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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

July 25, 2003

MEMORANDUM

SUBJECT: **REVISED Fosthiazate. Human Health Risk Assessment for Tolerances for** Fosthiazate Use in/on Imported Banana and Coffee, and Section 3 Registration for Fosthiazate Use in/on Peanut, Potato, and Tomato. PC Code 129022. **DP** Barcode D291003. Submission No. S592126.

FROM: Diana Locke (PhD), Risk Assessor
Reregistration Branch II
Health Effects Division (7509C)

Diana Locke 7/25/03

THROUGH: Alan Nielsen, Branch Senior Scientist
Reregistration Branch II
Health Effects Division (7509C)

Al Nielsen 7/25/03

TO: Rita Kumar, Product Manager
Insecticide-Rodenticide Branch
Registration Division (7505C)

Action Requested: The Office of Pesticide Programs' Registration Division (RD) has requested that the Health Effects Division (HED) evaluate hazard and exposure data and conduct dietary, residential, occupational, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from proposed new uses of the organophosphate (OP) fosthiazate with tomatoes, peanuts, potatoes, coffee (tolerance without U.S. registration), and bananas (tolerance without U.S. registration).

A summary of the findings and an assessment of human risk resulting from the proposed new uses of fosthiazate is provided in this document. The toxicology and hazard characterization were provided by Anna Lowit; the occupational risk assessment by Shanna Recore, the dietary and residue chemistry risk assessments by Sherrie Kinard, the risk characterization by Diana Locke,

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and the drinking water assessment by Thuy Nguyen/James Wolf/Henry Craven of the Environmental Fate and Effects Division (EFED).

Recommendations for Tolerances and Registration

Provided that revised Sections B and F with the modifications specified in Section 8.2 of this document are submitted, and appropriate mitigation (see below) for potential drinking water and occupational exposures of concern is made, the residue chemistry and toxicological databases support a conditional registration for the establishment of a permanent tolerance for residues of fosthiazate and its ASC-67131 metabolite (O-ethyl S-(1-methylpropyl)[2-(methylsulfonyl)ethyl] phosphoramidothioate) in/on the following raw agricultural commodities (RACs):

Tomato.....0.02 ppm

The results of the OP cumulative risk assessment conducted by the Agency do not permit the inclusion of additional OP residues on food from any source. Based on detectable residues of fosthiazate in banana, coffee, and potato field trial data above the limit of quantitation (LOQ), these uses were not included in the risk assessment. The data for peanut are insufficient to support a tolerance for residues in/on peanut (see p. 11).

The registrant proposed chemigation under plastic and shank injection as alternative methods of application of fosthiazate to tomato at 1.5 lbs active ingredient/acre/season. Estimated drinking water concentrations are potentially of little or no concern, using these methods and rate. Proposed lower acreages (25 acres) combined with the 1.5 lbs active ingredient/acre application rate and the chemigation under plastic method (only), potentially lower occupational risks to levels that are not of concern. These proposed changes and limitations support a conditional registration for the establishment of a permanent tolerance on tomato.

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1.0 Executive Summary

Fosthiazate (*O*-ethyl *S*-(1-methylpropyl)(2-oxo-3-thiazolidinyl)phosphonothioate) is a new active ingredient being proposed for registration by ISK Biosciences Corporation for use on banana, coffee, peanut, and potato[1], and tomato. The proposed use of fosthiazate on tomato is as a methyl bromide replacement (proposed tolerance of 0.02 ppm); the uses on coffee and banana are as tolerances without U.S. registration (import). Fosthiazate is an organophosphate (OP) pesticide that controls a broad spectrum of nematode species. It may be applied as a ground-directed spray through drip (trickle) irrigation systems or using ground equipment, and then immediately soil-incorporated. Fosthiazate is formulated as an emulsifiable concentrate (EC) at 75% active ingredient (a.i.) and 47.2% a.i. Application is made once per season, either prior to or at planting for all crops, or prior to or at transplanting for tomatoes. A maximum of one application at 4 lbs a.i. acre per season is proposed for peanuts and a maximum of one application at 4.5 lbs a.i. per acre per season is proposed for potatoes and tomatoes. Fosthiazate may be applied as a band application to tomatoes, which could result in an application rate for tomatoes of 1.5 lbs a.i. per acre per season. There are no current or proposed residential uses of fosthiazate.

Hazard Identification and FQPA Considerations

Fosthiazate has moderate toxicity via the dermal (toxicity category II) and oral (toxicity category II) routes of exposure and slight toxicity via the inhalation (toxicity category III) route of exposure. It is moderately irritating to the eyes (toxicity category II), and moderately irritating to the skin (toxicity category IV). Fosthiazate is classified as a dermal sensitizer. In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), and based on lack of evidence for carcinogenicity in mice and rats, the Agency has classified fosthiazate as "not likely to be carcinogenic to humans." There is no concern for mutagenicity resulting from exposure to fosthiazate.

The primary target for fosthiazate appears to be the nervous system, with a secondary target, the adrenal system. Inhibition of plasma, red blood cell (RBC), and brain cholinesterase (ChE) activities was noted in the acute, subchronic and chronic toxicity studies. Evidence of neurological impairment included impaired grip strength in female rats in the acute and subchronic neurotoxicity studies; ataxia, hunched posture, gasping, and tremors in male mice in the carcinogenicity study and in male and female rats in the 21-day dermal toxicity study; and inhibition of brain ChE in the 13-week and 4-week rat feeding studies, subchronic neurotoxicity rat feeding study, and the 21-day dermal toxicity study.

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[1]The Agency notes that proposed petitions for the use of fosthiazate on banana, coffee, peanut and potato are not included in this risk assessment. Due to detectable residues above LOQ in banana, coffee and potato, these uses could not be included in the fosthiazate risk assessment, in accordance with the results of the OP cumulative risk assessment. Numerous data gaps for peanuts precluded the inclusion of peanuts in the risk assessment (see p. 11).

Although the rat and rabbit developmental studies did not show increased sensitivity of the young, in the two-generation reproduction study, the observed effects on offspring (decreased pup weight, viability, and litter size) are considered to be more severe and occurred at a lower dose (2.09 mg/kg/day) than the dose at which effects on the parental animals (increased incidences of adrenal zona glomerulosa hypertrophy, centriacinar hepatocytic vacuolation and liver inflammation in females and periacinar hepatocytic hypertrophy in males) were seen (9.32 females and 7.21 males mg/kg/day). Therefore, there is qualitative and quantitative evidence of increased susceptibility of the fetus/pups. However, the Hazard Identification Assessment Review Committee (HIARC) indicated that there are no residual uncertainties for the effects seen in the reproduction study because: 1) the study was well conducted; 2) the dose-response in the offspring is well characterized; 3) clear NOAEL and LOAEL were established for the effects on the offspring; 4) although the decrease in pup survival seen at the LOAEL is severe, this could be attributed to exposure to higher levels of the chemical since the mortalities occurred during early lactation; and 5) although ChE activity was not measured in this study, cholinergic signs and ChEI were seen at comparable doses in other studies and thus could have been a cause for the pup mortality. Therefore, the Special FQPA factor was reduced to 1X since there are no residual uncertainties. The registrant is currently conducting a developmental neurotoxicity (DNT) study.

Toxicological endpoints selected for risk assessment purposes are based on the inhibition of plasma, RBC, and brain ChE. Dermal absorption is estimated to be 20% and inhalation absorption is assumed to be 100%. Risk assessments were conducted for the specific exposure durations listed below. The reference dose (RfD) is equal to the No-Observed-Adverse-Effect-Level, or NOAEL, divided by a 1000X uncertainty factor for the acute dietary risk and a 300X uncertainty factor for the chronic dietary risk: 10X for interspecies extrapolation, 10X for intraspecies variations, and a 10X/3X database uncertainty factor (UF_{DB}) for lack of a DNT study. The target Margin of Exposure (MOE) of 100 represents the level above which risks to occupational handlers are not of concern.

– acute dietary(general population):	NOAEL = 0.4 mg/kg/day	aRfD = 0.0004 mg/kg/day
– chronic dietary:	NOAEL = 0.05 mg/kg/day	cRfD = 0.00017 mg/kg/day
– short/intermediate-term dermal:	NOAEL = 0.5 mg/kg/day	Target MOE = 100
– short-term inhalation:	NOAEL = 0.10 mg/kg/day	Target MOE = 100
– intermediate inhalation:	NOAEL = 0.05 mg/kg/day	Target MOE = 100

HED proposes that consideration of the establishment of permanent tolerances be for the combined residues of fosthiazate and its ASC-67131 metabolite, O-ethyl S-(1-methylpropyl)[2-(methylsulfonyl)ethyl] phosphoramidothioate, in or on tomato. The Metabolism Assessment Review Committee (MARC) has determined that the residues of concern for plant and some rotational crop commodities are fosthiazate and its ASC-67131 metabolite. The metabolite of fosthiazate is assumed to be toxicologically equivalent to the parent. For the drinking water assessment, the MARC has determined that the only residue of concern is the parent fosthiazate.

Dietary Exposure

An acute and chronic dietary exposure assessment was conducted for fosthiazate on tomatoes using the Dietary Exposure Evaluation Model (DEEM-FCID™, version 1.3). Fosthiazate tomato field trial data were used, assuming 100% crop treated (%CT) and incorporating the default DEEM processing factors as well as processing data for tomato juice and puree, to estimate the acute and chronic dietary risk associated with the use of fosthiazate on tomatoes. Since no residues of concern were detected in the edible portion of the tomato plants in field trial studies, the residue value used consisted of half the LOQ for the parent, and half the LOQ for the metabolite ASC-67131; therefore, the residue value used in the dietary assessment was the LOQ (0.01 ppm). DEEM default values were used for all processed tomato commodities with the exception of tomato juice and puree. Dietary risk estimates are provided for the U.S. population (total) and various population subgroups. This assessment concludes that for all supported tomato commodities for registration, the acute dietary risk estimates are below the Agency's level of concern at the 95th exposure percentile for the U.S. population (total) and all population subgroups. The most highly exposed population subgroup in the acute dietary analysis is children 1-2 years of age (29% of acute population adjusted dose or aPAD). This assessment also concludes that for all commodities, the chronic dietary risk estimates are below the Agency's level of concern for the U.S. population (total) and all population subgroups. The most highly exposed population subgroup in the chronic dietary exposure analysis is also children 1-2 years of age (15% cPAD).

Residential Exposure

There are no current or proposed residential uses for fosthiazate; therefore, a residential exposure assessment has not been conducted.

Drinking Water Exposure

A drinking water assessment for fosthiazate was conducted based on Tier 2 surface water modeling (PRZM-EXAMS) and Tier 1 groundwater modeling (SCI-GROW) results. HED's MARC has determined that only the parent fosthiazate is to be included in the drinking water risk assessment. The metabolite of toxicological concern, ASC-67131, is not found in soil or water.

Estimated drinking water concentrations (EDWCs) of parent fosthiazate in surface water are 15 µg/L (chronic) and 41 µg/L (acute). These values incorporate an assumed maximum application rate of 4.5 lb a.i./acre to tomatoes by groundboom sprayer, and a default (and most likely conservative) percent cropped area (PCA) value of 87% for tomatoes. The acute and chronic EDWC in groundwater is 7 µg/L. This value also incorporates an assumed maximum application rate of 4.5 lbs. a.i./acre. No PCA adjustment is required for SCI-GROW, and a Tier 2 model for groundwater is not available at this time. Other conservative factors that contribute to the water assessments are 1) lacking data, it was assumed that fosthiazate is relatively stable in water, and 2) submitted adsorption/desorption studies in three different types of soil measured Kd values

(coefficient of adsorption/desorption) that ranged from 0.43 - 1.71. The lowest value (0.43) was used in the EDWC estimation though, in some cases the mobility of fosthiazate from source to water may be up to three times lower.

Since both the acute and chronic dietary food risks are less than 100% PAD, the drinking water levels of comparison (DWLOC) were calculated. The acute and chronic surface and ground water EDWCs of fosthiazate exceed the DWLOCs and therefore, exposures at these levels may pose a risk of concern.

It should be noted however, that application of fosthiazate on tomatoes by chemigation (via drip irrigation) under plastic and by shank injection is an option and EFED has determined that these methods are expected to result in reduced surface water concentrations of fosthiazate. Though EFED lacks sufficient in-depth information on the implications of these practices on drinking water, using the PRZM-EXAMS model, EFED predicts that the peak EDWC in surface water would be roughly 2.1 *u*g/L for a 1.5 lb ai/acre application rate and 1.1 *u*g/L for a 1 lb ai/acre rate. Note that these concentrations were modeled under the most conservative scenarios and are likely higher than the actual level of contamination in the environment. Using the SCI-GROW model and these lower application rates, EFED estimated that the ground water EDWCs would be 2.4 µg/L and 1.6 µg/L at the 1.5 and 1.0 lb ai/acre application rates, respectively. When compared to the calculated DWLOCs, there are slight exceedences of the chronic DWLOCs for infants and children for both surface water and ground water EDWCs. However, these EDWCs are conservative estimates and actual at-the-tap levels are expected to be lower.

Aggregate Exposure

Aggregate risk assessments consider the combined exposures from food, drinking water, and residential pathways of exposure. Since there are no current or proposed residential uses of fosthiazate, the aggregate risk assessments only consider exposure from food and drinking water. Aggregate risk assessments conducted for fosthiazate include acute (food and drinking water) and chronic (food and drinking water) assessments. Short- and intermediate-term aggregate risk assessments were not conducted since there are no short- or intermediate-term residential exposure scenarios.

Dietary (food) risk estimates, when considered alone, are not of concern. Estimated concentrations of fosthiazate in drinking water following groundboom applications at 4.5 lbs. a.i./acre exceed HED's DWLOC values, and therefore, acute and chronic aggregate risks may be of concern. However, concentrations of fosthiazate in drinking water following applications by chemigation under plastic or by shank injection at 1.5 and 1.0 lbs ai/acre are lower. The EDWCs at these lower application rates are below the acute DWLOC values and do not result in potential acute aggregate risks that are of concern. Though there are slight exceedances of the chronic DWLOCs, even at these lower application rates, the potential chronic aggregate risks are of little or no concern. It should also be noted that the EDWCs are modeled estimates, not at-the-tap measurements and are considered conservative (see EFED chapter and amendments 1 & 2).

Occupational Exposure

The level of concern for occupational exposures to fosthiazate is for margins of exposure (MOEs) less than 100. Based on the proposed use patterns, short-term (1 to 30 days) and possibly intermediate-term (30 days to 6 months) dermal and inhalation exposures are expected for pesticide handlers and postapplication workers. Since fosthiazate may be applied only one time per year, long-term (longer than 6 months) exposures to pesticide handlers or postapplication workers are not expected from the proposed use patterns.

HED has determined that there are potential exposures to mixers, loaders, applicators, and other handlers during the proposed use-patterns associated with fosthiazate. Based on the use patterns, four major occupational exposure scenarios were identified for fosthiazate:

- mixing/loading/applying liquids using chemigation systems
- mixing/loading liquids for groundboom applications;
- applying liquids with a groundboom sprayer; and
- cleaning equipment following groundboom applications.

At this time, HED has no data to assess handler exposures while handling pesticide-contaminated driplines or while laying tarps over a just-treated field. HED approximates exposures to handlers during chemigation applications by using data for mixing/loading only. Therefore, HED believes that estimates of handler risks for the dripline irrigation scenario underestimate likely risks for chemigation scenarios.

The handler exposure and risk assessments presented in this document are based on selected data from five fosthiazate-specific studies and the Pesticide Handler Exposure Database (PHED) Version 1.1 (August 1998). Five chemical-specific handler studies were submitted in support of the proposed registration. The Agency has concerns about the engineering control scenarios (i.e., closed mixing/loading system and enclosed tractor cab scenarios), because handlers were wearing maximum personal protective equipment (PPE) in addition to using the engineering controls. The Agency's policy is to allow handlers to wear reduced PPE when engineering controls are used. In addition, some of the study scenarios intended to represent open tractor cab exposures used enclosed cab equipment with open windows and doors. Due to these concerns, the Agency has determined that the only fosthiazate-specific handler data applicable for this risk assessment are the open mixing/loading, open tractor cab, and cleanup scenarios. In addition, PHED data for open mixing/loading and open tractor cab scenarios were used in this assessment because, for these two scenarios, there is a higher level of confidence in the PHED data which has many more replicates, than in the fosthiazate-specific studies.

The maximum application rate listed on the label was used to assess exposures and risks in all scenarios. In addition, an application rate of 1.5 lbs a.i. per acre was assessed for dripline irrigation applications to tomatoes, in order to reflect the possible rate reduction when the application is applied in banded areas only and not broadcast evenly across the treated area.

With one exception, the standard HED values for acreage were used. Based on information from the registrant regarding acres that can be treated per day when driplines are installed by hand following tomato transplanting, the assessment for dripline chemigation for tomatoes uses the standard value of 350 acres per day as well as the 25 acres per day proposed by the registrant.

To assess exposures during equipment cleanup, the fosthiazate-specific data first was adjusted to reflect the application rate of 4.5 pounds active ingredient per acre now proposed, rather than the 6.0 pounds active ingredient per acre used in the study. That exposure value (in milligrams) was assumed to be the daily exposure to cleanup workers.

Since both the dermal and inhalation toxicological endpoints of concern are based on inhibition of ChE, HED aggregated dermal and inhalation MOE values for both short- and intermediate-term exposures. The MOEs presented below represent the aggregated MOEs for each handler scenario.

All short- and intermediate-term handler risks are of concern based on HED's level of concern (MOE <100), *except* for dripline chemigation applications to tomatoes at 1.5 lbs a.i. and a maximum of 25 acres treated per day per handler. Using PHED data for mixing/loading liquid formulations with closed systems as a surrogate for closed-system dripline chemigation applications, MOEs are 120 for short-term and 110 for intermediate-term exposures. Using fosthiazate-specific data for mixing/loading liquid formulations with maximum dermal PPE (but not a respirator) as a surrogate for dripline chemigation applications, the MOEs are 250 for short-term and 240 for intermediate-term exposures.

The proposed label submitted by the registrant in support of fosthiazate registration requires mixers/loaders and applicators to use engineering controls, including closed mixing/loading systems and enclosed tractor cabs. As mandated in the Worker Protection Standard (WPS) for Agricultural Pesticides, the proposed label also permits handlers to wear reduced PPE when engineering controls are used.

HED recommends that if the proposed registration for dripline chemigation application to tomatoes is approved, pesticide labeling directions should limit drip-irrigation applications to 25 acres per day per handler and to a maximum application rate of 1.5 lbs a.i. per acre applied in bands.

Fosthiazate is applied directly to the soil before or at planting and postapplication exposure to fosthiazate may result from contact with treated soil. In particular, HED is concerned about transplanting tomatoes soon after a fosthiazate application. However, at this time, no postapplication assessment has been performed since there are no data on the soil residue dissipation of fosthiazate and no exposure data for activities resulting in contact with treated soil. Based on information provided by the registrant (i.e., the proposed label requires workers to wear gloves and boots when transplanting tomatoes within 7 days following applications to certain soil types) and fosthiazate-specific data indicating a relatively lengthy half-life in soils, HED is

proposing a 7-day restricted-entry interval (REI) following fosthiazate applications. HED notes that the Worker Protection Standard for Agricultural Pesticides (WPS) prohibits workers from performing routine early entry tasks while wearing PPE. Instead, the WPS requires that the Agency establish an REI for the length of time following application until risks are not of concern for workers entering treated areas and performing tasks requiring contact with the treated surface *without* the use of PPE.

The WPS prohibits routine entry to perform hand labor tasks during the REI and requires PPE to be worn for other early-entry tasks that require contact with treated surfaces. Based on the acute toxicity of fosthiazate a.i. (i.e., toxicity category II for dermal toxicity and eye irritation potential, and classified as a skin sensitizer) and using the default early entry PPE established by the WPS, HED recommends the following early entry PPE: long-sleeved coveralls over short-sleeved shirt and short pants, chemical-resistant gloves, chemical-resistant footwear plus socks, and protective eyewear.

Recommendations for Tolerances and Data Needs

HED concludes that the toxicological, residue chemistry, and occupational exposure databases are sufficient for establishment of a conditional registration and a tolerance for fosthiazate and its metabolite ASC-67131 pending mitigation of exposures of concern (drinking water and occupational) and the resolution of outstanding data requirements:

Tomato.....0.02 ppm

Petitions by the registrant for the establishment of tolerances for banana, coffee, peanut, and potato are not deemed appropriate at this time since detectable residues were found in banana, coffee, and potato field trial data and the results of the OP cumulative risk assessment preclude the inclusion of any additional OP residues.

The peanut data are insufficient to support consideration for a tolerance. Though no detectable residues were found in the nutmeat (edible portion), residues were detected in leafy peanut plant material, which is frequently used as fodder for farm animals. Feeding studies have been requested however, the registrant has volunteered to accept a feeding restriction. Though this might present an acceptable mitigation option for potential dietary risks from food, there are still potential unacceptable risks from drinking water and for occupational exposures. Therefore, the petition for peanut cannot be granted at this time.

A 28-day inhalation study in rats is required for fosthiazate, in order to better characterize exposure via the inhalation route of exposure. A DNT study in rats with comparative ChE measurements in adults and pups is also required, and is currently being conducted by the registrants. Various product and residue chemistry deficiencies, as well as occupational data gaps, have also been identified, and are explained in detail in Section 8.0 of this document.

2.0 Physical/Chemical Properties Characterization

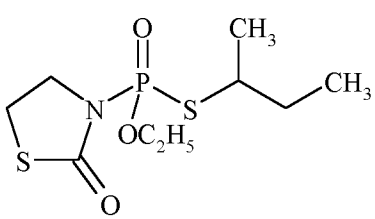
Technical fosthiazate is a light gold liquid with a boiling point of 198° C at 0.5 mm Hg, a low vapor pressure of 2.7×10^{-6} at 25° C, and a log P_{ow} of 1.752. Fosthiazate has a solubility of 9.85 g/L in water, 15.14 g/L in n-hexane, and is soluble in N-methyl-2-pyrrolidinone (NMP), isopropyl alcohol, and xylene (*Secondary Product Chemistry Review of Fosthiazate Technical. Shyam Mathur. November 8, 2001*).

It is not certain whether or not impurities of toxicological concern exist for fosthiazate since adequate data have not been provided.

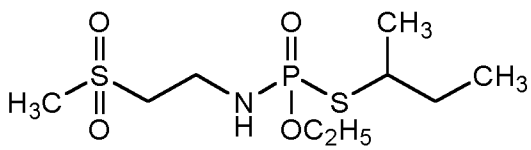
Various product chemistry data gaps have been identified for fosthiazate. These data gaps include, but are not limited to, the following: the nominal concentrations of all potential toxic impurities present in the technical, a discussion on the formation of impurities for all the impurities identified and listed in the CSF and also for theoretically possible impurities, a one year storage stability study on commercial packaging under warehouse conditions, and UV/Visible absorption data for technical fosthiazate. A complete listing of product chemistry data gaps and data requirements may be found in the Product Chemistry Review of Fosthiazate Technical (S. Mathur memo, 11/08/2001).

Empirical formula:	$C_9H_{18}NO_3S_2P$
Molecular weight:	251.29
CAS Registry No.:	98886-44-3
PC Code:	129022

Figure 1. Structures of fosthiazate and its metabolite ASC-67131.



Fosthiazate: *O*-Ethyl *S*-(1-methylpropyl)(2-oxo-3-thiazolidinyl)phosphonothioate



ASC-67131 or SDS-67131: (*RS*)-*S*-*sec*-Butyl *O*-ethyl *N*-[2-(methylsulfonyl)ethyl] phosphoramidothioate

3.0 Hazard Characterization

3.1 Hazard Profile

Fosthiazate has moderate toxicity in experimental animals by the inhalation (Category III), oral (Category II) and dermal (Category II) routes, is moderately irritating to the eyes (Category II), and minimally irritating to the skin (Category IV). It is a dermal sensitizer.

Table 1: Acute Toxicity Profile of Fosthiazate Technical

Guideline Number	Study Type	MRID	Results	Toxicity Category
870.1100	Acute Oral -Rat; 1989	41347622	LD_{50} = 73 mg/kg- M; = 51-64- F	II
870.1200	Acute Dermal- Rat; 1989	41347625	LD_{50} = 2396 mg/kg- M; =861 mg/kg- F	II
870.1300	Acute Inhalation- Rat (92% ai); 1989	41347626	LC_{50} = 0.83 mg/L- M = 0.56 mg/L- F	III
870.2400	Primary Eye Irritation - Rabbit; 1989	41347627 41347628	Mildly irritating; corneal opacity reversible within 7 days	II
870.2500	Primary Skin Irritation - Rabbit; 1989	41347629	Non-irritating	IV
870.2600	Dermal Sensitization- Guinea pig; 1989	41347630	Sensitizer	NA

The primary target of fosthiazate appears to be the nervous system; the adrenal organ appears to be a secondary target. Inhibition of plasma, RBC and brain ChE activities were noted in the subchronic (by oral and dermal routes), and chronic studies. Evidence of neurological impairment included impaired grip strength in female rats in the acute and subchronic neurotoxicity rat studies; ataxia, hunched posture, gasping and tremors in male mice in the carcinogenicity study and in male and female rats in a 21-day dermal toxicity study; inhibition of brain ChE in the 13-week and 4-week rat feeding studies, subchronic neurotoxicity rat feeding study, as well as in the 21-day dermal toxicity study. Adrenal histopathology, sometimes accompanied by increases in adrenal weights and adrenal cortico-medullary pigmentation, was seen at various doses in the rat subchronic and chronic toxicity studies, and in a mouse carcinogenicity study [*Fosthiazate (PC Code 129022): Revised Registration Toxicology Disciplinary Chapter. Anna Lowit. November 14, 2002*].

The oral rat and rabbit developmental studies did not reveal any developmental effects on the fetus exposed to fosthiazate *in utero*, while maternal toxicity resulted in reduced body weight/weight gain and abortions (rabbit only) at 10 and 2 mg/kg/day in rats and rabbits, respectively. In a 2-generation reproduction study, decreases in pup weight, as well as litter size and viability index were noted at 30 ppm (2.09 mg/kg/day). The next higher dose level [100 ppm (9.32 mg/kg/day)] produced parental toxicity (increased adrenal and liver hypertrophy). Thus, the effects on offspring are considered to be severe and occurred at a lower dose than those on the parental animals. Therefore, there is qualitative and quantitative evidence of increased susceptibility of the fetus/pups. Both the acute and subchronic neurotoxicity studies show that fosthiazate causes an adverse effect on the nervous system as noted above. The registrant is currently conducting a DNT study in rats (*Developmental Neurotoxicity Study Protocol. Susan Makris. May 30, 2001*).

Long-term dietary administration of fosthiazate resulted in an increased incidence of non-neoplastic histopathological changes in adrenal (in rats, mice and dogs) and pituitary (rats and mice) glands in one or both sexes. In addition, decreases in RBC parameters, and an increased

incidence of ovarian atrophy in female rats, as well as retinal atrophy and skeletal degenerative myopathy were noted in male rats. When tested at adequate dose levels, tumor rates were not increased in male or female rats, mice, and dogs after long-term dietary administration of fosthiazate.

Fosthiazate and one of its metabolites, 2-butane sulfonic acid (BSA), show no positive evidence of mutagenicity in *in vitro* or *in vivo* assays: including the gene mutation assay, cytogenetic assay for structural chromosomal aberrations, mouse lymphoma assay, and DNA Repair assay. *In vivo* micronucleus tests for chromosomal aberrations are negative.

The oral rat metabolism studies showed that fosthiazate is rapidly and extensively absorbed independent of dose; rapidly metabolized and excreted in the urine (>65%), expired air (>10%) and in feces (<9%) with only <5% detected in the tissues. No sex-related differences were noted in the absorption and distribution; absorption was not dose dependent. The peak concentration in the blood was at 0.33 hr in both sexes. Mean recovery was 95%-99%. Metabolism and excretion occurred within 24 hrs. Fosthiazate was metabolized by multiple processes including hydrolysis, oxidation, methylation and glutathione conjugation. The primary metabolite excreted was (RS)-S-sec-butyl 0-ethyl N-(2-methylsulfinylethyl) phosphoramidothioate, a.k.a. BESxP, [15% of the administered dose (AD)] in females and (RS)-S-sec-butyl 0-ethyl N-(2-sulfoethyl) phosphoramidothioate, a.k.a. BESaP, (11% of the AD) in males.

A 28-day inhalation study in rats with fosthiazate is required, as there is concern for toxicity by the inhalation route following occupational exposure on multiple days. Registrants are recommended to follow the protocol provided in OPPTS Guideline 870.3465 (90-day inhalation study) but cease exposure at 28 days. A DNT study in rats with comparative ChE measurements in adults and pups are also required.

Table 2: Subchronic and Chronic Toxicology Profile for Fosthiazate

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 13-Week Feeding Study-Rat	41347632 (1989) Acceptable/Guideline 10 rats/sex/dose at 0, 1.07, 10.7, 53.6 and 429 ppm (0.08, 0.77, 4.12 and 36.37 mg/kg/day for males; 0, 0.09, 0.89, 4.74, and 41.03 mg/kg/day for females).	**Systemic Toxicity LOAEL:** 0.08 and 0.09 mg/kg/day for males and females, respectively, based on microscopic lesions in the adrenals (males) and increased ALT (females) levels. **No NOAEL** was established. At higher doses, the severity of vacuolation of cells in zona fasciculata (≥1.07 ppm) and zona glomerulosa (≥53.6 ppm) of the adrenals increased in a dose-dependent manner; at ≥53.6 ppm, the brain ChEI was also noted. In addition, there was increase in adrenal gland weight at 429 ppm **LOAELfor ChEI:** 10.7 ppm (0.77 and 0.89 mg/kg/day for males and females, respectively) based on plasma and RBC ChEI. **NOAEL:** 1.07 ppm (0.08 and 0.09 mg/kg/day for males and females, respectively).

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
4-Week Range-Finding Feeding Study-Rat	44269905 (1989) Acceptable/Non-guideline 10/sex/dose at 0, 0.5, 1, 5, 10, 100 and 400 ppm (equivalent to 0, 0.05, 0.10, 0.48, 0.97, 9.69 and 40.87 mg/kg/day in males and 0, 0.05, 0.10, 0.50, 1.00, 10.67 and 43.52 mg/kg/day in females).	**Systemic LOAEL:** 400 ppm (equivalent to 40.87 mg/kg/day in males and 43.52 mg/kg/day in females) based on fur loss, muscle tremor, enlarged pale spongiocytes in the adrenals, increased adrenal weights, and increased alkaline phosphatase and alanine aminotransferase levels. **Systemic Systemic NOAEL**: 100 ppm (equivalent to 9.69 mg/kg/day in males and 10.67 mg/kg/day in females). **LOAEL for ChEI:** 5 ppm (equivalent to 0.48 mg/kg/day in males and 0.5 mg/kg/day in females) based on decreased plasma butyryl- and acetyl-cholinesterase, and brain acetyl-cholinesterase in females, and erythrocyte acetyl-cholinesterase in males. **NOAEL:** 1 ppm (equivalent to 0.10 mg/kg/day in males and females.
28-day Feeding Study- Rat with 2-Butanesulfonic acid **(BSA)**	43559701 (1999) Acceptable/Non-guideline 50/sex/dose at 0, 100, 250, 500, or 1000 mg/kg/day (limit dose)	**NOAEL:** 1000 mg/kg/day, the highest dose tested.
4-Week Range-Finding Feeding Study -Mice	43971902 (1989) Acceptable/Non-guideline 12 mice/sex/dose at 0, 5, 20, 100 or 400 ppm (males: 0, 0.90, 3.50, 17.59, 68.99; and females: 0, 0.97, 4.14, 21.43, 82.38 mg/kg/day)	**LOAEL:** 400 ppm (males: 68.99 and females: 82.38 mg/kg/day) based on increased tubular basophilia in the kidney. **NOAEL:** 100 ppm (equivalent to 17.59 mg/kg/day in males and 21.43 mg/kg/day in females).
870.3150 13-Weeks Subchronic Toxicity-Dog	41381108 (1989) Acceptable/Guideline 4 dogs/sex/dose at 0, 0.054, 0.11, 0.54, or 5.4 mg/kg/day in gelatin capsule	**Systemic Toxicity LOAEL**: 0.11 mg/kg/day, based on histopathological changes in the adrenal glands. **NOAEL**: 0.054 mg/kg/day. **LOAEL for plasma ChEI:** 0.11 mg/kg/day in females and 0.54 mg/kg/day in males. **NOAEL:** 0.054 mg/kg/day in females and 0.11 mg/kg/day in males.
870.3200 21 - Day Repeated Dermal Toxicity - Rat	43916806 (1989) Acceptable/Guideline 5 rats/sex/dose at 0, 0.5, 2.5, 25, or 250 mg/kg/day for 6 hours/day, 7 days/week, for a total of 21days	**Systemic LOAEL**: 250 mg/kg/day for males and females based on mortality, clinical signs (emaciation, torpor [lethargy or dullness], tremor, hunched posture, hypothermia, gasping, hypersensitivity to noise, pallor [paleness], tachypnea [labored breathing], and piloerection), decreased body weight gains, and histopathology of the adrenal cortex observed in both sexes; increased food conversion factor and hematology findings were observed in males only. **Systemic NOAEL**: 25 mg/kg/day. **LOAEL for ChEI**: 25 mg/kg/day in males and 2.5 mg/kg/day in females based on inhibition of plasma, erythrocyte, and brain ChE in both sexes. **NOAEL:** 2.5 mg/kg/day in males and 0.5 mg/kg/day in females.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700 Developmental Toxicity-Rat	43534505 (1990) Acceptable/Guideline 24 dams/dose at 0, 3, 5, 10 mg/kg/day from GD 6-15	**Maternal Toxicity LOAEL:** 10 mg/kg/day, based on reduced body weight gain. **NOAEL:** 5 mg/kg/day **Developmental Toxicity LOAEL:** Not determined. **NOAEL:** 10 mg/kg/day Although data were not provided on clinical signs in the dams during or after dosing, no cholinergic signs were seen in neurotoxicity studies at the same dose. Therefore, the study classification is upgraded to acceptable/ guideline.
870.3700 Developmental Toxicity- Rabbit	41381111; 41381110 (1989) Acceptable/Guideline 15-16 does/dose at 0, 0.5, 1.0, 1.5, or 2.0 mg/kg/day on GD 6 through 19 41381110 (1989) 7 does/dose at 0, 1.0, 2.0, 2.5, or 5.0 mg/kg/day on GD 6 though 19	**Maternal LOAEL:** 2 mg/kg/day based on weight loss, abortion, and cholinergic clinical signs noted in the range finding study (MRID 41381110). **NOAEL:** 1.5 mg/kg/day. **Developmental toxicity LOAEL:** Not determined. **NOAEL:** 2 mg/kg/day. No developmental toxicity was observed at any dose tested in the definitive prenatal developmental toxicity study. No developmental toxicity was observed at doses up to 2.5 mg/kg in a range-finding study.
870.3800 2-Generation reproduction--Rat	41381113; 44414501 (1989) Acceptable/Guideline 25 rats/sex/dose at 0, 3, 10, 30, or 100 ppm [approx. 0.21, 0.69, 2.09, or 7.21 mg/kg/day for males, and 0, 0.25, 0.91, 2.62, or 9.32 mg/kg/day for females, respectively]	**Parental Toxicity LOAEL:** 100 ppm (equivalent to 9.32 and 7.21 mg/kg/day in females, and males, respectively) based on increased incidences of adrenal zona glomerulosa hypertrophy, centriacinar hepatocytic vacuolation and liver inflammation in F_0 females and periacinar hepatocytic hypertrophy in F_0 males. **NOAEL:** 30 ppm (equivalent to 2.6 and 2.09 mg/kg/day) in females and males, respectively). in F_0 females and in males. **Reproductive Toxicity LOAEL:** >100 ppm. **NOAEL:** 100 ppm. **Offspring Toxicity LOAEL:** 30 ppm based on decreased litter size and decreased pup weight and viability index during lactation. **NOAEL:** 10 ppm

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4300 Combined Chronic/carcino-genicity- Rat	43559703 (1990) Acceptable/Guideline 60/sex/dose at 0, 1, 10, 50, or 200 ppm (0, 0.039, 0.38, 1.94, and 8.34 mg/kg/day for males, and 0.051, 0.50, 2.45, and 11.69 mg/kg/day for females, respectively).	**Systemic LOAEL:** 50 ppm (2.45 mg/kg/day) for females, based on decreased RBC parameters (packed cell volume, hemoglobin, and RBC count), and increased incidence of atrophy and foamy interstitial cells in the ovaries and 200 ppm (8.34 mg/kg/day) for males, based on increased incidences of retinal atrophy, skeletal degenerative myopathy and non-neoplastic lesions in the adrenal and pituitary glands. **NOAEL:** 10 ppm (0.50 mg/kg/day) and 50 ppm (1.94 mg/kg/day) for female and male rats, respectively. **The test material was not carcinogenic at the doses tested**. **LOAEL for ChEI:** 10 ppm for male rats (0.38 mg/kg/day) and 1 ppm for female rats (0.051 mg/kg/day) based on inhibition of plasma and RBC ChE activity. **NOAEL**: 1 ppm for male rats (0.039 mg/kg/day) and a NOAEL was not established for female rats.
870.4200b Carcinogenicity- Mouse	43534504 (1990) Acceptable/Guideline. 60/sex/dose at 0, 10, 30, 100, or 300 ppm (1.02, 3.10, 10.32, 30.51 mg/kg/day for males; and 1.11, 3.20, 10.43, 39.17 mg/kg/day for females) for 102 weeks	**Systemic LOAEL:** 10.43 mg/kg/day (100 ppm) for females, based on increased adrenal cortico-medullary pigmentation and 30.51 mg/kg/day (300 ppm) for males, based on decreased body weights and non-neoplastic lesions in the adrenals, pituitary and kidney. At 300 ppm, increase in cholinergic signs (ataxia, hunched posture, tremors) was observed. **NOAEL:** 3.20 mg/kg/day (30 ppm) and 10.32 mg/kg/day (100 ppm) for females and males, respectively. **The test material was not carcinogenic at the doses tested**.
8700.4100 1-Year Chronic Oral Toxicity - Dog;	43534503; 43559702; 43916805 (1990) Acceptable/Guideline 5 dogs/sex/dose at 0, 0.05, 0.1, 0.5 or 5.0 mg/kg/day in gelatin capsule for up to 12 months	**Systemic LOAEL:** 0.5 mg/kg/day in males based on increased alanine aminotransferase and 5 mg/kg/day in females based on microscopic lesions in the adrenal gland. **NOAEL:** 0.1 mg/kg/day in males and 0.5 mg/kg/day in females. **LOAEL for ChEI:** 0.5 mg/kg/day based on plasma acetyl- and butyryl-cholinesterase activity in males/females. **NOAEL:** 1.0 mg/kg/day based on plasma acetyl- and butyryl-cholinesterase activity. The erythrocyte and brain ChE activity LOAELs were not observed. The erythrocyte and brain cholinesterase NOAELs are 5 mg/kg/day.
870.5265 Gene Mutation Salmonella/ mammalian activation gene mutation assay	41347633 (1989) Acceptable/Guideline	Negative for mutagenic effects at dose levels up to 5000 ug/plate with or without metabolic activation
870.5300 *In vivo* Gene Mutation - Mouse Lymphoma Assay	43534508 (1993) Acceptable/Guideline	No evidence of increased mutation frequency at the thymidine locus in cells treated up to cytotoxic concentration with or without S-9. Cytotoxicity was evident at ≥640 μg/ml (-S9) and ≥160 μg/ml (+S9).

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5375 *In vitro* Cytogenetics (CHO) Assay	41347634 (1989) Acceptable/Guideline	No effects at concentrations up to 200 ug/ml (without S9) or 750 ug/ml (with S9). Cytotoxicity was evident at ≥50 μg/ml (-S9) and ≥93.75 μg/ml (+S9).
870.5395 *In vivo* mammalian cytogenetics assay	43559704 (1990) Acceptable/Guideline	No evidence of clastogenic or aneugenic effect at doses tested. Negative for induction of micronuclei at a dose approaching oral MTD, 50 mg/kg.
870.5500 *In vitro* DNA Repair Test	41347635 (1989) Acceptable/Guideline	Negative in the DNA repair test. Fosthiazate did not induce any clear differences in the diameter of growth inhibitory zones between H17 (rec^+) and M 45 (rec^-), either in the presence or absence of metabolic activation.
870.5100 Gene Mutation Salmonella/ mammalian activation gene mutation assay with **BSA**	43534506 (1993) Acceptable/guideline	Negative in Salmonella strains with or without S-9 activation. No cytoxicity response up to the limit dose.
870.5300 *In vivo* Mammalian Gene Mutation - Mouse Lymphoma Assay with **BSA**	43534507 (1993) Acceptable/Guideline	No evidence of increased mutation frequency in cells treated up to the limit dose with or without S-9.
870.5395 *In vivo* Mammalian Cytogenetics Micronucleus Assay with **BSA**	43534509 (1994) Acceptable/Guideline	No evidence of clastogenic or aneugenic effect at doses tested. Negative for induction of micronuclei.
8700.6100 Acute Delayed Neurotoxicity (ADNT) Study- Hen	41347631 (1989) Acceptable/Guideline 18 hens received 20 mg/kg IKI-1145; 6 hen received 600 mg/kg TCOP	Six hens treated with IKI-1145 (fosthiazate technical) died within 6 days; 2 had relapses and progressed to moribundity on days 13 and 26; 9 hens survived. No abnormal neuropathological changes were observed except for a minimal case of focal gliosis in the lumbar sacral area of one of the two relapsing hens. IKI-1145 did not cause ADNT.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.6200a Acute neurotoxicity screening battery	44269907 (1997) Acceptable/Guideline Neurobehavioral group: 10/sex/dose and a cholinesterase group: 30/sex/dose at single doses of 0, 0.4, 10, or 20/40 [F/M] mg/kg by gavage.	**Neurotoxicity LOAEL:** 10 mg/kg/day based on decreased forelimb grip strength in females. No abnormal neuropathological changes were observed. **NOAEL:** 0.4 mg/kg/day. **LOAEL for ChEI:** 10 mg/kg/day based on inhibition of plasma. Erythrocyte, and brain 3 hrs postdosing (plasma ChEI was reversible). **NOAEL:** 0.4 mg/kg/day.
Special Cholinesterase Inhibition study- rat	43534502 (1994) Acceptable/Non-guideline 5/sex/dose at 0, 0.04, 0.4 or 4 mg/kg/day	**LOAEL:** 4.0 mg/kg/day based on plasma ChEI. **NOAEL:** 0.4 mg/kg/day. Decrease plasma ChE activity was noted in the male and female rats 3 hours after a single dose at 4.0 mg/kg body weight. Brain and RBC ChE activities were unaffected
870.6200b Subchronic neurotoxicity screening battery	44269908 (1997) Acceptable/Guideline 30 rats/sex/dose at doses of 0, 0.05, 0.5, or 2.5 mg/kg/day (equivalent to 0, 0.07, 0.56, and 2.4 mg/kg/day for males and 0, 0.08, 0.57, and 2.5 mg/kg/day for females for 13 weeks.	**Systemic LOAEL:** 2.5 mg/kg/day based on decreased hind limb grip strength (21%; $p<0.01$) in females. No abnormal neuropathological changes were observed. **NOAEL:** 0.5 mg/kg/day. **LOAEL for ChEI:** 0.5 mg/kg/day based on significant inhibition of plasma, erythrocyte and brain ChE in females at weeks 5 and/or 9 and 14. **NOAEL:** 0.05 mg/kg/day.
870.7485 Metabolism- Rat	43534511 (1992); 43534513 (1993); 43534515 (1993); 43534519 (1994) Unacceptable/Guideline 5/sex/dose; single unlabeled low dose or repeat dose: 2 mg/kg; single unlabeled high dose: 20 mg/kg	IKI-1145 (fosthiazate technical) was rapidly absorbed and widely distributed with only >5% detected in the tissues. No sex-related differences noted in the absorption and distribution; absorption was not dose dependent. Peak concentration in the blood was at 0.33 hr in both sexes. Only one metabolite, BESxP, represented > 10% of the administered dose. Test material was rapidly eliminated primarily in the urine (57%-72%) within 24 hrs. Unacceptable/Guideline due to lack of identification of metabolites in fecal radioactivity (accounted for 9-15% of the administered dose). Mean recovery was 95%-99%. IKI-1145 was metabolized by multiple processes including hydrolysis, oxidation, methylation and glutathione conjugation.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism- Rat;	43534510 (1992); 43534512 (1992); 43534514 (1993); 43534518 (1994) Acceptable/guideline 5/sex/dose; single low dose or repeat dose: 2 mg/kg; single high dose: 20 mg/kg; 14/sex/dose; single labeled dose: 18 mg/kg;	IKI-1145 was rapidly and extensively absorbed independent of dose; rapidly metabolized and excreted in the urine (>65%), expired air (>10%) and in feces (<9%). Elimination was biphasic with first phase elimination half-life (t1/2) of 5-6 hrs and second phase of 85-112 hrs. Metabolism and excretion was rapid within 24 hrs. IKI-1145 was metabolized by multiple processes including hydrolysis, oxidation, methylation and glutathione conjugation. Female rats tended to excrete a metabolite containing a methylsulfinylethyl group while male rats excreted more containing a sulfoethyl group.
870.7485 Metabolism- Rat with **BSA**	43534516 (1993); 43534517 (1994) Acceptable/Guideline 1-2 males/dose; single iv or oral dose- 10 mg/kg	Recovery was 100-108%. BSA was rapidly eliminated unchanged following dosing via the iv (approx. 100% in the urine) or oral (63%-89% in the urine and 10%-28% in feces) routes. Tissue burden was low.

3.2 FQPA Considerations

Since there is evidence of increased susceptibility of the young following pre-and post-natal exposure to fosthiazate in the rat reproduction study, HIARC performed a Degree of Concern Analysis to: 1) determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. When residual uncertainties are identified, HIARC examines whether these residual uncertainties can be addressed by a special FQPA safety factor and, if so, the size of the factor needed.

In a 2-generation reproduction study, there is qualitative and quantitative evidence of increased susceptibility in offspring following pre- and post-natal exposure to fosthiazate since the effects on pups are considered to be severe and occurred at a lower dose than those on parental animals. In determining the degree of concern for these findings in the reproduction study, HIARC considered the overall quality of the study; the dose levels at which the pup effects were observed; the dose response of the pup effects; and the comparative severity of the effects seen. The majority of the HIARC agreed that there is a low degree of concern and no residual uncertainties for the susceptibility since: 1) the study was well conducted; 2) the dose-response in the offspring is well characterized; 3) clear NOAEL and LOAEL were established for the effects on the offspring; 4) although the decrease in pup survival seen at the LOAEL is severe, this could be attributed to exposure to higher levels of the chemical since the mortalities occurred during early lactation; and 5) although cholinesterase activity was not measured in this study, cholinergic signs and cholinesterase inhibition were seen at comparable doses in other studies and thus could have been a cause for the pup mortality.

The HIARC determined that the special FQPA Safety Factor can be reduced to 1X because: 1) there is no evidence (qualitative or quantitative) of increased susceptibility following *in utero* exposure to rats or rabbits and 2) there are no residual uncertainties for the effects seen in the reproduction study (see above).

Based on the weight of evidence presented, the HIARC concluded that a DNT study with comparative ChE measurements in adults and pups is required for fosthiazate. The available data base confirms that fosthiazate is a ChE inhibitor and the increased sensitivity for this effect can not be confirmed until the results of DNT study are known.

Based on the lack of a DNT study, the HIARC also concluded that a Database Uncertainty Factor (UF_{DB}) is necessary (*FOSTHIAZATE - 3rd Report of the Hazard Identification Assessment Review Committee. Anna Lowit. November 12, 2002*). The available data suggest that results of a DNT study could potentially impact the doses selected for risk assessment.

> A **UF_{DB} of 10x** is required for acute dietary risk assessment
> and a **UF_{DB} of 3x** is required for chronic dietary risk assessment.

The regulatory dose level for acute dietary risk assessment is the NOAEL of 0.4 mg/kg/day selected from the acute neurotoxicity study in adult rats (MRID# 44269907; see below). The regulatory dose level for chronic dietary risk assessment is the NOAEL of 0.05 mg/kg/day from the 2-year chronic/carcinogenicity toxicity study in rats (MRID# 43559703; see below). The dose levels in the reproductive toxicity study are estimated to be 0, 0.21, 0.69, 2.09, and 7.21 mg/kg/day. The offspring NOAEL and LOAEL are 0.69 mg/kg/day and 2.09 mg/kg/day, respectively, based on decreased pup weight, viability index, and litter size in the F_1 pups.

It can be assumed that doses used in a DNT study may be similar to those used in the reproductive toxicity study. ChEI has been shown to the be the most sensitive endpoint for fosthiazate in adults; it can also be assumed that ChEI may potentially be the most sensitive endpoint for pups.

The acute ChE NOAEL for pups may be lower than the established offspring NOAEL of 0.69 mg/kg/day and could be as low as 0.02 mg/kg/day (ie., 10x lower than the lowest dose in the reproductive toxicity study). In the absence of ChE data to compare the relative sensitivity of pups and adults to acute fosthiazate exposure, it is prudent to assume that the potential acute ChE NOAEL from a DNT study may be lower than the NOAEL of 0.4 mg/kg/day currently used for establishing the acute RfD. *Therefore, a 10x* UF_{DB} *is required for acute dietary risk assessment.*

The multi-dosing ChE NOAEL for pups may be lower than the established chronic ChE NOAEL of 0.05 mg/kg/day from the 2-year chronic/carcinogenicity study and could be as low as 0.02 mg/kg/day (ie., 10x lower than the lowest dose in the reproductive toxicity study). In the absence of ChE data to compare the relative sensitivity of pups and adults to exposure to fosthiazate, it is prudent to assume that the potential multi-dosing ChE NOAEL from a DNT study may be lower

than the established chronic ChE NOAEL. As opposed to a 10X, a 3X factor is considered adequate for chronic dietary risk assessment, because, the 0.05 mg/kg/day NOAEL currently used for risk assessment is approximately 3x higher than the potential lower NOAEL (0.02 mg/kg/day) that could be attained in the DNT. *Therefore, a 3x UF_{DB} is required for chronic dietary risk assessment.*

The dietary food exposure assessment is conservative, using field trial level residues and assuming 100% CT. Dietary drinking water exposure is based on conservative modeling estimates and there are no residential uses. These assessments will not underestimate the exposure and risks posed by fosthiazate.

Table 3: Summary of FQPA Safety Factors for Fosthiazate

	LOAEL to NOAEL (UF_L)	Subchronic to Chronic (UF_S)	Incomplete Database (UF_{DB})	Special FQPA Safety Factor (Hazard and Exposure)
Magnitude of Factor	1X	1X	**10X acute & 3X chronic**	**1X**
Rationale for the Factor	No LOAEL to NOAEL extrapolations performed	No subchronic to Chronic extrapolations performed	**For the lack of a Developmental Neurotoxicity Study and Comparative Cholinesterase Measures (adult/young).**	**No residual concerns regarding pre- or post-natal toxicity or completeness of the toxicity or exposure databases**
Endpoints to which the Factor is Applied	Not Applicable	Not Applicable	**All Dietary and Residential (when applicable) Non-Dietary exposure assessments. 10X for acute dietary & 3X for chronic dietary.**	**Not Applicable**

3.3 Dose Response Assessment

On April 23, 2002, HED's HIARC reviewed the recommendations of the toxicology reviewer for fosthiazate with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to fosthiazate was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in the report (*FOSTHIAZATE - 2nd Report of the Hazard Identification Assessment Review Committee. Sanju Diwan & Anna Lowit. August 20, 2002*). This report represents error-corrections to the previous HIARC report for fosthiazate (*Fosthiazate - 1st Report of the Hazard Identification Assessment Review Committee. Sanjivani Diwan. April 23, 2002*). A follow-up meeting on October 29, 2002 specifically to address the UF_{DB} resulted in changes to the prior two reports (*FOSTHIAZATE - 3rd Report of the Hazard Identification Assessment Review Committee. Anna Lowit. November 12, 2002*).

Acute Dietary

The acute reference dose (aRfD) of 0.0004 mg/kg/day is based on an acute oral neurotoxicity study in rats, and is calculated as the No-Observed-Adverse-Effect-Level (NOAEL) of 0.4 mg/kg/day divided by the total uncertainty factor of 1000X (10X for interspecies extrapolation, 10X for intraspecies variability, and an additional UF_{DB} of 10X for the lack of a DNT study). The acute endpoint is based on a significant decrease in plasma and brain ChE inhibition (ChEI) seen at the Lowest-Observed-Adverse-Effect-Level (LOAEL) of 10 mg/kg/day, as well as decreased forelimb grip strength in females. Since the hazard- and exposure-based special FQPA safety factor is reduced to 1X, the aRfD is equal to the acute population adjusted dose, or aPAD. The PAD is a modification of the acute or chronic RfD to accommodate the special FQPA safety factor, and is calculated as the RfD divided by the special FQPA safety factor. This dose is appropriate since the effects seen were observed three hours post-dosing following administration of a single dose, and is supported by the special acute ChE study.

Chronic Dietary

The chronic RfD of 0.00017 mg/kg/day is based on a chronic oral toxicity study in rats, and is calculated as the NOAEL of 0.05 mg/kg/day divided by the total uncertainty factor of 300X (10X for interspecies extrapolation, 10X for intraspecies variability, and an additional UF_{DB} of 3X for the lack of a DNT study). The chronic endpoint is based on the inhibition of plasma and RBC ChE activity seen at the LOAEL of 0.38 mg/kg/day in males. Again, since the hazard- and exposure-based special FQPA safety factor is reduced to 1X, the cRfD is equal to the cPAD. This study is appropriate for chronic risk assessment since the effects were seen after chronic feeding of the test material. The NOAEL for ChEI in rats is supported by the NOAEL in the rat subchronic neurotoxicity study.

Short- and Intermediate-Term Dermal

The short- and intermediate-term dermal endpoint is based on a 21-day dermal toxicity study in the rat. The NOAEL of 0.5 mg/kg/day in females is based on inhibition of plasma, RBC, and brain ChE seen at the LOAEL of 2.5 mg/kg/day in females. This study and dose are appropriate since the exposure duration and route are compatible, and the effects of concern are ChEI.

Long-term Dermal

The long-term dermal endpoint is based on a two year chronic/carcinogenicity study in the rat. The oral NOAEL of 0.05 mg/kg/day is based on inhibition of plasma and RBC ChE activity seen at the LOAEL of 0.38 mg/kg/day. The study is appropriate since the effects were seen after chronic feeding of the test material. The NOAEL for ChEI in rats is supported by the NOAEL in the rat subchronic neurotoxicity study. Because an oral endpoint is used, the dermal absorption factor of 20% should be applied.

Dermal Absorption

A dermal absorption study is not available. A dermal absorption factor of 20% was estimated using the LOAEL of 2.5 mg/kg/day for female rats in the 21-day dermal toxicity study and the LOAEL of 0.5 mg/kg/day for female rats in an oral four-week dietary range-finding study. Both studies have the same endpoint: inhibition of plasma, RBC, and brain ChE.

Short-term Inhalation

The short-term inhalation endpoint is based on a four-week range-finding study in the rat. The oral NOAEL of 0.10 mg/kg/day is based on decreased plasma butyryl- and acetyl-ChE, and brain acetyl-ChE in females, as well as decreased erythrocyte acetyl-ChE in males seen at the LOAEL of 0.5 mg/kg/day. The duration and dose are appropriate since the effects were observed four weeks post-treatment. Because an oral endpoint is used, the default inhalation absorption factor of 100% should be applied.

Intermediate-term Inhalation

The intermediate-term inhalation endpoint is based on a three month subchronic neurotoxicity study in rats. The NOAEL of 0.05 mg/kg/day is based on plasma, RBC, and brain ChEI in female rats, seen at the LOAEL of 0.5 mg/kg/day. The dose is appropriate since the effects of concern were observed after nine weeks of subchronic administration of the test material. Because an oral endpoint is used, the default inhalation absorption factor of 100% should be applied.

Long-term Inhalation

The long-term inhalation endpoint is based on the two-year chronic/carcinogenicity study in the rat. The oral NOAEL of 0.05 mg/kg/day is based on inhibition of plasma and RBC ChE activity seen at the LOAEL of 0.38 mg/kg/day. The study is appropriate since the effects were seen after chronic feeding of the test material. The NOAEL for ChEI in rats is supported by the NOAEL in the rat subchronic neurotoxicity study. Because an oral endpoint is used, the default inhalation absorption factor of 100% should be applied.

Target MOE for Occupational Exposure

A target MOE (NOAEL/exposure) is the level above which the Agency does not have a risk concern. For fosthiazate, a target MOE of 100 is considered adequate for occupational exposure to workers. The target MOE of 100 includes the 10X interspecies extrapolation factor and the 10X intraspecies variability factor. A target MOE of 100 is also appropriate for aggregate (dermal and inhalation) occupational exposure.

Table 4: Summary of Toxicological Doses and Endpoints for Fosthiazate for Use in Human Risk Assessment

Exposure Scenario	Dose (mg/kg/day) UF /MOE	Hazard and Exposure Based Special FQPA Safety Factor	Study and Toxicological Effects
Dietary Risk Assessments			
Acute Dietary general population including infants and children	NOAEL = 0.4 UF = 100 UF_{DB}* = 10	1x	Acute Oral Neurotoxicity / Rat LOAEL = 10 mg/kg/day based on inhibition of RBC ChE in males within 3 hrs post dosing
	Acute RfD and Acute PAD = 0.0004 mg/kg/day		
Chronic Dietary	NOAEL = 0.05 UF = 100 UF_{DB}* = 3	1x	Chronic Oral Toxicity / Rat LOAEL= 0.38 mg/kg/day based on inhibition of plasma and RBC ChE in males
	Chronic RfD and Chronic PAD = 0.00017 mg/kg/day		
Non-Dietary (Occupational) Risk Assessments			
Dermal Short-Term (1 - 30 days)	Dermal NOAEL =0.5 MOE=100	N/A	21-Day Dermal Toxicity/Rat LOAEL= 2.5 mg/kg/day based on inhibition of plasma, erythrocyte, and brain ChE in females
Dermal Intermediate-Term (1 - 6 Months)	Dermal NOAEL= 0.5 MOE=100	N/A	21-Day Dermal Toxicity/Rat LOAEL= 2.5 mg/kg/day based on inhibition of plasma, erythrocyte, and brain ChE in females
Dermal[1] Long-Term (> 6 Months)	Oral NOAEL= 0.05 MOE = 100	N/A	Chronic Oral Toxicity / Rat LOAEL= 0.38 mg/kg/day based on inhibition of plasma and RBC ChE in males
Inhalation[2] Short-Term (1 - 30 days)	Oral NOAEL= 0.10 MOE=100	N/A	4-Wk. Range-finding Subchronic Toxicity Study/Rat LOAEL = 0.5 mg/kg/day based on inhibition of plasma, RBC and brain ChE
Inhalation Intermediate-Term (1 - 6 Months)	Oral NOAEL= 0.05 MOE=100	N/A	90-Day Subchronic Neurotoxicity LOAEL = 0.5 mg/kg/day based on inhibition of plasma, RBC and brain ChE in females
Inhalation Long-Term (>6 Months)	Oral NOAEL=0.05 MOE=100	N/A	Chronic Oral Toxicity / Rat LOAEL = 0.38 mg/kg/day mg/kg/day based on inhibition of plasma and RBC ChE

1. Since an oral NOAEL was selected, a dermal absorption factor of 20% should be used in route-to-route extrapolation.
2. Absorption via the inhalation route is assumed to be equivalent to oral absorption.

MOE= For occupational exposure only; there are no residential exposures.

* UF_{DB} = database uncertainty factors of 10X & 3X are applied for lack of a DNT study

3.4 Endocrine Disruption

There is evidence of possible endocrine effects from exposure to fosthiazate in currently reviewed studies in which adrenal or pituitary effects were seen. EPA is required under the Federal Food,

Drug, and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, fosthiazate may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Exposure Assessment and Characterization

4.1 Summary of Registered Uses

Fosthiazate is a new OP a.i. that does not presently have any registered uses. The registrant, ISK Biosciences Corporation, is proposing registration for domestic use on tomatoes (as a methyl bromide replacement) to protect against a broad spectrum of nematode pest species. Pest species include, but are not limited to, the following: root-knot nematodes, root lesion nematodes, stubby root nematodes, stunt nematodes, ring nematodes, sheath nematodes, spiral nematodes, and sting nematodes. Although the registrant has proposed tolerances in/on bananas, coffee, potatoes and peanuts as well, these uses are not being included in this assessment, as bananas, coffee and potatoes have detectable residues in submitted field trial studies and peanuts have numerous data gaps at this time (*PP#6F4773, PP#6F4701, PP#6F04755, PP#6F04701, and PP# 6F04662. REVISED Registration for Fosthiazate use in/on Imported Banana and Coffee, and Section 3 Registration for Fosthiazate use in/on Peanut, Potato, and Tomato. Sherrie Kinard. June 26, 2003*). The results of the OP cumulative risk assessment conducted by the Agency do not permit the inclusion of any additional OP residues from any source.

Fosthiazate is formulated as an emulsifiable concentrate (75% a.i. and 47.2% a.i.). Application is as a ground-directed spray, either through drip (trickle) irrigation or by ground equipment. Aerial application is specifically prohibited on the labels. Fosthiazate must be soil-incorporated to a depth of four inches immediately after application. One application may be made either prior to or at planting/transplanting, and the maximum labeled application rate is 4.5 lbs. a.i./acre (tomato). Since the majority of field trials were conducted at the lower rate of 4.0 lbs ai/acre, the

registrant needs to lower the labeled rate or submit data in support of the 4.5 lbs. a.i./acre rate.

Based on the use pattern, occupational handlers are expected to have short-term (one to 30 days) and potentially intermediate-term (one to six months) exposure. Residential exposure was not assessed, as there are no current or proposed residential uses of fosthiazate.

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

The petitioner, ISK Biosciences Corporation, has submitted petitions for the establishment of permanent tolerances without U.S. registrations (imported commodities) for residues of the nematocide fosthiazate [O-ethyl S-(1-methylpropyl)(2-oxo-3-thiazolidinyl) phosphonothioate] and its metabolite, O-ethyl S-(1-methylpropyl)[2-(methylsulfonyl) ethyl] phosphoramidothioate (ASC-67131 or SDS-67131) in/on the raw agricultural commodity banana at 0.05 ppm, and in/on coffee at 0.05 ppm; the petitioner is also proposing the establishment of permanent tolerances (domestic uses) for the combined residues of fosthiazate and its metabolite, ASC-67131 in/on the raw agricultural commodities peanut nutmeats at 0.02 ppm and in/on peanut hay at 0.02 ppm, in/on potato at 0.03 ppm, and in/on tomato at 0.02 ppm.

The submitted metabolism studies on potatoes, tomatoes, and peaches are adequate. These data were presented to the HED MARC on July 10, 2002, which concluded that the parent and the metabolite ASC-67131 are the residues of concern for tolerance expression in plants [*Fosthaizate; Health Effects Division (HED) Metabolism Assessment Review Committee (MARC) Decision Document. Sherrie Kinard. August 27, 2002*].

The GC/FPD (phosphorus) method described for data collection on fosthiazate and ASC-67131 has undergone independent laboratory validation, radiovalidation, and has been determined to be adequate for data collection. The Agency has completed a successful Petition Method Validation (PMV) and has also concluded that the method is acceptable as an enforcement method for determining residues of fosthiazate and ASC-67131 in/on banana, coffee, peanut and peanut processed commodities, potato and potato processed commodities, and tomato and tomato processed commodities.

The previously submitted multiresidue method (MRM) testing for fosthiazate and its metabolite ASC-67131 have been reviewed and forwarded to FDA for publication in PAM Vol. I, Appendix 1. The 10/99 FDA PESTDATA database (PAM Volume I, Appendix I) indicates that fosthiazate and ASC-67131 are completely recovered (>80%) using Multiresidue Method Section 302 (Luke Method; Protocol D) and not recovered using Sections 303 (Mills, Onley, Gaither; Protocol E - nonfatty foods) and 304 (Mills; Protocol E - fatty foods).

The submitted banana, coffee and potato field trial data demonstrate that there are detectable residues of fosthiazate in/on banana, coffee, and potato commodities at < 1x the proposed

application rates. The submitted banana field trial data reflecting a single application at 2 g/mat represent an insufficient rate with respect to the proposed use and reflect maximum combined residues of < 0.04 ppm for fosthiazate and its metabolite ASC-67131 in/on whole bananas. The coffee bean field trials conducted in Brazil showed combined residues of < 0.04 ppm for fosthiazate and its metabolite ASC-67131 using the maximum proposed application rate. The submitted potato field trial data indicate that maximum combined residues in/on treated potato samples at 0.88x the maximum application rate were <0.04 ppm for fosthiazate and its metabolite ASC-67131.

The submitted peanut field trial data are insufficient to support the proposed use. The submitted data represent application rates of 1, 1.5, and 3x the proposed rate and show residues levels at < LOQ for fosthiazate and its metabolite ASC-67131 in/on all peanut nutmeat samples. Additional studies depicting residues in/on peanut hay following a 1x broadcast application are required from Region 2 (2 trials), Region 3 (1 trial), and Region 8 (1 trial).

The submitted tomato field trial data are adequate reflecting 1.3x the maximum proposed use pattern of fosthiazate on tomatoes and residues <0.01 ppm for each analyte in/on all treated tomato samples. The tomato processing study is also adequate and demonstrates that residues of fosthiazate and ASC-67131 did not significantly concentrate in puree (concentration factors of 1.2-1.3x), catsup (reduction factor of < 0.6x), juice (< 0.4x), or wet pomace (< 0.7-0.8x) processed from tomatoes treated at 9x and bearing quantifiable residues.

The Agency has determined that the residue data are adequate to support a permanent tolerance for the combined residues of fosthiazate and its metabolite ASC-67131 in/on tomato. This tolerance is conditional pending the data deficiencies being addressed. The Agency has also determined that the residue data are inadequate to support the permanent tolerances for the combined residues of fosthiazate and its metabolite ASC-67131 in/on peanut nutmeats and peanut hay. The Agency has also determined that the addition of any potential residues of an OP could or would pose a cumulative OP risk above the Agency's level of concern. Detectable residues at or above the LOQ were found in the banana, coffee and potato field trial data; therefore, peanuts as well as bananas, coffee and potatoes were not included in the dietary risk assessment. (*PP#6F4773, PP#6F4701, PP#6F04755, PP#6F04701, and PP# 6F04662. REVISED Registration for Fosthiazate use in/on Imported Banana and Coffee, and Section 3 Registration for Fosthiazate use in/on Peanut, Potato, and Tomato. Sherrie Kinard. June 26, 2003*).

There are currently no established Codex, Canadian, or Mexican maximum residue limits (MRLs) for residues of fosthiazate in/on plant or livestock commodities. Therefore, no compatibility issues exist with regard to the proposed U.S. tolerances discussed in this petition review.

4.2.2 Dietary Exposure

Fosthiazate acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™) software Version 1.3, which incorporates

consumption data from USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1994-96 and 1998. The 1998 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive days, and therefore represent more than 30,000 unique "person days" of data. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g., apples, peeled fruit-cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publically available recipe translation files developed jointly by USDA/ARS and EPA. Consumption data are averaged for the entire US population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment (*Fosthiazate. Acute and Chronic Dietary Exposure Assessments for the Section 3 Registration Action for Fosthiazate Use on Tomato. Sherrie Kinard. November 15, 2002*).

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., tomato or tomato paste) on the commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total estimated exposure. Exposure estimates are expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic exposure assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., those who reported eating relevant commodities/ food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis.

4.2.2.1 Acute Dietary

The acute dietary risk assessment was based on field trial residues in tomato (½ LOQ parent + ½ LOQ ASC-67131) and 100% CT. Risks of concern were considered at the 95th percentile because field trial data and 100% CT were used, which are considered conservative inputs. Acute dietary risk estimates are not a risk of concern (concern at $\geq$ 100% aPAD) for the general U.S. population and all population subgroups; highest exposed population subgroup is children 1-2 years of age (29%). See Table 5.

4.2.2.2 Chronic Dietary

The chronic dietary risk assessment was based on field trial residues in tomatoes, 100% CT, and average daily consumption estimates for each food/food form. Chronic dietary risk estimates are not a risk of concern for the general US population and all the population subgroups; children 1-2 years of age are the most exposed population subgroup (15% cPAD).

Table 5: Summary of Dietary Exposure Estimates for Fosthiazate in Tomatoes

Population Subgroup	Acute Dietary		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD at 95th %ile	Dietary Exposure (mg/kg/day)	% cPAD
U.S. Population (total)	0.000050	12	0.000011	7
All Infants (< 1 year)	0.000042	11	0.000006	4
Children 1-2 years	0.000117	29	0.000025	15
Children 3-5 years	0.000102	26	0.000023	13
Children 6-12 years	0.000073	18	0.000016	9
Youth 13-19 years	0.000050	13	0.000011	7
Adults 20-49 years	0.000041	10	0.000010	6
Adults 50+ years	0.000036	9	0.000008	5
Females 13-49 years	0.000039	10	0.000009	6

4.2.2.3 Cancer Dietary

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July 1999), the HIARC has classified fosthiazate as "Not likely to be carcinogenic to humans." This classification is based on the lack of evidence for carcinogenicity in studies with mice and rats. Therefore, a cancer dietary assessment has not been conducted.

4.3 Water Exposure/Risk Pathway

Based on laboratory studies, fosthiazate is expected to degrade slowly in the environment, with the major routes of dissipation being aerobic soil and anaerobic aquatic soil metabolisms with half-lives of approximately 45 and 37 days, respectively. Under alkaline conditions, fosthiazate may also dissipate quite rapidly via hydrolysis with a half-life of less than 1 week. Photo-degradation in water is not significant (*Tier 1 Estimated Drinking Water Concentrations of Fosthiazate. Thuy Nguyen. May 20, 2002*).

Although mobile in all soils tested under laboratory conditions, in the field fosthiazate residues were seen to remain mostly on the surface soils. Insignificant amounts of residues (< 10% of total applied) were found in the deeper 15-30 cm. soil layers, and no residues in soil below the 30 cm. layer. The half-lives of fosthiazate in the terrestrial field dissipation studies are between 10 - 17 days.

The major laboratory soil degradates, MBS (methyl sec-butyl sulfone) and BSA (2-butane sulfonic acid) were found in the field at concentrations less than 5% of the total applied and in the

surface soil layer only. Laboratory studies are not available to determine the level of toxicological concern of these degradates to the environment. HED's Metabolism Assessment Review Committee (MARC) has determined that, of the residues found in soil and water, only the parent compound is of toxicological concern. See *Fosthaizate; Health Effects Division (HED) Metabolism Assessment Review Committee (MARC) Decision Document. Sherrie Kinard. August 27, 2002.*

Estimated Drinking Water Concentrations (EDWCs) of Fosthiazate

A Tier 2 surface water assessment on tomatoes has been conducted for fosthiazate using PRZM-EXAMS, assuming a maximum application rate of 4.5 lbs ai/acre, and incorporating a percent cropped area (PCA) factor of 87% for tomatoes (*Tier 2 Estimated Drinking Water and Environmental Concentrations of Fosthiazate Use on Tomatoes. James K. Wolf. June 24, 2002*). The PCA factor is a generic adjustment that represents the maximum percent of any watershed that is planted to the crop being modeled and, thus, may potentially be treated with the pesticide in question. EDWC values for surface water are calculated to be 41 µg/L (acute) and 15 µg/L (chronic).

A Tier 1 groundwater assessment has been conducted for fosthiazate using SCI-GROW. Assumptions include the maximum application rate of 4.5 lbs ai/acre, and one application per year. SCI-GROW estimates likely groundwater concentrations if the pesticide is used at the maximum allowable rate in areas where groundwater is exceptionally vulnerable to contamination. In most cases, a large majority of the use area will have groundwater that is less vulnerable to contamination than the areas used to derive the SCI-GROW estimates. The EDWC value for groundwater is 7 µg/L (acute and chronic).

It should be noted that the default PCA value of 87% for tomatoes is most likely a high estimate; therefore, results may be conservative. Other conservative factors that contribute to the water assessments are 1) lacking data, it was assumed that fosthiazate is relatively stable in water, and 2) submitted adsorption/desorption studies in three different types of soil measured Kd values (coefficient of adsorption/desorption) that ranged from 0.43 - 1.71. The lowest value (0.43) was used in the EDWC estimation though, in some cases the mobility of fosthiazate from source to water may be up to three times lower.

The application of fosthiazate by chemigation (drip irrigation) under plastic and by shank injection were also considered as a potential "best case" scenario. Using either of these two methods of application, EFED believes would result in less run-off to streams and that surface water concentrations would be reduced. See EFED's *Fosthiazate Section 3 for Tomatoes Amendment 2 to the Previous Review. Thuy Nguyen. July 7, 2003.* In the initial *Fosthiazate Section 3 for Tomatoes Amendment to the Previous Review. Henry Craven. February 27, 2003*, EFED stated that the peak EDWC for drip irrigation under a plastic mulch would be less than 17 *u*g/L for a 1.5 lb ai/A application rate and 9 *u*g/L for a 1 lb ai/A rate, however EFED was not able to accurately quantify the amount. A further review of these methods of application led EFED to believe that

runoff as a result of this use may be unlikely from the day of application until the day of harvest (approximately 90 days) while the field is covered by the plastic mulch, unless an extremely heavy amount of rain falls immediately after application and causes runoff from under the mulch into the uncovered area. At this time, EFED is unable to predict and model such runoff due to lack of in-depth information on plastic mulch practices. Runoff after the removal of the plastic cover may be possible, however the amount of fosthiazate remaining in soil and available for runoff would be much less than the amount applied, due to chemical degradation and dissipation in soil, and to chemical uptake into plants. Assuming that half of the amount of fosthiazate applied is absorbed by plants and the remaining half dissipates in the soil within 45 days (based on laboratory and field studies), EFED expects that only about one eighth of what was originally applied would be available for runoff after the cover is removed (~ 90 days post application). Therefore, EFED predicts that the peak EDWC would be roughly **2.1 *u*g/L** for a 1.5 lb ai/acre application rate and **1.1 *u*g/L** for 1 lb ai/acre rate. Note that these concentrations were modeled under the most conservative scenarios and may likely exceed the actual level of contamination in the environment, unless there is excessive rain fall immediately following application, as stated above.

In its initial assessment, EFED performed a SCI-GROW estimation at 4.5 lbs ai/acre/season for broadcast application, which resulted in an EDWC of 7 *u*g/L. EFED is now estimating the ground water concentration at the proposed rate of 1.0 - 1.5 lb ai/acre/season using drip irrigation, resulting in EDWCs of **1.6** and **2.4 *u*g/L**, respectively. SCI–GROW assumes the pesticide is applied above ground and subsequent rainfall leaches some of the pesticide down to groundwater. Shank injection places all of the material slightly closer to the water table where degradation may be slower than at the surface. EFED believes that in all likelihood, drip irrigation under plastic will result in less pesticide reaching ground water then shank injection. This hypothesis is based on the assumption that more rainfall is conveyed off a field where plastic sheeting is used then in a field where plastic is not used. Regardless of the uncertainty, the modeled EDWC is considered upper bound.

Drinking Water Levels of Comparison (DWLOCs)

In the absence of chemical-specific monitoring data, the Agency uses drinking water levels of comparison to calculate aggregate risk. A drinking water level of comparison, or a DWLOC, is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. In other words, the DWLOC value represents the maximum theoretical exposure a person may have to pesticide residues through drinking water, after their exposure to the pesticide's residues through food and residential exposure have been taken into consideration. The Office of Pesticide Programs uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. DWLOC values are not regulatory standards for drinking water; however, they do have an indirect regulatory impact through aggregate exposure and risk assessments.

DWLOCs are calculated for each type of risk assessment as appropriate (acute, short-term,

intermediate-term, chronic, and cancer) and compared to the appropriate estimated concentration of a pesticide in surface and ground water, as provided by EFED. If the DWLOC is greater than the estimated surface and ground water concentration, (i.e., if the DWLOC > EDWC), the Agency concludes with reasonable certainty there is no drinking water risk of concern.

A summary of aggregate exposure and risk, including DWLOC calculations, may be found in Section 5.1.2 of this document.

4.4 Residential Exposure/Risk Pathway

4.4.1 Home and Recreational Uses

The registrant is not supporting any uses of fosthiazate in or around the home, around public buildings or recreational areas, or on rights-of-way. Therefore, the Agency did not include non-agricultural or residential exposures in its risk assessment.

4.4.2 Non-Occupational Off-Target Exposure (Spray Drift)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from groundboom application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation, and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

4.4.3 Other

The Agency's current approach for completing residential exposure assessments (when applicable) is based on the guidance provided in the *Draft: Series 875-Occupational and Residential Exposure Test Guidelines, Group B-Postapplication Exposure Monitoring Test Guidelines*, the *Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment*, and the *Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment* presented at the September 1999 meeting of the FIFRA Scientific Advisory Panel (SAP). The Agency is, however, currently in the process of revising its guidance for completing these types of assessments. Modifications to this assessment shall be incorporated as updated guidance becomes available. This will include expanding the scope of the

residential exposure assessments by developing guidance for characterizing exposures from other sources not already addressed, such as from spray drift; residential residue track-in; exposures to farm worker children; and exposures to children in schools.

4.5 Incidents Reports

Since fosthiazate is a new chemical and therefore, currently has no registered uses, an incident report was not generated.

5.0 Aggregate Risk Assessments and Risk Characterizations

The Food Quality Protection Act amendments to the Federal Food, Drug, and Cosmetic Act [FFDCA, Section 408(b)(2)(A)(ii)] require for establishing a pesticide tolerance "that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there is reliable information." Aggregate exposure will typically include exposures from food, drinking water, and residential uses of a pesticide. Aggregate risk assessments are conducted for acute (one day), short-term (one to 30 days), intermediate-term (one to six months), and chronic (lifetime) exposure. An acute aggregate risk assessment does not include residential exposure. Occupational exposure is not considered in any aggregate exposure assessment.

5.1 Acute Risk

5.1.1 Aggregate Acute Risk Assessment

The acute aggregate risk estimate to fosthiazate addresses exposure from food and drinking water. Fosthiazate has no registered residential uses; therefore, residential uses are not included in the aggregate assessment for fosthiazate.

Acute dietary food risks alone are below the Agency's level of concern. The % aPAD for the highest exposed population subgroup, children 1-2 years of age, is 29%, leaving 71% available for exposure through drinking water. However, the acute surface water EDWCs, resulting from groundboom applications, are potentially of concern based on exposure to water alone (i.e. > 100% aPAD). The estimated concentration in groundwater is also above HED's level of concern (> DWLOC) for exposure to fosthiazate in drinking water as a contribution to acute aggregate risk. It should be noted that these modeled estimates are likely conservative based on: the default PCA value of 87% for tomatoes is most likely a high estimate; it was assumed that fosthiazate is relatively stable in water; and the lowest Kd value (0.43) was used in the EDWC estimation resulting in a high estimation of mobility of fosthiazate from source to water (see EFED chapter). However, concentrations of fosthiazate in drinking water following applications by chemigation under plastic or by shank injection at 1.0 and 1.5 lbs ai/acre are lower and result in reduced aggregate risks.

5.1.2 Acute DWLOC Calculations

As show in Table 6, EFED's surface and ground water EDWCs at 4.5 lbs ai/acre by groundboom are above the Agency's back-calculated DWLOC values for the parent compound. The Agency concludes that acute aggregate risk estimates may be of concern for this application method and rate, based on conservatively modeled EDWCs.

The estimates surface water EDWCs following applications by chemigation under plastic sheeting or by shank injection, by the very nature of the application method, run-off or drift to bodies of water are expected to be greatly reduced and the resulting acute aggregate risks are potentially low or not of concern. Using the lower application rates, EFED estimated that the ground water EEC is 2.4 µg/L. When compared to the calculated acute DWLOCs, there are no exceedences and therefore, the potential acute aggregate risks are not of concern.

Table 6. Acute DWLOC Calculations

Population Subgroup[1]	Acute Scenario					
	aPAD mg/kg/d	Acute Food Exp mg/kg/day	Max Acute Water Exp mg/kg/day[2]	Ground Water EDWC µg/L[3] (4.5/1.5/1.0 lbs ai)	Surface Water EDWC µg/L[3] (4.5/1.5/1.0 lbs ai)	Acute DWLOC µg/L[4]
U.S. Population	0.0004	0.000050	0.00035	7/2.4/1.6	41/2.1/1.1	12
Infants <1 year	0.0004	0.000042	0.00036	7/2.4/1.6	41/2.1/1.1	4
Children 1-2 yrs	0.0004	0.00012	0.00028	7/2.4/1.6	41/2.1/1.1	3
Females 13-49	0.0004	0.000039	0.00036	7/2.4/1.6	41/2.1/1.1	11

[1] Population subgroups are representative of those with the highest dietary exposure values. Standard body weights and water consumption values are as follows: 70 kg/2L per day (adult male/general population); 60 kg/2L per day (adult female); 10 kg/1L per day (child).
[2] Maximum acute water exposure (mg/kg/day) = [(acute PAD (mg/kg/day) - acute food exposure (mg/kg/day)]
[3] EDWC values are modeled for tomato (crop with the maximum application rate).
[4] Acute DWLOC(µg/L) = $\frac{\text{[maximum acute water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$

5.2 Short- and Intermediate-Term Risk

5.2.1 Aggregate Short- and Intermediate-Term Risk Assessment

A short- and intermediate-term aggregate risk assessment considers potential exposure from food, drinking water, and short-/intermediate-term, non-occupational (residential) pathways of exposure. Fosthiazate has no currently registered or proposed residential uses; therefore, neither a short- nor intermediate-term aggregate risk assessments are required.

5.3 Chronic Risk

5.3.1 Aggregate Chronic Risk Assessment

The chronic aggregate risk estimate to fosthiazate addresses exposure from food, drinking water, and non-occupational (residential) pathways of exposure. Again, fosthiazate has no current or proposed registered residential uses; therefore, residential uses are not included in the aggregate assessment for fosthiazate.

Chronic dietary food risks are below the Agency's level of concern. The % cPAD for the highest exposed population subgroup, children 1-2 years of age, is 15%, leaving 85% for exposure through drinking water. The estimated chronic concentrations in surface and ground water following groundboom applications at 4.5 lbs ai/acre are above HED's level of concern for exposure to fosthiazate in drinking water as a contribution to chronic aggregate risk. However, concentrations of fosthiazate in drinking water following applications by chemigation under plastic or by shank injection at 1.5 lbs ai/acre are lower and result in reduced aggregate risks.

5.3.2 Chronic DWLOC Calculations

As show in Table 7, EFED's chronic surface and ground water EDWCs following groundboom applications are above the Agency's back-calculated DWLOC values for the parent compound. The Agency concludes that chronic aggregate risk estimates for this application method and rate may potentially be of concern.

Again, though the Agency has little information to estimate surface water EDWCs following applications by chemigation under plastic sheeting or by shank injection, by the very nature of the application method, run-off or drift to bodies of water are expected to be greatly reduced. Even peak EDWCs of 2.1 and 1.1 µg/L result in potential chronic aggregate risks that are low or not of concern. EFED believes that these are conservative estimates and that EDWCs are unlikely to reach these levels. Using the lower application rates, EFED estimated that the ground water EDWCs to be 2.4 and 1.6 µg/L. When compared to the calculated DWLOCs, there are slight exceedences of the chronic DWLOCs for infants and children. However, since SCI-GROW is a Tier 1 model and these estimates are considered screening level and upper bound (see EFED's amendment 2, July 7, 2003), the Agency does not expect exposures at this level from ground water to pose an aggregate risk of concern.

Table 7. Chronic DWLOC Calculations

Population Subgroup[1]	Chronic Scenario					
	cPAD mg/kg/day	Chronic Food Exp mg/kg/day	Max Chronic Water Exp mg/kg/day[2]	Ground Water EDWC µg/L[3] (4.5/1.5/1.0 lbs ai)	Surface Water EDWC µg/L[3] (4.5/1.5/1.0 lbs ai)	Chronic DWLOC µg/L[4]
U.S. Population	0.00017	0.000011	0.00016	7/2.4/1.6	15/2.1/1.1	6
Infants < 1 year	0.00017	0.000006	0.00016	7/2.4/1.6	15/2.1/1.1	2
Children 1-2 yrs	0.00017	0.000025	0.00015	7/2.41.6	15/2.1/1.1	2
Females 13-49	0.00017	0.000009	0.00016	7/2.4/1.6	15/2.1/1.1	5

[1] Population subgroups are representative of those with the highest dietary exposure values. Standard body weights and water consumption values are as follows: 70 kg/2L per day (adult male/general population); 60 kg/2L per day (adult female); 10 kg/1L per day (child).
[2]Maximum Chronic Water Exposure (mg/kg/day) = [Chronic PAD (mg/kg/day) - Chronic Dietary Exposure (mg/kg/day)]
[3]EDWC values are modeled for tomatoes (crop with maximum application rate).
[4] Chronic DWLOC(µg/L) = $\frac{\text{[maximum chronic water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$

5.4 Cancer Risk

5.4.1 Aggregate Cancer Risk Assessment

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the HIARC has classified fosthiazate into the category "Not likely to be carcinogenic to humans." This classification is based on the lack of evidence for carcinogenicity in mice and rats. Therefore, an aggregate cancer risk assessment has not been conducted.

6.0 Cumulative Risk

The Agency has completed its Revised Cumulative Risk Assessment for OPs, which can be found on the Agency's web site *www.epa.gov/pesticides/cumulative*. This assessment examined the cumulative effects of exposure to the OP pesticides. The relative potency factor (RPF) for fosthiazate was determined using the estimated BMD10 for female brain ChE data from feeding toxicity studies in the rat. The BMD10 is the estimated dose at which ChE is inhibited 10% compared to background inhibition. Although fosthiazate was considered in the cumulative hazard and dose-response assessment, it was not included in the OP cumulative exposure assessment since this OP pesticide is not monitored by the USDA's Pesticide Data Program (PDP) or other monitoring data sets used in the cumulative OP assessment. Residue data are available for fosthiazate from crop field trials conducted with tomatoes in which maximum (label) application rates and minimum (label) preharvest intervals were used. No residues were detected in these field trials (< 0.01 ppm). Thus, OPP concludes that there is no reasonable expectation that fosthiazate residues would be detected in monitoring data from use on tomato. Further, fosthiazate would not contribute to the total estimated cumulative dietary risk in the OP

cumulative risk assessment since non-detectable residues in monitoring data were considered to have a residue value of "zero."

7.0 Occupational Exposure

ISK Biosciences Corporation is proposing the use of the nematicide Fosthiazate 900 EC and Nemathorin® 500 EC for control of a broad spectrum of nematodes that attack peanuts, potatoes, and tomatoes. Fosthiazate may be applied prior to or at planting by ground equipment (groundboom or shank injection) to peanuts, potatoes, or tomatoes, and before or after transplant by chemigation (drip/trickle only) to tomatoes. A maximum of one application of 4 lbs ai/acre per season is proposed for peanuts and 4.5 lbs ai/acre per season for potatoes and tomatoes.

Based on the proposed use patterns, short-term (1 to 30 days) and possibly intermediate-term (1 to 6 months) dermal and inhalation exposures are expected for pesticide handlers and postapplication workers. Since fosthiazate may be applied only one time per year, long-term (longer than 6 months) exposures to pesticide handlers or postapplication workers are not expected from the proposed use patterns.

Fosthiazate is directly applied to the soil before or at planting and although postapplication exposure to fosthiazate may result from contact with treated soil, a postapplication assessment cannot be performed. At this time, there is also no data on the soil residue dissipation of fosthiazate and no exposure data exist for activities resulting in contact with treated soil. A worker exposure study done concurrently with a fosthiazate soil residue dissipation study is needed to assess this risk.

7.1 Use Patterns and Formulations

ISK Biosciences has proposed the registration of the technical fosthiazate (containing 94.0% of the active ingredient (a.i.) fosthiazate), and the preemergent nematocide Fosthiazate 900 EC (containing 75.0% fosthiazate a.i.) and Nemathorin® 500EC (containing 47.2% fosthiazate a.i.). Both of the proposed end-use products are EC formulations. According to the proposed labels, this product is applied as a dilute spray to the soil prior to or at planting to control a broad spectrum of nematode species on peanuts, potatoes, and tomatoes. A maximum of one application per season of 4 lbs ai/acre (peanuts) to 4.5 lbs ai/acre (potatoes and tomatoes) may be applied by groundboom equipment, shank injection, or by drip/trickle chemigation (tomatoes only). After fosthiazate is applied, it must be incorporated to a depth of four inches immediately after application. Aerial application is prohibited. Currently, there are no registered or proposed residential uses of fosthiazate. *NOTE: Peanuts and potatoes are included in the occupational assessment for informational purposes.*

7.2 Occupational Handler

HED has determined that there are potential exposures to mixers, loaders, applicators, and other handlers during the proposed use-patterns associated with fosthiazate. Based on the use patterns, four major occupational exposure scenarios were identified for fosthiazate:

- mixing/loading/applying liquids using chemigation systems
- mixing/loading liquids for groundboom application;
- applying liquids with a groundboom sprayer using data from PHED; and
- cleaning equipment following groundboom application.

At this time, HED has no data to assess exposures during chemigation applications while handlers are laying pesticide-contaminated driplines or laying tarps over a just-treated field. HED approximates exposures to handlers during chemigation applications by using data for mixing/loading only. *Therefore, HED believes that estimates of handler risks for the dripline irrigation scenario underestimates likely risks for chemigation scenarios.*

Based on the proposed use patterns, short-term (1 to 30 days) and possibly intermediate-term (30 days to 6 months), dermal and inhalation exposures are expected for pesticide handlers. Although intermediate-term exposure is not expected in most cases for the proposed uses, it is being assessed to determine potential risks in the event that such exposure does occur. Since fosthiazate may be applied only one time per year, long-term (longer than 6 months) exposures are not expected from the proposed use.

Chemical-Specific Data

The registrant submitted five fosthiazate-specific mixer/loader and applicator groundboom studies (MRID#s 443038-06, 443038-07, 443038-08, 443038-09, 43038-10). These studies included mixing/loading liquids to support groundboom application, groundboom sprayer application, and equipment cleanup tasks. The fosthiazate-specific applicator studies are performed with groundboom sprayers that are equipped with soil incorporation equipment and these unit exposure values are considered comparable to the PHED groundboom scenarios. There were some problems noted with each of the studies, including some quality assurance/quality control issues. The Agency has some concerns about the engineering control scenarios (i.e., closed mixing/loading system and enclosed tractor cab scenarios), because handlers were wearing maximum PPE in addition to using the engineering controls. The Agency's policy is to allow handlers to wear reduced PPE when engineering controls are used. In addition, some of the study scenarios intended to represent open tractor cab exposures used enclosed cab equipment with open windows and doors. Due to these concerns, the Agency has determined that the only fosthiazate-specific handler data applicable for this risk assessment are the date for the open mixing/loading, open tractor cab, and cleanup scenarios.

Unit exposure values from similar scenarios from each fosthiazate-specific study were considered together. The unit exposure values for applicators operating groundboom sprayers with semi-enclosed cabs (i.e., enclosed cabs where the door is removed and the windows are open) were not

included with the unit exposure values for the applicators operating groundboom sprayers with open cabs. There were five separate handler scenarios identified from the five studies:

- mixing/loading liquid formulations with open systems (21 replicates),
- mixing/loading liquid formulations with closed systems (9 replicates),
- applying sprays using open cab groundboom/soil incorporation equipment (6 replicates),
- applying sprays using semi-enclosed cab groundboom/soil incorporation equipment (24 replicates), and
- cleaning up the mixing, loading, and application equipment (15 replicates).

The Agency has made further adjustments to the fosthiazate-specific inhalation exposure values to reflect the inhalation exposure rates adopted by NAFTA and the EPA. NAFTA-recommended inhalation rates are 8.3 L/min for sedentary activities (e.g., driving a tractor), 16.7 L/m for light activities (e.g., flaggers and mixer/loaders handling containers less than 50 lbs) and 26.7 L/min for moderate activities (e.g., mixer/loaders handling containers greater than 50 lbs). The Agency adjusted mixer/loader and equipment cleaners inhalation values to reflect a breathing rate of 16.7 L/min and adjusted applicator inhalation values to reflect a breathing rate of 8.3 L/min.

HED Exposure Science Advisory Committee Policy 7 – *Use of Values from the PHED Surrogate Exposure Guide and from Analyses of Individual PHED Data Sets* – effective March 11, 1999 states: "It is the policy of HED to combine submitted chemical-specific data with those from the Pesticide Handlers Exposure Database (PHED) Version 1.1 to assess handler exposures for regulatory actions because individual studies may not encompass the variety of agricultural equipment in use throughout the country and the inter-variability of exposures among handlers." However, due to the complex issues involved in combining chemical-specific data with PHED data, HED has chosen to present the exposures and risks from each data source separately.

HED notes that PHED data for open mixing/loading of liquids at baseline protection and baseline protection plus gloves contain 72 to 122 replicates for dermal (nonhand) data and 53-59 replicates for hand data. In contrast, the fosthiazate-specific studies contain only 21 replicates for dermal and hand data. Also, PHED data for open cab groundboom application at baseline protection and baseline protection plus gloves contain 23 to 42 for dermal (nonhand) data and 21-29 replicates for hand data. In contrast, the fosthiazate-specific studies contain only 6 replicates for dermal and hand data.

Surrogate Data - PHED

The Pesticide Handlers Exposure Database (PHED) was designed by a task force of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide regulation, and member companies of the American Crop Protection Association. PHED is a software system consisting of two parts -- a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database

contains values for over 1,700 monitored individuals (i.e., replicates).

While data from PHED provide the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of a.i. handled) may not accurately represent labeled uses in all cases. HED has developed a series of tables of standard unit exposure values for many occupational scenarios that can be utilized to ensure consistency in exposure assessments.

HED has agreed to use inhalation rates recommended by NAFTA in place of the existing rate (29 L/min) in the OPPTS Harmonized Guidelines, Series 875 Group A. NAFTA-recommended inhalation rates are 8.3 L/min for sedentary activities (e.g., driving a tractor), 16.7 L/m for light activities (e.g., mixer/loaders handling containers less than 50 lbs) and 26.7 L/min for moderate activities (e.g., mixer/loaders handling containers greater than 50 lbs). Using the ratio of these inhalation rates, inhalation exposures should be reduced by a factor of (29/8.3) for sedentary activities, (29/16.7) for light activities, and (29/26.7) for moderate activities. Therefore, in this exposure and risk assessment, the Agency adjusted the PHED inhalation exposure values to reflect the new breathing rates adopted by NAFTA and EPA. The Agency used 16.7 L/min breathing rate for mixers/loaders and a 8.3 L/min breathing rate for applicators.

In addition, the Agency adjusted the PHED dermal exposure values by decreasing them 10%, since in PHED dermal exposure value calculations to estimate potential dose, the ratio of the body surface area to the body weight overestimates exposure by a factor of 1.1. Thus, exposures estimated using unit exposures from PHED are too high by a factor of 1.1. To include this factor, the exposure assessor can either divide the dermal unit exposures by a factor of 1.1 or 10 percent.

Data Sources for Handler Scenarios

Based on the use patterns, the following data sources were used to estimate fosthiazate handlers' exposure and risk:

- open mixing/loading liquids for groundboom application using data from PHED;
- open mixing/loading liquids for groundboom application using data from fosthiazate-specific studies;
- closed mixing/loading liquids for groundboom application using data from PHED;
- open mixing/loading/applying liquids for chemigation application using data from PHED;
- open mixing/loading liquids for chemigation application using data from fosthiazate-specific studies;
- closed mixing/loading/applying liquids for chemigation application using data from PHED;
- open cab application of liquids with a groundboom sprayer using data from PHED;
- open cab application of liquids with a groundboom sprayer using data from fosthiazate-specific studies;
- enclosed cab application of liquids with a groundboom sprayer using data from

PHED; and

- equipment cleanup following groundboom applications using data from fosthiazate-specific studies.

The maximum application rate listed on the label was used to assess exposures and risks in all scenarios. In addition, an application rate of 1.5 lbs a.i. per acre was assessed for dripline irrigation applications to tomatoes, in order to reflect the possible rate reduction when the application is applied in banded areas only and not broadcast evenly across the treated area.

With one exception, the HED's standard values for acreage were used. For dripline irrigation to tomatoes, the registrant asserts that: "The fosthiazate applications require the grower to lay drip/trickle irrigation lines in the beds as they are formed to allow application of fosthiazate through the lines after transplanting the tomatoes. The maximum acreage that can be treated per day through this system is about 25 acres." Since the proposed label allows dripline irrigation applications before transplanting tomatoes as well as after transplanting tomatoes, and the registrant's statement apparently applies only to dripline applications after transplanting tomatoes, the assessment for dripline chemigation to tomatoes uses the standard value of 350 acres per day as well as the 25 acres per day proposed by the registrant.

To assess exposures during equipment cleanup, the fosthiazate-specific data first was adjusted to reflect the application rate of 4.5 lbs a.i. per acre now proposed, rather than the 6.0 lbs a.i per acre used in the study and then that exposure value (in milligrams) was assumed to be the daily exposure to cleanup workers.

Table 8. PHED unit exposure values and fosthiazate study unit exposure values

Scenario	Dermal Protection	Dermal Exposure (mg/lb ai)		Inhalation Protection	Inhalation Exposure (µg/lb ai)	
		PHED	Fosthiazate Studies		PHED	Fosthiazate Studies
Mixing/loading liquids with an open system	Baseline (long-sleeve shirt and long pants)	2.6	Not available	Baseline: no respirator	0.69	0.019[c]
	PPE: double layers plus gloves	0.015	0.0037[a] plus boots, goggles, respirator, and apron	PPE: dust/mist respirator	0.14	Not available
Mixing/loading liquids with a closed system	Baseline plus gloves	0.0077	Not available	Baseline: no respirator	0.048	0.016[b]
	PPE: double layers plus gloves	Not available	0.00068[a,d] plus boots, goggles, respirator, and apron	Not applicable	Not applicable	Not applicable
Groundboom application of liquids with an open cab	Baseline (long-sleeve shirt and long pants)	0.013	Not available	Baseline: no respirator	0.21	0.74[b]
	PPE: double layers plus gloves	0.0099	0.0014[a] plus boots, goggles, and respirator	PPE: dust/mist respirator	0.043	Not available
Groundboom application of liquids with an enclosed cab with open doors and windows	PPE: double layers plus gloves	Not available	0.0056[a,d] plus boots, goggles, and respirator	Baseline: no respirator	Not available	0.18[a]
Groundboom application of liquids with an enclosed cab	Baseline (long-sleeve shirt and long pants)	0.0045	Not available	Baseline: no respirator	0.012	Not available
Cleanup of equipment	PPE: double layers plus gloves	Not available	1.1[a] plus boots, goggles, respirator, and apron	Baseline: no respirator	Not available	0.012[c]

Footnotes:

[a] Lognormal, geometric mean used
[b] Both normal and lognormal, arithmetic mean used
[c] Neither normal or lognormal, median used
[d] These exposure values were not used in the handler risk assessment due to the use of maximum personal protective equipment with engineering controls. EPA's policy is to allow handlers to wear reduced personal protective equipment when engineering controls are used.
Note: Double layers for PHED represents coveralls worn over long-sleeve shirt and long pants, whereas double layers for the fosthiazate studies represents coveralls worn over short-sleeve shirt and short pants.

7.3 Occupational Handler Risk Characterization

For the dermal and inhalation, short- and intermediate-term exposure, the target MOE is 100. The calculated dermal and inhalation MOE values were combined for both short- and intermediate-term exposures, because the dermal and inhalation endpoints were the same (i.e., ChEI). MOEs are calculated for all scenarios at baseline, with PPE, and with engineering control level exposures.

All short- and intermediate-term handler risks are of concern based on HED's level of concern (MOE $\geq$100), *except* for banded chemigation applications to tomatoes using engineering controls (using PHED data) and using maximum dermal PPE (using fosthiazate-specific data).

For **dripline irrigation applications to tomatoes** (using data for mixing/loading liquid formulations) at a maximum area treated per day of **25 acres** per handler, the MOEs are:

- **120** for short-term and **110** for intermediate-term exposures *using PHED data* for mixing/loading liquid formulations using closed systems and a maximum application rate of *1.5 lbs* a.i. per acre;
- 39 for short-term and 38 for intermediate-term exposures *using PHED data* for mixing/loading liquid formulations using closed systems and a maximum application rate of *4.5 lbs* a.i. per acre;
- **250** for short-term and **240** for intermediate-term exposures *using fosthiazate-specific data* for maximum dermal PPE (but no respirator) and a maximum application rate of *1.5 lbs* a.i.per acre;
- 82 for short-term and 80 for intermediate-term exposures *using fosthiazate-specific data* for maximum dermal PPE (but no respirator) and a maximum application rate of *4.5 lbs* a.i.per acre;
- 51 for short-term and 43 for intermediate-term exposures *using PHED data* for maximum dermal PPE (but no respirator) and a maximum application rate of *1.5 lbs* a.i. per acre; and
- 17 for short-term and 14 for intermediate-term exposures *using PHED data* for maximum dermal PPE (but no respirator) and a maximum application rate of *4.5 lbs* a.i. per acre.

For **dripline irrigation applications to tomatoes** (using data for mixing/loading liquid formulations) at a maximum area treated per day of **350 acres** per handler, the MOEs are:

- 8.4 for short-term and 8.1 for intermediate-term exposures *using PHED data* for mixing/loading liquid formulations using closed systems and a maximum application rate of *1.5 lbs* a.i. per acre;
- 2.8 for short-term and 2.7 for intermediate-term exposures *using PHED data* for mixing/loading liquid formulations using closed systems and a maximum application rate of *4.5 lbs* a.i. per acre;
- 18 for short-term and 17 for intermediate-term exposures *using fosthiazate-specific*

data for maximum dermal PPE (but no respirator) and a maximum application rate of *1.5 lbs* a.i. per acre;

- 6 for short-term and 5.9 for intermediate-term exposures *using fosthiazate-specific data* for maximum dermal PPE (but no respirator) and a maximum application rate of *4.5 lbs* a.i. per acre;
- 3.6 for short-term and 3 for intermediate-term exposures *using PHED data* for maximum dermal PPE (but no respirator) and a maximum application rate of *1.5 lbs* a.i. per acre; and
- 1.2 for short-term and 1.0 for intermediate-term exposures *using PHED data* for maximum dermal PPE (but no respirator) and a maximum application rate of *4.5 lbs* a.i. per acre.

HED notes that the exposure and risk assessment for handlers applying fosthiazate using dripline irrigation does not include exposure values for such handlers:

- while handling pesticide-contaminated driplines, or
- while laying tarps over a just-treated field.

Therefore, the dripline irrigation assessment is likely an underestimate of handler risks during chemigation. **HED recommends that if the proposed registration for dripline chemigation application to tomatoes is approved, pesticide labeling directions should limit dripline irrigation applications to 25-acres per day per handler and to a maximum application rate of 1.5 lbs a.i. per acre.**

For **groundboom scenarios** at a maximum area treated of 80 acres per day and application rate of 4.0 lbs a.i. per day for peanuts and 4.5 lbs a.i. per day for tomatoes and potatoes, MOEs range from:

- 12 to 14 for short-term and from 12 to 13 for intermediate-term exposures when mixing/loading to support groundboom applications with closed systems (engineering controls) *using PHED data*;
- 21 to 24 for short-term and intermediate-term exposures when applying with enclosed cab (engineering controls) groundboom equipment *using PHED data*;
- 26 to 29 for short-term and 25 to 28 for intermediate-term exposures when mixing/loading to support groundboom applications with maximum dermal PPE (no respirator) *using fosthiazate-specific data*;
- 45 to 51 for short-term and 34 to 38 for intermediate-term exposures when applying with open cab groundboom equipment and maximum PPE (including a respirator) *using fosthiazate-specific data*;
- 5.3 to 5.9 for short-term and 4.4 to 5 for intermediate-term exposures when mixing/loading to support groundboom applications with maximum dermal PPE (no respirator) *using PHED data*;
- 9.6 to 11 for short-term and 9.4 to 11 for intermediate-term exposures when

applying with open cab groundboom equipment and maximum PPE equipment (including a respirator) *using PHED data*;

HED notes that PHED data for open mixing/loading of liquids at baseline protection and baseline protection plus gloves contains 72 to 122 replicates for dermal (nonhand) data and 53-59 replicates for hand data. In contrast, the fosthiazate-specific studies contain only 21 replicates for dermal and hand data. Also, PHED data for open cab groundboom application at baseline protection and baseline protection plus gloves contains 23 to 42 for dermal (nonhand) data and 21-29 replicates for hand data. In contrast, the fosthiazate-specific studies contain only 6 replicates for dermal and hand data.

Equipment cleanup exposure values were assessed in the fosthiazate-specific studies and would be part of the typical activities associated with fosthiazate use. The proposed label specifies that the sprayer must be washed following each day of use. Since the Agency has no surrogate data in PHED to assess risks to equipment cleaners, the Agency assessed the risks to cleaners of equipment based on the dermal and inhalation unit exposure values from the fosthiazate-studies. For equipment cleanup tasks, the maximum acres treated per day and pounds of a.i. handled per day are only indirectly related to the amount of residue on the equipment. However, to assess exposures during equipment cleanup, the fosthiazate-specific data first were adjusted to reflect the currently proposed application rate of 4.5 lbs a.i. per acre, rather than the 6.0 lbs a.i. per acre used in the studies, and then that exposure value (in milligrams) was assumed to be the daily exposure to handlers involved in equipment cleanup.

The MOE for **cleaners of equipment** from short-term exposures was 39 and from intermediate-term exposures was 37. The Agency notes that in the studies the equipment cleaning function was performed by a handler who also mixed/loaded and/or applied fosthiazate on a given day. Since the time spent cleaning the equipment at the end of the work day ranged from about 30 to 60 minutes per day in the studies, the Agency believes it is likely that such tasks would be performed by handlers who also were involved in the mixing/loading and/or application of fosthiazate during that same day. In such situations, if the risks calculated for equipment were aggregated with the risks calculated for mixers/loaders or applicators, the total aggregated risks would be lower than 39 and 37 respectively, for short- and intermediate-term handler risks.

7.4 Occupational Postapplication Reentry Exposure

Fosthiazate is directly applied to the soil before or at planting and postapplication exposure to fosthiazate may result from contact with treated soil. In particular, HED is concerned about transplanting tomatoes soon after a fosthiazate application. However, at this time, no postapplication assessment has been performed since there are no data on the soil residue dissipation of fosthiazate and no exposure data for activities resulting in contact with treated soil. Based on information provided by the registrant (i.e., the proposed label requires workers to wear gloves and boots when transplanting tomatoes within 7 days following applications to certain soil types) and data indicating a relatively lengthy half-life in soils, HED is proposing a 7-day REI

following fosthiazate applications. HED notes that the WPS for Agricultural Pesticides prohibits workers from performing routine early entry tasks (such as transplanting tomato plants) while wearing PPE. Instead, the WPS requires that the Agency establish an REI for the length of time following application until risks are not of concern for workers to enter treated areas and perform tasks requiring contact with the treated surface *without* the use of PPE. A worker exposure study conducted concurrently with a fosthiazate soil residue dissipation study would be needed to assess this risk. HED recommends that the following postapplication exposure monitoring data be required as confirmatory support for the registration of fosthiazate on tomatoes: 875.2200 Soil Residue Dissipation and 875.2400 Postapplication Dermal Exposure.

The WPS prohibits routine entry to perform hand labor tasks during the REI and requires PPE to be worn for other early-entry tasks that require contact with treated surfaces. Based on the acute toxicity of the fosthiazate a.i. (i.e., toxicity category II for dermal toxicity and for eye irritation potential, and classified as a skin sensitizer) and using the default early entry PPE established by the WPS, HED recommends the following early entry PPE: long-sleeved coveralls over short-sleeved shirt and short pants, chemical-resistant gloves, chemical-resistant footwear plus socks, and protective eyewear.

8.0 Data Needs/Label Requirements

8.1 Product Chemistry

Various product chemistry data gaps have been identified for fosthiazate. These data gaps include, but are not limited to, the following: the nominal concentrations of all potential toxic impurities present in the technical, a discussion on the formation of impurities for all the impurities identified and listed in the CSF and also for theoretically possible impurities, a one year storage stability study in commercial packaging under warehouse conditions, and UV/Visible absorption data for technical fosthiazate. A complete listing of product chemistry data gaps and data requirements may be found in the *Product Chemistry Review of Fosthiazate Technical* (S. Mathur memo, 11/8/2001).

8.2 Residue Chemistry

Banana Data Needs

- A final report of the storage stability of fosthiazate and its metabolite ASC-6713 in banana pulp should be submitted to the Agency for review. Upon receipt and review of the continued storage stability data, HED will determine if corrections and/or tolerance adjustment are required.
- Data are required depicting the frozen storage stability of fosthiazate and ASC-67131 in a representative foliage commodity. The Agency notes that a tobacco storage stability study will be submitted.
- The petitioner must submit new banana field trials demonstrating residues resulting from the

lower proposed application rate of 2g ai/mat applied alternately with another nematicide.

- Analytical grade reference standards for the fosthiazate metabolite ASC-67131 must be submitted to the EPA standards repository.
- Additional data are required to characterize insoluble residues in 30-DAT rotated wheat commodities.
- Storage stability data are required to support the additional analyses required on the 30-DAT wheat forage, straw, and grain.
- Based upon the petitioner's data to support the proposed PBIs for rotated crops (30 days for cereal grains and root and tuber vegetables, and 90 days for leafy vegetables), extensive field rotational crop trials and rotational crop tolerances will be required for leafy vegetables, root and tuber vegetables, and cereal grains.
- If the petitioner amends the proposed label to specify a 90-day PBI for leafy vegetables, root and tuber vegetables, and crops with fosthiazate registrations, extensive field rotational crop trials and rotational crop tolerances may only be required for leafy vegetables and forages of cereal grains. Rotation to crops other than leafy vegetables, root and tuber vegetables, and crops with fosthiazate registrations is prohibited.

Coffee Data Needs

- A final report covering three years of storage stability of fosthiazate and ASC-67131 in coffee beans was submitted on May 6, 1997 (MRID# 44269902). These data are currently under review.
- Data are required depicting the frozen storage stability of fosthiazate and ASC-67131 in a representative foliage commodity. The Agency notes that a tobacco storage stability study will be submitted.
- Analytical grade reference standards for the fosthiazate metabolite ASC-67131 must be submitted to the EPA standards repository.
- Additional data are required to characterize insoluble residues in 30-DAT rotated wheat commodities.
- Storage stability data are required to support the additional analyses required on the 30-DAT wheat forage, straw, and grain.
- Based upon the petitioner's data to support the proposed PBIs for rotated crops (30 days for cereal grains and root and tuber vegetables, and 90 days for leafy vegetables), extensive field rotational crop trials and rotational crop tolerances will be required for leafy vegetables, root and tuber vegetables, and cereal grains.
- If the petitioner amends the proposed label to specify a 90-day PBI for leafy vegetables, root and tuber vegetables, and crops with fosthiazate registrations, extensive field rotational crop trials and rotational crop tolerances may only be required for leafy vegetables and forages of cereal grains. Rotation to crops other than leafy vegetables, root and tuber vegetables, and crops with fosthiazate registrations is prohibited.

Peanut Data Needs

- The detailed responses to the requested additional characterization data to upgrade the goat

metabolism study have been submitted and will be reviewed in the future.

- The dates of the sample storage data, as well as the analysis for the storage stability of fosthiazate and its metabolites in milk and tissues, have been submitted and will be reviewed in the future.
- The detailed analyses addressing the requested data characterizing fractions containing significant concentrations of residue or percentages of total radioactive residues (TRR) to upgrade the poultry metabolism study have been submitted and will be reviewed in the future.
- Dates and intervals of sample storage data in hen matrices have been submitted and will be reviewed in the future.
- Residue analytical methods for livestock commodities may be required if HED determines that secondary residues resulting from fosthiazate application to peanut and potato are to be regulated in meat, milk, poultry tissues, or eggs.
- Data are required depicting the frozen storage stability of fosthiazate and ASC-67131 in a representative foliage commodity. The Agency notes that a tobacco storage stability study will be submitted.
- Storage stability data are required for fosthiazate and ASC-67131 residues in/on peanut hay stored for at least 423 days (~14 months).
- Additional studies depicting residues in/on peanut hay are required from Region 2 (2 trials), Region 3 (1 trial), and Region 8 (1 trial).
- Analytical grade reference standards for the fosthiazate metabolite ASC-67131 must be submitted to the EPA standards repository.
- Additional data are required to characterize insoluble residues in 30-DAT rotated wheat commodities.
- Storage stability data are required to support the additional analyses required on the 30-DAT wheat forage, straw, and grain.
- Based upon the petitioner's data to support the proposed PBIs for rotated crops (30 days for cereal grains and root and tuber vegetables, and 90 days for leafy vegetables), extensive field rotational crop trials and rotational crop tolerances will be required for leafy vegetables, root and tuber vegetables, and cereal grains.
- If the petitioner amends the proposed label to specify a 90-day PBI for leafy vegetables, root and tuber vegetables, and crops with fosthiazate registrations, extensive field rotational crop trials and rotational crop tolerances may only be required for leafy vegetables and forages of cereal grains. Rotation to crops other than leafy vegetables, root and tuber vegetables, and crops with fosthiazate registrations is prohibited.

Potato Data Needs

- The petitioner must submit a revised section F proposing a tolerance level of 0.10 ppm for residues of fosthiazate and AS67131 in/on potato.
- The detailed responses to the requested additional characterization data to upgrade the goat metabolism study have been submitted and will be reviewed in the future.
- The dates of sample storage data and analysis for the storage stability of fosthiazate and its

metabolites in milk and tissues have been submitted and will be reviewed in the future.

- The detailed analyses addressing the requested data characterizing fractions containing significant concentrations of residue or percentages of total radioactive residues (TRR) to upgrade the poultry metabolism study have been submitted and will be reviewed in the future.
- Dates and intervals of sample storage data in hen matrices have been submitted and will be reviewed in the future.
- Residue analytical methods for livestock commodities will be required if HED determines that secondary residues resulting from fosthiazate application to potato are to be regulated in meat, milk, poultry tissues, or eggs.
- Data are required depicting the frozen storage stability of fosthiazate and ASC-67131 in a representative foliage commodity. The Agency notes that a tobacco storage stability study will be submitted.
- Analytical grade reference standards for the fosthiazate metabolite ASC-67131 must be submitted to the EPA standards repository.
- Additional data are required to characterize insoluble residues in 30-DAT rotated wheat commodities.
- Storage stability data are required to support the additional analyses required on the 30-DAT wheat forage, straw, and grain.
- Based upon the petitioner's data to support the proposed PBIs for rotated crops (30 days for cereal grains and root and tuber vegetables, and 90 days for leafy vegetables), extensive field rotational crop trials and rotational crop tolerances will be required for leafy vegetables, root and tuber vegetables, and cereal grains.
- If the petitioner amends the proposed label to specify a 90-day PBI for leafy vegetables, root and tuber vegetables, and crops with fosthiazate registrations, extensive field rotational crop trials and rotational crop tolerances may only be required for leafy vegetables and forages of cereal grains. Rotation to crops other than leafy vegetables, root and tuber vegetables, and crops with fosthiazate registrations is prohibited.

Tomato Data Needs

- The final report of the 3 year storage stability data for tomato must be submitted and reviewed.
- Data are required depicting the frozen storage stability of fosthiazate and ASC-67131 in a representative foliage commodity. The Agency notes that a tobacco storage stability study will be submitted.
- Analytical grade reference standards for the fosthiazate metabolite ASC-67131 must be submitted to the EPA standards repository.
- Additional data are required to characterize insoluble residues in 30-DAT rotated wheat commodities.
- Storage stability data are required to support the additional analyses required on the 30-DAT wheat forage, straw, and grain.
- Based upon the petitioner's data to support the proposed PBIs for rotated crops (30 days for

cereal grains and root and tuber vegetables, and 90 days for leafy vegetables), extensive field rotational crop trials and rotational crop tolerances will be required for leafy vegetables, root and tuber vegetables, and cereal grains.

- If the petitioner amends the proposed label to specify a 90-day PBI for leafy vegetables, root and tuber vegetables, and crops with fosthiazate registrations, extensive field rotational crop trials and rotational crop tolerances may only be required for leafy vegetables and forages of cereal grains. Rotation to crops other than leafy vegetables, root and tuber vegetables, and crops with fosthiazate registrations is prohibited.

8.3 Toxicology

- A 28-day inhalation study in rats with fosthiazate is required, as there is concern for toxicity by the inhalation route following exposure on multiple days in a commercial setting. Registrants are recommended to follow the protocol provided in OPPTS Guideline 870.3465 (90-day inhalation study) but cease exposure at 28 days.

- A DNT study in rats with comparative ChE measurements in adults and pups is also required. The protocol has been submitted and reviewed.

8.4 Occupational

- A worker exposure study for activities involving contact with treated soil conducted concurrently with a soil residue dissipation study is needed to assess postapplication risk. These data requirements are 875.2200 and 875.2400 in Group B-Postapplication Exposure Monitoring Test Guidelines in the Series 875-Occupational and Residential Exposure Test Guidelines.

9.0 References/Attachments

Developmental Neurotoxicity Study Protocol. Susan Makris. May 30, 2001.

Fosthiazate. Acute and Chronic Dietary Exposure Assessments for the Section 3 Registration Action for Fosthiazate Use on Tomato. Sherrie Kinard. November 15, 2002.

Fosthaizate; Health Effects Division (HED) Metabolism Assessment Review Committee (MARC) Decision Document. Sherrie Kinard. August 27, 2002.

Fosthiazate (PC Code 129022): Revised Registration Toxicology Disciplinary Chapter. Anna Lowit. November 14, 2002.

Fosthiazate - Report of the FQPA Safety Factor Committee. Brenda Tarplee. August 1, 2002.

Fosthiazate Section 3 for Tomatoes Amendment to the Previous Review. Henry Craven. February 27, 2003.

Fosthiazate Section 3 for Tomatoes Amendment 2 to the Previous Review. Thuy Nguyen. July 7, 2003.

Fosthiazate - 1st Report of the Hazard Identification Assessment Review Committee. Sanjivani Diwan. April 23, 2002.

FOSTHIAZATE - 2nd Report of the Hazard Identification Assessment Review Committee. Sanju Diwan & Anna Lowit. August 19, 2002.

FOSTHIAZATE - 3rd Report of the Hazard Identification Assessment Review Committee. Anna Lowit. November 12, 2002.

Occupational Exposure and Risk Assessment/Characterization for the Proposed Use of Fosthiazate on Peanuts, Potatoes and Tomatoes. Shanna Recore. July 16, 2003.

PP#6F4773, PP#6F4701, PP#6F04755, PP#6F04701, and PP# 6F04662. REVISED Registration for Fosthiazate use in/on Imported Banana and Coffee, and Section 3 Registration for Fosthiazate use in/on Peanut, Potato, and Tomato. Sherrie Kinard. June 26, 2003.

Secondary Product Chemistry Review of Fosthiazate Technical. Shyam Mathur. November 8, 2001. *Not attached.*

Tier 1 Estimated Drinking Water Concentrations of Fosthiazate. Thuy Nguyen. May 20, 2002.

Tier 2 Estimated Drinking Water and Environmental Concentrations of Fosthiazate Use on Tomatoes. James K. Wolf. June 24, 2002.

Table 9. Summary of Occupational Handler Short-term Dermal and Inhalation Total Exposure Variables

Exposure Scenario (Scenario #)	Crop	Application Rates[a] (lb ai/A)	Area Treated (A/day)	Total Short-Term Margin of Exposure[b]		
				Baseline	Personal Protective Equipment	Engineering Controls
Mixing/Loading						
Mixing/Loading Liquids for Groundboom Application (PHED)	Potatoes and Tomatoes	4.5	80	0.037 (open system plus single-layer body protection; no gloves or respirator)	6.2 (open system plus double layer body protection, gloves, and dust/mist respirator)	12 (closed system plus single-layer body protection plus gloves; no respirator)
Mixing/Loading Liquids for Groundboom Application (fosthiazate-specific studies)				N/A	26 (open system plus double layer body protection, gloves, boots, goggles, and apron; no respirator) 26 (open system plus double layer body protection, gloves, boots, goggles, and apron; and adding a dust/mist respirator using an 80% PF)	N/A
Mixing/Loading Liquids for Groundboom Application (PHED)	Peanuts	4.0	80	0.042 (open system plus single-layer body protection; no gloves or respirator)	7 (open system plus double layer body protection, gloves, and dust/mist respirator)	14 (closed system plus single-layer body protection plus gloves; no respirator)

Exposure Scenario (Scenario #)	Crop	Application Rates[a] (lb ai/A)	Area Treated (A/day)	Total Short-Term Margin of Exposure[b]		
				Baseline	Personal Protective Equipment	Engineering Controls
Mixing/Loading Liquids for Groundboom Application (fosthiazate-specific studies)				N/A	29 (open system plus double layer body protection, gloves, boots, goggles, and apron; no respirator) 29 (open system plus double layer body protection, gloves, boots, goggles, and apron; and adding a dust/mist respirator using an 80% PF)	N/A
Dripline Chemigation						
Mixing/Loading Liquids for Chemigation Application (PHED)	Tomatoes	4.5	25	0.12 (open system plus single-layer body protection; no gloves or respirator)	17 (open system plus double layer body protection, gloves, and no respirator)	39 (closed system plus single-layer body protection plus gloves; no respirator)
Mixing/Loading Liquids for Chemigation application (fosthiazate-specific studies)				N/A	82 (open system plus double layer body protection, gloves, boots, goggles, and apron; no respirator) 84 (open system plus double layer body protection, gloves, boots, goggles, and apron; and adding a dust/mist respirator using an 80% PF)	N/A

Exposure Scenario (Scenario #)	Crop	Application Rates[a] (lb ai/A)	Area Treated (A/day)	Total Short-Term Margin of Exposure[b]		
				Baseline	Personal Protective Equipment	Engineering Controls
Mixing/Loading Liquids for Chemigation Application (PHED)	Tomatoes	1.5	25	0.36 (open system plus single-layer body protection; no gloves or respirator)	51 (open system plus double layer body protection, gloves, and no respirator)	120 (closed system plus single-layer body protection plus gloves; no respirator)
Mixing/Loading Liquids for Chemigation application (fosthiazate-specific studies)				N/A	250 (open system plus double layer body protection, gloves, boots, goggles, and apron; no respirator) 250 (open system plus double layer body protection, gloves, boots, goggles, and apron; and adding a dust/mist respirator using an 80% PF)	N/A
Mixing/Loading Liquids for Chemigation Application (PHED)	Tomatoes	4.5	350	0.0085 (open system plus single-layer body protection; no gloves or respirator)	1.2 (open system plus double layer body protection, gloves, and no respirator)	2.8 (closed system plus single-layer body protection plus gloves; no respirator)
Mixing/Loading Liquids for Chemigation application (fosthiazate-specific studies)				N/A	5.9 (open system plus double layer body protection, gloves, boots, goggles, and apron; no respirator) 6 (open system plus double layer body protection, gloves, boots, goggles, and apron; and adding a dust/mist respirator using an 80% PF)	N/A

Exposure Scenario (Scenario #)	Crop	Application Rates[a] (lb ai/A)	Area Treated (A/day)	Total Short-Term Margin of Exposure[b]		
				Baseline	Personal Protective Equipment	Engineering Controls
Mixing/Loading Liquids for Chemigation Application (PHED)	Tomatoes	1.5	350	0.026 (open system plus single-layer body protection; no gloves or respirator)	3.6 (open system plus double layer body protection, gloves, and no respirator)	8.4 (closed system plus single-layer body protection plus gloves; no respirator)
Mixing/Loading Liquids for Chemigation application (fosthiazate-specific studies)				N/A	18 (open system plus double layer body protection, gloves, boots, goggles, and apron; no respirator) 18 (open system plus double layer body protection, gloves, boots, goggles, and apron; and adding a dust/mist respirator using an 80% PF)	N/A

Exposure Scenario (Scenario #)	Crop	Application Rates[a] (lb ai/A)	Area Treated (A/day)	Total Short-Term Margin of Exposure[b]		
				Baseline	Personal Protective Equipment	Engineering Controls
Applicator						
Sprays for Groundboom application (PHED))	Potatoes and Tomatoes	4.5	80	6.9 (open cab plus single-layer body protection; no gloves or respirator)	9.6 (open cab plus double layer body protection, gloves, and dust/mist respirator)	21 (enclosed cab plus single-layer body protection; no gloves or respirator)
Sprays for Groundboom application (fosthiazate-specific studies)				N/A	19 (open cab plus double layer body protection, gloves, boots, and goggles, and no respirator) 45 (open cab plus double layer body protection, gloves, boots, and goggles, and adding a dust/mist respirator using a 80% PF)	N/A
Sprays for Groundboom application (PHED)	Peanuts	4.0	80	7.8 (open cab plus single-layer body protection; no gloves or respirator)	11 (open cab plus double layer body protection, gloves, and dust/mist respirator)	24 (enclosed cab plus single-layer body protection; no gloves or respirator)
Sprays for Groundboom application (fosthiazate-specific studies)				N/A	21 (open cab plus double layer body protection gloves, boots, goggles; no respirator) 51 (open cab plus double layer body protection, gloves, boots, and goggles, and adding a dust/mist respirator using a 80% PF)	N/A
Equipment Cleanup Following Groundboom Application (fosthiazate-specific studies)	Peanuts, Potatoes, Tomatoes	4.0 and 4.5	N/A	N/A	39 (double layer body protection, gloves, boots, goggles, apron; no respirator)	N/A

Footnotes:

[a] Application Rates are based on the maximum application rates listed on the proposed fosthiazate labels.

[b] Total MOE (combined dermal and inhalation) = 1 / ((1/dermal MOE) + (1/inhalation MOE)).

Note: Double-layer body protection for PHED scenarios represents coveralls worn over long-sleeve shirts and long pants. Double-layer body protection for the fosthiazate-specific studies scenarios represents coveralls worn over short-sleeve shirts and short pants.

Table 10. Summary of Occupational Handler Intermediate-term Dermal and Inhalation Total Exposure Variables

Exposure Scenario (Scenario #)	Crop	Application rates[a] (lb ai/A)	Area Treated A/day	Total Intermediate-Term Margin of Exposure[b]		
				Baseline	Personal Protective Equipment	Engineering Controls
Mixing/Loading						
Mixing/Loading Liquids for Groundboom Application (PHED)	Potatoes and Tomatoes	4.5	80	0.037 (open system plus single-layer body protection; no gloves or respirator)	5.9 (open system plus double layer body protection, gloves, and dust/mist respirator)	12 (closed system plus single-layer body protection plus gloves; no respirator)
Mixing/Loading Liquids for Groundboom Application (fosthiazate-specific studies)				N/A	25 (open system plus double layer body protection, gloves, boots, goggles, and apron; no respirator) 25 (open system plus double layer body protection, gloves, boots, goggles, and apron; and adding dust/mist respirator using 80% PF)	N/A
Mixing/Loading Liquids for Groundboom Application (PHED)	Peanuts	4.0	80	0.042 (open system plus single-layer body protection; no gloves or respirator)	6.7 (open system plus double layer body protection, gloves, and dust/mist respirator)	13 (closed system plus single-layer body protection plus gloves; no respirator)

Exposure Scenario (Scenario #)	Crop	Application rates[a] (lb ai/A)	Area Treated A/day	Total Intermediate-Term Margin of Exposure[b]		
				Baseline	Personal Protective Equipment	Engineering Controls
Mixing/Loading Liquids for Groundboom Application (fosthiazate-specific studies)				N/A	28 (open system plus double layer body protection, gloves, boots, goggles, and apron; no respirator) 29 (open system plus double layer body protection, gloves, boots, goggles, and apron; and adding a dust/mist respirator using an 80% PF)	N/A
Chemigation						
Mixing/Loading Liquids for Chemigation Application	Tomatoes	4.5	25	0.12 (open system plus single-layer body protection; no gloves or respirator)	14 (open system plus double layer body protection, gloves, and no respirator)	38 (closed system plus single-layer body protection plus gloves; no respirator)
Mixing/Loading Liquids for Chemigation Application (fosthiazate-specific studies)				N/A	80 (open system plus double layer body protection, gloves, boots, goggles, and apron; no respirator) 83 (open system plus double layer body protection, gloves, boots, goggles, and apron; and adding a dust/mist respirator using an 80% PF)	N/A
Mixing/Loading Liquids for Chemigation Application	Tomatoes	1.5	25	0.36 (open system plus single-layer body protection; no gloves or respirator)	43 (open system plus double layer body protection, gloves, and no respirator)	110 (closed system plus single-layer body protection plus gloves; no respirator)

Exposure Scenario (Scenario #)	Crop	Application rates[a] (lb ai/A)	Area Treated A/day	Total Intermediate-Term Margin of Exposure[b]		
				Baseline	Personal Protective Equipment	Engineering Controls
Mixing/Loading Liquids for Chemigation Application (fosthiazate-specific studies)				N/A	240 (open system plus double layer body protection, gloves, boots, goggles, and apron; no respirator) 250 (open system plus double layer body protection, gloves, boots, goggles, and apron; and adding a dust/mist respirator using an 80% PF)	N/A
Mixing/Loading Liquids for Chemigation Application	Tomatoes	4.5	350	0.0085 (open system plus single-layer body protection; no gloves or respirator)	1 (open system plus double layer body protection, gloves, and no respirator)	2.7 (closed system plus single-layer body protection plus gloves; no respirator)
Mixing/Loading Liquids for Chemigation Application (fosthiazate-specific studies)				N/A	5.7 (open system plus double layer body protection, gloves, boots, goggles, and apron; no respirator) 5.9 (open system plus double layer body protection, gloves, boots, goggles, and apron; and adding a dust/mist respirator using an 80% PF)	N/A
Mixing/Loading Liquids for Chemigation Application	Tomatoes	1.5	350	0.26 (open system plus single-layer body protection; no gloves or respirator)	3 (open system plus double layer body protection, gloves, and no respirator)	8.1 (closed system plus single-layer body protection plus gloves; no respirator)

Exposure Scenario (Scenario #)	Crop	Application rates[a] (lb ai/A)	Area Treated A/day	Total Intermediate-Term Margin of Exposure[b]		
				Baseline	Personal Protective Equipment	Engineering Controls
Mixing/Loading Liquids for Chemigation Application (fosthiazate-specific studies)				N/A	17 (open system plus double layer body protection, gloves, boots, goggles, and apron; no respirator) 18 (open system plus double layer body protection, gloves, boots, goggles, and apron; and adding a dust/mist respirator using an 80% PF)	N/A

Exposure Scenario (Scenario #)	Crop	Application rates[a] (lb ai/A)	Area Treated A/day	Total Intermediate-Term Margin of Exposure[b]		
				Baseline	Personal Protective Equipment	Engineering Controls
Applicator						
Sprays for Groundboom Application (PHED)	Potatoes and Tomatoes	4.5	80	6.4 (open cab plus single-layer body protection; no gloves or respirator)	9.4 (open cab plus double layer body protection, gloves, and dust/mist respirator)	21 (enclosed cab plus single-layer body protection; no gloves or respirator)
Sprays for Groundboom Application (fosthiazate-specific studies)				N/A	11 (open cab plus double layer body protection, gloves, boots, goggles; no respirator) 34 (open cab plus double layer body protection, gloves, boots, and goggles, and adding a dust/mist respirator using a 80% PF)	N/A
Sprays for Groundboom Application (PHED)	Peanuts	4.0	80	7.2 (open cab plus single-layer body protection; no gloves or respirator)	11 (open cab plus double layer body protection, gloves, and dust/mist respirator)	24 (enclosed cab plus single-layer body protection; no gloves or respirator)
Sprays for Groundboom Application (fosthiazate-specific studies)				N/A	12 (open cab plus double layer body protection, gloves, boots, goggles; no respirator) 38 (open cab plus double layer body protection, gloves, boots, and goggles, and adding a dust/mist respirator using a 80% PF)	N/A
Equipment Cleanup Following Groundboom Application (fosthiazate-specific studies)	Peanuts, Potatoes, Tomatoes	4.0 and 4.5	N/A	N/A	37 (double layer body protection, gloves, boots, goggles, apron; no respirator)	N/A

Footnotes:

[a] Application Rates are based on the maximum application rates listed on the proposed fosthiazate labels.

[b] Total MOE (combined dermal and inhalation) = 1 / ((1/dermal MOE) + (1/inhalation MOE))

Note: Double-layer body protection for PHED scenarios represents coveralls worn over long-sleeve shirts and long pants. Double-layer body protection for the fosthiazate-specific studies scenarios represents coveralls worn over short-sleeve shirts and short pants.

Table 11. Occupational Handler Exposure Scenario Descriptions for the Use of Fosthiazate

Exposure Scenario (Scenario Number)	Data Source	Standard Assumption[a] (8-hr work day)	Comments[b]
MIXER/LOADER DESCRIPTORS			
Mixing/Loading Liquid Formulations	PHED V1.1	80 acres for groundboom to peanuts, potatoes, and tomatoes 25 acres for dripline chemigation application to tomatoes	**Baseline:** Hand, dermal, and inhalation data are AB grades. Dermal = 72 to 122 replicates; hand = 53 replicates; and inhalation = 85 replicates. High confidence in hand, dermal, and inhalation data. **PPE:** Hand data are AB grades, high confidence, and 59 replicates. Baseline dermal (minus head and neck) data is adjusted with a 50% protection factor to simulate double layer of clothing. Baseline inhalation data is adjusted with an 80% protection factor to simulate the use of a dust/mist respirator. **Engineering Controls:** Hand, dermal, and inhalation data are AB grades. Hand = 31 replicates; dermal =16 to 22 replicates; inhalation = 27 replicates. High confidence in hand, dermal, and inhalation data.
APPLICATOR DESCRIPTORS			
Applying Sprays with a Groundboom Sprayer	PHED V1.1	80 acres for groundboom to peanuts, potatoes, and tomatoes	**Baseline:** Hand, dermal, and inhalation data are AB grades. Hand = 29 replicates; dermal = 23 to 42 replicates; and inhalation = 22 replicates. High confidence in hand, dermal, and inhalation data. **PPE:** Hand data are ABC grades, medium confidence, and 21 replicates. Baseline dermal (minus head and neck) data is adjusted with a 50% protection factor to simulate double layer of clothing. Baseline inhalation data is adjusted with an 80% protection factor to simulate the use of a dust/mist respirator. **Engineering Controls:** Hand and dermal data are ABC grades, and inhalation are AB grades. Hand = 16 replicates; dermal =20 to 31 replicates; inhalation = 16 replicates. Medium confidence in hand and dermal data, and high confidence in inhalation data.

Footnotes

[a] Standard Assumptions based on an 8-hour work day as estimated by HED. BEAD data were not available.

[b] All handler exposure assessments in this document are based on the "Best Available" data as defined by OREB SOP for meeting Subdivision U Guidelines. Best available grades are assigned to data as follows: matrices with grades A and B data and a minimum of 15 replicates; if not available, then grades A, B and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality (i.e., All Grade Data) and number of replicates. High quality data with a protection factor take precedence over low quality data with no protection factor. Generic data confidence categories are assigned as follows:

High = grades A and B and 15 or more replicates per body part
Medium = grades A, B, and C and 15 or more replicates per body part
Low = grades A, B, C, D and E or any combination of grades with less than 15 replicates.