Appendix A. Multi-Active Ingredients Product Analysis for Acephate

The Agency does not routinely include, in its risk assessments, an evaluation of mixtures of active ingredients, either those mixtures of multiple active ingredients in product formulations or those in the applicator's tank. In the case of the product formulations of active ingredients (that is, a registered product containing more than one active ingredient), each active ingredient is subject to an individual risk assessment for regulatory decision regarding the active ingredient on a particular use site. If effects data are available for a formulated product containing more than one active ingredient, they may be used qualitatively or quantitatively (USEPA, 2004; USFWS/NMFS/NOAA, 2004).

Acute oral toxicity data (i.e., LD_{50} values) from mammalian studies for formulated products that contain acephate and one or more additional active ingredients are summarized in Table A.1 below. The results of an open literature search for data on formulated products that contain acephate using the EPA ECOTOX database are listed on page 3.

Currently, the Agency's guidance for assessing the potential risk of chemical mixtures is limited to human health applications (USEPA, 2000). However, the guidance includes principles for evaluating mixtures to assess potential interactive effects that are generally applicable. Consistent with EPA's Overview Document (USEPA, 2004), the Agency's mixture guidance (USEPA, 2000) discusses limitations in quantifying the risk of specified mixtures when there is differential degradation, transport and fate of chemical components following environmental release or application. The LD_{50} values are potentially useful only to the extent that a wild mammal would consume plants or animals immediately after these dietary items were directly sprayed by the product. Increasing time post application, the differential rates of degradation, transport, etc. for the active ingredients in the formulation only permit a qualitative discussion of potential acute risk (USEPA, 2004).

As discussed in USEPA (2000) a quantitative component-based evaluation of mixture toxicity requires data of appropriate quality for each component of a mixture. In this mixture evaluation LD_{50}s, with associated 95% confidence intervals, are needed for the formulated product. The same quality of data is also required for each component of the mixture. Given that some of the formulated products do not have LD_{50} values of the required quality and since LD_{50} values are not available for all the components of these formulations a quantitative analysis of potential interactive effects is not possible.

While a quantitative evaluation of the data is not possible with currently accepted scientific methods, as a screening tool, a qualitative analysis can be used to indicate if formulated products exhibit interactive effects (e.g., synergism or antagonism). In the case of acephate, a qualitative examination of the trends in LD_{50} values, with the associated confidence intervals, across the range of percent active ingredient, reveals no definitive conclusions but suggests synergistic (i.e., more than additive) interactions. In addition, when the product LD_{50}s, and associated confidence intervals, are adjusted for the percent acephate (a conservative assumption that attributes all of the observed toxicity of the formulated product to acephate) the adjusted 95% confidence intervals overlap with the confidence values of the adjusted LD_{50} value of acephate, 147-214 mg/kg, for only one (239-2595) of the four products that have LD_{50} values with associated

confidence intervals. The remaining three products have adjusted LD_{50}s and confidence intervals that are lower than the lower bound for acephate's 95% confidence interval (Table A.1).

Based on this qualitative evaluation of the best available data and the Agency's existing guidance it is reasonable to conclude that these formulations may exhibit a synergistic effect. Given that the active and inert ingredients would not be expected to have similar mechanisms of action, metabolites or toxicokinetic behavior it is also reasonable to conclude that an assumption of dose-addition would be inappropriate. However, the limited size of the data set and the variation in co-formulated pesticides prohibits any definitive conclusions. Additionally, as the registrations of three of the four products listed here have been cancelled by the registrants, the potential application of the analysis will be limited to the one remaining active registration (499-441). Consequently, an assessment of acephate's potential effect when it is co-formulated with other active ingredients will be based on the toxicity of acephate.

Table A.1. Pesticide products formulated with acephate and other pesticide active ingredients[1]

Product/Trade Name	EPA Reg. #	Formulation	Registrant Submitted Studies MRID	Product		Adjusted for Active Ingredient	
				LD_{50} (mg/kg)	95% CI (mg/kg)	LD_{50} (mg/kg)	95% CI (mg/kg)
Acephate TGAI	NA	Acephate (98%)	ECOTOX 38448	180.5	150-218	177	147-214
Ortho Systemic Rose & Floral Spray[2]	239-2476	Acephate (0.25%) Resmethrin (0.1%) Triforine (0.1%)	15297	3000	1700-5200	7.5	4.25-13
			46295408	5000	3408-20000	12.5	8.52-50
Orthenex Insect & Disease Control Formula III[3]	239-2594	Acephate (4%) Fenbutatinoxide (0.75%) Triforine (3.25%)	46295508	1030	550-1750	41.2	22-70
Isotox Insect Killer Formula IV[3]	239-2595	Acephate (8%) Fenbutatinoxide (0.5%)	46223005	3129	1750-5000	250.32	140-400
Whitmire TC 136	499-441	Acephate (1.5%) Fenpropathrin (1%)	43758602	1540	1050-2260	23.1	15.8-33.9

[1]From registrant submitted data to support registration. Compiled by Office of Pesticide Programs Health Effects Division. LD_{50} values are derived from small mammal studies.
[2]Product registration was cancelled by the registrant on June 1, 2011.
[3]Product registration was cancelled by the registrant on October 14, 2008.

ECOTOX Database literature with mixtures
Acephate – Screen of Ecotox Records for Possible Mixture Data

SEARCH_TERMS
ORTHO SYSTEMIC ROSE & FLORAL SPRAY
ORTHENEX INSECT & DISEASE CONTROL
FORMULA III
ISOTOX INSECT KILLER FORMULA IV
WHITMIRE TC 136
J & P SYSTEMIC ROSE & FLORAL SPRAY
Fenbutatin-oxide
Fenpropathrin
Resmethrin
Triforine

1. FIELD RP and HOY MA. EVALUATION OF GENETICALLY IMPROVED STRAINS OF METASEIULUS-OCCIDENTALIS ACARINA PHYTOSEIIDAE FOR INTEGRATED CONTROL OF SPIDER MITES ON ROSES IN GREENHOUSES. 1986(2): 1-32.
   Notes: Chemical of Concern: ACP
   Abstract: BIOSIS COPYRIGHT: BIOL ABS. RRM TETRANYCHUS-URTICAE ACEPHATE CARBARYL PIRIMICARB ENDOSULFAN HEXAKIS DIENOCHLOR BENOMYL TRIFORINE PARINOL PIPERALIN OXYCARBOXIN TOXICITY Biochemistry/ Poisoning/ Animals, Laboratory/ Plants/Growth & Development/ Herbicides/ Pest Control/ Pesticides/ Arachnida/ Entomology/Economics/ Pest Control, Biological/ Arachnida/ Entomology/Economics/ Insecticides/ Pest Control/ Pesticides/ Anatomy, Comparative/ Animal/ Arthropods/Physiology/ Physiology, Comparative/ Pathology/ Plants, Medicinal/ Arthropods

2. Morin, S.; Williamson, M. S.; Goodson, S. J.; Brown, J. K.; Tabashnik, B. E., and Dennehy, T. J. Mutations in the Bemisia tabaci para sodium channel gene associated with resistance to a pyrethroid plus organophosphate mixture. 2002 Dec; 32, (12): 1781-1791.
   Notes: Chemical of Concern: ACP
   Abstract: The voltage-gated sodium channel is the primary target site of pyrethroid insecticides. In some insects, super knockdown resistance (super-kdr) to pyrethroids is caused by point mutations in the linker fragment between transmembrane segments 4 and 5 of the para-type sodium channel protein domain II (IIS4-5). Here, we identify two mutations in the IIS4-5 linker of the para-type sodium channel of the whitefly, Bemisia tabaci: methionine to valine at position 918 (M918V) and leucine to isoleucine at position 925 (L925I). Although each mutation was isolated independently from strains >100-fold resistant to a pyrethroid (fenpropathrin) plus organophosphate (acephate) mixture, only L925I was associated with resistance in strains derived from the field in 2000 and 2001. The L925I mutation occurred in all individuals from nine different field collections that survived exposure to a discriminating concentration of fenpropathrin plus acephate. Linkage analysis of hemizygous male progeny of unmated heterozygous F1 females (L925Ixwild-type) shows that the observed resistance is tightly linked to the voltage-gated sodium channel locus. The results provide a molecular tool for better understanding, monitoring and managing pyrethroid resistance in B. tabaci. Insecticide/ Resistance/ Pyrethroid/ Voltage-gated sodium channel/ Bemisia tabaci

3. SIVASUPRAMANIAM, S.; JOHNSON, S.; WATSON TF; OSMAN AA , and JASSIM, R. A glass-vial technique for monitoring tolerance of Bemisia argentifolii (Homoptera: Aleyrodidae) to selected insecticides in Arizona. 1997(1): 66-74.

Notes: Chemical of Concern: ACP
Abstract: BIOSIS COPYRIGHT: BIOL ABS. A glass-vial bioassay technique was used to assess the toxicity of bifenthrin, endosulfan, fenpropathrin, and fenpropathrin+acephate (1:1) to adult Bemisia argentifolii Bellows & Perring. Initial surveys of B. argentifolii susceptibility to the test insecticides established a basis for monitoring possible changes in population sensitivity to these products. Data on tolerance of B. argentifolii adult populations were obtained in 1992 (20 populations) and 1993 (22 populations) with treated glass vials. Surveys on populations from different host crops (cotton, cole crops, and melons) were done in different geographical areas in Arizona. Probit analysis of the results indicated that the LC50s from many of the test sites were significantly different, exhibiting various levels of tolerance to the insecticides tested. Host plants, crop phenology, and the geographical region seemed to affect responses of B. argentifolii populations. Plants/Growth & Development/ Soil/ Textiles/ Vegetables/ Herbicides/ Pest Control/ Pesticides/ Arachnida/ Entomology/Economics/ Plants/ Arachnida/ Entomology/Economics/ Insecticides/ Pest Control/ Pesticides/ Plants/ Plants/ Plants/ Insects

4. Sivasupramaniam, S. and Watson, T. F. Selection for Fenpropathrin and Fenpropathrin + Acephate Resistance in the Silverleaf Whitefly (Homoptera: Aleyrodidae).
MORSOIL,ENV,MIXTURE; 2000; 93, (3): 949-954.
Notes: EcoReference No.: 58567
Chemical of Concern: ACP,FP