U. S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

DATE: Feb 22, 2007

SUBJECT: Human Health Risk Assessment for Ornamental Use of Cyclanilide.
PC Code: 026201 Chemical Class: Plant Growth Regulator
D333239 Trade Name: Cyclanilide 18% SC
Section 3 registration. No Aggregate risk.

TO: Tony Kish, PM-22
Fungicide Branch
Registration Division (7505P)

FROM: Greg Akerman, Toxicologist
Health Effects Division/Toxicology Branch (7509P)
Margarita Collantes, Biologist
Dennis McNeilly, Chemist/Risk Assessor
Health Effects Division/Registration Action Branch 2 (7509P)

THRU Kelly Schumacher, Biologist
PEER Douglas Dotson, Chemist
REVIEW Health Effects Division/Registration Action Branch 2 (7509P)

THRU: Kit Farwell, D.V.M.
Health Effects Division/Reregistration Branch 1 (7509P)
Christina Swartz, Chief
Health Effects Division/Registration Action Branch 2 (7509P)

MAR 1 4 REC'D

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY 4
2.0 Ingredient Profile 6
2.1 Summary of Registered/Proposed Uses 7
2.2 Structure and Nomenclature 8
2.3 Physical and Chemical Properties 8
3.0 Hazard Profile 8
3.1 Hazard and Dose-Response Characterization 8
3.1.1 Database Summary 8
3.1.2 Toxicological Effects 11
3.1.3 Dose-responses 12
3.1.4 FQPA 13
3.2 Absorption, Distribution, Metabolism, Excretion (ADME) 13
3.3 FQPA Considerations 14
3.3.1 Adequacy of the Toxicity Database 15
3.3.2 Evidence of Neurotoxicity 15
3.3.3 Developmental Toxicity Studies 16
3.3.4 Reproductive Toxicity Study 16
3.3.5 Additional Information from Literature Sources 17
3.3.6 Pre-and/or Postnatal Toxicity 18
3.3.6.1 Determination of Susceptibilit 18
3.3.6.2 Degree of Concern Analysis and Residual Uncertainties 18
3.3.7 Recommendation for a Developmental Neurotoxicity Study 18
3.3.8 Rationale for the UF_{DB} (when a DNT is recommended) 19
3.4 FQPA Safety Factor for Infants and Children 19
3.5 Hazard Identification and Toxicity Endpoint Selection 19
3.5.1 Acute Reference Dose (aRfD) - Females age 13-49 19
3.5.2 Acute Reference Dose (aRfD) - General Population 19
3.5.3 Chronic Reference Dose (cRfD) 20
3.5.4 Incidental Oral Exposure (Short- and Intermediate-Term) 20
3.5.5 Dermal Absorption 20
3.5.5 Dermal Absorption 20
3.5.6 Dermal Exposure (Short-, Intermediate- and Long-Term) 20
3.5.7 Inhalation Exposure (Short-, Intermediate- and Long-Term) 21
3.5.8 Level of Concern for Margin of Exposure 21
3.5.9 Recommendation for Aggregate Risk Assessment 21
3.5.10 Classification of Carcinogenic Potential 22
3.5.11 Summary of Toxicological Doses and Endpoints Assessments 22
3.6 Endocrine disruption 24
4.0 Public Health and Pesticide Epidemiology Data 24
4.1 Incident Reports 24
4.2 National Health and Nutritional Examination Survey (NHANES) 24

4.3 Agricultural Health Study (AHS) 24
4.4 Other Pesticide Epidemiology Published Literature 24
5.0 Dietary Exposure/Risk Characterization 24
5.1 Pesticide Metabolism and Environmental Degradation 24
5.1.1 Metabolism in Primary Crops 24
5.1.2 Metabolism in Rotational Crops 24
5.1.3 Metabolism in Livestock 24
5.1.4 Analytical Methodology 24
5.1.5 Environmental Degradation 24
5.1.6 Comparative Metabolic Profile 24
5.1.7 Toxicity Profile of Major Metabolites and Degradates 24
5.1.8 Pesticide Metabolites and Degradates of Concern 24
5.1.9 Drinking Water Residue Profile 24
5.1.10 Food Residue Profile 24
5.1.11 International Residue Limits 24
5.2 Dietary Exposure and Risk 24
5.2.1 Acute Dietary Exposure/Risk 27
5.2.2 Chronic Dietary Exposure/Risk 27
5.2.3 Cancer Dietary Risk 27
6.0 Residential (Non-occupatiuonal) Exposure/Risk 28
6.1 Residential Handler Exposure 29
6.2 Residential Postapplication Exposure 29
6.3 Other (Ppray Drift, etc.) 29
7.0 Aggregate Risk Assessments and Risk Characterization 29
8.0 Cumulative Risk Characterizatio/Assessment 30
9.0 Occupational Exposure/Risk Pathway 30
9.1 Short-/Intermediate/Long-Term Handler Risk 30
9.2 Short-/Intermediate/Long-Term Postapplication Risk 32
10.0 Data Needs and Label Recommendations 34
10.1 Toxicology 34
10.2 Residue Chemistry 34
10.3 Occupational and Residential Exposure 34
References 34
Appendix A: Toxicology Assessment 36
Appendix B: Metabolism Assessment 56
Appendix C: Tolerance Reassessment Summary and Table 56
Appendix D: Review of Human Research 56

1.0 EXECUTIVE SUMMARY

The Health Effects Division (HED) has peformed a human health risk assessment for the use of cyclanilide (1-[[(2,4-dichlorophenyl)amino]carbonyl]cyclopropanecarboxylic acid) on ornamentals. As the registration is for a non-food use, no tolerances are proposed or recommended. Cyclanilide is a plant growth regulator currently registered for use as a cotton harvest aid when used with other active ingredients. This would be the first registion of cyclanilide for use in a product without another active ingredient. Current registered uses for cyclanilide are as a synergist or co-active ingredient for use on cotton as a harvest aid. A Section 3 registration is being requested for the end-use product Cyclanilide 18% SC as the sole active ingredient. Cyclanilide will be used for increased branching of trees, shrubs, and cut flowers without the need to prune the central leader. HED conducted the most recent Section 3 registration human health risk assessment for cyclanilide in April 16, 1997 for the initial use on cotton.

Hazard Characterization

Adverse effects were identified at durations of exposure ranging from short-term (up to 30 days) to intermediate-term durations (> 30 days up to 6 months) and long-term durations (> 6 months). No cancer endpoint was identified; therefore, a cancer risk assessment is not required.

Dermal Route (noncancer). The short- and intermediate-term dermal risk assessment for cyclanilide is based on a NOAEL of 1,000 mg/kg/day from dermal study. No effects were observed at the highest dose level of 1,000 mg/kg/day. Long-term exposures to cyclanilide (i.e., greater than 6 months) are not expected.

Inhalation Route (noncancer). The short- and intermediate-term inhalation risk assessment for cyclanilide is based on a NOAEL of 4.0 mg/kg/day from a subchronic neurotoxicity study. The NOAEL is based on increased motor activity and decreased body weight in females. Long-term exposure to cyclanilide (i.e., greater than 6 months) is not expected.

Incidental Oral Route (noncancer). Incidental oral exposure is not expected based on the proposed use pattern (commercial nurseries).

Noncancer Level of Concern (LOC). HED's LOC for cyclanilide dermal and inhalation exposures is 100 (i.e., a margin of exposure (MOE) less than 100 exceeds HED's level of concern) for occupational assessments. The LOC is based on 10x for interspecies extrapolation and 10x for intraspecies variation.

Acute Toxicity. Cyclanilide is classified as category II for acute oral toxicity, category III for acute dermal toxicity, and category IV for acute inhalation toxicity. Cyclanilide is classified as category II for eye irritation potential and category IV for skin irritation potential. Results were negative for dermal sensitization in guinea pigs.

There are no registered residential uses for cyclanilide and none are proposed in this action. In addition, commercial applicators would not be applying cyclanilide in residential settings, as it is

not a use site on the draft proposed label.

Occupational Exposure

Based on the number of seasonal applications to ornamentals and cut flowers indicated on these product labels and information provided by the registrant (the registrant in an email to the Agency stated that the label will limit use to no more than three times per year), exposures are expected to be short-, and intermediate-term in duration. Long-term exposures (6 months of continuous exposure) are not expected to occur. Cyclanilide 18% SC can be applied at the maximum single application rate of 0.17 pound active ingredient per acre (lb ai/A) to ornamental plants in outdoor nurseries and plant production facilities. The product may be applied using groundboom equipment, backpack sprayer equipment, and low pressure handwand sprayer equipment.

Handler

Inhalation and dermal exposures of occupational handlers to cyclanilide were calculated using surrogate data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in the Agency's PHED Surrogate Exposure Guide (8/98). Defaults established by HED Science Advisory Council for Exposure (ExpoSAC) were used for acres treated per day, gallons handled per day, and body weight. Where data were available, the dermal and inhalation risks were below HED's level of concern at the baseline level (long-sleeve shirt, long pants, shoes, socks, and no respirator). There are no data to assess baseline dermal risks for mixing/loading/applying via backpack sprayer equipment. Dermal risks are below HED's level of concern for handlers of these scenarios when chemical-resistant gloves are worn in addition to baseline attire.

Under the Worker Protection Standard for Agricultural Pesticides, the personal protective equipment (PPE) for handlers is also based on acute toxicity of end-use products. Registration Division (RD) is responsible for ensuring that PPE listed on the label is in compliance with the Worker Protection Standard (WPS).

Postapplication

Postapplication exposures and risks to occupational workers were estimated using standard values established by HED since no chemical-specific data were submitted. The transfer coefficients (TCs) used for all postapplication activities were the TC's established by ExpoSAC in Policy 003.1. The dislodgeable foliar residue levels were estimated using HED standard values where it is assumed that the initial residue on treated foliage is 20 percent of the application rate and the residues degrade at a rate of 10 percent per day. MOEs on day 0 are above the target MOE of 100 for all crops and postapplication activities.

In cases where the risk assessment reveals little postapplication risk concern such as this, the Worker Protection Standard for Agricultural Pesticides mandates that a minimum restricted-entry interval be established based on the acute toxicity of the active ingredient for acute dermal toxicity, skin irritation potential, and eye irritation potential. Since cyclanilide is classified as toxicity category II for eye irritation potential (HIARC, 8/30/01; and reevaluated in this assessment), a REI of 24 hours is appropriate for all activities.

2.0 Ingredient Profile

Cyclanilide is a plant growth regulator registered for use as a cotton harvest aid when used with other active ingredients. A Section 3 registration is being requested for the end-use product Cyclanilide 18% SC (1-[[(2,4-dichlorophenyl)amino]carbonyl]cyclopropanecarboxylic acid) as the sole active ingredient for use on ornamental plants and cut flowers.

2.1 Summary of Registered/Proposed Uses

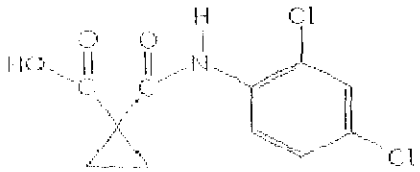
Cyclanilide 18% SC contains 18% cyclanilide in a soluble concentrate formulation for use as a plant growth regulator on ornamentals and cut flowers. The draft label restricts use of Cyclanilide 18% SC to use in outdoor nurseries and plant production facilities. The proposed or draft label states that: "Most varieties respond well to 1 to 2 applications of 50 to 200 ppm. Typically one application of 100 ppm is adequate." For lilacs, the proposed label specifies 1-3 applications of 100-200 ppm solution applied once a month for up to three months for the desired amount of branching. The seasonal maximum applications are 3 applications according to information provided by the registrant. No limit on the number of applications is specified on the draft label provided to HED. A maximum seasonal application rate was provided by the registrant as 0.34 lb a.i. A/season. This seasonal application rate limitation does not appear on the draft label. There is also a similar use with slightly lower application rates on non-bearing fruit trees, shown in Table 2.1

Cyclanilide is currently registered as a cotton harvest aid. It is used once per growing season, at the end of the cotton season, to promote boll opening, defoliation, and to inhibit foliar regrowth. It does not have any registered residential uses.

Table 2.1. Summary of Directions for Use of Cyclanilide.						
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Ornamentals						
Ornamentals, including flowers, foliage grow for cuttings	18% SC (432-RUUI)	0.17 or 0.0017 lb ai/gal	3	0.34	N/A	Registrant states that a typical application is 1 to 2 treatmentss of a 50 to 200 ppm solution.
Fruit tree (non-bearing)	"	0.085 or 0.0085 lb ai/gal	3	0.34	N/A	

2.2 Structure and Nomenclature

TABLE 2.2. Test Compound Nomenclature

Chemical Structure	
Empirical Formula	$C_{11}H_9Cl_2NO_3$
Common name	Cyclanilide
CAS name	1-[[(2,4-dichlorophenyl)amino]carbonyl]cyclopropanecarboxylic acid
CAS Registry Number	113136-77-9
End-use product/EP	Cyclanilide 18% SC
Chemical Class	Malonanilate
Known Impurities of Concern	NA

2.3 Physical and Chemical Properties

TABLE 2.3. Physicochemical Properties		
Parameter	Value	Reference
Molecular Weight	274.1	Cyclanilide Fact Sheet; May 19, 1997
Empirical formula	$C_{11}H_6Cl_2NO_2$	
Melting point/range	195.5 ± 1 C	
pH	3.8 (1% w/v in water, 21 C)	
Color/state	White/powder	
Density	1.469 - 1.482 g/mL (20 C)	
Odor	None	
Water solubility (20°C)	0.0037 g/100mL (distilled water)	
Solvent solubility (20°C to 25°C)	Acetone - 5.29 g/100 mL Acetonitrile - 3.50 g/100 mL Dichloromethane - 0.17 g/100 mL Ethylacetate - 53.18 g/100 mL Hexane - 0.0001 g/100 mL Methanol - 5.91 g/100 ml 1-octanol - 6.72 g/100 mL 2-propanol - 6.82 g/100 mL	
Vapor pressure (25°C)	$<10^{-7}$ Torr (25 C) 6.3×10^{-8} Torr (50 C)	
Octanol/water partition coefficient, $\log P_{OW}$	3.25 at 21 C	
UV/visible absorption spectrum	N/A	N/A

The stability of cyclanilide in storage is temperature dependent (Cyclanilide Fact Sheet). HED recommends that the registrant provide this information on the label section dealing with storage and stability of the product under high temperature conditions.

3.0 Hazard Characterization/Assessment

The available data are adequate to support the proposed Section 3 registration.

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

The available data are adequate to support the proposed Section 3 registration

TABLE 3.1.1: ACUTE TOXICITY PROFILE – CYCLANILIDE

GDLN	Study Type	MRID	Results	Tox Category
870.1100	Acute Oral	43368424	LD_{50}: 315/218 mg/kg (M/F)	II
870.	Acute Dermal - rat	43368425	LD_{50} > 2000 mg/kg	III
870.	Acute Inhalation	44651837	LC_{50}: > 2.64 mg/L	IV
870.	Primary Eye Irritation	43368430	*Conjunctivitis* and corneal opacity with epithelial sloughing; resolution by day 14.	II
870	Primary Skin Irritation	43368431	Slight erythema; resolution by 72 hours.	IV
870	Dermal Sensitization	43368433	Is not a sensitizer under conditions of study.	N/A

TABLE 3.1.2: *TOXICOLOGICAL* DOSES AND DIETARY/NON-OCCUPATIONS ENDPOINTS FOR CYCLANILIDE FOR USE IN HUMAN HEALTH ASSESSMENT

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	An acute dietary endpoint was not identified in the database for cyclanilide. This risk assessment is not required.		
Chronic Dietary	NOAEL = 3.0 UF = 100 FQPA SF = 1x all populations	*Decreases in absolute brain and liver weight, and lowered auditory startle amplitude at LOAEL of 6 mg/kg/day.*	Two-generation rat reproductive study.
		Chronic PAD = 0.03	
Carcinogenicity	"Not likely" to be carcinogenic to humans. Cyclanilide has been evaluated in at least two well conducted studies in two appropriate species without demonstrating carcinogenic effects.		
Incidental Oral (All durations)	No exposure expected		

Table 3.1.3 SUMMARY OF TOXICOLOGICAL DOSES AND ENDPOINTS FOR CYCLANILIDE FOR USE IN OCCUPATIONAL HUMAN HEALTH RISK ASSESSMENTS

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1-30 days)	NOAEL=1000 mg/kg/day	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	21-day dermal toxicity- rabbit LOAEL >1000 mg/kg
Dermal Intermediate-Term (1-6 months)	NOAEL=1000 mg/kg/day	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	21-day dermal toxicity- rabbit LOAEL >1000 mg/kg
Inhalation Short-Term (1-30 days)	NOAEL= 4.0 mg/kg/day	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	Subchronic (13-week) oral neurotoxicity-rat LOAEL: 35.8 mg/kg/day based on increased motor activity and decreased body weight in females.
Inhalation Intermediate-term (1-6 months)	NOAEL= 4.0 mg/kg/day	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	Subchronic (13-week) oral neurotoxicity-rat LOAEL: 35.8 mg/kg/day based on increased motor activity and decreased body weight in females.
Cancer (oral, dermal, inhalation)	Classification: "Not likely" to be carcinogenic to humans. Cyclanilide "has been evaluated in at least two well conducted studies in two appropriate animal species without demonstrating carcinogenic effects."			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.1.1.1 Studies available and considered (animal, human, general literature)

Studies available for review consisted of the data evaluation records (DERs) for the following:

- Acute toxicity- Oral rat, dermal rabbit, inhalation rat, eye irritation rabbit, dermal irritation rabbit, dermal sensitization guinea pig, acute neurotoxicity rat;
- Subchronic toxicity- Oral 90-day in rats, oral 90-day in mice, oral 90-day in dogs, subchronic neurotoxicity in rats, 21-day dermal toxicity in rabbits;
- Chronic toxicity/Carcinogenicity- Oral-rats (combined chronic/carcinogenicity), oral-mice (carcinogenicity) and oral-dogs (chronic);
- Mutagenicity- a battery of mutagenicity and genetic toxicity studies;

- Reproductive/developmental toxicity - Oral developmental in rabbits and rats; 2-generation reproductive in rats; and,

  Other- Metabolism and dermal penetration in rats.

3.1.1.2 Mode of action, metabolism, toxicokinetic data

Cyclanilide is a plant growth regulator that inhibits auxin activity, particularly in meristematic plant tissue. Cyclanilide is currently registered (as an ethephon synergist) for use on cotton harvest for boll opening, defoliation and growth suppression to aid in mechanical harvesting. The proposed new use is for use in outdoor nursery and plant production facilities to be applied as a broadcast spray on ornamental trees/shrubs and cut-flowers to promote increased branching. Metabolism and toxicokinetic data in the rat show that cyclanilide is rapidly absorbed after oral administration. The principal route of elimination of cyclanilide is by renal excretion of the parent compound and amino acid conjugates. Approximately 40% of the radioactivity from a single high dose of radiolabeled cyclanilide was excreted in urine and feces as unchanged parent compound within 72 hours. Methylation is a minor metabolic pathway. A methylated metabolite (RPA 93903) accounted for ≤5% of the dose. Ten amino acid conjugates of cyclanilide in feces (each at 0.11-5.22%) accounted for approximately 9-17% of the dose. Four amino acid conjugates totaling 1.5-2.5% were detected in urine. Also in urine were glucoside and glucuronide conjugates at 1.5-2.5%.

3.1.1.3 Sufficiency of studies/data

The available database was considered adequate to support the new uses proposed for this chemical. No additional studies are requested to support the new uses. A rat unscheduled DNA synthesis (UDS) assay was submitted as a condition-of-registration for use on cotton. This study was reviewed by HED. The UDS study was determined to be unacceptable (TXR# 0013902), but was later upgraded to acceptable (TXR# 0054472) after revisiting the data. The UDS study showed no evidence that unscheduled DNA synthesis was induced by the test material.

3.1.2 Toxicological Effects

The toxicological database provides adequate information to characterize potential hazards/effects. The acute toxicity of technical grade cyclanilide is high by the oral route (toxicity category II), but has low to medium dermal and inhalation acute toxicity (categories III and IV, respectively). The acute toxicity of cyclanilide is categorized as toxicity II for primary eye irritation and category IV for primary dermal irritation. Cyclanilide did not induce delayed contact sensitivity in the skin. In the 21-day dermal toxicity study, no dermal or systemic toxicity was observed at the limit dose (1000 mg/kg/day) for cyclanilide technical.

The oral studies in the mouse, rat and dog indicate the kidney and liver are the primary target organs. Increased liver weights were observed in the 90-day mouse and rat studies and in the mouse carcinogenicity study. Microscopic changes in the liver and elevated liver enzyme levels were observed in chronic dog and rat studies. The liver effects were only observed at the mid-high or highest dose tested in the subchronic and chronic studies. Increased renal mineralization was

observed in the adult females in the two-generation reproduction study. Increased renal mineralization was also observed in high dose males in the rat chronic/carcinogenicity study.

Developmental toxicity studies in the rat and rabbit showed no developmental effects. Maternal toxicity was observed at the highest dose tested (30 mg/kg/day in both species). Maternal effects in the rat included decreased body weight gain and food consumption. In the rabbit study, maternal toxicity was seen at the highest dose tested (decreased body weight gain and clinical signs including wobbly gait, partial hindlimb paralysis, decreased activity, salivation, emaciation, hair loss and no feces). In a two-generation reproduction study, no reproductive toxicity was observed at the highest dose tested (a dose level that produced parental systemic and offspring toxicities). The post-weaning decrease in bodyweight in the F_1 generation is not a susceptibility concern since it likely represents exposure to higher levels of cyclanilide due to the higher food intake to bodyweight ratio of the post-weaning pups. We note that the birth and pre-weaning bodyweights were not affected. In addition, only mid-high and high dose neurotoxicity effects were observed in the acute and subchronic neurotoxicity studies, subchronic oral, and developmental toxicity studies. Finally, potential susceptibility concerns for neurotoxicity are low at this time because: (1) this is not a food use pesticide and (2) the neurotoxicity in the rats were seen at the high dose of 75 mg/kg/day in the dose range finding study (main study high dose was 30 mg/kg/day). Thus, susceptibility issues are not of concern for cyclanilide at this time for this new use.

Mutagenicity studies were negative for cyclanilide in reverse and forward gene mutation assays. Cyclanilide was demonstrated to be an *in vitro* clastogen (inducing structural and numerical chromosomal aberrations) when tested with and without metabolic activation, but only at cytotoxic doses or over a narrow range that included severely cytotoxic doses. Cyclanilide was negative in the mouse micronucleus assay and *in vitro/in vivo* unscheduled DNA synthesis assay. Cyclanilide is classified as "not likely to be carcinogenic in humans" as demonstrated in at least two well conducted studies in two appropriate species without demonstrating carcinogenic effects.

3.1.3 *Dose-response*

The acute reference dose (aRfD) for females age 13-49 was not determined since an appropriate endpoint attributable to a single dose was not identified for this subpopulation. The acute neurotoxicity study in the rat was chosen for the aRfD for the general population. In this study, gait abnormalities, increased abdominal muscle tone, and slightly decreased motor activity test results were observed at 150 mg/kg (highest dose tested). The results are supported by a rangefinding acute neurotoxicity study in rats with resilient body tone, impaired gait and knuckling of forelimbs at $\geq$ 200 mg/kg, but not at 100 mg/kg. Forelimb paralysis and ataxia were also observed in an oral toxicity study at 150 mg/kg and greater. The rabbit developmental study reported wobbly gait, partial hindlimb paralysis and decreased activity at 30 mg/kg/day.

The two-generation reproduction toxicity rat study was chosen for the chronic reference dose (cRfD) based on reduced pre-mating bodyweights in males and females and increased renal mineralization of adult females (F1) at 2.0 mg/kg/day. A clear dose-related increase in renal mineralization was observed. Mineral deposits in the kidney were also observed in high dose

male rats in the chronic/carcinogenicity study, which is consistent with the evidence of kidney toxicity observed in the adult rats in the reproductive toxicity study.

No endpoint was chosen for the incidental oral exposure since incidental oral exposure is not likely based on the proposed non-residential use pattern.

A dermal absorption factor of 8.65% for cyclanilide was calculated from a rat dermal penetration study from the combined radioactivity absorbed and that remaining in/on the skin at the 10 hour exposure durations for the high dose. Although a low dermal absorption value was calculated in the rat, no systemic toxicity was observed at the limit dose (1000 mg/kg) in a 21-day dermal toxicity study in the rat. A dermal NOAEL of 1000 mg/kg was used as the point-of-departure for the occupational short- and intermediate-term exposure scenarios.

The subchronic oral neurotoxicity rat study was selected for short-term and intermediate-term occupational inhalation exposure. A 100% inhalation absorption rate was assumed. A NOAEL of 4.0 mg/kg/day was determined based on increased motor activity and decreased body weight (females) observed at 35.8 mg/kg/day in the subchronic neurotoxicity study.

3.1.4 FQPA

The available database is adequate to characterize any potential for prenatal or postnatal risks for infants and children based on the proposed new uses for cyclanilide. The data included an acceptable two-generation reproduction study in rats and prenatal developmental toxicity studies in rats and rabbits.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

The absorption, distribution, metabolism and excretion (ADME) of cyclanilide was investigated in a 7-day rat metabolism study (MRID 43868316). Radiolabeled cyclanilide administered orally to rats is rapidly absorbed and metabolized to some extent by methylation and conjugationed, although the majority is excreted unchanged. A 5 mg/kg dose, either single or the last in a series of 15 doses, is >70% eliminated within 24 hours. Absorption at a 50 mg/kg dose is delayed compared to the low dose, with the majority eliminated in 48 hours. Excreted radioactivity consists primarily of intact cyclanilide, along with conjugates of endogenous amino acids. Maximum plasma concentrations were attained within 1 hour of the low dose. High dose females reached maximum plasma concentrations in 5 hours versus 3 hours in high dose males. There was no difference in the relative pattern of excretion between male and female rats. After 168 hours, a majority of the excreted dose (single or repeated) was recovered in the urine (57-66% of dose) with 50-52% being recovered in the first 24 hours. Fecal excretion accounted for 27-40% of the low dose; 93-99% of the low dose was recovered in excreta after 168 hours. At 168 hours, approximately 30 and 60% respectively, of the high dose was recovered in the urine and feces, for a total recovery of 88-91% in excreta. Tissues accounted for 1.5 and 0.3% in the single low dose group, 0.66 and 0.65% in the repeated low dose group, and 6.08 and 1.05% from the high dose group. The relatively high percentage of the doses in tissues was accounted for by accumulation in skin/fur, which was dose-related and more pronounced in males in the single dose (low and high) groups. Metabolite analysis revealed that cyclanilide is not extensively metabolized,

although it may readily form amino acid conjugates. Approximately 40% of the radioactivity from a single high dose was excreted in urine and feces as unchanged parent compound within 72 hours. A methylated metabolite accounted for <5%. Ten amino acid conjugates (accounting for 9-17% of the dose) were identified in the feces and four amino acid conjugates (1.46-2.52% of dose) were identified in urine. The data indicated that the principal pathway for elimination of cyclanilide from rats is via renal excretion of the intact parent compound and various amino acid conjugates and that methylation is a minor pathway.

3.3 FQPA Considerations

An uncertainty factor (UF) of 100 was used to account for both the interspecies extrapolation and the intraspecies variability. An additional UF of 3 was also applied to the cRfD to account for the lack of a NOAEL in the two-generation reproductive toxicity study.

- The data provide no indication of increased sensitivity of fetal animals to in utero exposure to cyclanilide from the two developmental studies and the 2-generation reproductive toxicity studies.

- Although neurotoxicity occurred in several studies (acute and subchronic neurotoxicity in rats and both the rat and rabbit developmental studies), the dose levels at which they occur (150 mg/kg (rat acute neurotoxicity), 35.8 mg/kg/day (rat subchronic neurotoxicity) and 30 mg/kg/day (rat and rabbit developmental toxicity)) are all more than 10X higher than the LOAEL being used in the risk assessment from the 2-generation reproduction study (2.0 mg/kg/day).

- Reduced body weight gains in post-weaning young rats in the reproduction study, at a dietary level not affecting adult rats (30 ppm in young rats versus 300 ppm in adult rats), indicated the possibility of an increased sensitivity for young rats to cyclanilide. However, food and compound consumption were not determined for the pups after weaning when the apparent decreases in weight gain occurred. Since young rats are well known to consume considerably more food on a mg/kg/day basis than adult rats, even though both young and adult rats are given the same concentration of test material in the diet, it is likely that actual compound consumption in the young 30 ppm rats in this study was much more than 2.0 mg/kg/day calculated for the adults at the same dietary level. Therefore, it is uncertain if the young rats in this study were, in fact, more sensitive than the adult rats to the test material.

- The effect upon body weight of young weanling rats in the reproduction study was used to set the RfD. This endpoint by its very nature already addresses concerns for possible increased sensitivity in young animals since the effect was observed in young animals. Effects seen in other studies do not indicate potential pre- or postnatal effects of concern to infants or small children.

- The calculation of the RfD for cyclanilide already incorporates and additional uncertainty factor of 3 to account for the lack of a NOAEL in the reproduction study. A LOAEL to

NOAEL uncertainty factor of 3 is being used instead of 10 because the NOAELs in the existing chronic studies (dog-5.2, rat-8.1, mouse-42) are between 2 and 20x higher than the lowest dose in the 2-generation reproduction study. Dividing the LOAEL of 2.0 by 3, (0.7 mg/kg) appears to be a reasonable estimate for a slight temporary bodyweight change in growing pups.

Based on the considerations above, the population subgroups comprised of infants and children are sufficiently protected, and an additional uncertainty factor is not warranted for the current use.

3.3.1 Adequacy of the Toxicity Database

The available database is considered adequate to characterize any potential for prenatal or postnatal risks for infants and children based on the proposed new uses for cyclanilide. The data included an acceptable two-generation reproduction study in rats and prenatal developmental toxicity studies in rats and rabbits.

3.3.2 Evidence of Neurotoxicity

In an acute neurotoxicity screening study (MRID 43348436) twelve Sprague-Dawley rats/sex/group were administered a single gavage dose of 0, 15, 50, or 150 mg cyclanilide (technical). There were no gross or histopathological findings that could be attributed to the test article administration. Functional observational battery (FOB) tests and motor activity tests revealed no treatment-related effects in animals of the 15 or 50 mg/kg dose groups. On Day 0, 5/12 males and 8/12 females in the 150 mg/kg group exhibited a significantly ($p<0.05$ males; $p<0.01$ females) increased incidence of resilient body tone upon removal from their cages. This resiliency persisted through Day 1 in three males and one female. Females in the 150 mg/kg group also exhibited significantly ($p<0.01$) increased gait incapacity (8/12 animals) (accompanied by a delayed return of hindlimbs to the normal position in response to toe pinch), knuckling of the forelimbs (8/12 animals), and exaggerated/slow abducted movement (7/12 animals). Total activity counts were decreased 39% for high-dose males ($p<0.01$) on Day 0. A 23% decrease was observed for females, but the difference was not statistically significant. Based upon gait abnormalities, increased abdominal muscle tone, and slightly decreased motor activity test, a neurotoxicity LOAEL of 150 mg/kg is defined for male and female rats. The neurotoxicity NOAEL based upon these parameters is 50 mg/kg for male and female rats.

In a subchronic neurotoxicity screening study (MRID 43368435), twelve Sprague-Dawley rats/sex/group were fed 0, 50, 450 or 1200 ppm cyclanilide technical (98.8% a.i.; approximately equivalent to 3.3, 29.7 or 78.6 mg/kg/day for males and 4.0, 35.8, or 93.9 mg/kg/day for females) in the diet for 13 weeks. Body weights were 7-11% lower in mid-dose females on Days 42 to 91 ($P<0.05$ or $P<0.01$); terminal body weight gain was 27% less than controls. High-dose females exhibited 7-8% lower body weights ($P<0.05$) on Days 21, 42, 52, and 70; terminal body weight gain was 18% less than controls. Functional Observational Battery (FOB) tests showed a 28% ($P<0.01$) decrease in hindlimb splay measurements in high-dose females at Week 13 when compared to controls. Motor activity tests indicated a significant ($P<0.05$) increase in total activity counts in mid-dose females at Weeks 8 and 13 (31% and 50% increase, respectively, compared to controls). Marked increases (however, not statistically significant) in total activity counts were also observed

in mid-dose females at Week 4 (33% increase) and in high-dose females at Weeks 8 and 13 (20% and 32% increase). There were no gross or histopathological findings that could be attributed to the test article administration. The LOAEL is 450 ppm (35.8 mg/kg/day) based upon increased motor activity and decreased body weight in females. The NOAEL is 50 ppm (4.0 mg/kg/day).

Other evidence of neurotoxicity was observed as maternal toxicity in the prenatal development study in rabbits (MRID 43368445). The neurotoxicity effects were observed only at the highest dose tested (30 mg/kg/day) and included wobbly gait, partial hind limb paralysis, decreased activity and salivation.

3.3.3 Developmental Toxicity Studies

Cyclanilide (technical) was administered to 25 female Sprague Dawley rats per group, via a corn oil gavage at 0, 3.0, 10.0 or 30.0 mg/kg/day for gestational days 6 through 16. Developmental toxicity was studied externally, viscerally, and skeletally at gestational day 20. No dose related developmental toxicity was seen in the main study. Although the incidence of 14th rib was statistically significantly increased in litters at 30 mg/kg/day in the main study, it was within the historical control range and no dose relationship was seen at 10, 25 (screening study) and 30 mg/kg/day. Thus, the increase in the main study was considered incidental. Maternal body weight gain was decreased at 30.0 mg/kg/day gestational day 6-9, 6-16 (25% from control, $p \leq 0.01$) and food consumption was decreased at 30.0 mg/kg/day at gestational day 6-9 ($p \leq 0.01$), 9-12 ($p \leq 0.05$) and 6-16 (14% from control, $p \leq 0.01$). The incidences of mortality, ataxia and labored breathing were increased in the screening study at 75 mg/kg/day and reduced viable fetuses, increased post-implantation loss in 4/10 survivors at 75 mg/kg/day. The incidences of gastroschisis (hernia) and anopthalmia/micropthalmia (no eyes/small eyes) were increased in the survivors in the screening study at 75 mg/kg/day. The maternal NOAEL/LOAEL is 10.0/30.0 mg/kg/day based on decreased body weight gain and reduced food consumption. The developmental NOAEL/LOAEL is 30.0/>30.0 mg/kg/day based on no dose-related effects in the main study (MRID 43368443).

Technical cyclanilide (98.04%) was administered to artificially inseminated New Zealand White rabbits at doses of 0, 3, 10 and 30 mg/kg/day by oral gavage during gestation days 6-18. Animals were sacrificed on day 29. The maternal NOAEL/LOAEL is 10/30 mg/kg/day based on clinical signs and decreased body weight gain. Signs included wobbly gait, partial hindlimb paralysis, decreased activity, salivation, emaciation, hair loss and no feces. The high-dose group gained a mean of 22 g during treatment compared to a mean weight gain of 209 g for the controls. The NOAEL/LOAEL for developmental toxicity is 30/>30 mg/kg/day. Mean numbers of corpora lutea, implantation sites, viable fetuses, post-implantation loss, gravid uterine weight, fetal body weights, and fetal sex ratios were similar between all groups. Post-implantation loss was increased compared to concurrent controls (principally due to total resorptions by one female), but was within the historical control range. No treatment-related variations or malformations were seen (MRID 43368445).

3.3.4 Reproductive Toxicity Study

In a 2-generation reproduction study (MRID 43868313) cyclanilide (99.2% a.i.) was administered

to 30 Sprague Dawley rats/sex/dose in the diet at dose levels of 0, 30, 300, or 1000 ppm in the diet (equivalent to doses of 0, 1.9, 19.0, or 64.1 mg/kg/day for P males; 0, 2.0, 20.2, or 70.4 mg/kg/day for F_1 males; 0, 2.3, 21.8, or 84.5 for P females; 0, 2.4, 25.9, or 85.7 mg/kg/day for F_1 females). Exposure to P animals (30/sex/dose) began at 7 weeks of age, 10 weeks prior to mating to produce F_1 pups. Upon weaning, F_1 pups (30/sex/dose) were selected to become parents of the F_2 generation and were given the same concentration test diets as their dams beginning 11 weeks prior to mating. All animals were mated on a 1:1 ratio.

Parental toxicity at 1000 ppm included treatment-related reductions in mean body weights, body weight gains, and food consumption values in both sexes and generations; as well as treatment-related reductions in absolute and relative liver weights for the P (and F_1) males. At 300 ppm, treatment-related reductions in mean body weights, body weight gains and food consumption were observed occasionally in both sexes. Reduced body weight was observed in pre-mating F_1 males and females at 30 ppm. There were no treatment-related microscopic findings for any treatment group for the P parental generation. For the F_1 generation, treatment-related renal histopathology revealed mineralization of the renal papilla and microscopic calculi in the renal pelvis in the F_1 generation only (minimal to mild) at 1000 and 300 ppm of both sexes and in the 30 ppm group in females. The parental systemic LOAEL is 30 ppm (2.0 mg/kg bw/day in males, 2.4 mg/kg bw/day in females), based on reductions in mean body weights in both sexes and increased mineralization in the renal papilla of adult F_1 females. The parental systemic NOAEL was not established.

In the offspring, there were no treatment-related clinical signs or changes in mean litter size or viability indices in the F_1 or F_2 generation pups. Treatment-related decreases in mean pup weights were observed in both sexes at 300 and 1000 ppm. Mean pup weights were reduced 10-32% at 1000 ppm throughout lactation for both generations and by 9% on day 21 of lactation for the F_1 generation at 300 ppm. Relative liver weights were increased while absolute liver weights were decreased in F_1 and F_2 males and females at 1000 ppm. The offspring LOAEL is 300 ppm (21.8 mg/kg/day) based on decreases in mean pup weights. The offspring NOAEL is 30 ppm (2.3 mg/kg/day).

No adverse reproductive effects were observed at any dose. Estrous cycle length and periodicity, sperm measurements and sexual maturation measurements were not performed; however, there were no indications of treatment-related fertility abnormalities in this study. In a range-finding study, reproductive effects were seen at 1400 ppm (77.1 mg/kg/day) including reduced mating indices, reduced gestation index, decreased mean implantation sites, decreased pup weight, and increased pup mortality. Under the conditions of this study, the reproductive NOAEL is 1000 ppm (70.4 mg/kg/day in males and 85.7 mg/kg/day in females), the highest dose tested.

3.3.5 Additional Information from Literature Sources

No additional studies from the open literature were found.

3.3.6 Pre-and/or Postnatal Toxicity

3.3.6.1 Determination of Susceptibility

There was no quantitative or qualitative evidence of increased susceptibility following *in utero* exposure of cyclanilide in rats or rabbits in the developmental toxicity studies. No developmental toxicity was observed in the rat at the highest dose tested (30 mg/kg/day). Maternal toxicity effects observed at 30 mg/kg/day (LOAEL) dose included decreased body weight gain and food consumption. In the rabbit, there were no developmental effects observed at the highest dose tested (30 mg/kg/day), a dose level that produced maternal clinical signs of toxicity including wobbly gait, hindlimb paralysis, decreased activity, salivation, emaciation, hair loss and no feces. In the two-generation reproductive toxicity study, pup effects were observed at higher doses (≥ 21.8 mg/kg/day) than parental systemic effects (2.0/2.4 mg/kg/day in males/females, respectively). The available evidence (two developmental toxicity studies and one two-generation reproductive toxicity study) suggest there is no concern for pre- and/or post-natal toxicity resulting from exposure to cyclanilide.

3.3.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

The available evidence suggests there is no qualitative or quantitative evidence of pup susceptibility following exposure to cyclanilide in the developmental and reproductive toxicity studies.

3.3.7 *Recommendation for a Developmental Neurotoxicity Study*

Based on the available data, a developmental neurotoxicity study is not required for the proposed new use of cyclanilide on ornamentals and non-bearing fruit trees. There was no evidence of increased quantitative or qualitative susceptibility following *in utero* and/or postnatal exposure of cyclanilide in the developmental toxicity studies in rats and rabbits and in the two-generation reproduction study in rats. In the rat, no developmental toxicity was observed at the highest dose tested (30 mg/kg/day), although decreased body weight gait and food consumption was seen in the dam at this dose. In the rabbit, there were no developmental effects observed at the highest dose tested (30 mg/kg/day), a dose level that produced maternal clinical signs of toxicity including wobbly gain, hindlimb paralysis, decreased activity, salivation, emaciation, hair loss and no feces. In the two-generation reproductive toxicity study, pup effects (liver and body weight changes) were observed at higher doses (21.8 mg/kg/day) than similar parental systemic effects (2.0/2.4 mg/kg/day in males/females, respectively); signs of neurotoxicity were not observed in this study.

Signs of neurotoxicity were observed in adult animals following a single high dose (150 mg/kg) in the acute neurotoxicity study, at 30 mg/kg/day in the developmental rabbit study, and with repeated exposure (e.g., 4 weeks) to 35.8 mg/kg/day in the subchronic neurotoxicity study. While there might be some neurotoxicity concerns for the developing young, there is currently no major source of dietary exposure (registered uses are for cotton with proposed uses on ornamental plants/non-bearing fruit trees). If such uses are petitioned, the requirement for a DNT should be reconsidered. The following factors were also considered in the decision not to require a DNT at

this time and for these proposed uses.

1) Neurotoxicity was observed at high doses in the acute and developmental rat studies (150 mg/kg and 75 mg/kg/day, respectively)
2) None of the available studies indicated any neuropathological lesions.
3) Subchronic neurotoxicity LOAEL was 35.8 mg/kg/day
4) There were no developmental effects observed in either the rat or rabbit developmental studies.
5) There were no changes in birth weight or pre-weaning body weight at the low dose (2.0 mg/kg/day) in the 2-generation reproduction study.

The current uses are for cotton and ornamentals which have would result in limited dietary exposure to cyclanilide in meat and milk from dietary burden in animal feed. If in the future additional uses on food commodities are petitioned, the requirement for a DNT should be reconsidered

3.3.8 Rationale for the UF_{DB} (when a DNT is recommended)

N/A.

3.4 FQPA Safety Factor for Infants and Children

Based on the hazard and exposure data, the cyclanilide risk assessment team is recommending that the FQPA Safety Factor be reduced to 1X at this time because there is a complete toxicity database for cyclanilide and exposure data are complete or are estimated based on data that reasonably account for potential exposures. There is no evidence of susceptibility following *in utero* and or postnatal exposure in the developmental toxicity studies in rats or rabbits, and in the 2-generation rat reproduction study.

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 Acute Reference Dose (aRfD) - Females age 13-49

Study Selected: None

Comments about Study/Endpoint/Uncertainty Factors: An appropriate endpoint attributable to a single dose was not identified for this subpopulation.

3.5.2 Acute Reference Dose (aRfD) - General Population

Study Selected: Acute oral neurotoxicity- rat
MRID No.: 43368436

Executive Summary: See Appendix A, Guideline § 870.6200

Dose and Endpoint for Risk Assessment: NOAEL =50 mg/kg based on gait abnormalities, increased abdominal muscle tone, and slightly decreased motor activity test

seen at LOAEL = 150 mg/kg.

Comments about Study/Endpoint/Uncertainty Factors: An Uncertainty Factor (UF) of 100 was used to account for both interspecies extrapolation (10X) and intraspecies variations (10X).

3.5.3 Chronic Reference Dose (cRfD)

Study Selected: 2-Generation reproductive toxicity - rat
MRID No.: 43868313

Executive Summary: See Appendix A, Guideline § 870. 3800

Dose and Endpoint for Risk Assessment: Parental NOAEL not established. Parental LOAEL =2.0 mg/kg/day based on reduced pre-mating body weights of young F1 males and females and increased renal mineralization of adult F1 females.

Comments about Study/Endpoint/Uncertainty Factors: An Uncertainty Factor (UF) of 100 was used to account for both interspecies extrapolation (10X) and intraspecies variations (10X). An additional UF of 3 was also applied to account for the lack of a NOAEL in this study.

3.5.4 Incidental Oral Exposure (Short- and Intermediate-Term)

Incidental oral exposure not expected based on the proposed use pattern.

3.5.5 Dermal Absorption

Study Selected: Dermal Absorption- rat
MRID No.: 48368317

Executive Summary: See Appendix A, Guideline § 870. 7800

Dermal Absorption Factor = 8.65% calculated from the combined radioactivity absorbed and that remaining in/on the skin at the ten hour exposure duration.

3.5.6 Dermal Exposure (Short- and Intermediate-Term)

Study Selected: 21-day dermal toxicity- rabbit
MRID No.: 43868311

Executive Summary: See Appendix A, Guideline § 870.3200

Dose and Endpoint for Risk Assessment: NOAEL= 1000 mg/kg; LOAEL >1000 mg/kg; no toxicity observed at the highest dose tested.

Comments about Study/Endpoint/Uncertainty Factors: An Uncertainty Factor (UF) of 100 was used to account for both interspecies extrapolation (10X) and intraspecies variations (10X).

3.5.7 Inhalation Exposure (Short-, Intermediate- and Long-Term)

Study Selected: Subchronic (13-week) oral neurotoxicity – rat
MRID No.: 43368436

Executive Summary: See Appendix A, Guideline § 870. 6200

Dose and Endpoint for Risk Assessment: NOAEL =4.0 mg/kg/day based on increased motor activity and decreased body weight (females) seen at LOAEL = 35.8 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factors: An Uncertainty Factor (UF) of 100 was used to account for both interspecies extrapolation (10X) and intraspecies variations (10X).

3.5.8 Level of Concern for Margin of Exposure

Table 3.5.8 Summary of Levels of Concern for Risk Assessment.

Route	Short-Term (1 - 30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	N/A
Inhalation	100	100	N/A
Residential Exposure			
Dermal	N/A	N/A	N/A
Inhalation	N/A	N/A	N/A
Incidental Oral	N/A	N/A	N/A

3.5.9 Recommendation for Aggregate Exposure Risk Assessments

An aggregated exposure risk assessment is not required because the proposed use is a non-food use and there are no residential uses for cyclanilide. Dietary exposure to cyclanilide through drinking water and other currently established tolerances (cotton use) is being assessed.

3.5.10 Classification of Carcinogenic Potential

HED has determined that a full carcinogenicity peer review meeting is not necessary (TXR 012189; Memo date 4/9/1997). HED has also determined that cyclanilide has been tested adequately in two acceptable carcinogenicity studies in rats and mice. Based on the weight-of-the-evidence considerations, cyclanilide should not be considered at this time to be a carcinogen for the purposes of risk assessment. The appropriate descriptor for human carcinogenic potential is "Not Likely to be Carcinogenic to Humans."

3.5.11 Summary of Toxicological Doses and Endpoints for Cyclanilide for Use in Human Risk Assessments

Table 3.5.11a Toxicological Doses and Endpoints for Cyclanilide for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	NOAEL= 50 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	Acute RfD = 0.50 mg/kg/day aPAD = 0.50 mg/kg/day	**Acute oral neurotoxicity- rat** LOAEL: 150 mg/kg, based on gait abnormalities, increased abdominal muscle tone, and slightly decreased motor activity test.
Acute Dietary (Females 13-49 years of age)	An appropriate endpoint attributable to a single dose was not identified.			
Chronic Dietary (All Populations)	NOAEL=2.0 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x UF_L = 3x	Chronic RfD = 0.007 mg/kg/day cPAD=0.007 mg/kg/day	**Two-generation reproductive *toxicity- rat*** Parental LOAEL = (M/F) = 2.0/2.4 mg/kg/day (LDT) based on reduced pre-mating body weights of F1 males and females and increased renal *mineralization* of adult F1 females.
Incidental Oral Short-Term (All durations)	No exposure expected			
Dermal (All Terms)	*No non-occupational dermal exposure expected*			
Inhalation (All terms)	No non-occupational inhalation exposure expected			
Cancer (oral, dermal, inhalation)	"Not likely" to be carcinogenic to humans. Cyclanilide "has been evaluated in at least two well *conducted studies in two appropriate animal species* without demonstrating carcinogenic effects."			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = *extrapolation from animal to human (interspecies).* UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 3.5.11b Summary of Toxicological Doses and Endpoints for Cyclanilide for Use in Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1-30 days)	NOAEL=1000 mg/kg/day	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	**21-day dermal toxicity- rabbit** LOAEL >1000 mg/kg
Dermal Intermediate Term (1-6 months)	NOAEL=1000 mg/kg/day	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	**21-day dermal toxicity- rabbit** LOAEL >1000 mg/kg
Inhalation Short-Term (1-30 days)	NOAEL= 4.0 mg/kg/day	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	**Subchronic (13-week) oral neurotoxicity- rat** LOAEL: 35.8 mg/kg/day based on increased motor activity and decreased body weight in females.
Inhalation Intermediate term (1-6 months)	NOAEL= 4.0 mg/kg/day	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	**Subchronic (13-week) oral *neurotoxicity*- rat** LOAEL: 35.8 mg/kg/day based on increased motor activity and decreased body weight in females.
Cancer (oral, dermal, inhalation)	Classification: "Not likely" to be carcinogenic to humans. Cyclanilide "has been evaluated in at least two well conducted studies in two appropriate animal species without demonstrating carcinogenic effects."			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.6 Endocrine disruption

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 was scientific basis 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 has 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).

In the available toxicity studies on cyclanilide, there was no estrogen, androgen, and/or thyroid

mediated toxicity. When additional appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disruptor Screening Program (EDSP) have been developed, cyclanilide may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health and Pesticide Epidemiology Data

Not applicable.

4.1 Incident Reports

Not applicable.

4.2 National Health and Nutritional Examination Survey (NHANES)

Not applicable.

4.3 Agricultural Health Study (AHS)

Not applicable.

4.4 Other Pesticide Epidemiology Published Literature

Not applicable.

5.0 Dietary Exposure/Risk Characterization

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03) to include evaluation of the drinking water component for this new use. Treatment of ornamentals and cut flowers is considered to be a non-food use.

5.1 Pesticide Metabolism and Environmental Degradation

The estimates of cyclanilide concentrations in surface water were based on the FIRST Model, and include two significant degradates, 2,4-dichloroaniline, and RPA 110516 (rearranged, dechlorinated parent) because these two residues were present in some of the environmental fate studies.

5.1.1 Metabolism in Primary Crops

N/A, the proposed use is a non-food use on ornamentals and cut flowers.

5.1.2 Metabolism in Rotational Crops

N/A, the proposed use is a non-food use on ornamentals and cut flowers.

5.1.3 Metabolism in Livestock

N/A, the proposed use is a non-food use on ornamentals and cut flowers.

5.1.4 Analytical Methodology

N/A, the proposed use is a non-food use on ornamentals and cut flowers.

5.1.5 Environmental Degradation

In aerobic soil, at 0.25 ppm, the half-life is 95 days. The major metabolite is 2,4-dichloroaniline which degrades slowly. Under anaerobic conditions in a water-sediment system, cyclanilide did not degrade. Cyclanilide is mobile to moderately mobile in soils. Degradation rates are slow during dry and cooler autumn and winter months but increase with increased moisture and warmth during spring and summer.

5.1.6 Comparative Metabolic Profile

N/A, the proposed use is a non-food use on ornamentals and cut flowers.

5.1.7 Toxicity Profile of Major Metabolites and Degradates

The proposed use is a non-food use on ornamentals and cut flowers so there is no food use involved. However, residues of 2,4-dichloroaniline and RPA 110516 (dechlorinated and rearranged parent compound) were included in the drinking water assessment because they were observed in significant quantities in the environmental fate studies.

5.1.8 Pesticide Metabolites and Degradates of Concern

The proposed use on ornamental and cut flowers is considered a non-food use.

Table 5.1.8 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Not applicable	Not applicable
	Rotational Crop	Not applicable	Not applicable
Livestock	Ruminant	Not applicable	Not applicable
	Poultry	Not applicable	Not applicable

Table 5.1.8 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression		
Matrix	Residues included in Risk Assessment	Residues included in Tolerance Expression
Drinking Water	Estimates of cyclanilide in surface water include two significant degradates, 2,4-dichloroaniline, and RPA 110516 (rearranged, dechlorinated parent).	Not Applicable

5.1.9 Drinking Water Residue Profile

Drinking water concentrations are based on modeling estimates provided by EFED (D334063; Tier I Drinking Water Assessment for Cyclanilide; James Breithaupt; 12/11/2006). The use on outdoor nursery plants was chosen for modeling since this use scenario is proposed by the registrant. According to the label, up to three applications are allowed with a maximum annual rate of 0.34 lb ai/A. Modeling was conducted using the maximum annual rate. Additional modeling demonstrated that using the maximum annual rate provided higher EECs than running three equal applications of 0.113 lb ai/A. The estimates of cyclanilide concentrations in surface water were based on the FIRST Model, and include two significant degradates, 2,4-dichloroaniline, and RPA 110516 (rearranged, dechlorinated parent) because these two residues were present in some of the environmental fate studies.

The FIRST modeling was performed with Index Reservoir (IR) scenarios and a percent cropped area (PCA) adjustment factor of 0.87 as a default value, according to the IR/PCA guidance from R.D. Jones *et al* (March 21, 2000).

Table 5.1.9 Summary of Estimated Surface Water and Groundwater Concentrations for Cyclanilide.		
	Cyclanilide	
	Surface Water Conc., ppb [a]	Groundwater Conc., ppb [b]
Acute	20.2	0.1
Chronic (non-cancer)	4.9	0.1
Chronic (cancer)	N/A	N/A

[a] From the Tier II PRZM-EXAMS - Index Reservoir model.
[b] From the SCI-GROW Model assuming a maximum seasonal use rate of 0.34 lb ai/A, a K_{oc} of 304, and a half-life of 91 days

5.1.10 Food Residue Profile

N/A, the proposed use is a non-food use on ornamentals and cut flowers.

5.1.11 International Residue Limits

N/A, the proposed use is a non-food use, on ornamentals and cut flowers.

5.2 Dietary Exposure and Risk

Unrefined or Tier I dietary exposure analyses were performed for acute and chronic exposures to cyclanilide using the DEEM-FCID Model. Tolerance-level residues (40 CFR §180.506) were assumed for both assessments. Acute exposure estimates at the 95th percentile for cyclanilide are below HED's level of concern for the general U.S population and all population subgroups. Tolerance-level exposure estimates for cyclanilide are below HED's level of concern for chronic exposure to the U.S. general population and all population subgroups. Anticipated residue data and/or percent crop data, as well as typical treatment parameters could be used to significantly refine dietary risk estimates.

5.2.1 Acute Dietary Exposure/Risk

Tolerance-level residues and 100% crop treated were assumed for the acute exposure estimates at the 95th percentile for cyclanilide. Dietary exposure to cyclanilide through drinking water is also being assessed. Exposure levels for the general U.S population and all population subgroups are below HED level of concern.

5.2.2 Chronic Dietary Exposure/Risk

Tolerance-level residues and 100% crop treated were assumed for the chronic dietary exposure assessment. Exposure levels for the general U.S population and all population subgroups are below HED's level of concern. Dietary exposure to cyclanilide through drinking water is being assessed. See Table 5.2.3.

Anticipated residue data and/or percent crop data, as well as typical treatment parameters could be used to significantly refine dietary risk estimates.

5.2.3 Cancer Dietary Risk

No cancer endpoint has been identified; however, being protective for any chronic effects would be protective for cancer.

Table 5.2.3. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Cyclanilide

Population Subgroup	Acute Dietary (95 Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk
General U. S. Population	0.001981	0.4	0.000442	6.3	N/A	N/A

Table 5.2.3. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Cyclanilide

Population Subgroup	Acute Dietary (95 Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk
All Infants (< 1 year old)	**0.005088**	**1.0**	0.000870	12		
Children 1-2 years old	0.004666	0.9	**0.001771**	**25**		
Children 3-5 years old	0.003280	0.7	0.001231	18		
Children 6-12 years old	0.002166	0.4	0.000753	11		
Youth 13-19 years old	0.001355	0.3	0.000373	5.3		
Adults 20-49 years old	0.001237	0.25	0.000289	4.1		
Adults 50+ years old	0.001146	0.23	0.000279	4.0		
Females 13-49 years old	0.001289	0.26	0.000288	4.1		

Note: %PADs reported to 2 significant figures.

5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

Anticipated residues and percent crop data were not used in these analyses.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no existing or proposed residential uses. Therefore, an assessment for residential handler and post-application exposure is not required. As a result, no residential exposure/risk assessments are needed and none were performed. No exposure/risk assessments were performed

for either residential handlers or for those who could potentially be exposed after application.

6.1 Residential Handler Exposure

There are no existing or proposed residential uses.

6.2. Residential Postapplication Exposure

There are no existing or proposed residential uses.

6.3 Other (Spray Drift, etc.)

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 the ground application method employed for cyclanilide. 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. On a chemical by chemical basis, 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 database 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 with specific products with significant risks associated with drift.

7.0 Aggregate Risk Assessments and Risk Characterization

An aggregated exposure risk assessment is not required since there are no residential uses for cyclanilide at this time. In addition, the toxicological effects via different exposure routes are not the same.

No cancer endpoint of concern for cyclanilide was identified; therefore, cancer risk was not assessed. Protecting for chronic effects would be protective of any cancer effects.

8.0 Cumulative Risk Characterization/Assessment

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information concerning the cumulative effects" of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to cyclanilide and any other substances, and cyclanilide does not appear to produce a toxic metabolite produced by other substances. For the purposes of this non-tolerance action, therefore, EPA has not assumed that cyclanilide has a common mechanism of toxicity with

other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

There is a potential for exposure to cyclanilide in occupational scenarios from handling cyclanalide products during the application process (*i.e.*, mixer/loaders, applicators, mixer/loader/applicators). As a result, a risk assessment has been completed for occupational handler scenarios.

9.1 Short-/Intermediate-Term Handler Risk

Exposure to pesticide handlers is likely during the occupational use of cyclanilide. The proposed use patterns and proposed labeling indicate several occupational exposure scenarios based on the types of equipment and techniques that can potentially be used for cyclanilide applications. The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios.

The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios.

Mixer/Loaders:
(1) Mixing/loading liquids for groundboom applications (PHED).
Applicators:
(2) Applying liquids with groundboom equipment (PHED).
Mixer/Loader/Applicators:
(3) Mixing/loading/applying liquids with low pressure handwand sprayer (PHED);
(4) Mixing/loading/applying liquids with a backpack sprayer (PHED).

The following data, assumptions and calculations were used to determine dermal and inhalation handler exposure.

Application Rate:

- The maximum application rates listed on the proposed label were used for all exposure scenarios. The maximum application rate for cyclanilide on ornamentals (including cut flowers) is 0.17 lb ai/A or 0.0017 lb ai/gal and 0.085 lb ai/A or 0.00085 lb ai/gal for non bearing fruit trees.

Area Treated

- Based on HED's Exposure Science Advisory Council Policy 9.1, 40 acres per day treated are assumed for applications using groundboom sprayer, as well as for applications using low pressure handwand and backpack sprayer.

Body Weight

- Body weight of an average adult male (70 kg) was used to complete the dermal and inhalation exposure risk assessment

Unit Exposure

- Occupational exposure estimates are based on surrogate data from PHED.

A summary of the short- and intermediate-term risks for each exposure scenario are presented below in Table 9.1. There are no data to assess baseline dermal risks for mixing/loading/applying via backpack sprayer equipment. Dermal risks are below HED's level of concern for handlers of these scenarios when chemical-resistant gloves are used in addition to baseline attire.

Table 9.1 Cyclanilide Occupational Handler Exposure and Risk (Short- and Intermediate-Term) for Agricultural and Commercial Uses

Exposure Scenario	Crop or Target	Application Rate[a]	Area Treated Daily[b]	Baseline[c] MOE[d] (unless indicated otherwise)	
				Dermal (Target MOE =100)	Inhalation (Target MOE =100)
Mixer/Loader					
1) Mixing/Loading Liquid Concentrates for Groundboom Applications (PHED)	Ornamentals and Cut Flowers	0.017 lb ai/acre	40 acres	36,000	340,000
	Fruit Tree (non-bearing ornamental)	0.085 lb ai/acre	40 acres	7,100	69,000
Applicator					
2) Applying Sprays via Groundboom Equipment (PHED)	Ornamentals and Cut Flowers	0.017 lb ai/acre	40 acres	7,100,000	560,000
	Fruit Tree (non-bearing ornamental)	0.085 lb ai/acre	40 acres	1,500,000	110,000
Mixer/Loader/Applicator					
3) Mixing/Loading/ Applying Liquid Concentrates with Low - Pressure Handwand (PHED)	Ornamentals and Cut Flowers	0.0017 lb ai/gallon	40 gallons	10,000	140,000
	Fruit Tree (non-bearing ornamental)	0.00085 lb ai/gallon	40 gallons	20,000	270,000

Table 9.1 Cyclanilide Occupational Handler Exposure and Risk (Short- and Intermediate-Term) for Agricultural and Commercial Uses

Exposure Scenario	Crop or Target	Application Rate[a]	Area Treated Daily[b]	Baseline[c] MOE[d] (unless indicated otherwise)	
				Dermal (Target MOE =100)	Inhalation (Target MOE =100)
4) Mixing, Loading/ Applying Liquid Concentrates with a Backpack Sprayer (PHED)	Ornamentals and Cut Flowers	0.0017 lb ai/gallon	40 gallons	420,000 (w/gloves)	140,000
	Fruit Tree (non-bearing ornamental)	0.00085 lb ai/gallon	40 gallons	830,000 (w/gloves)	270,000

a Application rates are the maximum application rates determined from proposed cyclanilide label.

b Amount handled per day values are HED estimates of acres or gallons applied based on Exposure SAC SOP #9.1 "Standard Values for Daily Acres Treated in Agriculture," industry sources, and HED estimates.

c Exposures and risks are presented for baseline conditions, except for the backpack sprayer scenario. For the backpack sprayer scenario, dermal unit exposures are not available at the baseline level.
Baseline Dermal: Long-sleeve shirt, long pants, no gloves.
Baseline Inhalation: no respirator
PPE = i.e., long-sleeve shirt, long pants, gloves.

d Dermal MOE = NOAEL (1,000 mg/kg/day) dermal daily dose (mg/kg/day), where dermal dose = daily unit exposure (mg/lb ai) x application rate x amount handled per day/body weight (70 kg).
Inhalation MOE = NOAEL (4 mg/kg/day)/inhalation daily dose (mg/kg/day), where inhalation dose = daily unit exposure (µg/lb ai) x application rate x amount handled per day x conversion factor (1 mg/1,000 µg)/body weight (70 kg).

9.2 Short-/Intermediate-Term Postapplication Risk

HED uses the term "postapplication" to describe exposures to individuals that occur as a result of being in an environment that has been previously treated with a pesticide (also referred to as reentry exposure).

There is potential for postapplication worker exposure from entering areas previously treated with cyclanilide. For cyclanilide, the exposure durations for noncancer postapplication risk assessment were short-term (<30 days) and intermediate-term (greater than 30 days up to several months). However, since the short- and intermediate-term exposures are the same for the toxicological endpoints of concern, the short- and intermediate-term postapplication risks are numerically identical.

Inhalation exposures are thought to be negligible in outdoor postapplication scenarios, since cyclanilide has low vapor pressure and the dilution factor outdoors is considered infinite.

Data/Assumptions for Postapplication Exposure

A series of assumptions and exposure factors served as the basis for completing the occupational postapplication worker risk assessments. Each assumption and factor is detailed below on an individual basis. In addition to these values, transfer coefficient values were used to calculate risk estimates. The assumptions and factors used in the risk calculations are presented below:

- In the postapplication risk assessment, maximum application rates were considered.

- Levels of Concern: HED has established levels of concern (LOC) for occupational postapplication risks – margins of exposure of less than 100 for occupational noncancer dermal and inhalation risks are a concern.

- Dislodgeable Foliar Residues: No cyclanilide-specific dislodgeable foliar residue (DFR) data were available. Therefore, this assessment uses HED's default assumption that 20 percent of the application rate is available on day 0 and the residue dissipates at a rate of 10 percent per day.

- Exposures were calculated to reflect default DFR values over time coupled with surrogate transfer coefficients. The transfer coefficients were taken from HED's revised policy entitled Policy 003.1 Science Advisory Council for Exposure Policy Regarding Agricultural Transfer Coefficients (August 7, 2000).

Postapplication Exposure and Risk Estimates

Postapplication risks diminish over time because cyclanilide residues eventually dissipate in the environment. As a result, risks were calculated over time based on changing residue levels. A summary of the noncancer postapplication risks is provided in Table 9.2. The occupational

1. DAT = Days after treatment
2. DFR = Dislodgeable Foliar Residue = application rate (lb ai/A) x (1- daily dissipation rate) x 4.54E8 ug/lb x 24.7E-9 A/cm2 x % DFR after initial treatment.
3. Daily Dose = [DFR (ug/cm2) x Tc (cm2/hr) x 0.001 mg/ug x dermal absorption x 8 hrs/day] /body weight (70 kg)
4. MOE = NOAEL (1000 mg/kg/day)/Dose.

postapplication exposure and risk assessment for agricultural crop uses of cyclanilide indicates that risks are not a concern at day 0.

In cases where the risk assessment reveals little postapplication risk concern such as this, the Worker Protection Standard for Agricultural Pesticides mandates that a minimum restricted-entry interval be established based on the acute toxicity of the active ingredient for acute dermal toxicity, skin irritation potential, and eye irritation potential. Since cyclanilide is classified as toxicity category II for eye irritation potential, a REI of 24 hours is appropriate for all activities.

Table 9.2: Cyclanilide Postapplication Exposure and Risk

Crop	Crop Grouping	Application rate (lb ai/acre)	Transfer Coefficient	DAT [1] (Days)	Dose (mg/kg/day) [3]	MOE [4]
Ornamentals	N/A	0.17	400 (all tasks)	0	0.0017	57,000
Non-bearing Fruit Trees (ornamental)	N/A	0.085	400 (all tasks)	0	0.0087	115,000
Flowers or foliage grown for cuttings	Flowers, cut (ornamental)	0.17	5,100 (harvesting cut flowers)	0	0.22	4,500
			400 (transplanting, budding, crop maintenance tasks)	0	0.0017	57,000

10.0 Data Needs and Label Recommendations

The proposed label does not state the maximum seasonal application rate or the maximum number of applications. The registrant provided a maximum seasonal rate of 0.34 lb ai/acre and indicated that there would be up to three applications/season. The registrant must submit a revised label that reflects a maximum of 3 applications and a maximum seasonal application rate of 0.34 lbs ai/acre.

10.1 Toxicology

None.

10.2 Residue Chemistry

There are no residue chemistry data deficiencies.

10.3 Occupational and Residential Exposure

None.

References:

D334063; Tier I Drinking Water Assessment for Cyclanilide; James Breithaupt; 12/11/2006.

D334912; Cyclanilide: Occupational and Residential Exposure Assessment for the Ornamental Uses. Section 3 registration. Margarita Collantes.

D333238; Cyclanilide: Acute and Chronic Dietary Exposure Assessments for Cyclanilide including Drinking Water Estimates for Ornamental/Cut Flower Use. PC Code: 026201. Dennis McNeilly, Feb 7, 2007.

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for cyclanilide are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used. NOTE: The proposed use being evaluated is a non-food use on ornamentals; however, there is an existing use on cotton which is considered a food use.

Table A.1. Toxicology Data Requirements. Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	Yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	no	-
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	no	-
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200b	Carcinogenicity (mouse)	yes	yes
870.4300	Chronic Toxicity/Carcinogenicity (rat)	yes	yes
870.5100	Mutagenicity--Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity--Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity--Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity--Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90-Day Neuro. Screening Battery (rat)	yes	yes
870.6300	Develop. Neuro	no	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	yes

Table A.1. Toxicology Data Requirements. Test	Technical	
	Required	Satisfied
Special Studies for Ocular Effects		
Acute Oral (rat)	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)	no	-

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile - Test Substance				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral - rat	43368424	LD_{50} = 315 mg/kg (males) LD_{50} = 208 mg/kg (females)	II
870.1200	Acute dermal - rabbit	4336825	LD_{50} >2000mg/kg	III
870.1300	Acute inhalation - rat	43868310	LC_{50} > 2.64 mg/L	IV
870.2400	Acute eye irritation - rabbit	43368430	Conjunctivitis and corneal opacity with epithelial sloughing-Resolved by day 14.	II
870.2500	Acute dermal irritation - rabbit	43368431	Slight erythema, resolved by 72 hours. Primary irritation index= 0.17	IV
870.2600	Skin sensitization - guinea pig	43368433	Negative Buehler test	-

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	43368440 (1992) M/F: 0, 400, 800 and 1600 ppm M: 0, 27, 55 and 113 mg/kg/day F: 0, 32, 62 and 121 mg/kg/day Acceptable/guideline	NOAEL (M/F): 55/62 mg/kg/day LOAEL (M/F): 113/121 mg/kg/day based on decreases in body weight, body weight gain, increased absolute and/or relative liver weight, and the occurrence of handling-induced rigidity.
870.3100	90-Day oral toxicity (mouse)	43368439 (1993) M/F: 0, 40, 200, 2000 and 4000 ppm M: 0, 8, 38, 364 and 741 mg/kg/day F: 0, 9, 43, 416, and 788 mg/kg/day Acceptable/guideline	NOAEL (M/F): 38/43 mg/kg/day LOAEL (M/F) = 364/416 mg/kg/day based on mortality, elevated alkaline phosphatase, increased absolute liver weights, focal hepatocellular necrosis (1 male) and the occurrence of handling induced rigidity (1 male).
870.3200	21 - Day dermal toxicity (rabbit)	43868311 (1995) M/F: 0, 100, 500 or 1000 mg/kg Acceptable/guideline	NOAEL: 1000 mg/kg LOAEL: > 1000 mg/kg
870.3700a	Prenatal developmental in (rat)	43368443 (1990) 0, 3, 10 and 30 mg/kg/day for GD 6-16. Acceptable/guideline	**Maternal** NOAEL = 10 mg/kg/day **Maternal** LOAEL = 30 mg/kg/day based on decreased body weight gain and reduced food consumption. **Developmental** NOAEL = 30 mg/kg/day (HDT) **Developmental** LOAEL = >30 mg/kg/day based on no dose-related effects in the main study. Developmental effects however, were observed in the range-finding study at 75 mg/kg/day and included increased incidence of gastroschisis (hernia) and anophthalmia/microphthalmia (no eyes/small eyes).
870.3700b	Prenatal developmental in (rabbit)	43368445 (1991) 0, 3, 10 and 30 mg/kg/day (oral gavage) Acceptable/guideline	**Maternal** NOAEL = 10 mg/kg/day **Maternal** LOAEL = 30 mg/kg/day based on clinical signs and decreased body weight gain. Signs included wobbly gait, partial hindlimb paralysis, decreased activity, salivation, emaciation, hair loss, and no feces. **Developmental** NOAEL = 30 mg/kg/day **Developmental** LOAEL = >30 mg/kg/day based on no dose-related effects in the main study.

Table A.2.2	Subchronic, Chronic and Other Toxicity Profile		
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3800	Reproduction and fertility effects (species)	43868313 (1994) 0, 30, 300 and 1000 ppm P Males: 0, 1.9, 19.0 and 64.1 mg/kg/day F1 Males: 0, 2.0, 20.2 and 70.4 mg/kg/day P Females: 0, 2.3, 21.8 and 84.5 mg/kg/day F1 Females: 0, 2.4, 25.9 and 85.7 mg/kg/day Acceptable/guideline	**Parental Systemic** NOAEL (M/F) = not established **Parental Systemic** LOAEL (M/F)= 2.0/2.4 mg/kg/day based on reductions in mean body weights in both sexes and increased mineralization in the renal papilla of adult F1 females. **Offspring** NOAEL=2.3 mg/kg/day **Offspring** LOAEL= 21.8 mg/kg/day based on decreased mean pup weight. **Reproductive** NOAEL (M/F) = 70.4/85.7 mg/kg/day **Reproductive** LOAEL (M/F) = not observed.
870.4100b	Chronic toxicity (dog)	43368441 (1994) M/F: 0, 40 160 and 640 ppm M: 0, 1.5, 5.3 and 21.2 mg/kg/day F: 0, 1.3, 5.2, 21.5 and 21.5 mg/kg/day Acceptable/guideline	**NOAEL** M/F: 5.3/5.2 mg/kg/day **LOAEL** M/F: 21.2/21.5 mg/kg/day based on decreased weight gain, gross and histological liver lesions and increases in ALT and AST enzyme levels.
870.4100a	Chronic toxicity/ Carcinogenicity (rat)	43868314 (1995) M/F: 0, 50, 150, 450 and 1000 ppm M: 0, 2.0, 6.2, 18.9 and 43.1 mg/kg/day F: 0, 2.6, 8.1, 25.5 and 58.6 mg/kg/day Acceptable/guideline	**NOAEL** M/F: ≥43.1/8.1 mg/kg/day **LOAEL** M/F: not established / 25.5 mg/kg/day based on decreased body weight gains and microscopic changes in the liver in females (increased incidence of periportal and panlobular hypertrophy). **No evidence of carcinogenicity**
870.4300	Carcinogenicity (mouse)	43868312 (1995) M/F: 0, 50, 250 and 1000 ppm M: 0, 8.4, 41.8 and 168 mg/kg/day F: 0, 10.6, 52.4 and 206 mg/kg/day Acceptable/guideline	**NOAEL** M/F: 41.8/52.4 mg/kg/day **LOAEL** M/F: 168/206 mg/kg/day based on decreased body weight gain. **No evidence of carcinogenicity**

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5500	Gene Mutation *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay	43368446 (1992) 100, 333, 667, 1000, 3330 and 5000 µg/plate, +/- S9. *S. typhimurium* strains: TA98, TA100, TA1535, TA1537 and TA1538. Acceptable/guideline	Negative Cytotoxic at 3330 µg/plate and above.
870.5500	Gene Mutation. *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay	43868208 (1995) Six concentrations ranging from 100 to 5000 µg/plate +/- S9. *S. typhimurium* strains: TA98, TA100, TA1535 and TA1537; *E. coli* strain WP2*uvr*A Acceptable/guideline	Negative Cytotoxic at 3000 µg/plate and above.
870.5300	*In vitro* mammalian cell gene mutation test	43368449 (1994) Unacceptable	Repeat assay is required to confirm the stated "negative," especially under activation conditions.
870.5300	*In vitro* mammalian gene cell mutation test	43868211 (1995) Tested in CHO cells (+/- S9) for evaluation of induced forward mutations at the HGPRT locus up to doses resulting in severe cytotoxicity and/or precipitation (-S9: 800µg/mL , +S9: 600 µg/ml) Acceptable/Guideline	Negative
870.5375	Chromosomal Aberration *in vitro* (CHO cells)	43368448 (1994) Acceptable/guideline	-S9: Negative up to doses producing moderate to severe cytotoxicity (204-298 µg/mL) +S9: Induced aberrations and polyploidy in presence of only slight to moderate cytotoxicity (987, 1020 and 1270 µg/mL)

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5375	Chromosomal Aberration *in vitro* (CHO cells)	43868210 (1995) Acceptable/guideline	-S9: Negative at levels up to the cytotoxic doses (≥204 µg/ml; *18- or 42-hour cell treatments*) +S9: significant increases in structural chromosomal aberrations were observed over a narrow dose range (987-1270 µg/mL) that included severely cytotoxic doses (≥1270 µg/mL- 18-hour recovery). Structural aberrations and polyploidy cells were also significantly increased at 1020 and 1270 µg/mL after 41-hour recovery time.
870.5395	*In vivo* Mammalian Erythrocyte Micronucleus Test: Mouse	43868209 (1995) First exp: 20 h harvest -S9: 24.7 to 296 µg/mL +S9: 172 to 1480 µg/mL Repeat exp: 20 and 44 h harvest -S9: 25.5 to 255 µg/mL +S9: 255 to 1270 µg/mL Acceptable/guideline	Negative
870.5395	*In vivo* Mammalian Erythrocyte Micronucleus Test: Mouse	43368447 (1994) Single doses of test article up to 225 mg/kg, which caused ataxia and death. Acceptable/guideline	Negative
870.5550	*In Vivo/In Vitro* unscheduled DNA synthesis	44518601 (1998) Sprague Dawley rats were treated with 0, 60, 120 or 250 mg/kg. Primary hepatocyte cultures harvested at 2-4 hour or 15-16 hours. Acceptable/guideline	Negative

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	***MRID No. (year)*/ Classification /Doses**	**Results**
870.6200a	Acute neurotoxicity screening battery	43368436 (1994) M/F: 0, 15, 50 and 150 mg/kg Acceptable/guideline	**NOAEL**: 50 mg/kg **LOAEL**: 150 mg/kg, based on gait abnormalities, increased abdominal muscle tone, and slightly decreased motor activity test.
870.6200b	Subchronic neurotoxicity screening battery	43368435 (1994) M/F: 0, 50, 450 and 1200 ppm M: 0, 3.3, 29.7 and 78.6 mg/kg/day F: 0, 4.0, 35.8, 93.9 mg/kg/day Acceptable/guideline	**NOAEL**: 4.0 mg/kg/day **LOAEL**: 35.8 mg/kg/day based on increased motor activity and decreased body weight in females.
870.7485	Metabolism and pharmacokinetics (rat)	43868316 (1995) Acceptable/guideline	Rapidly absorbed after oral administration. Principal route of elimination by renal excretion of parent compound and amino acid conjugates. Methylation was a minor metabolic pathway.
870.7600	Dermal penetration (rat)	48368317 (1995) M: 0, 0.04, 0.4 and 4 mg/animal [U-phenyl ^{14}C]Cyclanilide Acceptable/guideline	A dermal absorption factor of **8.65%** from the combined radioactivity absorbed and that remaining in/on the skin at the 10 hour exposure duration for the high dose is considered appropriate for use in risk assessment.

A.3 Executive Summaries

0A.3.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity – Rat

In a subchronic dietary study (MRID 43368440), groups of 20 male and 20 female Sprague-Dawley CD® rats were fed diets containing RPA-90946 (purity 99.0%) at concentrations of 0, 400, 800, or 1600 ppm for 13 weeks. The mean consumption of RPA-90946 in the three dose groups was 27, 55, or 113 mg/kg/day for males and 32, 62, or 121 mg/kg/day for females. Handling-induced rigidity in high-dose males and females, judged to be treatment related, was the only clinical sign observed. High-dose males had significantly lower mean body weights (12-17%, $p < 0.01$) and body weight gains (18-68%, $p < 0.01$) relative to controls throughout the 13-week study; the differences from controls diminished with time. High-dose females had statistically significant decreases in mean body weights (5-8%), and in body weight gains (16-39%) relative to controls during the first two months of treatment ($p<0.05$ or $p<0.01$), but by week 9 the decreases were not statistically significant. Food consumption (g/kg/day) was

markedly lower during the first week of treatment in high-dose males (31% lower, $p<0.01$) and females (26% lower, $p<0.01$). For weeks 2-13, the g/kg food intake by high-dose males was increased (8-13%, $p<0.01$ for most weeks), whereas consumption by females was slightly decreased (6-9% lower; $p<0.05$ or $p<0.01$) compared to controls. In mid-dose males and females, there were small, statistically significant decreases in body weights, body weight gains, and food consumption primarily during the first and/or second week of treatment. Food efficiency was markedly lowered during the first week in male high-dose rats; minor decreases were seen during the first or second week in mid-dose males and females. A statistically significant increase (7%) in liver weight relative to body weight was noted in high-dose males. Slight increases in aspartate aminotransferase (30%) and alkaline phosphatase (60%) were also noted ($p\leq0.01$) in high-dose males but a clear correlation with the increase in relative liver weight could not be made because absolute liver weights were slightly decreased as were body weights at termination. High-dose females had increased ($p\leq0.01$) absolute and relative liver weights (15-20%) but no increases in enzyme activity. Although there were no histopathological findings in this study, the liver weight and enzyme changes taken together in both sexes at 1600 ppm suggest treatment-related effects in the liver, especially since other animal studies with this chemical have shown the liver to be a target organ. Minor, but statistically significant decreases in various clinical chemistry parameters (glucose, serum globulins, total protein, calcium) and alterations in several organ weights (kidney, ovary, testes, thyroid with parathyroid) in the 800 and/or 1600 ppm group rats were of questionable toxicological significance with no histopathological correlates, as were increases in liver weight relative to body weight (<10%, $p\leq0.05$) in the low and mid-dose females. The magnitude of the clinical chemistry parameter decreases was somewhat greater at 1600 ppm. The study report author set the NOAEL/LOAEL at 400/800 mg/kg/day based on changes in body weight, body weight gains, and food consumption primarily in the first 2 weeks of the study and on minor decreases in glucose, total protein, and globulins in the 800 ppm groups. Toxicology Branch does not think that the changes in the 800 ppm groups are of toxicological significance. The NOAEL for males and females is 800 ppm and the LOAEL is 1600 ppm for males and females based on decreases in body weight, body weight gain, increased absolute and/or relative liver weight, and the occurrence of handling-induced rigidity. This study is classified Core Guideline and satisfies the guideline requirement for a subchronic dietary toxicity study (82-1) in rats.

870.3100 90-Day Oral Toxicity – Mouse

In a subchronic oral toxicity study (MRID 43368439), technical cyclanilide (97.4%) was administered to CRL: CD-1 (ICR)BR mice. Ten males and 10 females per group were administered test material at dietary concentrations of 0, 40, 200, 2000, or 4000 ppm for 3 months, corresponding to average doses of 0, 8, 38, 364, and 741 mg/kg/day for males and 0, 9, 43, 416, and 788 mg/kg/day for females.

Three males and 1 female in the 2000 ppm dose groups and 1 male and 5 females in the 4000 ppm dose groups died, with 8/10 deaths occurring in the first 3 weeks of treatment. No cause of death could be determined. Males in the 4000 ppm group had statistically significantly ($p\leq0.05$) decreased body weight and body weight gains over the course of the study with a mean body weight gain of 14% compared to 23% for controls at week 13. Females in the 4000 ppm group

had statistically significantly decreased body weight from weeks 1-6 ($p \leq 0.5$) and body weight gains from weeks 1-9 ($p \leq 0.1$), with a mean body weight gain of 20% over the course of the study compared to 27% for controls. Generalized or hindquarter rigidity was seen in 2 males and 4 females in the 4000 ppm group, mostly during the first 2 weeks of the study, and in 1 male from the 2000 ppm group the day before dying. Non-specific signs seen in animals near the time of death included lethargy, hypothermia, pallor and/or yellow staining of the anogenital area, tremors, irregular gait, dyspnea, and/or poor condition. Serum alkaline phosphatase values were increased in the male and female 4000 ppm groups ($p \leq 0.01$) and the male and female 2000 ppm groups ($p \leq 0.05$). Absolute and relative liver weights were significantly higher for the male and female 2000 and 4000 ppm groups ($p \leq 0.01$). Focal hepatocellular necrosis was seen in 1 male from the 2000 ppm group which died as well as 1 surviving male and 1 surviving female from the 4000 ppm groups.

The NOAEL is 200 ppm in males and females (38/43 mg/kg/day for males/females) and the LOAEL is 2000 ppm in males and females (364/416 mg/kg/day males/females) based on mortality, elevated alkaline phosphatase, increased absolute and relative liver weights, focal hepatocellular necrosis (1 male), and the occurrence of handling induced rigidity (1 male). At 4000 ppm (741/788 mg/kg/day males/females), decreased body weights and body weight gains in males and females occurred. This study is Core Guideline and satisfies the 82-1 Guideline requirement for a subchronic mouse study. The absence of cholesterol was not critical.

870.3200 21/28-Day Dermal Toxicity – Rat

In a repeated dose dermal toxicity study (MRID 43868311), RPA 90946 (cyclanilide, 98.8% ai) was applied to the shaved skin of five adult Hra:(NZW)SPF rabbits/sex/dose at dose levels of 0, 100, 500, or 1000 mg/kg for 6 hours/day, 5 days/week, for 3 weeks.

RPA 90946 had no observed toxic effect on the rabbits in this study. For all treatment groups, there were no clinical signs of toxicity, and body weights, body weight gains, and food consumption were similar to the controls. There were no differences in hematology parameters, clinical blood chemistry, organ weights, or macroscopic or microscopic organ morphology between rabbits in the treated and the control groups. No neoplastic tissue was observed. Ophthalmoscopic examinations and urinalysis were not performed. No LOAEL was established in this study. The NOAEL was 1000 mg/kg.
This dermal toxicity study is classified acceptable and satisfies the guideline requirement for a repeated dose dermal toxicity study.

A.3.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat

Ccyclanilide technical (MRID 43368443) was administered to 25 female Sprague Dawley rats per group, via a corn oil gavage at 0, 3.0, 10.0 or 30.0 mg/kg/day for gestational days 6 through 16. Developmental toxicity was studied externally, viscerally and skeletally at gestational day 20.

No dose related developmental toxicity was seen in the main study. Although, the incidence of 14th rudimentary rib was statistically significantly increased in litters at 30 mg/kg/day in the main study, it was within historical control range and no dose relationship was seen at 10, 25 (Screening study) and 30 mg/kg/day. Thus, the increase in the main study was considered incidental.

Maternal body weight gain was decreased at 30.0 mg/kg/day gestational day 6-9 and 6-16 (25% from control, $p \leq 0.01$) and food consumption was decreased at 30.0 mg/kg/day and gestational day 6-9 ($p \leq 0.01$), 9-12 ($p \leq 0.05$) and 6-16 (14% from control, $p \leq 0.01$).

The incidence of mortality, ataxia and labored breathing were increased in the screening study at 75 mg/kg/day and reduced viable fetuses and increased post-implantation loss in 4/10 survivors at 75 mg/kg/day were observed. The incidence of gastroschisis (hernia) and anophthalmia/microphthalmia (no eyes/small eyes) was increased in the survivors in the screening study at 75 mg/kg/day.

The maternal NOAEL/LOAEL were 10.0/30.0 mg/kg/day based on decreased body weight gain and reduced food consumption. The developmental NOAEL/LEL were 30.0/>30 mg/kg/day based on no dose related effects in the main study.

Core classification: Guideline. The study (MRID# 43368443) is acceptable under guideline 83-3 for a developmental toxicity in rats.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

Cyclanilide technical (98.04%)(MRID 43368445) was administered to artificially inseminated New Zealand White rabbits at doses of 0, 3, 10, and 30 mg/kg/day by oral gavage during gestation days 6-18. Animals were sacrificed on day 29.

The maternal NOAEL/LOAEL is 10/30 mg/kg/day based on clinical signs and decreased body weight gain. Signs included wobbly gait, partial hindlimb paralysis, decreased activity, salivation, emaciation, hairloss, and no feces. The high-dose group gained a mean of 22 grams during treatment compared to a mean weight gain of 209 grams for controls.

The NOAEL/LOAEL for developmental toxicity is 30/>30 mg/kg/day. Mean numbers of corpora lutea, implantation sites, viable fetuses, post-implantation loss, gravid uterine weight, fetal body weights, and fetal sex ratios were similar between all groups. Post-implantation loss was increased compared to concurrent controls (principally due to total resorption by 1 female), but was within the historical range. No treatment induced variations or malformations were seen. This study is core guideline and satisfies the guideline requirement for a developmental study in rabbits.

A.3.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat

In a 2-generation reproduction study (MRID 43868313) RPA 90946 (cyclanilide, 99.2% a.i.) was administered to 30 Sprague Dawley rats/sex/dose in the diet at dose levels of 0, 30, 300, or 1000 ppm in the diet (equivalent to doses of 0, 1.9, 19.0, or 64.1 mg/kg/day for P males; 0, 2.0, 20.2, or 70.4 mg/kg/day for F_1 males; 0, 2.3, 21.8, or 84.5 for P females; 0, 2.4, 25.9, or 85.7 mg/kg/day for F_1 females). Exposure to P animals (30/sex/dose) began at 7 weeks of age, 10 weeks prior to mating to produce F_1 pups. Upon weaning, F_1 pups (30/sex/dose) were selected to become parents of the F_2 generation and were given the same concentration test diets as their dams beginning 11 weeks prior to mating. All animals were mated on a 1:1 ratio.

Parental toxicity at 1000 ppm included treatment-related reductions in mean body weights, body weight gains and food consumption values in both sexes and generations; treatment-related reductions in absolute and relative liver weights for the P (and F_1 males). At 300 ppm, treatment-related reductions in mean body weights, body weight gains and food consumption were observed occasionally in both sexes. Reduced body weight was observed in pre-mating F_1 males and females at 30 ppm. There were no treatment-related microscopic findings for any treatment group for the P parental generation. For the F_1 generation, treatment-related renal histopathology revealed mineralization of the renal papilla and microscopic calculi in the renal pelvis in the F_1 generation only (minimal to mild) at 1000 and 300 ppm of both sexes and in the 30 ppm group in females. The parental systemic LOAEL is 30 ppm (2.0 mg/kg bw/day in males, 2.4 mg/kg bw/day in females), based on reductions in mean body weights in both sexes and increased mineralization in the renal papilla of adult F_1 females. The parental systemic NOAEL was not established.

In the offspring, there were no treatment-related clinical signs or changes in mean litter size or viability indices in the F_1 or F_2 generation pups. Treatment-related decreases in mean pup weights were observed in both sexes at 300 and 1000 ppm. Mean pup weights were reduced 10-32% at 1000 ppm throughout lactation for both generations and by 9% on day 21 of lactation for the F_1 generation at 300 ppm. Relative liver weights were increased while absolute liver weights were decreased in F_1 and F_2 males and females at 1000 ppm. The offspring LOAEL is 300 ppm (21.8 mg/kg/day) based on decreases in mean pup weights. The offspring NOAEL is 30 ppm (2.3 mg/kg/day).

No adverse reproductive effects were observed at any dose. Estrous cycle length and periodicity, sperm measures and sexual maturation measurements were not performed; however there were no indications of treatment-related fertility abnormalities in this study. In a range-finding study, reproductive effects were seen at 1400 ppm (77.1 mg/kg/day) including reduced mating indices, reduced gestation index, decreased mean implantation sites, decreased pup weight and increased pup mortality. Under the conditions of this study, the reproductive NOAEL is 1000 ppm (70.4 mg/kg/day in males and 85.7 mg/kg/day in females), the highest dose tested. This study is acceptable (guideline) and satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800); OECD 416 in rat.

A.3.4 Chronic Toxicity

870.4300 Combined Chronic Toxicity/Carcinogenicity – Rat

In a combined chronic/carcinogenicity study (MRID 43868314), RPA 90946 (99.2% a.i.) was

administered to 50 CD rats/sex/dose in the diet at dose levels of 0, 50, 150, 450 or 1000 ppm (0, 2.0, 6.2, 18.9, or 43.1 mg/kg/day for males and 0, 2.6, 8.1, 25.5, or 58.6 mg/kg/day for females) for 23 months. In addition, a satellite group of 10 rats/sex/group was included for sacrifice at 12 months.

Chronic toxicity observed in females dosed at 450 or 1000 ppm (25.5 mg/kg/day or 58.6 mg/kg/day, respectively) included significantly decreased body weight gains (14% and 22% lower than in controls at 53 weeks) and an increased incidence of periportal and panlobular hypertrophy. Hepatocellular hypertrophy was detected in 30% (18/60) of the 450 ppm group females and 73% of the 1000 ppm group females compared to 0-5% in the controls and other treated groups. No compound-related toxicity was noted in males at the HDT of 1000 ppm (43.1 mg/kg/day).

The chronic LOAEL in females is 450 ppm, equivalent to 25.5 mg/kg/day, based on decreased body weight gains and microscopic changes in the liver. The chronic NOAEL in females is 150 ppm, equivalent to 8.1 mg/kg/day. The chronic LOAEL in males is > 1000 ppm (HDT) and the chronic NOAEL in males is ≥ 1000 ppm, equivalent to 43.1 mg/kg/day.

Combined hepatocellular adenomas and carcinomas were increased (0, 0, 1, 1, 4) in females at 1000 ppm (58.6 mg/kg/day).

Dosing was considered adequate based on decreased body weight gains and an increase in non-neoplastic lesions relative to the controls in the mid- and high-dose females. In addition, a previous 24-month study in rats was terminated at 6 months due to excessive mortality at 1600 ppm dietary concentration. This study is classified Acceptable/Guideline and satisfies the guideline requirements for a chronic toxicity study (§83-1) and a carcinogenicity study (§83-2) on the rat.

870.4100b Chronic Toxicity – Dog

In a chronic oral dietary study (MRID 43368441) initiated 3/18/92 and terminated 3/22/93, technical cyclanilide (97.4%) was administered to Beagle dogs. Five male and 5 females per group received doses of 0 ppm, 40 ppm, 160 ppm, or 640 ppm, equivalent to 0, 1.5, 5.3, and 21.2 mg/kg/day for males and 0, 1.3, 5.2, and 21.5 mg/kg/day for females. Treatment-related effects were seen in only the high-dose group of 640 ppm.

Males and females in the high-dose group had decreased body weights at termination with statistically significant decreases for males from weeks 46-52. Males in the high-dose group had a weight gain of 0% compared to 28% for male controls while females in the high-dose group had a weight gain of 1% compared to 23% for female controls at termination. Livers of 3/5 high-dose males had red and/or tan discoloration, rough surface, small size, cysts and/or nodules on gross exam. Histological findings in high-dose males and female livers included centrilobular degeneration and necrosis with subacute/chronic inflammation, post-necrotic scarring, and regenerative hypertrophy/hyperplasia; focal hemorrhages, hyperplastic bile ducts (males only), vascular congestion, extramedullary hematopoiesis, and brown pigment in reticuloendothelial cells and hepatocellular cytoplasm. Brown pigment in cytoplasm of epithelium lining the convoluted tubules of the kidney was seen in high-dose dogs. Elevations of ALT and AST

enzyme values in high-dose males were progressive with time, effects beginning after 3 months of treatment. Slight elevations of ALT enzyme values in high-dose females ($p \leq 0.05$) and serum alkaline phosphatase values in high-dose males occurred at termination. The increases in enzyme activity correlate with the gross and histological lesions seen in the livers of high-dose animals. Serum phosphorous was decreased in high-dose males and mid and high-dose females but was not clearly related to treatment.

The LOAEL of 640 ppm (21.2 and 21.5 mg/kg/day for males/females) is based on decreased weight gain, gross and histological liver lesions and increases in ALT and AST enzyme levels. The NOAEL is 160 ppm (5.3 and 5.2 mg/kg/day for males/females). This study is Core Guideline and satisfies the 83-1 guideline requirement for a chronic feeding study in dogs. Special Review Criteria: None.

A.3.5 Carcinogenicity

870.4200a- See above (Combined Chronic Toxicity/Carcinogenicity- Rat)
870.4200b Carcinogenicity (feeding) – Mouse

In a mouse carcinogenicity study (MRID 43868312), RPA 90946 (99.2% a.i., Lot# DA 674) was administered to 60 CD-1 mice/sex/dose in the diet at dose levels of 0, 50, 250, or 1000 ppm (0, 8.4, 41.8, or 168 mg/kg/day for males, and 0, 10.6, 52.4, or 206 mg/kg/day for females) for 18 months.

At 1000 ppm male and female mice exhibited significant decreases in weight gains. Liver weights in high dose animals were elevated significantly, relative to body weight, by 16% in high dose males and 11% in high dose females; absolute liver weight increased 10% in high dose males. The chronic LOAEL is 1000 ppm in males and females, equivalent to 168 mg/kg/day in males and 206 mg/kg/day in females, based on decreased body weight gain and elevated liver weights. The chronic NOAEL in males and females is 250 ppm, equivalent to 41.8 mg/kg/day in males and 52.4 mg/kg/day in females, respectively.

Under the conditions of this study, there was no evidence of carcinogenic potential. This study is classified as acceptable and satisfies the guideline requirements for a carcinogenicity study (§83-2b) on the mouse.

A.3.6 Mutagenicity

870.5100 Bacterial reverse mutation test MRID 43868446 Acceptable/Guideline	*Salmonella typhimurium*. The test with 98.09% a.i. was negative in all strains up to cytotoxic concentrations (≥3330 µg/plate –S9; 5000 µg/plate +S9)

870.5100 Bacterial reverse mutation test MRID 43868208 Acceptable Guideline	*Salmonella typhimurium/Escherichia coli*. Independently performed trials with 97.9% a.i. were negative up to doses (≥3330 µg/plate –S9; 5000 µg/plate ± S9) that were cytotoxic for the majority of *S. typhimurium* strains or up to the highest concentrations tested (5000 µg/plate ± S9) in *E. Coli*.

870.5300, *In vitro* mammalian cell gene mutation test MRID 43368449 Unacceptable	Reportedly negative for inducing forward mutations at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus in Chinese hamster ovary (CHO) cells exposed to test article up to cytotoxic concentration (600-800 µg/ml) ±S9. A repeat assay is required to confirm the stated "negative", especially under activation conditions.

870.5300, *In vitro* mammalian cell gene mutation test MRID 43868211 Acceptable Guideline	Forward gene mutation in mammalian cells in vitro (CHO/HGPRT)was negative for inducing forward mutations in hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus in Chinese hamster ovary (CHO) cells exposed to test article up to cytotoxic concentrations (600-800 µg/ml ±S9.

870.5395, *In vivo* mammalian erythrocyte micronucleus test: mouse MRID 43368447 Acceptable/Guideline	Negative for inducing micronuclei in polychromatic erythrocytes of mice treated orally with a single dose of test article up to 225 mg/kg, which caused ataxia and death.

870.5395, *In vivo* mammalian erythrocyte micronucleus test: mouse MRID 43868209 Acceptable/Guideline	Negative for inducing micronucleated polychromatic erythrocytes (24, 48 and 72 hours post-dose) up to doses producing severe clinical toxicity (hypoactivity, ataxia, dyspnea, death).

870.5375, Chromosomal aberration *in vitro* test (CHO cells) MRID 43368448 Acceptable/Guideline	Chromosomal damage in CHO cells was positive for inducing structural chromosomal aberrations in Chinese hamster ovary (CHO) cell cultures, with/without metabolic activation, to test article, but only at cytotoxic concentrations, 200 µg/ml - S9, and 1000-1250 µg/ml +S9.

870.5375 Chromosomal aberration *in vitro* test (CHO cells) MRID 43868210 Acceptable/Guideline	Negative for chromosomal damage in CHO cells without metabolic activation at levels up to the cytotoxic doses (≥204 µg/ml; 18- or 42-hour cell treatments). Positive for chromosomal damage in metabolically activated (+S9) over a narrow dose range (987-1270 µg/ml) that included severely cytotoxic doses (≥1270 µg/ml- 18-hour recovery). Structural aberrations and polyploidy cells were also significantly increased at 1020 and 1270 µg/ml after 41-hour recovery time

870.5550 *In vivo/in vitro* unscheduled DNA synthesis (UDS)[1] MRID 44518601 Acceptable	No evidence of induced unscheduled DNA synthesis in primary hepatocyte cultures harvested (2-4 hours or 15-16 hours) from Sprague Dawley rats treated with cyclanilide at 0, 60, 120 or 250 mg/kg.

[1] The UDS study was submitted as condition-of-registration toxicology data. The original data evaluation record (DER; TXR 0013902) executive summary was updated and the study was upgraded to Acceptable (TXR 0054472) based on a review of the study data.

A.3.7 Neurotoxicity

870.6200 Acute Neurotoxicity Screening Battery

In an acute neurotoxicity screening study (MRID 43348436) twelve Sprague-Dawley rats/sex/group were administered a single gavage dose of 0, 15, 50, or 150 mg RPA 90946 (tech, 98.8% a.i.)/kg in corn oil (5 mL/kg). Controls received an equal volume of the corn oil vehicle only. Functional observational battery (FOB) and motor activity tests were conducted pretreatment, on the day of dosing (day 0 at 6.5-7 hours post-dosing) and on days 7 and 14 post-dosing. Body weights and food consumption were measured weekly. On Day 15, 6 rats/sex/group were subjected to perfusion and those in the control and high-dose groups underwent neuropathological examination.

There were no gross or histopathological findings that could be attributed to the test article administration. FOB tests and motor activity tests revealed no treatment-related effects in animals of the 15 or 50 mg/kg dose groups. On Day 0, 5/12 males and 8/12 females in the 150 mg/kg group exhibited a significantly ($p<0.05$ males; $p<0.01$ females) increased incidence of resilient body tone upon removal from their cages. This resiliency persisted through Day 1 in three males and one female. Females in the 150 mg/kg group also exhibited significantly ($p<0.01$) increased gait incapacity (8/12 animals) (accompanied by a delayed return of hindlimbs to the normal position in response to toe pinch), knuckling of the forelimbs (8/12 animals), and exaggerated/slow abducted movement (7/12 animals). Total activity counts were decreased 39% for high-dose males ($p<0.01$) on Day 0. A 23% decrease was observed for females, but the difference was not statistically significant. Based upon gait abnormalities, increased abdominal muscle tone, and slightly decreased motor activity test, a neurotoxicity LOAEL of 150 mg/kg is defined for male and female rats. The neurotoxicity NOAEL based upon these parameters is 50 mg/kg for male and female rats. This study is classified as Core Guideline and satisfies the guideline requirements for an acute neurotoxicity study (§81-8) in rats.

870.6200 Subchronic Neurotoxicity Screening Battery

In a subchronic neurotoxicity screening study (MRID 43368435), twelve Sprague-Dawley rats/sex/group were fed 0, 50, 450 or 1200 ppm RPA 90946 (tech., 98.8%a.i.; approximately equivalent to 3.3, 29.7 or 78.6 mg/kg/day for males and 4.0, 35.8, or 93.9 mg/kg/day for females) in the diet for 13 weeks. Functional observational battery (FOB) and motor activity tests were conducted pretreatment, and at weeks 4, 8, and 13. Body weights and food consumption were measured weekly. At the completion of the study, 6 rats/sex/group were subjected to perfusion and those in the control and high-dose groups underwent neuropathological examination.

Body weights were 7-11% lower in mid-dose females on Days 42 to 91 ($P<0.05$ or $P<0.01$); terminal body weight gain was -27% less than controls. High-dose females exhibited 7-8% lower body weights ($P< 0.05$) on Days 21, 42, 52, and 70; terminal body weight gain was -18% less than controls. Functional Observational Battery (FOB) tests showed a 28% ($P<0.01$) decrease in hindlimb splay measurements in high-dose females at Week 13 when compared to controls. Motor activity tests indicated a significant ($P<0.05$) increase in total activity counts in mid-dose females at Weeks 8 and 13 (31% and 50% increase, respectively, compared to controls). Marked increases (however, not statistically significant) in total activity counts were also observed in mid-dose females at Week 4 (33% increase) and in high-dose females at Weeks 8 and 13 (20% and 32% increase). There were no gross or histopathological findings that could be attributed to the test article administration. The LOAEL is 450 ppm (35.8 mg/kg/day) based upon increased motor activity and decreased body weight in females. The NOAEL is 50 ppm (4.0 mg/kg/day).

This study is classified as Core Guideline and satisfies the guideline requirement for a subchronic neurotoxicity study (§82-7) in rats.

A.3.8 Metabolism

870.7485 Metabolism – Rat

In a 7-day rat metabolism study (MRID 43868316), [U-phenyl-^{14}C]cyclanilide (>99% ai) was administered to male and female CD rats (5 animals/sex/dose) by gavage as a single dose at levels of 5 or 50 mg/kg, or as a single dose at 5 mg/kg following a 14-day pretreatment with unlabeled cyclanilide at 5 mg/kg/day. Five additional rats/sex received a single 50 mg/kg oral dose in a 72-hour study for metabolite identification, and 5 rats/sex/dose were given single 5 or 50 mg/kg doses in a 7-day blood pharmacokinetics study.

[^{14}C]Cyclanilide was readily absorbed by rats following oral dosing; the low dose was absorbed more rapidly than the high dose. Maximum plasma concentrations were attained within 1 hour of the low dose. High dose females reached maximum plasma concentrations in 5 hours, versus 3 hours in high dose males.

There was no difference in the relative pattern of excretion between male and female rats. After 168 hours, the majority of the administered dose (single or repeated) was recovered in the urine (57-66% of dose) with 50-52% being recovered in the first 24 hours. Fecal excretion accounted for 27-40% of the low dose; 93-99% of the low doses were recovered in excreta after 168 hours. At 168 hours, approximately 30 and 60%, respectively, of the high dose was recovered in urine and feces, for a total recovery of 88-91% in excreta. Tissues in males and females accounted for 1.5 and 0.3% in the single low dose group, 0.66 and 0.65% in the repeated low dose rats, and 6.08 and 1.05% from the high dose. The relatively high percentage of the doses in tissues was accounted for by accumulation in skin/fur, which was dose-related and more pronounced in males in the single dose (5 or 50 mg/kg) groups. Concentration of radioactivity in skin/fur of males and females, respectively, was 0.269 and 0.056 ppm from the single low dose, 10.9 and 2.48 ppm from the single high dose, and 0.141 and 0.162 ppm from the repeated low dose. Extraction and HPLC analysis of skin/fur radioactivity revealed a single component identified as the parent compound. Kidneys contained 0.028-0.045 ppm (single or repeated) and 0.21-0.27 ppm (single high dose) of radioactivity, and the tissue/plasma ratios of radioactivity in kidneys were 4-5 for a single low dose and 1.9-2.6 for a single high dose.

Metabolite analysis revealed that cyclanilide is not extensively metabolized, although it may readily form amino acid conjugates. Approximately 40% of the radioactivity from a single high dose was excreted in urine and feces as unchanged parent compound within 72 hours. A methylated metabolite (RPA 93903) accounted for ≤5%. Ten amino acid conjugates of cyclanilide in feces (each at 0.11-5.22%) accounted for approximately 9-17% of the dose. Four amino acid conjugates were detected in urine, each at 0.01-1.59%, totaling 1.46-2.52%. Also in urine were glucoside and glucuronide conjugates at 1.49-2.54%. Recovery of radioactivity in the metabolite identification study was >90% of the total radioactivity in the 72-hour feces and urine samples used for analysis. The data indicate that the principal pathway for the elimination of cyclanilide from rats is *via* renal excretion of the intact parent compound and various amino acid

conjugates. Methylation is a minor pathway.

This metabolism study in the rat is classified acceptable and satisfies the guideline requirement for a metabolism study (85-1) in the rat.

870.7600 Dermal Absorption – Rat

In a dermal penetration study (MRID 43868317), Cyclanilide ([U-phenyl-^{14}C] Cyclanilide, 98.8% ai, Lot 3169-043) was applied to Charles River CRL:CD®BR male rats at dose levels of 0.044 mg (0.004 mg/cm^2), 0.399 mg (0.032 mg/cm^2) and 516 mg (0.413 mg/cm^2) per animal. A single dermal application of the test material prepared in 1% carboxymethylcellulose (CMC) was made to the shaved dorsal skin (approximately 12.5 cm^2) of a total of 72 animals (4 per time group/24 per dose) and the animals were monitored for absorption at 0.5, 1, 2, 4, 10 and 24 hours after dosing. Skin washing occurred immediately prior to sacrifice. Two control animals received vehicle (1% CMC) only. A summary of the mean percent absorption at each time point is presented in the table below.

Dermal Absorption Rate Summary[a]

Dose level (mg/cm^2)	Mean percentage of Dose Absorbed & In/On Skin											
	0.5 h		1 h		2 h		4 h		10 h		24 h	
	Abs*	Skin**	Abs.	Skin	Abs.	Skin	Abs.	Skin	Abs.	Skin	Abs.	Skin
0.004	0.01	32.50	0.03	29.40	0.21	38.80	0.45	30.10	0.75	37.90	2.00	38.90
0.032	0.02	4.50	0.06	3.47	0.25	3.85	0.37	4.04	1.91	6.74	3.79	11.20
0.413	0.01	0.72	0.23	1.33	0.29	0.85	1.26	0.78	4.25	2.37	21.60	2.18

a Data summarized by reviewer from pages 25-34 of the study report, MRID 43868317.
* Abs= radioactivity absorbed (sum of blood, carcass, urine, feces and cage wash)
**Amount of radioactivity in/on skin after skin wash

The mean total recovery of applied radioactivity ranged from 88–117% for all treatment groups. Most of the applied radioactivity was recovered in the skin washes with a recovery range of 49-62 % at 0.004 mg/cm^2, 80-113% at 0.032 mg/cm^2, and 75-100% at 0.413 mg/cm^2. The site of application accounted for a majority of the remaining radioactivity in the low and mid-dose groups with 29-39% of the radioactivity found in the skin application site for the 0.004 mg/cm^2 group and 4-11% for the 0.032 mg/cm^2 group. At the high dose, 0.7%-2.4% of the applied radioactivity was found at the application site with a majority of the radioactivity found in the urine after 24 hours (13%). Radioactivity present in the carcass at all exposure durations ranged from 0.2%-3.4% of the applied dose. Negligible amounts of radioactivity were found in the blood. Less than 1.6% of the radioactivity was found in the feces for all doses and exposure periods. The mean percentage of absorbed radioactivity (represented as the sum of the percent radioactivity found in blood, carcass, urine feces and cage washes) was 0.01%-1.99%, 0.02%-3.8% and 0.01%-21.6% for 0.004, 0.032 and 0.413 mg/cm^2, respectively.

Total radioactivity absorbed clearly increased with increasing exposure time for all doses and the highest absorption rate consistently occurred at the 24 hour exposure duration. The total radioactivity absorbed increased with increasing dose. This pattern of increasing absorption with

increasing dose is indicative of a skin irritant. Typically for a non-skin irritant, radioactivity decreases with increasing dose as the skin approaches saturation of penetration at higher doses.

Typically, the highest dermal absorption factor (DAF), which usually corresponds to the lowest dose, is select for use in risk assessment. Additionally, skin bound residues are typically considered absorbed unless data indicate otherwise. However, use of the ten hour DAF of 38.65% (including bound skin residue) from the lowest dose is not recommended in this case. As noted, this compound appears to be a dermal irritant based on the dermal absorption pattern. Additionally, the very high radioactivity remaining in/on the skin at the low dose (37.9% at ten hours) is consistent with a dermal irritant, i.e. a skin irritating compound would reasonably be expected to penetrate but not breach the skin barrier for systemic uptake at a very low dose. Consequently, in this case, the low dose is considered too low to provide meaningful dermal absorption information. Therefore, a dermal absorption factor of 8.65% calculated the combined radioactivity absorbed and that remaining in/on the skin at the ten hour exposure duration for the next highest dose tested (0.32 mg/cm^2) is considered more appropriate for use in risk assessment in this case.

This study in the rat is acceptable/guideline and satisfies the guideline requirement for a dermal penetration study (870.7600) in rats.

A.3.9 Special/Other Studies

None

A.4 References (in MRID order)

43368401 Robinson, K.; Brooks, W.; Broxup, B. (1994) A Time of Peak Behavioral Effects Study of a Single Oral Administration of RPA 90946 in Rats: Lab Project Number: 97324. Unpublished study prepared by Bio-Research Labs Ltd. 174 p.

43368435 Robinson, K.; Brooks, W.; Broxup, B. (1994) A 13-Week Dietary Study of the Potential Effects of RPA 90946 on Behavior and Neuromorphology in Rats: Lab Project Number: 97275. Unpublished study prepared by Bio-Research Labs, Ltd. 580 p.

43368436 Robinson, K.; Brooks, W.; Broxup, B. (1994) An Acute Study of the Potential Effects of Orally Administered RPA 90946 on Behavior and Neuromorphology in Rats: Lab Project Number: 97274. Unpublished study prepared by Bio-Research Labs, Ltd. 575 p.

43368437 Auletta, C. (1991) A Four-week Range-finding Oral Toxicity Study of RPA-90946 in the Rat via Dietary Administration: Final Report: Lab Project Number: 90-3555. Unpublished study prepared by Bio/Dynamics, Inc. 505 p.

43368438 Auletta, C. (1992) A 6-Week Oral Toxicity Study of RPA 90946 in the Mouse via Dietary Administration: Final Report: Lab Project Number: 91-3720. Unpublished study prepared by Bio/Dynamics, Inc. 316 p.

43368439 Auletta, C. (1993) A Subchronic (3-Month) Oral Toxicity Study of RPA 90946 in the Mouse via Dietary Administration: Final Report: Lab Project Number: 91-3721. Unpublished study prepared by Bio/Dynamics, Inc. 593 p.

43368440 Auletta, C. (1992) A Subchronic (3-Month) Oral Toxicity Study of RPA 90946 in the Rat via Dietary Administration: Final Report: Lab Project Number: 90-3556. Unpublished study prepared by Bio/Dynamics, Inc. 534 p.

43368441 Auletta, C. (1994) A Chronic (12-Month) Oral Toxicity Study of RPA 90946 in the Dog via Dietary Administration: Final Report: Lab Project Number: 91-3725. Unpublished study prepared by Pharmaco LSR, Inc. 667 p.

43368442 Rodwell, D. (1990) A Screening Teratology Study in Rats with RPA 90946: Final Report: Lab Project Number: 3147.46A. Unpublished study prepared by Springborn Labs, Inc. 210 p.

43368443 Rodwell, D. (1990) Teratology Study in Rats with RPA-90946: Final Report: Lab Project Number: 3147.71. Unpublished study prepared by Springborn Labs, Inc. 234 p.

43368444 Rodwell, D. (1990) Range-finding Teratology Study in Rabbits with RPA-90946: Final Report: Lab Project Number: 3147.72. Unpublished study prepared by Springborn Labs, Inc. 128 p.

43368445 Rodwell, D. (1991) Teratology study in Rabbits with RPA-90946: Final Report: Lab Project Number: 3147.73. Unpublished study prepared by Springborn Labs, Inc. 222 p.

43368446 Lawlor, T. (1992) Mutagenicity Test on RPA-90946 in Salmonella/Mammalian-Microsome Reverse Mutation Assay (Ames Test): Final Report: Lab Project Number: 14777-0-401. Unpublished study prepared by Hazleton Washington, Inc. 34 p.

43368447 Murli, H. (1994) Mutagenicity Test on RPA 90946 in an In vivo Mouse Micronucleus Assay: Final Report: Lab Project Number: 15990-0-45CO. Unpublished study prepared by Hazleton Washington, Inc. 41 p.

43368448 Murli, H. (1994) Mutagenicity Test on RPA 90946 Measuring Chromosomal Aberrations in Chineese Hamster Ovary (CHO) Cells: with a Confirmatory Assay with Multiple Harvests: Final Report: Lab Project Number: 15990-0-437CO. Unpublished study prepared by Hazleton Washington, Inc. 58 p.

43368449 Cifone, M. (1994) Mutagenicity Test on RPA 90946 in the CHO/HGPRT Forward Mutation Assay: Final Report: Lab Project Number: 15990-0-435. Unpublished study prepared by Hazleton Washington, Inc. 29 p.

43379801 Auletta, C. (1993) A 6-Week Oral Toxicity Study of RPA 90946 in the Dog via Dietary Administration: Final Report: Lab Project Number: 91-3724. Unpublished study prepared by Bio/dynamics, Inc. 163 p.

43379803 Auletta, C. (1994) A 24-Month Oral Toxicity/Oncogenicity Study of RPA 90946 in the Rat via Dietary Administration: One-year Interim Final Report: Lab Project Number: 92-3844. Unpublished study prepared by Pharmaco LSR, Inc. 1487 p.

43868207 Auletta, C. (1995) A 4-Week Oral Toxicity Study of Cyclanilide (RPA 90946) in the Rat via Dietary Adminstration: Audited Terminal Status Report: Lab Project Number: 95-2402. Unpublished study prepared by Pharmaco LSR. 260 p.

43868208 Lawlor, T. (1995) Mutagenicity Test with Cyclanilide (RPA 90946) in the Salmonella--Escherichia coli/Mammalian-Microsome Reverse Mutation Assay (Modified Ames Test) with a Confirmatory Assay: Amended Final Report: Lab Project Number: 17013-0-409R: 17013-A1. Unpublished study prepared by Corning Hazleton, Inc. 43 p.

43868209 Murli, H. (1995) Mutagenicity Test on Cyclanilide (RPA 90946) in an in vivo Mouse Micronucleus Assay: Final Report: Lab Project Number: 17013-0-455CO. Unpublished study prepared by Corning Hazleton, Inc. 46 p.

43868210 Murli, H. (1995) Mutagenicity Test on Cyclanilide (RPA 90946): Measuring Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells: With a Confirmatory Assay with Multiple Harvests: Final Report: Lab Project Number: 17013-0-437CO: 437CO. Unpublished study prepared by Corning Hazleton, Inc. 55 p.

43868211 Cifone, M. (1995) Mutagenicity Test on Cyclanilide (RPA 90946) in the CHO/HGPRT Forward Mutation Assay with a Confirmatory Assay: Final Report: Lab Project Number: 17013-0-435R: 22207. Unpublished study prepared by Corning Hazleton, Inc. 38 p.

43868311 Trutter, J. (1995) 21-Day Dermal Toxicity Study in Rabbits with RPA 90946: Final Report: Lab Project Number: HWA 656-188. Unpublished study prepared by Hazleton Washington, Inc. 185 p.

43868312 Auletta, C. (1995) An 18-Month Oncogenicity Study of RPA 90946 in the Mouse via Dietary Administration: Final Report: Lab Project Number: 91-3722. Unpublished study prepared by Pharmaco LSR, Inc. 2208 p.

43868313 Tyl, R.; Myers, C.; Marr, M. (1994) Two-Generation Reproductive Toxicity Study of RPA 90946 Administered in the Feed to CD (Sprague-Dawley) Rats: Final Report: Lab Project Number: 65C-5250: RTI-426. Unpublished study prepared by Research Triangle Institute. 1188 p.

43868314 Auletta, C. (1995) A Chronic Oral Toxicity/Oncogenicity Study of RPA 90946 in the Rat via Dietary Administration: Final Report: Lab Project Number: 92-3844. Unpublished study prepared by Pharmaco LSR, Inc. 3414 p.

43868315 Cifone, M. (1995) Mutagenicity Test on RPA 90946 in the CHO/HGPRT Forward Mutation Assay: Revised Final Report: Lab Project Number: 15990-0-435: 22207. Unpublished study prepared by Hazleton Washington, Inc. 31 p.

43868316 Fisher, P. (1995) Cyclanilide: Absorption, Distribution, Metabolism and Excretion in the Rat: Lab Project Number: SA 92184: 92184: STUDY SA 92184. Unpublished study prepared by Rhone-Poulenc Agrochimie. 170 p.

43868317 Cheng, T. (1995) Dermal Absorption of (carbon 14)-RPA090946 in Male Rats: (Preliminary and Definitive Phases): Final Report: Lab Project Number: 6224-217: HWI 6224-217. Unpublished study prepared by Hazleton Wisconsin, Inc. 171 p

43901501 Auletta, C. (1995) A 4-Week Oral Toxicity Study of Cyclanilide (RPA 90946) in the Rat via Dietary Administration: Final Report: Lab Project Number: 95-2402. Unpublished study prepared by Huntingdon Life Sciences. 349 p.

44166601 Auletta, C. (1996) Historical Control Data to Support MRID No. 43868314: A Chronic Oral Toxicity/Oncogenicity Study of RPA 90946 in the Rat via Dietary Administration: Lab Project Number: 92-3844. Unpublished study prepared by Huntingdon Life Sciences. 10 p.

44073701 Powell, G. (1996) Two-Generation Reproductive Toxicity Study of RPA 90946 Administered in the Feed to CD (Sprague-Dawley) Rats: Addendum to Final Report: Lab Project Number: 45124: RPAC 45124. Unpublished study prepared by Rhone-Poulenc Ag Co. 8 p.

44389904 Cifone, M. (1997) Mutagenicity Test on Cyclanilide (RPA 90946) in the CHO/HGPRT Forward Mutation Assay with a Confirmatory Assay: Revised Final Report: Lab Project Number: CHV 17013-0-435R: 17013-0-435R: 17013-0-435. Unpublished study prepared by Corning Hazleton, Inc. 39 p.

44518601 Ham, A. (1998) Cyclanilide: In Vivo/In Vitro Unscheduled DNA Synthesis in Rat Primary Hepatocyte Cultures at Two Timepoints: Amended Final Report: Lab Project Number: 18871-0-494. Unpublished study prepared by Covance Laboratories, Inc. 41 p.

TXR 0012172: G. Ghali; 02/19/1997; RfD/Peer Review Report of Cyclanilide.

TXR 0012189: E.Budd; 04/09/1997; Carcinogenicity peer review decision.

Appendix B: Metabolism Assessment

B.1 Metabolism Guidance and Considerations

N/A. This is a non-food use on ornamentals and cut flowers.

Appendix C: Tolerance Reassessment Summary and Table

N/A. This is a non-food use on ornamentals and cut flowers.

Appendix D: Review of Human Research

Studies reviewed for ethical conduct:

No MRID - PHED Surrogate Exposure Guide

00031050 Feldman, R.J., Maibach, H.I. (1974) Percutaneous penetration of some pesticides and herbicides in man. Toxicology and Applied Pharmacology 28(?):126-132. (Also In unpublished submission received Apr 23, 1980 under 10279-7; submitted by Purdue Frederick Co., Norwalk, Conn.; CLD:242321-R)

Studies reviewed by the Human Studies Review Board:

44416201 Gledhill, A. (1997) Dichlorvos: A Study to Investigate Erythrocyte Cholinesterase Inhibition Following Oral Administration to Healthy Male Volunteers: Lab Project Number: XH5170: Y09341: C05743. Unpublished study prepared by Zeneca Central Toxicology Lab. 104 p.

13544

R142127

Chemical: Cyclanilide

PC Code: 026201
HED File Code: 14000 Risk Reviews
Memo Date: 2/22/2007
File ID: DPD333239
Accession #: 000-00-0119

HED Records Reference Center
4/24/2007