEL values of 0.12 mg/kg/d (rat) and 0.09 mg/kg/d (estimated, dog) were obtained, for the inhibition of brain AChE, in dietary studies lasting for 13-wks and 1-yr., respectively. These NOELs were used for the determination of seasonal and annual MOE values, respectively. Acephate has been examined for genotoxic effects in four types of assay: microbial gene mutation, mammalian gene mutation, mammalian chromosome assays and DNA damage/repair. It caused reverse mutations in one strain (TA100) of *S. typhimurium* in 5 of 5 experiments, with or without metabolic activation. It also caused an increased mutation frequency at the TK locus of mouse lymphoma cells *in vitro*, with or without metabolic activation. In both types of assay, acephate had a low potency compared with standard mutagens, but it did consistently show a dose-response. In a series of (6) *in vivo* studies indicative of chromosomal mutation, in the mouse and monkey, acephate gave no evidence of genotoxicity. There was mutagenicity and UDS in (2) strains of *S. cerevisiae* and in human fibroblasts *in vitro*, at relatively high concentrations, with or

without metabolic activation. Reports were reviewed according to TSCA guidelines. It is concluded that, although acephate is weakly genotoxic in isolated systems, its potential for causing genotoxicity in humans, *in vivo,* is limited.

The toxicity of acephate in a multi-generation rat reproduction study included reduced body weight and increased incidence of soft/liquid feces in male adults, at 500 ppm, the HDT. In offspring, there was a reduction in the number of pups/litter, without a significant reduction in litter weight, and reduced viability, at 500 ppm. Thus, the NOEL for reproductive and adult/parental toxicity was 50 ppm, equivalent to 2.8 mg/kg/d.

Developmental toxicity in the rat and rabbit was only recorded at doses that were maternally toxic and could thus be due to secondary effects. In the rat, the maternal NOEL was 5 mg/kg/d for reduced body weight, body weight gain and food intake; the developmental toxicity NOEL was 20 mg/kg/d for reduced mean live litter weight (4.7%) and increased incidence of a skeletal variation (13%). In a rat developmental neurotoxicity study, in which dams were dosed by daily, oral gavage during pregnancy and pups were also dosed by daily oral gavage during lactation, it was found that pups were not more sensitive than adults to the inhibition of brain AChE. In the rabbit, the maternal NOEL was 3 mg/kg/d for maternal toxicity, in the form of nasal discharge and abortion and there was no developmental toxicity, giving a NOEL of ≥10 mg/kg/d.

Occupational Exposure

The potential occupational exposure associated with the use of technical acephate in formulations used as insecticides was assessed for workers during mixing, loading, application and flagging activities; post-application scenarios were also addressed in the report of Zhao and Formoli, 2008. Estimated exposure for golf course and Home & Garden uses have also been estimated, even though many of these uses should have been cancelled in 2003 (RCD, Volume 2). The bulk of the exposure estimates were made using PHED. Estimates of acute ADD values during applications to food crops were 52 to 7580 μg/kg/d for the aerial M/L; 4.6 to 468 μg/kg/d for the ground A; 63.1 to 7490 μg/kg/d for the ground M/L; 8.3 to 1170 μg/kg/d for the ground M/L/A; for non-food crop applications, the acute ADDs ranged from 6.7 (F) to 11,100 (M/L) μg/kg/d for aerial applications and 31.6 to 2530 μg/kg/d (M/L) and 3.6 to 1170 μg/kg/d, for the ground A. For field workers the acute ADDs ranged from 0.8 (for succulent bean harvesting) to 162 μg/kg/d (for citrus pruning) and 433 μg/kg/d (for stone fruit thinning). For golf course pesticide handlers the acute ADDs were from 0.1 to 191 μg/kg/d (M/L). For Home & Garden uses, the range of acute ADDs was 1.3 to 516 μg/kg/d (M/L/A, fire ant PCO); 0.5 to 15.1 μg/kg/d for post-application on lawns and 0.22 to 1.00 μg/kg/d, for indoor uses of acephate. SADDs for agricultural workers on food crops ranged from 1.1 (ground A) to 1680 (aerial M/L) μg/kg/d; for non-food crop applications, SADDs were from 0.9 (ground A) to 306 (aerial A) μg/kg/d. For field workers the SADDs ranged from 0.1 to 68.3 μg/kg/d. Seasonal and annual ADDs were not estimated for golf course and residential exposure scenarios. AADDs for agricultural workers on food crops were from 0.5 (ground A) to 701 (aerial M/L) μg/kg/d; for non-food crop applications, AADDs were from 0.4 to 128 μg/kg/d (aerial A). For field workers the AADDs ranged from 0.03 to 28.5 μg/kg/d. The lowest margin of exposure or MOE (calculated as acute Human NOEL of 1 mg/kg/d / Estimated Human Exposure) for short-term exposure was <10 for at least one classification of worker in each category for food and non-food crops (aerial M/L, ground M/L, ground A, ground M/L/A for crop applications; aerial or ground M/L

and ground A on non-food crops), based on a 95th percentile of exposure. Indeed, for each category, except the ground A, the lowest MOE was below 1. MOE values for field workers were >10 except for citrus tree pruners, where the calculated MOE was 6. Similarly, for golf course applications, the MOE values were above 10, except for the M/L of a SP formulation, where the MOE was 5. For residential/institutional applications, the MOE values were above 10, except for the PCO treating fire ant mounds using a backpack sprayer (MOE=2) and for the use of a hose-end sprayer on ornamental or shade trees or hedges (MOE=6). Residential post-application and indoor uses gave MOE values ranging from 66 to 4,500. For seasonal exposure (the 90% upper bound C.L. of the acute ADD), the MOE values, based on an animal NOEL (0.12 mg/kg/d, in a rat subchronic study) was <100 for almost every type of application, with the exception of the a tractor-drawn A of a granular formulation on cotton (MOE=110) and a non-crop ground A of a SP on pasture (MOE=130). For field workers, the seasonal MOE values ranged from 2 (citrus tree pruning) to 1200 (succulent bean harvesting). Likewise for annual exposure (using AADD values), the MOE values, based on an animal NOEL (0.09 in a dog chronic study) was <100 for almost every type of application, with the exception of a tractor-drawn A of a granular formulation on cotton (MOE=130), the Flagger of an aerial application to pasture (MOE=130) and the ground boom A on pasture (MOE=230). For field workers, the MOE values ranged from 3 (citrus tree pruning) to 3000 (succulent bean harvesting). A MOE or margin of safety of >10 is generally considered adequate to protect human health whenever the NOEL is from a human study (acute MOE) and >100 whenever the NOEL is based on toxicology data from animal studies (seasonal and annual MOEs).

Dietary Exposure

Calculations conducted by DPR of dietary acute and chronic (annual) exposure used residue data or tolerances. Residue data were obtained primarily from the USDA/PDP program. The exposure has been calculated for all crops, combined, for which there are U.S. EPA. tolerances, using the DEEM® Monte Carlo program *i.e.* head lettuce, cotton, beans (all types), celery and peppers (all types), Brussel's sprouts, cottonseed, cranberry, macadamia nut, peanut, soybean, plus secondary residues in cattle, egg, goat, horse, pork, poultry, sheep. Short-term exposure at the 95th percentile ranged from 0.056 to 0.181 μg/kg/d, for females (13-19 yrs., not pregnant or nursing) and Seniors (55+ yrs.) at the low exposure end and Children (1-6 yrs.) at the high end. Exposure at the 99.9th percentile, the range was 1.063 to 2.427 μg/kg/d, for females (13 -19 yrs. not pregnant or nursing) and Infants (nursing), respectively. Potential chronic dietary exposure was also estimated at the annualized mean level of exposure to all commodities for which there are tolerances, and using percent of crop treated, giving a range of exposures from 0.01 to 0.045 μg/kg/d. Acute, tolerance level exposure at the 95th percentile was also estimated for the (3) main commodities treated with acephate that are consumed in California. These are head lettuce (tolerance 10 ppm), celery (10 ppm), beans (3 ppm). MOEs were 5,530 to 18,000 (95th percentile) and 410 to 910 (99.9th percentile) for acute dietary exposure and 1,980 to 9,090 for chronic exposure. For acute exposure at tolerance levels (95th percentile), the MOEs were as follows: head lettuce (29 - 252), celery (55 - 180), beans (25 – 195) These values are above those considered adequate to protect people from the toxic effects of a pesticide when the toxicity is from a human (MOE≥ 10, acute) or animal (MOE≥ 100, chronic) study.

Combined Exposure

For all conventional crop applications (food crop and non-food crop), for all occupational tasks involving acephate, the addition of estimated acute dietary exposure (0.116 μ, US population, 16+ yrs.) increases occupational exposure by <3%. However, for the following low-exposure tasks, the increases in occupational exposure after the addition of dietary exposure are >3%: for harvesting cauliflower, 1.6 to 1.7 μg/kg/d (6.3%), succulent beans, 0.8 to 0.9 μg/kg/d (13%); turfgrass or golfcourse mowing, 1.0 to 1.1 (10%) and 1.3 to 1.4 (7%) μg/kg/d, respectively and golfing, 0.1 to 0.2 μg/kg/d (100%). For Home & Garden applications, the addition of dietary exposure to that experienced during or after application was also <3%, with the exceptions of low exposure scenarios such as the use of a shaker cup on roses, 1.3 to 1.4 (7%) μg/kg/d, child grass ingestion after application to lawns, 0.5 to 0.6 (20%) μg/kg/d. All modeled indoor residential tasks, which were associated with low exposures, gave increases >3%. These included adult dermal (hard surface or carpet), 0.6 to 0.7 (17%) μg/kg/d; child dermal (hard surface or carpet), 1.0 to 1.1 (10%) μg/kg/d; child (hand-to-mouth), 0.22 to 0.32 (45%) μg/kg/d. Likewise, for estimated chronic dietary exposure (0.02μg/kg/d, US population, all seasons) added to occupational exposure, for the great majority of occupational tasks involving acephate, increased occupational exposure by <3%. However, for the following low exposure tasks, the increases in the AADD after the addition of chronic dietary exposure are: 0.40 to 0.42 (5%) μg/kg/d for the A of groundboom on pasture; 0.47 to 0.49 (4%) μg/kg/d for harvesting cauliflower; 0.03 to 0.05 (67%) μg/kg/d for harvesting succulent beans; 0.22 to 0.24 (9%) μg/kg/d for child hand-to-mouth exposure after indoor residential use.

The corresponding MOE values were generally decreased by <3%, with the exception of some low exposure scenarios: MOE from 625 to 590 (6%) and 1200 to 1100 (8%) for harvesting cauliflower and succulent beans, respectively; from 1,000 to 910 (9%) for turfgrass or 770 to 710 (8%) for golf course mowing; from 10,000 to 5,000 (50%) for golfing. For Home & Garden applications, the decrease in MOE with the addition of dietary exposure was also <3%, except for low exposure scenarios such as the use of a shaker cup on roses, 770 to 710 (8%), child grass ingestion after application to lawns, 2000 to 1700 (18%). All modeled indoor residential tasks, which were associated with low exposures, gave decreases in MOE >3%. These included adult dermal (hard surface or carpet), 1700 to 1400 (21%); child dermal (hard surface or carpet), 1000 to 910 (9%); child (hand-to-mouth), 4500 to 3100 (45%). Likewise, for estimated chronic dietary exposure (0.02μg/kg-d, US population, all seasons) added to occupational exposure, for the great majority of occupational tasks involving acephate, increased occupational exposure by <3%. However, for the following low exposure tasks, the increases in the AADD/decreases in MOE after the addition of chronic dietary exposure were: 230 to 210 (9%) for the A of groundboom on pasture; 190 to 180 (5%) for harvesting cauliflower; 3000 to 1800 (40%) for harvesting succulent beans.

II. INTRODUCTION

A. CHEMICAL IDENTIFICATION

Acephate (*O,S*-dimethyl acetylphosphoramidothioate) is a broad spectrum insecticide with both systemic and contact activity. It is an organophosphate which was originally discovered and developed by Chevron Chemical Company but is now marketed by Valent, under the name Orthene.™ It is registered on a variety of crops for the control of various pests. In California, the main applications are on lettuce, celery, cotton and beans (various types). It is currently also registered for use on golf courses and sod farms; it is not currently registered for home and garden uses. It is inactive against acetylcholinesterase (AChE) but is readily de-acetylated in insects (and to a lesser extent in mammals) to methamidophos (*O,S*-dimethyl phosphoramidothioate), which is an inhibitor of AChE.

B. REGULATORY HISTORY

During the SB 950 study evaluation, possible adverse effects were identified in chronic, oncogenicity and mutagenicity studies. Low NOEL values also presented a concern for risk assessment.

On Feb. 2, 2000, U.S. EPA established NOEL values for risk assessment of 0.5 mg/kg/d (from a rat neurotoxicity study) for acute dietary exposure and 0.12 mg/kg/d (from a 13-week rat study) for chronic dietary exposure. The endpoint of brain AChE inhibition was common to both studies. Other NOEL values used by USEPA for risk assessment were: 12 mg/kg/d from a 21-day rat dermal toxicity study for short and intermediate-term dermal exposure risks in occupational and residential settings; 0.14 mg/kg/d (based on 0.5 μg/L) from a 4-week rat inhalation toxicity study for assessing risks of similar duration from inhalation exposure.

In October, 2001, the principal registrant, Valent, requested that USEPA cancel all residential indoor and outdoor uses, with the exception of golf courses, sod farms and harvester and fire ant control (spot or mound). Valent also requested the cancellation of one acephate product registered under Section 3 (of FIFRA) and 8 products under Section 24(c), special local needs. The timing of these withdrawals was such that it was anticipated that Manufacturing Use Products would be depleted by October 31, 2002 and End Use Products would be depleted by December 31, 2002 (USEPA, 2001).

Similar requests for deletions of labeled uses were received from three other registrants of technical acephate: Drexel Chemical Co, United Phosphorus, Inc. and Micro Flo Company, LLC. The other (3) end use product registrants also made similar requests for cancellation: Whitmire Micro-Gen Research Labs, The Scotts Company and Pursell Technologies, Inc. In January 2002, USEPA issued an interim risk management decision for acephate whereby it was agreed, that by reducing home and garden exposure, the remaining acephate residues (aggregate) in the diet (food and water) did not pose risk concerns. Acephate was considered not to exceed but instead, to fit into its own “risk cup.” It was also established that occupational exposure and ecological risks were below USEPA’s levels of concern. However, it was also pointed out that this was an interim risk management decision. A cumulative risk assessment was currently being conducted for the organophosphate insecticides as a group by USEPA and, when

completed, this could require additional risk mitigation measures to be implemented for acephate. In particular, under FQPA (1996), exposure to acephate was to be combined with exposure to methamidophos. A further cancellation, for grass (pasture and rangeland) was agreed by USEPA in 2002 (Fed. Reg., 2002). Tolerances for residues of acephate in RACs (40CFR 180-108) have been expressed in terms of combined residues of acephate and methamidophos.

In August 2007, USEPA announced proposed rule changes affecting certain tolerances (Fed. Reg., 2007). It was announced that for tolerances on beans (succulent and dry forms), Brussels sprouts, cauliflower, celery, cranberry, lettuce, mint hay and pepper, that "acephate per se" was the (sole) residue of concern. Furthermore, a footnote was to be added to dietary risk assessments for acephate, stating that "Residues of the acephate metabolite, methamidophos, are regulated under 40CFR 180.315." This is an intriguing policy change by USEPA because none of these RACs currently has a tolerance for methamidophos. Therefore, any such (methamidophos) residues on any of these crops would make their sale illegal!

C. TECHNICAL and PRODUCT FORMULATIONS

There are 59 products containing acephate registered in California. Some of these are commercial formulations but they also include several Home & Garden ones. The formulations comprise a mixture of liquid and granular types, with a large range of percentage of active ingredient.

D. USAGE

Acephate use in the past six years in California has been declining, from 283,000 lb./annum (active ingredient) in 2000 to 194,000 lb/annum in 2005. The major uses are listed in Table 1. The main crops are lettuce, cotton, beans (various) and celery. Other non-crop uses include landscape, nurseries and structural pests.

Table 1 Major usage of acephate (a.i.) in California, 2000-2005.[1/,2/]

CROP	2000		2001		2002		2003		2004		2005	
	LB.	AC.	LB.	AC.	LB.	AC.	LB.	AC.	LB.	AC.	LB.	AC.
Beans, various	56.5	62.7	29.0	36.8	24.9	29.1	20.8	24.3	8.7	10.3	11.3	12.4
Celery	19.0	21.4	19.2	21.8	56.4	18.2	14.7	16.8	17.0	19.0	14.1	15.6
Cotton	66.4	61.7	55.7	52.3	39.8	34.2	54.8	51.6	54.8	52.0	51.6	47.4
Landscape	8.4	N/A	4.5	N/A	5.0	N/A	4.5	N/A	6.5	N/A	4.2	N/A
Lettuce	98.6	112	95.8	111	98.4	116	81.5	96.0	82.9	95.3	71.9	83.0
Flowers, Greenhouse	1.4	1.6	4.6	4.4	4.0	3.0	3.9	2.7	4.0	2.9	3.5	2.5
Flowers, Outdoors	3.2	6.9	15.2	23.5	14.8	20.2	11.7	15.7	14.0	19.1	14.7	20.1
Peppers, all	7.9	9.7	8.7	10.8	5.9	6.9	6.4	7.6	5.3	7.1	5.9	7.9
Structural pest Control	4.5	N/A	4.6	N/A	6.2	N/A	20.6	N/A	5.7	N/A	11.5	N/A
Uncultivated non-ag uses, all	0.004	N/A	0.06	N/A	0.000	N/A	0.02	N/A	0	N/A	0	N/A
TOTAL LBS.	283		240		259		224		205		194	

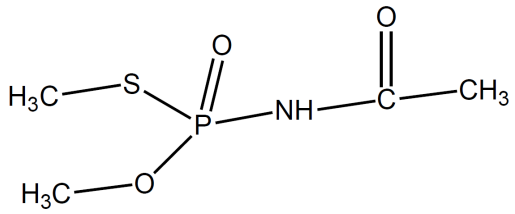
1/ DPR PUR 2001 to 2006; all numbers for lbs and acres are in 1000s.
2/ Crops accounting for ≥5,000 lbs./annum in any year quoted, plus other uses, are included.

E. ILLNESS REPORTS

There are fewer cases of reported illnesses associated with acephate than with many other organophosphate and carbamate insecticides (Volume 2). Over the period 1996-2000, there were 70 cases reported in California (Calvert *et al.*, 2001) but only 15 of these involved acephate alone. Most of the illness cases were field workers (residue and drift) and ingestion (accidental or deliberate) rather than from mixing/loading/applying acephate. The number of cases of definite/probable and possible systemic illnesses arising from acephate exposure in California, is as follows: 1 definite/probable plus 1 possible in 2000, 3 definite/probable plus 2 possible in 2001, 1 definite/probable in 2002, none in 2003, 1 definite/probable in 2004 and none in 2005. There were no topical cases (eye and skin effects, but excluding cholinergic signs) attributed to acephate (www.cdpr.ca.gov/docs/whs) in any of the years.

F. PHYSICAL/CHEMICALPROPERTIES

1. Common Name: Acephate (EPA,1987)
2. Chemical name: O,S-dimethyl N-acetylphosphoramidothioate (EPA, 1987)
3. Trade Names: Orthene; Ortho 12420 (Merck, 1989)
4. CAS Registry No: 30560-19-1 (Merck, 1989)
5. Molecular Weight: 183.16 (Chevron, 1972a)
6. Structural Formula



(Chevron, 1972a)

7. Empirical Formula: $C_4H_{10}NO_3PS$ (Merck, 1989)
8. Physical State: white solid
9. Density: 1.35 g/cm^3 (Chevron, 1972a)
10. Melting Point: 92 - 93 ºC (Chevron, 1972a)
11. Solubility: water: 700 mg/mL
    methylene chloride: 515 mg/mL; ethyl alcohol: 340 mg/mL
    acetone: 151 mg/mL; ethyl acetate: 34.7 mg/mL
    benzene: 15.7 mg/mL; toluene: 6.8 mg/mL
    ether: 6.1 mg/mL; hexane: 0.1 mg/mL (Chevron, 1972a)
12. Vapor Pressure: 1.7 x 10^{-6} mmHg at 23 - 25ºC (Chevron, 1972a)
13. Henry's Law Constant: 5.85 x 10^{-13} atm m^3 mol^{-1} at 25ºC (Chevron, 1972a)
14. log K_{OW}: –0.89, K_{OW}: 0.13 at 25ºC (Chevron, 1972a)

15 Types of Formulations: granular, pressurized liquid, soluble concentrates (both liquids and solids), and cartridge (EPA, 1987).

G. ENVIRONMENTAL FATE

Summary: Acephate is hydrolyzed to the degradates DMPT (O,S-dimethyl phosphorothioate) and RE 17,245 (S-methyl acetylphosphoramidothioate). It does not undergo photolysis. Soil microorganisms rapidly degrade acephate under both aerobic and anaerobic conditions. The products of this are RE 18,420 (O-methyl N-acetylphosphoramidate), methamidophos, and DMPT. Acephate's metabolites are very weakly adsorbed to the soil. They will be readily leached but will be quickly degraded in the soil. Acephate will not volatilize in any significant quantity to cause air contamination. Plants readily degrade acephate to methamidophos and DMPT. Its rapid degradation makes acephate non-threatening to groundwater or surface water. Metabolic pathways are summarized in Figure 1. Acephate and methamidophos do not have any measurable effect on soil microorganisms.

Hydrolysis

The hydrolysis rates of acephate were measured at various pH ranges. At pH 5 to 7, the $t_{1/2}$ was 50 days at 21ºC and 20 days at 40ºC. At pH 3 and 9, the $t_{1/2}$ was 65 and 16 days respectively, at 21ºC. Thus, acephate is more stable in acidic conditions and less stable in alkaline conditions (Chevron, 1972b).

The products of the hydrolysis of acephate were studied using ^{14}C- acephate in 0.25 N HCl, phosphate buffer (pH 7) and 0.02 N NaOH, at 40ºC. In both acid and base, it was hydrolyzed by cleavage of the P—N bond to O,S-dimethyl phosphorothioate (DMPT). At pH 7, S-methyl acetylphosphoramidothioate (RE 17,245) was formed (Chevron, 1972c).

Szeto *et al.* (1979) also measured the effect of pH on acephate hydrolysis. At pH 4.0 to 6.9, there was no significant difference in hydrolysis rate at 20ºC compared to 30ºC. At pH 6.9, less than 20% of the initial acephate was hydrolyzed in 20 days. At pH 8.2, the hydrolysis rate was affected by temperature. The remaining acephate at 20ºC was 77.9%, while at 30ºC there was only 17.8% remaining.

Photolysis

Acephate does not undergo photolysis. When acephate is in water or adsorbed onto glass or paper, it is stable to sunlight. Experiments have shown that acephate samples exposed to sunlight and those that are kept in the dark exhibit essentially the same degree of stability (Chevron, 1972d).

Soil Metabolism

Acephate is rapidly degraded in soil by microorganisms under aerobic and anaerobic conditions, the $t_{1/2}$ ranging from 0.5 to 3 days. The soil types in this experiment included loamy sand, sandy clay, silty clay loam, loam, and clay (Chevron, 1972e and 1972f). The same products were formed under both aerobic and anaerobic conditions: O,S-dimethyl phosphoramidothioate (methamidophos) and O-methyl N-acetylphosphor-amidate (RE 18,420) (Chevron, 1972g and 1972h).

According to EPA, 1987, acephate dissipates rapidly with $t_{1/2}$ values of less than 3 and 6 days in aerobic and anaerobic soils, respectively. The major, terminal metabolite was CO_2 in both soil types. The leaching data included a soil TLC and a soil column study. The data indicate that acephate is mobile in most soils; however, aged acephate

residues are immobile in sandy loam soil. Most of the applied (^{14}C) acephate and the degradate methamidophos become immobile in 20 days (EPA, 1987).

Field Dissipation

The leaching potential was studied by using ^{14}C-labeled acephate. It was applied to Oakley sandy loam at 2 ppm and incubated for 20 days. The treated soil was then placed on top of 12 inch columns of the same soil and leached with a ½ inch of water daily for 46 days. Leachates were analyzed for radioactivity. The analyses showed that 14 to 18% of the applied acephate remained in the treated soil after the 20-day incubation period (Chevron, 1972i). Only 0.27% of the ^{14}C was recovered in the leachates during the 46 days. Since acephate and its metabolite methamidophos are water-soluble and freely move in the soil, the findings indicate that neither chemical remained in significant quantities at the time leaching was initiated. Following leaching, residual ^{14}C was found to be almost entirely in the top 3 inches of the soil column. Only 1.1% of this was extractable with acetone during 2 hours in a soxhlet extractor, a method known to remove acephate and methamidophos from soil. This indicates that the residual ^{14}C is neither of the two chemicals but has probably been incorporated into the soil organic matter by soil microorganisms (Chevron, 1972i).

There was found to be no difference in the rate of acephate leaching in soil moistened to its field capacity or air-dried soil. In both cases, the acephate moves readily with water. Acephate and its soil metabolite, methamidophos, were degraded three times faster in soil moistened to its field capacity than in air-dried soil (Chevron, 1972j).

Soil Adsorption

The adsorption coefficients of acephate, methamidophos, and DMPT were studied. The Freundlich soil adsorption/desorption coefficient (K_d) and the K_{OC} (adsorption based on organic carbon) were determined in five soils: sand, sandy loam, clay loam, silty loam, and clay, at 0.1, 0.2, 0.5, and 1 µg/g dry weight soil. Acephate had a $K_d \leq 0.090$ and a $K_{OC} \leq 2.73$. Methamidophos had a $K_d \leq 0.29$ and a $K_{OC} \leq 0.88$. DMPT's K_d was ≤ 0.30 with a $K_{OC} \leq 0.91$ (Chevron, 1988b). All three chemicals are very weakly adsorbed by soil. They have a high leaching potential, but they also degrade rapidly (Chevron, 1973).

Mobility

Soil

In a greenhouse, mobility of acephate in soil was measured, as follows: soil samples were sprayed with acephate at 9 lbs./A. and aged, undisturbed except for watering for 21 weeks. At this time, the soil contained ≤ 0.05 ppm acephate. No methamidophos was detected. The acephate level was about 0.5% of the applied dose. This remaining acephate was entirely leachable with the equivalent of 10 inches of rain. There was no bound acephate or methamidophos present in the soil (Chevron, 1973).

Water:

Hydrolysis of acephate is very slow, depending on pH and temperatures, being hydrolyzed more quickly at basic pH. Photodegradation of acephate is also very slow. Acephate is very water soluble and also rapidly degraded in soil (Chevron, 1973). Szeto *et al.* studied the mobility of acephate in water. Acephate remained more in solution than partitioned into sediments. After 2 days in a pond and 7 days in a creek, only 20%

of the applied acephate was in the bottom sediments. This is due to the high water solubility of acephate. It was also demonstrated that acephate did not volatilize from water because of its high water solubility (Szeto et al, 1979).

Air:

Acephate is not expected to contaminate the air and should not pose any vapor hazard to animals including humans. It was calculated, from the vapor pressure, that at ambient temperatures the concentration of acephate in saturated air would be only 0.02 mg/m^3 or 0.002 ppm (Chevron, #54161).

Plant Metabolism

Acephate (^{14}C) is readily degraded by plants, as is evident from both field and greenhouse studies. The $t_{1/2}$ was 5 to 10 days. Only about 5 to 10% of acephate degraded to methamidophos (O,S-dimethyl phosphoramidothioate), the remainder resulting in innocuous salts. No metabolites of toxicological concern have been observed or suspected, except for methamidophos. Possible degradation products of acephate and methamidophos are those in which the P—N, P—O, and/or P—S bonds are broken yielding P—OH acids. Conversion of any of these bonds to the P—OH group is sufficient to detoxify these compounds completely (Chevron, #54161).

Acephate is adsorbed onto leaf surfaces. Washing of field-treated broccoli, lettuce, and cotton leaves with water removed $\leq$ 5% of the acephate residues. Translocation studies using ^{14}C-labeled acephate in potatoes and sugar beets have shown that there is only slight movement from the treated leaf to other parts of the plant, including roots and tubers (Chevron, #54161).

Groundwater Monitoring

Acephate moves readily in soil with water giving it the potential to contaminate ground water. However, because of its rapid degradation in soil it is not expected that it would exist long enough in the soil to have enough time to move into the ground water (Chevron, #54161).

An experiment was conducted in Florida to determine acephate's potential to move into groundwater. This was done in extreme conditions where the rainfall was heavy and the soil was porous sand. Lettuce was sprayed several times with 1 lb./acre acephate. Three months later the same plot was treated at 3 lbs./acre (three times the recommended label rate). The amount of acephate in water at one foot varied from 0 to 2 ppm, with highest amount found on the 3 lb. treatment 0 to 4 hours after application. The degradation product of acephate, methamidophos, was only detected at a maximum of 0.06 ppm. Acephate was detected in the soil but at shallow depth, maximum occurring in the 6 to 12 inch sample. Traces of methamidophos were found in that sample also. No acephate or methamidophos was detected in any sample of water or soil at 2 ½ feet or deeper. This held true even after 7 treatments and 12 inches of rain (Chevron, #54161).

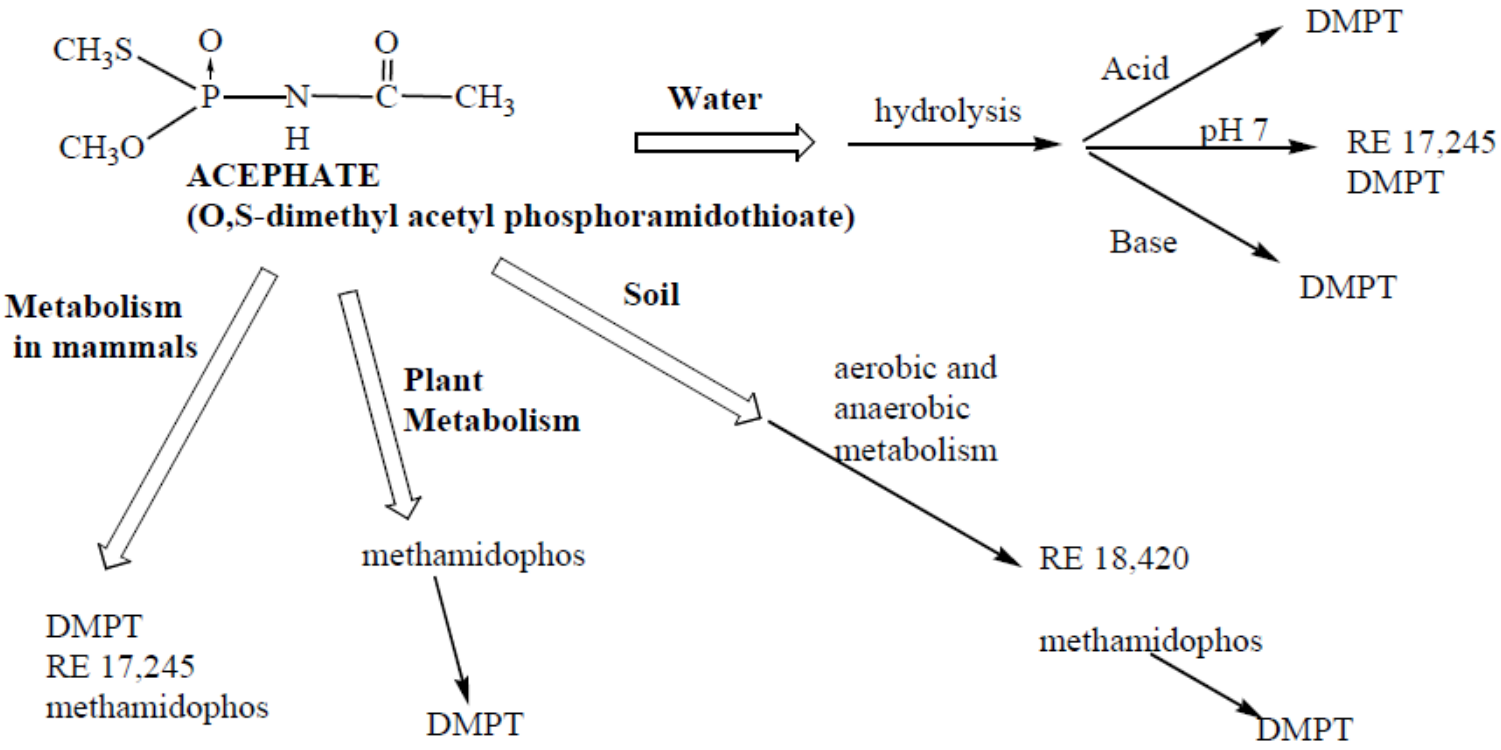
Yen, *et al*, 2000, using the behavior assessment model (BAM) and the groundwater potential model (GWP) assessed the contamination of groundwater by acephate and methamidophos. Acephate was found to have a longer half-life than methamidophos in soil as well as having greater mobility in two soil types than methamidophos. Acephate

may therefore lead to greater contamination of groundwater than methamidophos, under equivalent conditions.

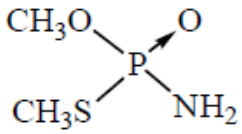
Surface Water Monitoring

Acephate is not intended for use directly in bodies of water (ponds or lakes). It could become a contaminant from runoff or accidental spills. An experiment was done to determine the acephate residues in water. Several ponds were treated with acephate at 0.1 ppm. Residues in the water decreased below 0.1 ppm within a week. The residue was undetectable in 6 weeks. There was no methamidophos detected. It is thus concluded that even if a body of water was contaminated, within a short time no residues would remain either in the water or in the mud or vegetation (Chevron, #54161).

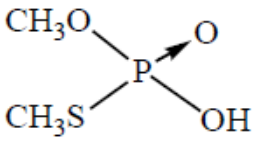
Figure 1. Degradation of Acephate



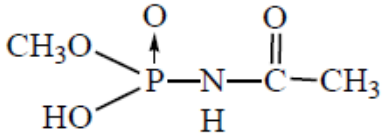
methamidophos
(O,S-dimethyl phosphoramidothioate)



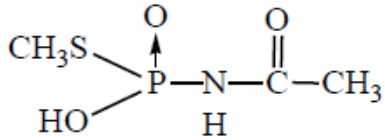
DMPT
(O,S-dimethyl phosphorothioate)



RE 18,240
(O-methyl N-acetyl phosphoramidate)



RE 17,245
(S-methyl N-acetyl phosphoramidothioate)



III. TOXICOLOGY PROFILE

A. PHARMACOKINETICS

Summary: ^{14}C-acephate studies were conducted on mammals to determine the nature of the metabolites. In rat urine, over 90% of the orally administered ^{14}C was acephate. The remainder comprised metabolites: 3-6% was DMPT and 3-4% was *S*-methyl acetyl phosphoramidothioate and *ca.*1% was methamidophos (Figure 1). There was no methamidophos found in milk. In birds there was a small amount of methamidophos in feces and traces in eggs. Neither acephate nor its metabolite methamidophos bioconcentrated in any organism tested from simple organisms to mammals and birds. Humans absorbed, metabolized and excreted acephate in a similar way to the rat, with little opportunity to bioaccumulate. It is considered that absorption following oral dosing is essentially complete.

Oral-Rat

Three rats per sex were given S-methyl ^{14}C-acephate by oral gavage, following pre-conditioning doses of 25 mg/kg/d for 7 successive days (Chevron, 1972k). Most of the excretion of ^{14}C occurred within the first 12 h and *ca.* 95% of the recovered label was acephate, in the urine. Recovery, over 72 h, was 88 to 100%. Two minor biotransformation products were identified as DMPT (Fig. 1) *O,S*-dimethyl phosphorothioate (3 – 6%) and RE 17,245 (Fig. 1) *S*-Me-acetylphosphoramidothioate (3 – 4%). In addition, a small amount (1 - 4.5%) was identified as $^{14}CO_2$ in exhaled air. The amount of ^{14}C in feces was *ca.*1% and at 72 h, following sacrifice, ^{14}C in tissues was measured at *ca.*0.4%. No methamidophos was found in this study. Because only 1% of ^{14}C was found in feces, it can be assumed that acephate is completely absorbed into the blood following oral administration.

Oral-Human

Acephate was given to groups of human volunteers in oral capsule form, at levels of 0.35, 0.7, 1.0 and 1.25 mg/kg/d (M) and a single group at 1.0 mg/kg/d (F) (Freestone & McFarlane, 2001). The study involved monitoring urine and blood at time intervals of 0, 1, 2, 4, 8, 12, 24, 48 and 72 h, since dosing. A small amount of the acephate was isolated as methamidophos in blood or urine (1 - 2%). Blood plasma concentrations of acephate peaked at 2 to 2.7 h after dosing and clearance from the blood had a relatively short $t_{1/2}$ of 4.3 to 6.6 h (Tozer, 2000). In a computer modeling exercise it was concluded that, because of its rapid clearance, chronic (daily) exposure to acephate would not result in any further accumulation of acephate or methamidophos (Tozer, 2000). The inhibition of plasma and RBC AChE in this experiment are described in Section III.K.

B. ACUTE TOXICITY

Summary: studies were conducted on mammals to determine the acute toxicity of acephate: it was determined to be Category III for oral, dermal, inhalation and eye irritation and Category IV for dermal irritation. Skin sensitization was considered negative. The results are summarized in Table 2.

Table 2. The acute toxicity of technical acephate

Route/species	Sex	Dose/effect	Ref.
Oral LD_{50}			
Rat	M	945 (720-1240) mg/kg/d	Chevron, 1970a
	F	866 (500-1490) mg/kg/d	Chevron, 1970a
Rat	M	1400 (670-2800) mg/kg/d	Chevron, 1979a
	F	1000 (490-2100) mg/kg/d	Chevron, 1979a
Mouse	M/F	362±36.7 (S.D.) mg/kg/d	Chevron, 1970b
Dog, beagle	M/F	681 mg/kg/d MLD	Chevron, 1970c
Dermal LD_{50}			
Rabbit	M	>2000 mg/kg/d (0% mort.)	Chevron, 1970d
Rabbit	M	>10,000 mg/kg/d (0% mort.)	Chevron, 1977a
Rabbit	M/F	>2000 mg/kg/d (0% mort.)	Chevron, 1980
Inhalation LD_{50}			
Rat	M/F	>1.81 mg/L (0% mort.)	Bio-Test, 1972
Eye Irritation			
Rabbit	unknown	no corneal opacity or iritis	Chevron, 1971a
Rabbit	unknown	no corneal opacity or iritis	Chevron, 1971b
		75S form. Grade 1 iritis, grade 4 chemosis	Chevron, 1971b
Dermal Irritation			
Rabbit	unknown	no edema; grade 2 erythema in intact skin	Chevron, 1979b
Skin sensitization			
Rabbit	M	no sensitization	Chevron, 1970e
Guinea pig	unknown	no sensitization	Chevron, 1971c

C. SUBCHRONIC TOXICITY

Summary:

The two rat subchronic studies using acephate are described in Section III.I, Neurotoxicity.

D. CHRONIC TOXICITY AND ONCOGENICITY

Summary: In acceptable studies, the chronic toxicity of acephate has been studied in the rat, mouse and dog. In none of these species were there any clinical signs. There was a fall in body weight in the rat and mouse but not in the dog, without a significant reduction in food intake. The inhibition of ChE, in plasma, erythrocyte (RBC) and brain was measured in the rat and dog. In both species, brain AChE was inhibited more than the plasma or RBC enzyme. In the rat, inhibition of brain AChE was from 66% to 83% at 700 ppm, in both sexes, with a NOEL of 5 ppm at 22 months, equivalent to 0.24 mg/kg/d. At 28 months, however, significant inhibition (9 – 11%) of brain AChE was reported in this study at 5 ppm. In the dog, inhibition of brain AChE ranged from 66% at 800 ppm, to 11% (F) to 17%(M) at 10 ppm, for both sexes. Because the inhibition in males at 10 ppm (0.27) was significantly different from controls ($p<0.05$), this is considered the LOEL, giving an estimated NOEL of 0.09 mg/kg/d (NOEL=LOEL/3). An uncertainty factor of 3 is supported by benchmark dose calculations. This estimated NOEL was used to calculate MOEs for annual occupational and dietary exposure. Oncogenicity was assessed in the rat and mouse. In the former a significant increase in adrenal medullary adenomas/ carcinomas (combined) was observed at the top two dose levels (50 and 700 ppm) in males but not females. The vast majority were adenomas; there was no treatment-related increase in adenocarcinoma incidence. In the mouse, females but not males at the HDT had a significantly increased incidence of hepatocellular tumors. There was evidence of toxicity to the liver in both sexes. It is possible that tumors in both species were secondary to excessive toxicity. Effects and chronic NOEL are summarized in Table 8.

Dietary-Rat

Acephate (92.4% purity, lot SX-992) was fed in the diet to SD rats (80/sex/group) for 28 months, at 0, 5, 50 or 700 ppm, equivalent to 0, 0.24, 2.44 or 38.2 mg/kg/d for males and 0, 0.31, 3.06 or 47.2 mg/kg/d for females (Biodynamics, 1981). Interim sacrifices were conducted at 4 and 12 months on 10 rats/sex/dose and on 4 or 5 rats/sex/dose at 22 months. Reduced group mean body weights (4 - 18%) were reported at 700 ppm in males, although food intake was higher (5 - 18%). Females consumed more food than controls (4 - 24%) at 700 ppm, but body weight was not significantly affected. Transient effects on body weight and food intake were observed at 5 and 50 ppm. Sporadic changes in relative organ weight were likely a result of body weight changes since there were no changes in absolute organ weights. No clinical signs were exhibited by any rats during the study.

Brain AChE was inhibited in both sexes at all (4) sampling times at 50 and 700 ppm ($p<0.01$), but only occasionally at 5 ppm (Table 3). At 700 ppm, this enzyme was inhibited by 69 to 77% below concurrent controls for males and by 66 to 83% for females. At 50 ppm, the equivalent figures were 35 to 43% (males) and 33 to 45% (females). At 5 ppm however, the inhibition of brain AChE was sporadic and only occasionally significant *e.g.* by 11% for males ($p<0.01$) and by 9% ($p<0.05$) for females at 28 months but by 0% and 0.9% at 22 months. The NOEL was, therefore, 5 ppm, equivalent to 0.24 mg. Two other ChE enzymes, which serve as markers of exposure to OPs, blood plasma ChE and RBC ChE, were also evaluated. Inhibition of plasma ChE was less marked than was brain AChE: at 700 ppm, it was inhibited by 21 to 50% compared to controls for males and 52 to 68% for females; at 50 ppm, inhibition was 17 to 29% (males) and 0 to 36% (females); at 5 ppm, inhibition was 0% for males and 0 to 19% for females. RBC ChE was also inhibited less than brain AChE: at 700 ppm, inhibition was 21 - 57% (males) and 37 - 58% (females); at 50 ppm, inhibition was 0 - 26% (males) and 10 - 42% (females); at 5 ppm, inhibition was 0 - 22% (males) and 0 - 29% (females).

Table 3. Mean inhibition of cholinesterase by acephate in the SD rat at 7, 12, 22 and 28 months (% reduction *vs.* control)[1/]

Time/ChE assay		0	5	50	700 ppm
7 months					
Blood plasma:					
(μmol/ml/min)	M	1.7±0.6	1.7±0.8 (-)	1.2±0.3 (29)	1.0±0.2 (41)
	F	3.1±0.4	2.5±0.3 (19)	2.0±0.8* (36)	1.0±0.5** (68)
RBC:	M	3.4±1.1	3.6±1.0 (-)	2.8±1.2 (18)	2.0±1.1 (41)
(μmol/ml/min)	F	3.8±1.9	2.7±0.3 (29)	2.2±0.7 (42)	1.6±0.5* (58)
Brain:	M	15.6±0.9	14.2±0.7* (9.0)	10.2±0.9** (35)	3.6±0.5** (77)
(μmol/g/min)	F	14.0±0.7	12.2±2.7 (13)	7.7±0.5** (45)	2.4±0.2** (83)
12 months					
Blood plasma:					
	M	1.4±0.4	1.4±0.3 (-)	1.1±0.4 (21)	1.1±0.2 (21)
	F	3.1±0.5	3.1±0.7 (-)	2.6±0.3 (16)	1.3±0.2** (58)
RBC:	M	3.2±1.1	2.5±0.4 (22)	2.8±0.7 (12)	1.6±0.5** (50)
	F	2.9±0.6	2.8±0.5 (3.5)	2.6±0.6 (10)	1.8±0.5** (38)
Brain:	M	12.1±1.2	10.5±1.0** (13)	7.1±1.2** (41)	3.6±0.5** (70)
	F	11.9±1.1	11.3±0.5 (5.0)	8.0±1.1** (33)	3.5±0.5** (70)
22 months					
Blood plasma:					
	M	1.7±0.2	1.9±0.5 (+12)	1.3±0.2 (24)	1.2±0.2 (29)
	F	2.7±0.5	2.7±0.8 (-)	2.8±0.2 (+3.7)	1.3±0.4** (52)
RBC:	M	2.8±0.4	3.3±0.8 (+18)	3.1±0.7 (+11)	2.2±0.5 (21)
	F	2.7±0.4	2.8±0.5 (+3.7)	2.2±0.3 (19)	1.7±0.5* (37)
Brain:	M	10.8±0.5	10.8±0.7 (-)	6.2±0.5** (43)	3.4±0.3** (69)
	F	10.8±0.6	10.7±0.5 (0.9)	6.5±0.4** (40)	3.7±1.6** (66)
28 months					
Blood plasma:					
	M	1.2±0.3	1.6±0.6* (+33)	1.0±0.2 (17)	0.6±0.1** (50)
	F	2.1±0.5	1.9±0.4 (9.5)	1.5±0.3** (29)	0.9±0.1** (57)
RBC:	M	2.3±0.5	2.4±0.6 (+4.4)	1.7±0.6* (26)	1.0±0.2** (57)
	F	2.4±0.5	2.3±0.4 (4.2)	1.9±0.2** (21)	1.3±0.2** (46)
Brain:	M	10.8±0.8	9.6±0.6** (11)	6.5±1.0** (40)	3.1±0.5** (71)
	F	10.8±0.4	9.8±0.6* (9.3)	6.8±1.2** (37)	3.3±0.4** (69)

1/ data from Biodynamics, 1981.
* significantly different from control at $p<0.05$ (Dunnett's test)
** significantly different from control at $p<0.01$ (Dunnett's test)

Oncogenicity was also evaluated in this study. An elevated incidence of adrenal medullary adenomas, and to a lesser extent, carcinomas, was reported in males. A less clear-cut increase in the incidence of adrenal cortical tumors was also observed. Table 4A gives the incidence of these tumors in rats at terminal sacrifice (28 months) combined with unscheduled deaths and 22 month sacrifice animals. No such increase was observed for female rats (Table 4B).

Table 4A. Incidence of tumors in male rat adrenal gland(s) after acephate[a/]

Tumor type	0	5	50	700 PPM
Medullary[b/]	2/55 (3.6%)	7/55 (13%)	11/52** (1) (21%)	9/54* (1) (17%)
Cortical[b/]	7/55 (13%)	10/55 (1) (19%)	15/55* (1) (27%)	9/54 (1) (17%)

a/ data from Biodynamics,1981: unscheduled deaths, 22- and 28-mon. sacrifice
b/ includes adenoma and carcinoma (in parenthesis), unilateral and bilateral
* significantly different from control @ $p<0.05$ (Fisher's exact test)
** significantly different from control @ $p<0.01$ (Fisher's exact test)
no significant trend using the Cochran-Armitage test.

Table 4B. Incidence of tumors in female rat adrenal gland after acephate[a/]

Tumor type	0	5	50	700 PPM
Medullary[b/]	2/56 (3.6%)	0/55 (0%)	1/51 (2.0%)	1/55 (1.8%)
Cortical[b/]	11/56 (1) (20%)	11/55 (1) (20%)	11/51 (22%)	14/55 (27%)

a/ data from Biodynamics,1981: unscheduled deaths, 22- and 28-mon. sacrifice
b/ includes adenoma and carcinoma (in parenthesis), unilateral and bilateral
no significant trend using the Cochran-Armitage test.

Because of the appearance of these tumors late in life, it is considered appropriate to exclude rats sacrificed at earlier time intervals from consideration. The study authors considered the medullary tumors not to be compound-related but rather, to be the result of low control incidence. The authors quoted other rat chronic studies conducted at Biodynamics over the same period, which showed adrenal medullary tumors of 0.9%, 2.6%, 6.0%, 7.1% and 15.0%. These compared with 2/75 or 2.7% (for males) in the study described above.[1/] The study authors also quote literature reports on the "spontaneous" incidence of male rat adrenal medullary tumors: 1.1%, 2.0%, 5.8%, 11.6%, 15.6% and 20.3% (Chen, 1980); 1.7% and 5.0% (Mackenzie *et al.*, 1973) and 5.9% (Cohen *et al.*, 1978). Taken together, nine batches of control rats had a higher incidence of these tumors and five had a lower incidence than the concurrent controls in the Biodynamics, 1981 study. It is therefore difficult to agree with the authors' theory about low control incidence. It is, however, possible that the MTD was exceeded for males (mean body weight was reduced by 18%, $p<0.01$, at 700 ppm, at 22 months), though not for females (mean body weight was reduced by 0.7%, N.S., at 700 ppm, at 22 months). Because the tumors were benign, did not show a clear monotonic increase with dose and because they may have been secondary to general toxicity, rather than have been a result of genotoxicity, they were not subjected to a quantitative assessment.

[1/] Biodynamics included rats sacrificed at earlier time points, thus giving a larger denominator than DPR and a lower apparent incidence (2.7% *vs.* 3.6%).

Dietary-Mouse

Acephate technical (92.7% and 92.1% purity) was fed to CD1 mice (75/sex/level) at dietary levels of 0, 50, 250 or 1000 ppm (7, 36 or 146 mg/kg/d, males, and 8, 42 or 167 mg/kg/d, females) in a 104-week study (IRDC, 1982). An interim sacrifice was conducted at 52 weeks on 10 mice/sex/dose. The inhibition of AChE (or ChE) was not measured in this study. Group mean body weights, for both sexes, were similar for controls and 50 ppm mice at most time intervals measured; at 250 ppm, group mean body weights for males were similar to controls through week 13, and for females through week 39, before becoming consistently lower ($p<0.05$ or $p<0.01$) at all subsequent weighing times; at 1000 ppm, group mean body weights were depressed significantly ($p<0.01$), in both sexes, at all intervals analyzed. The terminal body weight data are summarized in Table 5.

Table 5. Group mean body weights in CD-1 mice; dietary acephate for 104 weeks.[1/]

endpoint/dose	0	50	250	1000 PPM
Group mean, M body wt. (g)	38	37 (2.6%)	34** (11%)	29** (24%)
Group mean, F body wt. (g)	35	33 (5.7%)	30** (14%)	25** (29%)

1/ data from IRDC,1982.

A decrease in food consumption probably accounts for most of this reduction in body weight: at 1000 ppm, after 104 weeks, males reduced their food intake by 18% and females by 22%, compared with concurrent controls. At 250 ppm, both sexes reduced their food intake by 7.8% and at 50 ppm, food intake was unaffeted by acephate administration. These numbers are similar to the lower body weight reported (Table 5). Toxicity to the lung included “pigmented alveolar macrophages” and “eosinophilic foreign bodies,” at all dose levels, in both sexes. Survival at 104 wks. for males was longer at 250 ppm (72%, $p<0.05$) and 1000 ppm (72%, $p<0.05$) than control (52%); for females, survival at 1000 ppm was 55% (n.s.) vs. 51% for control.

Oncogencity was assessed through a full histopathological examination. There was an increased incidence of hepatic tumors (principally carcinomas) at the HDT for females (Table 6B). This was associated with hepatic toxicity, which was also most marked at 1000 ppm, but was often found also at 250 ppm. However, for males, there was not an increased incidence of hepatic tumors, although measures of hepatic toxicity (Table 6A) indicated similar effects to those found in females, with the exception of an increased incidence of hyperplastic nodules, found only in females. Because these tumors, along with the other markers for hepatic toxicity, were found only in the second year of the study, interim (12-month) sacrifice animals were excluded from the incidence Tables (6A and 6B). Since females at 1000 ppm experienced a large (29%) decrease in group mean body weight (Table 5) it appears that the MTD may have been exceeded, making these tumors of limited relevance for risk assessment purposes.

Table 6A. Acephate hepatic toxicity in male CD1 mice: 2-yr. diet study[1/]

Endpoint\Dose	0	50	250	1000 PPM
Hepatocellular Tumors[2/]	4/65 (4)[3/] (6.2%)	3/65 (2) (4.6%)	4/65 (3) (6.2%)	4/65 (3) (6.2%)
Hyperplastic nodules	12/65 (18%)	7/65 (11%)	3/65 (4.6%)	13/65 (20%)
Hepatocyte hypertrophy	0/65 (0%)	0/65 (0%)	9/65** (14%)	55/65*** (85%)
Intracellular inclusion bods.	0/65 (0%)	0/65 (0%)	13/65*** (20%)	57/65*** (88%)
Mononuclear cell foci	9/65 (14%)	20/65* (31%)	19/65* (29%)	42/65*** (65%)
Karyomegaly	0/65 (0%)	4/65 (6.2%)	17/65*** (26%)	43/65*** (66%)

*/ **/ *** significantly different from control @ p<0.05, p<0.01, p<0.001 (Fisher's exact test)
1/ data from IRDC,1982: unscheduled deaths + terminal sacrifice
2/ includes adenoma and carcinoma, unilateral and bilateral
3/ number of carcinomas in parenthesis.

Table 6B. Acephate hepatic toxicity in female CD1 mice: 2-yr. diet study[1/]

Endpoint\Dose	0	50	250	1000 PPM
Hepatocellular Tumors[2/]	1/65 (1)[3/ +++] (1.5%)	3/64 (1) (4.7%)	0/64 (0) (0%)	15/66*** (12) (23%)
hyperplastic nodules	2/65 (3.1%)	1/65 (1.5%)	0/64 (0%)	17/66*** (26%)
hepatocyte hypertrophy	0/65 (0%)	0/65 (0%)	12/64*** (19%)	45/66*** (68%)
intracellular inclusion bodies	0/65 (0%)	0/65 (0%)	6/64* (9.4%)	31/66*** (47%)
mononuclear cell foci	19/65 (29%)	26/65 (40%)	23/64 (36%)	48/66*** (73%)
karyomegaly	0/65 (0%)	0/65 (0%)	12/64*** (19%)	38/66*** (58%)

1/ data from IRDC,1982: unscheduled deaths + terminal sacrifice
2/ includes adenoma and carcinoma, unilateral and bilateral
3/ number of carcinomas in parenthesis.
*/ *** significantly different from control @ p<0.05, p<0.001 (Fisher's exact test)
+++ significant trend @ p<0.001 (Cochran-Armitage test).

Dietary-Dog

In a one-year dietary study, acephate (99.9% purity) was administered to beagle dogs (5/sex/level) in the feed at 0, 10, 120,[2] or 800 ppm (Hazleton, 1991). These doses are equivalent to composite mean values of 0.27, 3.11 and 20.16 mg/kg/d during the entire study. No treatment-related clinical signs were recorded. The activity of plasma ChE was not reduced significantly at any dose level or time point (Table 7); at 800 ppm, inhibition compared with concurrent controls was only 7.2% (M) or 11% (F). However,

[2]/ the mid-dose started as 200 ppm, but was lowered to 120 ppm during week 2.

RBC ChE was inhibited by 85% (F) to 86% (M) at 800 ppm and by 43% (M) to 47% (F) at 120 ppm, both $p<0.05$. At 10 ppm, ChE in RBCs was not significantly affected. Brain AChE was inhibited ($p<0.05$) at the two highest doses, in both sexes, by 66% at 800 ppm and 49% (F) to 53% (M) at 120 ppm (Table 7). There was significant inhibition of brain AChE ($p<0.05$) in male (17%) but not in female (11%) beagles at 10 ppm (Table 7). Because of the inhibition of brain AChE at 10 ppm, (or 0.27 mg/kg/d) this is considered the LOEL for chronic toxicity. An estimated NOEL for this effect (LOEL/3) is 0.09 mg/kg/d (see Section IV.A).

There was little change in body weight for either sex (Table 7). Mean absolute liver weight was increased at 800 ppm by 28% (M) or 17% (F). Relative to brain weight,[3] liver weight was increased by 21% (M) and 11% (F) at 800 ppm. No other organ weights were markedly affected by acephate. The clinical hematology data indicated a dose-related increase in APTT (activated partial thromboplastin time), in both sexes, which was significantly elevated ($p<0.05$) only for males, at 120 and 800 ppm at 26 weeks and at 800 ppm at 52 weeks. The length of the APTT was increased by 13% and 96% for males, at 120 ppm and 800 ppm respectively, at 26 weeks, and by 8.7% and 42% at these doses respectively, at 52 weeks (Table 7). The corresponding increases in APTT for females were 0% and 40% at 26 weeks and 3.4% and 36% at 52 weeks (n.s.). There was not a corresponding increase in plasma prothrombin time, or PT, (data not shown) nor was there a reduction in the levels of platelets in the blood. There was a dose-related reduction in erythrocyte (RBC) count, which reached significance ($p<0,05$) only in males. The decrease at 26 weeks was from 10% to 17% and at 52 weeks, from 8.8% to 20%. For females, the corresponding figures were 5.5% to 21%, at 26 weeks, and 4.4% to 7.6% at 52 weeks (Table 7). At 800 ppm, the effect was observed at each of the (5) sampling times, from 4 weeks onwards, for males but not females.

The accumulation of ACh at the vagal nerve terminals in the heart would normally be expected, in a severe case, to result in hypovolemic hypotension with stasis, which would increase the possibility of thrombosis (Ruben *et al.*, 1992), rather than cause a delay in clotting, as observed with acephate. The toxicological significance of the clinical hematology findings is thus unclear.

[3]/ Brain weight increased by 4.6% (M) to 6.9% (F) at 800 ppm compared with controls.

Table 7. Mean inhibition of cholinesterase, organ weight and hematology data: effects of acephate in the beagle dog, 1-yr. diet study[1/]

ChE Assay	0	10	120	800 ppm
Blood plasma				
M	---	6.7%	13%	7.2%
F	---	6.2%	9.4%	11%
RBC				
M	---	8.2%	43% *	86% *
F	---	16%	47% *	85% *
Brain				
M	---	17% *	53% *	66% *
F	---	11%	49% *	66% *
mean body wt. (kg) M	11.6±0.86	12.1±1.22(4.3%↑)	11.8±1.70(1.7%↑)	13.2±1.54(14%↑)
F	10.0±1.74	10.2±1.63(2.0%↑)	9.3±1.99 (7.0%↓)	10.6±1.19(6.0%↑)
mean liver wt. (g) M	279±44	277±30 (0.7%↓)	285±40 (2.2%↑)	358±79 (28%↑)
F	268±22	268±58 (0%)	212±33 (21%↓)	313±29 (17%↑)
liver:brain wt. M	3.9±0.8	3.6±0.5 (7.7%↓)	3.7±0.4 (5.1%↓)	4.7±0.6 (21%↑)
F	3.6±0.3	3.7±0.7 (2.8%↑)	3.0±0.6 (17%↓)	4.0±0.4 (11%↑)
APTT (sec.)				
M (26 wk.)	10.3±0.5	10.3±0.6 (0%)	11.6±1.1* (13%↑)	20.2±5.9* (96%↑)
M (52 wk.)	10.4±0.9	10.0±0.5 (3.9%↓)	11.3±1.1 (8.7%↑)	14.8±1.9* (42%↑)
F (26 wk.)	13.6±4.3	11.2±0.8 (18%↓)	11.5±1.6 (15%↓)	19.1±5.6 (40%↑)
F (52 wk.)	11.8±1.8	11.6±2.3 (1.7%↓)	12.2±0.4 (3.4%↑)	16.0±6.8 (36%↑)
RBC (MI/UL)				
M (26 wk.)	6.75±0.23	6.07±0.30*(10%↓)	6.08±0.34*(9.9%↓)	5.58±0.43*(17%↓)
M (52 wk.)	7.03±0.56	6.41±0.35(8.8%↓)	6.26±0.35*(11%↓)	5.60±0.32*(20%↓)
F (26 wk.)	7.10±0.65	6.71±1.02(5.5%↓)	6.30±0.95(11%↓)	5.60±0.86(21%↓)
F (52 wk.)	6.42±0.90	6.14±1.0(4.4%↓)	6.12±0.80(4.7%↓)	5.93±0.47(7.6%↓)

1/ data from Hazleton, 1991; % inhibition of ChE *vs*. controls.
* different from control, $p<0.05$ (Dunnett's test, raw data).

Table 8. Summary of chronic effects caused by acephate.

CHRONIC TOXICITY & ONCOGENICITY

Species/Route		Effect	LOEL/NOEL (mg/kg/d)		Ref.[a/]
Rat	oral	Clinical signs	-----	47.2	1[b/]
2-yr.	diet	Body wt. M	38.2	2.44	
		ChE inhibition (plasma, RBC, brain)	2.44[c/]	0.24	
		Increased incidence of adrenal medullary adenomas/carcinomas in males at 2.44 and 38.2 mg/kg/d.			
Mouse	oral	Clinical signs	----	146	2[b/]
2-yr.	diet	Body wt. M	36	7	
		Hepatic toxicity, M and F	36	7	
		Increased incidence of hepatocellular carcinomas/adenomas in females at 167 mg/kg/d.			
Dog	oral	clinical signs	-----	20.2	3[b/]
1-yr.	diet	Body wt.	----	20.2	
		ChE inhibition (plasma, RBC, brain)	0.27[d/]	0.09[e]	

a/ References: 1. Biodynamics, 1981; 2. IRDC, 1982; 3. Hazleton, 1991
b/ study acceptable to DPR, according to FIFRA guidelines.
c/ inhibition of ChE was 29% (M) - 36% (F), plasma; 26%(M) - 42%(F), RBC and 43% (M) - 45% (F), brain.
d/ inhibition of ChE was 17%(M) - 11%(F) for brain AChE.
e/ estimated NOEL (LOEL/3); critical NOEL used for chronic risk assessment.

E. GENOTOXICITY

Summary: Acephate has been examined for genotoxic effects in four types of assay: microbial gene mutation, mammalian gene mutation, mammalian chromosome assays and DNA damage/repair. It caused reverse mutations in one strain (TA100) of *S. typhimurium* in 5 of 5 experiments, with or without metabolic activation. It also caused an increased mutation frequency at the TK locus of mouse lymphoma cells *in vitro*, with or without metabolic activation. In both types of assay, acephate had a low potency compared with standard mutagens, but it did consistently show a dose-response. In a series of (6) *in vivo* studies indicative of chromosomal mutation, in the mouse and monkey, acephate gave no evidence of genotoxicity. There was mutagenicity and UDS in (2) strains of *S. cerevisiae* and in human fibroblasts *in vitro*, at relatively high concentrations, with or without metabolic activation. Reports were reviewed according to TSCA guidelines. Genotoxicity tests with acephate are summarized in Table 9. The impurity methylthioacetate was negative in microbial gene mutation, rat chromosomal aberration and mouse micronucleus assays. It is concluded that, although acephate is weakly genotoxic in isolated systems, its potential for causing genotoxicity in humans, *in vivo,* is limited.

Gene Mutation

Acephate (92.4% purity) was tested at 1 to 10,000 μg/plate on *Salmonella typhimurium* strains TA98, TA100 and TA1537 with and without S-9 rat liver homogenate activation (Chevron, 1977b). The rate of reversion of these histidine auxotrophic strains was measured. A weak positive response was detected for TA100, with or without metabolic activation (S-9). This strain detects base-pair substitution mutations and is recognized as sensitive to various types of mutagens. The magnitude of the effect was not large, but showed a dose-response. The report was acceptable to DPR.

In another study, acephate (93.5% purity) was tested at 1 to 10,000 μg/plate on *S. typhimurium* on strains TA98, TA100, TA1535, TA1537, TA1538 and on *E. coli*, with and without S-9 rat liver homogenate activation (SRI, 1979a). It was weakly mutagenic in one strain, TA100, at concentrations 2.5 mg/plate, with or without S-9. Acephate also increased mitotic recombination in D3 of *S. cerevisiae* without S-9 (at 1-5%) and induced UDS in WI-38 (at 100 μg/ml), without S-9. The report was considered unacceptable to DPR and probably not upgradeable.

Acephate (purity unstated) was tested at 0 and five concentrations, from 1,000 to *ca*. 40,000 μg/plate on *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and on *E. coli,* with and without S-9 from rat liver (Inst. Environ. Toxicol., 1982). A positive dose-response was noted for the TA100 strain, but only at concentrations above 5,000 μg /plate and for *E. coli* (WP2 *hcr*), with or without S-9. Because no data were given and there was no verification of the dosing solutions, the study was unacceptable to DPR.

The effects of six batches of acephate (Lot No. SX-911, -941, -978, -984, -986 and -988) were tested against *S. typhimurium* strain TA100 in one trial at 0 to 50 mg/plate, without S-9 metabolic activation (Chevron, 1982a). All batches were considered weakly mutagenic. The report was considered unacceptable to DPR and was not upgradeable.

The effects of eight batches of acephate (Lot No. SX-257, -284, -357, -911, -941, -976, -978 and -979) were tested against *Salmonella typhimurium* strains TA98, TA100 and TA1537 in one trial at 0 to 50 mg/plate, without S-9 metabolic activation (Chevron, 1982b). Seven of the (8) lots were considered weakly mutagenic in TA100. The report was considered unacceptable to DPR and was not upgradeable.

The effect of acephate (unstated purity) at 10 ppm in the diet was studied in a sex-linked recessive lethal assay in *Drosophila melanogaster* (WARF, 1981b). No genotoxic effects were reported. The report was considered unacceptable to DPR.

Mammalian Systems

Acephate (93.5% purity, SX-734) was tested on mouse lymphoma cells at 10 concentrations between 1000 and 5000 μg/ml, with and without rat liver S-9 metabolic activation (SRI, 1980a). The mutation frequency at the TK locus was increased dose-dependently at 1000 to 5000 μg/ml without S-9 and at 2000 to 5000 μg/ml, with S-9 mix. The study was unacceptable because of the inadequate characterization of the dosing solutions.

Acephate (98.7% purity, SX-1102) was tested on mouse lymphoma cells at 5 concentrations between 2429 and 5000 μg/ml, with and without rat liver S-9 metabolic activation (Microbiol. Assoc., 1982a). There were duplicate cultures per dose level, a 4-hr. exposure time and a 48-h. expression time. The mutation frequency was increased dose-dependently at all dose levels, with and without S-9 mix. The study was acceptable to DPR.

Acephate (93.5% purity, SX-762) was tested on mouse lymphoma cells at 5 concentrations between 2429 and 5000 μg/ml, with and without rat liver S-9 metabolic activation (Microbiol. Assoc., 1982b). The experiment was identical to Microbiol. Assoc., 1982a, above, except that a different batch of acephate was used. The mutation frequency was increased dose-dependently at the TK locus at all dose levels, with and without S-9 mix. The study was acceptable to DPR.

Acephate (98.7% purity, SX-1102) did not induce somatic cell mutations in mouse fetuses following dietary administration to dams at 0, 50, 200, 600 or 800 ppm on days 8 to 12 of gestation (Hazleton, 1986). Pups were examined for recessive coat spots on days 14 and 28 of lactation, but no increase was observed. Although the positive control was acceptable and dams at the two highest doses displayed cholinergic signs, there was no evidence that fetuses were exposed to acephate and the report was unacceptable to DPR.

Chromosome Mutation

The monkey, *Macaca fascicularis,* was dosed with acephate (98.7% purity, SX-1102) at 0 or 2.5 mg/kg/d by gavage for 20 days (LSR, 1983). SCE and chromosome aberrations were measured in peripheral lymphocytes. Although ChE inhibition was reported, no genotoxic effects were detected. The study was rejected by DPR because of a lack of data.

In a micronucleus assay, acephate (96.6% purity, SX-734) was administered by gavage (2x over 24 hr.) to male mice at 0, 75, 150 or 300 mg/kg/d, 24/group (SRI, 1980b). Mice were sampled at 48, 72 and 96 hr. (8/sacrifice time) and 500 PCEs (polychromatic erythrocytes) were evaluated for each animal. There were no genotoxic effects but the report was rejected by DPR because there were no females, too few PCEs evaluated and poor animal husbandry.

In a dominant lethal assay, acephate (99% purity, SX-1102) was fed in the diet at levels of 0, 50, 500 and 1000 ppm for 5 days to 12 male mice mated with 190 female CD-1 mice per group over 8 wks. at 2/wk/male (Chevron, 1982c). There were no dominant lethal effects and the report was acceptable to DPR.

In a cytogenetics assay, Swiss white mice were given acephate by oral gavage at 0, 11.2, 37.3 or 112 mg/kg/d (EG&G Mason, 1982). There were cholinergic signs at the HDT (ataxia, inactivity, eye exudate) but bone marrow showed no signs of genotoxicity. The report was acceptable to DPR.

In a SCE assay, acephate (99% purity, SX-1102) was given by oral gavage at 0, 29 or 96 mg/kg/d to CD-1 mice, five per sex per dose (Litton, 1983). Bone marrow was examined for SCE activity and none was found using acephate, although positive controls were adequate. The report was rejected by DPR because of a lack of individual data and because the doses used were unjustified and probably too low.

The effects of acephate (93.5% purity, SX-734) was tested for SCEs in CHO cells at 0, 125, 250, 500, 1000 or 2000 μg/ml for 21.5 hr, without rat S-9 mix and at 0, 312.5, 625, 1250, 2500 or 5000 μg/ml for 2 hr., with rat S-9 mix (SRI, 1980c). Increased SCEs were found at 500 μg/ml without S-9 and at 5000 μg/ml, with S-9. The report was acceptable to DPR.

DNA Damage/Repair

Four strains of *S. typhimurium* were tested for genotoxicity using acephate (93.5% purity, SX-734) at 0, 1 or 5 mg/disc (SRI, 1981). Two platings per dose level and two trials per dose were run but none included a metabolic activation (S-9) system, resulting in a rejection of the report by DPR. No adverse effects were reported in the first trial but SL 4525 (*rec*+) and SL 4700 (*rec*-) gave differential growth in the second trial whereas TA 1978 and TA1538 were negative in both trials.

Using strains of *E. coli* (W3110/p3478) and of *B. subtilis* (H17/M45), acephate (93.5%, SC-7562) was examined in a spot test at 0.01, 0.1, 1.0 or 5.0 mg/disc/plate (SRI, 1979b). No adverse effects were found but, because the study lacked both replicates and repetition, it was rejected by DPR.

S. cerevisiae (D3) was tested for genotoxicity and UDS in a mitotic recombination assay using acephate (93.5% purity, SX-7562) at 0, 0.1, 0.5, 1.0 or 5.0% (trial 1) and at 1, 2, 4 or 5% (trial 2) (SRI, 1979c). Positive results were obtained, with or without rat liver S-9 mix, at $\geq$1%. However, the study was rejected by DPR because of a lack of dose justification and individual data and also because of the use of DMSO as a solvent.

S. cerevisiae (D7) was tested in mitotic crossing over, gene conversion and reverse mutation assays using acephate (93.5% purity, SX-734) at 0, 1, 2, 3, 4 or 5% (trial 1) and at 3, 3.5, 4, 4.5 or 5% (trial 2) (SRI, 1980d). Positive results were obtained, in mitotic crossing over and reverse mutation assays, with rat liver S-9 mix, at 2% and in increased frequency of gene conversion at 1%. In the absence of rat S-9 mix, acephate gave positive results in all (3) assays, at all doses. However, the study was rejected by DPR because of a lack of dose justification and individual data.

Acephate (93.5% purity, SX-734) was tested for its ability to induce UDS in human fibroblasts (WI-38) at 0.1 to 4000 μg/ml (SRI, 1979d). A slight increase in UDS was reported at concentrations ≥1000 μg/ml. The study was acceptable to DPR.

Impurity: Methylthioacetate

Methylthioacetate (98.2% purity, SX-1732) was tested at 100 to 10,000 μg/plate on *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538, triplicate plates, with and without S-9 mix and repeated (Microbiol. Assoc.,1987). There was no increase in revertants, at any dose. The study was considered supplemental by DPR.

A rat bone marrow assay was used to examine chromosome aberrations caused by methylthioacetate (98.2% purity, SX-1732) (Hazleton, 1987). F-344 rats (5/sex/group) were exposed to vapors at 400, 600 or 800 ppm for 6 hr./day for 4 successive days and sacrificed at 19 hr. post-dosing. Fifty cells/rat were scored for clastogenicity. No such effects were observed although clinical signs were noted at all dose levels including 80% mortality at 800 ppm. The study was considered a supplemental, pilot study by DPR.

Micronuclei formation was measured using Swiss mouse bone marrow erythrocytes following inhalation of methylthioacetate (99.2% purity, SX-1763) at 445, 651 or 796 ppm (measured) for 4 hrs. (Chevron, 1988a). Mice (5/sex/group) were sacrificed at 24, 48 or 72 hrs. after commencing dosing and PCEs were determined in 1000 cells per mouse. No adverse chromosomal effects were detected although 33% mortality was found at 796 ppm and all animals showed treatment-related lung lesions. The study was judged supplemental by DPR.

Table 9. Summary of genotoxicity tests with acephate.

Gene Mutation

Test	Route	Dose	Results	Reference
S. typhimurium/ ±S9	*in vitro*	1-10,000 μg/plate	TA98 neg. ±S9 TA100 weak pos. ±S9 (2x) TA1537 neg. ±S9	Chevron, 1977b[a/]
S. typhimurium/ ±S9 *E. coli* WP2 *S. cerevisiae* D3	*in vitro*	1-10,000 μg/plate	TA98, 1535, 1537, 1538 neg. ±S9 TA100 weak pos. ±S9 UDS pos. -S9 mitotic recombination pos. -S9	SRI, 1979a[b/]
S. typhimurium/ ±S9 *E. coli,* WP2*hcr*	*in vitro*	0-50 mg/plate	TA98, 1535, 1537, 1538 neg. ±S9 TA100 weak pos. ±S9 UDS pos. ±S9	*Inst. Environ. Toxicol.,* 1982[d/]
S. typhimurium/ ±S9	*in vitro*	0-50 mg/plate	TA100 weak pos. - 6 lots of acephate	Chevron, 1982a[b/]
S. typhimurium/ ±S9	*in vitro*	0-50 mg/plate	TA100 weak pos. - 7 of 8 lots of acephate	Chevron, 1982b[b/]
Drosophila melanogaster	*in vitro*	10 ppm, diet	no effects	WARF, 1981[b/]

Mammalian Gene Mutation

Test	Route	Dose	Results	Reference
Mouse lymphoma ±S9	*in vitro*	1,000-5,000 μg/ml	pos. @ TK locus, ±S9	SRI, 1980a[c/]
Mouse lymphoma ±S9	*in vitro*	2,429-5,000 μg/ml	dose-dep. increase in mutn. frequency, ±S9	Microbiol. Assoc., 1982a[a/]
Mouse lymphoma ±S9	*in vitro*	2,429-5,000 μg/ml	dose-dep. increase in mutn. frequency @TK locus, ±S9	Microbiol. Assoc., 1982b[a/]
Mouse somatic cell	*in vivo*	50-800 ppm, diet	neg. - no increase in recessive coat spots in litters	Hazleton, 1986[b/]

a/ study acceptable to DPR, according to TSCA guidelines.
b/ study unacceptable and not upgradeable.
c/ study unacceptable and upgradeable;
d/ literature publication

Table 9. **continued**

Chromosome Mutation

Test	Route	Dose	Results	Reference
Monkey *(Macaca fascicularis)* lymphocytes	*in vivo* gavage	2.5 mg/kg/d for 20 days	SCE and chromosome aberrations – neg.	LSR, 1983[b/]
Mouse, micronucleus	*in vivo* gavage	75 – 300 mg/kg/d x2	PCEs - neg.	SRI, 1980b[c/]
Mouse, dominant lethal assay	*in vivo* diet	50 – 1000 ppm	neg.	Chevron, 1982c[a/]
Mouse, bone marrow Marrow cytogenetics	*in vivo* gavage	11.2 - 112 mg/kg/d	neg.	Mason and Mason, 1982a[a/]
Mouse, bone marrow SCE	*in vivo*	29-96 mg/kg/d	neg.	Litton, 1983[b/]
SCE in CHO cells	*in vitro*	125-2000 μg/ml w/o S9 312-5000 μg/ml w/ S9	pos. at 500 μg/ml w/o S9 pos. at 5000 μg/ml w/ S9	SRI, 1980c[a/]

DNA Damage/Repair

Test	Route	Dose	Results	Reference
S. typhimurium	*in vitro*	1, 5 mg/disc (2x)	SL4525 differential growth SL4700 differential growth TA1978 negative TA1538 negative	SRI, 1981[b/]
E coli and *B. subtilis* Genotoxicity	*in vitro*	0.01-5 mg/disc	*E coli* W3110/p3478 – neg. *B. subtilis* H17/M45 - neg.	SRI, 1979b[b/]
S. cerevisiae, D3 ±S9 Genotoxicity	*in vitro*	0.1 - 5%	positive at 1%, ±S9	SRI, 1979c[b/]
S. cerevisiae, D7 ±S9 Mutagenicity, Mitotic crossing-over, gene conversion	*in vitro*	1 - 5%	positive at 1% w/S9 positive at 2% w/o S9	SRI, 1980d[c/]
Human fibroblasts WI-38, UDS ±S9	*in vitro*	0.1 - 4000 μg/ml	positive at ≥1000 μg/ml, w/o S9	SRI, 1979d[a/]

a/ study acceptable to DPR, according to TSCA guidelines.
b/ study unacceptable and not upgradeable.
c/ study unacceptable and upgradeable.
d/ literature publication

F. REPRODUCTIVE TOXICITY

Summary: The toxicity of acephate in a multi-generation rat reproduction study included reduced body weight and soft/liquid feces in male adults, at 500 ppm, the HDT. This was not associated with reduced food intake; for some groups, such as F_0 males, there was a significant increase in food consumption, especially during the first 16 weeks, when measured in mg. In offspring, there was a reduction in the number of pups/litter, without a significant reduction in litter weight, and reduced viability, at 500 ppm. Thus, the NOEL for reproductive and adult/parental toxicity was 50 ppm, equivalent to 2.8 mg/kg/d.

Dietary-Rat

In a study with two generations, and two litters per generation, acephate (98.5% purity) was fed to Sprague-Dawley rats at 0, 25, 50 and 500 ppm (30 rats/sex/dose level) (Argus, 1987). Because of low fertility in the 2nd. litters of each generation, a single litter from a third generation was also analyzed. The equivalent dosages were, for F_0 males: 1.4 - 2.8, 2.8 - 5.7 and 29.2 - 56.9 mg/kg/d, at the three doses, respectively and for F_o females: 1.6 - 2.8, 2.8 - 5.6 and 29.2 - 55.9 mg/kg/d; for F_{2a} males the equivalent dosages were: 1.4 - 4.0, 2.8 - 8.0 and 30.4 - 82.2 mg/kg/d and for F_{2a} females: 1.7 - 3.7, 3.3 - 7.5 and 35.0 - 78.9 mg/kg/d, respectively. A decrease in body weight, without a reduction in food consumption in mg, and soft or liquid feces for adults at 500 ppm gave a parental NOEL of 50 ppm (Table 10). Reductions in litter size, without a correspondingly lower litter weight, and reduced post-natal survival, at 500 ppm yielded a reproductive NOEL of 50 ppm. The study was based in part on a preliminary study (Huntingdon, 1983) below and was acceptable to DPR.

Acephate (92.8% purity) was fed to SD rats at levels of 0, 50, 150 or 500 ppm for three generations, two litters per generation (Huntingdon, 1983). Each group consisted of 12 males and 24 females. Fertility (male) and pup viability were reduced at 500 ppm, but also at 50 ppm. The study was rejected by DPR because of insufficient animals per group, incomplete histopathology and several GLP violations.

Table 10. Mean adult (M) and pup body weight (g) and clinical signs after dietary acephate in a rat reproductive toxicity study[1]

Generation	0 (n=30)	25 (n=30)	50 (n=30)	500 PPM (n=30)
adults/ F_0 **(M)**				
1 day	215	215	214	213
8	281	276	276	267** (5.0%)[2]
78	537	544	541	497** (7.0%)
113	604	621	617	566* (6.0%)
197	694	714	706	649* (6.5%)
adults/ F1b **(M)**				
1 day	59.8	59.1	58.5	55.8 (6.7%)
28	92.7	96.9	98.0	93.0 (+0.3%)
78	517	503	514	483** (6.6%)
113	588	576	585	527** (10%)
194	679	670	681	602** (11%)
adults/ F2b **(M)**				
1 day	58.0	55.4	54.8	57.2 (1.4%)
8	98.9	91.7*	94.3	89.4** (9.6%)
78	503	491	490	491 (2.4%)
113	567	562	553	552 (2.6%)
131	597	594	585	584 (2.2%)
		Clinical Signs		
soft/liquid feces (M)				
No. days/No. rats				
F_0	0/0	1/1	6/3	12/5
F_{1b}	101/9	75/10	97/12	422/21**
F_{2b}	135/7	171/15**	196/11	509/20**
F1a pups				
no.pups/litter	12.6±3.1	12.2±2.9	11.3±3.8	11.3±2.5 (10%)
live pups/litter:				
day 0	12.3±3.0	12.0±2.8	11.1±3.8	11.1±2.6 (10%)
day 4	12.3±3.0	11.8±2.8	10.9±4.0	10.8±2.6 (12%)
litter wt. (g)				
day 0	6.3±0.6	6.3±0.9	6.5±0.6	6.4±0.5 (+1.6%
day 4	10.6±1.4	10.6±2.1	10.7±1.8	10.7±1.2 (+0.1%

Table Table 10 cont.				
F1b pups				
no.pups/litter	13.1±1.8	10.4±4.7	11.1±2.1	9.7±3.0* (26%)
live pups/litter:				
day 0	12.8±1.5	10.4±4.7	11.1±2.1	9.6±2.9* (25%)
day 4	12.8±1.5	10.3±4.5	11.1±2.1	9.5±2.7* (26%)
litter wt. (g)				
day 0	6.5±0.6	6.8±1.1	6.6±0.8	6.7±0.7 (3.1%)
day 4	10.9±1.1	10.8±2.6	11.3±1.8	11.8±1.6 (+8.3%)
F2a pups				
no.pups/litter	13.6±3.2	13.5±1.6	12.6±3.9	10.2±3.4** (25%)
live pups/litter:				
day 0	13.4±3.4	13.4±1.8	12.5±3.8	10.6±2.8** (21%)
day 4	13.2±3.3	13.1±1.7	12.2±3.7	10.4±2.9** (21%)
litter wt (g).				
day 0	6.0±0.8	6.1±0.5	6.2±0.7	6.2±0.7 (+3.3%)
day 4	9.7±1.6	9.9±0.8	10.0±1.6	10.5±1.7 (+8.3%)
F2b pups				
no.pups/litter	13.2±2.2	13.8±2.6	14.3±3.0	9.9±3.4** (25%)
live pups/litter:				
day 0	13.2±2.2	13.5±2.8	14.2±3.0	9.8±3.3** (26%)
day 4	13.1±2.2	13.2±2.8	14.0±3.0	9.8±3.3* (25%)
litter wt. (g)				
day 0	6.3±0.5	6.0±0.5	6.0±0.7	6.4±0.7 (+1.6%)
day 4	10.6±1.4	10.1±1.3	10.1±1.7	11.1±2.1 (+4.7%)
F3a pups				
no.pups/litter	13.8±2.6	13.5±1.7	12.3±2.8*	9.7±2.8** (30%)
live pups/litter:				
day 0	13.7±2.6	13.3±1.7	12.0±2.6*	9.4±2.7** (31%)
day 4	13.5±2.5	13.0±1.7	11.9±2.6*	9.0±2.7** (33%)
litter wt. (g)				
day 0	6.0±0.5	6.1±0.4	6.0±0.6	6.2±0.6 (+3.3%)
day 4	10.0±1.2	9.9±0.8	10.4±1.5	10.5±1.4 (+5.0%)

1/ Argus, 1987
2/ % decline compared with control
* significantly different from control, $p<0.05$ (Dunnett's test).
** significantly different from control, $p<0.01$ (Dunnett's test).

G. DEVELOPMENTAL TOXICITY

Summary: in the rat and rabbit, developmental toxicity was only recorded at doses that were maternally toxic and could thus be due to secondary effects. In the rat, the maternal NOEL was 20 mg/kg/d for clinical signs, 5 mg/kg/d for reduced body weight, body weight gain and food intake; the developmental toxicity NOEL was 20 mg/kg/d for reduced mean live litter weight (4.7%) and increased incidence of a skeletal variation (13%). In the rabbit, the maternal NOEL was 3 mg/kg/d for maternal toxicity, in the form of nasal discharge and abortion and there was no developmental toxicity giving a NOEL of ≥10 mg/kg/d.

Gavage-Rat

Acephate (98.7 – 99.5% purity) was administered by oral gavage to groups of 25 mated Sprague-Dawley rats at 0, 5, 20 and 75 mg/kg/d on days 6 – 15 of presumed gestation (Argus, 1989). Maternal toxicity was expressed as an increased incidence of clinical signs at 75 mg/kg/d and also as a decrease in body weight and body weight gain (Table 11). The gain in body weight was particularly reduced over the 6 – 9 and 6 – 16 day periods ($p<0.01$) and correlated with reduced food intake at 20 and 75 mg/kg/d ($p<0.01$). Based on these endpoints, the maternal NOEL for acephate toxicity was therefore established at 5 mg/kg/d. Developmental toxicity of acephate was found, at 75 mg/kg/d, in the forms of a reduced mean live litter weight for females (4.7%,) and a reduced mean number of phalanges in the hindpaw of fetuses (13%). Both effects (Table 11) were significant ($p<0.05$) only at 75 mg/kg/d, thus giving a developmental NOEL of 20 mg/kg/d. Measurements of ChE inhibition were not made. It thus appears, from this study, that developmental toxicity to acephate is only likely to appear in the rat as a secondary result of maternal toxicity.

The dose selection for the above study was based, at least in part, on an earlier study (IBT, 1971). In this study, acephate (*ca.* 90% purity) was administered to groups of 17 – 21 mated albino female rats at 0, 25, 100 and 200 mg/kg/d on days 6 – 15 of presumed gestation. Maternal toxicity, consisting of dose-related reductions in body weight gain, was considered by the study authors to contribute to a slightly increased resorption rate at 200 mg/kg/d. Therefore, it was considered that no developmental toxicity could be attributed to acephate. However, this study was rejected by DPR, for several reasons: no individual animal data, no dose level justification, no analysis of dosing solutions and no statistical analysis.

Gavage-Rabbit

Acephate (92.8% purity) was administered by oral gavage to groups of 16 mated Dutch belted rabbits at 0, 1, 3 and 10 mg/kg/d on days 6 – 27 of presumed gestation (IRDC, 1980). There was no evidence of toxicity in either dams or fetuses with the exception of a slight increase in the incidence of nasal discharge at 3 and 10 mg/kg/d. In addition, there were two abortions on gestation days 25 and 27 at 10 mg/kg/d. It was considered that the maternal LOEL was 10 mg/kg/d, giving a NOEL of 3 mg/kg/d. The developmental NOEL was determined to be $\geq$10 mg/kg/d. It thus appears, from this study, that developmental toxicity to acephate is only likely to appear in the rabbit as a secondary result of maternal toxicity.

Table 11. Developmental toxicity of acephate in the rat[a/]

	0	**5**	**20**	**75** mg/kg/d [b/]
MATERNAL				
clinical signs[c/]				
a. Tremors↑	0/375 0/25	0/375 0/25	0/375 0/25	191/375 25/25**
b. motor activity↓	0/375 0/25	0/375 0/25	0/375 0/25	6/375** 4/25**
Mean body wt., g	n=21	n=23	n=24	n=24
day 6	304.6 ± 17.1	304.6 ± 12.6	304.9 ± 11.4	309.0 ± 17.2
day 7	310.2 ± 17.8	306.8 ± 11.9	305.8 ± 11.9	300.4 ± 20.2
day 8	314.4 ± 17.9	311.1 ± 11.7	309.2 ± 11.1	298.0 ± 19.8*
day 9	319.8 ± 17.8	314.6 ± 12.3	312.9 ± 12.4	297.0 ± 18.8**
day 6-9	15.1 ± 5.2	10.0 ± 4.0**	8.06 ± 6.4**	-11.9 ± 9.5**
day 6-16	+69.0 ± 9.4	+67.1 ± 10.0	+58.1±11.1**	+32.5 ± 11.6**
Food consumed, g/d				
Day 6-7	24.3 ± 2.9	23.0 ± 2.4	21.2 ± 2.9**	16.5 ± 4.1**
Day 6-9	23.9 ± 2.7	22.9 ± 1.8	21.5 ± 2.6*	15.6 ± 3.7**
Day 6-16	24.9 ± 2.3	24.6 ± 1.7	23.0 ± 2.4**	18.2 ± 2.2**
DEVELOPMENTAL				
mean pup wt., M, g	3.54 ± 0.19	3.62 ± 0.25	3.57 ± 0.16	3.51 ± 0.27
mean pup wt., F, g	3.38 ± 0.20	3.44 ± 0.22	3.41 ± 0.13	3.22 ± 0.23*
Hindpaw phalanges Mean no./fetus/litter	4.74 ± 0.65	4.66 ± 0.69	4.63 ± 0.54	4.12 ± 1.10*

a/ data from Argus, 1989.
b/ dams were dosed by oral gavage on each of days 6 to 15 of gestation.
c/ clinical signs as a function of 375 measurements on 25 dams
*/** significantly different from control at $p<0.05$ or $p<0.01$

H. DEVELOPMENTAL NEUROTOXICITY

Summary: Pregnant rats were dosed with acephate via daily oral gavage on GD6 to LD6. Pups were dosed via daily oral gavage LD7 to LD21. The inhibition of brain AChE was the principal toxic effect recorded. This was measured at several ages in pups and adults. There was no evidence that the pups' AChE was more sensitive to inhibition than the adults' enzyme. The LOEL/NOEL values for pups and adults were 0.5 and <0.5 mg/kg/d, respectively.

In a definitive developmental neurotoxicity study, pregnant SD rats received daily doses of acephate at 0, 0.5, 1.0 or 10 mg/kg/d by oral gavage on gestation day 6 (GD6) through lactation day 6 (LD6) (Hoberman, 2003a). Pups were also dosed by gavage from LD7 to LD21 (weaning). None of the dams showed clinical signs but measurements of ChE activity in dams were not made. In pups, there was no effect on ChE (plasma, RBC, brain) in animals dosed *via* the dam *i.e.* GD6 to PND4. However, for pups dosed by gavage until postnatal day 21 (PND21), there was significant inhibition of all 3 types of ChE at 10 mg/kg/d (26 to 62%, males, $p<0.01$ and 43 to 63%, females, $p<0.01$). At 1.0 mg/kg/d, only brain ChE was significantly inhibited, by 34%, males ($p<0.01$) and 26%, females (n.s.). Likewise, at 0.5 mg/kg/d, brain ChE was inhibited by 29%, males ($p<0.01$) and by 25% for females (n.s.). The inhibition of plasma and RBC ChE did not show a consistent dose/response in either sex except for the clear inhibition at the HDT. It is therefore concluded that the LOEL and NOEL for the inhibition of brain ChE are 0.5 and <0.5 mg/kg/d, respectively. The equivalent values for plasma and RBC ChE are 1.0 and 0.5 mg/kg/d . In this study there were no effects of acephate on neurohistology, passive avoidance and water maize, motor activity and auditory startle habituation or abnormal clinical signs. There were also no effects of acephate on reproductive toxicity parameters or body weight.

Several studies were conducted with acephate prior to the definitive study, above. These were conducted to develop the protocol and also to establish the best range of doses to use. Early attempts to use a dietary rather than gavage administration of acephate were quickly discontinued because, in goat and sheep lactation studies, less than 1% of the acephate given to the mother appeared in the milk. In Hoberman, 2003b, a comparison was made between neonatal and adult rats in terms of their sensitivity to ChE inhibition. The doses selected were 0, 0.5, 1.0, 2.5 or 10 mg/kg/d, administered by single oral gavage to pups on PND11 or PND21 or else to adults of 68 days. All measurements were made on rats that had been dosed *ca.* 3 hr earlier, since this was shown to approximate the period of peak brain ChE inhibition (2 – 6 hr.). The brain ChE inhibition results were as follows: at 0.5 mg/kg/d, there were no effects; at 1.0 mg/kg/d, PND11 pups' enzyme was inhibited by 23%, males ($p<0.01$) to 30%, females ($p<0.05$) and adults' by 35%, males (n.s.); at 2.5 mg/kg/d, PND11 ChE was inhibited by 27%, males ($p<0.01$) and 14%, females ($p<0.05$), PND21 pups' ChE was unaffected and adults' was inhibited by 20%, males ($p<0.05$) and 8%, females (n.s.); at 10 mg/kg/d, PND11 pups' ChE was inhibited by 41%, males and 35%, females (both $p<0.01$) and the analogous figures for PND21 and adult animals were 35%, males ($p<0.05$) and 36%, females (n.s.) and 53%, males ($p<0.01$) and 45%, females ($p<0.05$), respectively. The main conclusion from this study is that pups are not more susceptible to ChE inhibition than adults.

In another similar study, multiple doses (n=11), at the same dose levels as above

(Hoberman, 2003c) were administered to pups over the period PND11 – PND21 as well as to 71 to 77 day old adults (Hoberman, 2003c). At 0.5 mg/kg/d, there was no effect on brain ChE in pups, with males showing 5% inhibition and females, 5% apparent stimulation of the enzyme, relative to controls. Adults at this dosage showed inhibition of 29%, males ($p<0.01$) and 8%, females (n.s.). At 1.0 and 2.5 mg/kg/d, significant brain ChE inhibition was reported in adults of both sexes and in male, but not female, pups. At the HDT, inhibition of brain ChE was similar for adults and pups. Once again, it can be concluded that rat pups are not more sensitive to ChE inhibition than are adults. The developmental neurotoxicity studies for acephate were accepted by DPR after the submission of historical control data (Argus Research, 2003).

I. NEUROTOXICITY

Summary: in two single-dose oral gavage studies and two sub-chronic dietary studies, the main effects observed were the inhibition of ChE and clinical signs. In the acute studies, a NOEL of *ca.* 25 mg/kg/d was established for clinical signs, and NOELs of $\geq$ 5 mg/kg/d for plasma ChE inhibition, 2.5 mg/kg/d for RBC ChE inhibition and 0.5 mg/kg/d for regional brain AChE inhibition. In 13-wk. studies, NOELs of 10 ppm were obtained for plasma and RBC ChE inhibition and 2 ppm for brain AChE inhibition. The latter value, equivalent to 0.12 mg/kg/d, was used for assessing risks following seasonal occupational exposure to acephate. Subchronic dermal toxicity in the rat was addressed in two studies, with a combied NOEL of 50 mg/kg/d, for brain AChE inhibition.

Acute Dermal-Rat

A single administration of acephate to the shaved dorsal skin of the SD rat was followed, at 72 h, by sacrifice and the measurement of brain, RBC and plasma ChE (Brorby & Rosenberg, 1986). Groups of 5 rats/sex/dose were subjected to acephate (Lot SX-1102, 98.2%) in distilled water containing 0.1% Tween 80, at 0, 7.9, 37, 107 and 201 mg/kg (M) or 0, 9.4, 52, 154 and 306 mg/kg (F), for 72 h. No clinical signs were observed throughout the study. At the two highest doses, marked, significant inhibition of brain AChE was reported, of 29-34% (M) and 37-51% (F), giving NOEL values of 37(M) and 52 (F) mg/kg. At these doses, non-significant inhibition of 16% (M) and 9.8% (F) was observed. The inhibition of plasma and RBC ChE was similar to that of brain AChE, but lacked the clear-cut monotonic dose-response characteristics of the inhibition of the brain enzyme. The study was considered a valid supplemental one by DPR, but of uncertain usefulness for risk assessment purposes, owing to the unusual protocol.

Acute Gavage-Rat

In phase 1 of this study, acephate (99.4% pure) was administered by oral gavage to two Sprague-Dawley rats per sex per dose at 0, 5, 25, 125 and 500 mg/kg/d (Nemec, 1995). In phase 2 of this study, five females/group were dosed with 0, 0.5, 2.5 or 5 mg/kg/d. Detailed examinations of clinical signs were made at 15 min, 30 min, 1 h, 2h and 2.5 h post-dosing, in phase 1 and at 2.5 h in phase 2. This was the time at which toxic signs reached a peak and at which rats were sacrificed for the measurement of plasma, RBC and brain (sectional) ChE, in phase 2. The clinical signs and inhibition of ChE from phase 1 are summarized in Table 12. All of the rats dosed at 125 or 500 mg/kg/d displayed one or more of the signs listed whereas none of the rats at 5 mg/kg/d showed

any of these signs. The inhibition of ChE was marked (57-90%) at 500 mg/kg/d and was quite pronounced (19%-31%) even at 5 mg/kg/d.

In phase 2 of this study, 5 mg/kg/d gave rise to inhibition of plasma ChE of 10% (n.s.) and RBC ChE of 19% ($p<0.001$), as shown in Table 13. In 5 regions of the brain, AChE was also significantly inhibited, by *ca*. 30%. At 2.5 mg/kg/d, neither plasma nor RBC ChE were inhibited significantly, but all (5) brain regions showed significant inhibition, generally of *ca.* 20%. At 0.5 mg/kg/d, ChE activity was unaffected by acephate, making this the NOEL for this study.[4/] Although brain stem AChE was significantly ($p<0.01$) inhibited at this dose, because the level of inhibition was only 6.8% and, because it was the only brain region affected, it is considered to be probably due to chance variation, and unlikely to be of toxicological significance. The study was considered acceptable by DPR as supplemental study.

Table 12. Clinical signs and AChE activity after acephate dosing of the rat.[1/]

Effect/Dosage	**0**	**5**	**25**	**125**	**500** mg/kg/d
Clinical signs					
None	4/4	4/4	3/4	0/4	0/4
Rep. mouth moves	0/4	0/4	1/4	1/4	1/4
Tremor (legs,body)	0/4	0/4	0/4	4/4	4/4
Salivation	0/4	0/4	0/4	1/4	3/4
Altered gait	0/4	0/4	0/4	4/4	4/4
Ear twitching	0/4	0/4	1/4	1/4	0/4
Hypothermia	0/4	0/4	0/4	0/4	4/4
Mean ChE I (%)					
Plasma, M	--	30%↓	56%↓	77%↓	84%↓
Plasma, F	--	25%↓	41%↓	69%↓	90%↓
RBC, M	--	25%↓	31%↓	50%↓	57%↓
RBC, F	--	14%↓	41%↓	52%↓	58%↓
Brain, M	--	19-31%↓	50-59%↓	69-77%↓	77-81%↓
Brain, F	--	24-31%↓	55-66%↓	75-79%↓	80-85%↓

1/ data taken from Nemec, 1995; 2 male and 2 female SD rats /dose.

Acute Gavage-Rat

Another acute neurotoxicity study in the SD rat was conducted in which animals were subjected to both ChE measurements and FOB tests (Nemec, 1996). Groups of 30 rats of each sex were dosed with 0, 10, 100 or 500 mg/kg/d of acephate technical (Lot SX1725, 99.0% pure) by oral gavage; 12 of these were evaluated in FOB tests and neuropathological examinations and 6 rats/sex/group were sacrificed at 2.5 hr., 7 and 14 days for the measurement of ChE activity. There were no compound-related mortalities. Clinical signs and FOB effects were generally observed only at 100 and 500 mg/kg/d. Increases were found in incidences of abnormal mobility, gait, clonic convulsions, tremors, arousal and rearing in both sexes at these two doses. At 10 mg/kg/d, the only effect was a reduction in rotorod performance ($p<0.01$) in males, but not females. Mean ChE activity was reduced ($p<0.01$) in plasma, RBC and in all (6) brain regions measured in males on the day of dosing (2.5 h). In females, similar reductions in ChE activity were observed, except for a statistically non-significant decrease of 34% in plasma ChE activity. At 7 and 14 days, plasma and RBC ChE activity had both returned to normal (pre-dosing). However, a significant reduction ($p<0.01$) in ChE activity was found at 7 days in most brain regions but not at 14 days. It was concluded that NOELs were 10 (clinical signs) and <10 mg/kg/d (ChE inhibition).

Table 13. Mean AChE activity after acephate dosing: female rat at 2.5 hrs.[1/]

Source of ChE	DOSAGE mg/kg/d			
	0	0.5[4/]	2.5	5.0
Plasma[2/]	1240±149	1292±344 (4%↑)	1062±273 (14%↓)	1111±208 (10%↓)
RBC[2/]	3984±261	3680±463 (7.6%↓)	3846±132 (3.5%↓)	3229±172*** (19%↓)
Hippocampus[3/]	8.59±0.31	7.91±0.29 (7.9%↓)	7.44±0.67* (13%↓)	6.04±0.82* (30%↓)
Midbrain[3/]	16.72±1.22	15.98±0.40 (4.4%↓)	13.24±0.42*** (21%↓)	11.65±0.33*** (30%↓)
Brain stem[3/]	15.79±0.57	14.71±0.37** (6.8%↓)	12.38±0.41*** (22%↓)	10.37±0.73*** (33%↓)
Cerebellum[3/]	7.10±0.38	7.13±0.93 (0%)	5.66±0.34*** (20%↓)	4.77±0.51*** (33%↓)
Cortex[3/]	13.80±1.01	14.18±0.60 (3%↑)	10.95±0.94*** (21%↓)	9.49±0.40*** (31%↓)

1/ data taken from Nemec, 1995; 5 female SD rats /dose.
2/ International units per L
3/ International units per g
4/ NOEL used by USEPA to establish acute MOE values for dietary exposure (2/2/2000).
*/**/*** p<0.05, <0.01, 0.001 (Student's t test)

Sub-chronic Dermal-Rat

A subchronic toxicity study was conducted in which acephate (Lot R23044/VS-9B-40, purity 97.8%) was applied to the shaved dorsal skin of the SD rat in physiological saline (0.9%) at 1 ml/kg at 0, 12, 60 or 300 mg/kg/d (Blaszak, 1998). Dosing was for 6 h/day, 5 d/week to 10 rats/sex/dose for 3 weeks. Treated skin was covered with a dressing and a fresh application was administered on each day. Necropsy occurred on the day after the last dose, giving a total of 15 or 16 applications. No clinical signs or effects on body weight/food consumption were observed and no skin lesions were observed at the application site(s). Hematology was also unaffected by acephate, with the exception of brain AChE inhibition. At 300 mg/kg/d, inhibition was 9.3% (M) and 14% (F), both p<0.01. At 60 mg/kg/d, inhibition was 5.5% (M, n.s.) and 6.6% (F, p<0.01). The NOEL values for brain AChE inhibition are therefore considered to be 60 mg/kg/d (M) and 12 mg/kg/d* (F). This study is considered by DPR to be a valid pilot study.

Another subchronic toxicity study was conducted in which acephate (Lot VJI-001TG-21, purity 98.8%) was applied to the clipped dorsal skin of the SD rat in physiological saline (0.9%) at 1 ml/kg at 0, 20, 30, 40 or 50 mg/kg/d (Hoffman, 2000). Dosing was for 6 h/day, 5 d/week to 10 rats/sex/dose for 3 weeks. Treated skin was covered with a dressing and a fresh application was administered on each day. Necropsy occurred on the day after the last dose, giving a total of 16 applications. No clinical signs or effects on body weight/food consumption were observed and no skin lesions were observed at the application site(s). Brain, RBC and plasma ChE were all unaffected by acephate. The NOEL values for brain AChE inhibition are therefore considered to be 50 mg/kg/d for males and females, with no LOEL. This study is considered by DPR to be a valid supplementary study.

* This NOEL was used by USEPA as the critical one for calculating risk for worker exposure

Sub-chronic Dietary-Rat

A sub-chronic neurotoxicity study in the SD rat was conducted in which animals were subjected to both FOB tests and plasma, RBC and (6) regional brain ChE measurements (Nemec, 1997). Groups of 30 SD rats of each sex were fed on diets containing 0, 5, 50 or 700 ppm of acephate technical (Lot SX1725, 99.0%) for 13 weeks. These doses were equivalent to mean measured dosages of 0, 0.33, 3.31 and 48.63 (M) and 0, 0.41, 3.95 and 58.27 (F). Measurements were made of FOB effects, body weight changes and ChE inhibition at 3, 7 and 13 weeks after dosing commenced. There were no consistent, dose-related effects on FOB or neuropathological parameters during or after the study. There were also no consistent, dose-related effects on body weight during the study. The inhibition of ChE is summarized in Table 14. At 700 ppm, there was generally a significant ($p<0.01$) inhibition of plasma (55%-57%, M and 67%-74%, F), RBC (37%-46%, M and 25%-43%, F) and brain (63%-82%, M and F) enzyme. At 50 ppm, there was only a low, insignificant level of plasma (9.7%-25%, M and 5.8%-41%, F) and RBC (7.9%-13%, M and 7.9%-26, F) ChE inhibition, but there was generally a significant ($p<0.01$) inhibition of regional brain AChE (29%-49%, M and 18%-55%, F). At 5 ppm, there was no inhibition of plasma or RBC ChE. However, three (of six) brain regions had significantly inhibited AChE ($p<0.01$) at 7 and 13 weeks: the midbrain, brainstem and cortex in males; midbrain, olfactory bulb in females ($p<0.05$). It was therefore concluded that, following sub-chronic dietary dosing of the rat with acephate, 5 ppm was the LOEL for brain AChE inhibition and a NOEL was not established in this study.

Table 14. Mean ChE inhibition (%) in rats after sub-chronic oral acephate.[1/]

Site/ Time			Dose,	ppm		
	5 (M)	**50 (M)**	**700 (M)**	**5 (F)**	**50 (F)**	**700 (F)**
Plasma						
Wk 3	4.5	25*	57**	22	41**	74**
Wk 7	3.5	11	55**	0.1	22	73**
Wk 13	18↑	9.7	55**	16↑	5.8	67**
RBC						
Wk 3	18	13	46**	7.5	26	42*
Wk 7	0.9↑	7.9	37**	3.9↑	7.9	43**
Wk 13	0.4	11	37**	9.9↑	9.4	25
H'campus						
Wk 3	14**	38**	79**	6.0	48*	78**
Wk 7	7.4	47**	82**	4.7	50**	82**
Wk 13	16	29	81**	28**	55**	82**
Olfactory						
Wk 3	4.8	45**	77**	13↑	23	79**
Wk 7	12	40**	82**	24*	54**	82**
Wk 13	4.9	39**	79**	18*	45**	79**
Midbrain						
Wk 3	9.5**	36**	73**	19**	45**	77**
Wk 7	14**	40**	77**	15**	47**	78**
Wk 13	14**	38**	78**	9.0*	35**	73**
Brainstem						
Wk 3	15**	31**	68**	6.7	18	68**
Wk 7	9.4**	34**	71**	8.4	36**	72**
Wk 13	10**	28**	68**	4.2	30**	69**
Cerebellum						
Wk 3	11**	27**	63**	2.7	27**	64**
Wk 7	3.5	28**	65**	16**	38**	69**
Wk 13	5.5	24**	63**	4.2	25**	63**
Cortex						
Wk 3	16**	44**	80**	6.7	39**	81**
Wk 7	10**	46**	82**	2.4	44**	81**
Wk 13	17**	49**	80**	14**	51**	81**

1/ data from Nemec, 1997; % inhibition compared with concurrent control.
*/** Significantly different from control, $p<0.05$ or $p<0.01$ (using raw data)

Sub-chronic Dietary-Rat

An earlier sub-chronic neurotoxicity study in the SD rat was conducted in which plasma, RBC and brain ChE measurements were made at 4, 9 and 13 weeks (Brorby & Rosenberg, 1987). Groups of 30 SD rats of each sex were fed on diets containing 0, 2, 5, 10 or 150 ppm of acephate technical (Lot SX110, 98.2%) for 13 weeks. Ten rats per sex per dose were sacrificed at each timepoint. These doses were equivalent to mean measured dosages of 0, 0.12, 0.28, 0.58 and 8.90 (M) and 0, 0.15, 0.36, 0.76 and 11.48 (F). There was no mortality in the study and no consistent, compound-related effects on body weight, food consumption, clinical signs or necropsy.

The inhibition of ChE is summarized in Table 15. At 150 ppm, there was inhibition of plasma ChE ($p<0.01$) only in females and only at 13 weeks, by 43%. RBC ChE was inhibited sporadically, by ≤42% in males in week 4 ($p<0.01$), but not significantly at week 13 and in females, by 44% ($p<0.01$) at 13 weeks, but not significantly at week 4. Brain AChE was inhibited significantly ($p<0.01$) by 44 - 53% at all timepoints in both sexes at 150 ppm. At 10 ppm, plasma and RBC ChE were not significantly inhibited, in either sex, at any of the timepoints. However, brain ChE was inhibited ($p<0.01$) by 11-16% (M) and 9.6%-14% (F) at each timepoint. Similarly, 5 ppm caused no significant inhibition of plasma or RBC ChE but brain AChE was inhibited ($p<0.01$) at each timepoint, by 7.3 - 9.9% (M) and 5.4% - 10% (F). At 2 ppm, inhibition of plasma and RBC ChE did not occur. The brain AChE was inhibited, but only sporadically, by 1.1% (n.s.) at week 4 to 7.4% ($p<0.01$) at week 13 for males and 2.1.% (n.s.) at 4 weeks to 9.2% ($p<0.01$) at 9 weeks for females. Inhibition of brain AChE is not necessarily considered significant toxicologically, even though significant statistically, depending on other considerations. Therefore, 5 ppm is considered the LOEL and 2 ppm the NOEL for AChE inhibition in this study. Because AChE inhibition at 13 weeks is generally similar to that in the same animal system at one or two years, this sub-chronic NOEL (*i.e.* 2ppm, or 0.12) was used by USEPA for assessing chronic dietary risks from acephate exposure.[4]

Table 15. Mean ChE inhibition (%) in rats after sub-chronic dietary acephate.[1/]

Site/ Time	Dose, ppm							
	2 (M)	**5 (M)**	**10 (M)**	**150 (M)**	**2 (F)**	**5 (F)**	**10 (F)**	**150 (F)**
Plasma								
Wk 4	3.5↑	2.0	3.1↑	28	9.6	19	18	27
Wk 9	2.1↑	6.5	4.2↑	26	10	6.4	13	46
Wk 13	1.6	12	19	36	29	15	23	43**
RBC								
Wk 4	10↑	2.8↑	3.5	42**	4.3	0.5	11↑	30
Wk 9	2.8↑	4.2↑	1.5↑	32*	10↑	6.8	18	44**
Wk 13	4.6↑	12↑	1.5↑	22	2.7	8.4	10	44**
Brain								
Wk 4	1.1	7.3**	11**	46**	2.1	5.4**	9.6**	44**
Wk 9	3.0	7.2**	14**	49**	9.2**	10**	14**	52**
Wk 13	7.4**	9.9**	16**	52**	8.5**	9.8**	14**	53**

1/ data from Brorby & Rosenberg, 1987; % inhibition compared with concurrent control.
*/** Significantly different from control, $p<0.05$ or $p<0.01$ (using raw data).

[4] / Final RED published in September, 2001.

J. IMMUNOTOXICITY

Summary: the administration of acephate to the rat *via* single intraperitoneal injection resulted in a suppression of the immune system, with a LOEL of 100 mg/kg/d and a NOEL of 10 mg/kg/d.

Intraperitoneal-Rat

After the injection of acephate into the female SD rat (n=5), at 0, 10, 100, 250 or 500 mg/kg/d, various immunological parameters were measured in the blood and brain (Sing & Jiang, 2002). No clinical signs were observed with the exception of minor tremors at the HDT, commencing 45 to 60 min. after dosing, and there was no mortality. The blood levels of acephate increased in a dose and time- dependent fashion, peaking at 1 - 3 hr. At the HDT, the blood concentration peaked at *ca.* 12 mg/ml., at 1, 2 and 3 hr., before falling to zero at 24 hr. In brain, the accumulation was somewhat slower. Peak level was *ca.* 6 mg/g brain at 2, 3 and 10 hr, decreasing to *ca.* 4 mg/g at 24 hr. There was no apparent increase with 10 mg/kg/d. These changes in acephate concentration were paralleled by reductions in AChE activity in blood and brain (hypothalamus) as well as increases in corticosterone in the blood. The inhibition of AChE at the HDT peaked at *ca.* 75%, from 30 min to 3 hr. (blood) and from 30 min. to 10 hr. (brain). The dose and time dependencies of the increases in corticosterone levels in the blood were similar to the decreases in AChE activity, especially in the brain. A 30 to 50% increase was observed at 30 min, 1, 2 and 3 hr. ($p<0.05$) at the HDT and similar though lesser increases were recorded at 250 and 100. The levels of corticosterone were still elevated at 24 hr., by *ca.* 20%, at 100, 250 and 500 mg/kg/d. No significant increase in corticosterone concentration was seen at 10 mg/kg/d of acephate.

Over the period 30 min. to 10 hr., acephate caused a significant ($p<0.05$) reduction in WBC (white blood cells), but only at the HDT. A decrease of 20 – 25% was observed at 1, 2, 3 and 10 hr, with a return almost to normal by 24 hr. There were parallel falls in CD4, CD8, B cell and monocyte levels compared with controls, with a similar time course, significant ($p<0.05$) at 250 and 500 mg/kg/d. However, WBC levels were still slightly reduced, by *ca.* 10% ($p<0.05$) at 24 hr. Another component of the (cellular) immune system, the neutrophils, was affected by acephate administration. Here, there was an increase ($p<0.05$) at 30 min. to 10 hr., of 30 – 50% above control, at the HDT. The neutrophil counts were still elevated by *ca.* 25% (n.s.) at 24 hr. At 250 mg/kg/d, there was a similar though less marked increase in neutrophils of *ca.* 20%, significant ($p<0.05$) at only 3 and 10 hr. All of these effects of acephate on immune system parameters were abolished following adrenalectomy.

The authors considered the role of IL-1 in the immune system changes. This was injected intraperitoneally at 250 mg/kg/d either at time zero or 1 hr. after the acephate dosing. IL-1 injection caused an increase in the levels of WBC and CD4 cells along with other immune system marker cells. This increase was *ca.* 30% by 5 min. and peaked at *ca.* 50% at 10 min. Acephate co-administration resulted in a dose-dependent reduction in the IL-1 induced increases, but they followed the same time courses. When IL-1 was injected 1 hr. after acephate, the increases were less marked, and were only observed at 10 mg/kg/d acephate, the LDT. At all of the other acephate doses there was a decrease to below the control level in the concentration of these markers. For neutrophils, however, the increase seen with acephate was accentuated in the presence of acephate plus IL-1, whether co-administered or IL-1 was given 1 hr. after the acephate.

It was concluded that acephate, at intraperitoneal doses above 10 mg/kg/d, could suppress the normal immune response by increasing corticosterone and reducing immune cell numbers. This is supported by the absence of acephate immunological effects in the adrenalectomized rats. However, it is possible that acephate could also impair the body's normal immune response to injury or foreign tissue by increasing neutrophil numbers. The literature on possible immunotoxicity by organophosphate insecticides allows few clear conclusions (Rodgers, 2001). A reduction in immune function is the predominant effect observed but it is unclear whether the mediator of the response is ACh accumulation, some other parameter associated with increased cholinergic activity or (secondary) increases in corticosterone levels. However, effects of OPs on aspects of immune system function were measured *in vitro* in Rogers, 2001, indicating that direct effects of OPs may be involved in causing some immunotoxicity *in vivo*.

K. SPECIAL STUDIES

Summary: the pharmacokinetics and inhibition of plasma and RBC ChE were monitored in groups of male or female human adults, dosed by oral capsule, at 0.35 to 1.25 mg/kg/d. Samples of urine and blood were taken from each person before dosing and at 10 time points from 1 hr. to 14 d after dosing. No individuals reported clinical signs. Peak plasma concentrations appeared at 2 to 2.7 hr after dosing and clearance occurred with a $t_{1/2}$ of 4.8 to 5.4 hr. The presence of methamidophos was confirmed in the blood and urine, at 1 to 2% of the level of acephate, at all doses except the lowest. Significant inhibition of plasma ChE was from 8.9% to 12.8% from 12 hr to 48 hr. after dosing at 1.25 mg/kg/d in males and was not significant at 1.0 (1.6% to 4.2%). In females, significant inhibition of 10.5% to 12.7% was observed at 8 to 24 hr. after dosing at 1.0 mg/kg/d. However, this was not considered to be toxicologically relevant because plasma ChE activity in controls ranged from 6.7% stimulation (48 hr) to 7.5% inhibition (7 days), compared with time zero, during the experiment. Inhibition of RBC ChE was significant, by 6.8%, at only one sampling time (12 hr), only in males, at the HDT. It is concluded that 1.0 mg/kg/d is the NOEL for this study.

Acute Oral-Human

Groups of 10 male volunteers were dosed orally (once) with gelatin capsules containing acephate (Lot No. 80121, 99.0% pure) at 0.35, 0.7, 1.0 or 1.25 mg/kg/d (Freestone & McFarlane, 2001). A single group of females received 1.0 mg/kg/d of acephate. In each dose group, 7 individuals received acephate and 3 received placebo (lactose). A baseline ChE activity for each individual was established by averaging plasma and RBC ChE activity from 6 blood samples taken pre-dosing. Vital signs and EKG were recorded at 2, 4, 8 and 24 hr post-dosing. Samples of blood were taken at 10 time points after dosing, from 1 h to 14 days. The blood levels of acephate and methamidophos were measured in addition to the ChE activity. The excretion of acephate in urine was also measured. Acephate had no effects on vital signs, EKG, hematology, clinical chemistry or urinalysis. Statistically significant inhibition of plasma ChE was reported at 1.25 mg/kg/d in males, at 12, 24 and 48 hrs. and at 1.0 mg/kg/d in females at 8, 12 and 24 hrs. (Table 16A). However, the degree of inhibition was only from 9 to 13% (males) or 10 to 13% (females) making it of doubtful toxicological significance. There was also significant inhibition ($p<0.01$) of RBC ChE in males at 12 h at 1.25 mg/kg/d, but only by 6.8%, making this also of doubtful toxicological significance (Table 16B). This was the sole case of significant inhibition of RBC ChE in the study (M or F).

DPR has no requirement for human testing of pesticides and there are currently no FIFRA guidelines in place for this type of study. However, the study was conducted in a double-blind

manner following "Good Clinical Practices" guidelines and had an extensive informed consent form. The protocol and volunteer information was approved by an institutional review board (Independent Research Ethics Committee of Inveresk Research) and the study was conducted in accordance with the guidelines set out in the Declaration of Helsinki, 1964. Furthermore, the study by Freestone & McFarlane, 2001, was one of those addressed by Charnley & Patterson, 2003 in terms of the ethical status of 15 studies with pesticides on humans (deliberate dosing). It was concluded that all of these studies were conducted in a manner "...substantially consistent with the fundamental protections of the Common Rule – voluntary participation, informed consent, and review by an ethical committee or institutional review board."

Table 16A. Mean % inhibition of plasma ChE in humans after oral acephate [1/]

Time			Dosage,	mg/kg/d			
	0 (M) n=12	**0.35 (M) n=7**	**0.7 (M) n=7**	**1.0 (M) n=7**	**1.25 (M) n=7**	**0 (F) n=3**	**1.0 (F) n=7**
1-4 h	5.3-7.5↓	6.8-8.8↓	6.8-10.5↓	4.7-5.6↓	4.7-6.4↓	0.6-4.6↓	6.5-9.1↓
8h	6.6↓	9.3↓	8.3↓	4.8↓	10.9↓	1.6↓	12.7*↓
12h	4.9↓	10.9*↓	10.1↓	2.9↓	12.8**↓[2/]	2.3↓	12.1*↓
24h	1.4↓	5.8↓	4.7↓	1.6↓	8.9**↓	3.5↑	10.5**↓
48h	0.4↓	1.1↓	4.7↓	4.2↓	9.1***↓	6.7↑	0.3↑
72h	1.3↑	3.8↓	0.6↓	0.2↓	8.7↓	1.0↑	3.6↓
7-14 d	2.6↓	3.5-4.9↓	0.5-1.3↑	+1.5-4.4↓	+0.14-4.8↓	1.4-7.5↓	+4.0-6.9↓

1/ data from Freestone & McFarlane, 2001; % difference from pre-dosing.
2/ mean RBC ChE was also inhibited (p<0.01), by 6.8%.
*/ **/ *** Significantly different from control, p<0.05, p<0.01, p<0.001

Table 16B. Mean % inhibition of RBC ChE in humans after oral acephate [1/]

Time			Dosage,	mg/kg/d			
	0 (M) n=12	**0.35 (M) n=7**	**0.7 (M) n=7**	**1.0 (M) n=7**	**1.25 (M) n=7**	**0 (F) n=3**	**1.0 (F) n=7**
1-4 h	3.3↑-0.5↓	2.8-6.4↑	1.8↑-2.2↓	0.6-4.1↑	0.3-3.1↑	0.3-8.8↓	2.2-4.6↓
8h	1.3↑	0.9↓	0.1↑	0.3↑	7.5↓	2.4↓	0.3↓
12h	2.9↑	1.0↑	8.2↑	2.5↓	6.8**↓	1.6↓	10.7↓
24h	0.4↑	2.5↑	1.7↓	6.5↓	3.0↓	8.3↓	5.0↓
48h	0.1↑	8.0↑	3.3↓	1.5↓	3.1↓	1.9↓	5.5↓
72h	3.2↓	8.9↑	8.8↓	5.3↓	0.9↓	13.8↓	11.4↓
7-14 d	0.7↑-0.8↓	0.4↑-2.9↑	5.5↑-1.1↓	1.4↑-3.6↓	5.4↑-4.6↓	0.8↑-10.1↓	0.3↑-10.7↓

1/ data from Freestone & McFarlane, 2001; % difference from pre-dosing.
** Significantly different from control, p<0.01.

The magnitude of inhibition of plasma ChE was considered in the context of the variation of this enzyme's activity in controls. In males, apparent inhibition in controls was 4.9 to 7.5% over the first 12 hrs. of the study; for females, 0.6 to 4.6% inhibition was recorded in the first 12 hrs. and from 6.7% apparent stimulation at 48 hr to 7.5% apparent inhibition over the 7 – 14 day period. There was little or no dose/response relationship for either plasma or RBC ChE at any time

point during the study. It was concluded that the NOEL for plasma ChE inhibition was 1.0 mg/kg/d (M) and (F). For males, 1.0 mg/kg/d was also the NOEL for RBC ChE, whereas for females it was ≥1.0 mg/kg/d. It should be noted that in Table 16B, the greatest (apparent) inhibition of RBC ChE, 13.8%, was observed in female controls at 72 hr. A NOEL of 1.0 mg/kg/d from this experiment was used for acute risk assessment purposes.

The pharmacokinetics of acephate absorption and elimination was also studied in this human experiment. At 1.0 and 1.25 mg/kg/d, in both sexes, the maximum concentration achieved in blood plasma, 1.45 to 1.69 μg/ml (~10 μM), was reached at 2 to 2.7 hr after dosing. Clearance occurred with a $t_{1/2}$ (of elimination) of 4.8 to 5.4 hr at a rate of 77 to 79 ml/hr/kg. Very little acephate remained in plasma at 24 hr. and it was undetectable at 48 hr. (<0.01 ppm). Methamidophos was not isolated from plasma at 0.35 mg/kg/d but constituted about 1.3% at the other doses tested, independent of dose or sex. The mean recovery of acephate in urine (over 48 hr.), as parent and methamidophos, averaged 26% to 53%. Methamidophos represented *ca.* 1% of the total acephate + methamidophos species recovered (Table 17). A summary of the acephate neurotoxicity/special studies is provided in Table 18.

Table 17. Mean concentration of acephate and methamidophos in urine of acephate – dosed humans, 0 – 12 hr.[1/]

	DOSAGE ng/ml			
	0.35	**0.7**	**1.0[2/]**	**1.5**
Acephate (n=7)	9536±3106	21457±12422	34951±21973	27371±8152
Methamidophos (n=7)	83±24 (0.9%)	187±92 (0.9%)	296±141 (0.8%)	325±71 (1.2%)

1/ data taken from Freestone & McFarlane, 2001.

2/ for females dosed at 1.0 mg/kg/d, acephate was 31,000±16,700 ng/ml and methamidophos 383±133 ng/ml (0.9%) over 0 –12 hr.

Table 18 Summary of Neurotoxicity / Special studies using acephate.

Species/Route	Effect	LOEL/NOEL mg/kg/d	Reference
Rat/gavage, acute	brain ChE ↓ RBC ChE ↓ Clinical signs	2.5 / 0.5[a/] 5.0 / 2.5 25 / 5	Nemec, 1995
Rat/gavage, acute	Plasma, RBC, brain ChE ↓ Clinical signs	10 / <10 100 / 10	Nemec, 1996
Rat/diet, 13-wks.	brain ChE ↓ plasma, RBC ChE ↓ Clinical signs, FOB	0.33 / <0.33 48.6 / 3.31 >48.6 / 48.6	Nemec, 1997
Rat/diet, 4, 9, 13-wks.	brain ChE ↓ plasma, RBC ChE ↓ Clinical signs	0.28 / 0.12[b/] 8.9 / 0.58 >8.9 / 8.9	Brorby & Rosenberg, 1987
Human/oral (M/F) capsule, acute	plasma, RBC ChE ↓ Clinical signs	>1.0 / 1.0[c/] >1.0 / 1.0	Freestone& McFarlane, 2001

a/ critical NOEL used by USEPA for assessing acute dietary risk.

b/ critical NOEL used by USEPA for assessing chronic dietary risk and by DPR for assessing risks from seasonal occupational exposure.

c/ critical NOEL used by DPR for assessing acute occupational and dietary risk.

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

The Birth Defect Prevention Act of 1984 (SB 950) requires DPR to review the toxicological data for all active ingredients currently registered in California. DPR placed acephate in risk assessment based on low NOEL values identified in laboratory animal studies. In acute, sub-chronic and chronic studies, acephate consistently inhibited cholinesterase activity (plasma, RBC and brain), although generally in the absence of clinical signs. The degree of inhibition tended to be greater for the brain enzyme. Cholinesterase inhibition was the most sensitive endpoint and was used to characterize the human risk from potential acute, subchronic and chronic exposure. There was no evidence of developmental or reproductive toxicity in appropriate rat and rabbit toxicity tests. Gene mutations and UDS were reported in mammalian cells *in vitro*, at high concentrations, but acephate was inactive in genotoxicity studies in mammals, *in vivo.* There was an increase in adrenal adenoma incidence in the male rat and an increase in carcinoma incidence in the female mouse liver in 2-year dietary studies. Both tumors may have resulted from excessive toxicity of the doses used.

Acute Toxicity

Acephate and its formulations have low acute toxicity to rodents and rabbits orally, (LD_{50} 360-1400 mg/kg/d) and dermally, (LD_{50} >2000 mg/kg/d) both Category III. Although eye irritation was also considered Category III, a formulated product caused iritis (Grade 1) and chemosis (Grade 4) in the rabbit. Dermal irritation was mild, Category IV. There was no dermal sensitization in the rabbit or guinea pig. By inhalation, acephate caused no mortality in the rat at 1.81 mg/L. Data describing the acute toxicity of metabolites and impurities are limited, with the exception of methamidophos. This is the bioactive form of acephate and is used as an insecticide in its own right. However, there is evidence that methamidophos inhibits the enzyme that de-acetylates acephate to methamidophos in mammals, an example of endproduct inhibition (Mahajna *et al.*, 1997). This would have the effect of reducing the bioactivation of acephate.

Developmental toxicity tests are commonly used for acute risk assessment, because developing organisms are sometimes more sensitive than adults. However, in such tests using rats and rabbits for acephate, this was not the case. Reduction of mean fetal body weight was reported only at doses that were several fold higher than doses causing body weight loss in dams (Table 11). In these experiments, ChE inhibition was not measured in fetuses or dams. An acceptable reproductive toxicity study did not show evidence of developmental or reproductive toxicity in the rat (Table 10). However, ChE measurements were not made in this experiment. In a developmental neurotoxicity study for acephate (Section III.H.), brain AChE was shown not to be more sensitive to inhibition in fetuses/pups than in adults. This is similar to the situation for the active metabolite, methamidophos.

In common with other organophosphate insecticides, the inhibition of ChE was the most sensitive endpoint in both acute and chronic toxicity tests. In acute, single dose, neurotoxicity tests in the rat, the NOEL for ChE inhibition (regional brain) was 0.5 mg/kg/d, with a LOEL of 2.5 mg/kg/d (Nemec, 1995; 1996). In these studies, plasma and RBC ChE had a NOEL of 2.5 mg/kg/d and a LOEL of 5 mg/kg/d, in females. However, for acute risk assessment purposes, the use of an apparently well conducted human study is proposed. A NOEL of 1.0 mg/kg/d was obtained for clinical signs/symptoms and plasma/ RBC ChE inhibition (Freestone & McFarland,

2001). It was also found that the peak level of methamidophos in blood plasma was only 1.3% of the administered dose. Because of Its rapid oral absorption and excretion in humans (Tozer, 2000), acephate is unlikely to accumulate.

Subchronic Toxicity

Two rat dietary studies of 4, 9 and 13 weeks duration have been conducted, giving the following LOEL/NOEL values: for plasma and RBC ChE inhibition, 150 ppm/ 50 ppm, respectively and for brain AChE, 5 ppm/ 2 ppm, respectively. The latter value (2 ppm) was equivalent to 0.12 mg/kg/d. This value has been used by USEPA for conducting chronic (dietary) risk assessments for acephate (USEPA RED, 2001b). It was used by DPR to determine MOE values for seasonal occupational exposure. Although two rat dermal toxicity studies have been conducted, with a NOEL of 50 mg/kg/d for brain AChE inhibition, they are of much lower quality than the dietary studies and DPR has therefore decided not to use them for risk assessment.

Chronic Toxicity

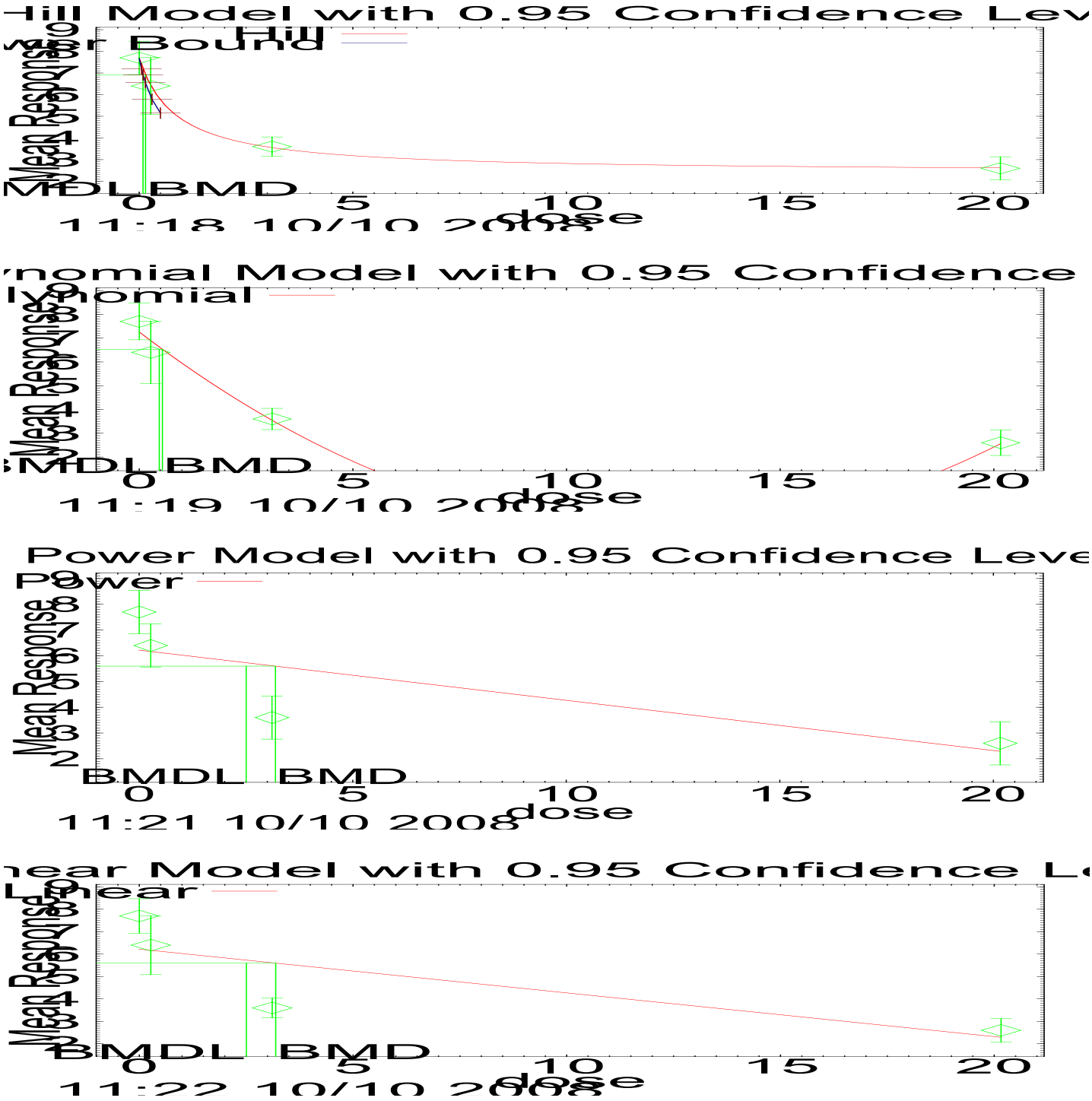
Body weight loss was observed in the rat and mouse, but not the dog. There were no clinical signs in these studies. There was some evidence of inhibition of ChE in plasma and clear evidence in erythrocytes, and of AChE in brain. The LOEL for the inhibition of brain AChE was 10 ppm, equivalent to 0.27 mg/kg/d, in the dog, at 1-yr. This was based on 17% ($p<0.05$) inhibition in males and 11% (n.s.) in females. Because there was no clear NOEL for brain AChE inhibition in this study, an estimated chronic NOEL was obtained by dividing the LOEL by 3 *i.e.* 0.09 mg/kg/d.

Support for the use of a factor of 3 rather than the common default of 10 in estimating the NOEL from the LOEL was provided by the calculation of Benchmark Doses (BMDs). The mean and S.D. for brain AChE inhibition (Table 7) were analyzed using BMDS, Version 1.3.1, developed for USEPA (2002) by the National Centre for Environmental Assessment. Four programs were run for continuous data (Hill, Polynomial, Power and Linear models) and the BMD and BMDL (95% lower confidence limit of the BMD) were determined by each one, based on 10% enzyme inhibition. For male dogs, BMDLs were 0.09, 0.47, 2.51 and 2.51 mg/kg/d, for the four models, respectively. The AIC (Akaike Information Criteria) were 7.86, 11.1, 41.5 and 37.5 respectively. From the AIC values (the lower the better) and an inspection of the dose/response curves (Figure 2), it would appear that the Hill model provides the best analysis of the data, thus giving a BMDL of 0.09 mg/kg/d. It is therefore concluded that the use of 0.09 mg/kg/d as an estimated NOEL from this study should be relatively close to the "true" NOEL. This estimated NOEL of 0.09 mg/kg/d, based on 11-17% inhibition of brain AChE activity at 0.27 mg/kg/d (LOEL) in the 1-yr. dog study (Hazelton, 1991), was used as the critical value for chronic risk characterization.

Oncogenicity

Chronic feeding of acephate to the rat or mouse resulted in a dose-related increase in tumors, as follows: rat, male adrenal gland adenoma at the top two doses and, mouse, female hepatic cancer at the HDT. There was significant evidence of liver toxicity and it is considered possible that the MTD was exceeded, based on body weight effects. It is probable that both tumor types resulted from secondary (systemic) toxicity rather than being primarily due to a genotoxic event, and it is therefore not deemed appropriate to conduct a quantitative cancer risk assessment.

Figure 2. Benchmark Dose plot for chronic brain AChE inhibition in the male dog dosed with dietary acephate.*



* Mean response (brain AChE activity) plotted against Dose (mg/kg/d) using four BMD models: Hill, Polynomial, Power and Linear. The green vertical lines drawn to the abscissa denote the BMD (on the right) and the lower bound on the BMD, the BMDL (on the left).

B. EXPOSURE ASSESSMENT

1. Occupational Exposure (Volume 2)

Summary: The potential occupational exposure associated with the use of technical acephate was assessed for workers during mixing (M), loading (L), application (A) and flagging (F) activities. Post-application scenarios are also addressed. Estimated exposure for golf course and Home & Garden uses have also been estimated, even though many of these uses should have been cancelled in 2003 (RCD, Volume 2). The bulk of the exposure estimates were made using PHED. Estimates of acute ADD values during applications to food crops were 52 to 7580 μg/kg/d for the aerial M/L; 4.6 to 468 μg/kg/d for the ground A; 63.1 to 7490 μg/kg/d for the ground M/L; 8.3 to 1170 μg/kg/d for the ground M/L/A; for non-food crop applications, the acute ADDs ranged from 6.7 (F) to 11,100 (M/L) μg/kg/d for aerial applications and 31.6 to 2530 μg/kg/d (M/L) and 3.6 to 1170 μg/kg/d (A) for ground applications. For field workers the acute ADDs ranged from 0.8 to 443 μg/kg/d for stone fruit thinning and for applying acephate to or using golf courses, the acute ADDs were from 0.1 to 191 μg/kg/d. For Home & Garden uses, the range of acute ADDs was 1.3 to 516 μg/kg/d (M/L/A); 0.5 to 15.1 μg/kg/d for post-application on lawns and 0.22 to 1.00 μg/kg/d, for indoor uses of acephate. SADDs for agricultural workers on food crops ranged from 1.1 (ground A) to 1680 (aerial M/L) μg/kg/d; for non-food crop applications, SADDs were from 0.9 (ground A) to 306 (aerial A) μg/kg/d. For field workers the SADDs ranged from 0.1 to 68.3 μg/kg/d. Seasonal and annual ADDs were not estimated for golf course and residential exposure scenarios. AADDs for agricultural workers on food crops were from 0.7 (ground A) to 701 (aerial M/L) μg/kg/d; for non-food crop applications, AADDs were 0.4 to 128 μg/kg/d (aerial A). For field workers the AADDs were 0.01 to 28.5 μg/kg/d.

Volume 2 of this RCD was prepared by the Worker Health & Safety Branch of DPR (Zhao & Formoli, 2008). The exposure estimates were derived using five monitoring studies and PHED, for aerial and ground-based methods of application, four types of work task for aerial application (mixer, loader, applicator, flagger or M/L/A/F) with the appropriate personal protective equipment and engineering controls for each separate task. For ground-based applications, a variety of methods are listed in Table 19. Five types of formulation were considered: WP (water-soluble pellet); SP (soluble powder); DF (dry flowable); L (liquid); G (granular). The first part of Table 19 considers foodcrop applications and the second page of Table 19 addresses applications to turf, pasture, forest, sod, flowers and golf course turf. Four types of post-application exposure estimates have also been considered: scouting, harvesting, pruning and mowing (Table 20). Possible exposure to acephate on golf courses has been estimated (Table 20) along with residential exposure (Table 21).

The (acute) ADD for M/L (aerial) ranged from 52 to 7580 μg/kg/d (1200 A/day, 1 lb AI/A, 7.6% dermal absorption, 69.7 kg body weight). The lower value was obtained from a field study using a water-soluble pellet and the higher, using PHED with a soluble powder. For the M/L (ground), acute ADDs ranged from 47.5 to 7490 μg/kg/d (200 A/day, 1 lb AI/A etc.). The former was value obtained using PHED and the lower value was for a tractor-drawn spreader of a granular formulation on cotton whereas the latter was obtained for a hopper-box seed application of a soluble powder to cotton. Chemigation of acephate at 1.0 lb/A on cranberry resulted in an acute ADD estimate of 115 μg/kg/d. For the ground applicator, acute ADDs ranged from 4.6 to 468 μg/kg/d, for PHED calculations involving a tractor-drawn spreader application of a granular formulation to cotton (200 A/day, 1 lb AI/A) and handgun application of a soluble powder

formulation to trees, shrubs and outdoor floral crops (10 lbs AI/1000 gallons). The M/L/A (ground) had a range of PHED estimates of acute ADD from 8.3 to 1170 μg/kg/d. These were for a handtool shaker of a soluble powder on fire ant mounds (0.0029 lb/mound, 10 mounds/A/day) and a belly grinder application of a granular formulation to trees, shrubs and ornamentals (0.1125 lb/1000 ft^2 and 87,000 ft^2 per day), respectively. For non-crop applications of acephate (Table 19, 2nd page), PHED estimates of exposure were made, exclusively. Aerial and ground-based methods were used for 4 types of task (M/L/A/F), with 3 formulation types (SP, L, G). The (acute) ADD for aerial applications ranged from 6.7 to 11,100 μg/kg/d. The lower value was obtained for a flagger on pasture (350 A/day, 0.125 lb/A) and the higher for a M/L on turf (350 A/day, 5 lb/A). In each case a SP formulation was considered. For ground applications, the (acute) ADD estimates for the M/L ranged from 31.6 to 2530 μg/kg/d. The lower value was obtained for an airblast application to outdoor flowers (2400 gallons/day, 0.5 lb/100 gallons) and the higher for a groundboom on sod (80 A/day, 5 lb/A). The formulations used were both SP. For the ground applicator, the range of (acute) ADDs was from 3.6 to 1170 μg/kg/d. The lower value was obtained for a groundboom on pasture (80 A/day, 0.125 lb/A) and the higher for handgun on turf (5 A/day, 5 lb/A). In each case a SP formulation was considered.

Fieldworkers performing tasks such as scouting, harvesting and thinning had estimated (acute) ADD values from 0.8 to 433 μg/kg/d, for stone fruit thinning (Table 20). The lower value was for harvesters of succulent beans, 14 days after the last acephate application and the latter acute ADD was for stone fruit triming on the day after the last acephate application. For golf courses, the range of acute ADD values was from 0.1 to 191 μg/kg/d. The former value was estimated for a golfer playing 18 holes of golf in 4 hrs. *ca.* 12 hrs after acephate was applied and the latter, for a M/L preparing 100 gallons of SP formulation containing 12 lbs AI. Estimates of acute residential exposure to acephate are given in Table 21. The range of acute ADD values for the M/L/A was from 1.3 to 86.5 μg/kg/d for using a shaker cup on roses at 0.1125 lb/1000 ft^2 and using a hose-end sprayer on turf at 0.035 lb/gallon, respectively. Exposure estimates for home and garden uses of acephate are also included (Table 21) because, although withdrawn by the registrants in 2001, many of these products may still be in use. The highest acute ADD for residential use was 171 μg/kg/d for using a hose-end sprayer on ornamentals, shade trees and hedges at 0.01175 lb AI/gallon (from a monitoring study). Residential post-application exposures to acephate were also estimated, following use on lawn, and ranged from 0.5 to 15.1 μg/kg/d. These were for estimated grass ingestion by children and children's dermal exposure, respectively, following the application of 5 lb AI/A. For indoor acephate use, the range of estimated human acute ADD values were 0.22 to 1.0 μg/kg/d. These were for child hand-to-mouth exposure following a spot spray of 0.088 lb/gallon and child dermal (carpet) after a spot spray of the same formulation or child dermal (hard surface) following the use of acephate as a crack/crevice spot spray at 0.088 lb/gallon.

Seasonal and annual occupational exposure estimates are also provided in Tables 19 and 20. The (acute) ADD values were calculated as the 90% upper confidence limit on the 95th percentile of the absorbed daily dosage whereas the (seasonal) SADD estimates were calculated as the 90% upper bound confidence limit on the ADD. The (annual) AADD is the SADD amortized over the whole year, based on the number of months' exposure in the season. The LADD is the AADD amortized over a lifetime and these values were also determined in Volume 2. However, they were not used in the RCD because LADD values are generally used in cancer risk assessments, but these calculations are not considered appropriate for acephate.

The ranges of SADD and AADD values for foodcrop applications were 9.6 to 1680 μg/kg/d for the former and 4.0 to 701 μg/kg/d for the latter for the M/L (aerial); 14.0 to 1310 μg/kg/d for the

former and 8.2 to 765 μg/kg/d for the latter for the M/L (hopper box); Chemigation resulted in SADD and AADD estimates of 42.0 and 24.5, respectively; 11.9 to 6.90 μg/kg/d for tractor-drawn spreader (G) and 1310 and 765 μg/kg/d for the hopper box seed (SP), both on cotton. For the ground A, the ranges were 1.1 to 187 μg/kg/d for the former and 0.7 to 109 μg/kg/d for the latter; 10.7 to 292 μg/kg/d for the former and 6.3 to 171 μg/kg/d for the latter for the M/L/A (ground). For non-foodcrop applications, the equivalent SADD and AADD values were 61.3 and 25.5 μg/kg/d, respectively for the M/L (aerial); 14.9 to 306 μg/kg/d for the former and 6.2 to 128 μg/kg/d for the latter for the A (aerial); 1.7 to 34.7 μg/kg/d for the former and 0.7 to 14.4 μg/kg/d for the latter for the F (aerial). For the ground M/L, the corresponding SADD and AADD values were: 7.0 to 14.0 μg/kg/d for the former and 4.1 to 8.2 μg/kg/d for the latter. For the A (ground), the equivalent ranges were 0.9 to 13.0 μg/kg/d for the former and 0.4 to 7.6 μg/kg/d for the latter.

For fieldworkers, the corresponding SADD and AADD values ranged from 0.1 to 68.3 μg/kg/d and 0.01 to 28.5 μg/kg/d, respectively and for golf course exposure estimates, the SADD and AADD ranges were not determined (Table 20). Similarly, these exposure estimates were not calculated for residential uses of acephate (Table 21).

Table 19. Occupational exposure estimates for acephate in agriculture.[a/]

Job category/ Formulation [b/]	Crop/ Use rate (lb AI/A or gallon)	Acute ADD[c/] µg/kg/d	SADD[d/] µg/kg/d	AADD[e/] µg/kg/d
AERIAL				
M/L (WP) [f/]	Cotton 1.0	**52** [g/]	**9.6**	**4.0**
M/L (SP)	Ag. 1.0	**7580** [g/]	**1680**	**701**
A (SP)	Ag. 1.0	1220	408	170
F (SP)	Ag. 1.0	185	46.2	19.3
GROUND M/L				
Groundboom (SP)	Ag. 1.0	**1260**	**280**	**164**
Airblast (SP)	Citrus, non-bear 0.5	126	28.0	16.3
	Trees/shrubs 1.0	**63.1**	**14.0**	**8.2**
Handgun (SP)	Trees/shrubs/floral 1.0/100 gallon	**63.1**	**14.0**	**8.2**
Slurry seed treatment				
(SP)	Cotton 0.04/ 100 lb	505	112	65.4
(DF)	do.	63.6	15.9	9.3
Chemigation (SP)	Cranberry 1.0	115	42.0	24.5
Hopper box seed (SP)	Cotton 0.225	**7490**	**1310**	**765**
Tractor-drawn sp. (G)	Cotton 1.0	**47.5**	**11.9**	**6.9**
GROUND A				
Groundboom (SP)	Ag. 1.0	35.8	8.9	5.2
Airblast (SP)	Citrus 0.5	87.0	21.7	12.7
	Trees/shrubs 1.0/100 gallon	104	26.0	15.2
Handgun (SP)	Trees/shrubs/floral 1.0/100 gallon	**468**	**187**	**109**
Tractor-drawn sp. (G)	Cotton 1.0	**4.6**	**1.1**	**0.7**
GROUND M/L/A [c/]				
Hopper box (SP)	Cotton seed 0.225	542	111	64.6
Low pressure handwand (SP)	Trees/shrubs/floral 1.0/100 gallon	57.2	11.4	6.7
	Wasps 0.075 lb/gall.	53.6	**10.7**	**6.3**
Backpack sprayer (SP)	Trees/shrubs/floral 1.0/100 gallon	59.0	19.7	11.5
	Wasps 0.075 lb/gall.	55.3	18.4	10.7
High press. sprayer (SP)	Trees/shrubs/floral 1.0/100 gallon	468	187	109
Handtool/shaker (SP)	Fire ants 2 tsp./mnd.	**8.3**		
Belly grinder (G)	Trees/shrubs/orn. 0.1125 lb/1000 ft^2	**1170**	**292**	**171**
Shaker can (G)	Trees/shrubs/orn. 0.1125 lb/1000 ft^2	134	33.6	19.6
	0.00099 lb/pot	546	109	106
By hand (G)	Fire ants 2 tsp./mnd.	44.2		
	Trees/shrubs/orn. 0.1125 lb/1000 ft^2	62.1	12.4	7.2

Table 19 cont. Job category/ Formulation [b/]	Crop/ Use rate (lb AI/A or gallon)	Acute ADD [c/] (95th perc.) μg/kg/d	SADD [d/] (90% U.L.) μg/kg/d	AADD [e/] μg/kg/d
AERIAL				
M/L (SP)	Turf 5.0	**11,100**		
(SP)	Pasture 0.125	276	61.3	25.5
(L)	Forest 0.75	5680	**1240**	**516**
A (SP, L)	Turf 5.0	1770		
(SP, L)	Pasture 0.125	76.4	14.9	6.2
(SP, L)	Forest 0.75	458	306	128
F (SP, L)	Turf 5.0	270		
(SP, L)	Pasture 0.125	**6.7**	1.7	0.7
(SP, L)	Forest 0.75	139	34.7	14.4
GROUND M/L				
Groundboom (SP)	Pasture 0.125	63.1	14.0	8.2
	Sod 5.0	**2530**		
	Golf course turf 5.0	1260		
Airblast (SP)	Outdoor floral 0.5/100 gallon	**31.6**	7.0	4.1
Handgun (SP)	Sod 5.0	158		
Tractor-drawn sp. (G)	turf 5.0	95.0		
	Golf course 5.0	47.5		
GROUND A				
Groundboom (SP)	Pasture 0.125	**3.6**	**0.9**	**0.4**
	Sod 5.0	71.6		
	Golf course turf 5.0	35.8		
Airblast (SP)	Outdoor floral 0.5/100 gallon	52.2	13.0	7.6
Handgun (SP)	Turf 5.0	**1170**		
Tractor-drawn sp. (G)	Sod 5.0	9.1		
	Golf course turf 5.0	4.6		
Paintbrush (WP)	Window frame etc. 0.083 lb/gal w/ 2 gal.	62.2		

a/ data from Zhao & Formoli, 2008, Table 49.
b/ M/L/F/A = Mixer/Loader/Flagger/Applicator. WP= water-soluble pellet; SP= soluble powder; DF= dry flowable; L= liquid; G= granular
c/ ADD = Absorbed Daily Dosage (95^{th} percentile)
d/ SADD = Seasonal Average Daily Dosage (90% upper bound CL on ADD)
e/ AADD = Annual Average Daily Dosage (SADD x months of use per year/12)
f/ calculated from a field monitoring study, otherwise using PHED
g/ highest and lowest are bolded for each job category.

Table 20. Exposure estimates for acephate: post-application or golf courses.[a/]

Job category [b/] REI/PHI (days) [h/]	Crop/ Use rate (lb AI/A)	Acute ADD [c/] (95th perc.) μg/kg/d	SADD [d/] (90% U.L.) μg/kg/d	AADD [e/] μg/kg/d
FIELD WORKERS[b/]				
scout (1)	Cotton	32.7	1.9	0.63
harvest (14)	Cauliflower	1.6	0.5	0.47
harvest (14)	Succulent bean	**0.8**	**0.1**	**0.01**
pruning (1)	Citrus tree	**163** [g/]	**68.3**	**28.5**
thinning	Stone fruit	433	-	-
pruning/ harvest (1)	Greenhouse rose	7.4	5.9	5.9
mowing (0.5)	Turfgrass	1.0		
harvest (0.5)	Sod	12.9		
tying/pruning	Grape	90		
nursery pruning	Ornamental	4.2		
GOLF COURSE EXPOSURE				
M/L (SP [f/]	5.0 lb AI/A	**191**		
A (SP) [f/]	5.0 lb AI/A	56.4		
mowing	5.0 lb AI/A	1.3		
golfing	5.0 lb AI/A	**0.1**		
maintaining	5.0 lb AI/A	20.8		

a/ data from Zhao & Formoli, 2008

b/ M/L/A = Mixer/Loader/Applicator; SP= soluble powder

c/ ADD = Absorbed Daily Dosage(95^{th} percentile)

d/ SADD = Seasonal Average Daily Dosage (90% upper bound CL on ADD)

e/ AADD = Annual Average Daily Dosage (SADD x months of use per year/12)

f/ calculated from a field monitoring study, otherwise using PHED

g/ highest and lowest are bolded for each job category.

h/ REI = Re-Entry Interval; PHI = Pre-Harvest Interval. These were assumed in the PHED calculations.

Table 21. Exposure estimates for acephate: residential.[a/]

Application category[b/]	Crop / pest / use rate (lb AI/A or gallon)	Acute ADD[c/] µg/kg/d
Residential/Institute M/L/A		
Low pressure wand	Ornamentals, flowers, shrubs, trees, fire ants = 0.023 lb/gallon	6.6
Backpack sprayer	Turf = 0.035 lb/gallon	10.3
	Fire ant (non-crop) = 0.47 lb/5 gal.	68.9
	PCO = 0.088 lb/gallon	**516**
Hose-end sprayer	Fire ants = 0.023 lb/gallon	56.8
	Turf = 0.035 lb/gallon	86.5
	Roses, flowers, shrubs, trees = 0.0076 lb/gallon	18.8
	Ornam., turf = 0.058 lb/1000 ft^2	57.3
Hose-end sprayer	Ornam., shade trees, hedges = 0.01175 lb/gallon	171
Sprinkling can	Ornamentals, flowers, shrubs, trees, fire ants = 0.023 lb/gallon	NA
	Turf = 0.035 lb/gallon	NA
	Roses, flowers, shrubs, trees = 0.0076 lb/gallon	NA
Handtool/shaker can	Fire ants = 0.0069 lb/mound	5.6
Shaker cup	Ornamentals = 0.5 lb/1000 ft^2	5.8
	Roses == 0.1125 lb/1000 ft^2	**1.3**
Aerosol can	Crack & crevice = 0.01 lb/can	27.7
	Ornamentals = 0.03 lb/can	83.0
Low pressure hand wand	Wasps = 0.075 lb/gallon	53.6
	Fire ants (non-crop) = 0.47 lb/gal.	67.2
	PCO (residential) = 0.088 lb/gal.	57.8
	PCO (commercial) = 0.088 lb/gal.	62.6
Paintbrush	Window frame = = 0.083 lb/gal.	65.6
Residential Post-application: lawns		
Adult dermal	Turf = 5.0	9.1
Children dermal	Turf = 5.0	**15.1**
Children hand-to-mouth	Turf = 5.0	3.8
Children grass ingestion	Turf = 5.0	**0.5**
Residential Indoor		
Adult dermal (hard surf.)	Crack/crev. spot spray = 0.088 lb/g	0.60
Child dermal (hard surf.)	Crack/crev. spot spray = 0.088 lb/g	**1.00**
Adult dermal (carpet.)	spot spray = 0.088 lb/g	0.60
Child dermal (carpet)	spot spray = 0.088 lb/g	**1.00**
Child hand-to-mouth	spot spray = 0.088 lb/g	**0.22**

a/ data from Zhao & Formoli, 2008

b/ M/L/A = Mixer/Loader/Applicator; SP= soluble powder

c/ ADD = Absorbed Daily Dosage(95^{th} percentile)

d/ SADD = Seasonal Average Daily Dosage (90% upper bound CL on ADD)

2. Dietary Exposure

DPR evaluates the dietary exposure to an active ingredient using two processes: (1) use of residue levels detected in RACs (raw agricultural commodities) to estimate the exposure from all label uses, and (2) use of tolerance levels to estimate the exposure to individual commodities (see Section VI). For the evaluation of risk to detected residue levels, the total exposure in the diet is determined for all label-approved raw agricultural commodities, processed forms, and animal products (meat and milk) that have established U.S. EPA tolerances. Tolerances may be established for the parent compound and associated metabolites. DPR considers these metabolites and other degradation products that may be of toxicological concern in the dietary assessment.

The percentage of a commodity (crop) that is treated with a particular pesticide is often considered relevant for dietary exposure. For short-term (acute) dietary exposure, it is assumed that 100 percent of each commodity has been treated and therefore contains a residue. However, for long-term (chronic) dietary exposure, it is reasonable to suppose that only a proportion of any specific commodity has been treated with a particular pesticide. Therefore, a percentage crop-treated adjustment can be made for specific commodities.

Residue Data

Primary and Secondary Residues

Data for potential pesticide residues associated with U.S. EPA and California label-approved direct food uses with tolerances, and with any secondary residues in animal tissues, are necessary for estimating human dietary exposures. The sources of residue data for dietary exposure assessment include DPR and federal monitoring programs, field trials, and survey studies by registrants. Residue data obtained from the monitoring programs are often preferred because they represent a realistic estimate of potential exposure. When residues are at levels higher than established tolerances, they are not utilized in the dietary exposure assessments since they are illegal. Additionally, DPR evaluates the potential risk from consuming commodities with residues over tolerance levels using an expedited acute risk assessment process. In the absence of data, surrogate data are used from the same crop group as defined by U.S. EPA, or theoretical residues equal to U.S. EPA tolerances are used.

The U. S. Department of Agriculture (USDA) is responsible for the Pesticide Data Program (PDP), a nationwide cooperative monitoring program. The PDP is designed to collect objective, comprehensive pesticide residue data for risk assessments. There have also been determinations of residues in secondary animal products because there are tolerances for such commodities. Because of its short persistence in the field, there is little likelihood of acephate leaching into groundwater. Analysis was for parent and methamidophos because this is the only degradate anticipated to have significant toxicity. When no residue was detected in a sample, it was assumed that acephate was present at the LOD or zero, if the RAC was not treated with acephate. Residue data in RACs for the determination of potential dietary exposure to acephate were obtained from (1) registrant field and processing studies and (2) USDA 1994-7 PDP monitoring program.

Acute Exposure

Estimates of potential acute dietary exposure use the highest measured residue values at or below the tolerance for each commodity. The following assumptions are used to estimate potential acute dietary exposure from measured residues: (1) the residue does not change over time, (2) the concentration of residue does not decrease when the raw agricultural commodity is washed, (3) processing is assumed to result in a residue level equivalent to or higher than that in the raw agricultural commodity; an adjustment factor may be used and (4) all foods that are consumed will contain the highest reported residue. The default procedure assumed that "below detection limit" residues were equal to 100% of the LOD for each commodity.

Residue trials show that acephate and methamidophos residues would be anticipated on an acute basis, following the use of acephate, in head lettuce, cotton, beans (all types), celery, peppers (all types), Brussel's sprouts, cottonseed, cranberry, macadamia nut, peanut, soybean, plus secondary residues in cattle, egg, goat, horse, pork, poultry, sheep. (Table 1 and Appendix B). Default residues of the LOD were used for each commodity for the estimation of potential acute dietary exposure when no residue was detected in a sample. However, for unprocessed RACs, when using a probabilistic (Monte Carlo) program, it is considered appropriate to use zero residue, in place of the LOD, for a proportion of the samples to better reflect "percentage of crop-treated" or PCT. In practice, PCT data were used for head lettuce, green beans, celery, peppers and cauliflower (Table 22) because these are the only five RACs for which good PCT data are available for acephate.

Chronic Exposure

Estimates of potential chronic dietary exposure used the average of measured and "below detection limit" residue values for each commodity. The default procedure assumed that "below detection limit" residues were equal to 50% of the LOD for each commodity. The following assumptions were used to estimate potential chronic dietary exposures from measured residues: (1) the residue level does not change over time, (2) residues are not reduced by washing the RAC, (3) processing is assumed to be at a level equivalent to the RAC residue level that may be multiplied by an adjustment factor (4) exposures to a commodity at all reported residue levels do occur, *i.e.* a commodity with the average calculated residue is consumed every day at an annual average level (dosage) and (5) except where stated, 100% of each crop was treated with a particular pesticide.

Field residue trials (Table 1, Appendix B) showed that acephate (parent) and methamidophos residues would be anticipated on an annual basis in head lettuce, cotton, beans (all types), celery and peppers (all types), Brussel's sprouts, cottonseed, cranberry, macadamia nut, peanut, soybean, plus secondary residues in cattle, egg, goat, horse, pork, poultry, sheep. Default residues of 50% of LOD were used for each commodity to estimate potential chronic (annual) dietary exposure when no residue was detected. Otherwise, the mean annualized residue was assumed, namely, 0.026 ppm (head lettuce), 0.0086-0.0166 ppm (beans) and 0.027 ppm (celery) – Appendix B.

Dietary Exposure Analysis

Acute Exposure

Acute dietary exposure analyses were conducted using the DEEM™ program (Novigen, 1998). This program estimates the distribution of user-day (consumer-day) exposure for the overall U.S. population and specific population subgroups. A user-day is any day in which at least one food from the specific commodity list is consumed. The analysis uses data from the USDA CSFII (Continuing Survey of Food Intakes of Individuals) from a 1994-1998 survey. The program was used to calculate the 95th and 99.9$^{th.}$ percentile of user-day exposures (Table 22).

The potential acute dietary exposure to acephate from all labeled uses at the 95th percentile ranged from 0.056 to 0.181 μg/kg/d (Monte Carlo) using the 1994-1998 CSFII survey data (Table 20). Females (13-19 yrs., not pregnant or nursing) and Seniors (55+) were the low exposure groups and Children (1-6 yrs) were the high exposure group. Potential acute dietary exposure to acephate, from all labeled uses, at the 99.9$^{th.}$ percentile, ranged from 1.063 for Females (13-19 yrs.), not pregnant or nursing to 2.427 μg/kg/d (Infants, nursing) (Table 22). Appendix B gives the complete dietary analysis.

Chronic Exposure

The potential chronic dietary exposure was also calculated using DEEM™ software. The food consumption data for the chronic analysis was also based on the 1994-98 USDA Nationwide Food Consumption Survey. Calculations of annualized mean dietary exposure were made, adjusting for percentage of crop-treated with acephate in California (Appendix B), using the point estimate approach (Table 23).

All potential dietary exposure was pooled by combining acephate residues in all commodities on which acephate use is registered. The mean potential annual dietary exposure ranged from 0.01 (nursing infants) to 0.045 μg/kg/d (children 1-6 yrs.) using the 1994-1998 CSFII survey data. Percentage of crop-treated data (Appendix B) indicate that approximately 70% of head lettuce, 10-60% of beans (all), 70% of celery, 50% peppers and 30% cauliflower are treated with acephate in California.

Lifetime Exposure

The results of the chronic toxicity studies in rodents and in the genotoxicity tests (described in Section IIID and IIIE) suggest that there is little or no risk of cancer from the use of acephate. Therefore, lifetime exposure and risk are not considered relevant in the dietary assessment of the toxicology of acephate.

3. Combined Occupational and Dietary Exposure.

For all conventional crop applications (food crop and non-food crop), for all occupational tasks involving acephate (Table 19), the addition of estimated acute dietary exposure (0.116μg/kg/d, US population, 16+ yrs.) increases occupational exposure by <3%. However, for the following low-exposure tasks (Table 20), the increases in occupational exposure after the addition of dietary exposure are >3%: for harvesting cauliflower, 1.6 to 1.7 μg/kg/d (6.3%), succulent beans, 0.8 to 0.9 μg/kg/d (13%); turfgrass or golfcourse mowing, 1.0 to 1.1 (10%) and 1.3 to 1.4 (7%) μg/kg/d, respectively and golfing, 0.1 to 0.2 μg/kg/d (100%). For Home & Garden

applications (Table 21), the addition of dietary exposure to that experienced during or after application was also <3%, with the exceptions of low exposure scenarios such as the use of a shaker cup on roses, 1.3 to 1.4 (7%) μg/kg/d, child grass ingestion after application to lawns, 0.5 to 0.6 (20%) μg/kg/d. All modeled indoor residential tasks, which were associated with low exposures, gave increases >3%. These included adult dermal (hard surface or carpet), 0.6 to 0.7 (17%) μg/kg/d; child dermal (hard surface or carpet), 1.0 to 1.1 (10%) μg/kg/d; child (hand-to-mouth), 0.22 to 0.32 (45%) μg/kg/d.

Likewise, for estimated chronic dietary exposure (0.02 μg/kg/d, US population, all seasons) added to occupational exposure, for the great majority of occupational tasks involving acephate, increases occupational exposure by <3%. However, for the following low exposure tasks, the increases in the AADD after the addition of chronic dietary exposure are: 0.40 to 0.42 μg/kg-d (5%) for the A of groundboom on pasture; 0.47 to 0.49 μg/kg/d (4%) for harvesting cauliflower; 0.03 to 0.05 μg/kg/d (67%) for harvesting succulent beans; 0.22 to 0.24 μg/kg/d (9%) for child hand-to-mouth exposure after indoor residential use.

Table 22. Potential acute dietary exposure to acephate at the 95th and 99.9th. percentile in all commodities with U.S. EPA tolerances – Monte Carlo (probabilistic) model.[a/]

Population subgroup	ACUTE EXPOSURE (μg/kg/d) 95th	99.9th. percentile [b/]
US Pop. all seasons	0.093	1.404
Western Region	0.104	1.488
Hispanics	0.114	1.661
Non-Hispanic Whites	0.091	1.366
Non-Hispanic Blacks	0.079	1.257
Non-Hispanic Other	0.109	1.674
All Infants	0.145	2.099
Infants (nursing)	0.064	**2.427**[c/]
Infants (non-nursing)	0.158	2.038
Children (1-6 yrs)	**0.181**	2.034
Children (7-12 yrs)	0.089	1.346
Females (13-19 yrs, not preg. or nurs.)	**0.056**	**1.063**[c/]
Females (13+ yrs, pregnant, not nurs.	0.061	1.659
Females (13+ yrs, nursing)	0.060	1.112
Females (20+ yrs, not preg. or nurs.)	0.057	1.320
Females (13-50 yrs.)	0.058	1.286
Males (13-19 yrs)	0.065	1.103
Males (20+ yrs)	0.059	1.311
Seniors (55+ yrs)	**0.056**	1.281
US Population (16+ yrs)	0.058	1.301

a/ DEEM™ was used to calculate estimates of acute dietary exposure for all registered RACs, including head lettuce, cotton, beans (all types), celery and peppers (all types). These are the major use crops, accounting for >82% of acephate used in agriculture, 1996-2000 (Appendix B). Based on user-day exposure estimates.

b/ %CT data were used for 5 RACs, for which good use data are available: head lettuce, green beans, celery, bell and chili peppers and cauliflower.

c/ highest and lowest values are in bold type.

Table 23. Potential chronic dietary exposure to acephate in all commodities with U.S. EPA tolerances. [a/]

Population subgroup	CHRONIC EXPOSURE (annualized mean) μg/kg/d
	Percent Crop Treated (%CT)
US Pop. all seasons	0.022
Western Region	0.024
Hispanics	0.026
Non-Hispanic Whites	0.021
Non-Hispanic Blacks	0.017
Non-Hispanic Other	0.025
All Infants	0.021
Infants (nursing)	**0.010**[b/]
Infants (non-nursing)	0.025
Children (1-6 yrs)	**0.045**[b/]
Children (7-12 yrs)	0.027
Females (13-19 yrs, not preg or nursing	0.016
Females (13+ yrs, preg not nursing	0.021
Females (13+ yrs, nursing)	0.023
Females (20+ yrs, not preg or nursing	0.018
Females (13-50 yrs.)	0.018
Males (13-19 yrs)	0.018
Males (20+ yrs)	0.018
Seniors (55+ yrs)	0.018

a/ DEEM™ annualized average dietary exposure head lettuce, cotton, beans (all types), celery and peppers (all types),cauliflower, Brussel's sprouts, cottonseed, cranberry, macadamia nut, peanut, soybean, plus secondary residues in cattle, egg, goat, horse, pork, poultry, sheep.

b/ highest and lowest values are in bold type.

C. RISK CHARACTERIZATION

The risk characterization process consists of calculating a margin of exposure (MOE) by dividing the critical acute, subchronic or chronic NOEL value for a specific toxicological endpoint (Section IV A) by an estimate of human exposure (Section IV B). The critical NOEL values were derived from studies using oral capsules in humans (acute) and dietary in the rat and dog, for seasonal and annual exposure, respectively. Because acephate is considered to be absorbed completely after oral exposure (Section III A), no route-to-route extrapolation was necessary in dividing these NOEL values by absorbed daily dosage to calculate MOE values for occupational exposure.

Occupational Exposure

The estimates of occupational and residential exposure (Tables 19-21) were used to calculate MOE values for various work tasks (Tables 24-26). The acute MOEs were obtained by dividing the acute NOEL (1.0 mg/kg/d, human study) by the acute ADD (90% UCL on 95th percentile). The (acute) MOEs for the M/L (aerial) ranged from 0.1 (PHED with a soluble powder) to 19 (field study using a water-soluble pellet on cotton). For the M/L (ground), MOEs ranged from 0.8 (groundboom application of a soluble powder) to 21 (tractor-drawn spreader of a granular formulation on cotton). For the ground applicator, MOEs ranged from 2 (handgun application of a soluble powder to trees, shrubs and outdoor floral crops) to 220 (tractor-drawn spreader application of a granular formulation to cotton). The M/L/A (ground) gave a range of PHED estimates of MOE, from 0.9 (belly grinder application of a granular formulation to trees, shrubs and ornamentals) to 120 (handtool shaker with a soluble powder on fire ant mounds). For non-foodcrop applications of acephate (Table 24, 2nd page), PHED estimates of exposure were made, exclusively. Aerial and ground-based methods were used for 4 types of task (M/L/A/F), with 3 formulation types (SP, L, G). The (acute) MOE for aerial applications ranged from 0.1 (M/L on turf) to 150 (flagger on pasture). For ground applications, the (acute) MOE estimates for the M/L ranged from 0.4 (groundboom on sod) to 30 (airblast spray on outdoor flowers). The formulations used were SP. For the ground applicator, the range of (acute) MOEs was from 0.9 (handgun on turf) to 280 (groundboom on pasture). In each case a SP formulation was considered. For the use of a paintbrush on window frames, the estimated MOE was 16.

Fieldworkers performing tasks such as scouting and harvesting had estimated (acute) MOE values from 6 (pruning citrus trees) to 1,200 (harvesters of succulent beans) (Table 25). For golf courses, the range of MOE values was from 5 (M/L preparing 100 gallons of SP formulation containing 12 lbs AI.) to 10,000, for a golfer playing 18 holes of golf in 4 hrs. *ca.* 12 hrs after acephate was applied.

Had the lowest, acute animal NOEL (0.5 mg/kg/d, for AChE inhibition in a rat neurotoxicity study) been used for the calculation of MOEs (instead of a human NOEL), then the MOEs for acute exposure would have been halved. Furthermore, there would be an extra 10-fold factor applied to the MOE for it to be considered adequate *i.e.* a MOE of 100 would be needed instead of MOE=10, when a human study is used for risk assessment.

In residential/institutional settings, the MOEs for the M/L/A were from 2 to 770. These were for the PCO using a backpack sprayer on fire ants and for the use of a shaker cup on roses, respectively. Post-application exposures resulted in MOEs from 66 to 2000. These were for children (dermal) and grass ingestion, associated with turf use. Residential indoor MOEs ranged from 1000 to 4500. These were for children (dermal) on hard surface or carpet after

spot spray and children, for hand-to-mouth exposure.

Seasonal and annual occupational MOE estimates are also provided in Tables 24 to 26. These estimates are (acute) MOE values at the 90% upper bound CL (seasonal) or the seasonal amortized over a full year (annual). MOE estimates for home and garden uses of acephate have been included in this RCD even though these labels were withdrawn in 2002.
The seasonal MOEs were derived by dividing the subchronic NOEL (0.12 mg/kg/d, rat dietary neurotoxicity study) by the (seasonal) SADD for each task (Tables 19 to 21). Similarly, the annual MOE values were calculated by dividing the chronic, estimated NOEL (0.09 mg/kg/d, dog, 1-yr dietary study) by the AADD for each task (Tables 19 to 21).

The MOE values for seasonal exposure (Table 24) had the following ranges, for generally the same sub-groups of tasks as for acute workers: M/L (aerial) 0.1 to 12; M/L (ground) 0.1 to 10; A (ground) 0.6 to 110 and M/L/A (ground) 0.4 to 11, for food crops, and M/L (aerial) 0.1 to 70; M/L (ground) 9 to 17 and A (ground) 9 to 130, for non-food crops. The MOE values for corresponding annual occupational exposure were, as follows: M/L (aerial) 0.1 to 22; M/L (ground) 0.1 to 13; A (ground) 0.8 to 130 and 0.5 to 14, for food crops and for the M/L (aerial) 0.1 to 4, F (aerial) 6 to 130; M/L (ground) 11 to 22 and A (ground) 12 to 230, for non-food crops.

Post-application tasks resulted in the following ranges of MOE values: seasonal MOE values ranged from 2 to 1200 and annual MOE values from 3 to 3000, for citrus tree pruning and harvesting succulent beans, respectively, for both exposure durations. Seasonal and annual MOE values have not been determined for golf course and residential exposure scenarios.

Table 24. MOE estimates after occupational exposure to acephate in agriculture.[a/]

Job category/ Formulation [b/]	Crop/ Use rate (lb AI/A or gallon)	Acute MOE[c/]	Seasonal MOE[d/]	Annual MOE [e/]
AERIAL				
M/L (WP) [f/]	Cotton 1.0	**19** [g/]	**12**	**22**
M/L (SP)	Ag. 1.0	**0.1**[g/]	**0.1**	**0.1**
A (L)	Ag. 1.0	0.8	0.3	0.5
F (L)	Ag. 1.0	5	3	5
GROUND M/L				
Groundboom (SP)	Ag. 1.0	**0.8**	**0.4**	**0.5**
Airblast (SP)	Citrus, non-bear 0.5	8	4	6
	Trees/shrubs 1.0	**16**	**9**	**11**
Handgun (SP)	Trees/shrubs/floral 1.0/100 gallon	**16**	**9**	**11**
Slurry seed treatment				
(SP)	Cotton 0.04/ 100 lb	2	1	1
(DF)	do.	16	8	10
	Cranberry 1.0	9	3	4
Chemigation (SP)				
Hopper box seed (SP)	Cotton 0.225	**0.1**	**0.1**	**0.1**
Tractor-drawn sp. (G)	Cotton 1.0	**21**	**10**	**13**
GROUND A				
Groundboom (SP)	Ag. 1.0	28	13	17
Airblast (SP)	Citrus 0.5	11	6	7
	Trees/shrubs 1.0/100 gallon	10	5	6
Handgun (SP)	Trees/shrubs/floral 1.0/100 gallon	**2**	**0.6**	**0.8**
Tractor-drawn sp. (G)	Cotton 1.0	**220**	**110**	**130**
GROUND M/L/A [c/]				
Hopper box (SP)	Cotton seed 0.225	1.8	1	1
Low pressure handwand (SP)	Trees/shrubs/floral 1.0/100 gallon	17	11	13
	Wasps 0.075 lb/gall.	19	**11**	**14**
Backpack sprayer (SP)	Trees/shrubs/floral 1.0/100 gallon	17	6	8
	Wasps 0.075 lb/gall.	18	7	8
High press. sprayer (SP)	Trees/shrubs/floral 1.0/100 gallon	2	0.6	0.8
Handtool/shaker (SP)	Fire ants 2 tsp./mnd.	**120**		
Belly grinder (G)	Trees/shrubs/orn. 0.1125 lb/1000 ft^2	**0.9**	**0.4**	**0.5**
Shaker can (G)	Trees/shrubs/orn. 0.1125 lb/1000 ft^2	7	4	5
By hand (G)	0.00099 lb/pot	2	1	0.8
	Fire ants 2 tsp./mnd.	23		
	Trees/shrubs/orn. 0.1125 lb/1000 ft^2	16	10	12

Table 24 cont. Job category/ Formulation [b/]	Crop/ Use rate (lb AI/A or gallon)	Acute MOE [c/]	Seasonal MOE [d/]	Annual MOE [e/]
AERIAL				
M/L (SP)	Turf 5.0	**0.1**		
(SP)	Pasture 0.125	4	0.2	4
(L)	Pasture/forest 0.75	1	0.3	0.5
(L)	Forest 0.75	0.31	**0.1**	**0.1**
A (SP, L)	Turf 5.0	0.6		
(SP, L)	Pasture 0.125	13	8	15
(SP, L)	Forest 0.75	2	0.4	0.7
F (SP, L)	Turf 5.0	4		
(SP, L)	Pasture 0.125	**150**	70	130
(SP, L)	Forest 0.75	7	3	6
GROUND M/L				
Groundboom (SP)	Pasture 0.125	16	9	11
	Sod 5.0	**0.4**		
	Golf course turf 5.0	0.8		
Airblast (SP)	Outdoor floral 0.5/100 gallon	**30**	17	22
Handgun (SP)	Sod 5.0	6		
Tractor-drawn sp. (G)	turf 5.0	11		
	Golf course 5.0	20		
GROUND A				
Groundboom (SP)	Pasture 0.125	**280**	**130**	**230**
	Sod 5.0	14		
	Golf course turf 5.0	28		
Airblast (SP)	Outdoor floral 0.5/100 gallon	19	9	12
Handgun (SP)	Turf 5.0	**0.9**		
Tractor-drawn sp. (G)	Sod 5.0	110		
	Golf course turf 5.0	220		
Paintbrush (WP)	Window frame etc. 0.083 lb/gal w/ 2 gal.	16		

a/ data from Zhao & Formoli, 2008, Table 49.
b/ M/L/F/A = Mixer/Loader/Flagger/Applicator. WP= water-soluble pellet; SP= soluble powder; DF= dry flowable; L= liquid; G= granular
c/ Acute MOE = ratio of critical acute (human) NOEL of 1 mg/kg/d to ADD.
d/ Seasonal MOE = ratio of critical subchronic (rat) NOEL of 0.12 mg/kg/d to SADD.
e/ Chronic MOE = ratio of critical chronic (dog) NOEL of 0.09 mg/kg/d to AADD.
f/ calculated from a field monitoring study, otherwise using PHED
g/ highest and lowest are bolded for each job category.

Table 25. MOE estimates for acephate: post-application or golf courses.[a/]

Job category[b/] REI/PHI (days)[f/]	Crop/ Use rate (lb AI/A)	Acute MOE[c/]	Seasonal MOE[d/]	Annual MOE[e/]
FIELD WORKERS[b/]				
scout (1)	Cotton	31	63	140
harvest (14)	Cauliflower	630	240	190
harvest (14)	Succulent bean	**1200**[g/]	**1200**[g/]	**3000**[g/]
pruning (1)	Citrus tree	**6**[g/]	**2**[g/]	**3**[g/]
pruning/ harvest (1)	Greenhouse rose	130	20	15
mowing (0.5)	Turfgrass	1000		
harvest (0.5)	Sod	78		
tying/pruning	Grape	11		
nursery pruning	Ornamental	240		
GOLF COURSE EXPOSURE				
M/L (SP[h/]	5.0 lb AI/A	**5**[g/]		
A (SP)[h/]	5.0 lb AI/A	18		
mowing	5.0 lb AI/A	770		
golfing	5.0 lb AI/A	**10,000**[g/]		
maintaining	5.0 lb AI/A	48		

a/ data from Zhao & Formoli, 2008.

b/ M/L/A = Mixer/Loader/Applicator; SP= soluble powder.

c/ Acute MOE = ratio of critical acute (human) NOEL of 1 mg/kg/d to ADD (Absorbed Daily Dosage, 90% UCL on 95th percentile).

d/ Seasonal MOE = ratio of critical subchronic (rat) NOEL of 0.12 mg/kg/d to SADD (Seasonal Average Daily Dosage, 90% UCL on ADD).

e/ Chronic MOE = ratio of critical chronic (dog) NOEL of 0.09 mg/kg/d to AADD (Annual Average Daily Dosage, SADD x months of use per year/12).

f/ REI = Re-Entry Interval; PHI = Pre-Harvest Interval. These were assumed in the PHED calculations.

g/ highest and lowest are bolded for each job category.

h/ calculated from a field monitoring study, otherwise using PHED.

Table 26. MOE estimates for acephate: residential.[a/]

Application category [b/]	Crop / pest / use rate (lb AI/A or gallon)	MOE [c/]
Residential/Institute M/L/A		
Low pressure wand	Ornamentals, flowers, shrubs, trees, fire ants = 0.023 lb/gallon	150
Backpack sprayer	Turf = 0.035 lb/gallon	97
	Fire ant (non-crop) = 0.47 lb/5 gal.	14
	PCO = 0.088 lb/gallon	**2**
Hose-end sprayer	Fire ants = 0.023 lb/gallon	18
	Turf = 0.035 lb/gallon	12
	Roses, flowers, shrubs, trees = 0.0076 lb/gallon	53
	Ornam., turf = 0.058 lb/1000 ft^2	17
Hose-end sprayer	Ornam., shade trees, hedges = 0.01175 lb/gallon	6
Sprinkling can	Ornamentals, flowers, shrubs, trees, fire ants = 0.023 lb/gallon	NA
	Turf = 0.035 lb/gallon	NA
	Roses, flowers, shrubs, trees = 0.0076 lb/gallon	NA
Handtool/shaker can	Fire ants = 0.0069 lb/mound	180
Shaker cup	Ornamentals = 0.5 lb/1000 ft^2	170
	Roses == 0.1125 lb/1000 ft^2	**770**
Aerosol can	Crack & crevice = 0.01 lb/can	36
	Ornamentals = 0.03 lb/can	12
Low pressure hand wand	Wasps = 0.075 lb/gallon	19
	Fire ants (non-crop) = 0.47 lb/gal.	15
	PCO (residential) = 0.088 lb/gal.	17
	PCO (commercial) = 0.088 lb/gal.	16
Paintbrush	Window frame = = 0.083 lb/gal.	15
Residential Post-application: lawns		
Adult dermal	Turf = 5.0	110
Children dermal	Turf = 5.0	**66**
Children hand-to-mouth	Turf = 5.0	260
Children grass ingestion	Turf = 5.0	**2000**
Residential Indoor		
Adult dermal (hard surf.)	Crack/crev. spot spray = 0.088 lb/g	1700
Child dermal (hard surf.)	Crack/crev. spot spray = 0.088 lb/g	**1000**
Adult dermal (carpet.)	spot spray = 0.088 lb/g	1700
Child dermal (carpet)	spot spray = 0.088 lb/g	**1000**
Child hand-to-mouth	spot spray = 0.088 lb/g	**4500**

a/ data from Zhao & Formoli, 2008

b/ M/L/A = Mixer/Loader/Applicator; PCO is pest control officer.

c/ MOE = Ratio of critical acute (human) NOEL of 1 mg/kg/d to ADD.

Dietary Exposure

Acute Exposure

The margin of exposure (MOE) for each population subgroup for potential acute dietary exposure to acephate is given in Table 27. These values were derived from the dietary exposure values (Table 22) for the 8 registered commodities with the highest residue contribution of the 33 RACs with human consumption. These are beans, Brussel's sprouts, cauliflower, celery, cottonseed meal, head lettuce, chili and bell peppers and soybean. The MOE values, for exposure at the 95th percentile, ranged from 5,530 for Children, 1-6 yrs, to 18,000, for Females, 13+ (not pregnant or nursing) and Seniors (55+) yrs. At the 99.9$^{th.}$ percentile of exposure, the equivalent MOE figures were 410 to 910 for Infants (nursing) and Males (13-19 yrs.), respectively.

Chronic Exposure

The margin of exposure for each population subgroup following potential chronic (annual, average) dietary exposure to acephate has been calculated, with DEEM® software, using point estimates (Table 28). These values were derived from the chronic exposure values (Table 23) using all registered commodities, with adjustment for percentage of crop-treated. The MOE values ranged from 1980, for children (1-6 yrs.), to 9090 for nursing infants (<1 yr.) using %CT.

Combined Occupational and Dietary Exposure

For the great majority of occupational tasks involving acephate, the addition of estimated acute dietary exposure reduced occupational MOE values by <3%. For the following (low exposure) tasks, the reductions in occupational MOEs after the addition of dietary exposure are >3%: MOE from 625 to 590 (6%) for harvesting cauliflower; from 1,200 to 1100 (8%) for harvesting succulent beans; from 1,000 to 910 (9%) for turfgrass or 770 to 710 (8%) for golf course mowing; from 10,000 to 5,000 (50%) for golfing. For Home & Garden applications, the decrease in MOE associated with the addition of dietary exposure to that experienced during or after application was also <3%, with the exceptions of low exposure scenarios such as the use of a shaker cup on roses, 770 to 710 (8%), child grass ingestion after application to lawns, 2000 to 1700 (18%). All modeled indoor residential tasks, which were associated with low exposures, gave decreases in MOE >3% when dietary exposure was added. These included adult dermal (hard surface or carpet), 1700 to 1400 (21%); child dermal (hard surface or carpet), 1000 to 910 (9%); child (hand-to-mouth), 4500 to 3100 (45%).

Likewise, for estimated chronic dietary exposure (0.02 μg/kg/d, US population, all seasons) added to occupational exposure, for the great majority of occupational tasks involving acephate, increases occupational exposure by <3%. However, for the following low exposure tasks, the increases in the AADD resulted in decreases in MOE after the addition of chronic dietary exposure of >3%: 230 to 210 (9%) for the A of groundboom on pasture; 190 to 180 (5%) for harvesting cauliflower; 3000 to 1800 (40%) for harvesting succulent beans.

Table 27. MOE values for potential acute dietary exposure to acephate at the 95th and 99.9th. percentile using DEEM® in all commodities with U.S. EPA tolerances.[a,b/]

Population subgroup	MOE for ACUTE EXPOSURE[c/]	
	95th [d/]	99.9th. percentile [d/]
US Pop. all seasons	10,700	710
Western Region	9,600	670
Hispanics	8,770	600
Non-Hispanic Whites	11,000	730
Non-Hispanic Blacks	12,700	800
Non-Hispanic Other	9,170	600
All Infants	6,880	480
Infants (nursing)	15,500	**410** [e/]
Infants (non-nursing)	6,330	490
Children (1-6 yrs)	**5,530** [e/]	490
Children (7-12 yrs)	11,200	740
Females (13-19 yrs, not preg or nursing	**18,000** [e/]	940
Females (13+ yrs, preg, not nursing	16,400	600
Females (13+ yrs, nursing)	16,800	900
Females (20+ yrs, not preg. or nursing	17,500	760
Females (13-50 yrs.)	17,400	780
Males (13-19 yrs)	15,300	**910** [e/]
Males (20+ yrs)	16,900	760
Seniors (55+ yrs)	**18,000** [e/]	780
U.S. Population (16+ yrs.)	17,400	770

a/ from Carr, 2002 (Appendix B).
b/ Residues on all labeled RACs (see Table 20).
c/ MOE= NOEL / Acute Dietary intake
NOEL of 1.0 mg/kg/d based on plasma ChE inhibition in a human study (Freestone & McFarlane, 2001).
d/ DEEM™ probabilistic (Monte Carlo) estimate of dietary exposure (Table 20).
e/ highest and lowest values are in bold type.

Table 28. MOE values for chronic dietary exposure to acephate residues using DEEM® in all commodities with U.S. EPA tolerances.[a/]

Population subgroup	MOE for CHRONIC EXPOSURE [b/] Percent Crop Treated (%CT)
US Pop. all seasons	4170
Western Region	3700
Hispanics	3420
Non-Hispanic Whites	4200
Non-Hispanic Blacks	5180
Non-Hispanic Other	3620
All Infants	4390
Infants (nursing)	**9090** [c/]
Infants (non-nursing)	3670
Children (1-6 yrs)	**1980**[c/]
Children (7-12 yrs)	3370
Females (13-19 yrs, not preg or nursing	5670
Females (13+ yrs, preg, not nursing	4290
Females (13+ yrs, nursing)	3860
Females (20+ yrs, not preg or nursing	4880
Females (13-50 yrs.)	4910
Males (13-19 yrs)	4920
Males (20+ yrs)	4920
Seniors (55+ yrs)	5070

a/ DEEM® annual average dietary exposure, all labeled RACs (Table 21).

b/ MOE= NOEL / Chronic Dietary intake
estimated NOEL of 0.09 mg/kg/d based on brain AChE inhibition in a dog 1-yr. study, with a LOEL of 0.27 mg/kg/d (Hazleton, 1991).

c/ highest and lowest values are in bold type.

V. RISK APPRAISAL

A. Introduction

Risk assessment is the process that is used to evaluate the potential for exposure and the likelihood that the toxic effects of a substance will occur in humans under specific exposure conditions. Every risk assessment has inherent limitations and uncertainties in the application of existing data to estimate the potential risk to human health. Therefore, certain *a priori* assumptions are incorporated into the hazard identification, dose-response assessment and exposure assessment processes. These, in turn, result in uncertainty in the risk characterization, which integrates all of the information in these three processes. Qualitatively, risk assessment for all chemicals has similar types of uncertainty. However, the degree or magnitude of the uncertainty varies depending on the availability and quality of the data and the exposure scenarios being assessed. Varying degrees of uncertainty are involved in the estimation of these parameters, affecting the accuracy of the risk characterization. Specific areas of uncertainty associated with this risk assessment for acephate are delineated in the following discussion.

B. Hazard Identification

Acute toxicity tests measure the effects of a chemical after a single or brief period of exposure. Developmental toxicity tests, which are often used for acute risk assessment, did not show increased susceptibility of the developing organism to the effects of acephate relative to the dam in the rat and rabbit. However, it should be noted that measurements of ChE inhibition were not made in these studies. Instead, the most sensitive acute endpoint (inhibition of regional brain AChE activity) was observed when acephate was evaluated in two acute neurotoxicity studies in the SD rat that gave LOEL and NOEL values of 2.5 and 0.5 mg/kg/d, respectively. At 2.5 mg/kg/d, four of the five brain regions had 20 to 22% inhibition ($p<0.001$) and for the fifth, the hippocampus, AChE was inhibited by 13% ($p<0.05$), making this a potentially adverse effect. At 0.5 mg/kg/d, only the brain stem had statistically significant inhibition of AChE ($p<0.01$), but only by 6.8%, relative to control. Because of the low level of inhibition, and the fact that in the cortex, for example, in this experiment there was apparently 3% stimulation, it is considered unlikely that brain stem AChE inhibition at 0.5 mg/kg/d is toxicologically relevant. It remains possible, however, that 0.5 mg/kg/d is actually the LOEL rather than being the NOEL. At 2.5 mg/kg/d, the inhibition of plasma ChE (14%) and RBC ChE (3.5%) was not statistically significant. Only at ≥ 5 mg/kg/d was RBC ChE significantly inhibited, by 19% ($p<0.001$) at 5 mg/kg/d, for example. The NOEL for clinical signs was 5.0 mg/kg/d and the LOEL, 25 mg/kg/d. The lowest acute animal NOEL of 0.5 mg/kg/d, in the rat, was used by USEPA for acute dietary risk assessment.

The rat reproductive and developmental toxicity studies did not indicate a greater sensitivity of the pups than adults to acephate. The developmental neurotoxicity study makes it clear that brain AChE inhibition in fetuses and pups is less or equally sensitive compared with adults. This is analogous to the situation for methamidophos, the bioactive transformation product of acephate, where there is also evidence that the enzyme in pups/ fetuses is less or equally sensitive to inhibition as AChE in adults. However, for methamidophos, the pesticide was administered in the diet rather than by oral gavage as for acephate. In the case of acephate, a human study is available. This was conducted in an effort to demonstrate that humans were no more susceptible than rats and also to measure the pharmacokinetic properties of acephate in humans. Although statistically significant inhibition of plasma ChE was reported sporadically,

this was not considered to be of toxicological significance; for example, in males, 10.9% inhibition at 12 h in the 0.35 mg/kg/d group was not dose-dependent; at 1.25 mg/kg/d, although significant inhibition was measured at 12h, 24h and 48h, it was only inhibited by 12.8%, 8.9% and 9.1%, respectively, relative to mean pre-dosing values. In control (undosed) males, variation in ChE activity indicated 4.9% - 7.5% apparent inhibition over the first 12h after dosing. In females, in controls, there was from 6.7% apparent stimulation to 7.5% apparent inhibition, relative to pre-dosing mean ChE values. It must therefore remain doubtful whether the inhibition of 10.5% to 12.7% at 8h to 24h ($p<0.01$ or $p<0.05$) is of toxicological significance at 1.0 mg/kg/d in females. It should be emphasized that there were no clinical signs or symptoms in this study attributable to acephate. RBC ChE was significantly inhibited ($p<0.01$) at only 12 hrs., for males only at the HDT, but only by 6.8%. There was no increase in inhibition with dose at any timepoint and the greatest (apparent) inhibition of RBC ChE (13.8%) was observed in control (undosed) females at 72 hr (compared with time zero). It is clear that the rat and human have similar susceptibility to ChE inhibition following acephate exposure.

In the evaluation of chronic toxicity, the most sensitive endpoint in the rat and dog was the inhibition of brain AChE. A statistically significant level of inhibition (17%) was recorded at the LDT of 10 ppm in the diet (0.27 mg/kg/d) in the male, but not the female, dog. Therefore, an estimated NOEL (from the dog study), equivalent to 0.09 mg/kg/d was calculated, by dividing the LOEL by a default UF of 3. This estimated NOEL was used for chronic risk characterization. The use of a default factor of 3 in estimating a NOEL from a LOEL is supported by BMD calculations. Chronic feeding studies also resulted in an increased incidence of adenomas in the adrenal medulla in male rats and in hepatocellular carcinomas in female mice. Because these tumors were gender-specific, were benign in the case of adrenal tumors, were associated with liver toxicity in the mouse which appeared to be more severe in the case of the female and could have been secondary to overall systemic toxicity at doses >MTD, they were not subjected to quantitative risk assessment. In the IRIS for acephate (USEPA, 1993) it is stated that, for female mice, “the MTD may have been exceeded at the high dose.” It was also noted that liver toxicity (hyperplastic nodules) were elevated at the HDT for female mice, but not for males and not for lower dose females. This correlates with the elevated incidence of carcinomas only in females and only at the HDT. However, because acephate was (weakly) genotoxic in some assays, it is possible that the tumors arose through such a mechanism. Nonetheless, although female mouse liver carcinomas were subjected to quantitative risk assessment in IRIS (USEPA, 1993), neither tumor type was considered by USEPA in the acephate RED (USEPA, 2001a) or in the Organophosphate Cumulative Risk Assessment (USEPA, 2006), thus supporting a non-genotoxic mechanism.

The lower bound on the dose giving a 10% reduction of brain AChE activity was 0.09 mg/kg/d, using the Hill model, indicating that this value would be close to the "true" chronic NOEL. However, it is also apparent that brain and RBC AChE are more susceptible to inhibition by acephate than plasma ChE in the dog (Table 7); for the rat, brain AChE appears to be more susceptible than RBC or plasma ChE in acute (Table 13) or sub-chronic (Tables 14, 15) studies. The toxicological consequences of these findings with respect to human health risk assessments for acephate are presently unclear. On the one hand, because the acute NOELs for rat and human are so similar, it is possible that the 10x UF from animal to human is overly conservative for subchronic and chronic exposure situations. On the other hand, there is a lack of data for human brain AChE inhibition; the lack of clinical symptoms and signs in humans may be an insensitive measure of acephate toxicity when considered with respect to clinical signs and toxicity (AChE inhibition) in animals.

There is currently controversy about the choice of the appropriate percentage of inhibition for

risk assessment. On the one hand, 10% inhibition of RBC or brain AChE has been suggested as an adequate level of inhibition for LOEL selection, preferably with statistical significance, but for ethical reasons brain AChE can only be measured in animals studies. On the other hand, according to the Worker Protection standards (CCR 6728), plasma or RBC ChE inhibition in workers' blood must reach 20% before the worker must be notified and an investigation of exposure begun. However, for a farmworker to be removed from his task, inhibition of ChE needs to be $\geq$40% (plasma) or $\geq$30% (RBC). There must therefore remain some uncertainty about the validity of NOEL selection for inhibitors of ChE.

It should also be noted that, owing to its high hydrophilicity (K_{ow} = 0.13; log K_{ow} = -0.89), acephate would be anticipated to penetrate the blood brain barrier poorly, in the absence of a carrier-mediated specific uptake mechanism. It has been suggested recently (CDPR, 2004; Gammon *et al.*, 2005) that the inhibition of brain AChE that was measured in response to methamidophos administration may have been predominantly localized in glial cells rather than having been neuronal (synaptic). The inhibition of brain glial AChE would not be anticipated to result in clinical signs to the same extent as would the inhibition of synaptic AChE. This (presence of glial AChE inhibition) may thus explain, at least in part, the relatively high inhibition of brain AChE that was reported in chronic and sub-chronic dietary studies in rodents and dogs, without any clinical signs. By analogy, it is possible that acephate dosing may result in brain glial AChE inhibition, as suggested for methamidophos.

There is also evidence that organophosphates (*e.g.* chlorpyrifos and diazinon) may play a role in disrupting glial cell growth (Qiao *et al.,* 2001). Such an event would be anticipated to result in the alteration of glial cells and thus of blood-brain-barrier properties, perhaps leading to greater access of acephate/ methamidophos to neuronal AChE. The disruption of glial DNA synthesis could, in turn, result in altered glial cell structure, with consequent changes in the properties of the blood-brain-barrier. However, counting against this theory to explain acephate's action is the finding that the parent organothiophosphates were more potent than their oxon metabolites, the form of acephate.

Likewise, it is possible that acephate disrupts the P-Glycoprotein transporters (PGTs) in the rat brain, also known as the multi-drug-resistance or MDR-protein mechanism. Such PGTs remove a variety of molecules from the brain, including the carbamate insecticide thiodicarb (Lenning *et al.*, 1996). Disruption of the PGT system could result in higher levels of acephate/methamidophos in the brain being maintained (due to reduced removal) than in the presence of an intact PGT system. However, the late ontological development of the PGT system in rodents (Lankas *et al.,*1989) would lead to an anticipation of greater inhibition of brain AChE in neonatal rats than in adults, and yet there is experimental evidence that this is not the case, for acephate and methamidophos.

Finally, following the inhibition of brain AChE, it is also possible that the ACh receptor(s) become desensitized to ACh in the continued presence of this transmitter at the synapse. This would lead to reduced postsynaptic signaling capability at those synapses affected by AChE inhibition.

C. Exposure Assessment

Occupational Exposure

As mentioned in Section II.E., during the 5-year period 2002-2006, 12 cases of worker illness associated with acephate use were reported to DPR, but in 55 of these, multiple pesticide applications obscured the identity of the causative agent(s). There were only two reported definite/probable cases of worker illness in the four years from 2002 to 2005. A MOE of 10 is generally considered adequate to protect human health whenever the NOEL is from a human study (acute) and 100, whenever the NOEL is from an animal study (seasonal, annual). The vast majority of the occupational exposure calculations gave MOE values well below 10 or 100, respectively. It is thus difficult not to consider acephate a risk factor in the development of illnesses following its use, even in the presence of competing risk factors. Solid formulations, such as water-soluble pellet (WP) and granule (G), tended to have higher MOEs than liquid (L) or soluble powder (SP) ones, with the exception of the use of granules in a belly grinder (Table 24), but the latter may be an inherently hazardous application method for acutely toxic pesticides. It is likely that liquid formulations present greater dermal absorption than solid ones, thus accounting for these MOE differences. In support of this contention, it should be noted that the only aerial application in Table 24 with an adequate MOE (19) was based on a field study rather than PHED. Nonetheless, seasonal and annual MOEs based on this study were inadequate, with MOEs of 12 and 22, respectively, based on animal NOELs. Because some formulations of acephate are considered Category I for acute toxicity, it suggests that possible mitigation measures may be needed.

Dietary Exposure

Acephate is an insecticide that is used on foliage and it is therefore often detected, along with its degradate methamidophos, in RACs at harvest. Therefore, the residue values used for calculating possible dietary exposure are considered reasonable estimates rather than “worst-case” ones. For acute (distributional) and chronic exposure, the percentage of crop treated factor has been used, which will have the effect of reducing dietary exposure and increasing the MOE values.

The DEEM® program (Monte Carlo) used for calculating acute dietary exposure resulted in only slightly different dietary exposure estimates and corresponding MOE values based on PCT data. This is because, using a distributional approach, the main practical effect of using PCT will have been to convert a proportion of non-detects to zeros. In dietary risk assessment, non-detects are assumed to contain a residue equivalent to the LOD (or 50% of LOD, chronic), thus encouraging the development and use of increasingly sensitive crop residue analysis methods. For methamidophos, where point estimates were compared with Monte Carlo simulations, the Monte Carlo program generally yielded lower dietary exposure estimates than the point estimate, the former being generally 20% to 40% of the latter. It is often considered that the Monte Carlo probabilistic simulation of acute dietary exposure is more appropriate than the point estimate, deterministic approach. Because the (Monte Carlo) exposure values are lower, this will have the effect of underestimating dietary exposure wherever the point estimate approach would have been more appropriate.

Acephate is the *N*-acetyl analog of methamidophos, to which it is enzymically converted, in both

insects and mammals. Because acephate is inactive against AChE, it is considered to owe its toxicity to this conversion, *in vivo*. The tolerance expression for acephate has traditionally included methamidophos residues, but it has recently been decided by USEPA (2007) that methamidophos residues should be considered separately from acephate (see Section II.B). Methamidophos is widely used in California, on cotton, tomato and potato, giving rise to potential additional exposure. Following the completion of risk assessments for acephate and methamidophos, risk will be considered from the perspective of "cumulative" and aggregate exposure, under FQPA (1996). This could be especially important for the high-consumption RACs tomato and potato, for which there are no acephate tolerances. Various FQPA adjustment factors will be used for other organophosphates, as appropriate.

D. Issues Related to the Food Quality Protection Act

Introduction

The Food Quality Protection Act of 1996 mandated US EPA to "upgrade its risk assessment process as part of the tolerance setting procedures" (US EPA, 1997a,b). The changes to risk assessment were based in part on recommendations from the National Academy of Sciences report, "Pesticides in the Diets of Infants and Children" (NRC, 1993). The act required an explicit determination that tolerances were safe to children. US EPA was required to use an extra 10-fold safety factor to take into account both pre-/post natal developmental toxicity and the completeness of the database, unless US EPA determined, based on reliable data, that a different factor would be safe. In addition, US EPA must consider available information on: 1/ aggregate exposure from all non-occupational sources; 2/ effects of cumulative exposure to the pesticide plus others with a common mechanism of toxicity; 3/ effects of *in utero* exposure; 4/ the potential for endocrine disrupting effects.

Aggregate Exposure(s)

This refers to the possibility that an individual might be exposed to a particular chemical by more than one route. In the case of acephate, non-occupational exposure is likely to be entirely *via* the oral route. Home and garden registrations for acephate have been canceled (USEPA, 2001) but exposure from such uses has been determined because of acephate in the channels-of-trade. Therefore, dietary exposure will be the only likely route; acephate is unlikely to be found in potable water. Although not mandated under FQPA, DPR has previously conducted, and will continue to conduct, aggregate exposure and risk estimations based on dietary and occupational exposure pathways, where appropriate.

Cumulative Exposure(s)

There is a possibility that an individual could be exposed to multiple chemicals sharing the same mechanism of toxicity. An effort is to be made under FQPA to attempt to combine these "cumulative exposure(s)" to related chemicals. In the case of acephate, such multiple chemical exposure(s) include exposure to methamidophos, the cholinesterase-inhibiting degradate of acephate. The determination of cumulative risk (USEPA, 2006) awaits the completion of risk assessments for methamidophos and acephate by DPR.

Pre-/Post Natal Sensitivity

Developmental toxicity studies in the rat and rabbit showed no evidence of fetal or embryonic

toxicity at doses of acephate less than those affecting dams. No evidence was forthcoming from these experiments that there was an increase in sensitivity among fetal/embryonic animals compared with adults. Therefore no additional factor should be required to protect against greater pre-/post natal sensitivity to acephate. Developmental neurotoxicity studies for both methamidophos and acephate also indicate that fetal/young rats are not more sensitive than adults.

In a 2-generation (SD) rat reproductive toxicity study, reduced body weight was reported in adults and reduced numbers of pups per litter and reduced viability, with the same LOEL and NOEL values. It is therefore unlikely that acephate has adverse effects on reproduction in the absence of parental toxicity.

Endocrine Effects

Endocrine effects caused by a pesticide are also to be addressed under FQPA. The main hormonal systems under consideration are male and female reproductive hormones and thyroid hormones. There are no indications that acephate may be toxic on any of these systems.

E. Comparison of endpoints/NOELs used by DPR and by USEPA

Inhibition of brain AChE, sometimes accompanied by plasma and RBC AChE inhibition, is the endpoint chosen for risk assessment by both DPR and USEPA. The latter used a NOEL of 0.5 mg/kg/d from a rat, single oral gavage dosing experiment, whereas DPR used a human NOEL (Tables 16-18). Although DPR agrees with the choice of NOEL from this rat study, DPR also may consider data from ethically conducted studies employing human subjects. Similarly, OEHHA (part of Cal/EPA) notes that ethically obtained human data should be used for risk assessment, wherever possible, so as to limit the uncertainty in the final risk evaluation (OEHHA, 2001). As stated in the OEHHA guidelines: “Laboratory studies using human volunteers are better able to gauge some health effects because chemical exposures can then be measured with precision.” And subsequently “Nevetheless, human studies are preferred for risk assessment, so OEHHA makes every effort to use them when they are available.” It is clearly unethical to measure brain AChE inhibition in humans, but instead, in humans, plasma and RBC AChE were measured, along with clinical signs and symptoms in Freestone & McFarlane, 2001. Because there were no significant effects on any of these parameters, it is considered unlikely that brain AChE was affected in the human study. Furthermore, it would appear that humans are probably of similar susceptibility to the toxic effects of acephate as are animals. For chronic, annual dietary exposure, DPR used the lowest NOEL from an acceptable study, 0.09 mg/kg/d (estimated) from a 1-yr. dog study for the inhibition of brain AChE, whereas USEPA used 0.12 mg/kg/d from a 4, 9 and 13-wk. rat study for the same endpoint in the female rat. This difference is based in part on USEPA’s desire to use a standardized NOEL (8-wk. female rat, brain AChE inhibition) for the purpose of aggregating OP exposure under FQPA. USEPA used a 21-day rat dermal toxicity study (Table 29) for acute and seasonal occupational risk assessment, (NOEL 12 mg/kg/d).* DPR used the human oral capsule and a rat oral gavage study, for acute and seasonal exposure, respectively. Because there is a contemporary human toxicity study available for acephate, DPR prefers to use an estimate of oral absorption (100%) in comparing absorbed dose in a human study for risk assessment purposes, rather than using an absorbed dose (7.6% estimated absorption) from a rat dermal toxicity study. It is noted that dermal absorption (in the rat) is dose- and exposure duration-dependent (Vol. 2, p. 21).

Table 29. Comparison of critical NOELs used by DPR and USEPA for acephate.

Exposure type	DPR	USEPA
Acute worker	1.0 mg/kg/d [a/] human,oral	12 mg/kg/d [b/] rat, dermal
Acute dietary	1.0 mg/kg/d [a/] human,oral	0.5 mg/kg/d [c/] rat, oral
Seasonal worker	0.12 mg/kg/d [d/] rat, oral	12 mg/kg/d [b/] rat, dermal
Chronic worker	0.09 mg/kg/d [e/] dog, oral	N/A [f/]
Chronic dietary	0.09 mg/kg/d [e/] dog, oral	0.12 mg/kg/d [d/] rat, oral
Inhalation	N/A [g/]	0.14 mg/kg/d [h/] rat, inhalation

a/ single dose oral capsule, Freestone & McFarlane, 2001
b/ 21-day dermal study.*
c/ single dose oral gavage study, Nemec, 1995
d/ 13-week, oral gavage study, Brorby & Rosenberg, 1987
e/ 1-year dietary study, Hazleton, 1991
f/ not applicable: USEPA does not conduct chronic worker risk assessments
g/ inhalation not relevant for this A.I.
h/ based on 0.5 μg/L, 4-week, nose-only, Hoffman, 2000b.

* when Blaszcak, 1998 and Hoffman, 2000a are both considered, DPR has concluded that the dermal subchronic NOEL in the rat for acephate is 50 mg/kg/d.

FQPA considerations

Because the developmental neurotoxicity study (Section III.H) showed that immature rats were no more susceptible to acephate toxicity than adults, there is little reason for an additional uncertainty factor, at this time. USEPA has reduced the FQPA factor to unity in the latest IRED that addresses aggregate risk for acephate (USEPA, 2000). However, it is noted that a cumulative risk assessment requires other OPs to also be considered.

VI. TOLERANCE ASSESSMENT

A. INTRODUCTION

A tolerance is the maximum amount of pesticide residue that may lawfully be present in or on a raw agricultural commodity, or processed food, or animal feed, expressed as parts per million by weight of the pesticide chemical residue in the food or feed (U.S. EPA, 2007). The U.S. EPA tolerance program was developed as an enforcement mechanism to identify illegal residue concentrations resulting from potential non-compliance with the product label requirements (e.g. improper application rates or methods, inadequate pre-harvest intervals, direct or indirect application to unapproved commodities). Tolerances are enforced by the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and state enforcement agencies (*e.g.* Enforcement Branch of DPR).

The data requirements established by U.S. EPA for tolerances include: (1) residue chemistry which includes measured residue levels from field studies, (2) environmental fate studies, (3) toxicology studies which evaluate the hazards to humans, domestic animals, and non-target organisms, (4) product performance such as efficacy, and (5) product chemistry which includes physical-chemical characteristics and analytical methods (Code of Federal Regulations, 1992). The field studies must reflect the proposed use with respect to the rate and mode of application, number and timing of applications, and formulations proposed (U.S. EPA, 1982).

Currently, the tolerances set by U.S. EPA are at levels necessary for the maximum application rate and frequency, and are not expected to produce deleterious health effects in humans from dietary exposure (U.S. EPA, 1991). U.S. EPA uses the Reference Dose for non-cancer risks, and negligible risk level for cancer as guides to determine the appropriate levels for dietary exposure. Assembly Bill 2161 (Bronzan and Jones, 1989) requires the DPR to "conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides". In the situation where "any pesticide use represents a dietary risk that is deleterious to the health of humans, the DPR shall prohibit or take action to modify that use or modify the tolerance.....". As part of the tolerance assessment, a theoretical dietary exposure for a specific commodity and specific population subgroups can be calculated from the product of the tolerance and the daily consumption rate.

For a pesticide allowed to be used on numerous commodities, tolerance assessments are conducted for selected fruits and vegetables. Generally, commodities are selected from all the uses based on the potential for high levels of dietary exposure. For acephate, there are currently 33 tolerances for human consumption in the United States. Eight of these were selected for tolerance evaluation based on consumption and acephate usage patterns (Appendix II). Of these, the three main commodities, beans, celery and head lettuce are tabulated (Table 30).

B. ACUTE EXPOSURE

An acute exposure assessment using the residue level equal to the tolerance was conducted for each individual label-approved commodity. The DEEM® software program and the USDA Continuing Survey of Food Intakes of Individuals (CSFII) 1994-1998 were used in this assessment. The acute tolerance assessment does not routinely address multiple commodities at the tolerance levels since the probability of consuming multiple commodities at the tolerance decreases as the number of commodities included in the assessment increases. The ranges of

potential dietary exposure values at the 95th. percentile for each of the three main registered commodities are given in Table 30. In summary, the MOEs were between 25 and 195 for beans; 55 to 171 for celery and 29 to 252 for head lettuce. The population subgroups with the lowest MOE values (greatest exposure) were (all and) nursing infants (< 1yr.) for beans and children (1-6 yrs.), for celery and head lettuce. Tolerance assessment for other RACs were, as follows: Brussel's sprouts (tolerance 3 ppm), MOE = 37 - 517; cauliflower (2 ppm), MOE = 71-1820; cottonseed meal (8 ppm), MOE = 351-2,370; chile and bell peppers (4 ppm), MOE = 89 – 491; soybean (1 ppm), MOE = 135 – 1480.

Table 30. MOE values after consumption of commodities with residues of acephate at U.S. EPA tolerances.[a/]

Population Subgroup	**(Acute) Margin of Exposure at the 95th. Percentile [b/]**		
	Beans[d/] (3 ppm)	**Celery[e/] (10 ppm)**	**Head Lettuce[f/] (10 ppm)**
U.S. Pop. all seasons	107	113	45
Western Region	114	96	42
Hispanics	110	96	44
Non-Hispanic Whites	116	118	45
Non-Hispanic Blacks	81	147	56
Non-Hispanic Other	89	74	37
All Infants	**25** [1/]	76	170
Infants (nursing, <1 yr.)	**25** [1/]	102	**252** [2/]
Infants (non-nursing, <1 yr.)	26	73	169
Children (1-6 yrs.)	53	**55** [1/]	**29** [1/]
Children (7-12 yrs.)	86	72	38
Females (13-19 yrs.) not preg or nursing	151	123	45
Females (13+ yrs.) preg not nursing	**195** [2/]	171	45
Females (13+ yrs.) nursing	109	**180** [2/]	44
Females (20+ yrs.) not preg or nursing	140	133	45
Females (13-50 yrs.)	139	127	44
Males (13-19 yrs.)	126	95	47
Males (20+ yrs.)	138	132	51
Seniors (55+ yrs.)	144	142	53

a/ from Carr, 2008 (Appendix B). Tolerances are: 3 ppm (beans), 10 ppm (celery, head lettuce).
b/ MOE= NOEL / Acute Dietary intake
NOEL of 1.0 mg/kg/d based on plasma and RBC ChE inhibition in a human study (Freestone & McFarlane, 2001).
c/ determined using the DEEM® program, using the 1994-1996,1998 CSFII data.
d/ 1/ highest exposure to acephate,38.6 μg/kg/d at 95th percentile.
2/ lowest exposure to acephate, 5.1 μg/kg/d at 95th percentile.
e/ 1/ highest exposure to acephate, 18.1 μg/kg/d at 95th percentile.
2/ lowest exposure to acephate, 5.8 μg/kg/d at 95th percentile.
f/ 1/highest exposure to acephate, 33.6 μg/kg/d at 95th percentile.
2/ lowest exposure to acephate, 4.0 μg/kg/d at 95th percentile.

C. CHRONIC EXPOSURE

A chronic exposure assessment using residues equal to the established tolerances for individual or combinations of commodities was not conducted because it is highly improbable that an individual would habitually consume single or multiple commodities with pesticide residues at tolerance levels. This conclusion is supported by data from both federal and DPR pesticide monitoring programs which indicate that less than one percent of all sampled commodities have residue levels at or above the established tolerance (CDFA, 1990-1993).

VII. CONCLUSIONS

The toxicological risk from potential occupational and dietary exposure to acephate has been estimated. Residues in all crops for which there are currently tolerances were considered. Methamidophos, the degradate of acephate, was included in the exposure/risk estimates, whenever it was a result of acephate application. It is not anticipated that acephate will be a contaminant of potable water. Home and Garden uses of acephate have been cancelled, but such exposures were estimated because of channels-of-trade issues.

A MOE of at least 10 is generally considered adequate to protect people from the toxic effects of a chemical when the NOEL is based on toxicology data from human studies and 100 when based on animal toxicology studies. Animal and human data for acephate indicated that the inhibition of ChE was likely to be the endpoint of toxicological concern. Acute dietary exposure to acephate gave MOEs above 10, based on a human NOEL (1.0 mg/kg/d), and for chronic (annual) dietary exposure, above 100, based on an estimated chronic dog NOEL (0.09 mg/kg/d). For occupational exposure, estimates were obtained for a variety of application and post-application tasks, predominantly using PHED. Acute MOEs were below 10 for 14 of 30 tasks involving the application of acephate to crops and 12 of 25 tasks involving non-crop applications. For post-application tasks, only two of 14 tasks resulted in estimated acute MOEs below 10: pruning citrus, 12 hrs after treatment (PHED) and mixing/loading acephate for applications to a golf course (field study). Seasonal and annual application tasks to agricultural crops resulted in estimated MOEs below 100, (based on rat and dog NOELs, respectively, of 0.12 and 0.09 mg/kg/d) for 29 of 30 tasks. For non-food crop applications, the equivalent MOEs were also below 100 for 10 of 11 tasks. For post-application tasks, 3 of 5 MOEs for seasonal exposure were below 100 and 2 of 5 annual MOEs were below 100. For combined occupational and dietary exposure, MOEs were reduced by less than 3%, with respect to occupational MOEs, for the majority of tasks, the exceptions being those with the least occupational exposure.

The consumption of crops with residues at tolerance resulted in (acute) MOE values above 10, for all (8) of the major crops, for all population sub-groups, based on a human NOEL.

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IX. APPENDICES

APPENDIX A

TOXICOLOGY SUMMARIES

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
ACEPHATE

Chemical Code # 001685, DPN # 00108
SB 950 # 125

October 1, 1986
Revised 2/5/87; 1/25/88; 7/2/88; 11/7/88; 4/6/90; 5/5/93, 2/8/02, 6/7/02, 10/01/03, 1/06/04, 2/9/04 and 8/17/05

I. DATA GAP STATUS

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

Toxicology one-liners are attached.
** Indicates an acceptable study.
Bold face indicates a possible adverse effect.
FILE NAME: T050817
Revised by M. Silva, 11/88 and 4/90; Kellner, 5/5/93 and Gee, 2/8/02, 6/7/02, 10/01/03, 1/5/04, 2/9/04 and 8/17/05
All relevant records indexed as of 1/6/04 were included in this summary.
These pages contain summaries only. Each individual worksheet may contain additional effects.

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/d, 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 108-46, 037723-8 --Diet analysis data. Samples from cage hoppers after 3-4 days were 93.1% of nominal for the 5 ppm level, 81.8% 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 DPR review of 037723-8.

CHRONIC TOXICITY, RAT

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

CHRONIC TOXICITY, DOG

**** 108-238 096115** "One-Year Oral Toxicity Study in Dogs with Chevron Acephate Technical." (D.W. Dalgard, Hazleton Washington, HWA 2107-165, 1/25/91). Acephate technical, purity of 99.9%, was administered in the feed at concentrations of 0, 10, 120 (reduced from 200 ppm during week 2 of study), or 800 ppm to 5 Beagle dogs/sex/group for 1 year. High-dose groups had lower red cell mass indices, elevated APTT and increased liver weights. Liver pathology (perivascular pleocellular infiltrate and pigment in the reticuloendothelial cells) was noted in most high-dose animals and one mid-dose male (NOEL =

10 ppm/day). Significant RBC cholinesterase (ChE) inhibition for mid- and high dose groups was reported in addition to brain ChE inhibition for mid- and high dose females and all dose levels for males. ChE NOEL (females) = 10 ppm; males < 10 ppm. **Possible Adverse Effect:** Significant brain ChE inhibition (no NOEL in males). ACCEPTABLE. Kishiyama, Kellner and Aldous, 4/30/93.

108-237 095950. This submission was an adverse effect disclosure for 096115. Adverse Effect consisted of a significant (16%) inhibition of brain ChE in low dose (10 ppm) males by the end of the study. No worksheet. Kishiyama and Kellner, 4/30/93.

108-225 85614 "Four-Week Pilot Oral Toxicity Study in Dogs with Chevron Acephate Technical." (Hazleton Laboratories, Chevron Report #2107-164). Levels of acephate of 250 and 500 ppm in the feed resulted in brain ChE levels of 6.2 and 5.0 mmol/g, respectively. A brain ChE NOEL was established at 20 ppm. No worksheet. Kellner, 5/6/93.

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, was fed in the diet at 0, 10, 30 or 100 ppm for two years with 4/sex/group. There was a 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 $\geq$ 100 ppm (HDT) for systemic toxicity; cholinesterase activity NOEL = 30 ppm; core grade--minimum.

161 Rebuttal of 11/20/86 to DPR 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 out 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.

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 was 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 the discovery of an impurity in the test article - the impurity was not identified. The 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 the diet to CD1 mice for 104 weeks at 0 (vehicle = chow), 50, 250 or 1000 ppm (7, 36 or 146 mg/kg/d) for males; 8, 42, or 167 mg/kg/d for females) with 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 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. DPR 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 DPR 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 DPR review of 037729.

161 050991 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 with CrL:cobs CD(SD)BR rats, 12 males and 24 females per group. There was 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.

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 (DPR # 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.

209 072152 "Two-Generation (Two Litter) Reproduction Study in Rats with Chevron Acephate Technical." This volume contains a final revision of the definitive rat reproduction study (182 060979). Two changes were made: 1. post natal survival at 25 ppm for first generation F1a litter was changed to not be statistically lower than the value for the control. 2. # of pups dying Days 1-4 at 500 ppm for first generation F1a litter was changed to not be statistically significant when compared to control. The data were accompanied by a summary letter. The changes did not alter the outcome of the study, nor did it alter its acceptability. D. Shimer & M. Silva, 3/30/90.

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

Summary: The study conducted at Huntingdon, DPR 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 (DPR 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

** 219, 230 074315, 088434 "Oral Teratogenicity and Developmental Toxicity Study in Rats with Chevron Acephate Technical." (Argus Research Laboratories, Study No. 303-008, 2-13-89). Acephate technical (Lot #: SX-1725; purity = 99.5%, or Lot #: SX-1102; purity = 98.7%) was administered to mated Crl:CD®(SD)BR rats (25/dose) by gavage on days 6 - 15 of presumed gestation (presence of vaginal sperm or copulatory plug = day 0 of gestation) at 0, 5, 20 or 75 mg/kg/d. Maternal NOEL = 5 mg/kg/d (increase in tremors, decrease in motor activity, body weight and food consumption). Developmental NOEL = 20 mg/kg/d (decreased fetal body weight, and delay in ossification of hindpaw phalanges--historical controls for malformations and alterations were provided in the report). No adverse effects**.** Volume/record # 230/088434 contained an analysis of dosing solution. ACCEPTABLE**.** D. Shimer & M. Silva, 4/2/90.

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/d on days 6-15 of gestation, 17-21 pregnant females/group. There was a 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/d and 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/d, slightly more resorption sites per female at 200 mg/kg/d than in controls, less wt. gain at 100 mg/kg/d level and 200 mg/kg/d by females during gestation; core grade--minimum.

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

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/d on days 6-27 of gestation, not adjusted for purity, with 16 per group. No significant developmental effects. Slight maternal toxicity at high dose. Developmental NOEL = >10 mg/kg/d, maternal NOEL = 3 mg/kg/d. Initially reviewed as unacceptable (McGee, 5/2/86) based on incomplete necropsy data, no analysis of dosing solutions and fetuses which 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/d, fetotoxic NOEL => 10 mg/kg/d, maternal toxic NOEL = 3 mg/kg/d; 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 DPR 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) was tested at 0.001 to 10 μg/plate with Salmonella strain TA100 and at 1, 2 and 10 μg/plate with strains TA 98 and 1537, with and without rat liver S9. There were 2 plates/dose level. Results indicated weak mutagenic activity 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 ug/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) was 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), with and without rat liver S9 on Salmonella strains TA98, TA100, TA1535, TA1537, and TA1538. Results indicated acephate was weakly mutagenic in TA 100. 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) was tested at 0 to 40,000 μg/plate. No data - results given as "+" for TA100 and E. coli; **an increase 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 μg/plate on Salmonella strain TA100 in 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 016927 "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) were tested at 0 - 50 μg/plate on Salmonella strains TA98, 100 and 1537 without activation, one trial, no individual plate counts. Seven **of 8 lots weakly positive in TA100.** 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.

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 μg/plate) and without (6000 μg/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) was 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) was tested at 10 levels between 1000-5000 ug/ml +/- rat liver S9 on mouse lymphoma cells (L5178Y). Duplicate platings/dose level with 4 hour exposure, 2-day expression time with a repeat trial. I**ncreased 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%) was tested at 2429, 3071, 3714, 4357 and 5000 ug/ml +/- rat liver S9 on mouse lymphoma cells (L5178Y). There were duplicate cultures/dose level, 4 hour exposure, 48 hr expression time. A **dose-dependent increase in mutation frequency** over entire dose

range +/- S9. ACCEPTABLE. Wong, 5/21/85.
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/ml +/- 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 and J. Gee, 1/4/88.

Summary: Multiple reports on file with DPR 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) was tested for SCE (028968) and chromosome aberrations (028969) at 0 and 2.5 mg/kg/d only by gavage for 20 days. Peripheral lymphocytes of monkey (Macaca fascicularis) were stimulated with phytohemagglutinin. Cells arrested in mitosis after 45 hours were incubated 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 was 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/d 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/d to mice for micronucleus assay; justification of dose based on an oral LD50 in mice of 361 mg/kg/d; 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/d 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/d; 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/d 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/d; core grade--acceptable as supplementary.

158 045233 More complete version of record #973222. JGee, 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/d 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/d.

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.

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 survivors x 10^{-5} and 3 plates for mitotic recombinants x 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.) Wong, 5/17/85.

EPA one-liner: Positive at 1% and above; core grade--acceptable.

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 semiconservative DNA synthesis; DNA was extracted, DNA determined by diphenylamine reaction and tritium quantitated by liquid scintillation counting; in the absence of activation, 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 DPR 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 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/d, redosed after 21 days, 5 mg/kg/d 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 note. 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/d by gavage, one dosing, 5 mg/kg/d 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.

**** 108-286 153408** " Subchronic (13-Week) Neurotoxicity Study of ORTHENE Technical in Rats." (M.D. Nemec; WIL Research Laboratories, Inc., Ashland, OH; Project ID. No. WIL-194014; 1/16/97) Thirty Sprague-Dawley rats/sex/group were dosed orally in the diet with 0, 5, 50 or 700 ppm of ORTHENE Technical (lot no. SX1725, purity: 99.0%) for up to 13 weeks ((M): 0, 0.33, 3.31, 48.63 mg/kg/d, (F) 0, 0.41, 3.95, 58.27 mg/kg/d). There were no treatment-related effects upon mean body weights or food consumption. Although some of the FOB parameters and motor activity measurements for the treated animals were statistically different from that of the control group, there was no consistent pattern of effect noted over the course of the study. The mean cholinesterase (ChE) activity levels for plasma were lower than that of the control at 3 weeks for the 50 ppm males and females ($p<0.05$ or $p<0.01$) and at 3, 7 and 13 weeks for the 700 ppm males and females ($p<0.01$). The mean red blood cell activity levels

were less at 3, 7 and 13 weeks for the 700 ppm males ($p<0.01$) and at 3 and 7 weeks for the 700 ppm females ($p<0.05$ or $p<0.01$). In the 6 subregions of the brain for which ChE activity was assayed, the activity levels were less than that of the control at 50 ppm and above for all of the regions at least twice for the 3 time points assayed ($p<0.1$). The mean percent of control activity for the 50 ppm males ranged from 50.6% in the cortex (week 13) to 75.8% in the cerebellum (week 13). For the 50 ppm females, the percent of control activity ranged from 45.4% in the hippocampus (week 13) to 81.5% in the brainstem (week 3). For the 5 ppm treatment group males , ChE activity was reduced in the hippocampus (week 3, $p<0.01$, 86.1% of control), midbrain (weeks 3, 7,13, $p<0.01$, 85.5 to 90.5%), brainstem (weeks 3, 7, 13, $p<0.01$, 85.0 to 90.6%), cerebellum (week 3, $p<0.01$, 89.1%), and cortex (weeks 3, 7, 13, $p<0.01$, 82.4 to 89.9%). Similarly, for the 5 ppm females, ChE activity was less in the hippocampus (week 13, $p<0.01$, 71.6% of control), olfactory lobe (weeks 7, 13, $p<0.05$, 75.7, 82.2%), midbrain (weeks 3, 7, 13, $p<0.1$ or $p<0.05$, 80.9 to 91.0%), cerebellum (week 7, $p<0.1$, 83.9%) and cortex (week 13, $p<0.01$, 86.2%). No treatment-related effects were noted in the histopathological examination. **Possible adverse effect:** significant brain ChE inhibition; **NOEL (Clinical Signs):** (M/F) 700 ppm ((M): 48.63 mg/kg/d, (F): 58.27 mg/kg/d) (based upon the lack of treatment effects in the FOB determinations for the 700 ppm group); **NOEL (ChE Inhibition):** < 5 ppm ((M): < 0.33 mg/kg/d, (F) < 0.41 mg/kg/d) (based upon significant brain ChE inhibition at 5 ppm). **Study acceptable.** (Moore, 2/6/02)

** **108-285 153407** "An Acute Neurotoxicity Study of Orthene® Technical in Rats" (M.D. Nemec; WIL Research Laboratories, Inc., Ashland, OH; Project ID No. WIL-194013; 12/9/96.) Thirty Sprague-Dawley rats/sex/group were dosed by oral gavage with 0, 10, 100 or 500 mg/kg/d of Orthene Technical (lot no. SX1725; purity: 99.0%). Twelve animals/sex/group were evaluated in the Functional Observational Battery (FOB) and for locomotor activity as well as in the neuropathology examination. The other 18 animals/sex/group were euthanized for cholinesterase (ChE) activity evaluation, 6 animals/sex/group at 2.5 hours and 7 and 14 days post-dose. No animals died as a result of the treatment. The mean body weight for the males in the 500 mg/kg/d group was less than that of the controls at 7 days post-dose ($p<0.05$). Clinical signs included whole body tremors, repetitive movement of the mouth, tremors of the forelimbs and/or hindlimbs, and alterations in the posture/gait of the animals in the 100 and 500 mg/kg/d groups in a dose-related manner. The earliest observation of these signs was at 30 minutes and the time to peak effect was between 2 and 2.5 hours and persisted up to 8 hours post-dose in the high dose group. The signs were no longer present by the next day. Salivation, lacrimation and chromodaccryorrhea were observed only in the 500 mg/kg/d animals. In the FOB, at 2.5 hours post-dose, the 100 and 500 mg/kg/d animals exhibited in a dose-related manner, abnormal posture, whole body tremors which ranged from slight to extremely coarse, slightly impaired to totally impaired mobility, walking on tiptoes to ataxia, decreased arousal and rearing, diminished response to a tail pinch, impaired righting reflex, and reduced body temperature. In addition, the high dose animals exhibited signs of lacrimation, salivation, poor grooming, diminished startle, touch and approach responses and catalepsy. The males in the high dose group had no pupilary response. The hindlimb extensor strength was reduce for the males in both the 100 and 500 mg/kg/d groups and the females in the 500 mg/kg/d group. The fore and hindlimb grip strength for the high dose males was reduced from that of the controls ($p<0.01$ and $p<0.05$, respectively). The rotorod performance was affected in all of the male treatment groups ($p<0.01$) and for the high dose females ($p<0.01$). In the motor activity evaluation, total activity and ambulatory activity counts were reduced for the animals in the 100 and 500 mg/kg/d groups. All of these parameters had returned to normal by day 7. In the ChE activity determinations, all of the treatment groups for both sexes exhibited reduced activity levels in the plasma, red blood cells and subregions of the brain at 2.5 hours post-dose

(p<0.01). At 7 days post-dose, reduced activity was still evident in the following tissues: hippocampus, females, 500 mg/kg/d; midbrain, males, 500 mg/kg/d, females, 500 mg/kg/d; brainstem, males and females, 500 mg/kg/d; cerebellum, males and females, 500 mg/kg/d; cortex, males, 500 mg/kg/d, females, 10, 100, 500 mg/kg/d (p<0.05 or p<0.01). At 14 days, activity was reduced in the red blood cells and the midbrain of the 500 mg/kg/d males (p<0.05 and p<0.01, respectively). No treatment related lesions were evident in the neuropathology examination. **Possible Adverse effect:** extensive neurtoxic signs; **NOEL(clinical signs) (M/F):** 10 mg/kg/d (based upon the clinical signs manifested by the 100 mg/kg/d treatment animals); **NOEL (cholinesterase inhibition):** < 10 mg/kg/d (based upon ChE inhibition evident in the plasma, red blood cells and subregions of the brain of the 10 mg/kg/d treatment group); **Study acceptable.** (Moore, 10/16/01)

108-284 153406 " Range-Finding Acute Study of Orthene® Technical in Rats" (M.D. Nemec; WIL Research Laboratories, Inc., Ashland, OH; Project No. WIL-194015; 4/27/95) Two Sprague-Dawley rats/sex/group were dosed by oral gavage with 0, 5, 25, 125 or 500 mg/kg/d of Orthene® Technical (batch no. SX 1725, purity: 99.4%) in Phase I. In Phase II, five females/group were dosed orally with 0, 0.5, 2.5 or 5 mg/kg/d of the test material. In Phase I, animals received detailed clinical examinations at 15 and 30 minutes and 1, 2 and 2.5 hours post-dose. In Phase II, the animals were examined at the time of euthanization, 2.5 hours post-dose. Plasma, red blood cell and sections of the brain were assayed for cholinesterase (ChE) activity at the time of when peak toxic signs were manifested, 2.5 hours post-dose. No animals died as a result of the treatment. Clinical signs of repetitive mouth movements, tremors in the forelimbs/hindlimbs or whole body, salivation and altered gait were noted in the 125 and 500 mg/kg/d groups. One male in the 25 mg/kg/d group exhibited repetitive mouth movements. Twitching of both ears was noted for animals in the 25, 125 and 500 mg/kg/d treatment groups. Hypothermia was exhibited by the animals in the 500 mg/kg/d. In Phase I, cholinesterase activity was reduced in a dose-related manner with the activity level ranging from 68.9 to 80.5% and 69.6 to 85.9% of the control activity for the males and females, respectively, in the 5 mg/kg/d treatment group. In Phase II, at 2.5 mg/kg/d, female ChE activity in the various brain sections ranged from 78.4 (brain stem) to 86.6% (hippocampus) of the control activity. At 0.5 mg/kg/d, the activity levels in the brain ranged from 92.1 to 102.8% of control activity. **Possible adverse effects**: signs of neurotoxicity. **NOEL (ChE inhibition): (M)** < 5 mg/kg/d (based upon the brain ChE inhibition exhibited by the males in the 5 mg/kg/d group), **(F)** 0.5 mg/kg/d (based upon the inhibition of ChE in the brain of the females in the 2.5 mg/kg/d group); **NOEL (clinical signs): (M/F)** 5 mg/kg/d (based upon the signs observed in the 25 mg/kg/d animals). **Study supplemental.** (Moore, 10/19/01)

108-315 183892 " A Single Oral Dose Study with Acephate Technical in Humans" (S. Freestone and P. McFarlane; Inveresk Research, Elphinstone Research Centre, Tranent, EH33 2NE, Scotland; Project ID. ICR 013072; 5/3/00, 1st Amend. 6/26/00, 2nd Amend. 3/23/01) Four groups of 10 male subjects each and one group of 10 female subjects were included in the study. For each group, 7 people were dosed with the test material and 3 received the lactose placebo. The male groups were treated with one dose in a gelatin capsule of 0.35, 0.7, 1.0 or 1.25 mg/kg/d of Acephate Technical (lot no. 80121 (SCC), purity: 99.0%). The female group received 1.0 mg/kg/d of the test material. Each subject was screened prior to treatment in which hematology, clinical chemistry, vital signs and ECG were evaluated. Plasma and red blood cell (RBC) cholinesterase (ChE) activities were measured 6 times prior to dosing with the mean values being used as the base line. During the study, blood samples were recovered at 1, 2, 4, 8, 12, 24, 48 and 72 hours and 7 and 14 days post-dose. ChE activity measurements and analysis of acephate and methamidophos levels were performed. Hematology, clinical

chemistry and urinalysis parameters were evaluated at 24 hours post-dose. Vital signs and ECG were measured at 2, 4, 8, and 24 hours post-dose. No treatment-related effects were noted for the vital signs, ECG, hematology, clinical chemistry and urinalysis. Analysis of the ChE activity data revealed a statistically significant % change from baseline for plasma ChE at 12 (-12.77%, $p<0.01$), 24 (-8.89%, $p<0.01$) and 48 (-9.12, $p<0.001$) hours post-dose for the males in the 1.25 mg/kg/d group and at 8 (12.73%, $p<0.05$), 12 (-12.08%, $p<0.05$) and 24 (-10.50%, $p<0.01$) hours for the females in the 1.0 mg/kg/d group. For RBC ChE, a statistically significant % change from baseline was noted for the males at 12 hours post-dose (-6.75%, $p<0.01$). In the pharmacokinetic analysis, the $T_{1/2}$ elimination ranged from 4.39 to 5.42 hours. The time to maximal concentration in the blood (T_{max}) ranged from 1.29 to 2.71 hours. The highest mean concentration of both acephate and methamidophos recovered in the urine occurred during the 0 to 12 hours post-dose interval. For the males, the mean percentage of the administered dose recovered in the urine up to 48 hours post-dose ranged from 43.3% for the 0.35 mg/kg/d group to 52.5% for the 1.0 mg/kg/d group. The mean percentage of the administered dose recovered in the urine from 0 to 48 hours post-dose from the 1.0 mg/kg/d females was 26.0%. **No adverse effects indicated. NOEL: (M)** 1.0 mg/kg/d (based upon a statistically significant reduction in the plasma ChE activity for the 1.25 mg/kg/d males); **(F)** < 1.0 mg/kg/d (based upon a statistically significant reduction in plasma ChE activity for the 1.0 mg/kg/d females). **Study supplemental.** (Moore, 12/4/01)

108-200 067747 "The Cholinesterase Inhibition Potential of Acephate Techical (SX-1102) Following 4-, 9-, or 13-Week Dietary Administration in Male and Female Rats"; (G.P. Brorby, and D.W. Rosenberg; Chevron Environmental Health Center, Inc., Richmond, CA; Study No. S-3068; 12/30/87); Thirty Sprague-Dawley rats/sex/group were treated in the diet with 0, 2, 5, 10 or 150 ppm of Orthene Technical (lot no. SX-110,; purity: 98.2%) for up to 13 weeks ((M), 0, 0.12, 0.28, 0.58, or 8.90 mg/kg/d, (F) 0, 0.15, 0.36, 0.76 or 11.48 mg/kg/d). Ten animals/sex/group were euthanized after 4, 9 and 13 weeks on study. There were no mortalities during the study. There were no treatment-related clinical signs or effects on food consumption. There was no apparent treatment-related effect on body weight gain. Significant brain cholinesterase (ChE) inhibition was noted for the 5 ppm group and above for both sexes after 4, 9 and 13 weeks of treatment ($p<0.01$) (% of control activity: 5 (M) 92.5 to 92.7%, (F) 89.3 to 91.2%, 10 (M) 85.8 to 89.1%, (F) 83.1 to 88.5%, 150 (M) 48.3 to 52.7%, (F) 45.2 to 54.0%). For the 2 ppm treatment group, only the females demonstrated significant brain ChE inhibition at all of the time points ($p<0.01$) (% of control activity: 90.3 to 91.9%). A dose-response for ChE inhibition in the plasma and red blood cells was not well demonstrated with statistical significance only at the 150 ppm treatment level. The necropsy examination did not reveal any treatment-related lesions. Possible adverse effect: inhibition of brain cholinesterase; NOEL: (M) 2 ppm (0.12 mg/kg/d) (based upon significant brain ChE inhibition in the 5 ppm treatment group, (F) < 2 ppm (< 0.15 mg/kg/d) (based on the significant brain ChE inhibition in the 2 ppm treatment group). Study acceptable. (Moore, 2/27/02)

DEVELOPMENTAL NEUROTOXICITY

328 206825 "Dietary dose range-finding developmental neurotoxicity study of acephate technical in rats." (Argus Research, October 30, 2001 draft protocol) This document is the draft protocol 222-002P for a developmental neurotoxicity study in rats. The protocol indicates that 15 females per group will be given diets containing 0, 5, 25, 50 and 100 ppm from day 6 of presumed gestation to day 22 of lactation. The dose selection was based on a subchronic neurotoxicity study in adults (record 153408 in volume 286) in which it was stated that no inhibition of cholinesterase was seen through week 7 at 5 ppm. Samples for RBC, plasma

and brain cholinesterase activity will be collected on day 20 of presumed gestation (5 dams) or day 22 of lactation (10 dams) from the F0 generation. For F1 offspring, blood and brain samples will be collected from 4 fetuses per sex (DG 20) or two pups per sex per litter (maximum of 10 litters per group, days 5 and day 22) for cholinesterase determination. A gross necropsy will be performed on dams and pups. This is a draft protocol. No worksheet. (Gee, 10/1/03).

328 206826 "Dietary developmental neurotoxicity study of acephate technical in rats." (Argus Research, October 30, 2001 draft protocol) This document is a draft protocol (number not assigned) for a study to be conducted following completion of the range-finding study described in record 206825 above. No doses had been selected for the definitive study. Because cholinesterase activity will have been measured in the range-finding study, it will not be determined in the definitive study. Twenty-five presumed pregnant rats will be assigned per group. On day 5 of lactation, pups will be assigned (1/sex/litter) to one of 4 subgroups for day 22 brain weights and histology, watermaze and passive avoidance, motor activity and startle habituation and brain weights and pathology at day 70. The draft protocol states that litters with fewer than 8 pups will not be retained. Sexual maturation will be evaluated. Addendum 4 contains the protocol (222-002) for brain weight measurements and histological evaluations. No worksheet. (Gee, 10/1/03)

** 108 - 0331 208523 “Oral (gavage) developmental neurotoxicity study of acephate technical in rats.” (Hoberman, A. M., Argus Research, Laboratory Project VP-23747, Argus protocol 222-002, December 4, 2003). Presumed pregnant Crl:CD7(SD)IGS BR VAF/Plus7 female rats were given doses of 0 (water), 0.5, 1 or 10 mg/kg/d, gestation days 6 through termination of pregnancy and days 0 through 6 of lactation. Pups were dosed at these same doses beginning day 7 of lactation through weaning at day 21. There were 25 dams per dose with 20 litters selected for continuation of the study. There were 5 subsets of pups with 1/sex/litter when possible per subset. Subset 1 were sacrificed on PND 21 for neurohistological examination or ChE assays. Subset 2 were sacrificed on PND 71 following evaluation of passive avoidance and watermaze testing. Subset 3 were sacrificed on PND 71 following testing for motor activity (days 13, 17, 21 and 58) and auditory startle habituation (days 22 and 62). Subset 4 were examined outside of the home cage on days 4, 11, 21, 35, 45 and 60 for abnormal signs and sacrificed on PND 71 for neurohistological examination. Subset 5 were sacrificed on PND 21 and were used to standardize litter size and for ChE assays. Litters were standardized to 10/litter on PND 4 with extra pups being used for ChE assays (plasma, RBC and brain). All parental dams survived with no adverse clinical signs. Body weights, weight gains, food consumption and necropsy findings were comparable among groups. Acephate did not affect sexual maturation, learning, motor activity or weight of pups. Administration from gestation day 6 through lactation day 4 did not affect brain, plasma or RBC cholinesterase activity on PND 4. Direct dosing from lactation day 7 through day 21 did result in a statistically significant and biologically relevant reduction in all three measurements at 10 mg/kg/d, PND 21. At 0.5 and 1 mg/kg/d, brain ChE was reduced > 20%, being significant in male pups (-28.7%** and -33.7%**) and in sexes combined but not in females (-25.4% and -25.8%). Plasma and RBC cholinesterase activities were lower at 0.5 and 1 mg/kg/d but not clearly dose-related. No affects on brain weight, neuromorphometric or neurohistopathology were noted. Systemic NOAEL = 10 mg/kg/d with brain ChE NOEL < 0.5 mg/kg/d when given directly to pups. No positive control data for neurotoxicity were included in the report. Unacceptable but possibly upgradeable with submission or citation of positive control data mentioned in the text of the report. (Gee, 1/5/04). Positive and negative historical control data were submitted on a CD as record 209229, upgrading the study. (Gee, 2/9/04).

108 - 0337 209229 "Historical control data." (Argus Research, 2003) The record consists of a CD with 2174 pages. There are seven sections addressing negative and positive control data for the FOB, motor activity, neuropathology (R. H. Garman), passive avoidance, sexual maturation, and watermaze. Data were collected from approximately 1990 through 2001. These data apparently have been accumulated by Argus Research for all of the neuropathology studies conducted at the laboratory. This worksheet is supplemental to the developmental neurotoxicity study in 108-0331, record 208523. These data upgrade that study to acceptable status. (Gee, 2/9/04).

108 - 0332 208524 "Oral (gavage) acute relative sensitivity study of acephate technical in neonatal and adult rats." (Hoberman, A. M., Argus Research, Laboratory Project VP-25072, Argus protocol 222-005, December 9, 2003) Crl:CD®(SD)IGS BR VAF/Plus® rats were given a single dose of acephate technical (lot AS 40s, batch VDL-622-37a, 99.2%) at doses of 0 (water), 0.5, 1, 2.5 or 10 mg/kg/d in 10 ml. Pups were dosed on PND 11 or 21 and adults at approximately 68 days of age. There were 10/sex/dose group. Blood and brains were collected at approximately 3 hours after dosing for ChE determinations. The dose of 0.5 mg/kg/d did not result in toxicologically meaningful reduction in brain or plasma ChE in any group. At 1.0 mg/kg/d, statistically significant reduction was found in brain ChE in PND 11 male pups (-22.7%**) and adult females (-30.1%*). Adult male brain ChE was reduced by 34.7% (NS). Plasma ChE activities were comparable with controls. At 2.5 mg/kg/d, brain ChE was significantly reduced in both male (-26.6%**) and female (-14.2%*) pups on PND 11 but not on PND 21. In adults given 2.5 mg/kg/d, brain activity was reduced in adult males (-19.8%*) but not in adult females (-8.3%). At 10 mg/kg/d, brain activities were reduced in all groups (PND 11 males, -40.9%**, PND 11 females, -34.6%**; PND 21 males, -34.6%*, PND 21 females, -35.8% not significant; adult males, -53.2%** and adult females, -45.2%*). Plasma ChE activity was significantly reduced in all groups at 10 mg/kg/d. RBC activity was quite variable with no clear dose response. Pups were of equal or less sensitivity than adults. All animals survived to scheduled sacrifice with no adverse clinical observations reported. No gross lesions were seen at necropsy. Supplemental study. No worksheet. (1/2/04).

108 - 0333 208525 "Oral (gavage) dosage-range study of acephate technical in adult rats." (Hoberman, A. M., Argus research, Laboratory Project VP-25064, Protocol 222-004, November 25, 2003) Crl:CD®(SD)IGS BR VAF/Plus® adult rats were treated with acephate technical (lot AS 40s, batch VDL-622-37a, 99.2%). In Part A, fourteen per sex were given a single dose of 0 (water), 2.5 or 10 mg/kg/d. Two per sex per dose were sacrificed at 0 (predosage), 1, 2, 3, 4, 8 and 24 hours after dosing. Blood was collected for RBC and plasma ChE and brains were excised, weighed and assayed for ChE activity. Peak reduction in brain ChE occurred between 4 and 8 hours at 2.5 mg/kg/d and between 3 and 4 hours at 10 mg/kg/d, single dose. Peak plasma reduction in ChE activity occurred between 1 and 8 hours. RBC levels were variable with peak reduction around 8 hours postdose. In Part B, two per sex were given doses of 0, 2.5 or 10 mg/kg/d for 11 days. Blood was collected approximately 3 hours after the final dose and processed for ChE determinations. The brain was excised, weighed and assayed for ChE. Brain ChE was reduced by 40.7% at 2.5 mg/kg/d and by 67.5% at 10 mg/kg/d, sexes combined. Plasma ChE was reduced by 18.6% at 2.5 mg/kg/d and by 54.5% at 10 mg/kg/d, sexes combined. RBC ChE was lower by 9.8% at the low dose and by 53.3% at the high dose of 10 mg/kg/d, day 11 of dosing. A gross necropsy was performed on all animals. All animals survived and body weights were comparable. No adverse clinical signs were noted. Supplemental study. No worksheet. (Gee, 1/2/04).

108 - 0334 208526 "Oral (gavage) maternal and fetal exposure study of acephate technical in rats." (Hoberman, A. M., Argus Research, Laboratory Project VP-25267, Argus protocol 222-007, conducted Sept./Oct. 2002, report date December 1, 2003) Eight presumed pregnant Crl:CD®(SD)IGS BR VAF/Plus® rats were given doses of technical acephate (lot AS 40s, batch VDL-622-37a, purity 99.2%) of 0 (water), 0.5, 1, 2.5, or 10 mg/kg/d on day 6 through day 21 of gestation, 10 ml/kg, given approximately the same time each day. Doses were selected based on studies VP-25056 (record 208528) and VP-25064 (record 208525). Rats were observed before dosing and at 60 minutes and 3 hours postdosage. On day 21, blood was collected approximately 3 hours after dosing for plasma and RBC cholinesterase and brains were excised, weighed and processed for ChE assay. Fetuses were weighed, examined for gross changes and the blood and brain collected for ChE determinations. All dams survived until scheduled sacrifice. There were no treatment-related findings for clinical observations, body weights, food consumption, or fetal gross changes. Brain weights and brain to body weight ratios were comparable. ChE activity of male and female fetuses were similar. RBC ChE activity was variable with no evident dose-dependency up to 10 mg/kg/d. Plasma ChE of dams was lower at 10 mg/kg/d (-55.0 %**) and of combined fetuses (-60.0%**). At 2.5 mg/kg/d, plasma activity was reduced by 21% (not statistically significant) in dams and by 31%** in fetuses, sexes combined. At 0.5 and 1 mg/kg/d, plasma activity in male fetuses was also reduced (-21.7% at -.5 and 13.3% at 1 mg/kg/d). Brain ChE activity was significantly reduced in dams at all doses (-16.7%*, -18.1%*, -40.8%** and -61.5%** with increasing dose). The decreases at 0.5 and 1 mg/kg/d were considered by the author to be within the variability of the assay. For fetuses, brain cholinesterase was considered reduced at 10 mg/kg/d (-40.0%**). Other values (-7.3%, -12.1%* and -14.3%*) were considered by the author to be within the variability of the assay. [*, $p \leq 0.05$, **$p \leq 0.01$.} The conclusions were that exposure of the dam results in fetal exposure, male and female fetuses respond similarly and fetuses were found to be equally or less sensitive than the dams at 2.5 and 10 mg/kg/d. Supplemental study. No worksheet. (Gee, 12/31/03).

108 - 0335 208527 "Oral (gavage) repeated dose relative sensitivity study of acephate technical in neonatal and adult rats." (Hoberman, A. M., Argus Research, Laboratory Project VP-25081, Argus protocol 222-006, conducted in Sept./Oct., 2002, report date of November 25, 2003) Crl:CD®(SD)IGS BR VAF/Plus® rats were used. The purpose was to compare the effects of acephate on neonatal (part A) and adult (part B) rats, including cholinesterase inhibition. Doses were 0 (water), 0.5, 1, 2.5 or 10 mg/kg/d, given PNDS 11 through 21 (11 days total) to neonates and to adults (males were 77 days and females were 71 days of age) for 11 days at the same doses. Doses were selected based on studies VP-25056 (record 208528) and VP-25064 (record 208525). Technical acephate (lot AS 40s, batch VDL-622-37a, 99.2%) was used. Part A: Pups: One pup/sex/group/litter (total of 10/sex) were given the above doses. Clinical observations were made each day before dosing and approximately 60 minutes after dosing as well as at 3 hours postdosage. Pups were sacrificed on PND 21 and a gross necropsy conducted. Blood was collected 3 hours after dosing for RBC and plasma ChE determinations. The brain was excised for ChE levels. All pups survived until sacrifice and no clinical signs or gross lesions were observed. Body weights were generally comparable. Part B: Adults with ten/sex/dose: Observations were made prior to dosing and at 60 minutes and 3 hours postdosage. A gross necropsy was performed and blood drawn for ChE determinations. Brains were excised, weighed and assayed for ChE. Cholinesterase: At 0.5 mg/kg/d, brain ChE was significantly inhibited by 28.5%** in adult males but not in adult females (-8.2%) or in pups (M: -5.2%; F: +5.2%). At 1 and 2.5 mg/kg/d, significant inhibition of brain ChE occurred in all groups except female pups

(both doses). At 10 mg/kg/d, similar levels of inhibition of brain ChE occurred in pups and adults (>50 %). For plasma ChE, no inhibition occurred at 0.5 mg/kg/d in any group. At 1 mg/kg/d, significant inhibition was found in adult females (-34.9%**) but no other group. At 2.5 mg/kg/d, inhibition was greater in adults (-33.9 %*, sexes combined) than in pups (-21.1%**). At 10 mg/kg/d, plasma ChE was inhibited to a greater extent in adults, sexes combined (-53.7 %**), than in pups (-38.9%**). The RBC data did not indicate any clear pattern. The conclusion of the author was that adult rats were as sensitive or more sensitive than pups to cholinesterase inhibition by acephate. Supplemental study. No worksheet. (Gee, 12/31/03).

108 - 0336 208528 "Oral (gavage) dosage-range study of acephate technical in neonatal rats." (Hoberman, A. M., Argus Research, Laboratory Project VP-25056, Argus protocol No. 222-003, conducted in May/June of 2002, December 9, 2003) The study was conducted in three parts, using acephate technical, lot number AS 40s, batch VDL-622-37a, 99.2% with water as the vehicle. Neonatal Crl:CD®(SD)IGS BR VAF/Plus® rats were used. Part A: One pup/sex/litter (4 litters, n = 4/sex) were given a dose of 0 (water), 0.5, 2.5, 5 or 10 mg/kg/d on postnatal day 11 or 21. Pups were observed at 60 minutes, 2, 3 and 4 hours and at the 24-hour post-dose sacrifice. Body weights were recorded. A gross necropsy was conducted. F0 females were discarded without further evaluation. All pups survived until scheduled sacrifice with no adverse clinical signs observed. Body weights and weight gains were comparable among groups. Part B: Four/sex/dose were given doses of 0 (water), 0.5, 2.5, 5 or 10 mg/kg/d technical acephate on postnatal days 11 through 21 by gavage. Clinical observations were recorded daily before dosing and 60 minutes after dosing. Body weights were recorded. Pups were sacrificed on PND 22, a gross necropsy conducted and any lesions retained. All pups survived until scheduled sacrifice with no adverse clinical signs observed. Body weights and weight gains were comparable among groups. Part C: Two pups/sex/litter (7 litters) were given doses of 0, 5 or 10 mg/kg/d on PND 11 or 21. Pups were observed daily for clinical signs with body weights recorded on day of dosing and at scheduled sacrifice. Blood samples were collected for cholinesterase determinations at 0 (predose), 1, 2, 3, 4, 8 and 24 hours postdosage. Samples were processed for RBC and for plasma ChE levels. Brains were collected for ChE. Duplicate analyses were performed per sample. Two pups per sex were used per time point. All pups survived until scheduled sacrifice and all appeared normal at necropsy. Due to the small number (2) per sampling time per sex, the peak time of inhibition of ChE was difficult to determine but the author concluded that the maximal inhibition occurred between 2 and 8 hours with no significant difference with sex or with age (PND 11 versus PND 21). A peak sampling time of 3 hours was proposed. Inhibition of brain, plasma and RBC ChE was slightly greater at 10 mg/kg/d. Supplemental study. No worksheet. (Gee, 12/30/03)

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 DPR 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 0.9 to 1.2 % w/w 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/d) or in rats (3.0 mg/kg/d). 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/d) (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.

Twelve studies on methylthioacetate to support continued registration of acephate were submitted by Valent U.S.A. Corp. with a letter dated 12/5/88. The studies include acute, subchronic and mutagenicity. These studies are under tolerance number 51656. One-liners created in the 950 review follow.

108-128 16926 Review of the results of mutagenicity testing of Acephate technical (Orthene): Gene Mutation, Primary DNA Damage, Chromosome Alteration. No worksheet. Kellner, 5/5/93.

SUBCHRONIC, DERMAL

51656-003 72296 "Ninety Day Dermal Toxicity Study in Rabbits with Methylthioacetate (MTA)" (Chevron Environmental Health Center, Inc. No. CEHC 2822, 1-15-88) Methylthioacetate, SX-1732, 98.9%, was placed on the backs of New Zealand White rabbits for 6 hours/day, 5 days/week at dose levels of 0, 5, 20 or 60 mg/kg/d, deaths by percent were 7, 50, 53 and 50, respectively. There were 15/sex/group initially except for the low dose group which had 10/sex. The majority of deaths were attributed to mucoid enteritis. Clinical signs include inappetence, diarrhea, no stool and decreased activity related to mucoid enteritis. At 20 and 60 mg/kg/d severe skin irritation occurred until the site of application was varied on the animal. Histopathology revealed no compound related lesions of the optic nerve or liver, the known target organs in acute studies. Supplemental since not an active pesticidal ingredient, otherwise UNACCEPTABLE, and not upgradeable. The occurrence of disease compromised the value of the study and reduced animal numbers to unacceptable levels. D. Shimer, 7/13/89.

GENE MUTATION

51656-004 072297 "Salmonella/Mammalian Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with Methylthioacetate (SX-1732)," (Microbiological Associates, Study No. T5771.501014, 12-23-87) Methylthioacetate (98.2% pure; LOT #: SX-1732), was tested for mutagenicity with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 at concentrations of 10,000, 5000, 2500, 500 or 100 ug/plate (triplicate plates). Assays were done in the presence and absence of metabolic activation. A confirming repeat test was performed. No increase in the number of revertants was observed. No adverse effects.

Supplemental. This is not a registered pesticide, but a contaminant present at a very low concentration in Acephate. D. Shimer & M. Silva, 3/30/90.

CHROMOSOME MUTATION

51656-004 072298 "Clastogenic Evaluation of Methylthioacetate (SX-1732) in the Rat Bone Marrow Cytogenetic Assay Following a Four-Day Inhalation Pilot Study," (Hazleton Laboratories America, Inc., Study No. 2107-147, 11-12-87). Fischer 344 rats, 5/sex/group, were exposed to methylthioacetate (Lot #: SX-1732; 98.2% pure) vapors at concentrations of 400, 600 or 800 ppm for 6 hours/day for 4 consecutive days. Animals were sacrificed 19 hours after their last exposure and 50 cells/dose/animal were scored (50 spreads/animal). NOEL < 400 ppm (Clinical signs were observed at $\geq$ 400 ppm; body weights in both sexes were significantly decreased at $\geq$ 400 ppm; there was a significant decrease in food consumption at $\geq$ 400 ppm; 80% mortality--all males and 3/5 females--at 800 ppm). NOAEL = 600 ppm. No positive control, was used in this study, however, the high dose was acceptable, due to the degree of mortality at 800 ppm. No adverse effects. Supplemental. The study was considered to be a pilot study. This is not a registered active ingredient, but a contaminant in Acephate. D. Shimer & M. Silva, 3/29/90.

DNA DAMAGE/REPAIR

51656-004 072299 "Micronucleus Assay in Mouse Bone Marrow Erythrocytes Following Inhalation Exposure to Methylthioacetate (SX-1763, 99.2% Purity)," (Chevron Environmental Health Center, Inc., No. CEHC 2751, 1-15-88). Methylthioacetate (Lot #: SX-1763; 99.2% pure) was used, as a vapor, on Swiss albino mice ($\geq$ 15 mice/sex/group) for 4 hours at actual concentrations of 0, 445, 651 or 796 ppm. Five/sex/group were sacrificed at 24, 48 and 72 hours after the start of exposure. 1000 PCE were examined/slide/animal, 1000 cells were counted to determine NCE:PCE ratio. No adverse chromosome effects. No treatment related increase in the number of micronucleus was observed, however, 5 animals died at 796 ppm and histopathology revealed treatment related lesions in lungs of all methylthioacetate dosed animals. Supplemental. This is not a registered ingredient, but has been submitted because it is a contaminant in Acephate. D. Shimer & M. Silva,

OTHER

315 - 0281 211501 “A study of the effects of Orthene and Monitor on plasma and erythrocyte cholinesterase activity in human subjects during subacute oral administration.” (Garofalo, M., Industrial Bio-Test Laboratories, Inc., IBT No. 636-02498, Report No. 98473, March 7, 1973)
Note: This study has been evaluated by US EPA as “S” for supplementary and not as “I”, invalid. Pages 49 and following contain evaluations of the study made in 1977/1978, comparing the report with the available raw data. The major problem was the lack of some raw data to support the values in the IBT report, especially for the 0.4 mg/kg/d females.
Study: The test materials were mixtures of methamidophos (Monitor) and acephate (Orthene) in ratios of either 1:9 or 1:4 parts of Monitor/Orthene. The materials were taken three times daily in corn oil in gelatin capsules for daily doses of 0.1, 0.2, 0.3 or 0.4 (females only) mg/kg/d. The subjects were seven male and seven female volunteers with 2/sex in the control and 1:4 groups and 3/sex in the 1:9 group. Ages ranged from 21 to 48 years. Exposure was for a total

of 21 consecutive days for 0.1, 0.2 and 0.3 mg/kg/d and 10 days for 0.4 mg/kg/d in females. Baseline plasma and erythrocyte cholinesterase activities were determined 5 times during the 2 weeks preceding exposure. ChE activities were determined on days 1, 3, 7, 14 and 21 during the test period. Each subject was given increasing doses of the test materials, same ratio, in sequence of increasing dose. After exposure to 0.3 mg/kg/d, there was a 7-day rest period with evaluation of ChE activities. ChE was determined by an AutoAnalyzer using the procedure of Levine, J. B. et. al. Limited hematology parameters were also evaluated pretest and at the end of the exposure period. Additional observations included blood pressure, muscle tone, pulse rate, pupil size, light reflex, eye accommodation, knee jerk, tongue tremor and finger tremor. Subjects were also to report any abnormal symptoms. Results There was no effect on erythrocyte ChE in any group. There was no effect on ChE at 0.1 mg/kg/d with either ratio. At 1:4, 0.2 mg/kg/d, plasma ChE was depressed in both sexes (considered to be the minimum effect level by the author) but not at 1:9 ratio. At 1:9, 0.3 mg/kg/d caused depression in plasma ChE in males [1:4 was not tested at this dose]. At 0.4 mg/kg/d,1:9, in three females, plasma, but not erythrocyte, ChE was depressed. ChE was considered affected if there were two consecutive measurements with depression greater than 2 standard deviations below the mean pretest value. The report states that there were no significant effects on hematology or the other parameters evaluated. Individual data were presented for hematology and clinical chemistry. Corrected pages, based on raw data, are included in the reevaluation pages. Supplemental study. No worksheet. (Gee, 6/18/04)

APPENDIX B

DIETARY EXPOSURE ASSESSMENT

ACEPHATE (Orthene)

DIETARY EXPOSURE ASSESSMENT

Wesley C. Carr, Jr.

HEALTH ASSESSMENT SECTION

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CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

September 16, 2003

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I. Summary

Acute and chronic dietary exposure analyses were performed for the pesticide acephate. No lifetime dietary exposure analysis was conducted since there was no clear evidence of cancer in experimental animal studies. Over 30 raw agricultural commodities (RACs) and 100 food form residues were included in the dietary assessment. The residue data were derived from registrant supplied field trials, DPR, FDA, and USDA PDP monitoring data (Tables 2A and 2B).

Exposures were calculated for an acute dietary exposure intake using the combined RACs residue values which had been adjusted to reflect processing factors. The acute dietary scenario was evaluated using the acute no-observed-effect-level (NOEL) of 1.0 mg/kg/d based on plasma and red blood cell cholinesterase inhibition measured in an oral human volunteer study. The acute percent crop treated adjustment factors ranged from 5% treated for dry beans to 70% treated for head lettuce. The acute dietary exposure values at the 99.9th% ranged from 0.001063 mg/kg/d, females 13-19 years, to 0.002427 mg/kg/d, nursing infants < 1 year (Table 3C).

Exposures were calculated for a chronic dietary exposure intake using combined averaged RACs. The dietary scenario was evaluated using the chronic estimated NOEL of 0.09 mg/kg/d based on brain cholinesterase inhibition measured in a 1-year dog study. The residue data used in the chronic dietary analyses included a percent of the crop treated (%CT) adjustment for most all of the commodities. The percent crop treated adjustment factors ranged from 1% treated for Brussel's Sprouts, macadamia nuts, and soybeans to 50% treated for celery and head lettuce crops. The acephate percent crop treated calculations were based on U.S. EPA Benefits and Economic Analysis Division (BEAD) estimates using multi-year use data. The chronic dietary exposure analysis was also modified by commercial processing data. The chronic dietary exposures ranged from 0.000010 mg/kg/d, nursing infants, to 0.000045 mg/kg/d, children 1-6 years of age population subgroups (Table 4).

An acute tolerance assessment was performed for acephate using the current U.S. EPA tolerances (U.S.EPA, 2001). The acephate acute NOEL of 1.0 mg/kg/d was used to calculate dietary margins of exposure based on a human study (plasma and red blood cell ChE inhibition). There are currently 33 human consumption RACs that have acephate tolerances (CFR, 2002). A total of 8 individual commodities were analyzed for tolerance level acute dietary exposure at the maximum residue contribution (MRC).

II. Introduction

Acute and chronic dietary exposure analyses were conducted for acephate. All available acephate raw agricultural commodities (RAC) residue data were evaluated (Tables 2A and 2B). A tolerance assessment was also conducted for established 40 CFR 180 tolerance that characterizes acephate (CFR, 2002). **The acephate listing under 40 CFR 180.108 includes residues for both acephate and its degradate methamidophos.**

Several federal and state regulatory pesticide residue monitoring programs routinely analyze for acephate or the degradate product methamidophos. These include the Food and Drug Administration (FDA) monitoring program (McMahannon and Wirtz, 1998, 1999, 2000), the California Department of Pesticide Regulation (DPR, 1998, 1999a, 2001a), and the United States Department of Agriculture (USDA) Pesticide Data Program (PDP) (USDA, 1997c, 1998c,d and 2000).

Residues analyzed by the FDA regulatory monitoring surveillance program (statistically based commodity survey) for acephate were collected through the 1990s for domestic and imported commodities. The FDA has monitored for acephate; therefore, recent FDA residue data were considered for use in the DPR dietary exposure assessment (McMahonnan and Wirtz, 1998, 1999, 2000). The FDA multiple screen residue databases for 1997 and 1998, and 1999 were reviewed. The residue screens are located on the FDA homepage and must be downloaded to use. The FDA residue methods screen for acephate residues (McMahonnan and Wirtz, 1998, 1999, 2000). The limits of detection (LOD) for acephate are difficult to discern from the FDA database. Cranberry, which is not grown in California, was the only commodity that used FDA residue data in the DPR dietary assessment.

The USDA monitors for acephate using either their multi-residue screen or individual analyte programs and, therefore, data are available or reported in their annual surveys for the Pesticide Data Program (PDP) but not for the Food Safety Inspection Service (FSIS). The PDP program targets specific raw agricultural commodities that are likely to be heavily consumed by infants and children (USDA, 1996, 1997, 1998a,b, 2000). The FSIS monitors for chemical residues, including some pesticides, on various commercial meat animals, such as cattle, pork, poultry and sheep (USDA, 1994). Residue data for milk, non-processing and processing green beans were taken from the PDP annual summaries. The range for the limits of detection (LOD) was between 0.002 ppm for California specific processing green beans to 0.003 ppm for non-processing green beans (USDA, 1997c, 1998c,d and 2000).

The DPR also monitors for acephate in its market basket surveillance pesticide program (DPR, 1998, 1999a, 2001a). Acephate is part of the DPR organophosphate multiple residue screen analysis program. The range for the limits of detection (LOD) was between 0.02 ppm for cauliflower and celery to 0.04 ppm for peppers (DPR, 1998, 1999a, 2001a).

The primary registrant for acephate is Valent U.S.A. (Orthene®). There are 12 other active secondary acephate registrants; Bonide Products, Inc., Drexel Chemical Company, Florida Silvics, Inc., Platte Chemical Co., The Scotts Co., Whitmire Micro-Gen, Creative Sales, Inc., Ecolab, Inc., Micro-Flo Co., Pursell Technologies, Inc., United Phosphorus, Inc., and Value Gardens Supply (DPR, 2002). The pesticide name used in the submitted field trial residue studies is acephate (Trade Names: Orthene® and Lancer) or Acetylphosphoramidothioic acid O,S,-dimethyl ester (IUPAC). The active ingredient acephate appears as a whitish solid at room temperature (25^{o} C). Acephate is occasionally formulated together with a miticide active ingredient for broad spectrum pest control (insects and mites) in home and garden products.

There were 50 products containing acephate registered with the U.S. EPA as of September 2002

(DPR, 2002). The percent acephate active ingredient per EPA registered product ranges from 0.25% for a crack and crevice formulation to 99.2% for technical material.

As of September 2002, there were 60 active acephate product registrations approved by DPR for use in California (DPR, 2002). The product registrations include agricultural (pre-plant, field or post-harvest applications), home and garden, and crack and crevice uses (both commercial pest control operator and over the counter formulations)(DPR, 2002). The agricultural products are for broad-spectrum insect control in pre-plant seed preparations, post-emergence sprays, and post-harvest treatment of raw agricultural commodities. The percentages of California registered acephate formulations range from a low of 0.25% (Orthene home and garden product and crack and crevice products) to a maximum of 97.4% (pest control operator applied pelletized product).

The pre-harvest intervals for agricultural commodities ranged from 1 day for succulent beans to 90 days for cranberry for U.S. EPA registered acephate products. The maximum amount of acephate active ingredient (a.i.) that can be applied on any commodity in any single year is 6 pounds (lbs.) per acre. The 6 applications at 1 lb. a.i./acre amount is the label approved maximum for cotton. This maximum acephate amount is found on both the U.S. EPA and California DPR labels (DPR, 2002). The next highest seasonal maximum amount is 4 lbs. a.i./acre for both peanuts and tobacco. The agricultural commodity pre-harvest intervals for DPR registered acephate products are the same as those for the U.S. EPA registrations (DPR, 2002).

The total national use of acephate is approximately 4-5 million pounds per year. The 3 largest uses are on cotton, tobacco, and home and garden applications (USEPA, 2000). The use on cotton constitutes about 23% of the 4-5 million pounds applied nationally each year. Applications on tobacco represent another 21% of national acephate usage. Home and garden applications in and around the residential outdoors represent another 20% of national use (Fort, 2000). The 3 largest uses account for over 60% (approximately 2.7 million pounds) of the annual national acephate applications.

There were 355,350 lbs. of acephate used in California during 1996 (DPR, 1998). There were 343,840 lbs. applied during 1997 and for 1998, 384,091 lbs. (DPR, 1999c, 2000a). A total of 307,687 lbs. was applied during 1999 and for 2000, 283,284 lbs. (DPR, 2000b, 2001b). The California 5 year (1996-2000) average annual use is 334, 850 lbs. of acephate active ingredient (DPR, 2002). The average annual use of acephate in California is summarized in Table 1. California use represents about 13 percent of the total national annual average. The top 5 crops receiving acephate applications in California are head lettuce, cotton, beans (all), celery, and peppers (all) (Table 1). The top 5 crops in Table 1 comprise about 88% of the total acephate use in California. Cotton is the only commodity found on both the national and California top use lists. California cotton acephate use represents less than 8% of the national cotton use.

Table 1. Average Annual Acephate Use In California

Commodity	Average Annual Use (in Pounds) [1]
Total California Acephate Agricultural Use	356,970
Top 5 Crop Uses Combined	293,543
Head lettuce [2]	112,952
Cotton	82,342
Beans (all varieties)	67,239
Celery	21,857
Peppers (all varieties)	8,551

1. Average of 5 Years (1996 - 2000) California DPR Pesticide Use Report (PUR) data.
2. The top 5 crops based on average annualized pounds used from DPR PUR (1996-2000).

III. Acephate Residues

A. Acephate Residue Database

The acephate residue data used in the DPR dietary exposure assessment were derived entirely from federal and state residue monitoring programs or submitted by the acephate registrant. More than 100 registrant acephate residue studies were received and evaluated by the DPR staff. Most of the older studies (more than 50) were ultimately not used because they were replaced by more recent studies for the same commodities or regulatory pesticide residue monitoring data. The regulatory residue monitoring data and the more recent registrant studies had lower limits of detection and more precise data validation (Tables 2A and 2B).

Almost all of the fresh commodities analyzed for acephate residues by the DPR and the USDA PDP programs were collected from the contiguous United States and were analyzed primarily in California. All composite samples (domestic and foreign origin) were randomly selected before extraction and chemical analysis. The acephate analytical protocols for certifying concentration levels, accuracy, temperature and retention times were included in the registrant magnitude of the residue reports.

Acephate residues for the commodities used in the dietary exposure assessment were analyzed by either registrant laboratories (Chevron, Inc.) or from available government regulatory pesticide monitoring programs (California Department of Pesticide Regulation, Food and Drug Administration, or the United States Department of Agriculture Pesticide Data Program) and then used in the DPR dietary exposure assessment. The limits of detection (LOD) used for the acephate residues ranged from 0.002 ppm (processing green beans, USDA PDP) to 0.04 ppm (both bell and chili peppers, DPR). Most of the analyzed commodities had a LOD of between 0.01 ppm or 0.02 ppm depending on the commodity or processed food form and the age of the monitoring data or field study (Tables 2A and 2B). Acephate raw and processed agricultural commodity residue data used to conduct the DPR dietary exposure assessment are presented in Tables 2A and 2B. If a commodity did not have any residue data, a residue value from another commodity in the same or similar U.S. EPA crop grouping was used as a surrogate representative. For example, green beans (non-processing and processing) were used as the surrogate commodity residue to represent dry beans (CFR, 2002, U.S. EPA crop group 6 - legume vegetables - including beans and garden peas).

The Health Assessment Section (HAS) of the Medical Toxicology Branch of the DPR has a set of guidelines to help interpret and determine what data sources (field study or market basket) and which measures (highest, average, etc.) of the residues to use to represent the anticipated acute and chronic dietary exposure pesticide residue levels. All the residue data used in the dietary exposure assessment came from either registrant field trial or government regulatory agencies market basket survey residue data.

The DPR default guideline for acute dietary exposure residues is to select the highest detected residue for a raw agricultural commodity (i.e., whole cauliflower, pepper, etc.) or the acute average for mixtures (soybean oil and flour, etc.) to represent a commodity. An acute distributional analysis can be used if sufficient residue information is available. Either a high end (95^{th}% of the detects) or a distributional residue value was selected for each RAC depending on the number of analyzed samples. The acute average was used to represent acute mixtures and consisted of a simple average of all the detected values together with the non-detectable residues reported at the LOD.

The chronic residue values in the dietary exposure assessment used the average of all the reported residues for both the raw agricultural commodities (i.e., whole cauliflower, etc.) and mixtures (soybean oils and flour, etc.). The chronic average consisted of a simple average of all the utilized residue values in the study. Any non-detect residues were reported at ½ the LOD.

All of the residue values used in the acephate dietary exposure assessment were derived from composited samples. The analyzed samples from the regulatory monitoring programs were taken from composites of multiple, randomized selections which were equally distributed within the commodities. The registrant supplied magnitude of the residue field trials were composite samples taken from randomized field plots. The sample weights for residue analysis range from several grams to several pounds (five pounds), depending on the commodity. Commodities that have liquid food forms (e.g. juices, oils) also used the same sampling methodology.

B. Commodity Residue Studies

There were 100 commodities and food forms included and analyzed in both the acute and chronic portions of the DPR dietary exposure assessment. The residue information presented in Tables 2A and 2B is in summary form for most of the commodities analyzed in the dietary exposure assessment. Major contributing commodities to the acute dietary exposure that used the distributional Monte Carlo method for residue estimation are discussed below in greater detail.

Green Beans (Both Non-Processing and Processing Food Forms)

Green Beans (non-processed and processed forms) represent the major acute dietary contribution for upper percentile consumers (99.5th - 99.9th%) for several population subgroups. The commodity green beans can be broken down into 9 distinct food forms; 3 non-processed and 6 processed forms based on U.S. EPA commodity codes. The non-processed food forms are uncooked, cooked, and boiled. The processed forms are canned, canned: cooked, canned: boiled, frozen: cooked, frozen: boiled, and cured. The combined green beans acute dietary contribution at the 99.5th - 99.9th% level of consumption for the nursing infants population subgroup is *ca.* 88% and for the non-nursing infants population subgroup is *ca.* 78%. Green beans are a moderate dietary contributor for the children 1-6 years (*ca.* 29%), western U.S. (*ca.* 13%), females 13+ nursing (*ca.* 13%), females 13-50 years (*ca.* 10%), and females 13+ pregnant and not nursing (*ca.* 10%) population subgroups. If applied to green beans, acephate could likely be found as a residue since beans are frequently consumed raw and unwashed. The majority of green beans consumed in the United States are domestically grown. Any green beans imported into the United States would be assumed to have been treated with acephate.

A. Non-Processed Green Beans

There were 4 green beans studies submitted by the registrant. Three were magnitude of the residue studies and the other was a multiple commodity farm-gate residue decline study (Lai, 1989b). The non-processing green beans residue value was generated from two years of USDA PDP 1994 and 1995 monitoring data collected and analyzed in California (USDA, 1996, 1997)[5]. The California specific LOD value for the green beans monitoring data was 0.003 ppm. The residues ranged from 0.003 - 1.03 ppm (N = 285) with an acute average of 0.011 ppm (SD; ± 0.067 ppm) and a chronic average of 0.01 ppm. The value used for the acute dietary exposure was a distributional estimate derived from 500 Monte Carlo iterations using 285 samples with a range of 0.003 - 1.03 ppm, a standard deviation of ± 0.067 ppm, and an acute percent of the crop treated estimate of 40%. The green bean residue value used

[5] DPR 1996 - 98 monitoring program green bean data exist (DPR, 1998, 1999a, 2001a). The data were considered but not used because very few samples were collected and analyzed.

for the chronic dietary exposure was 0.009 ppm and reflects a U.S. EPA BEAD chronic percent of the crop treated (%CT) estimate of 30% (U.S. EPA, 1999).

B. Processed Green Beans

The same 4 registrant submitted green bean studies were also available for the processed fraction of the commodity. Three years of green bean residue data were available from the DPR market basket monitoring program (DPR, 1998, 1999a, 2001a). These data were not used for the same reason previously discussed. The processing green beans residue value was generated from USDA PDP 1996 - 1998 monitoring data collected and analyzed in California (USDA, 1998a,b, 2000). The green beans destined for processing California specific LOD was 0.002 ppm. The residues ranged from 0.002 - 0.7 ppm (N = 400) with an acute average of 0.018 ppm (SD; ± 0.063 ppm) and a chronic average of 0.017 ppm. The value used for the acute dietary exposure was a distributional estimate derived from 500 Monte Carlo iterations using 400 samples with a range of 0.002 - 0.7 ppm, a standard deviation of ± 0.063 ppm, and an acute %CT estimate of 60%. The destined for processing green bean residue used for the chronic dietary exposure was 0.0166 ppm and reflects a U.S. EPA BEAD chronic %CT estimate of 35% (U.S. EPA, 1999).

C. Dry Beans

The USDA PDP non-processing and processing green beans residue data were used as surrogate data to represent dry beans. Non-processed green beans residue data were used to represent non-processing dry beans. Green beans destined for processing were used to represent processed dry beans. The same four registrant submitted green bean studies were also intended to represent residues on dry beans. There were not any dry bean data available from either the DPR or USDA PDP market basket monitoring programs (DPR, 1998, 1999a, 2001a, USDA, 1998a,b, 2000). These data were not used. Instead, processed and non-processed green beans were used as surrogate residue data for processing and non-processed dry beans respectively. The same California specific LOD and total number of samples were applied to the surrogate data. The only differences were the acute and chronic %CT estimates used. The processed and non-processed dry beans both used an acute %CT estimate of 10%. Both the processed and non-processed dry beans used a chronic %CT estimate of 5% (U.S. EPA, 1999).

Head Lettuce (Non-Leaf Lettuce Varieties)

Head lettuce is a major dietary contributor for the population subgroups females 13-50 years (ca. 56%), western U.S. (ca. 41%), females 13+ pregnant and not nursing (ca. 38%), females 13+ nursing (ca. 35%), and children 1-6 years (ca. 31%). The commodity is only a minor dietary contributor for nursing infants (<1%), and non-nursing infants (<1%). If applied to head lettuce, acephate could likely be found as a residue since it is primarily consumed raw. The majority of head lettuce consumed in the United States is domestically grown. An economically important percentage of head lettuce is imported into the United States during the winter months. Any lettuce imported into the United States would be assumed to have been treated with acephate.

There were 3 head lettuce studies submitted by the registrant. Two were magnitude of the residue studies and the other was a multiple commodity farm-gate residue decline study (Lai, 1989b). There was one year, 1994, of USDA PDP head lettuce monitoring data available (USDA, 1996). The head lettuce residue value was generated from DPR 1996 - 98 market basket monitoring data (DPR, 1998, 1999a, 2001a). The average LOD value for the head lettuce monitoring studies was 0.03 ppm. The residues ranged from 0.03 - 5.7 ppm (N = 468) with an acute average of 0.047 ppm (SD; ± 0.27 ppm) and a chronic mean of 0.033 ppm. The residue used for the acute dietary exposure was a distributional value based on 500 Monte Carlo iterations from the 468 residues and an acute %CT estimate of 70%. The residue value used for the chronic dietary exposure was 0.026 ppm and reflects a %CT adjustment of 50%.

Chili Pepper

Chili pepper is a major dietary contributor for the population subgroup females 13+ pregnant and not nursing (ca. 34%). The commodity is a modest dietary contributor for the western U.S. (ca. 14%), and females 13-50 years (ca. 12%) population subgroups. Chili pepper is only a minor dietary contributor for the children 1-6 years (ca. 6%), females 13+ nursing (ca. 4%), nursing infants (<1%), and non-nursing infants (ca. 2%) population subgroups. If applied to chili pepper, acephate could be found as a residue since peppers are routinely consumed raw. The majority of chili pepper consumed in the United States is domestically grown. An economically important percentage of chili pepper is imported into the United States.

There was 1 study for chili and 3 bell peppers as surrogate chili pepper studies submitted by the registrant. Each study was a magnitude of the residue field trial. No USDA PDP chili pepper monitoring data were available (USDA, 1996-2001). The chili pepper residue value was generated from DPR 1996 - 98 market basket monitoring data (DPR, 1998, 1999a, 2001a). The average LOD value for the chili pepper monitoring data was 0.04 ppm. The residues ranged from 0.04 - 1.8 ppm (N = 629) with an acute average of 0.075 ppm (SD; ± 0.16 ppm) and a chronic mean of 0.058 ppm. The residue value used for the acute dietary exposure was a distributional one based on 500 Monte Carlo iterations from the 629 residues. The residue value used for the chronic dietary exposure was 0.043 ppm and reflects a %CT adjustment of 25%.

Bell Pepper

This commodity is a major dietary contributor for the small population subgroup females 13+ nursing (ca. 37%). Bell pepper is a modest dietary contributor for the females 13-50 years (ca. 9%), and western U.S. (ca. 6%) population subgroups. However, bell pepper is only a minor dietary contributor for children 1-6 years (ca. 4%), females 13+ pregnant and not nursing (ca. 4%), nursing infants (ca. 4%), and non-nursing infants (ca. 2%) population subgroups. If applied to an agricultural crop, acephate likely could be found as a residue since bell pepper is routinely consumed raw. The majority of bell pepper consumed in the United States is primarily domestically grown. Any imported bell peppers into the United States would be assumed to have been treated with acephate.

There were 3 studies submitted by the registrant for bell peppers. Each one was a magnitude of the residue study. No USDA PDP bell pepper monitoring data were available (USDA, 1996-2001). The bell pepper residue value was generated from DPR market basket monitoring data (DPR, 1998, 1999a, 2001a). The average LOD value for the bell pepper monitoring data was 0.04 ppm. The residues ranged from 0.04 - 3 ppm (N = 1010) with an acute average of 0.102 ppm (SD; ± 0.23 ppm) and a chronic mean of 0.086 ppm. The residue value used for the acute dietary exposure was a distributional value based on 500 Monte Carlo iterations from the 1010 residues. The residue value used for the chronic dietary exposure was 0.071 ppm and reflects a %CT adjustment of 25%.

Celery

Celery is a modest dietary contributor for the western U.S. (Ca. 7%) and children 1-6 years (ca. 6%) population subgroups. The commodity is also a minor contributor to nursing and non-nursing infants (ca. 3%) and the females, 13-50 years (ca. 2%) population subgroups. Acephate, when applied, likely could be found as a residue because celery is commonly consumed raw. The majority of celery consumed in the United States is primarily domestically grown. Any imported celery would be assumed to have been treated.

There were 4 magnitude of the residue celery studies submitted by the registrant. There was 1 year of USDA PDP celery monitoring data from 1994 available (USDA, 1996). The celery residue value

was generated from DPR market basket monitoring data from 1996 - 98 (DPR, 1998, 1999a, 2001a). The LOD value for the celery monitoring data was 0.02 ppm. The residues ranged from 0.02 - 0.8 ppm (N = 203) with an acute mean of 0.041 ppm (SD; ± 0.084 ppm) and a chronic mean of 0.032 ppm. The residue value used for the acute dietary exposure was a distributional value based on 500 Monte Carlo iterations. The residue value used for the chronic dietary exposure was 0.027 ppm and reflects a %CT adjustment of 50%.

Cauliflower

This commodity is a minor dietary contributor for the children 1-6 years (ca. 2%), females 13-50 years (ca. 2%), and females 13+ nursing (ca. 3%) population subgroups. Acephate, when applied, likely could be found as a residue because cauliflower is routinely consumed raw. The majority of cauliflower consumed in the United States is primarily domestically grown. Any cauliflower imported into the continental United States would be assumed to have been treated.

There were 2 studies submitted by the registrant for cauliflower. One was a magnitude of the residue study and the other was a multiple commodity farm-gate residue decline study (Lai, 1989b). No USDA PDP cauliflower monitoring data were available (USDA, 1996-2001). The cauliflower residue value was generated from DPR market basket monitoring data (DPR, 1998, 1999a, 2001a). The LOD value for the cauliflower monitoring data was 0.02 ppm. The residues ranged from 0.02 - 0.6 ppm (N = 173) with an acute mean of 0.029 ppm (SD; ± 0.064 ppm) and a chronic average of 0.02 ppm. The residue value used for the acute dietary exposure was a distributional value based on 500 Monte Carlo iterations. The residue value used for the chronic dietary exposure was 0.015 ppm and reflects a %CT adjustment of 15%.

Table 2A. Summary of Acephate Acute Probabilistic and Chronic Point Estimate Residues

Commodity	Data Source	Year	Number of Samples	Number Detected Samples	Detected Residues (ppm)	Range LOD (ppm)	Acute % Crop treated [A]	Adjust factor B	Acute Residue (ppm) Point Estimate	Acute Residue (ppm) Monte Carlo
Beans, Dry (raw forms)	PDP C- from green beans	1994 1995 CA only	Refer to PDP raw green beans	Refer to PDP raw green beans	Refer to PDP raw green beans	0.003	10	1.0	0.15	
Beans, Dry (processed forms)	PDP - from green beans	1996 1997 1998 CA	Refer to process green beans	Refer to process green beans	Refer to process green beans	0.002	10	1.0	0.14	
Beans, Green (raw forms)	PDP data	1994 1995 CA only	285	17	0.003 - 1.03	0.003	40	1.0	0.15	
Beans, Green (processed forms)	PDP data	1996 1997 1998 CA	400	94	0.002 - 0.7	0.002	60	1.0	0.14	
Cauliflower	DPR [E] data	1996 1997 1998	173	11	0.02-0.6	0.02	30	1.0	0.16	
Celery	DPR data	1996 1997 1998	203	31	0.02-0.8	0.02	70	1.0	0.21	
Lettuce - Head types	DPR data	1996 1997 1998	468	32	0.03-5.7	0.03	70	1.0	0.58	
Pepper - Bell (sweet varieties)	DPR data	1996 1997 1998	1010	184	0.04-3.0	0.04	50	1.0	0.56	
Pepper - Chili (hot varieties)	DPR data	1996 1997 1998	629	78	0.04-1.8	0.04	50	1.0	0.4	

A.) Percent crop treated estimate generated by the U.S. EPA Biological and Economic Analysis Division (BEAD).

B.) DEEM ™ default factors to account for food hydration state changes. **C**.) Pesticide Data Program (PDP) of the United States Department of Agriculture (USDA). **D**.) Residue Distribution File containing all reported residue values and used to generate a Monte Carlo method dietary exposure distribution. **E**.) DPR Market Basket pesticide residue surveillance program.

Table 2B. Summary of Acephate Point Estimate Acute and Chronic Residues

Commodity	Source a/ (Reference/Year)	Residue (PPM) Acute	Chronic	N b/	Additional Information
Brussel's Sprouts	DPR (1996-98)	0.12	0.005	132	Acute=95th% of detected residues, chronic=mean 1%
Cattle (fat)	EPA (Fort, 1999)	0.000016	0.000009	--	Registrant tissue to feed ratios for residues --
Cattle (kidney, mbyp)	EPA (Fort, 1999)	0.000050	0.000033	--	Registrant tissue to feed ratios for residues --
Cattle (liver)	EPA (Fort, 1999)	0.000006	0.000004	--	Registrant t--
Cattle (meat)	EPA (Fort, 1999)	0.000023	0.000015	--	Registrant tissue to f
Cottonseed meal/oil	REG (Lai, 1992)	0.13	0.013	12	Field trial, average residue. 0.2x oil process factor10%
Cranberry	FDA (1997-99)	0.006	0.0057	26	Acute = a
Egg	EPA (Fort, 1999)	0.000026	0.000022	--	REG beef tissue to feed ratios as surrogate data--
Goat (fat)	EPA (Fort, 1999)	0.000016	0.000009	--	REG beef tissue to feed ratios as surrogate data--
Goat (kidney, mbyp)	EPA (Fort, 1999)	0.000050	0.000033	--	REG beef tissue to feed ratios as surrogate data--
Goat (liver)	EPA (Fort, 1999)	0.000006	0.000004	--	REG beef tissue to feed ratios as surrogate data--
Goat (meat)	EPA (Fort, 1999)	0.000023	0.000015	--	REG beef tissue to feed ratios as surrogate data--
Horse (all forms)	EPA (Fort, 1999)	0.000023	0.000015	--	REG beef tissue to feed ratios as surrogate data--

Macadamia nut	EPA (Fort, 1999)	0.01	0.0001	6	REG field trial, non- detect residue, LOD = 0.01 1%
Milk (fat, sugar, water)	PDP (1997-98)	0.002	0.001	1322	All non-detects,
Peanut (nut, oil forms)	EPA (Fort, 1999)	0.01	0.0005	4	REG study, N detect, LOD=0.01, 0.13x oil process 5%
Peanut (butter)	EPA (Fort, 1999)	0.01	0.0005	4	REG study, N detect, LOD=0.01, 0.13x processing 5%
Pork (fat)	EPA (Fort, 1999)	0.000016	0.000009	--	REG beef tissue to feed ratios as surrogate data--
Pork (kidney, mbyp)	EPA (Fort, 1999)	0.000050	0.000033	--	REG beef tissue to feed ratios as surrogate data--
Pork (liver)	EPA (Fort, 1999)	0.000006	0.000004	--	REG beef tissue to feed ratios as surrogate data--
Pork (meat)	EPA (Fort, 1999)	0.000023	0.000015	--	REG beef tissue to feed ratios as surrogate data--
Poultry (fat)	EPA (Fort, 1999)	0.000001	0.000001	--	Registrant poultry tissue to feed ratios for residues--
Poultry (liver, giblets)	EPA (Fort, 1999)	0.000001	0.000001	--	Registrant poultry tissue to feed ratios for residues--
Pork (mbyp)	EPA (Fort, 1999)	0.000012	0.000007	--	Registrant poultry tissue to feed ratios for residues--
Poultry (meat)	EPA (Fort, 1999)	0.000007	0.000007	--	Registrant poultry tissue to feed ratios for residues--

Table 2B. Summary of Acephate Point Estimate Acute and Chronic Residues (Continued)

Commodity	Source [a/] (Reference/Year)	Residue (PPM) Acute	Chronic	N [b/]	Additional Information
Sheep (fat)	EPA (Fort, 1999)	0.000016	0.000009	--	REG beef tissue to feed ratios as surrogate data --
Sheep (kidney, mbyp)	EPA (Fort, 1999)	0.000050	0.000033	--	REG beef tissue to feed ratios as surrogate data --
Sheep (liver)	EPA (Fort, 1999)	0.000006	0.000004	--	REG beef tissue to feed ratios as surrogate data --
Sheep (meat)	EPA (Fort, 1999)	0.000023	0.000015	--	REG beef tissue to feed ratios as surrogate data --
Soybean (flour, oil)	REG (Lai, 1989a)	0.02	0.0001	2	Acute = LOD (0.02 ppm), processing factor used 1% [c/]
Soybean (protein)	REG (Lai, 1989a)	0.03	0.0003	2	Acute = LOD (0.03 ppm), processing facts used 1% [c/]

List of Abbreviations: **LOD**, Limit of Detection; **mbyp**, meat by products; **ppm**, parts per million.
a/ **DPR** = Residues from Department of Pesticide Regulation, **EPA** = U.S. EPA memo, **FDA** = Food and Drug Administration, **PDP** = Residues from USDA Pesticide Data Program, and **REG** = Residues from registrant field study.
b/ **N** = The number of RAC composite samples analyzed from the selected submitted studies.
c/ **%CT** = Percent of the crop treated adjustment made to the chronic dietary residues when sufficient use data are available.

IV. Residue Adjustments

A. Processing Effects

The DEEM® Dietary Exposure program residue file contains two adjustment factors (AF#1 and AF#2) which can be used to modify the residue concentrations used in a dietary assessment. Adjustment factor #1 (AF#1 in Table 2A) in the program commodity residue file is set to a specific default value depending on the commodity and its food form (fresh, dried, etc.). The default values range from 1.0 for most raw commodities to14.3 for dried tomato and are based on those concentration values used by U.S. EPA in its DEEM® (Dietary Estimated Exposure Model) dietary exposure program (Novigen, 2001). These default values account for the potential concentration of pesticide residues in processed foods (e.g. concentrated fruit juices, peels and dried forms) due primarily to the removal of water (Novigen, 2001). Since acephate is relatively non-volatile, the concentration of residues from processing procedures such as cooking or drying, is possible. There potentially may be a concentration of acephate as a result of repeated field applications to some agricultural crops. This situation could occur as the raw agricultural commodities are refined into their processed food forms. All of the primary commodities (excludes eggs, milk, and all meats) reported in Tables 2A and 2B were in their raw forms (fresh and dried fruit, raw vegetables and nuts, fresh juice, etc.) and most were also in market distribution channels.

Adjustment Factor #2 (AF#2) used registrant provided commodity studies showing acephate residue disappearance due to processing effects post-harvest (Fort, 1999, Lai, 1989b and 1992). Therefore, AF#2 was used to modify the default DEEM ™ concentration factors (AF#1) used for some specific commodities in the dietary exposure assessment. Also included was information related to the effects of commodity processing on acephate residues. Most of the liquids and other processed forms were based on residues measured after treatment of the raw commodity (i.e. cranberry); therefore, processing factors dependent on the extent of preparation of the raw commodity into a processed form were also determined. Based on the registrant supplied data, it appears that acephate residues are reduced after various forms of processing (washing, peeling, boiling, pasteurizing, cooking and baking) are performed on the raw commodity (Lai, 1989b).

Commodities destined for commercial processing (canned; cooked and frozen; cooked green beans, concentrated fruit juices, etc.) are likely to have residues reduced by the commercial processor. However, if these pre-commercially processed commodities did receive a treatment while in their raw form, the AF#2 processing and dissipation reductions presented in Table 3 would still apply. Table 3 lists the changes made to adjustment factor #2 of the food code file for a number of commodities analyzed in the dietary exposure assessment. The changes are due to the effects of processing. Registrant residue processing data for cottonseed, peanuts, and soybeans were used (Fort, 1999, Lai, 1989b and 1992).

Table 3. Residue File Adjustment Factor #2 Changes Based on Processing Effects.

COMMODITY [a]	FACTOR [b]	SOURCE [c]
Cottonseed oil	0.2	Cottonseed residue reduction based on processing into refined oil. (Lai, 1992)
Peanut oil	0.13	Peanut residue reduction based on processing into refined oil. (Fort, 1999)
Peanut butter	0.13	Residue reduction adjustment based on processing into peanut butter. (Fort, 1999)
Soybean flour	0.38	Bean residue reduction based on processing into fat and fat free forms. (Lai, 1989a)
Soybean oil	0.007	Soybean seed residue reduction based on processing into refined oil. (Lai, 1989a)
Soybean protein	0.54	Residue reduction based on processing and separation into protein form. (Lai, 1989a)
Soybean seeds/other	0.54	Residue reduction based on processing into edible forms. (Lai, 1989a)

a. The commodity name and, when necessary, the specific food form (i.e. oil, flour).
b. Residue reduction factor value used (all < 1.0X). Derived from residue processing (baking, cooking, etc.) reductions.
(For example: 1 ppm X 0.2 factor = 80% reduction in the residue).
c. Lists residue reduction method and reference.

B. Percent of the Crop Treated

The current DPR dietary exposure analysis default assumption is that 100% of any commodity is treated with the pesticide under consideration. When data are available that indicate less than 100% of a commodity is treated with a specific pesticide, exceptions to the default assumption are made on an individual crop and pesticide combination basis. The percent crop treated (%CT) adjustment was made to five commodities (cauliflower, celery, raw and processed green beans, head lettuce, and bell and chili peppers) for the acute distributional dietary exposure analysis. Percent crop treated adjustments were also made to all of the primary raw agricultural commodities (RACs) in the chronic dietary exposure analysis. Extensively blended commodities (e.g. milk, all meats, and eggs - secondary commodities) were excluded from any %CT adjustments in both the acute and chronic dietary exposure analyses.

Chronic %CT

The basic assumption in chronic exposure is that people under daily eating patterns would be continuously exposed to the averaged residue level of a pesticide for every labeled commodity for either for 1 year (chronic) or 70 years (lifetime). This exposure level based on an average residue and a 1/2 the non-detect as a residue value does not take into account the fact that a significant amount of a commodity may be untreated with the pesticide. The actual %CT with a specific pesticide varies from year to year depending upon biotic and abiotic factors. The U.S. EPA Benefits and Economic Assessment Division

(U.S. EPA BEAD) derived less than 100% of the crop treated adjustments for many commodities using acephate active ingredient national use and sales marketing data (Fort, 1999). Commodities residue values in the chronic dietary exposure analysis that were obtained from registrant field trial, state, or federal residue monitoring data were considered for %CT adjustments. Chronic %CT estimates available from the U.S. EPA BEAD were used exclusively in the DPR acephate dietary exposure analysis (Fort, 1999).

A percent of the crop treated adjustment has been made on all of the primary commodities in the chronic dietary exposure assessment. Excluded commodities from any %CT adjustments were the milk, meat, and eggs foods (secondary commodities). Most of the primary commodities have reported acephate use at the federal and state levels for both pre-plant and foliar application activities. Macadamia nut use information was unavailable, therefore registrant sales estimates were substituted instead. There are comprehensive use data available from the DPR Pesticide Use Reports, CDFA crop statistics, and the USDA Agricultural Field Crops Summary annuals. However, the U.S. EPA BEAD estimates were used because the BEAD numbers had already factored these use and product sales information into their acephate estimates (Fort, 1999). The U.S. EPA BEAD generated chronic %CT estimates were used to directly modify the commodity residue. The DPR chronic dietary exposure analysis used the %CT formula shown:

$$\text{Chronic Anticipated Residue (AR)} = \frac{\sum R_1 + [MDL/2 \times (N \times PCT - N_1)]}{N}$$

Where:

Anticipated Residue = Resulting residue value after %CT adjustment made (See Tables 3a,b)
$\mathbf{R_1}$ = All of the commodity samples with detected residues,
MDL = Minimum detection limit for the pesticide / commodity combination,
N = The total number of commodity samples analyzed, and
$\mathbf{N_1}$ = The number of commodity samples with pesticide residue detections.

Refer to Tables 2A and 2B for the commodities that had %CT adjustments made to their chronic dietary residue values using the above formula. The %CT adjustment can also appear as a value less than 1.0 under the column titled "Adjustment Factor #2" in the DEEM® dietary food code file (Novigen, 2001). The "Adjustment Factor #2" method may over-estimate the impact of the %CT adjustments. This method was not used in the DPR acephate chronic dietary exposure analysis.

Acute %CT

A %CT adjustment was made to each of the following primary commodities; cauliflower, celery, raw and processed green beans, dry beans, head lettuce, and both bell and chili peppers. Only commodities that used distributional residue data were modified with acute %CT adjustments. All the remaining commodities in the acute dietary exposure analysis used the default assumption that 100% of the commodity was treated with acephate. The U.S. EPA BEAD estimates were used based on product use and sales information described in the chronic %CT section (Fort, 1999).

The acute %CT estimates generated by U.S. EPA BEAD were used to modify the commodity residue distribution. The chronic %CT formula previously described was not used to modify acute dietary residue distributions. Each U.S. EPA BEAD estimate was factored into the acute residue distribution to represent untreated commodity (true zeros) instead of using the LOD.

For example, if there were 100 samples in a hypothetical residue distribution with 20 detections and 80 non-detects that was modified using a BEAD generated %CT estimate of 50 percent, then there would be a change in the distribution. If 50% of the crop was treated, then 50 detected residues would be

expected. Therefore, the 50% crop treated BEAD estimate would result in the use of the 20 detected residues, then 30 non-detected residues at the LOD changed to ½ LOD, and finally 50 of the non-detects at the LOD would be changed to zero. The 30 non-detects changed to ½ LOD represent residues expected but not found based on the 50% CT estimate. The resulting acute residue distribution would consist of the same 100 total samples with 20 detections but now also have 30 residues at ½ LOD, and 50 samples at zero to represent the 50% crop treated BEAD estimate. This method was used to modify the 5 commodities that used residue distributions in the DPR dietary exposure analysis (DPR, 2002b). Refer to Table 2A for the commodities that had acute %CT adjustments made to their residue distribution data sets.

V. Dietary Exposure

A. Acute Dietary Exposure

The acute dietary exposure analysis includes all current U.S. EPA and DPR label approved acephate uses. The acute dietary exposure analysis margins of exposure (MOE) are presented in Tables 4 A and B (Novigen, 2001, USDA, 1994-98). The MOEs are based on an acute NOEL of 1.0 (lack of statistically significant ChE inhibition, human oral study) and are reported for the 95th and 99.9th percentiles of anticipated dietary exposure (Freestone and McFarlane, 2001). The revised DPR policy is to report the 95th percentile of exposure for an acute dietary when a commodity residue is represented by a point estimate value. Also, the revised DPR policy for acute dietary exposure reports at the 99.9th percentile of exposure when a commodity value is represented by a distributional estimate derived from a range of residue samples (Monte Carlo analysis). The 99.9th percentile MOEs are reported for acephate since distributional estimates were used for several commodities in the acute dietary exposure analysis. The acute dietary exposure data for some of the commodity food forms were modified to reflect lower residues due to the effects of processing. The 99.9th percentile acute dietary exposure ranged from 0.001063 mg/kg/d, (females 13-19 years not pregnant/not nursing) to 0.002427 mg/kg/d, (nursing infants < 1 year old)

B. Seasonal Dietary Exposure

Acephate, because of its extensive use on a limited number of agricultural commodities, presents a clearly defined seasonal exposure scenario. This seasonal dietary exposure can impact workers applying the pesticide to the fields. The population subgroup females 20^{+} years (not pregnant, not nursing) was used as the surrogate population subgroup to represent anticipated exposure for workers in the subchronic/seasonal dietary exposure.

The DEEM® dietary exposure program does not calculate subchronic duration exposure; therefore, the DPR uses either acute or chronic dietary exposure values to represent the subchronic dietary exposure. The choice is dependent on the approximate time frame of exposure that is based on the anticipated duration of the seasonal exposure. If the duration likely is to be less than 1 week, then an acute dietary exposure value would be used. A chronic exposure value would be used if the subchronic duration is expected to be >1 week to three months. The population subgroup selected to represent seasonal exposure should best represent the potential exposure to workers and also indicate relative exposure to other population subgroups. The seasonal calculated dietary exposure was 0.000018 mg/kg/d (Table 5).

Table 4A. Acute Dietary Exposures from Anticipated Acephate Residues 95 th Percentile.

Population Subgroups	Monte Carlo Acute Dietary Exposure [a/] 95 th Percentile Exposure	Margins of Exposure [b/]
U.S. Population, all seasons	0.000093	10,700
Western Region	0.000104	9,600
Hispanics	0.000114	8,770
Non-Hispanic Whites	0.000091	11,000
Non-Hispanic Blacks	0.000079	12,700
Non-Hispanic Other	0.000109	9,200
All Infants	0.000145	6,900
Infants (nursing, < 1 year)	0.000064	15,500
Infants (non-nursing, < 1 year)	0.000158	6,300
Children (1-6 years)	0.000181	5,500
Children (7-12 years)	0.000089	11,200
Females (13-19 years) (not pregnant, not nursing)	0.000056	18,000
Females (20+ years) (not pregnant, not nursing)	0.000057	17,500
Females (13-50 years)	0.000058	17,400
Females (13+ years) (pregnant, not nursing)	0.000061	16,400
Females (13+ years) (nursing)	0.000060	16,800
Males (13-19 years)	0.000065	15,300
Males (20+ years)	0.000059	16,900
Seniors (55+ years)	0.000056	18,000
U.S. Population (16^{+} years) [C]	0.000058	17,400

a/ Exposure levels rounded to 3 significant figures, based on the 1994-1998 Continuing Survey of Food Intakes of Individuals (CSFII). Anticipated residue values (mg/kg/d) used for the commodities.
b/ MOE = NOEL ÷ Exposure. The acute NOEL value of 1.0 mg/kg/d was used (human oral study: lack of significant ChE inhibition, Freestone and McFarlane, 2001).
c/ This custom population subgroup.

Table 4B. Acute Dietary Exposures from Anticipated Acephate Residues -99.9 th Percentile.

Population Subgroups	Monte Carlo Acute Dietary Exposure [a/] 99.9 th Percentile Exposure	Margins of Exposure [b/]
U.S. Population, all seasons	0.001404	710
Western Region	0.001488	670
Hispanics	0.001661	600
Non-Hispanic Whites	0.001366	730
Non-Hispanic Blacks	0.001257	800
Non-Hispanic Other	0.001674	600
All Infants	0.002099	480
Infants (nursing, < 1 year)	0.002427	410
Infants (non-nursing, < 1 year)	0.002038	490
Children (1-6 years)	0.002034	490
Children (7-12 years)	0.001346	740
Females (13-19 years) (not pregnant, not nursing)	0.001063	940
Females (20+ years) (not pregnant, not nursing)	0.001320	760
Females (13-50 years)	0.001286	780
Females (13+ years) (pregnant, not nursing)	0.001659	600
Females (13+ years) (nursing)	0.001112	900
Males (13-19 years)	0.001103	910
Males (20+ years)	0.001311	760
Seniors (55+ years)	0.001281	780
U.S. Population (16^{+} years) [C/]	0.001301	770

a/ Exposure levels rounded to 3 significant figures, based on the 1994-1998 Continuing Survey of Food Intakes of Individuals (CSFII). Anticipated residue values (mg/kg/d) used for the commodities.
b/ MOE = NOEL ÷ Exposure. The acute NOEL value of 1.0 mg/kg/d was used (human oral study: lack of significant ChE inhibition, Freestone and McFarlane, 2001).
c/ Custom population subgroup.

C. Chronic Dietary Exposure

The chronic dietary exposure values are presented in Table 5 (Hazleton, 1991, Novigen, 2001, USDA, 1994-98). The chronic dietary exposure data for most commodities were modified with percent of the crop treated estimates based on U.S. EPA BEAD data. The commodity food form changes reflect lower and/or lack of residues due to processing effects or non-use. The

changes made to the commodity food forms were based on registrant supplied processing and/or acephate residue dissipation data. The data indicate that acephate residues decline over time (post treatment) and are also removed by the effects of processing (baked, canned, cooked, fried, etc.). When dissipation and/or processing data were available, then the food forms of many commodities were modified to reflect the reduced levels of acephate residues. These adjustments were used only with registrant field trial data. These food form adjustments (residue file adjustment factor #2 set to between 1 and zero) did slightly reduce the over-all potential dietary exposure compared to the unmodified forms. The main reason for only the modest reduction was that the majority of residues used in the dietary exposure assessment were derived from regulatory agencies in which no adjustments were used. The impact of percent of the crop treated adjustments to the commodities food form residues was much more significant. The percent of the crop treated (%CT) values were derived from the average weighted acephate use information from the U.S. EPA BEAD. The percentages of the crop treated adjustment factors for the chronic dietary exposure analysis were based on this %CT information for each commodity. The MOEs are based on a chronic ENEL (estimated-no-effect-level) of 0.09 mg/kg/d (statistically significant AChE inhibition in males, dog 1 year feeding study, 0.27 mg/kg/d LOEL) and are reported as the average anticipated dietary exposure (Hazleton, 1991). The chronic dietary exposure ranged from 0.000010 mg/kg/d, (nursing infants) to 0.000045 mg/kg/d, (children 1-6 years) (Table 5). Refer to the Critical Commodity Contribution paragraphs of the Commodity Contribution Effects (section D.) for details.

Table 5. Chronic Dietary Exposures from Anticipated Acephate Residues.

Population Subgroup	Chronic Dietary Exposure [a/] Annualized Averages Exposure	Margins of Exposure [b/]
U.S. Population, all seasons	0.000022	4,170
Western Region	0.000024	3,700
Hispanics	0.000026	3,420
Non-Hispanic Whites	0.000021	4,200
Non-Hispanic Blacks	0.000017	5,180
Non-Hispanic Other	0.000025	3,620
All Infants	0.000021	4,390
Infants (nursing, < 1 year)	0.000010	9,090
Infants (non-nursing, < 1 yr.)	0.000025	3,670
Children (1-6 years)	0.000045	1,980
Children (7-12 years)	0.000027	3,370
Females (13-19 years) (not pregnant, not nursing)	0.000016	5,670
Females (20+ years) (not pregnant, not nursing)	0.000018	4,880
Females (13-50 years)	0.000018	4,910
Females (13+ years) (pregnant, not nursing)	0.000021	4,290
Females (13+ years) (nursing)	0.000023	3,860
Males (13-19 years)	0.000018	4,920
Males (20+ years)	0.000018	4,920
Seniors (55+ years)	0.000018	5,070

a/ The chronic residue file used anticipated residue values (mg/kg/d) for the commodities and are based on the 1994-1998 Continuing Survey of Food Intakes of Individuals (CSFII), USDA.

b/ MOE = NOEL ÷ Exposure. The chronic estimated NOEL value of 0.09 mg/kg/d was used (dog; 1 year: brain AChE inhibition, Hazleton, 1991). Residue values are adjusted for percent of the crop treated.

D. Commodity Contribution Effects

Several population subgroups were selected to best characterize the significant groups of interest for the anticipated dietary exposures to acephate. The following population subgroups were selected: western region of the United States, females 13-50 years of age, nursing infants, non-nursing infants <1 year and children 1-6 years of age. The western region of the U.S. (11 western states) population represents the most appropriate exposure group to characterize all Californians. The females 13-50 years of age population subgroup represents women of child bearing age and can account for dietary exposure to the unborn from the consumption of pesticide residues in food. The nursing and non-nursing infants <1 year population groups are populations of interest especially in light of the U.S. EPA Food Quality Protection Act (FQPA) mandates. The highest chronic dietary exposure value for any of the populations listed in Table 5 came from the children 1-6 years of age population subgroup (0.000045 mg/kg/d).

A *Critical Commodity Contribution Analysis* (chronic module, DEEM® software) was done for the selected representative population subgroups to ascertain which commodities were contributing significant exposure to the chronic DPR dietary exposure analysis (Novigen, 2001, USDA, 1994-98). There remained several commodities that are significant contributors to chronic dietary exposure after all of the processing, residue dissipation and percent of the crop treated (%CT) adjustments were made to the chronic dietary residue food file.

The following three commodities contributed 10 % or more to the total chronic dietary exposure for one or more of the representative populations: **milk products** (western, females 13-50 years, nursing infants, non-nursing infants and children 1-6 years), **head lettuce** (western, females 13-50 years, non-nursing infants and children 1-6 years), and **green beans; canned: cooked** (nursing and non-nursing infants). Residue data sources for the commodities are described in III. B. Commodity Residue Studies. All 3 of the commodities, in reality, are likely significant contributors to the overall dietary burden based on the CSFII consumption information (Table 6).

The milk value came from the USDA PDP program and represents non-detected residues (USDA; 1997-98). Therefore, the total milk dietary contribution to the 5 population subgroups is based on the non-detect, theoretical ½ LOD value of 0.001 ppm (Table 2B). A majority of the national milk supply may not contain any acephate residues. However, no %CT treated adjustments were made to the milk food forms to represent this possibility.

The head lettuce residue derives from the average value (N = 468) of raw lettuce samples measured in the DPR pesticide monitoring program (DPR; 1996-98) (Table 6). The head lettuce residue is likely a reasonable representation of the actual value due to consumption primarily in the raw and often unwashed form. A %CT adjustment of 50% was made to the lettuce food form to account for the known amount of untreated commodity.

The canned, cooked form of succulent green beans (Table 6) value is based on the average residue (N = 400) of California collected green beans destined for canning measured in the PDP program (PDP; 1996-98).

The canned, cooked green bean average residue is possibly an over-estimation of the actual residue because no adjustment was made to account for the effects of processing on acephate. A registrant supplied study indicated that acephate residues on green beans dissipate 54% during transport from the field to the processing plant and are reduced by an additional 28-35% when processed and put into cans (Lai, 1989b). However, the USDA PDP surveyed specifically for processed green beans in

their monitoring program (USDA PDP, 2000). Therefore, the PDP processed green bean samples would likely already account for residue dissipation noted in the registrant study. The additional removal of acephate residues when processed into cans, also noted in the registrant study, were not included in the DPR dietary exposure assessment because this reduction would also likely be reflected in the PDP canned bean samples.

The DPR dietary exposure guidelines specify that when market basket origin residue samples are used that no adjustment be made to account for processing effects. Only when field trial studies are used can residues be adjusted to reflect potential reduction due to processing. Field trials have 100% of the crop treated and therefore most residue reduction is likely due to the effects of dissipation over time or commodity processing. The registrant study indicated just such effects (Lai, 1989b). The reason why the PDP data were used preferentially over the registrant's green bean data were previously explained in section III.B.A. (page 9). Basically, the market basket's average residue may already reflect reduction due to dissipation, processing, and non-detects may, in fact, be untreated samples. To account for these variables, the DPR guidelines specify keeping the residue unadjusted for processing when market basket source values are used.

Table 6. Ten percent or More Contribution to the Total Chronic Dietary Exposure

Population Subgroup	**Commodity** Milk Products [1]	Head Lettuce [1]	Green Beans [1]
Western United States	25%	28%	<10%
Nursing Infants	32%	<10%	53%
Non-nursing Infants	60%	<10%	26%
Children 1-6 Years	51%	10%	<10%
Females 13-50 Years	15%	37%	<10%

1. Includes all the milk food forms. Head lettuce represents a single food form. Green bean is specific for the canned: cooked food form of succulent green beans.

A *Critical Commodity Contribution Analysis* (CEC) (DEEM® program) was done for selected representative population subgroups to ascertain which commodities were contributing significant exposure to the acute DPR dietary exposure analysis (Novigen, 2001, USDA, 1994-98). The acute CEC is a much more complex analysis than the chronic commodity contribution analysis. Whereas the chronic looks at only the average contribution of a commodity to the average consumer, the CEC looks at all the individual upper bound consumption records for all consumers. The acute CEC methodology is described in the DEEM® program manual (Novigen, 2001). Two additional female population subgroups were added to the females 13-50 years of age population subgroup to represent women of child-bearing age during the more variable acute dietary consumption analysis. The two additional populations subgroups are females 13+ years (pregnant and not nursing) and females 13+ (nursing) which can provide additional information accounting for dietary exposure to the unborn due to the consumption of commodities that may contain pesticide residues.

Several commodities remained that are significant contributors to the acute dietary exposure after all of the processing, distributional residue ranges, and %CT adjustments were made to the dietary residue file. The following 3 commodities contributed 10 % or more to the total acute dietary exposure for one or more of the 7 representative populations: **head lettuce** (western U.S., children 1-6 years, females 13-50 years, females 13+ years [pregnant and not nursing], and females 13+ [nursing]), **green beans, all succulent food forms** (western, nursing infants, non-nursing infants, children 1-6 years,

females 13-50 years, females 13+ years [pregnant and not nursing], and females 13+ [nursing]), **Chili pepper** (western, females 13-50 years, and females 13+ years [pregnant and not nursing]). Residue data sources for the commodities are described in III. B. Commodity Residue Studies. Each of the 3 commodities is a significant upper bound (99.5 - 99.9 th%) contributor to the overall acute dietary burden of specific individuals based on the CSFII consumption information (Table 7).

The head lettuce residue is the probabilistic estimate derived from the acute distribution (N = 468) of raw lettuce samples measured in the DPR pesticide monitoring program (DPR; 1996-98) (Table 7). The head lettuce value is likely a reasonable representation of the actual residue primarily due to consumption in the raw and often unwashed form. An acute %CT adjustment of 70% was made to the residue distribution in the probabilistic analysis to account for the estimated amount of untreated commodity.

The succulent green beans (all food forms) residue is a probabilistic estimate derived from an acute distribution (N = 400) of succulent green bean samples measured in the USDA PDP pesticide monitoring program (USDA; 1996-98) (Table 7). The succulent green bean probabilistic residue distribution is possibly still an over-estimation of the actual residue because no adjustment was made for the effects of processing on acephate. Refer to the registrant supplied study by Lai (1989b) that was discussed in the prior chronic commodity contribution section.

The chili pepper residue is a probabilistic estimate derived from the acute distribution (N = 629) of raw chili pepper samples measured in the DPR pesticide monitoring program (DPR; 1996-98) (Table 7). The chili pepper probabilistic residue distribution is likely an over-estimate of the actual residue because no adjustment was made to account for the effects of acephate dissipation. A registrant supplied study indicated that acephate residues on bell peppers dissipate 3-29% during transport from the field to the grocery store (Lai, 1989b). The bell pepper dissipation data would also be applicable to chili peppers. In addition, the 1994-98 CSFII chili pepper consumption data were analyzed differently than prior CSFII data. Earlier data only considered specific chili pepper consumption and not chili peppers included in ethnic menu recipes. However, the 1994-98 CSFII analysis included chili pepper consumption from ethnic recipes (e.g. Carne asada). Based on the percentage of chili peppers included in the USDA ethnic recipes, the consumption of chili peppers may be over-estimated. The percentage of chili peppers in USDA meal recipe was discussed in more detail in a DPR methamidophos and chili peppers over-tolerance assessment (Schreider and Carr, 2001).

Table 7. 10% or More Contribution to the Total Acute Dietary Exposure

	Commodity		
Population Subgroup	Head Lettuce [1]	Green Beans [1]	Chili Pepper [1]
Western United States	41%	13%	14%
Nursing Infants	<10%	88%	<10%
Non-nursing Infants	<10%	78%	<10%
Children 1-6 Years	31%	29%	<10%
Females 13-50 Years	56%	10%	12%
Females 13+ (Preg/NN)	38%	10%	34%
Females 13+ (Nursing)	35%	13%	<10%

1. Head lettuce represents a single food form. Green bean includes all of the succulent green bean food forms (9). Chili pepper includes all chili pepper food forms

VI. Acute Tolerance Assessment

An acute tolerance assessment was performed for acephate using the current U.S. EPA tolerances (Code of Federal Regulations, 2002). The acephate acute NOEL of 1.0 mg/kg/d was used to calculate tolerance level margins of exposure based on the results from a human oral study (lack of plasma and red blood cell ChE inhibition). There are currently 33 human consumption RACs that have acephate tolerances (Code of Federal Regulations, 2002). Eight individual commodities were analyzed at the tolerance level maximum residue contribution (MRC) for acute dietary exposure using the NOEL of 1.0 mg/kg/d. The 8 commodity tolerances analyzed were dry and succulent beans (3 ppm tolerance), Brussel's sprouts (3 ppm), cauliflower (2 ppm), celery (10 ppm), cottonseed meal (8 ppm), head lettuce (10 ppm), chili and bell peppers (4 ppm), and soybean (1 ppm tolerance).

The MOEs and exposure ranges for each commodity are reported at the 95th percentile of MRC dietary consumption. The RAC dry bean tolerance MOE range is children 1-6 yrs: 74 (0.013407 mg/kg/d) - females 13^{+} years (pregnant/not nursing): 223 (0.004480 mg/kg/d). The commodity succulent bean tolerance MOE range is non-nursing infants <1 yr.: 24 (0.040232 mg/kg/d) – females 13+ yr. (pregnant/not nursing): 196 (0.005100 mg/kg/d). The Brussel's sprouts tolerance MOE range is non-nursing infants: 37 (0.026829) – Hispanics: 517 (0.001933 mg/kg/d). The MOE range for the cauliflower tolerance is non-nursing infants: 71 (0.014009 mg/kg/d) - nursing infants < 1 year: 1,819 (0.000550 mg/kg/d). The celery tolerance MOE range is children 1-6 years: 55 (0.018067) - females 13^{+} years (nursing): 180 (0.005829 mg/kg/d). The RAC cottonseed meal tolerance MOE range is Hispanics: 18,212 (0.000055 mg/kg/d) - seniors 55^{+} years: 472,727 (0.000002 mg/kg/d). The MOE range for the head lettuce tolerance is children 1-6 years: 29 (0.033606 mg/kg/d) - nursing infants < 1 year: 252 (0.003956 mg/kg/d). The peppers (chile and bell) tolerance MOE range is females 13^{+} years (pregnant/not nursing): 89 (0.011200 mg/kg/d) – females 13-19 yrs: 491 (0.002036 mg/kg/d) - seniors 55^{+} years: 1,482 (0.000675 mg/kg/d). The soybean seed tolerance MOE range is non-nursing infants <1 yr: 218 (0.004579 mg/kg/d) – seniors 55+: 7,727 (0.000129 mg/kg/d).

The MOEs were greater than 10 at the 95th % of exposure for all of the population subgroups for each of the 9 commodities at tolerance when the acephate acute NOEL of 1.0 mg/kg/d was used. The highest acute MRC exposure (lowest MOE) was 0.040232 mg/kg/d (MOE: 24), that occurred in the non-nursing infants <1 yr population subgroup, from consumption of tolerance level succulent beans at the 95th % of exposure. The lowest MRC (highest MOE) was obtained from the cottonseed meal tolerance for the seniors 55^{+} years population subgroup with an exposure of 0.000002 mg/kg/d (MOE: 472,727). In addition, there were 4 population subgroups that had MOEs of less than 10 at the 99.9th % of tolerance level commodity consumption. The population subgroup children 1-6 yr had a MOE of 8 for the RAC succulent beans at the 99.9th % of exposure. The same RAC resulted in MOEs of 9 at the 99.9th% for the nursing and all infants populations. Also, the combination of Hispanics and head lettuce had a MOE of 9 at the 99.9th %. The three commodities (beans, celery and head lettuce) with the highest tolerance level exposures are presented in Table 8 with each of their individual population subgroups' MOEs.

Table 8. Margins of Exposure [a/] for Population Subgroups From Three Individual Commodities Using Tolerance Levels of Acephate.

	Acute 95 th Percentile Margins of Exposure [b/]			
Commodity:	**Beans**	**Beans**	**Celery**	**Head Lettuce**
Population Subgroup	**(Dry)**	**(Succ.)**		
	(3 ppm)	**(3 ppm)**	**(10 ppm)**	**(10 ppm)**
US Pop. all seasons	144	96	113	45
Western Region	125	115	96	42
Hispanics	117	121	96	44
Non-Hispanic Whites	191	100	118	45
Non-Hispanic Blacks	131	79	147	56
Non-Hispanic Other	89	90	74	37
All Infants	105	25	76	170
Infants (nursing, < 1 year)	197	25	102	**252**
Infants (non-nursing, < 1 year)	99	**24**	73	169
Children (1-6 years)	**74**	46	**55**	**29**
Children (7-12 years)	116	78	72	38
Females (13-19 years) (not pregnant, not nursing)	179	138	123	45
Females (20+ years) (not pregnant, not nursing)	210	134	133	45
Females (13-50 years)	198	135	127	44
Females (13+ years) (pregnant, not nursing)	**223**	**196**	171	45
Females (13+ years) (nursing)	109	158	**180**	44
Males (13-19 years)	139	123	95	47
Males (20+ years)	183	126	132	51
Seniors (55+ years)	201	136	142	53

a/ MOEs based on label approved commodities. Acute NOEL of 1.0 mg/kg/d from human study used. Exposure levels have been rounded off to 3 significant figures and were based on the 1994-1998 Continuing Survey of Food Intakes of Individuals.

b/ The residue files used tolerance level values for the commodities. The number of user days from the 1994-98 CSFII database are acceptable for each commodity. High and low MOE values are bolded.

VII. Acephate Dietary Exposure References

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ATTACHMENT A
Acute Dietary Exposure
All Labeled Commodities

Acephate Residue Distribution Files (RDF)

Cauliflower
DPR data from 1996- 1998 (173 samples, 11 detects)
Data used directly (not decomposited)
6% Detected (Actual residues ranged from 0.01 - 0.6 ppm)
30% CT, Cauliflower-DPR

TOTALZ=121
41 @ 0.01
0.6,0.54,0.27,0.21,0.07,0.06,0.02,0.02,0.02,0.02,0.01

Celery
DPR data from 1996- 1998 (203 samples, 30 detects)
Data used directly (not decomposited)
15% Detected (Actual residues ranged from 0.02 - 0.8 ppm)
70% CT, Celery-DPR

TOTALZ=60
112 @ 0.01
0.8,0.45,0.41,0.3,0.28,0.27,0.26,0.22,0.17,0.1,0.026,0.02
3×0.29, 5×0.05, 5×0.04, 6×0.03

Head Lettuce
DPR data from 1996- 1998 (448 samples, 32 detects)
Data used directly (not decomposited)
7% Detected (Actual residues ranged from 0.02 - 5.7 ppm)
70% CT, Head Lettuce-DPR

TOTALZ=140
296 @ 0.01
5.7,0.52,0.46,0.28,0.26,0.25,0.2,0.16,0.11,0.1,0.07,0.06
2×0.19, 5×0.05, 2×0.04, 2×0.03, 9×0.02

Bell Pepper
DPR data from 1996- 1998 (1010 samples, 184 detects)
Data used directly (not decomposited)
18% Detected (Actual residues ranged from 0.02 - 3 ppm)
50% CT, Bell Pepper-DPR

TOTALZ=505
321 @ 0.02
3,1.5,1.49,1.3,1.2,1.16,1.14,0.98,0.93,0.82,0.79,0.78,0.64,0.61,0.58,0.57,0.54,0.48,0.47,0.46,0.41,

0.39,0.37,0.35,0.29,0.28,0.27,0.177,0.15,0.14,0.1,0.035,0.01

2×2, 4×1.4, 2×1.26, 2×1.1, 2×0.96, 2×0.88, 2×0.72, 2×0.66, 2×0.62, 2×0.6, 4×0.56, 3×0.53, 3×0.52,
2×0.45, 2×0.43, 2×0.42, 2×0.4, 2×0.38, 2×0.36, 3×0.34, 2×0.32, 2×0.31, 2×0.3, 3×0.26, 2×0.25,
2×0.24, 3×0.23, 4×0.22, 5×0.21, 4×0.2, 3×0.19, 2×0.18, 6×0.16, 4×0.13, 3×0.12, 6×0.11, 6×0.09,
4×0.08, 8×0.07, 7×0.06, 6×0.05, 7×0.04, 6×0.03, 7×0.02,

Chili Pepper
DPR data from 1996- 1998 (629 samples, 78 detects)
Data used directly (not decomposited)
12% Detected (Actual residues ranged from 0.02 - 1.8 ppm)
50% CT, Chili Pepper-DPR

TOTALZ=314
237 @ 0.02
1.8,1.5,1.22,0.92,0.7,0.67,0.55,0.52,0.47,0.46,0.45,0.4,0.32,0.29,0.27,0.22,0.19,0.17,0.16,0.15,
0.11,0.06

2×1.35, 2×1.0, 2×0.48, 2×0.43, 2×0.38, 2×0.37, 2×0.33, 2×0.31, 2×0.3, 3×0.24, 3×0.23, 4×0.18,
2×0.13, 3×0.12, 2×0.1, 3×0.08, 3×0.07, 4×0.04, 4×0.03, 7×0.02

Green Beans - raw
PDP California collected data from 1994 and 1995 (285 samples, 17 detects)
Data used directly (not decomposited)
6% Detected (Actual residues ranged from 0.003 - 1.03 ppm)
40% CT, Green Beans - raw - PDP

TOTALZ=173
99 @ 0.0015
1.03,0.29,0.23,0.21,0.17,0.12,0.06,0.026,0.014,0.01

2×0.13, 2×0.015, 3×0.005

Green Beans - destined for processing
PDP California collected data from 1996, 1997, and 1998 (400 samples, 94 detects)
Data used directly (not decomposited)
24% Detected (Actual residues ranged from 0.002 - 0.7 ppm)
60% CT, Green Beans - processed - PDP
TOTALZ=161
149 @ 0.001

0.7,0.47,0.4,0.34,0.3,0.29,0.28,0.27,0.26,0.24,0.19,0.18,0.13,0.12,0.1,0.096,0.093,0.078,0.076,0.067,0.05
7,0.052,0.051,0.048,0.045,0.044,0.043,0.037,0.036,0.035,0.032,0.031,0.03,0.026,0.024,0.022,0.02,0.019,
0.018,0.013,0.007

2×0.16, 2×0.15, 2×0.034, 2×0.027, 3×0.025, 2×0.023, 3×0.017, 2×0.016, 4×0.015, 2×0.014, 2×0.012,
2×0.011, 5×0.01, 3×0.009, 6×0.008, 11×0.003

Dry Beans - Raw (Surrogate)
PDP California green beans from 1994 and 1995 as surrogate data (285 samples, 17 detects)
Data not decomposited
6% Detected (Actual residues ranged from 0.003 - 1.03 ppm)
10% CT, Dry Beans - raw - PDP

TOTALZ=260

12 @ 0.0015
1.03,0.29,0.23,0.21,0.17,0.12,0.06,0.026,0.014,0.01

2×0.13, 2×0.015, 3×0.005

Green Beans - destined for processing (Surrogate)
PDP California green beans from 1996, 1997, and 1998 as surrogate (400 samples, 94 detects)
Data not decomposited
24% Detected (Actual residues ranged from 0.002 - 0.7 ppm)
10% CT, Dry Beans - processed - PDP

TOTALZ=310
TOTALLOD=0

0.7,0.47,0.4,0.34,0.3,0.29,0.28,0.27,0.26,0.24,0.19,0.18,0.13,0.12,0.1,0.096,0.093,0.078,0.076,0.067,0.057,0.052,0.051,0.048,0.045,0.044,0.043,0.037,0.036,0.035,0.032,0.031,0.03,0.026,0.024,0.022,0.02,0.019,0.018,0.013,0.007

2×0.16, 2×0.15, 2×0.034, 2×0.027, 3×0.025, 2×0.023, 3×0.017, 2×0.016, 4×0.015, 2×0.014, 2×0.012, 2×0.011, 5×0.01, 3×0.009, 6×0.008, 11×0.003

END OF ACEPHATE RDF FILES

California Department of Pesticide Regulation Ver. 7.76
DEEM Acute analysis for ACEPHATE
Residue file name: D:\deem\Resi-files\acephate acute3.RS7
Analysis Date 03-19-2003 Residue file dated: 08-23-2002
DPR Acute NOEL = 1 mg/kg bw/day
Comment: Dietary exposure (180.108), human NOEL using REG & GOV residue data.

RDL indices and parameters for Monte Carlo Analysis:

Index #	Dist Code	Parameter #1			
1	6	DPR-ace-cauliflower.rdf			
2	6	DPR-ace-celery.rdf			
3	6	DPR-ace-Head Lettuce.rdf			
4	6	DPR-ace-bell pepper.rdf			
5	6	DPR-ace-chili pepper.rdf			
6	6	PDP-ace-Raw Green Beans.rdf			
7	6	PDP-ace-Processed Green Beans.rdf			
8	6	PDP-ace-Raw Green Beans as surrogate.rdf			
9	6	PDP-ace-Processed Green Beans as surrogate.rdf			

Food Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	#2	RDL Ind
8	O	Cranberries	0.054000	1.00	1.00	
		Full comment: FDA domes resi (1997-99): 95th% value				
9	O	Cranberries-juice	0.006000	1.10	1.00	
		Full comment: FDA domes residues (1997 - 99): ac avg				
46	14	Macadamia nuts (bush nuts)	0.010000	1.00	1.00	
		Full comment: EPA value from REG study				
139	8	Paprika	0.560000	1.00	1.00	4
		Full comment: DPR bell pepper as surrogate residue				
155	8	Peppers-sweet(garden)	0.560000	1.00	1.00	4
		Full comment: DPR (1996 - 98): 95th % residue				
156	8	Peppers-chilli incl jalapeno	0.400000	1.00	1.00	5
		Full comment: DPR (1996 - 98): 95th % residue				
157	8	Peppers-other	0.400000	1.00	1.00	5
		Full comment: DPR chilli pepper as surrogate				
158	8	Pimientos	0.400000	1.00	1.00	5
		Full comment: DPR chilli pepper as surrogate				
166	4B	Celery	0.210000	1.00	1.00	2
		Full comment: DPR (1996 - 98): 95th % residue				
169	5A	Brussels sprouts	0.120000	1.00	1.00	
		Full comment: DPR (1996 - 98): 95th % residue				
171	5A	Cauliflower	0.160000	1.00	1.00	1
		Full comment: DPR (1996 - 98): 95th % residue				

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 192 4A   Lettuce-head varieties              0.580000   1.00 1.00 3
    Full comment: DPR (1996 - 98):  95th% residue
 227 6C   Beans-dry-great northern
            14-Boiled                         0.150000   1.00 1.00 8
           Full comment: PDP CA only greenbean as surrogate
            32-Canned: Cooked                 0.140000   1.00 1.00 9
           Full comment: PDP CA only greenbean as surrogate
 228 6C   Beans-dry-kidney
            12-Cooked: NFS                    0.150000   1.00 1.00 8
           Full comment: PDP CA only greenbean as surrogate

Food Crop Food Name                           Def Res     Adj.Factors
RDL
Code  Grp                                      (ppm)       #1    #2
Ind
---- ---- -------------------------------  ----------  ------ ------
----
            13-Baked                          0.150000   1.00 1.00 8
           Full comment: PDP CA only greenbean as surrogate
            14-Boiled                         0.150000   1.00 1.00 8
           Full comment: PDP CA only greenbean as surrogate
            32-Canned: Cooked                 0.140000   1.00 1.00 9
           Full comment: PDP CA only greenbean as surrogate
            34-Canned: Boiled                 0.140000   1.00 1.00 9
           Full comment: PDP CA only greenbean as surrogate
            42-Frozen: Cooked                 0.140000   1.00 1.00 9
           Full comment: PDP CA only greenbean as surrogate
 229 6C   Beans-dry-lima
            14-Boiled                         0.150000   1.00 1.00 8
           Full comment: PDP CA only greenbean as surrogate
            32-Canned: Cooked                 0.140000   1.00 1.00 9
           Full comment: PDP CA only greenbean as surrogate
 230 6C   Beans-dry-navy (pea)
            14-Boiled                         0.150000   1.00 1.00 8
           Full comment: PDP CA only greenbean as surrogate
            32-Canned: Cooked                 0.140000   1.00 1.00 9
           Full comment: PDP CA only greenbean as surrogate
            34-Canned: Boiled                 0.140000   1.00 1.00 9
           Full comment: PDP CA only greenbean as surrogate
 231 6C   Beans-dry-other
            12-Cooked: NFS                    0.150000   1.00 1.00 8
           Full comment: PDP CA only greenbean as surrogate
            13-Baked                          0.150000   1.00 1.00 8
           Full comment: PDP CA only greenbean as surrogate
            14-Boiled                         0.150000   1.00 1.00 8
           Full comment: PDP CA only greenbean as surrogate
            15-Fried                          0.150000   1.00 1.00 8
           Full comment: PDP CA only greenbean as surrogate
            34-Canned: Boiled                 0.140000   1.00 1.00 9
           Full comment: PDP CA only greenbean as surrogate
 232 6C   Beans-dry-pinto
            12-Cooked: NFS                    0.150000   1.00 1.00 8
           Full comment: PDP CA only greenbean as surrogate
            13-Baked                          0.150000   1.00 1.00 8
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Food Crop	Food Name	Def Res	Adj.Factors		RDL
Code Grp		(ppm)	#1	#2	Ind
	Full comment: PDP CA only greenbean as surrogate				
	14-Boiled	0.150000	1.00	1.00	8
	Full comment: PDP CA only greenbean as surrogate				
	15-Fried	0.150000	1.00	1.00	8
	Full comment: PDP CA only greenbean as surrogate				
	32-Canned: Cooked	0.140000	1.00	1.00	9
	Full comment: PDP CA only greenbean as surrogate				
	42-Frozen: Cooked	0.140000	1.00	1.00	9
	Full comment: PDP CA only greenbean as surrogate				
233 6B	Beans-succulent-lima				
	11-Uncooked	0.150000	1.00	1.00	6
	Full comment: PDP Green beans (raw) - 95th%				
	12-Cooked: NFS	0.150000	1.00	1.00	6
	Full comment: PDP Green beans (raw) - 95th%				
	14-Boiled	0.150000	1.00	1.00	6
	Full comment: PDP Green beans (raw) - 95th%				
	32-Canned: Cooked	0.140000	1.00	1.00	7
	Full comment: PDP Green beans (proc) - 95th% residue				
	42-Frozen: Cooked	0.140000	1.00	1.00	7
	Full comment: PDP Green beans (proc) - 95th% residue				
	44-Frozen: Boiled	0.140000	1.00	1.00	7
	Full comment: PDP Green beans (proc) - 95th% residue				
234 6A	Beans-succulent-green				
	11-Uncooked	0.150000	1.00	1.00	6
	Full comment: PDP Green beans (raw) - 95th%				
	12-Cooked: NFS	0.150000	1.00	1.00	6
	Full comment: PDP Green beans (raw) - 95th%				
	14-Boiled	0.150000	1.00	1.00	6
	Full comment: PDP Green beans (raw) - 95th%				
	31-Canned: NFS	0.140000	1.00	1.00	7
	Full comment: PDP Green beans (proc) - 95th% residue				
	32-Canned: Cooked	0.140000	1.00	1.00	7
	Full comment: PDP Green beans (proc) - 95th% residue				
	34-Canned: Boiled	0.140000	1.00	1.00	7
	Full comment: PDP Green beans (proc) - 95th% residue				
	42-Frozen: Cooked	0.140000	1.00	1.00	7
	Full comment: PDP Green beans (proc) - 95th% residue				
	44-Frozen: Boiled	0.140000	1.00	1.00	7
	Full comment: PDP Green beans (proc) - 95th% residue				
	51-Cured: NFS (smoked/p	0.150000	1.00	1.00	7
	Full comment: PDP Green beans (raw) - 95th%				
235 6A	Beans-succulent-other				
	34-Canned: Boiled	0.140000	1.00	1.00	7
	Full comment: PDP Green beans (proc) - 95th% residue				
236 6A	Beans-succulent-yellow/wax				
	14-Boiled	0.150000	1.00	1.00	6
	Full comment: PDP Green beans (raw) - 95th%				
	32-Canned: Cooked	0.140000	1.00	1.00	7

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            Full comment: PDP Green beans (proc) - 95th% residue
             42-Frozen: Cooked                0.140000   1.00 1.00 7
            Full comment: PDP Green beans (proc) - 95th% residue
 249 6C   Beans-dry-broadbeans                0.150000   1.00 1.00 9
    Full comment: PDP CA only greenbean as surrogate
 250 6B   Beans-succulent-broadbeans          0.150000   1.00 1.00 6
    Full comment: PDP Green beans (raw) - 95th%
 251 6C   Beans-dry-pigeon beans              0.150000   1.00 1.00 9
    Full comment: PDP CA only greenbean as surrogate
 253 6    Beans-unspecified                   0.150000   1.00 1.00 6
    Full comment: PDP Green beans (raw) - 95th%
 255 6A   Soybeans-sprouted seeds             0.030000   0.33 1.00
    Full comment: DPR - REG FT AR + EPA processing
 256 O    Beans-dry-hyacinth                  0.150000   1.00 1.00 9
    Full comment: PDP CA only greenbean as surrogate
 257 O    Beans-succulent-hyacinth            0.150000   1.00 1.00 6
    Full comment: PDP Green beans (raw) - 95th%
 258 6C   Beans-dry-blackeye peas/cowpea      0.150000   1.00 1.00 9
    Full comment: PDP CA only greenbean as surrogate
 259 6C   Beans-dry-garbanzo/chick pea
             12-Cooked: NFS                   0.150000   1.00 1.00 8
            Full comment: PDP CA only greenbean as surrogate
             14-Boiled                        0.150000   1.00 1.00 8
            Full comment: PDP CA only greenbean as surrogate

Food Crop Food Name                          Def Res     Adj.Factors
RDL
Code  Grp                                     (ppm)       #1    #2
Ind
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             15-Fried                        0.150000   1.00 1.00 8
            Full comment: PDP CA only greenbean as surrogate
             32-Canned: Cooked               0.140000   1.00 1.00 9
            Full comment: PDP CA only greenbean as surrogate
 287 6C   Guar beans
             13-Baked                        0.140000   1.00 1.00 6
            Full comment: PDP CA only greenbean as surrogate
             34-Canned: Boiled               0.150000   1.00 1.00 7
            Full comment: PDP CA only greenbean as surrogate
 290 O    Cottonseed-oil                      0.130000   1.0 0.200
    Full comment: REG field trial data
 291 O    Cottonseed-meal                     0.130000   1.00 1.00
    Full comment: REG field trial data
 293 O    Peanuts-oil                         0.010000   1.00 0.13
    Full comment: EPA cited REG Field Trial w/ processing
 297 6A   Soybeans-oil                        0.020000   1.0 0.007
    Full comment: DPR - REG FT AR + EPA processing
 303 6A   Soybean-other                       0.030000   1.00 0.54
    Full comment: DPR - REG FT AR + EPA processing
 304 6A   Soybeans-mature seeds dry           0.030000   1.0 0.540
    Full comment: DPR - REG FT AR + EPA processing
 305 6A   Soybeans-flour (full fat)           0.020000   1.00 0.38
    Full comment: DPR - REG FT AR + EPA processing
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 306 6A   Soybeans-flour (low fat)           0.020000   1.00 0.38
    Full comment: DPR - REG FT AR + EPA processing
 307 6A   Soybeans-flour (defatted)          0.020000   1.00 0.38
    Full comment: DPR - REG FT AR + EPA processing
 318 D    Milk-nonfat solids                 0.002000   1.00 1.00
    Full comment: USDA PDP LOD (1997, 98)
 319 D    Milk-fat solids                    0.002000   1.00 1.00
    Full comment: USDA PDP LOD (1997, 98)
 320 D    Milk sugar (lactose)               0.002000   1.00 1.00
    Full comment: USDA PDP LOD (1997, 98)
 321 M    Beef-meat byproducts               0.000050   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 322 M    Beef-other organ meats             0.000050   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 323 M    Beef-dried                         0.000023   1.92 1.00
    Full comment: EPA - REG derived anticipted residues
 324 M    Beef-fat w/o bones                 0.000016   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 325 M    Beef-kidney                        0.000050   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 326 M    Beef-liver                         0.000006   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 327 M    Beef-lean (fat/free) w/o bones     0.000023   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 328 M    Goat-meat byproducts               0.000050   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 329 M    Goat-other organ meats             0.000050   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 330 M    Goat-fat w/o bone                  0.000016   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 331 M    Goat-kidney                        0.000050   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
Food Crop Food Name                          Def Res     Adj.Factors
RDL
Code  Grp                                     (ppm)       #1    #2
Ind
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 332 M    Goat-liver                         0.000006   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 333 M    Goat-lean (fat/free) w/o bone      0.000023   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 334 M    Horsemeat                          0.000023   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 336 M    Sheep-meat byproducts              0.000050   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 337 M    Sheep-other organ meats            0.000050   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 338 M    Sheep-fat w/o bone                 0.000016   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 339 M    Sheep-kidney                       0.000050   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
 340 M    Sheep-liver                        0.000006   1.00 1.00
    Full comment: EPA - REG derived anticipted residues
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341	M	Sheep-lean (fat free) w/o bone	0.000023	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
342	M	Pork-meat byproducts	0.000050	1.00	1.00	
		Full comment: EPA ruminant AR as surrogate				
343	M	Pork-other organ meats	0.000050	1.00	1.00	
		Full comment: EPA ruminant AR as surrogate				
344	M	Pork-fat w/o bone	0.000016	1.00	1.00	
		Full comment: EPA ruminant AR as surrogate				
345	M	Pork-kidney	0.000050	1.00	1.00	
		Full comment: EPA ruminant AR as surrogate				
346	M	Pork-liver	0.000006	1.00	1.00	
		Full comment: EPA ruminant AR as surrogate				
347	M	Pork-lean (fat free) w/o bone	0.000023	1.00	1.00	
		Full comment: EPA ruminant AR as surrogate				
355	P	Turkey-byproducts	0.000012	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
356	P	Turkey-giblets (liver)	0.000001	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
357	P	Turkey--fat w/o bones	0.000001	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
358	P	Turkey- lean/fat free w/o bones	0.000012	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
360	P	Poultry-other-lean (fat free) w/	0.000012	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
361	P	Poultry-other-giblets(liver)	0.000001	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
362	P	Poultry-other-fat w/o bones	0.000001	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
363	P	Eggs-whole	0.000026	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
364	P	Eggs-white only	0.000026	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
365	P	Eggs-yolk only	0.000026	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
366	P	Chicken-byproducts	0.000012	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
367	P	Chicken-giblets(liver)	0.000001	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				

Food Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	#2	RDL Ind
368	P	Chicken-fat w/o bones	0.000001	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
369	P	Chicken-lean/fat free w/o bones	0.000012	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
384	4B	Celery juice	0.041000	1.00	1.00	2
		Full comment: DPR (1996 - 98): avg acute residue				
385	P	Chicken-giblets (excl. liver)	0.000001	1.00	1.00	
		Full comment: EPA - REG derived anticipted residues				
389	O	Cranberries-juice-concentrate	0.006000	3.30	1.00	

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   Full comment: FDA domes residues (1997 - 99): ac avg
 398 D    Milk-based water                    0.002000   1.00 1.00
   Full comment: USDA PDP LOD (1997, 98)
 403 O    Peanuts-butter                      0.010000   1.00 0.13
   Full comment: EPA cited REG Field Trial w/ processing
 424 M    Veal-fat w/o bones                  0.000016   1.00 1.00
   Full comment: EPA - REG derived anticipted residues
 425 M    Veal-lean (fat free) w/o bones      0.000023   1.00 1.00
   Full comment: EPA - REG derived anticipted residues
 426 M    Veal-kidney                         0.000050   1.00 1.00
   Full comment: EPA - REG derived anticipted residues
 427 M    Veal-liver                          0.000006   1.00 1.00
   Full comment: EPA - REG derived anticipted residues
 428 M    Veal-other organ meats              0.000050   1.00 1.00
   Full comment: EPA - REG derived anticipted residues
 429 M    Veal-dried                          0.000023   1.92 1.00
   Full comment: EPA - REG derived anticipted residues
 430 M    Veal-meat byproducts                0.000050   1.00 1.00
   Full comment: EPA - REG derived anticipted residues
 449 P    Turkey-other organ meats            0.000001   1.00 1.00
   Full comment: EPA - REG derived anticipted residues
 467 19B  Celery seed                         0.041000   1.00 1.00
   Full comment: DPR (1996 - 98): avg acute residue
 482 O    Soybeans-protein isolate            0.020000   1.00 0.54
   Full comment: DPR - REG FT AR + EPA processing
 940 O    Peanuts-hulled                      0.010000   1.00 1.00
   Full comment: EPA cited REG Field Trial
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California Department of Pesticide Regulation Ver. 7.76
DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
1994-98 DATA Adjustment factor #2 used
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500 MC list in residue file MC seed = 1
Dietary exposure (180.108), human NOEL using REG/GOV residue data

U.S. POP - ALL SEASONS

Daily Exposure Analysis /a (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000031	0.000031
Standard Deviation	0.000186	0.000187
Margin of Exposure /2	32,354	32,223

Percent of Person-Days that are User-Days = 99.60%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000002	541,703	90.00	0.000057	17,437
20.00	0.000004	274,324	95.00	0.000093	10,749
30.00	0.000006	169,176	97.50	0.000150	6,676
40.00	0.000009	115,505	99.00	0.000291	3,439
50.00	0.000012	84,074	99.50	0.000469	2,131
60.00	0.000016	62,628	99.75	0.000748	1,337
70.00	0.000022	45,741	99.90	0.001404	712
80.00	0.000032	31,046			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000002	559,912	90.00	0.000057	17,491
20.00	0.000004	279,280	95.00	0.000093	10,776
30.00	0.000006	171,248	97.50	0.000149	6,692
40.00	0.000009	116,433	99.00	0.000290	3,448
50.00	0.000012	84,585	99.50	0.000468	2,138
60.00	0.000016	62,952	99.75	0.000746	1,340
70.00	0.000022	45,925	99.90	0.001400	714
80.00	0.000032	31,154			

a/ Analysis based on all two-day participant records in CSFII 1994-98 survey.
2/ Margin of Exposure = NOEL/ Dietary Exposure.

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Western region

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000035	0.000035
Standard Deviation	0.000196	0.000196
Margin of Exposure	28,699	28,531

Percent of Person-Days that are User-Days = 99.42%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	486,817	90.00	0.000065	15,473
20.00	0.000004	234,729	95.00	0.000104	9,598
30.00	0.000007	139,427	97.50	0.000167	5,975
40.00	0.000010	95,782	99.00	0.000329	3,037
50.00	0.000014	71,415	99.50	0.000526	1,900
60.00	0.000019	53,273	99.75	0.000812	1,231
70.00	0.000026	38,936	99.90	0.001488	672
80.00	0.000037	26,913			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	512,943	90.00	0.000064	15,534
20.00	0.000004	241,177	95.00	0.000104	9,643
30.00	0.000007	141,730	97.50	0.000167	5,999
40.00	0.000010	96,932	99.00	0.000327	3,053
50.00	0.000014	71,988	99.50	0.000525	1,906
60.00	0.000019	53,687	99.75	0.000808	1,236
70.00	0.000026	39,155	99.90	0.001482	674
80.00	0.000037	27,079			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Hispanics

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000037	0.000037
Standard Deviation	0.000199	0.000200
Margin of Exposure	27,185	27,031

Percent of Person-Days that are User-Days = 99.43%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	545,663	90.00	0.000072	13,797
20.00	0.000004	257,943	95.00	0.000114	8,769
30.00	0.000007	150,388	97.50	0.000179	5,581
40.00	0.000010	99,108	99.00	0.000341	2,929
50.00	0.000014	71,355	99.50	0.000551	1,814
60.00	0.000019	51,904	99.75	0.000889	1,125
70.00	0.000027	36,801	99.90	0.001661	602
80.00	0.000040	24,731			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	574,682	90.00	0.000072	13,862
20.00	0.000004	264,796	95.00	0.000114	8,802
30.00	0.000007	153,222	97.50	0.000179	5,596
40.00	0.000010	100,303	99.00	0.000340	2,940
50.00	0.000014	71,959	99.50	0.000549	1,821
60.00	0.000019	52,300	99.75	0.000886	1,129
70.00	0.000027	36,986	99.90	0.001655	604
80.00	0.000040	24,858			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Non-hispanic whites

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000031	0.000031
Standard Deviation	0.000188	0.000188
Margin of Exposure	32,538	32,438

Percent of Person-Days that are User-Days = 99.69%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	465,605	90.00	0.000056	17,861
20.00	0.000004	249,122	95.00	0.000091	11,022
30.00	0.000006	158,465	97.50	0.000147	6,794
40.00	0.000009	110,772	99.00	0.000288	3,472
50.00	0.000012	82,304	99.50	0.000457	2,186
60.00	0.000016	62,179	99.75	0.000728	1,374
70.00	0.000022	46,340	99.90	0.001366	732
80.00	0.000032	31,607			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	476,233	90.00	0.000056	17,906
20.00	0.000004	252,204	95.00	0.000091	11,047
30.00	0.000006	159,787	97.50	0.000147	6,808
40.00	0.000009	111,435	99.00	0.000287	3,480
50.00	0.000012	82,659	99.50	0.000456	2,191
60.00	0.000016	62,429	99.75	0.000726	1,376
70.00	0.000022	46,465	99.90	0.001363	733
80.00	0.000032	31,681			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Non-hispanic blacks

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000025	0.000025
Standard Deviation	0.000150	0.000150
Margin of Exposure	39,545	39,259

Percent of Person-Days that are User-Days = 99.28%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	>1,000,000	90.00	0.000049	20,396
20.00	0.000002	511,102	95.00	0.000079	12,709
30.00	0.000003	288,588	97.50	0.000131	7,638
40.00	0.000006	180,736	99.00	0.000249	4,009
50.00	0.000008	123,131	99.50	0.000417	2,398
60.00	0.000012	84,901	99.75	0.000694	1,440
70.00	0.000018	56,855	99.90	0.001257	795
80.00	0.000027	37,006			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	>1,000,000	90.00	0.000049	20,515
20.00	0.000002	528,162	95.00	0.000078	12,789
30.00	0.000003	297,510	97.50	0.000130	7,680
40.00	0.000005	184,302	99.00	0.000248	4,037
50.00	0.000008	124,849	99.50	0.000415	2,409
60.00	0.000012	85,815	99.75	0.000691	1,447
70.00	0.000017	57,530	99.90	0.001250	799
80.00	0.000027	37,282			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Non-hisp/non-white/non-black

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000036	0.000036
Standard Deviation	0.000220	0.000221
Margin of Exposure	28,012	27,819

Percent of Person-Days that are User-Days = 99.31%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	936,202	90.00	0.000067	14,827
20.00	0.000003	309,718	95.00	0.000109	9,167
30.00	0.000006	166,324	97.50	0.000173	5,784
40.00	0.000010	101,563	99.00	0.000328	3,053
50.00	0.000014	73,221	99.50	0.000552	1,810
60.00	0.000019	53,164	99.75	0.000882	1,134
70.00	0.000026	38,624	99.90	0.001674	597
80.00	0.000038	26,237			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	>1,000,000	90.00	0.000067	14,914
20.00	0.000003	319,979	95.00	0.000108	9,221
30.00	0.000006	170,552	97.50	0.000172	5,828
40.00	0.000010	102,900	99.00	0.000326	3,071
50.00	0.000013	74,184	99.50	0.000549	1,820
60.00	0.000019	53,721	99.75	0.000878	1,138
70.00	0.000026	38,860	99.90	0.001667	600
80.00	0.000038	26,401			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

All infants

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000041	0.000046
Standard Deviation	0.000135	0.000143
Margin of Exposure	24,631	21,691

Percent of Person-Days that are User-Days = 88.07%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000007	139,507	90.00	0.000073	13,661
20.00	0.000014	69,890	95.00	0.000145	6,883
30.00	0.000018	54,494	97.50	0.000239	4,185
40.00	0.000022	44,812	99.00	0.000345	2,897
50.00	0.000026	38,331	99.50	0.000468	2,136
60.00	0.000030	33,016	99.75	0.001091	916
70.00	0.000036	27,742	99.90	0.002099	476
80.00	0.000045	22,048			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000065	15,349
20.00	0.000006	170,364	95.00	0.000124	8,089
30.00	0.000015	68,679	97.50	0.000211	4,743
40.00	0.000019	52,650	99.00	0.000322	3,106
50.00	0.000023	42,707	99.50	0.000405	2,468
60.00	0.000028	35,621	99.75	0.000940	1,063
70.00	0.000033	29,967	99.90	0.001927	518
80.00	0.000042	23,774			

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DEEM ACUTE ANALYSIS FOR ACEPHATE   Section 3 Registration
Residue file name: Acephate acute3         Analysis date: 08-26-2002
DPR NOEL (Acute) =   1.0 mg/kg body-wt/day
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Nursing infants (<1 yr old)        Daily Exposure Analysis
---------------------------        (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000016     0.000027
            Standard Deviation        0.000120     0.000155
            Margin of Exposure          61,899       36,378

       Percent of Person-Days that are User-Days = 58.77%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile Exposure    MOE             Percentile   Exposure   MOE
-----------------------------------------------------------------------
10.00   0.000000 >1,000,000             90.00      0.000038 26,422
20.00   0.000001 >1,000,000             95.00      0.000064 15,506
30.00   0.000004    274,459             97.50      0.000126  7,911
40.00   0.000007    143,183             99.00      0.000271  3,687
50.00   0.000010     98,994             99.50      0.000520  1,924
60.00   0.000016     63,962             99.75      0.001182    845
70.00   0.000020     49,069             99.90      0.002427    411
80.00   0.000026     37,882

  Estimated percentile of per-capita days falling below calculated
exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile Exposure    MOE           Percentile   Exposure    MOE
-----------------------------------------------------------------------
10.00   0.000000 >1,000,000             90.00      0.000030 33,473
20.00   0.000000 >1,000,000             95.00      0.000040 24,848
30.00   0.000000 >1,000,000             97.50      0.000074 13,523
40.00   0.000000 >1,000,000             99.00      0.000179  5,581
50.00   0.000000 >1,000,000             99.50      0.000277  3,616
60.00   0.000004    236,723             99.75      0.000647  1,545
70.00   0.000009    105,993             99.90      0.001704    586
80.00   0.000018     56,795
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DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Non-nursing infants (<1 yr old)

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000050	0.000050
Standard Deviation	0.000140	0.000140
Margin of Exposure	20,048	19,886

Percent of Person-Days that are User-Days = 99.19%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000014	73,957	90.00	0.000083	12,076
20.00	0.000018	56,081	95.00	0.000158	6,327
30.00	0.000022	46,325	97.50	0.000252	3,966
40.00	0.000025	40,405	99.00	0.000347	2,878
50.00	0.000029	34,934	99.50	0.000451	2,215
60.00	0.000033	30,444	99.75	0.001048	953
70.00	0.000039	25,894	99.90	0.002038	490
80.00	0.000049	20,465			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000013	76,270	90.00	0.000081	12,355
20.00	0.000018	56,883	95.00	0.000157	6,350
30.00	0.000021	46,761	97.50	0.000250	3,995
40.00	0.000025	40,673	99.00	0.000347	2,880
50.00	0.000028	35,114	99.50	0.000447	2,237
60.00	0.000033	30,577	99.75	0.001040	961
70.00	0.000038	26,011	99.90	0.002021	494
80.00	0.000049	20,526			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Children 1-6 yrs

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000077	0.000077
Standard Deviation	0.000215	0.000216
Margin of Exposure	13,056	13,043

Percent of Person-Days that are User-Days = 99.90%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000014	69,171	90.00	0.000134	7,446
20.00	0.000026	39,072	95.00	0.000181	5,526
30.00	0.000035	28,973	97.50	0.000248	4,025
40.00	0.000044	22,978	99.00	0.000439	2,276
50.00	0.000053	18,852	99.50	0.000723	1,383
60.00	0.000064	15,617	99.75	0.001143	874
70.00	0.000078	12,885	99.90	0.002034	491
80.00	0.000096	10,396			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000014	69,776	90.00	0.000134	7,449
20.00	0.000026	39,181	95.00	0.000181	5,530
30.00	0.000034	29,025	97.50	0.000248	4,027
40.00	0.000043	23,004	99.00	0.000439	2,278
50.00	0.000053	18,871	99.50	0.000723	1,384
60.00	0.000064	15,629	99.75	0.001142	875
70.00	0.000078	12,893	99.90	0.002033	491
80.00	0.000096	10,401			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Children 7-12 yrs

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000042	0.000042
Standard Deviation	0.000181	0.000181
Margin of Exposure	23,937	23,933

Percent of Person-Days that are User-Days = 99.98%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000006	154,334	90.00	0.000068	14,612
20.00	0.000013	78,287	95.00	0.000089	11,174
30.00	0.000017	57,615	97.50	0.000130	7,705
40.00	0.000022	45,194	99.00	0.000272	3,681
50.00	0.000028	35,967	99.50	0.000460	2,174
60.00	0.000034	29,616	99.75	0.000743	1,346
70.00	0.000040	25,049	99.90	0.001346	742
80.00	0.000050	20,117			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000006	154,552	90.00	0.000068	14,614
20.00	0.000013	78,320	95.00	0.000089	11,175
30.00	0.000017	57,633	97.50	0.000130	7,706
40.00	0.000022	45,202	99.00	0.000272	3,681
50.00	0.000028	35,972	99.50	0.000460	2,174
60.00	0.000034	29,620	99.75	0.000743	1,346
70.00	0.000040	25,051	99.90	0.001346	742
80.00	0.000050	20,119			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Females 13+ (preg/not nursing)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000029	0.000030
Standard Deviation	0.000172	0.000174
Margin of Exposure	34,649	33,771

Percent of Person-Days that are User-Days = 97.47%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	516,754	90.00	0.000051	19,562
20.00	0.000005	199,213	95.00	0.000061	16,387
30.00	0.000009	112,315	97.50	0.000104	9,590
40.00	0.000011	87,091	99.00	0.000247	4,043
50.00	0.000016	64,342	99.50	0.000432	2,312
60.00	0.000019	52,828	99.75	0.000872	1,147
70.00	0.000023	42,607	99.90	0.001659	602
80.00	0.000031	32,786			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	682,144	90.00	0.000050	19,915
20.00	0.000004	240,749	95.00	0.000060	16,712
30.00	0.000009	117,485	97.50	0.000104	9,639
40.00	0.000011	91,707	99.00	0.000243	4,120
50.00	0.000015	66,005	99.50	0.000425	2,353
60.00	0.000019	53,452	99.75	0.000866	1,155
70.00	0.000023	42,916	99.90	0.001621	617
80.00	0.000030	33,182			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Females 13+ (nursing)

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000029	0.000029
Standard Deviation	0.000164	0.000164
Margin of Exposure	33,951	33,951

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000004	269,349	90.00	0.000039	25,969
20.00	0.000007	141,968	95.00	0.000060	16,797
30.00	0.000011	89,625	97.50	0.000125	7,986
40.00	0.000014	71,345	99.00	0.000308	3,244
50.00	0.000017	59,495	99.50	0.000514	1,945
60.00	0.000020	50,814	99.75	0.000691	1,448
70.00	0.000022	44,456	99.90	0.001112	899
80.00	0.000027	37,340			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000004	269,349	90.00	0.000039	25,969
20.00	0.000007	141,968	95.00	0.000060	16,797
30.00	0.000011	89,625	97.50	0.000125	7,986
40.00	0.000014	71,345	99.00	0.000308	3,244
50.00	0.000017	59,495	99.50	0.000514	1,945
60.00	0.000020	50,814	99.75	0.000691	1,448
70.00	0.000022	44,456	99.90	0.001112	899
80.00	0.000027	37,340			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Females 13-19 (not preg or nursing) Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000023	0.000023
Standard Deviation	0.000176	0.000176
Margin of Exposure	43,781	43,643

Percent of Person-Days that are User-Days = 99.69%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	632,879	90.00	0.000037	27,185
20.00	0.000003	341,230	95.00	0.000056	17,977
30.00	0.000005	210,046	97.50	0.000087	11,436
40.00	0.000007	135,486	99.00	0.000217	4,598
50.00	0.000011	94,317	99.50	0.000330	3,028
60.00	0.000014	72,816	99.75	0.000558	1,793
70.00	0.000018	55,742	99.90	0.001063	940
80.00	0.000024	42,529			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	644,824	90.00	0.000037	27,237
20.00	0.000003	345,439	95.00	0.000056	18,008
30.00	0.000005	212,520	97.50	0.000087	11,475
40.00	0.000007	136,380	99.00	0.000217	4,614
50.00	0.000011	94,709	99.50	0.000329	3,035
60.00	0.000014	73,081	99.75	0.000556	1,798
70.00	0.000018	55,854	99.90	0.001062	942
80.00	0.000023	42,577			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Females 20+ (not preg or nursing)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000024	0.000024
Standard Deviation	0.000196	0.000196
Margin of Exposure	41,627	41,520

Percent of Person-Days that are User-Days = 99.74%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	697,263	90.00	0.000033	30,619
20.00	0.000003	352,063	95.00	0.000057	17,522
30.00	0.000004	224,105	97.50	0.000115	8,689
40.00	0.000006	156,353	99.00	0.000283	3,535
50.00	0.000009	114,148	99.50	0.000455	2,199
60.00	0.000011	87,230	99.75	0.000703	1,422
70.00	0.000015	66,708	99.90	0.001320	757
80.00	0.000021	48,690			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	712,197	90.00	0.000033	30,674
20.00	0.000003	355,932	95.00	0.000057	17,565
30.00	0.000004	225,785	97.50	0.000115	8,714
40.00	0.000006	157,300	99.00	0.000282	3,544
50.00	0.000009	114,555	99.50	0.000454	2,204
60.00	0.000011	87,471	99.75	0.000702	1,424
70.00	0.000015	66,849	99.90	0.001316	759
80.00	0.000021	48,757			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Females 13-50 yrs

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000024	0.000024
Standard Deviation	0.000205	0.000206
Margin of Exposure	41,249	41,086

Percent of Person-Days that are User-Days = 99.60%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	700,046	90.00	0.000035	28,874
20.00	0.000003	356,783	95.00	0.000058	17,352
30.00	0.000004	224,540	97.50	0.000110	9,050
40.00	0.000007	152,481	99.00	0.000272	3,673
50.00	0.000009	110,230	99.50	0.000436	2,295
60.00	0.000012	82,893	99.75	0.000683	1,465
70.00	0.000016	62,418	99.90	0.001286	777
80.00	0.000022	46,075			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	721,672	90.00	0.000035	28,963
20.00	0.000003	363,512	95.00	0.000057	17,407
30.00	0.000004	227,322	97.50	0.000110	9,075
40.00	0.000006	154,015	99.00	0.000271	3,689
50.00	0.000009	110,869	99.50	0.000434	2,302
60.00	0.000012	83,286	99.75	0.000681	1,469
70.00	0.000016	62,655	99.90	0.001283	779
80.00	0.000022	46,224			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Males 13-19 yrs

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000027	0.000027
Standard Deviation	0.000158	0.000158
Margin of Exposure	36,971	36,954

Percent of Person-Days that are User-Days = 99.95%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	454,945	90.00	0.000045	22,044
20.00	0.000004	234,344	95.00	0.000065	15,268
30.00	0.000007	135,289	97.50	0.000109	9,183
40.00	0.000011	91,528	99.00	0.000226	4,419
50.00	0.000014	72,064	99.50	0.000412	2,429
60.00	0.000018	56,526	99.75	0.000602	1,659
70.00	0.000022	44,505	99.90	0.001103	906
80.00	0.000030	32,873			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	456,435	90.00	0.000045	22,046
20.00	0.000004	235,132	95.00	0.000065	15,275
30.00	0.000007	135,455	97.50	0.000109	9,185
40.00	0.000011	91,618	99.00	0.000226	4,421
50.00	0.000014	72,120	99.50	0.000411	2,430
60.00	0.000018	56,547	99.75	0.000602	1,660
70.00	0.000022	44,517	99.90	0.001102	907
80.00	0.000030	32,881			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Males 20+ yrs

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000024	0.000024
Standard Deviation	0.000174	0.000174
Margin of Exposure	41,729	41,614

Percent of Person-Days that are User-Days = 99.73%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	614,718	90.00	0.000034	29,497
20.00	0.000003	327,103	95.00	0.000059	16,909
30.00	0.000005	210,864	97.50	0.000122	8,210
40.00	0.000007	147,643	99.00	0.000265	3,774
50.00	0.000009	110,488	99.50	0.00043	2,282
60.00	0.000012	84,364	99.75	0.000708	1,412
70.00	0.000016	64,478	99.90	0.001311	762
80.00	0.000021	47,463			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	629,122	90.00	0.000034	29,570
20.00	0.000003	330,495	95.00	0.000059	16,960
30.00	0.000005	212,716	97.50	0.000121	8,235
40.00	0.000007	148,381	99.00	0.000264	3,781
50.00	0.000009	110,926	99.50	0.000437	2,286
60.00	0.000012	84,626	99.75	0.000706	1,415
70.00	0.000015	64,625	99.90	0.001308	764
80.00	0.000021	47,562			

DEEM ACUTE ANALYSIS FOR ACEPHATE Section 3 Registration
Residue file name: Acephate acute3 Analysis date: 08-26-2002
DPR NOEL (Acute) = 1.0 mg/kg body-wt/day

Seniors 55+

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000023	0.000023
Standard Deviation	0.000158	0.000158
Margin of Exposure	42,820	42,787

Percent of Person-Days that are User-Days = 99.92%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	604,367	90.00	0.000032	31,566
20.00	0.000003	314,644	95.00	0.000056	17,999
30.00	0.000005	200,611	97.50	0.000115	8,706
40.00	0.000007	144,269	99.00	0.000261	3,837
50.00	0.000009	109,615	99.50	0.000436	2,292
60.00	0.000012	84,871	99.75	0.000679	1,473
70.00	0.000015	66,218	99.90	0.001281	780
80.00	0.000020	49,499			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	608,258	90.00	0.000032	31,580
20.00	0.000003	315,689	95.00	0.000056	18,013
30.00	0.000005	201,037	97.50	0.000115	8,713
40.00	0.000007	144,465	99.00	0.000260	3,840
50.00	0.000009	109,724	99.50	0.000436	2,293
60.00	0.000012	84,934	99.75	0.000678	1,473
70.00	0.000015	66,260	99.90	0.001280	781
80.00	0.000020	49,526			

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DEEM ACUTE ANALYSIS FOR ACEPHATE   Section 3 Registration
Residue file name: Acephate acute3         Analysis date: 08-26-2002
DPR NOEL (Acute) =   1.0 mg/kg body-wt/day
=======================================================================

Custom demographics 1: Workers (16+ Years)
All Seasons, All Regions, Sex: M/F-all, All Races
Age-Low: 16 yrs   High: 99 yrs
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	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000024	0.000024
Standard Deviation	0.000184	0.000185
Margin of Exposure	41,677	41,557

Percent of Person-Days that are User-Days = 99.71%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	653,032	90.00	0.000034	29,465
20.00	0.000003	336,119	95.00	0.000058	17,361
30.00	0.000005	214,769	97.50	0.000116	8,620
40.00	0.000007	148,313	99.00	0.000267	3,745
50.00	0.000009	110,034	99.50	0.000440	2,274
60.00	0.000012	83,807	99.75	0.000698	1,433
70.00	0.000016	64,210	99.90	0.001301	768
80.00	0.000021	47,165			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	668,400	90.00	0.000034	29,534
20.00	0.000003	340,117	95.00	0.000057	17,407
30.00	0.000005	216,691	97.50	0.000116	8,648
40.00	0.000007	149,234	99.00	0.000266	3,753
50.00	0.000009	110,450	99.50	0.000439	2,279
60.00	0.000012	84,055	99.75	0.000696	1,436
70.00	0.000016	64,363	99.90	0.001298	770
80.00	0.000021	47,255			

ATTACHMENT B
Chronic Dietary Exposure
All Labeled Commodities

California Department of Pesticide Regulation Ver. 7.76
DEEM Chronic analysis for ACEPHATE 1994-98 data
Residue file: D:\deem\Resi-files\acephate chronic.RS7 Adjust. #2 used
Analysis Date 08-26-2002 Residue file dated: 08-23-2002
Reference dose (RfD) = 0.0012 (NOEL) = 0.09 mg/kg bw/day
Comment:Dietary exposure (180.108), dog NOEL using REG & GOV residue data.

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	Adj.Factors #1	#2
8	O	Cranberries	0.005700	1.00	1.00
		Full comment: %CT, FDA (1997-99): avg residue			
9	O	Cranberries-juice	0.005700	1.10	1.00
		Full comment: %CT, FDA (1997-99): avg residue			
46	14	Macadamia nuts (bush nuts)	0.000100	1.00	1.00
		Full comment: %CT, EPA cited REG Field Trial			
139	8	Paprika	0.043000	1.00	1.00
		Full comment: %CT, DPR (1996-98): avg residue			
155	8	Peppers-sweet(garden)	0.071000	1.00	1.00
		Full comment: %CT, DPR (1996-98): avg residue			
156	8	Peppers-chilli incl jalapeno	0.043000	1.00	1.00
		Full comment: %CT, DPR (1996-98): avg residue			
157	8	Peppers-other	0.043000	1.00	1.00
		Full comment: %CT, DPR (1996-98): avg residue			
158	8	Pimientos	0.043000	1.00	1.00
		Full comment: %CT, DPR (1996-98): avg residue			
166	4B	Celery	0.027000	1.00	1.00
		Full comment: %CT, DPR (1996-98): avg residue			
169	5A	Brussels sprouts	0.005000	1.00	1.00
		Full comment: %CT, DPR (1996-98): avg residue			
171	5A	Cauliflower	0.012000	1.00	1.00
		Full comment: %CT, DPR (1996-98): avg residue			
192	4A	Lettuce-head varieties	0.026000	1.00	1.00
		Full comment: %CT, DPR (1996-98): avg residue			
227	6C	Beans-dry-great northern			
		14-Boiled	0.008600	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		32-Canned: Cooked	0.016300	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
228	6C	Beans-dry-kidney			
		12-Cooked: NFS	0.008600	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		13-Baked	0.008600	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		14-Boiled	0.008600	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		32-Canned: Cooked	0.016300	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		34-Canned: Boiled	0.016300	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			

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            42-Frozen: Cooked              0.016300    1.00 1.00
  Full comment: %CT, PDP CA greenbean as surrogate
229 6C   Beans-dry-lima
            14-Boiled                      0.008600    1.00 1.00
  Full comment: %CT, PDP CA greenbean as surrogate
            32-Canned: Cooked              0.016300    1.00 1.00
  Full comment: %CT, PDP CA greenbean as surrogate
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Food Code	Crop Grp	Food Name	RESIDUE (ppm)	Adj.Factors #1	#2
230	6C	Beans-dry-navy (pea)			
		14-Boiled	0.008600	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		32-Canned: Cooked	0.016300	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		34-Canned: Boiled	0.016300	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
231	6C	Beans-dry-other			
		12-Cooked: NFS	0.008600	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		13-Baked	0.008600	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		14-Boiled	0.008600	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		15-Fried	0.008600	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		34-Canned: Boiled	0.016300	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
232	6C	Beans-dry-pinto			
		12-Cooked: NFS	0.008600	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		13-Baked	0.008600	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		14-Boiled	0.008600	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		15-Fried	0.008600	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		32-Canned: Cooked	0.016300	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
		42-Frozen: Cooked	0.016300	1.00	1.00
		Full comment: %CT, PDP CA greenbean as surrogate			
233	6B	Beans-succulent-lima			
		11-Uncooked	0.009000	1.00	1.00
		Full comment: %CT, PDP (1996-98 CA) avg residue			
		12-Cooked: NFS	0.009000	1.00	1.00
		Full comment: %CT, PDP (1996-98 CA) avg residue			
		14-Boiled	0.009000	1.00	1.00

```
  Full comment: %CT, PDP (1996-98 CA) avg residue
             32-Canned: Cooked                0.016600  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
             42-Frozen: Cooked                0.016600  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
             44-Frozen: Boiled                0.016600  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
234 6A   Beans-succulent-green
             11-Uncooked                      0.009000  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
             12-Cooked: NFS                   0.009000  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
             14-Boiled                        0.009000  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
             31-Canned: NFS                   0.016600  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
             32-Canned: Cooked                0.016600  1.00  1.00




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Food Crop                                      RESIDUE      Adj.Factors
Code  Grp  Food Name                            (ppm)       #1   #2
---- ---- --------------------------------     ------ ------ --------
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  Full comment: %CT, PDP (1996-98 CA) avg residue
             34-Canned: Boiled                0.016600  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
             42-Frozen: Cooked                0.016600  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
             44-Frozen: Boiled                0.016600  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
             51-Cured: NFS (smoked/pickled/saltd)
                                              0.016600  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
235 6A   Beans-succulent-other
             34-Canned: Boiled                0.016600  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
236 6A   Beans-succulent-yellow/wax
             14-Boiled                        0.009000  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
             32-Canned: Cooked                0.016600  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
             42-Frozen: Cooked                0.016600  1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
249 6C   Beans-dry-broadbeans
             14-Boiled                        0.008600  1.00  1.00
  Full comment: %CT, PDP CA greenbean as surrogate
250 6B   Beans-succulent-broadbeans          0.009000   1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
251 6C   Beans-dry-pigeon beans              0.008600   1.00  1.00
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  Full comment: %CT, PDP CA greenbean as surrogate
253 6    Beans-unspecified                  0.009000   1.00  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
255 6A   Soybeans-sprouted seeds            0.000300  0.330  1.00
  Full comment: %CT, DPR - REG Field Trial
256      Beans-dry-hyacinth                 0.008600  1.000  1.00
  Full comment: PDP CA only greenbean as surrogate
257      Beans-succulent-hyacinth           0.050000  1.000  1.00
  Full comment: EPA cited REG FT/Grn bean processing
258 6C   Beans-dry-blackeye peas/cowpea
             14-Boiled                      0.008600  1.000  1.00
  Full comment: %CT, PDP CA greenbean as surrogate
259 6C   Beans-dry-garbanzo/chick pea
             12-Cooked: NFS                 0.008600  1.000  1.00
  Full comment: %CT, PDP CA greenbean as surrogate
             14-Boiled                      0.008600  1.000  1.00
  Full comment: %CT, PDP CA greenbean as surrogate
             15-Fried                       0.008600  1.000  1.00
  Full comment: %CT, PDP CA greenbean as surrogate
             32-Canned: Cooked              0.016300  1.000  1.00
  Full comment: %CT, PDP CA greenbean as surrogate
287 6C   Guar beans
             13-Baked                       0.008600  1.000  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
             34-Canned: Boiled              0.016300  1.000  1.00
  Full comment: %CT, PDP (1996-98 CA) avg residue
290 O    Cottonseed-oil                     0.013000  1.000 0.200
  Full comment: %CT/proc, REG field trial - avg residue
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Food Code	Crop Grp	Food Name	RESIDUE (ppm)	Adj. Factors #1	#2
291	O	Cottonseed-meal	0.013000	1.00	1.00
	Full comment: %CT, REG field trial - avg residue				
293	O	Peanuts-oil	0.000500	1.00	0.13
	Full comment: %CT/proc, EPA cited REG Field Trial				
297	6A	Soybeans-oil	0.000100	1.0	0.007
	Full comment: %CT/proc, DPR - REG Field Trial				
303	6A	Soybean-other	0.000300	1.00	0.54
	Full comment: %CT/proc, DPR - REG Field Trial				
304	6A	Soybeans-mature seeds dry	0.000300	1.00	0.54
	Full comment: %CT/proc, DPR - REG Field Trial				
305	6A	Soybeans-flour (full fat)	0.000200	1.00	0.38
	Full comment: %CT/proc, DPR - REG Field Trial				
306	6A	Soybeans-flour (low fat)	0.000100	1.00	0.38
	Full comment: %CT/proc, DPR - REG Field Trial				
307	6A	Soybeans-flour (defatted)	0.000100	1.00	0.38
	Full comment: %CT/proc, DPR - REG Field Trial				
318	D	Milk-nonfat solids	0.001000	1.00	1.00
	Full comment: USDA PDP 1/2 LOD (1997, 98)				
319	D	Milk-fat solids	0.001000	1.00	1.00
	Full comment: USDA PDP 1/2 LOD (1997, 98)				
320	D	Milk sugar (lactose)	0.001000	1.00	1.00
	Full comment: USDA PDP 1/2 LOD (1997, 98)				
321	M	Beef-meat byproducts	0.000033	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
322	M	Beef-other organ meats	0.000033	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
323	M	Beef-dried	0.000015	1.92	1.00
	Full comment: REG derived anticipted chronic residues				
324	M	Beef-fat w/o bones	0.000009	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
325	M	Beef-kidney	0.000033	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
326	M	Beef-liver	0.000004	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
327	M	Beef-lean (fat/free) w/o bones	0.000015	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
328	M	Goat-meat byproducts	0.000033	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
329	M	Goat-other organ meats	0.000033	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
330	M	Goat-fat w/o bone	0.000009	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
331	M	Goat-kidney	0.000033	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
332	M	Goat-liver	0.000004	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
333	M	Goat-lean (fat/free) w/o bone	0.000015	1.00	1.00
	Full comment: REG derived anticipted chronic residues				

334	M	Horsemeat	0.000015	1.00	1.00
Full comment: EPA ruminant AR as surrogate					
336	M	Sheep-meat byproducts	0.000033	1.00	1.00
Full comment: REG derived anticipted chronic residues					
337	M	Sheep-other organ meats	0.000033	1.00	1.00
Full comment: REG derived anticipted chronic residues					

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	Adj.Factors #1	#2
338	M	Sheep-fat w/o bone	0.000009	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
339	M	Sheep-kidney	0.000033	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
340	M	Sheep-liver	0.000004	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
341	M	Sheep-lean (fat free) w/o bone	0.000015	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
342	M	Pork-meat byproducts	0.000033	1.00	1.00
	Full comment: EPA ruminant AR as surrogate				
343	M	Pork-other organ meats	0.000033	1.00	1.00
	Full comment: EPA ruminant AR as surrogate				
344	M	Pork-fat w/o bone	0.000009	1.00	1.00
	Full comment: EPA ruminant AR as surrogate				
345	M	Pork-kidney	0.000033	1.00	1.00
	Full comment: EPA ruminant AR as surrogate				
346	M	Pork-liver	0.000004	1.00	1.00
	Full comment: EPA ruminant AR as surrogate				
347	M	Pork-lean (fat free) w/o bone	0.000015	1.00	1.00
	Full comment: EPA ruminant AR as surrogate				
355	P	Turkey-byproducts	0.000007	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
356	P	Turkey-giblets (liver)	0.000001	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
357	P	Turkey--fat w/o bones	0.000001	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
358	P	Turkey- lean/fat free w/o bones	0.000007	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
360	P	Poultry-other-lean (fat free) w/	0.000007	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
361	P	Poultry-other-giblets(liver)	0.000001	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
362	P	Poultry-other-fat w/o bones	0.000001	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
363	P	Eggs-whole	0.000022	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
364	P	Eggs-white only	0.000022	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
365	P	Eggs-yolk only	0.000022	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
366	P	Chicken-byproducts	0.000007	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
367	P	Chicken-giblets(liver)	0.000001	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
368	P	Chicken-fat w/o bones	0.000001	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
369	P	Chicken-lean/fat free w/o bones	0.000007	1.00	1.00
	Full comment: REG derived anticipted chronic residues				

384	4B	Celery juice	0.027000	1.00	1.00
	Full comment: %CT, DPR (1996-98): avg residue				
385	P	Chicken-giblets (excl. liver)	0.000001	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
389	O	Cranberries-juice-concentrate	0.005700	3.30	1.00
	Full comment: %CT, FDA (1997-99): avg residue				

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	Adj. Factors #1	#2
398	D	Milk-based water	0.001000	1.00	1.00
	Full comment: USDA PDP 1/2 LOD (1997, 98)				
403	O	Peanuts-butter	0.000500	1.00	0.13
	Full comment: %CT/proc, EPA cited REG Field Trial				
424	M	Veal-fat w/o bones	0.000009	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
425	M	Veal-lean (fat free) w/o bones	0.000015	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
426	M	Veal-kidney	0.000033	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
427	M	Veal-liver	0.000004	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
428	M	Veal-other organ meats	0.000033	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
429	M	Veal-dried	0.000015	1.92	1.00
	Full comment: REG derived anticipted chronic residues				
430	M	Veal-meat byproducts	0.000033	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
449	P	Turkey-other organ meats	0.000001	1.00	1.00
	Full comment: REG derived anticipted chronic residues				
467	19B	Celery seed	0.027000	1.00	1.00
	Full comment: %CT, DPR (1996-98): avg residue				
482	O	Soybeans-protein isolate	0.000100	1.00	0.54
	Full comment: %CT/proc, DPR - REG Field Trial				
940	O	Peanuts-hulled	0.000500	1.00	1.00
	Full comment: %CT, EPA cited REG Field Trial				

California Department of Pesticide Regulation Ver. 7.76 (1994-98 data)
DEEM **Chronic** analysis for ACEPHATE (**Adjustment factor #2 USED**)
Analysis Date 08-26-2002. Residue file dated: 08-23-2002 File Name: acephate chronic.RS7
Chronic RfD (U.S. EPA) = .0012 mg/kg bw/day. DPR NOEL (Chronic) = .09 mg/kg bw/day
COMMENT 1: Dietary exposure analysis for 180.108 using REG & monitoring residue data.

Total exposure by population subgroup

Population Subgroup	mg/kg body wt/day	Margin of Exposure 1/	Percent of RfD
U.S. Population (total)	0.000022	4,167	1.8%
U.S. Population (spring season)	0.000022	4,141	1.8%
U.S. Population (summer season)	0.000021	4,378	1.7%
U.S. Population (autumn season)	0.000023	3,997	1.9%
U.S. Population (winter season)	0.000022	4,177	1.8%
Northeast region	0.000021	4,203	1.8%
Midwest region	0.000022	4,022	1.9%
Southern region	0.000019	4,623	1.6%
Western region	0.000024	3,702	2.0%
Hispanics	0.000026	3,421	2.2%
Non-hispanic whites	0.000021	4,197	1.8%
Non-hispanic blacks	0.000017	5,181	1.4%
Non-hisp/non-white/non-black	0.000025	3,615	2.1%
All infants (< 1 year)	0.000021	4,387	1.7%
Nursing infants	0.000010	9,090	0.8%
Non-nursing infants	0.000025	3,667	2.0%
Children 1-6 yrs	0.000045	1,982	3.8%
Children 7-12 yrs	0.000027	3,374	2.2%
Females 13-19 (not preg or nursing)	0.000016	5,668	1.3%
Females 20+ (not preg or nursing)	0.000018	4,876	1.5%
Females 13-50 yrs	0.000018	4,914	1.5%
Females 13+ (preg/not nursing)	0.000021	4,291	1.7%
Females 13+ (nursing)	0.000023	3,860	1.9%
Males 13-19 yrs	0.000018	4,916	1.5%
Males 20+ yrs	0.000018	4,919	1.5%
Seniors 55+	0.000018	5,072	1.5%

1. MOE = NOEL ÷ Exposure

DRAFT - 09-16-2003

APPENDIX C

OEHHA REVIEW OF DRAFT FINAL RCD

Office of Environmental Health Hazard Assessment's Comments on the Draft Risk Characterization Document (RCD) for Acephate

The Office of Environmental Health Hazard Assessment (OEHHA) reviews risk assessments prepared by the Department of Pesticide Regulation (DPR) under the general authority of the Health and Safety Code, Section 59004, and also under the Food and Agricultural code, Section 13129, in which OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticide active ingredients.

Acephate is an organophosphate insecticide used for the control of a broad spectrum of pests on lettuce, cotton, celery, and beans. DPR initiated this risk assessment because of the need to assess health risks associated with exposure to acephate. This draft risk characterization document (RCD) evaluates occupational, dietary, and combined occupational and dietary exposure for acute, subchronic, and chronic durations. Acephate is not heavily used in California, and its use is declining. A leading factor in the decreased use, which is an important consideration for the general population exposure, is the suspension of home and garden uses. DPR previously prepared a RCD on methamidophos, a principal degradate of acephate, which OEHHA also reviewed.

General comments on the draft RCD:

1) OEHHA agrees with DPR's choices of critical studies and toxicological endpoints for determining the critical no-observed-effect levels (NOELs). DPR's determination of the critical values for acute and chronic worker and dietary exposure differs from those of the U.S. Environmental Protection Agency (U.S. EPA) by a small margin (except for acute worker and seasonal worker scenarios). For chronic worker and dietary exposures, DPR uses depression of dog brain cholinesterase with the use of an uncertainty factor of three to derive a NOEL from the Lowest Observed Effect Level (LOEL). DPR ordinarily would use a factor of (up to) ten to estimate a NOEL from the effect of depression of brain cholinesterase. They used a factor of three in this case because the benchmark dose modeling result indicates that the 95% lower confidence limit on the 10% response level ($BMDL_{10}$) (point of departure) is only about 3-fold lower than the LOEL. We support this dose estimation.

2) We also support the use of depression of cholinesterase in the acute human dosing study as the basis for deriving a NOEL for acute worker and acute dietary exposure. Although there are many studies showing depression of all types of cholinesterases with acephate in experimental animals, DPR chose to go with an experimental human study in which groups of ten individuals were dosed at 0.35, 0.7, 1, or 1.25 mg/kg/day. Significant inhibition of red blood cell (RBC) cholinesterase was only observed at 1.25 mg/kg/day, but not lower. The use of the NOEL of 1 mg/kg-day based upon the human data reduces the uncertainty of extrapolating from animal effects to human.

3) OEHHA is not fully supportive of DPR's approach on the carcinogenicity assessment. We have not evaluated the carcinogenicity of acephate for any OEHHA program, so we have no formal position on the carcinogenicity of acephate at this time. However, the U.S. EPA positions on these issues in the available documents can be compared with those of DPR. We have reviewed U.S. EPA's discussion on the carcinogenicity of acephate in IRIS (U.S. EPA, 1993), the Federal Register (1996), and an undated U.S. EPA review (1982?), and made the following observations:

The U.S. EPA concluded from the female mouse study that the increase in liver tumors at the highest dose is treatment related, and considered the study to be suggestive of possible carcinogenicity (U.S. EPA, 1993). It is noteworthy that liver tumors found in 12/15 of the high-dose females were hepatocellular carcinomas, and no treatment-related effects on clinical toxicity or survival were observed. The U.S. EPA (1993) computed a cancer potency factor based on the liver tumor incidence data from this study. However, DPR does not consider these tumors to be treatment related. They concluded that the high dose was excessive based on reduced body weight and observations of liver toxicity consisting of increases in hyperplastic nodules, hypertrophy, intracellular inclusion bodies, mononuclear cell foci, and karyomegaly in both males and females.

OEHHA questions DPR's conclusion that the maximum tolerated dose (MTD) may have been exceeded in the high-dose groups, thus rendering the statistically significant increase in liver tumors observed in the female mice of limited relevance for risk assessment purposes. First, liver toxicity, as indicated by the non-neoplastic liver changes

(i.e., increases in hyperplastic nodules, hypertrophy, intracellular inclusion bodies, mononuclear cell foci, and karyomegaly), was observed in both males and females. DPR suggests that these changes resulted in the liver tumors in the high-dose females, yet there appears to be no satisfactory mechanism to explain the absence of liver tumors in the high-dose males. Second, while the decrease in body weight of mice in the high-dose group is significant, 29 percent in females and 24 percent in males, it is unclear why the decrease in body weight would only cause liver tumors in females, but not in the males. Third, one can argue that the depression in body weight, at least in part, could be attributed to a decrease in food consumption (22 percent in females and 18 percent in males) in the high-dose groups. This makes the decrease in body weight less useful as an indicator of toxicity than when a decrease in body weight is observed together with a normal or higher rate of food consumption.

The basis for DPR's conclusion that the MTD may have been exceeded is not consistent with U.S. EPA guidance (U.S. EPA, 2005). The U.S. EPA Guidelines for Carcinogenic Risk Assessment state that an "adequate high dose would generally be one that produces some toxic effects without unduly affecting mortality from effects other than cancer or producing significant adverse effects on the nutrition and health of the test animals." The guidelines further state that the high dose would generally be considered inadequate if neither toxicity nor change in weight gain is observed" (U.S. EPA, 2005). Thus, decreased weight gain is one indicator of adequate dosing. U.S. EPA Guidelines state that significantly increased mortality (from effects other than cancer) is usually an indication that an adequate high dose has been exceeded (U.S. EPA, 2005), but this is not the case in this mouse study as there are no clinical signs of toxicity or lethality at the high dose. U.S. EPA Guidelines also state that a significant reduction in body weight gain (e.g. greater than 10%) *may* also be associated with an excessive high dose (U.S. EPA, 2005). But, clearly, decreased body weight is not by itself an indication of an excessive high dose (U. S. EPA, 2005). As noted before in the U.S. EPA (1993) review of this study, they were very concerned that there were no other substantial signs of toxicity, apart from body weight loss, whereupon to dismiss this study's results as indicative of possible carcinogenicity.

DPR dismisses the significant increase in adrenal tumors in male rats as indicative of carcinogenicity based on the lack of a dose-response relationship and the likelihood that the MTD was exceeded. OEHHA agrees that there is no apparent dose-response. The authors of the study attributed the statistically higher incidence of adrenal tumors in the males to the unusually low incidence of adrenal tumors in the controls. DPR states that this explanation is debatable since some of the provided historical control data showed lower tumor levels than those reported in this study.

In reviewing the tumor data of the male rats, U.S. EPA (1993) found the incidence of pheochromocytomas (medullary adrenal tumors) in [all dosed groups] was within the range of historical incidences and other published results for that rat strain. Due to the high variability of pheochromocytomas in rats, U.S. EPA has been reluctant to use them as an endpoint for carcinogenicity assessment. Also, U.S. EPA noted that there was no increase in malignancy in the lesions or decrease in the latency period in the treated males. After obtaining an independent review of the slides, U.S. EPA concluded that the increase in adrenal tumors was not treatment-related.

OEHHA questions DPR on its determination concerning the significance of the exceedance of the MTD and the increased adrenal tumor in male rats. A significant decrease in body weight (18 percent) with an increase in food consumption can be used as an indication of toxicity in the high-dosed males. However, there were only transient decreases in body weight and food consumption in the mid-dose males and their tumor rates were about the same as that of the high-dose males. DPR needs to strengthen its argument to defend this point.

U.S. EPA has updated some of its conclusions on these two cancer studies, prepared in support of the Interim Reregistration Eligibility Document (U.S. EPA, 2006a) and the Organophosphate Pesticides Cumulative Risk Assessment (2006b). We have recently obtained the additional documentation from U.S. EPA in the form of a DVD of the docket for many old pesticide risk assessments. We have delivered a copy to DPR (to the library) for your reference. The DVD provides the acephate human risk assessment (U.S. EPA, 1999), which explains that although U.S. EPA still considers acephate a Group C carcinogen, it no longer recommends using the slope factor from the mouse study in risk assessment as stated in the IRIS (U.S. EPA, 1993).

In summary, OEHHA does not agree that the liver tumors observed in female mice can be dismissed, based entirely on MTD considerations. The increased incidence of malignant and benign liver tumors observed in the high-dose female mice suggests possible carcinogenicity of acephate. The rat adrenal tumors should also be

reevaluated in light of the work already conducted by the U.S. EPA. Hence, we encourage DPR to obtain and review the U.S. EPA work in this area and reevaluate and/or provide additional support for its determination of carcinogenicity on acephate.

DPR response: pages 2 (Summary), 20 (Toxicology Profile) and 74 (Risk Appraisal) have been modified, as follows to address the issue of oncogenicity:

Page 2

In chronic toxicity studies conducted according to FIFRA guidelines, oncogenicity was assessed in the rat and mouse. In the former a significant increase in adrenal medullary adenomas/ carcinomas (combined) was observed at the top two dose levels (50 and 700 ppm) in males but not females. The vast majority were adenomas *i.e.* benign; there was no treatment-related increase in carcinoma incidence. It is possible that the MTD was exceeded at the HDT for male though not for female rats because the body weight was reduced by 18% ($p<0.01$) and 0.7% (n.s.) for males and females, respectively, compared with controls. In the mouse, females but not males at the HDT had a significantly increased incidence of hepatocellular carcinomas, without a significant effect on survival. There was evidence of toxicity to the liver in both sexes. In particular, there was a significant elevation of hyperplastic nodules in females ($p<0.001$), but not in males, at the HDT of 1000 ppm. It is possible that tumors in both species were secondary to excessive toxicity, based on body weight deficits, compared with controls, at the HDT of 18% (male rat) and 29% (female mouse), both $p<0.01$.

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Because of the appearance of these tumors late in life, it is considered appropriate to exclude rats sacrificed at earlier time intervals from consideration. The study authors considered the medullary tumors not to be compound-related but rather, to be the result of low control incidence. The authors quoted other rat chronic studies conducted at Biodynamics over the same period, which showed adrenal medullary tumors of 0.9%, 2.6%, 6.0%, 7.1% and 15.0%. These compared with 2/75 or 2.7% (for males) in the study described above.[1]/ The study authors also quote literature reports on the "spontaneous" incidence of male rat adrenal medullary tumors: 1.1%, 2.0%, 5.8%, 11.6%, 15.6% and 20.3% (Chen, 1980); 1.7% and 5.0% (Mackenzie *et al.*, 1973) and 5.9% (Cohen *et al.*, 1978). Taken together, nine batches of control rats had a higher incidence of these tumors and five had a lower incidence than the concurrent controls in the Biodynamics, 1981 study. It is therefore difficult to agree with the authors' theory about low control incidence. It is, however, possible that the MTD was exceeded for males (mean body weight was reduced by 18%, $p<0.01$, at 700 ppm, at 22 months), though not for females (mean body weight was reduced by 0.7%, N.S., at 700 ppm, at 22 months). Because the tumors were benign, did not show a clear monotonic increase with dose and because they may have been secondary to general toxicity, rather than have been a result of genotoxicity, they were not subjected to a quantitative assessment.

Page 74

In the evaluation of chronic toxicity, the most sensitive endpoint in the rat and dog was the inhibition of brain AChE. A statistically significant level of inhibition (17%) was recorded at the LDT of 10 ppm in the diet (0.27 mg/kg/d) in the male, but not the female, dog. Therefore, an estimated NOEL (from the dog study), equivalent to 0.09 mg/kg/d was calculated, by dividing the LOEL by a default UF of 3. This estimated NOEL was used for chronic risk characterization. The use of a default factor of 3 in estimating a NOEL from a LOEL is supported by BMD calculations. Chronic feeding studies also resulted in an increased incidence of adenomas in the adrenal medulla in male rats and in hepatocellular carcinomas in female mice. Because these tumors were gender-specific, were benign in the case of adrenal tumors, were associated

with liver toxicity in the mouse which appeared to be more severe in the case of the female and could have been secondary to overall systemic toxicity at doses >MTD, they were not subjected to quantitative risk assessment. However, because acephate was (weakly) genotoxic in some assays, it is possible that the tumors arose through such a mechanism. Nontheless, neither tumor type was considered by USEPA in the acephate RED (USEPA, 2001a) or in the Organophosphate Cumulative Risk Assessment (USEPA, 2006), thus supporting a non-genotoxic mechanism.

4) In OEHHA's review of the draft methamidophos RCD (DPR, 2003), we noted that the document did not include exposure to methamidophos residues as a result of acephate applications (methamidophos is a major degradate of acephate). At that time, OEHHA noted that U.S. EPA's risk assessment for methamidophos (U.S. EPA, 2000) evaluated dietary exposures with and without acephate contributions. Significant exposures to methamidophos in children were noted with combined contributions. Therefore, OEHHA recommended that DPR complete an exposure assessment for acephate in order to assess cumulative risks from exposure to methamidophos. DPR states in this draft acephate RCD (p. 76), that upon completion of the RCDs for acephate and methamidophos, it will consider the risks from cumulative and aggregate exposure under the Food Quality Protection Act (FQPA) of 1996. DPR notes that to do so would be especially relevant because certain high consumption foods such as potatoes and tomatoes do not have tolerance levels for acephate. The lack of tolerance levels is the result of acephate being applied directly to foliage and not to the fruit or root of the plant, i.e., potatoes and tomatoes. While acephate does not migrate, these commodities can still be affected from migration of residues from acephate's major metabolite, methamidophos. This is why we agree with DPR and continue to support and encourage the completion of the combined risk assessment.

DPR response: however, as noted on page 76, "The tolerance expression for acephate has traditionally included methamidophos residues, but it has recently been decided by USEPA (2007) that methamidophos residues should be considered separately from acephate (see Section II.B)."

5) As to FQPA considerations, OEHHA agrees with DPR that toxicity data indicate young and immature animals are not more sensitive to acephate than adults and it is acceptable to use a factor of one for the FQPA adjustment. In what DPR describes as a definitive developmental neurotoxicity study, all measured parameters (including cholinesterase inhibition) showed no increased sensitivity of the offspring relative to the parent. U.S. EPA (2006a,b,c) has done the same in its evaluation. DPR notes that when other organophosphates (OPs) are considered this may have to change. We recommend that DPR specifically state here that when other OPs are considered together with acephate, their own FQPA factors (such as the factor of two for methamidophos) should be included.

DPR response: at the end of page 76, it now reads: Various FQPA adjustment factors will be used for other organophosphates, as appropriate.

6) OEHHA agrees with the DPR conclusion that occupational risks present a concern, as the estimated margin of exposure (MOE) values are less than ten. We agree that mitigation measures are needed to reduce the risk to farm workers.

Specific comments on the draft RCD:
In Table 18, the grouping of lowest-observed-effect levels (LOELs) with NOELs, distinguished by a slash between them, might be confusing to a non-technical reader. A further separation or delineation between these values would be helpful. In addition, we recommend that real values and estimated values should be distinguished in the table, perhaps by the use of parentheses or brackets with explanatory footnotes. In addition, the NOEL/LOEL of the human study should be explained as a combined analysis for both sexes or a NOEL/LOEL should be designated for each sex.

Table 29, typographical error in the title.

The U.S. EPA reference on p. 84 should be in the "U.S. EPA" subtitle later in the list.

On p. 45, please specify how often vital signs and EKG were monitored. It seems doubtful that they would have been done at the same time as the blood draws.

Please update the web sites in the reference list, as the U.S. EPA ones have changed.

Please reference IRED, RED and cumulative risk documents in the reference section.

DPR response: all of these have been corrected, as suggested.

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