13544

069089 0014000 113099 TX013887 R000805

Chemical:	**Diethyl-2-(4-methylbenzyloxy)ethylamine**
PC Code:	**069089**
HED File Code	**14000 Risk Reviews**
Memo Date:	**11/30/99**
File ID:	**TX013887**
Accession Number:	**412-01-0045**

HED Records Reference Center
11/13/2000

Image

013887

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 11/30/99

SUBJECT: PP#8F04998 -- **FQPA Human Health Risk Assessment for PT807-HCl -** Proposal for Tolerance of Residues in/on Oranges.

DP Barcode:	D260121	PRAT Case:	290274
Submission No.:	S551488	Caswell No.:	none
Chemical#:	069089	Class:	Plant Growth Regulator
Trade Name:	ECOLYST	EPA Reg#:	XXX
40 CFR:	§180.XXX		

TO: Rose Kearns/C. Parker, PM Team 22
Registration Division (7505C)

FROM: Yan Donovan, Chemist Yan Donovan
John Whalan, Toxicologist
Margarita Collantes, Biologist
RAB2/HED (7509C)

THRU: Mike Doherty, Chemist
SanYvette Williams-Foy, Toxicologist
Shih-Chi Wang, Biologist
RAB2/HED (7509C)

THRU: Richard A. Loranger, Branch Senior Scientist R. Loranger
RAB2/HED (7509C)

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

General Background:

The petitioner, GMJA Specialties (GMJA), through its authorized representative Jellinek, Schwartz & Connolly, Inc., is proposing a permanent tolerance for residues of the plant growth regulator PT807-HCl [N, N-diethyl-2-(4-methylbenzyloxy)ethylamine hydrochloride] be established in/on **oranges, whole fruit** at **0.01 ppm**.

PT807-HCl is a systemic plant growth regulator which has been shown to be effective at shortening the time to maturation of citrus when applied during the spring bloom. This Section 3 registration is being requested for an end-use product (Product Name = Ecolyst) which contains PT807-HCL as the sole active ingredient. This product is a 3.3% a.i. soluble concentrate (SC) formulation (concentration equivalent to 1 g ai/fl oz solution).

PT807-HCl is a member of a new chemical class, and currently it has no registered food or residential uses. This petition PP# 8F04998 proposes the first food use (on oranges). There are no Codex maximum levels established for residues of Ecolyst.

HED has evaluated the toxicological, residue chemistry and exposure databases for PT807-HCl.

The toxicology data base is complete, and the quality of the data is high and sufficient to characterize the toxicity of this chemical. There is high confidence in the hazard and dose-response assessments conducted. Although there are no inhalation data with which to do a route-specific risk assessment, this is not considered a data gap because current practice is to use oral data as a surrogate.

PT807-HCl has low acute toxicity by the oral, dermal, and inhalation routes (Toxicity Categories III, IV, and IV, respectively). Although it is a slight to moderate eye irritant (Toxicity Category III), it is not a notable dermal irritant or sensitizer. Based on a comparison of NOAEL's and LOAEL's, there is no sex-related difference in sensitivity. There is little evidence of cumulative toxicity, even when acute, subchronic, and chronic data are compared. This is most likely due to the fact that PT807-HCl is rapidly excreted, primarily in the urine and secondarily in the feces.

Neurotoxicity was observed in several studies, but only in adult animals. No developmental effects were observed in rats or rabbits, even at doses far in excess of the maternal LOAELs. In the rat reproductive toxicity study, anomalies were found in the pups, but at a parentally toxic dose. There is no evidence of increased developmental or neurologic susceptibility in the prenatal and pre/postnatal studies.

At the dose levels tested, no toxicity or tumors were observed in the chronic mouse and dog studies. The high-dose in the mouse study exceeded the limit dose (1000 mg/kg/day). An increased incidence of hepatocellular adenomas and carcinomas in the high-dose male rats was attributed to the fact that the high-dose animals lived significantly longer than the other groups, that is, they lived long enough to develop more tumors. PT807-HCl is clastogenic in an in *vitro*

study in Chinese hamster ovary cells; however, there is no evidence of clastogenic potential in whole animals.

The HED HIARC Committee met on 9/16/99 to determine appropriate toxicological endpoints and to evaluate the Food Quality Protection Act (FQPA) aspects of PT807-HCl. Since PT807-HCl will be applied using an air-blast sprayer, the most likely routes of worker exposure are dermal and inhalation. The HIARC has determined that no dermal risk assessments are necessary since no systemic toxicity was observed in a 21-day dermal toxicity limit test in rats at 2.5-times the limit dose, but inhalation and dietary risk assessments will be required.

The HIARC selected an **acute dietary RfD of 0.5 mg/kg/day** based on a NOAEL of 50 mg/kg/day in an acute neurotoxicity study in rats, and an uncertainty factor of 100. The LOAEL was 200 mg/kg/day based on slight ataxia in 1 of 11 males. The HIARC selected a **chronic dietary RfD of 0.14 mg/kg/day** based on a systemic NOAEL of 14.1 mg/kg/day in a reproductive toxicity study in rats, and an uncertainty factor of 100. The systemic LOAEL is 114 mg/kg/day based on decreased body weight and body weight gain. In the absence of acceptable inhalation data, other than an acute study, inhalation risk assessments for all time periods will use the oral NOAEL of 30 mg/kg/day from the 90-day gavage toxicity study in rats. The HIARC classified PT807-HCl as a "not likely human carcinogen" according to the EPA *Proposed Guidelines for Carcinogen Risk Assessment* (4/10/96) so a cancer risk assessment is not required.

On 10/4/99, the FQPA Safety Factor Committee met to determine the FQPA Safety Factor needed to protect infants and children. **The FQPA Safety Factor for enhanced sensitivity of infants and children was reduced to 1x** (HED FQPA Safety Factor Committee, memo of 10/15/99). Rationales for removing the FQPA factor include: 1) the toxicology database is complete for the assessment of the effects following *in utero* and/or postnatal exposure to PT807-HCl; 2) the toxicity data provided no indication of quantitative or qualitative increased susceptibility of rats or rabbits to **in utero** and/or postnatal exposure; 3) the requirement of a developmental neurotoxicity study is not based on the criteria reflecting some special concern which are generally used for requiring a DNT study and an FQPA safety factor (e.g.: neuropathy in adult animals; CNS malformations following prenatal exposure; brain weight or sexual maturation changes in offspring; and/or functional changes in offspring)[1] and therefore does not warrant an FQPA safety factor; and 4) the exposure assessment will not underestimate the potential dietary(food and water) exposures for infants and children from the use of PT807-HCl (currently no residential exposure is expected).

On 9/21/99, the HED's Metabolism Assessment Review Committee (MARC) determined that only parent compound needs to be included in the tolerance expression and used for dietary risk assessment purposes for oranges. The nature of the residue in plant and animal is adequately understood for the purpose of this use on oranges.

The crop field trials submitted by the petitioner are not adequate to support the proposed zero day PHI on oranges. About 40% of oranges (i.e., Valencia oranges) have mature fruit from the previous year still present at the time the trees bloom and thus potentially may have fruit harvested immediately after treatment with Ecolyst. The normal data requirement for oranges is

16 field trials or, if residues are below the method's limit of quantitation, 12 trials. Only two of the trials included samples with a zero day PHI. HED has concluded that at least three more studies reflecting the zero day PHI are required. Unless these additional crop trials supporting 0-day PHI are submitted, the PHI should be increased to 30 days for which more data are available to allow a conclusion that residues are not likely to exceed the 0.01 ppm tolerance.

The Hazard endpoints to be used for risk assessment purposes are as follow:

Acute Dietary Exposure **Acute RfD: 0.5 mg/kg/day.** The systemic NOAEL of 50 mg/kg/day in the acute neurotoxicity study in rats is based on slight ataxia in 1/11 males at the LOAEL of 200 mg/kg/day. The FQPA Safety Factor for enhanced sensitivity of infants and children was reduced to 1x. The acute population adjusted dose (**aPAD**) is determined by dividing the acute RFD by the FQPA factor: **aPAD** = 0.5 / 1 = **0.5 mg/kg /day**. Since the HED FQPA Safety Factor Committee determined to remove the 10X safety factor, the acute RfD is identical to the aPAD. This aPAD applies to all population subgroups.

Chronic Dietary Exposure **Chronic RfD: 0.14 mg/kg/day**. The systemic NOAEL of 14.1 mg/kg/day in the reproductive toxicity study in rats is based on decreased body weight and body weight gain at the systemic LOAEL of 114 mg/kg/day. This is the lowest NOAEL in the most sensitive species. The FQPA Safety Factor for enhanced sensitivity of infants and children was reduced to 1x. The chronic population adjusted dose (cPAD) is determined by dividing the chronic RfD by the FQPA factor: **cPAD** = 0.14 / 1 = **0.14 mg/kg/day**. Since the HED FQPA Safety Factor Committee determined to remove the 10X safety factor, the chronic RfD is identical to the cPAD. This cPAD applies to all population subgroups.

Occupational Dermal Exposure This risk assessment **is not required** because no systemic toxicity was seen at the limit dose in a 21-day dermal toxicity study, and because no developmental effects were observed in rats or rabbits.

Occupational Inhalation Exposure. In the absence of acceptable inhalation data, HED HIARC used oral data as a surrogate. The oral NOAEL of 30 mg/kg/day from the 90-day gavage toxicity study in rats has been selected for use in inhalation risk assessments. Neurotoxic signs were observed at the LOAEL of 300 mg/kg/day in that study.

Cancer

PT807-HCl has been classified by HED HIARC as a "not likely human carcinogen." A cancer risk assessment **is not required**.

The risk assessments conducted in this review are acute and chronic aggregates. In conducting the acute and chronic exposure assessment for food, HED used Dietary Exposure Evaluation Model (DEEM) program and Tier 1 approach. Tier 1 assumptions are: tolerance level residues and 100% crop treated. This DEEM analysis concluded that both acute and chronic exposures to PT807-HCl from food for the general US population, infants and children are all **<1%** of the **aPAD/cPAD.**

EFED provided the environmental fate analysis and the results of maximum estimated environmental concentrations (EECs) of PT807-HCl in surface and ground water for acute exposure. This chemical is very soluble in water and stable in the environment. Based on its chemical properties it is likely that this chemical will move to surface water and groundwater, and it may accumulate in the environment. According to information included in the proposed Ecolyst label, the maximum application rate for this chemical is 0.013 lb a.i./acre/year. Using the PRZM/EXAMS model, the calculated surface water acute EEC and chronic EEC are **4.0 ppb** and **3.9 ppb,** respectively. These values represent the 1-in-10 year peak surface water concentration and 1-in-10 year mean yearly concentration, and therefore, these estimates are considered very conservative. EFED notes that the calculated concentration in surface water increases over time as the compound builds up in the environment, and continued use will result in increasing concentration over time. The groundwater screening concentration, calculated using SCI-GROW is **0.02 ppb**. However, the properties of this compound are outside the range of values used to develop SCI-GROW. Because of its stability in the environment this chemical can be expected to accumulate in groundwater and the actual concentrations may be much higher.

Ecolyst currently has no registered or proposed residential uses (REFS 10/99). Therefore a residential exposure assessment is not required at this time.

Risk Assessment Conclusions:

Acute Aggregate Risk (Food + Water)

Acute aggregate risk estimates do not exceed HED's level of concern. (Acute aggregate risk takes into account of food and water only). Using the most conservative Tier I approach, the Dietary Exposure Evaluation Model (DEEM) for acute dietary risk estimates concluded that the acute exposures to PT807-HCl from food for the general US population, infants and children will utilize **<1%** of the **aPAD**. EFED provided maximum estimated environmental concentrations (EECs) of PT807-HCl in surface and ground water for acute exposure, and the highest value (4.0 ppb) is well below HED's calculated drinking water level of comparison (DWLOC), which ranged from 5000 to 18000 ppb for various population subgroups. HED concludes that there is a reasonable certainty that no harm will result to adults, infants and children from acute aggregate exposure to PT807-HCl residues.

Chronic Aggregate Risk (Food + Water + Residential)

Chronic aggregate risk includes exposures from food, water, and residential uses. Using the most conservative Tier I analysis, it is estimated that the chronic exposures to PT807-HCl from food for general US population, infants and children will utilize **<1%** of the cPAD. EFED's EEC of PT807-HCl in surface and ground water for chronic exposure (3.9 ppb) is very small compared to the DWLOC, which ranged from 1400 to 4900 ppb. Currently there is no registered or proposed residential uses that could result in residential exposures. Therefore, HED concludes that there is a reasonable certainty that no harm will result to adults, infants and children from chronic aggregate exposure to PT807-HCl residues.

Short- and Intermediate- Term Aggregate risk (Residential + Chronic Food + Chronic Water)

There are no registered residential uses of PT807-HCl. Therefore, a short- and intermediate-term aggregate risk assessment for PT807-HCl is **not required.**

Cancer

PT807-HCl has been classified by HED HIARC as a "not likely human carcinogen." A cancer risk assessment **is not required**.

Occupational Exposure

Workers may be exposed to Ecolyst during mixing, loading, application and postapplication activities. Based on the proposed use patterns, short and intermediate-term exposures may occur. Chronic exposures (6 months of continuous exposure) are not expected.

Since no chemical-specific data for assessing human exposures during pesticide handling activities were submitted to the Agency in support of the registration of Ecolyst, it is the policy of HED to use data from the Pesticide Handlers Exposure Data Base (PHED) Version 1.1 to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure, Policy .007, "Use of Values from the PHED Surrogate Table and Chemical-Specific Data." Health Effects Division, Office of Pesticide Programs, January 1999.)

All inhalation MOEs were above 100. For workers, MOEs equal to or greater than 100 do not exceed HED's level of concern.

Although the potential for postapplication (dermal) exposure does exist, dermal exposure/risk assessment was not required because no dermal endpoints were selected by the HIARC.

Recommendations:

HED concludes that there is a reasonable certainty that no harm will result to the U.S. Population including infants and children from acute, short- and intermediate- term and chronic aggregate exposure to PT807-HCl residues. Contingent on successful Agency analytical method validation, and the submissions of either a revised Section B specifying a 30-day PHI, or three additional crop field trials with 0-day PHI (and the resulted residues all < 0.01 ppm), HED has no objection to the establishment of permanent tolerances for the residues of PT807-HCl, expressed as parent, in or on **oranges at 0.01 ppm.**

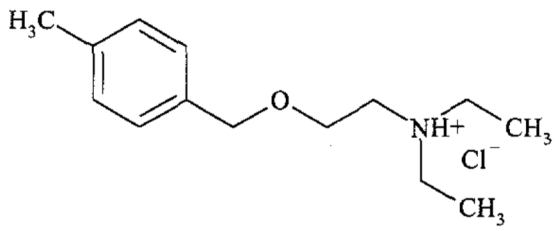
Data Needs:

● Three additional crop field studies with 0-day PHI, unless petitioner submits a revised Section B specifying 30-day PHI.

● A more specific confirmatory method or interference study (recommend this be made a conditional requirement).

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

The chemical structure of PT807-HCl is as follows:



Product chemistry for PT807-HCl has been previously reviewed by RD (RD memo of 03/17/99, S. Mathur, D252109). Some of the physical properties of PT-807 HCl are summarized below:

Color:	Colorless		
Physical State:	Slightly viscous liquid		
Odor:	Like sweet alcohol		
B.P.:	$105.9^0 \pm 1.5^0$C		
Density:	1.0596 ± 0.0001 g/cm^3		
Vapor pressure:	8.93×10^{-8} Torr		
Dissociation Constant:	pKa = 9.55 ± 0.08		
PH: Neat	1.98 ± 0.01 @ 25^{0}C		
	: 1% aq. Soln. 4.57 ± 0.03 @ 25.1^0C		
Octanol/Water Partition Coefficient:			
	$K_{o/w}$ at pH 5 and 7 = < 1.0		
	$K_{o/w}$ at pH 9 based on total ^{14}C-activity = 94.4 ± 06.3		
	$K_{o/w}$ at pH 9 based on total ^{14}C-PT807-HCl = 235.0 ± 16.0		
Solubility:	Aqueous Buffer solution:	pH 5-9	100%
	Organic solvents:	Acetonitrile	100% at 25^{0}C
		Methanol	100%
		Methylene chloride	100%
		Octanol	100%
Hydrolysis:	Stable		
Half-life:	Stable (photolysis)		
	1005 days (aerobic soil metabolism)		
	Stable (aerobic aquatic metabolism)		

3.0 HAZARD CHARACTERIZATION (Attachment 1)

3.1 Hazard profile

Acute Toxicity: The data base adequately characterizes PT807-HCl as having low acute oral, dermal, and inhalation toxicity. It is Toxicity Category IV for acute dermal toxicity, acute inhalation toxicity, and primary dermal irritation; Toxicity Category III for acute oral and primary eye irritation; and it is not a dermal sensitizer. The acute toxicity profile for PT807-HCl is presented in **Table 1.**

Table 1. Acute Toxicity Profile of PT807-HCl Technical

OPPTS No./Study Type	MRID	Results
870.1100 Acute Oral - Rat	44344512	LD_{50} = 494 mg/kg ♂ LD_{50} = 602 mg/kg ♀ LD_{50} = 531 mg/kg ♂ + ♀ **Toxicity Category III**
870.1200 Acute Dermal - Rabbit	44354513	LD_{50} >5050 mg/kg ♂ + ♀ (2.5x the limit dose) **Toxicity Category IV**
870.1300 Acute Inhalation - Rat	44354514	LC_{50} >2.08 mg/L ♂ + ♀ (limit concentration) **Toxicity Category IV**
870.2400 Primary Eye Irritation - Rabbit	44354515	slight to moderate ocular irritant. **Toxicity Category III**
870.2500 Primary Skin Irritation - Rabbit	44354516	Not a notable dermal irritant. **Toxicity Category IV**
870.2600 Dermal Sensitization - Guinea Pig	44354517	Not a dermal sensitizer.

Non-Acute Toxicity: Table 2 presents the non-acute toxicity profile for PT807-HCl:

Table 2. Toxicity Profile of PT807-HCl Technical		
OPPTS No./Study Type	**MRID**	**Results**
870.3100 Subchronic Feeding - Mouse	44380003	NOAEL = 7000 ppm (1004 / 1272 mg/kg/day, M/F; limit dose) **NOTE:** Due to faulty dose concentration analyses, the regulatory usefulness of this NOAEL is in doubt.
870.3100 Subchronic Gavage - Rat	44380005	NOAEL = 30 mg/kg/day LOAEL = 300 mg/kg/day based on increased mortality; hyperactivity, hyperreflexivity, lack of coordination, tremors, convulsions, and increased salivation in males and females; and elevated urinary protein in males.
870.3150 Subchronic Feeding - Dog	44354519	NOAEL = 2500 ppm (equivalent to 71/78 mg/kg/day [M/F]). LOAEL = 7500 ppm (equivalent to 211/233 mg/kg/day [M/F]), based on pathological changes to the male reproductive organs and possibly the uterus in females.
870.3200 21-Day Dermal - Rat	44595002	Systemic NOAEL >1000 mg/kg/day (limit dose). Dermal NOAEL = 1000 mg/kg/day(nonadverse dermal irritation was observed at 1000 mg/kg/day).
870.3700 Developmental Toxicity - Rat	44354521	Maternal NOAEL = 50 mg/kg/day Maternal LOAEL = 250 mg/kg/day, based on clinical signs (post-dosing rooting in the bedding and lethargy) and reduced body weight gains. Developmental NOAEL = 500 mg/kg/day Developmental LOAEL was not observed
870.3700 Developmental Toxicity - Rabbit	44354522	Maternal NOAEL = 10 mg/kg/day Maternal LOAEL = 100 mg/kg/day, based on increased mortality in the mid- and high-dose animals Developmental NOAEL >200 mg/kg/day Developmental LOAEL was not observed

Table 2. Toxicity Profile of PT807-HCl Technical		
OPPTS No./Study Type	**MRID**	**Results**
870.3800 Reproductive Toxicity - Rat	44595004	Systemic NOAEL = 14.1 mg/kg/day ppm Systemic LOAEL = 114 mg/kg/day based upon decreased body weight and body weight gains. Reproductive NOAEL = 14.1 mg/kg/day for both sexes. Reproductive LOAEL = 114 mg/kg/day for both sexes based on decreased pup body weight and body weight gains, delayed sexual development, reductions in absolute and relative uterus and ovary weights, and histological changes in the uterus, vagina, and ovaries in the females.
870.4100 Chronic Toxicity - Dog	44612101	NOAEL >5000 ppm. (135.7/151.5 mg/kg/day, M/F) LOAEL was not observed.
870.4200 Carcinogenicity - Mouse (18 months)	44612102	NOAEL = 7000 ppm (1010/1250 mg/kg/day, M/F) LOAEL was not observed **Mice were dosed at greater than the limit dose of 1000 mg/kg/day with no evidence of carcinogenic potential.**
870.4300 Chronic Toxicity/Carcinogenicity-Rat	44612103	NOAEL = 500 ppm (20/28 mg/kg/day, M/F) LOAEL = 5,000 ppm (213/308 mg/kg/day, M/F) based on decreased body weight and body weight gains. An increased incidence of hepatocellular adenomas and carcinomas in the high-dose males (5000 ppm) was attributed to significantly increased survival. **There was no clear evidence of carcinogenic potential.**
870.5100 Bacterial Reverse Gene Mutation Test	44354523	Negative for cytotoxicity and genotoxic response at the limit dose (5,000 µg/plate) with and without metabolic activation in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, and *E. coli* WP2 *uvr*A strain.
870.5300 CHO/HGPRT/Mammalian Activation Gene Mutation Assay	44354524	Negative for induction of forward mutation at the HGPRT locus in this *in vitro* assay with or without metabolic activation.

Table 2. Toxicity Profile of PT807-HCl Technical		
OPPTS No./Study Type	**MRID**	**Results**
870.5375 *In Vitro* Mammalian Chromosome Aberrations in CHO Cells	44354526	Clastogenic with or without metabolic activation in Chinese hamster ovary cells cultured *in vitro*.
870.5395 *In Vivo* Mammalian Cytogenetics - Micronucleus Assay in Mice	44354525	Testing at toxic concentrations, with mortality at ≥116.5 mg/kg, did not induce significant increases in micronucleated polychromatic erythrocytes (MPCEs).
870.5550 Unscheduled DNA Synthesis in Rat Hepatocytes	44595005	UDS was not induced.
870.6200 Acute Neurotoxicity - Rats	44380001	Neurotoxicity NOAEL = 50 mg/kg/day Neurotoxicity LOAEL = 200 mg/kg based on slight ataxia in 1 of 11 males. Neurotoxicity at 400 mg/kg included increases in FOB clinical signs and decreases in motor activity.
870.6200 Subchronic Neurotoxicity - Rats	44595003 44703101	Neurotoxicity NOAEL is >5000 ppm. (323/386 mg/kg/day; M/F) Neurotoxicity LOAEL was not observed

Table 2. Toxicity Profile of PT807-HCl Technical		
OPPTS No./Study Type	**MRID**	**Results**
870.7485 Metabolism - Rat	44595006	[^{14}C]PT807-HCl was readily absorbed from the GI tract of male and female rats. Within 24 hours of dosing, 75.2 and 66.5% of the administered dose was recovered in urine (plus cage wash) from males and females, respectively. Within 168 hours, 79.3% of the dose was recovered in urine (plus cage wash) and 13.8% was recovered in feces from males, and 73.8% was recovered in urine (plus cage wash) and 18.3% was recovered in feces from females. Only ≤0.34% of the dose was associated with tissues, and no radioactivity was found in expired air. Radioactivity was generally 2-3x higher in tissues and blood of females than males, except in kidney and spleen. However, the pattern of distribution among tissues was similar between the sexes. With the exception of the uterus, radioactivity was highest in liver, spleen, and carcass and lowest in fat and gonads. In females, radioactivity was highest in the uterus and was >2.3x higher than in the liver and carcass. The metabolism of PT807-HCl in male and female rats was qualitatively and quantitatively similar. Only minor amounts of parent, PT807 (0.4-0.8% dose), were identified in urine and feces. The primary metabolite identified in excreta was the carboxylic acid metabolite, M-7 (54.2-55.3% of the dose), which accounted for 45.2-45.8% of the dose in urine and 8.5-10.1% of the dose in feces. Five other metabolites each account for >5% of the dose in excreta. Biotransformation of PT807-HCl in rats appears to occur primarily via oxidation of the 4-methyl group on the phenyl ring to form the carboxylic acid metabolite (M-7) which then undergoes conjugation to glucuronic acid (M-3) or hydroxylation on the alkyl portion of the molecule (RU-10b). Other secondary reactions involved in the metabolism of PT807 included deamination, N-de-ethylation, hydroxylation of the N-ethyl group, and oxidation of the benzyl carbon.

Dermal Absorption: A dermal penetration study was not performed. A dermal absorption factor is not needed because dermal risk assessments are not required.

Cumulative Toxicity and Metabolism: There is little evidence of cumulative toxicity. The oral LD_{50} in rats (531 mg/kg) is not markedly greater than the oral subchronic rat LOAEL (300 mg/kg/day). Similarly, a comparison of subchronic and chronic LOAELs reveals no evidence of cumulation in the rat (300 mg/kg/day v 213/308, M/F) and dog (211/233 mg/kg/day v >135.7/141.5 mg/kg/day, HDT). The rat metabolism study reveals why there is a minimum of cumulation. Rats rapidly excrete PT807-HCl, primarily in the urine and secondarily in the feces, with very little remaining in the tissues after 7 days (≤0.34%). There may also be some adaptation due to enzyme induction.

Neurotoxicity: Neurotoxicity was observed in several studies. Hyperactivity, hyperreflexivity, lack of coordination, tremors, convulsions, and ptyalism were observed at 300 mg/kg/day in the subchronic gavage study in rats. Rooting in the bedding and lethargy were observed at 250 mg/kg/day in the developmental toxicity study in rats. In the acute neurotoxicity study, the HIARC designated the LOAEL to be 200 mg/kg/day based on slight ataxia in 1 of 11 males. At a dose of 400 mg/kg/day, there was an increase in clinical signs in the functional observation battery, and decreases in motor activity. No toxicity was observed in the subchronic neurotoxicity study in rats at doses of 323 mg/kg/day in males and 386 mg/kg/day in females.

Developmental and Reproductive Toxicity: In the developmental toxicity study in rats, there was an increased incidence of enlarged lateral ventricles in pups at 500 mg/kg/day. The incidences were within historical limits, however, and occurred at a dose far in excess of the maternal NOAEL of 50 mg/kg/day. No developmental effects were seen in rabbit pups at 200 mg/kg/day, whereas the maternal NOAEL was 10 mg/kg/day. In the rat reproductive toxicity study, the systemic and reproductive LOAELs were both 114 mg/kg/day at which dose the parents exhibited decreased body weight and body weight gains, and the pups had decreased body weight and body weight gains, delayed sexual development, reductions in absolute and relative uterus and ovary weights, and histological changes in the uterus, vagina, and ovaries in the females.

Prenatal and Postnatal Susceptibility: There is no evidence of increased developmental or neurologic susceptibility in the prenatal and pre/postnatal studies.

Chronic/Carcinogenicity and Mutagenicity Studies: No toxicity or tumors were observed in the mouse carcinogenicity study. The high-dose in the mouse study exceeded the limit dose (1000 mg/kg/day). In the chronic toxicity/carcinogenicity study in rats, survival was markedly increased in the high-dose (213/308 mg/kg/day, M/F) compared to the controls. The HIARC considers this dose to be excessive based on decreases in body weight and body weight gain. No other toxicity was seen. Although there was an increased incidence of hepatocellular adenomas and carcinomas in the high-dose males, the HIARC attributes this to increased survival; that is, these rats lived long enough to develop more tumors. PT807-HCl was clastogenic with or without metabolic activation in Chinese hamster ovary cells cultured *in vitro*, but all other mutagenicity studies were negative. Thus, there is no evidence of clastogenic potential in whole animals. Based on these findings, the HIARC classified PT807-HCl as a "not likely human carcinogen."

3.2 FQPA Consideration (Attachment 2)

The FQPA Safety Factor Committee has determined that the safety factor should be reduced to 1x. Rationales for removing the FQPA factor include: 1) the toxicology database is complete for the assessment of the effects following *in utero* and/or postnatal exposure to PT807-HCl; 2) the toxicity data provided no indication of quantitative or qualitative increased susceptibility of rats or rabbits to **in utero** and/or postnatal exposure; 3) the requirement of a developmental neurotoxicity study is not based on the criteria reflecting some special concern which are generally used for requiring a DNT study and an FQPA safety factor (e.g.: neuropathy in adult animals; CNS malformations following prenatal exposure; brain weight or sexual maturation changes in offspring; and/or functional changes in offspring)[1] and therefore does not warrant an FQPA safety factor; and 4) the exposure assessment will not underestimate the potential dietary(food and water) exposures for infants and children from the use of PT807-HCl (currently no residential exposure is expected).

3.3 Dose Response Assessment

The doses and toxicological endpoints selected by the HIARC for various exposure scenarios are summarized below.

Table 3. Summary of Toxicological Endpoints for Use in Human Risk Assessment

EXPOSURE SCENARIO	DOSE (mg/kg/day)	UF*	ENDPOINT	STUDY
Acute Dietary	NOAEL = 50 mg/kg/day	100	Acute RfD = 0.5 mg/kg/day. Based on slight ataxia in 1/11 males at the LOAEL of 200 mg/kg/day.	Acute Neurotoxicity in Rats
Chronic Dietary	NOAEL = 14 mg/kg/day	100	Chronic RfD = 0.14 mg/kg/day. Based on decreased body weight and body weight gains in parents and pups; delayed sexual development, reductions in uterus and ovary weights, and histological changes in the uterus, vagina, and ovaries of pups at LOAEL of 114 mg/kg/day.	Reproductive Toxicity in Rats

Table 3. Summary of Toxicological Endpoints for Use in Human Risk Assessment				
Dermal (all time intervals)	This risk assessment is not required because no systemic toxicity was seen at the limit dose in a 21-day dermal toxicity study.			
Inhalation (all time intervals)	Oral NOAEL = 30 mg/kg/day**	100	Based on neurotoxic signs at LOAEL = 300 mg/kg/day	90-Day Toxicity in Rats

* An MOE generally exceeds HED's level of concern if it is less than the Uncertainty Factor (UF).
**Since an oral NOAEL was selected, an oral/inhalation absorption ratio of 1 shall be used in risk assessments.

Rationale for Selection of an Acute Dietary RfD:

The systemic NOAEL of 50 mg/kg/day in the acute neurotoxicity study in rats is based on slight ataxia in 1/11 males at the LOAEL of 200 mg/kg/day. The HIARC considers this NOAEL to be appropriate for assessing acute risk because this neurotoxic effect resulted from a single dose.

Rationale for Selection of a Chronic Dietary RfD:

The systemic NOAEL of 14.1 mg/kg/day in the reproductive toxicity study in rats is based on decreased body weight and body weight gain at the systemic LOAEL of 114 mg/kg/day. This is the lowest NOAEL in the most sensitive species. The HIARC considers this NOAEL appropriate for assessing chronic risk because the dosing duration was 14 weeks.

Rationale for Not Requiring a Dermal Risk Assessment:

Dermal risk assessments are not required because no systemic toxicity was observed in a 21-day dermal toxicity study in rats at the limit dose of 1000 mg/kg/day, and because no developmental effects were observed in rats or rabbits.

Rationale for Selection of an Inhalation Risk Assessment:

In the absence of acceptable inhalation data, it is current HIARC policy to use oral data as a surrogate. The oral NOAEL of 30 mg/kg/day from the 90-day gavage toxicity study in rats has been selected for use in inhalation risk assessments. This is a very conservative endpoint because 1.) no mortality occurred in an acute inhalation toxicity study at the limit concentration, 2.) bolus dosing (gavage) bears no resemblance to continuous exposure during tidal breathing, and 3.) the toxic signs seen by the oral and inhalation routes are different.

Adequacy of the Data Base:

There are no data gaps. Although there is no evidence of increased developmental or neurologic susceptibility in the prenatal and pre/postnatal studies, the HIARC has requested a prenatal developmental neurotoxicity study (DNT) based on the fact that this chemical is a neurotoxicant

in adult animals following oral (gavage) administration. This requirement is not based on the criteria generally used for requiring a DNT study and an FQPA safety factor (e.g., neuropathy in adult animals; CNS malformations following prenatal exposure; brain weight or sexual maturation changes in offspring; and/or functional changes in offspring).[1]

4.0 EXPOSURE ASSESSMENT

No tolerances have been established for the residues of PT807-HCl since this is the first food use application.

4.1 Summary of Registered Uses

Proposed use on Oranges

PT807-HCl is a plant growth regulator (end use product = Ecolyst). Ecolyst is a 3.3% a.i. soluble concentrate (SC) formulation (concentration equivalent to 1 g ai/fl oz solution) which is proposed to be used as a single foliar application to orange trees at 6 g ai/A (equivalent to 0.21 oz ai/A or 16 ppm concentration in spray solution) in 100 gallons of finished spray using ground equipment (airblast sprayer). Application should be made during spring bloom (approximately 50% open flower through petal drop).

About 40% of oranges (i.e.,Valencias) will have mature fruit present at the time of application (i.e., fruit require more than one year from bloom to mature) (information from Bernie Schneider, HED).

The proposed direction for use of Ecolyst on oranges is not adequate because no preharvest interval (PHI) was specified. Based on the conversation with the petitioner, the intended PHI is 0-day. However, considering 40% of oranges may have fruit present at application, there are not enough crop field trials to support a 0-day PHI in the submitted studies, and RAB2 concluded that the submitted data do support a 30-day PHI. Therefore, the petitioner should submit a **revised Section B specifying a 30-day PHI, unless additional field trial data reflecting the proposed 0-day PHI are submitted .**

4.2 Dietary Exposure

Residue chemistry data for the proposed use of PT807-HCl on oranges have been previously reviewed by HED. Below are summaries from that review (Memo of 11/22/99, Y. Donovan, D250965).

Product Properties

The review of product chemistry data is under the purview of RD.

Proposed Uses

The proposed use pattern is not adequate for the purposes of this Section 3 registration of PT807-HCl on oranges. **A revised Section B specifying a 30-day PHI is needed unless additional field trial data reflecting the proposed 0-day PHI are submitted.**

Nature of the Residue in Plants

The qualitative nature of the residue in oranges is adequately understood for purpose of this use on oranges. **Future uses on crops other than tree fruit will require additional plant metabolism studies**. The HED Metabolism Assessment Review Committee (MARC) has determined that the residue of concern in plants is parent compound only (HED memo of 9/30/99, Y. Donovan, D 259693). No new orange metabolism data are needed to support the Section 3 registration of PT807-HCl on oranges.

Approximately 89-91% total radioactive residue (TRR) (16.086 ppm) was characterized/identified in orange leaves and immature and mature oranges. PT807-HCl was the major component identified in leaves (53.29% TRR, 14.191 ppm), immature oranges (13.32% TRR, 0.093 ppm), and 50-DAT mature oranges from the previous season (71.93% TRR, 0.386 ppm).

Nature of the Residue in Animals

Ruminants
Based on an acceptable goat metabolism study, the qualitative nature of the residue in ruminants is adequately understood. Future uses with significantly higher residues in feed items may require an additional study with dosing levels higher than 7.55 ppm. For the purpose of the proposed use, the residue of concern is parent compound only as determined by MARC (HED memo of 9/30/99, Y. Donovan, D 259693).

Following oral administration of [^{14}C]PT807-HCl to a lactating goat for 5 consecutive days at 7.55 ppm in the feed (3775x the maximum theoretical dietary burden for beef and dairy cattle), the TRR were <0.001-0.017 ppm in milk, 0.057 ppm in liver, 0.024 ppm in kidney, and 0.002 ppm each in leg muscle, loin muscle, and fat. Analysis of the urine, feces, and cage wash indicated that nearly 100% of the administered dose was excreted, with less than 0.2% of the administered dose found in edible tissues and milk. In milk, TRR levels were 0.015-0.017 ppm in each of the five PM collections made after dosing and dropped to 0.001 ppm in the following AM collections, confirming that PT807-HCl was rapidly metabolized and/or eliminated.

Day 5 PM milk, liver, and kidney samples were subjected to further analysis. None of the components in milk, liver, or kidney corresponded to the parent or other reference metabolite standards.

Poultry
A poultry metabolism study is not required because no poultry feed items are associated with oranges.

Residue Analytical Method - Plant Commodities

For tolerance enforcement, the petitioner proposes an HPLC/UV method with a limit of quantitation of 0.01 ppm and a limit of detection of 0.001 ppm. Method validation recoveries indicate that this method adequately recovers residues of PT807-HCl from oranges and orange processed commodities (orange juice, oil, and dried pulp). Adequate independent method validation and radiovalidation data have been submitted for this method. This method has been sent to BEAD for petition method validation (PMV). Contingent on a successful PMV, this method is considered adequate to enforce the proposed tolerance on oranges.

Confirmatory procedures and method specificity: The petitioner suggested that using the column-switching technique (usage of two columns: C_1 and C_{18}) is an alternative determination step. RAB2 concludes that this confirmatory method is not acceptable. Due to the lack of specificity in the method (UV detection), RAB2 recommends that the registration be made conditional on a more specific confirmatory method (preferably MS detection). Alternatively, the petitioner may submit data showing whether any pesticide registered for use on oranges interferes with determination of PT807-HCl in the HPLC/UV procedure (interference study).

The petitioner utilized the proposed HPLC/UV enforcement method for the determination of residues of PT807-HCl in/on orange samples collected from the storage stability, crop field, and processing studies. The concurrent method recovery data indicate that the method is adequate for data collection.

Residue Analytical Methods - Animal Commodities

The petitioner has requested a waiver from developing a residue analytical method for animal commodities because no detectable residues of PT807-HCl are anticipated. Based on the results of the goat metabolism study, RAB2 agrees with the petitioner that there is no reasonable expectation of residues in milk and ruminant tissues [40 CFR 180.6 (a) (3)]. **Therefore, a residue analytical method for animal tissues, milk, and eggs is not required at this time.**

Multiresidue Methods

The petitioner has submitted data concerning the recovery of residues of PT807-HCl using FDA multiresidue method protocols (PAM Vol. I). PT807-HCl is not recoverable by the multiresidue methods. These data will be forwarded to FDA for evaluation.

Storage Stability Data

The submitted storage stability data are adequate. Fortified residues of PT807-HCl have been demonstrated to be stable during frozen storage for 3.3-3.7 months in/on oranges, orange juice, orange oil, and dried pulp. These data support and validate the storage intervals and conditions of samples collected from the orange field and processing studies.

Crop Field Trials

Following a single foliar application of the 3.3% SC formulation at 6 g ai/A/application (1x the proposed maximum seasonal application rate), residues of PT807-HCl were below the LOQ (<0.01 ppm) in/on all samples. These samples included mature oranges from the previous season harvested 0-68 DAT (4 trials) and oranges from the treatment season harvested 197-359 DAT (13 trials). **RAB2 concludes that, with only two crop field trials reflecting the proposed 0 day PHI, the number of crop field trials for the proposed use of 0-day PHI is not adequate. An additional three crop field studies at 0-day PHI are needed to support the proposed use. Unless new data supporting 0-day PHI are submitted, a revised Section B specifying a 30 day PHI is required.** With the two residue decline studies plus the two trials reflecting 19 and 28 day PHI's, RAB 2 concludes sufficient data are available to support a 30-day PHI taking into account only about 40% of the crop can have harvest intervals in this range.

Processed Food/Feed

The submitted orange processing data are adequate. At 5X application rate, residues of PT807-HCl were less than the LOQ (<0.01 ppm) in/on whole oranges harvested at 19 days PHI. Residues were below the analytical method's LOQ in orange juice and oil processed from treated oranges bearing non-detectable residues. In dried pulp, residues ranged from 0.015 ppm to 0.017 ppm. Because no quantifiable residues were found in the RAC at the 5x application rate and the tolerance for oranges is being proposed at the LOQ, the residue levels in dried pulp can be adjusted for the degree of exaggeration. The adjusted residues would be <0.01 ppm. Therefore, provided that the PHI is increased to 30-days (see Crop Field Trials), the proposed tolerance of 0.01 ppm for oranges would be appropriate for any residues expected in dried pulp as a result of processing. **No tolerances are required for orange processed commodities. An additional processing study may be required to support a 0-day PHI. RAB2 suggests that some 5X rate fruit samples be analyzed in any future trials reflecting a 0-day PHI to address whether additional processing data required.**

Meat, Milk, Poultry, Eggs

Ruminants

The petitioner has requested a waiver from the requirement to conduct a ruminant feeding study. The waiver request is based on the results of the processing study, the maximum theoretical dietary burden of PT807-HCl for ruminants, and the results of the goat metabolism study. The only ruminant feed item associated with this petition is dried orange pulp. The maximum theoretical dietary burden of PT807-HCl for ruminants is 0.002 ppm.

The goat metabolism study reviewed in this petition was conducted at a feeding level of 7.55 ppm, which is equivalent to 3775x the maximum theoretical dietary burden for beef and dairy cattle. Assuming a linear relationship between dose and total radioactive residues, the expected PT807-HCl residues in meat and milk would be well below the likely LOD for methods used to measure residues in livestock products. Therefore, **RAB 2 concludes that a feeding study is**

not required as there is no reasonable expectation of finite residues [40 CFR§180.6(a)(3)] in milk and ruminant tissues.

Poultry
There are no poultry feed commodities associated with this petition. **Therefore, data pertaining to the magnitude of PT807-HCl residues in poultry commodities are not required.**

Confined/Field Accumulation in Rotational Crops

No confined or field rotational crop studies were submitted with this petition. The Agency has determined that rotational crop studies are not required for uses of pesticides on oranges as they are not routinely rotated to other crops.

Codex Issues

The Codex Alimentarius Commission, Mexico, and Canada have not established maximum residue limits (MRLs) for residues of PT807-HCl in/on plant and animal commodities.

4.2.1 Food Exposure (Attachment 3)

Acute Dietary Exposure and Risk. **aPAD = acute RfD = 0.5 mg/kg bwt/day.**

For the acute dietary (food) exposure analyses, tolerance level residues and 100% crop treated (%CT) were used. The Dietary Exposure Evaluation Model (DEEM™) acute dietary risk analysis estimates the distribution of single-day exposures for the overall U.S. population and certain subgroups. The analysis evaluates individual food consumption as reported by respondents in the USDA 1989-92 Continuing Survey of Food Intake by Individuals (CSFII) and accumulates exposure to the chemical for each commodity. Each analysis assumes uniform distribution of PT807-HCl in the commodity supply.

The resulting analysis is summarized below (Table 4) as a percent of the acute PAD (%aPAD) at the 95th percentile of exposure (Memo of 10/27/99, W. Cutchin, D259992). The acute exposures are all less than 1% of the aPAD. This acute dietary risk estimate should be viewed as conservative since these calculated exposures are based on tolerance level residues and 100% CT (i.e., Tier I assessment). Therefore, any additional refinements could reduce risk estimates significantly. In making a safety determination for the requested use, HED is taking into account this conservative exposure assessment. HED is generally concerned with acute exposures that exceed 100% of the aPAD.

Table 4. **Acute** Dietary (Food Only) Exposure Analysis by DEEM for PT807-HCl		
Population Subgroup	Exposure @ 95th Percentile (mg/kg bwt/day)	Percent aPAD[1]
U.S. Population (48 states)	0.000068	<1
Non-nursing infants (< 1 yr)	0.000134	<1
Children (1-6 yrs)	0.000175	<1
Female (13 +/nursing)	0.000083	<1
Males (13-19 yrs)	0.000062	<1

[1] Percentage Acute PAD (% aPAD) = $\frac{\text{Exposure X 100}}{\text{aPAD}}$

Chronic Dietary Exposure and Risk. **cPAD = chronic RfD = 0.14 mg/kg bwt/day.**

The DEEM analysis evaluates individual food consumption as reported by respondents in the USDA 1989-91 Continuing Survey of Food Intake by Individuals (CSFII) and accumulates exposure to the chemical for each commodity.

A DEEM chronic exposure analysis was performed using tolerance level residues and 100% CT to estimate the Tier I exposure for the general population and subgroups of interest (Memo of 10/27/99, W. Cutchin, D259992). Summaries of the exposure and their representations as percentages of PAD are in the following Table 5. Exposures for all population subgroups are less than 1% of the cPAD, and HED's level of concern is greater than 100% cPAD.

Table 5. **Chronic** Exposure Analysis by the DEEM System for PT807-HCl		
Population Subgroup	Exposure (mg/kg/day)	Percent cPAD[1]
U.S. Population	0.000012	<1
Non-nursing infants	0.000013	<1
Children (1-6 years old)	0.000034	<1
Female 13+ (nursing)	0.000015	<1
Males (13-19 yrs)	0.000012	<1

[1] Percentage cPAD = $\frac{\text{Exposure X 100}}{\text{cPAD}}$

4.2.2 Drinking Water (Attachment 4, EFED memo of 9/23/99, Laurence Libelo, D258699.)

4.2.2.1 Environmental Fate Properties

N,N-diethyl-2(4-methylbenzyloxy) ethylamine hydrochloride (PT807-HCl or Ecolyst) is very soluble in water and stable in the environment. Based on its chemical properties it is likely that this chemical will move to surface water and groundwater, and it may accumulate in the environment.

4.2.2.2 Ground Water Modeling

According to information included in the proposed Ecolyst label, the maximum application rate for this chemical is 0.013 lb a.i./acre/year. The groundwater Estimated Environmental Concentration (EECs), calculated using SCI-GROW is **0.02 ppb**. However, the properties of this compound are outside the range of values used to develop SCI-GROW. Because of its stability in the environment this chemical can be expected to accumulate in groundwater and the actual concentrations may be much higher.

4.2.2.3 Surface Water Modeling

According to information included in the proposed Ecolyst label, the maximum application rate for this chemical is 0.013 lb a.i./acre/year. The surface water acute EEC is **4.0 ppb** using PRZM/EXAMS. The surface water chronic EEC is also **3.9 ppb**. These values represent the 1-in-10 year peak surface water concentration and 1-in-10 year mean yearly concentration. EFED notes that the calculated concentration in surface water increases over time as the compound builds up in the environment, and continued use will result in increasing concentration over time.

Acute

For purposes of this acute risk assessment, the estimated acute maximum concentration for PT807-HCl in surface and ground waters (4.0 ppb = 4.0 μg/L) should be used for comparison to the back-calculated DWLOCs for the acute endpoint. These DWLOCs for various population categories are summarized in Table 6.

Table 6. Drinking Water Levels of Comparison for **Acute** Exposure to PT807-HCl[1]

Population Category[2]	aPAD (mg/kg/day)	Food Exposure (mg/kg/day)	Max. Water Exposure[3] (mg/kg/day)	DWLOC [4,5,6] (μg/L)	EEC[7] (μg/L)
U.S. Population (48 states)	0.5	0.000068	0.5	18,000	4.0
Females 13 +	0.5	0.000083	0.5	15,000	4.0
Children (1-6 year)	0.5	0.00018	0.5	5,000	4.0

[1] Values are expressed to 2 significant figures.
[2] Within each of these categories, the subgroup with the highest food exposure was selected.
[3] Maximum Water Exposure (Chronic or Acute) (mg/kg/day) = [aPAD (mg/kg/day) - Food Exposure (mg/kg/day)].
[4] DWLOC(μg/L) = Max. water exposure (mg/kg/day) x body wt (kg) ÷ [(10^{-3} mg/μg) x water consumed daily (L/day)].

[5] HED Default body weights are: General U.S. Population, 70 kg; Males (13+ years old), 70 kg; Females (13+ years old), 60 kg; Other Adult Populations, 70 kg; and, All Infants/Children, 10 kg.
[6] HED Default daily drinking rates are 2 L/day for adults and 1 L/day for children.
[7]EEC: Estimated Environmental Concentration. (Acute value).

Chronic

For purposes of chronic risk assessment, the estimated chronic maximum concentration for PT807-HCl in surface and ground waters (which is 3.9 ppb = 3.9 μg/L) should be used for comparison to the back-calculated human health DWLOCs from the chronic (non-cancer) endpoint. These DWLOCs for various population categories are summarized in Table 7.

Table 7. Drinking Water Levels of Comparison for **Chronic** Exposure to PT807-HCl[1]

Population Category[2]	cPAD (mg/kg/day)	Food Exposure (mg/kg/day)	Max. Water Exposure[3] (mg/kg/day)	DWLOC [4,5,6] (μg/L)	EEC[7] (μg/L)
U.S. Population (48 states)	0.14	0.000012	0.14	4,900	3.9
Female 13+	0.14	0.000015	0.14	4,200	3.9
Children (1-6 years)	0.14	0.000034	0.14	1,400	3.9

[1] Values are expressed to 2 significant figures.
[2] Within each of these categories, the subgroup with the highest food exposure was selected.
[3] Maximum Water Exposure (Chronic or Acute) (mg/kg/day) = cPAD (mg/kg/day) - Food Exposure (mg/kg/day).
[4] DWLOC(μg/L) = Max. water exposure (mg/kg/day) x body wt (kg) ÷ [(10^{-3} mg/μg) x water consumed daily (L/day)].
[5] HED Default body weights are: General U.S. Population, 70 kg; Males (13+ years old), 70 kg; Females (13+ years old), 60 kg; Other Adult Populations, 70 kg; and, All Infants/Children, 10 kg.
[6] HED Default daily drinking rates are 2 L/day for adults and 1 L/day for children.
[7]EEC: Estimated Environmental Concentration. (Chronic 90-day average).

4.3 Occupational Exposure (Attachment 5, HED memo of 10/29/99, D259538)

Workers may be exposed to Ecolyst during mixing, loading, application and postapplication activities. Based on the proposed use patterns, short and intermediate-term exposures may occur. Chronic exposures (6 months of continuous exposure) are not expected.

TABLE 8: USE PATTERNS AND FORMULATION FOR Ecolyst

FORMULATION	METHOD OF APPLICATION	USE SITES	APPLICATION RATES	TIMING OF APPLICATION
Liquid Formulation (3.3% ai)	By ground air-blast sprayer equipment.	oranges	0.0124 lbs ai/A	Apply during spring bloom. Do not apply more than 1 application per season.

4.3.1. Handler

Since no chemical-specific data for assessing human exposures during pesticide handling activities were submitted to the Agency in support of the registration of Ecolyst, it is the policy of HED to use data from the Pesticide Handlers Exposure Data Base (PHED) Version 1.1 to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure, Policy .007, "Use of Values from the PHED Surrogate Table and Chemical-Specific Data." Health Effects Division, Office of Pesticide Programs, January 1999).

The unit exposure values calculated by PHED generally range from the geometric mean to the median of the selected data set. To add consistency and quality control to the values produced from this system, the PHED Task Force has evaluated all data within the system and has developed a set of grading criteria to characterize the quality of the original study data. The assessment of data quality is based on the number of observations and the available quality control data. These evaluation criteria and the caveats specific to each exposure scenario are summarized in **Table 9.** While data from PHED provide the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. HED has developed a series of tables of standard unit exposure values for many occupational scenarios that can be utilized to ensure consistency in exposure assessments (PHED Surrogate Exposure Guide. Health Effects Division, Office of Pesticide Program, August 1998).

Defaults established by the HED Science Advisory Council for Exposure were used for body weight, and the level of personal protective equipment worn by handlers. A short- and intermediate-term inhalation NOAEL of **30** mg/kg/day and **100%** inhalation absorption factor were established by the HIARC (9/16/99) for estimating risk from inhalation exposure. The HIARC did not select a dermal endpoint and determined that a risk assessment was **not** required for dermal exposure.

A summary of the exposure and risk estimates for handlers are included as **Table 9.** All MOEs are above 100. The inhalation MOEs ranged from 2,000,000 for mixer/loader to 500,000 for applicators. For workers MOEs equal to or greater than 100 do not exceed HED's level of concern.

Per the Worker Protection Standard (WPS), the minimum level of PPE for handlers is based on the acute toxicity of the end-use product. RD is responsible for ensuring that PPE listed on the label is in compliance with WPS.

Table 9: OCCUPATIONAL HANDLER INHALATION EXPOSURE RISK TO ECOLYST											
PHED Scenario [1]	Personal Protective Equipment [2]	Route of Exposure [3]	PHED Unit Exposure [4] (mg/lb ai)	PHED Data Conf [5]	AR [6] (lb ai/acre)	% AF [7]	Acres Treated [8] (A/day)	BW [9] (kg)	Daily Dose [10] (mg/kg/day)	Inhalation Short- and Intermediate-term	
										NOAEL [11] (mg/kg/day)	MOE [12]
Mixer/ Loader Exposure											
Mixing/Loading Liquid Formulation for Airblast Spray	Long Sleeves, Long Pants, Gloves	inhalation	0.0012	high	0.0124	1 (100%)	74	70	1.5 x 10-5	30	2,000,000
Applicator Exposure											
Applying Sprays to Orchard with Airblast (open-cab)	Long Sleeves, long Pants, Gloves	inhalation	0.0045	high	0.0124	1 (100%)	74	70	5.9 x 10-5	30	500,000

Footnotes:

1. Pesticide Handler Exposure Database (PHED) scenarios - Self-explanatory.
2. Personal Protective Equipment - Based on the acute toxicity of the end-use product.
3. Self-explanatory
4. Unit Exposure (UE) is from Pesticide Handlers Exposure Database (PHED) version 1.1, 8/98.
5. Unit exposure data quality is based on Subdivision U Guidelines
6. Application rate (AR) is from the label for Ecolyst Plant Growth Regulator
7. % Absorption Factor (AF) determined by HIARC 9/99
8. Acres treated per day are based on US Agricultural Census.
9. Body weight for an adult male = 70 kg.
10. Daily Dose (DD) = [(lb ai/A) x (A/day) x UE (mg/lb ai handled) x AF] ÷ Body Weight (kg)
11. Short and Intermediate-term Inhalation NOAEL = 30 mg/kg/day established by HIARC based on 90-day gavage study in rats.
12. MOE = NOAEL/ Daily Dose

4.3.2 Post-Application

Although the potential for postapplication (dermal) exposure does exist, no systemic toxicity was observed in the 21-day dermal toxicity study in rats at the limit dose of 1000 mg/kg/day. Therefore no dermal endpoints were selected by the HIARC and a postapplication exposure risk assessment is not required.

Restricted Entry Interval (REI). The REI is based on the acute toxicity of the technical material, which is classified in acute toxicity category III/IV (HIARC, 9/99). Acute toxicity category III and IV chemicals require a 12-hour REI. Thus, the 12-hour REI that appears on the PT807-HCL label is adequate.

4.4 Non- Occupational (Residential) Exposure

Ecolyst currently has no registered uses that could result in residential exposures (REFS 10/99). Therefore a residential exposure risk assessment is **not** required at this time.

5.0 AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION

In examining aggregate exposure, FQPA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures. The primary non-food sources of exposure the Agency looks at include drinking water (whether from ground or surface water), and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor and/or outdoor uses). In evaluating food exposures, EPA takes into account varying consumption patterns of major identifiable subgroups of consumers, including infants and children.

5.1 Acute Aggregate Risk (Food + Water)

Using the most conservative Tier I approach, it is estimated the acute exposure to PT807-HCl from food for the general US population, infants and children will utilize **<1%** of the **aPAD**, as shown in Table 4. Despite the potential for exposure to PT807-HCl in drinking water, HED does not expect the aggregate exposure to exceed 100% of the aPAD for adults, infants and children. As seen in Table 6, EFED's maximum concentration of PT807-HCl in surface and ground water for acute exposure is well below the DWLOC. HED concludes that there is a reasonable certainty that no harm will result to adults, infants and children from acute aggregate exposure to PT807-HCl residues.

5.2 Chronic Aggregate Risk (Food + Water + Residential)

Using the most conservative analysis described above, it is estimated that the chronic exposure to PT807-HCl from food for the general US population, infants and children will utilize **<1%** of the cPAD, as shown in Table 5. Despite the potential for exposure to PT807-HCl in drinking water, HED does not expect the aggregate exposure to exceed 100% of the cPAD. As indicated in Table 7, EFED's maximum concentration of PT807-HCl in surface and ground water for chronic exposure is very small compared to the DWLOC. Currently there is no registered or proposed uses that could result in residential exposures. Therefore, HED concludes that there is a reasonable certainty that no harm will result to adults, infants and children from chronic aggregate exposure to PT807-HCl residues.

5.3 Short- and Intermediate-Term Aggregate Risk (Residential + Chronic Food + Chronic Water)

There are no registered residential uses of PT807-HCl. Therefore, a short- and intermediate-term aggregate risk assessment for PT807-HCl is **not required.**

5.4 Determination of Cancer Risk

PT807-HCl has been classified by HED HIARC as a "not likely human carcinogen." A cancer risk assessment **is not required**.

5.5 Endocrine Disrupter Effects

The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." EPA has been working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine Disrupter Screening Program was published in the Federal Register of December 28, 1998 (63 FR71541). The Program uses a tiered approach and anticipates issuing a Priority List of chemicals and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of PT807-HCl and its end-use products for endocrine effects may be required.

5.6 Cumulative Exposure To Substances with a Common Mechanism of Toxicity

PT807-HCl is a new plant growth regulator. HED does not have, at this time, available data to determine whether PT807-HCl has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, HED has not assumed that PT807-HCl has a common mechanism of toxicity with other substances.

6.0 DATA NEEDS

There are no data gaps pertaining to toxicity studies. The HIARC has requested a developmental neurotoxicity study in rats.

RAB2 has previously concluded that data gaps pertaining to residue chemistry are as follow:

- Revised Section B specifying the preharvest interval of 30 days, or additional three crop field trials with 0-day PHI
- More specific confirmatory method or interference study (recommend this be made a conditional requirement).

1. This is an interim step towards accordance with the proposed 'OPP POLICY ON DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTOR(S) FOR USE IN THE TOLERANCE-SETTING PROCESS' which was presented to the FIFRA SAP meeting in May, 1999 and placed in the Docket for Public Comment (64FR37001; 7/8/99; Docket No. 37001).

Attachments: 1. HIARC report on PT807-HCl (10/19/99);
2. FQPA report on PT807-HCl (10/15/99);
3. DEEM summaries (10/27/99, D259992);
4. EFED memo (9/23/99, D258699);
5. HED memo (ORE report of 10/29/99, D259538).

cc with Attachments: Y.W. Donovan.

cc without Attachments: John Whalan, Margarita Collantes, RAB2 reading file, PP#8F04998.

Attachment 1

HED DOC. NO. 013819

DATE: **October 19, 1999**

MEMORANDUM

SUBJECT: ***PT807-HCl (Ecolyst®)***: - Report of the Hazard Identification Assessment Review Committee.

FROM: John E. Whalen, Toxicologist
Registration Action Branch 2
Health Effects Division (7509C)

THROUGH: Pauline Wagner, Co-Chair
and
Jess Rowland, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Richard Loranger, Branch Senior Scientist
Registration Action Branch 2
Health Effects Division (7509C)

PC Code: 069089

On September 16, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of PT807-HCl, the active ingredient in the formulated product Ecolyst®. The HIARC selected toxicology endpoints for oral and inhalation exposure risk assessments, dismissed carcinogenicity concerns, and addressed the potential enhanced sensitivity of infants and children from exposure to PT807-HCl as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present on September 16, 1999 include Pauline Wagner, Jess Rowland, Pam Hurley, Karen Hamernik, Yiannakis Ioannou, Virginia Dobozy, Nicole Paquette, Kathy Raffaele, Sue Makris, P.V. Shah, Bill Burnam, Tina Levine, and Dave Andersen. Member *in absentia* was Nancy McCarroll who provided written comments regarding mutagenicity. Data were presented by John E. Whalan of Registration Action Branch 2.

Data Presentation &
Report Preparation: _____

John E. Whalan
Toxicologist

Executive Secretary: _____

Brenda Tarplee

I. INTRODUCTION

PT807-HCl is a plant growth regulator which has been shown to be effective at shortening the time to maturation of citrus when applied during the Spring bloom. It will be applied to trees as a single foliar application at a rate of 6 grams a.i./A in 100 gallons of finished spray using an airblast sprayer.

On September 16, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of PT807-HCl, the active ingredient in Ecolyst®. The HIARC selected toxicology endpoints for oral and inhalation exposure risk assessments, dismissed carcinogenicity concerns, and addressed the potential enhanced sensitivity of infants and children from exposure to PT807-HCl as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

II. HAZARD IDENTIFICATION

A. ACUTE DIETARY (Acute RfD)

Study Selected: Acute Neurotoxicity in Rats 870.6200

MRID No.: 44380001

Executive Summary: In an acute neurotoxicity screening battery study (MRID 44380001), male and female Sprague-Dawley rats (11 animals/sex/group) were given a single dose of PT807-HCl (99.7% a.i.) in water by gavage at levels of 0, 50, 200, or 400 mg/kg and observed through day 14. Functional Observation Battery (FOB) and motor activity tests were performed on day -7, 0 (approximately 0.75-1.25 hours postdosing), 7, and 14.

No differences of toxicological concern were observed in mortality, non-functional observation battery clinical signs, body weights, food consumption, landing hindlimb splay, forelimb grip strength, brain parameters, gross pathology, and histopathology. In the FOB, all groups were comparable during the pretest evaluation and at days 7 and 14.

At 400 mg/kg, treatment-related effects were observed in the FOB and motor activity tests on day 0 and are as follows: clinical signs seen were slight ataxia (3/11 males, 3/11 females vs 0/22 controls), hypotonic gait (1/11 males vs 0/11 controls), dilated pupils (1/11 males, 1/11 females vs 0/22 controls), muzzle staining (2/11 males vs 0/11 controls), flaccid body tone (1/11 males vs 0/11 controls), reduced locomotor activity (5/11 females vs 0/11 controls), and reduced rearing (females, ↓42%, $p<0.05$). The following differences ($p<0.05$) were observed in the females only: reduced body temperature (↓0.7°C), increased hindlimb grip strength (↑27%) and decreased overall motor activity (↓26%).

At 200 mg/kg, treatment-related effects were limited to slight ataxia (1/11 males vs 0/11 controls) during the FOB. There were no findings of toxicological concern in the 50 mg/kg dose group.

Neurotoxicity NOAEL = 50 mg/kg/day
Neurotoxicity LOAEL = 200 mg/kg based on slight ataxia in 1 of 11 males.

Dose and Endpoint for Risk Assessment: The NOAEL is 50 mg/kg/day for systemic effects based on slight ataxia in 1/11 males at the LOAEL of 200 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factor(s): The neurotoxic effect (slight ataxia) was seen following a single dose, thus it is relevant for this acute risk assessment.

This risk assessment is required.

B. CHRONIC DIETARY [Reference Dose (RfD)]

Study Selected: Reproductive Toxicity Study in Rats 870.3800

MRID No.: 44595004

Executive Summary: In a 2-generation reproduction toxicity study (MRID 44595004), diethyl-2-(4-methylbenzyloxy)ethylamine hydrochloride (PT-807-HCl; 0.5 g a.i./mL) was administered continuously in the diet to Sprague-Dawley rats (32/sex/dose) at dose levels of 0, 250, 2000, or 4000 ppm (equivalent to 14.1/20.8, 114.0/168.0, and 229.3/350.3 in the P animals [M/F] and 19.5/26.8, 168.8/231.6, and 360.5/490.7 mg/kg/day in F_1 animals [M/F], respectively). Exposure to P animals began at 10-11 weeks of age and lasted for 10 weeks prior to mating. F_1 pups selected (25/sex/dose) to produce the F_2 generation were exposed to the same dosage as their parents beginning at postnatal day (PND) 21. F_1 animals were administered the test article for approximately 14 weeks prior to mating to produce the F_2 litters. Mating to produce a second F_{2b} generation was not performed. F_2 animals (20/sex/dose) were given the same diet as their dams, and necropsied 1 to 2 weeks after weaning. Exposure of all animals to the test material was continuous throughout the study.

There were no treatment-related clinical signs observed in the P or F_1 adults. There were no changes of toxicological concern in reproductive performance.

In the 2000 ppm group, body weights were decreased ($p<0.01$ or 0.001) compared to concurrent controls throughout the study in the F_1 males and females (↓9-15%). Body weight gains were decreased over the course of the study in P females and in F_1 males and females (↓6-89%, $p<0.05$, 0.01, or 0.001).

In the 4000 ppm group, body weights were decreased ($p<0.001$) in the F_1 males and females throughout the study (↓15-24%) and in P females during gestation and lactation (↓7-13%). Body weight gains were decreased ($p<0.05$, 0.01, or 0.001) in P males and females (↓21-100%) and in F_1 males and females (↓9-65%). Decreases ($p<0.001$) in food consumption were observed in P and F_1 females during gestation and lactation (↓9-27%).

Systemic NOAEL = 14.1 mg/kg/day
Systemic LOAEL = 114 mg/kg/day based upon decreased body weight and body weight gains.

No treatment-related effects on mortality or clinical signs were observed at any time in the F_1 and F_2 litters. There were no differences of toxicological concern in anogenital distance or organ weights in the F_1 or F_2 litters. There were no differences in static righting reflex, startle response, and pupillary light reflex in the F_1 and F_2 pups. There were no treatment-related findings at necropsy in the F_1 or F_2 pups.

In the 2000 ppm groups, sexual development was delayed in F_1 females (delay in vaginal perforation - ↑9%, $p<0.001$). In the P females, decreases ($p<0.05$ or 0.01) in absolute and relative ovary weights (↓10%) occurred, along with an increased number of animals showing no estrous cycle activity, diffuse uterine atrophy, diffuse vaginal atrophy, vaginal mucification, and ovarian interstitial gland atrophy (9-19/32 treated vs 3-5/31 controls). The number of corpora lutea were reduced 48% ($p<0.05$). Body weights and body weight gains were decreased ($p<0.05$, 0.01, or 0.001) during lactation in F_1 and F_2 pups (↓8-19%). There was a delay ($p<0.05$ or 0.01) in developmental parameters in F_1 and F_2 pups (pinna detachment: ↓30-31%; eyes open: ↓26-50%). These delays are in part attributable to the decreased body weights of the treated animals.

In the 4000 ppm groups, sexual maturation was delayed ($p<0.001$) in F_1 males (delay of preputial separation -↑7%) and females (delay of vaginal perforation - ↑21%). In P dams, decreases occurred in the absolute weights ($p<0.001$) of the uterus (↓37%) and ovaries (↓30%); decreased ($p<0.001$) relative (to body) weights of the uterus (↓28%) and ovaries (↓21%) were also observed. In the F_1 females, decreases in absolute ovarian weights occurred (↓15%, $p<0.01$). In the P dams, an increased number of animals showed no estrous cycle activity, diffuse uterine atrophy, diffuse vaginal atrophy, vaginal mucification, and ovarian interstitial gland atrophy (21-27/32 treated vs 3-5/31 controls). Enumeration of the ovarian follicles and corpora lutea revealed a decrease ($p<0.05$, 0.01, or 0.005) in the number of medium (↓26%) and large follicles (↓29%), and corpora lutea (↓60%). Changes in F_1 dams were limited to a decrease in the number of large ovarian follicles (↓25%, $p<0.01$). Body weights and body weight gains were decreased ($p<0.001$) in all F_1 and F_2 pups throughout lactation (↓10-30%). There was a delay ($p<0.01$ or 0.001) in development in F_1 and F_2 pups (pinna detachment - ↓43-44%; eyes open - ↓63-88%). These delays are in part attributable to the decreased body weights of the treated animals. No observations of toxicological significance were made at the low-dose (250 ppm).

Reproductive NOAEL = 14.1 mg/kg/day for *both sexes (nontoxic)*
Reproductive LOAEL = 114 mg/kg/day for both sexes based on decreased pup body weight and body weight gains, delayed sexual development, reductions in absolute and relative uterus and ovary weights, and histological changes in the uterus, vagina, and ovaries in the females.

Dose and Endpoint for Risk Assessment: Systemic NOAEL = 14.1 mg/kg/day in males.

Comments about Study/Endpoint/Uncertainty Factor(s): This is the lowest NOAEL in

the most sensitive species. The HIARC considers this NOAEL appropriate for assessing chronic exposure because the dosing duration was 14 weeks.

This risk assessment is required.

C. OCCUPATIONAL / RESIDENTIAL EXPOSURE—DERMAL

1. DERMAL ABSORPTION

A dermal absorption factor is not needed because dermal risk assessments are not required.

2. SHORT-TERM DERMAL (1 - 7 days)

Study Selected: The only applicable study is a 21-day dermal toxicity in rats (MRID 44595002). Because no toxic effects were observed at the limit dose, no study was selected.

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not applicable

Comments about Study/Endpoint/Uncertainty Factor(s): A short-term dermal risk assessment is not required because no systemic toxicity was observed in a 21-day dermal toxicity study in rats at the limit dose of 1000 mg/kg/day.

This risk assessment is not required.

3. INTERMEDIATE-TERM DERMAL (1-Week to Several Months)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not applicable

Comments about Study/Endpoint/Uncertainty Factor(s): See Short-Term Dermal.

This risk assessment is not required.

4. LONG-TERM DERMAL (Several Months to Lifetime)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not applicable

Comments about Study/Endpoint/Uncertainty Factor(s): See Short-Term Dermal.

This risk assessment is not required.

5. INHALATION EXPOSURE

Study Selected: 90-Day Gavage Toxicity Study in Rats 870.3100

MRID No.: 44380005

Executive Summary: In a 13-week subchronic toxicity study (MRID 44380005), PT807-HCl (100% a.i. assumed) was administered to Sprague-Dawley Crl:CD(SD)BR albino rats (10/sex/dose) by gavage at dose levels of 0, 30, 300, or 600 mg/kg/day for 13 weeks.

No treatment related differences compared to controls were detected in body weight, food consumption, food efficiency, hematology, opthalmology, gross pathology, or histopathology (other than spontaneous and agonal lesions). Between Weeks 5 and 13 in the high-dose group, 6/10 males and 7/10 females died following convulsions and a reduction in activity, and in some cases labored breathing. One female (1/10) in the 300 mg/kg/day treatment group died during Week 4 following a lack of coordination and reduced activity.

All rats in the 600 and 300 mg/kg/day treatment groups exhibited hyperactivity, hyperreflexivity, lack of coordination, tremors, and convulsions beginning between 5 minutes and 4 hours after dosing. This acute reaction was followed by a period of relative inactivity. Increased salivation was observed pre- and post-dosing in nearly all rats in the 600 and 300 mg/kgk/day groups.

Phosphorus levels were increased in both sexes (↑ 32-36%) at the high dose, compared to controls. A majority of males in the 300 and 600 mg/kg/day treatment groups had elevated urinary protein levels, but the females had normal urine protein levels.

Rats in the 600 mg/kg/day treatment groups had increased ($p<0.01$) absolute and relative liver weights (↑31-38 and 22-40%, respectively) compared to controls. This

marked increase in liver weight is considered an adaptive response because there were no corroborating clinical chemistry values or histopathologic lesions. Males in the high-dose group had increased absolute brain weights (9%; $p<0.01$), while female brain weight increased 4%. The increase in male brain weight may be an adverse finding.

NOAEL = 30 mg/kg/day
LOAEL = 300 mg/kg/day based on increased mortality; hyperactivity, hyperreflexivity, lack of coordination, tremors, convulsions, and increased *salivation in males and females; and elevated urinary protein in males.*

Dose and Endpoint for Risk Assessment: Oral NOAEL = 30 mg/kg/day. The following "3-C's route-to-route extrapolation" should be used:

Step I. The inhalation exposure component (i.e.,µg a.i/lb) using a 100% absorption rate (default value) should be *converted to* an *equivalent oral dose* (mg/kg/day)

Step II. Not applicable because a dermal risk assessment is not required.

Step III The dose from Step I should then be *compared to the oral dose* to calculate the MOE's.

Comments about Study/Endpoint/Uncertainty Factor(s): This is a very conservative endpoint because 1.) no mortality occurred in an acute inhalation toxicity study at the limit concentration, 2.) bolus dosing (gavage) bears no resemblance to continuous exposure during tidal breathing, and 3.) the toxic signs seen by the oral and inhalation routes are different. In the absence of acceptable inhalation data, it is current HIARC policy to use oral data as a surrogate.

This risk assessment is required.

D. Margin of Exposure (MOE): An MOE of 100 is adequate for occupational exposure.

E Recommendation for Aggregate (Food, Water, Dermal, Inhalation) Exposure Risk Assessments

There are no registered residential uses, so aggregate exposure risk assessment will be limited to food and water.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 44612103

Executive Summary: In a combined chronic/oncogenicity study (MRID 44612103), PT807-HCl (0.5 g/mL a.i.) was administered in the diet for 104 weeks to 60 Sprague-Dawley rats/sex/group at levels of 0, 250, 500, 5,000, or 10,000 ppm (equivalent to approximately 0, 10/14, 20/28, 213/308, or 443/621 mg/kg/day [M/F]). In addition, 10 rats/sex/dose each were terminated at approximately 52 weeks.

No differences of toxicological concern were observed in survival rates in either sex of the treated groups throughout the study when compared to the respective control groups. Clinical signs, food consumption and utilization, ophthalmoscopic parameters, hematological parameters, clinical chemistry, and urinalysis were unaffected by treatment.

At 5,000 ppm, decreased body weights (↓5-27%; $p \leq 0.05$-0.01) and body weight gains (↓11-43%; $p \leq 0.05$-0.01) relative to concurrent controls were observed in males and females. At the interim necropsy, an increased incidence of hepatocellular hypertrophy was seen in males and females (5/20 treated vs 0/20 controls). When the data from all animals were examined, an increase in hepatocellular hypertrophy was observed in females (22/70 treated vs 3/70 controls).

At 10,000 ppm, decreased body weights (↓15-41%; $p \leq 0.01$) and body weight gains (↓28-118%; $p \leq 0.01$) relative to concurrent controls were observed in males and females. At termination (24 months), the males had increased relative (to body) liver weights (↑26%, $p \leq 0.01$) and the females had an increased incidence of discolored foci in the lungs (29/70 treated vs 8/70 controls). At the interim necropsy, an increased incidence of hepatocellular hypertrophy was seen in the males and females (7/20 treated vs 0/20 controls). When the data from all animals were examined, an increase in hepatocellular hypertrophy was observed in males and females (25-31/70 treated vs 2-3/70 controls). In addition, there was an increase in the incidence of acidophilic hepatocellular alterations in the 10,000 ppm males (9/70 treated vs 3/70 controls). No differences of toxicological concern were noted at the 500 and 250 ppm doses.

Dosing was considered adequate by decreases in body weights and body weight gains in the 5,000 and 10,000 ppm groups.

NOAEL = 20/28 mg/kg/day, M/F
LOAEL = 213/308 mg/kg/day, M/F, based on decreased body weight and body weight gains.

When data from all animals were combined, there was a significant increase relative to concurrent controls in the incidence of hepatocellular adenomas in the 10,000 ppm males (5/70 treated vs 0/70 controls, $p \leq 0.05$). Although the incidence of carcinomas was not

significantly increased (3/70 treated vs 0/70 controls), the combined hepatocellular adenoma/carcinoma incidence was significantly increased in the 10,000 ppm males (8/70 treated vs 1/70 controls, $p \leq 0.05$). When corrected for survival, no statistically significant differences were observed among groups, but a dose-related trend was observed. Therefore, under the conditions of this study, there was no clear evidence of carcinogenic potential.

Discussion of Tumor Data: Survival rates in the PT807-HCl male rats showed a signficant increasing trend (i.e., the higher dose rats lived longer), and significant differences between the 5,000 and 10,000 ppm dose groups and the controls, all at $p < 0.01$. Female rats indicated a significant increasing trend for survival, and a significant difference between the 10,000 ppm dose group and the the controls, both at $p < 0.01$.

Tumor rates were analyzed by the company using the 2X2 Chi-square, Cox's test and the Generalized K/W Analysis. Males showed significant trends for hepatocellular adenomas at $p < 0.01$ and for hepatocellular adenomas and/or carcinomas combined at $p < 0.05$. There was a significant difference in the pair-wise comparison of the 10,000 ppm dose group with the controls for hepatocellular adenomas and/or carcinomas combined at $p = 0.039$ by the 2X2 Chi-square test, while these other tests did not indicate significance. HED's statistician confirmed these results by the Fisher's Exact test for pair-wise comparisons and the Exact test for trend.

The liver tumors in male rats should have been evaluated by the Peto Prevalence test which takes into account the significant increasing survival with increasing doses. Due to time constraints, this could not be done by HED's statistician and was not done by the company. Because the male 10,000 ppm dose group survived significantly longer than the controls, the statistics presented above are a worst-case scenario. The use of the Peto Prevalence test would only reduce the borderline pair-wise significance of 0.039 found between controls and the high dose, probably resulting in a significant trend, but no significant pair-wise comparisons.

Female rats showed no statistically significant trends or pair-wise comparisons for hepatocellular tumors in either the analyses completed by the company, or those completed by HED's statistician. The HIARC agreed with this evaluation and concluded that there is no evidence of carcinogenicity in rats.

Adequacy of the Dose Levels Tested: The HIARC considered the high-dose in this study (10,000 ppm) to be excessive based on decreases in body weight (↓15-41%, $p<0.01$) and body weight gain (↓28-118%).

2. Carcinogenicity Study in Mice

MRID No.: 44612102

Executive Summary: In a mouse oncogenicity study (MRID 44612102), PT807-HCl (50% w/v) was administered in the diet to male and female Crl:CD-1®(ICR)BR mice at levels of 0, 500, 3500 or 7000 ppm [0, 66.5/86.2, 484/624, or 1010/1250 mg/kg/day (M/F)] for 78

weeks.

No treatment-related effects in mortality rates, clinical signs, body weights, body weight gains, food consumption, differential leukocyte counts, or organ weights were observed in either sex of the treated groups throughout the study when compared to the respective control groups. No treatment-related gross or microscopic pathological findings were observed when treated groups were compared to concurrent controls.

NOAEL = 7000 ppm (1010/1250 mg/kg/day, M/F)
LOAEL = not observed

Discussion of Tumor Data: There was no evidence of compound-related carcinogencity.

Adequacy of the Dose Levels Tested: The highest dose tested exceeded the limit dose for a carcinogenicity study (1000 mg/kg/day).

3. Mutagenicity - The HIARC determined that PT807-HCl has intrinsic clastogenic potential which is not expressed in whole animals. The following table presents the mutagenicity findings for PT807-HCl:

OPPTS No./Study Type	MRID	Results
870.5100 Bacterial Reverse Gene Mutation Test	44354523	Negative for cytotoxicity and genotoxic response at the limit dose (5,000 µg/plate) with and without metabolic activation in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, and *E. coli* WP2 *uvr*A strain.
870.5300 CHO/HGPRT/Mammalian Activation Gene Mutation Assay	44354524	Negative for induction of forward mutation at the HGPRT locus in this *in vitro* assay with or without metabolic activation.
870.5375 *In Vitro* Mammalian Chromosome Aberrations in CHO Cells	44354526	Clastogenic with or without metabolic activation in Chinese hamster ovary cells cultured *in vitro*.
870.5395 *In Vivo* Mammalian Cytogenetics - Micronucleus Assay in Mice	44354525	Testing at toxic concentrations, with mortality at ≥116.5 mg/kg, did not induce significant increases in micronucleated polychromatic erythrocytes (MPCEs).
870.5550 Unscheduled DNA Synthesis in Rat Hepatocytes	44595005	UDS was not induced.

4. Classification of Carcinogenic Potential: In accordance with the proposed guideline for cancer risk assessment (April 10, 1996), the HIARC classified PT807-HCl as a "not likely human carcinogen"based on the lack of evidence of carcinogenicity in mice or rats.

IV. FQPA CONSIDERATIONS

1. Adequacy of the Data Base

The toxicity data base is complete.

2. Neurotoxicity Data

A. Acute Neurotoxicity Study in Rats

MRID No. 44380001

Executive Summary: See Acute Dietary

B. Subchronic Neurotoxicity Study in Rats

MRID Nos. 44595003 and 44703101

Executive Summary: In a 90-day subchronic oral neurotoxicity study (MRIDS 44703101 and 44595003), PT807-HCl (>99% a.i.) was administered for 90 days to Charles River Crl:CD®BR VAF/Plus rats (11/sex/dose) at dietary concentrations of 0, 500, 2500, or 5000 ppm, equivalent to actual mean doses of 32, 164, or 323 mg/kg/day for males and 37, 186, or 386 mg/kg/day for females.

No animals died during the study. No treatment-related clinical signs, gross lesions, neoplastic tissue, or ophthalmoscopic findings were observed. Reduced ($p \leq 0.05$ or 0.01) body weights were observed in the high- and mid-dose females (↓9-15%, each) throughout the study (Weeks 2 through 13) and in the low-dose females (↓10-15%) during weeks 9 through 13. Reduced ($p \leq 0.05$ or 0.01) food consumption was observed only during Weeks 1 and 2 in all treated females (high-dose, ↓8-18%; mid-dose, ↓9%; low-dose, ↓6-8%).

No treatment-related findings indicative of neurotoxicity were noted during the homecage, handling, open field, sensorimotor, and grip-strength observations of the Functional Observation Battery (FOB) in this study. No neuropathological changes were observed in any of the treatment groups.

Decreased ($p \leq 0.01$ or 0.05) horizontal motor activity (↓24-42%) and stereotypy counts (↓38-50%) compared to controls were observed in the high-, mid-, and low-dose females during Week 8. These decreases occurred only at one interval (Week 8), did not increase in severity with time, did not occur in the males, and /or were not dose dependent and are therefore not considered to be treatment related.

Neurotoxicity LOAEL was not observed
Neurotoxicity NOAEL is >5000 ppm (323/386 mg/kg/day; M/F)

3. **Developmental Toxicity Data**

A. Developmental Toxicity Study in Rats

MRID No. 44354521

Executive Summary: In a developmental toxicity study (MRID 44354521), PT807-HCl (99.6% a.i.) was administered by gavage at 0, 50, 250, or 500 mg/kg/day to pregnant rats (25 females/dose) on days 6-15 of gestation. A single nonpregnant high-dose female exhibited seizures on the first day of dosing and again on day two prior to dosing and her subsequent death. A high-dose pregnant dam died on gestation day 8.

Maternal toxicity at the mid-dose was characterized by clinical signs of toxicity observed over the 10 day dose period including rooting in bedding (35 incidences treated vs 0 controls) and lethargy (2 incidences treated vs 0 controls). When compared to concurrent controls, mid-dose body weight gains were significantly reduced (↓46% vs controls, $p<0.05$) on gestation days 6-9. Mid-dose body weight gains increased non-significantly over the remaining study interval.

Observations of clinical signs of toxicity in high-dose dams included: lethargy (45 incidences treated vs 0 controls), salivation (3 incidences treated vs 0 controls), prone positioning (21 incidences treated vs 0 controls), piloerection (24 incidences treated vs 3 controls), and rooting in bedding (64 incidences treated vs 0 controls). Body weight gains were significantly ($p<0.01$) reduced at the high-dose level during gestation days 6-9 (↓98%) and for the overall treatment interval (↓29%, days 6-15); high-dose weight gains rebounded significantly during the post-treatment interval (↑17%, days 15-20, $p<0.05$).

When compared to concurrent controls, high-dose absolute (g/rat/day) and relative (g/kg body weight/day) food consumption were significantly reduced ($p<0.05$ or 0.01) during gestation days 6-9, 9-12, and 12-15 (absolute, ↓13-25%; relative, ↓8-22% vs controls) and for the overall treatment interval (absolute, ↓18%; relative, ↓14%, days 6-15). Food consumption significantly increased ($p<0.05$ or 0.01) at the high-dose level during post-treatment (absolute, ↑12%; relative, ↑8-14% days 18-20).

There were no treatment-related effects in organ weights, gross pathologic findings, or cesarean section parameters at any dose level. Sixteen of the 17 apparently nonpregnant females (including 3 controls) displayed ovarian corpora lutea with no uterine implantation sites, a relatively infrequent finding.

Maternal NOAEL = 50 mg/kg/day
Maternal LOAEL = 250 mg/kg/day, based on clinical signs (post-dosing rooting

in the bedding and lethargy) and reduced body weight gains.

There were no treatment-related effects on developmental parameters noted at any dose level.

Developmental NOAEL = 500 mg/kg/day based on increased incidence of enlarged lateral ventricles within historical limits
Developmental LOAEL = Not observed

B. Developmental Toxicity Study in Rabbits

MRID No. 44354522

Executive Summary: In a developmental toxicity study (MRID 44354522), PT807-HCl (99.6% a.i.) was administered by gavage at 0, 10, 100, or 200 mg/kg/day to pregnant rabbits (16 females/dose) on gestation days (GDs) 7-19. One 100 mg/kg doe and three 200 mg/kg does died during the study; the single mid-dose doe displayed convulsions prior to death on GD 12. No treatment-related effects were noted regarding maternal body weights, body weight gains, liver weights, food consumption, or reproductive parameters. Negative corrected body weight gains were indicative of poor animal husbandry in all animals, treated and control.

There were no treatment-related gross pathologic findings at scheduled necropsy. Treatment-related necropsy findings for unscheduled deaths included: dilated blood vessels in the thoracic and abdominal organs in one mid-dose doe that died on GD 12, and dilated blood vessels in the uterus and intestines of two high-dose does that died on GD 9.

Maternal NOAEL = 10 mg/kg/day
Maternal LOAEL = 100 mg/kg/day, based on increased mortality in the mid- and high-dose animals

There were no treatment-related developmental parameters observed at any dose level.

Developmental NOAEL >200 mg/kg/day
Developmental LOAEL = Not observed

4. **Reproductive Toxicity**

MRID No. 44595004

Executive Summary: In a 2-generation reproduction toxicity study (MRID 44595004), diethyl-2-(4-methylbenzyloxy)ethylamine hydrochloride (PT-807-HCl; 0.5 g a.i./mL) was administered continuously in the diet to Sprague-Dawley rats (32/sex/dose) at dose levels of 0, 250, 2000, or 4000 ppm (equivalent to 14.1/20.8,

114.0/168.0, and 229.3/350.3 in the P animals [M/F] and 19.5/26.8, 168.8/231.6, and 360.5/490.7 mg/kg/day in F_1 animals [M/F], respectively). Exposure to P animals began at 10-11 weeks of age and lasted for 10 weeks prior to mating. F_1 pups selected (25/sex/dose) to produce the F_2 generation were exposed to the same dosage as their parents beginning at postnatal day (PND) 21. F_1 animals were administered the test article for approximately 14 weeks prior to mating to produce the F_2 litters. Mating to produce a second F_{2b} generation was not performed. F_2 animals (20/sex/dose) were given the same diet as their dams, and necropsied 1 to 2 weeks after weaning. Exposure of all animals to the test material was continuous throughout the study.

There were no treatment-related clinical signs observed in the P or F_1 adults. There were no changes of toxicological concern in reproductive performance.

In the 2000 ppm group, body weights were decreased ($p<0.01$ or 0.001) compared to concurrent controls throughout the study in the F_1 males and females (↓9-15%). Body weight gains were decreased over the course of the study in P females and in F_1 males and females (↓6-89%, $p<0.05$, 0.01, or 0.001).

In the 4000 ppm group, body weights were decreased ($p<0.001$) in the F_1 males and females throughout the study (↓15-24%) and in P females during gestation and lactation (↓7-13%). Body weight gains were decreased ($p<0.05$, 0.01, or 0.001) in P males and females (↓21-100%) and in F_1 males and females (↓9-65%). Decreases ($p<0.001$) in food consumption were observed in P and F_1 females during gestation and lactation (↓9-27%).

Systemic NOAEL = 14.1 mg/kg/day
Systemic LOAEL = 114 mg/kg/day based upon decreased body weight and body weight gains.

No treatment-related effects on mortality or clinical signs were observed at any time in the F_1 and F_2 litters. There were no differences of toxicological concern in anogenital distance or organ weights in the F_1 or F_2 litters. There were no differences in static righting reflex, startle response, and pupillary light reflex in the F_1 and F_2 pups. There were no treatment-related findings at necropsy in the F_1 or F_2 pups.

In the 2000 ppm groups, sexual development was delayed in F_1 females (delay in vaginal perforation - ↑9%, $p<0.001$). In the P females, decreases ($p<0.05$ or 0.01) in absolute and relative ovary weights (↓10%) occurred, along with an increased number of animals showing no estrous cycle activity, diffuse uterine atrophy, diffuse vaginal atrophy, vaginal mucification, and ovarian interstitial gland atrophy (9-19/32 treated vs 3-5/31 controls). The number of corpora lutea were reduced 48% ($p<0.05$). Body weights and body weight gains were decreased ($p<0.05$, 0.01, or 0.001) during lactation in F_1 and F_2 pups (↓8-19%). There was a delay ($p<0.05$ or 0.01) in developmental parameters in F_1 and F_2 pups (pinna detachment: ↓30-31%; eyes open: ↓26-50%). These delays are in part attributable to the decreased body weights of the treated animals.

In the 4000 ppm groups, sexual maturation was delayed ($p<0.001$) in F_1 males (delay of preputial separation - ↑7%) and females (delay of vaginal perforation - ↑21%). In P dams, decreases occurred in the absolute weights ($p<0.001$) of the uterus (↓37%) and ovaries (↓30%); decreased ($p<0.001$) relative (to body) weights of the uterus (↓28%) and ovaries (↓21%) were also observed. In the F_1 females, decreases in absolute ovarian weights occurred (↓15%, $p<0.01$). In the P dams, an increased number of animals showed no estrous cycle activity, diffuse uterine atrophy, diffuse vaginal atrophy, vaginal mucification, and ovarian interstitial gland atrophy (21-27/32 treated vs 3-5/31 controls). Enumeration of the ovarian follicles and corpora lutea revealed a decrease ($p<0.05$, 0.01, or 0.005) in the number of medium (↓26%) and large follicles (↓29%), and corpora lutea (↓60%). Changes in F_1 dams were limited to a decrease in the number of large ovarian follicles (↓25%, $p<0.01$). Body weights and body weight gains were decreased ($p<0.001$) in all F_1 and F_2 pups throughout lactation (↓10-30%). There was a delay ($p<0.01$ or 0.001) in development in F_1 and F_2 pups (pinna detachment - ↓43-44%; eyes open - ↓63-88%). These delays are in part attributable to the decreased body weights of the treated animals.

No observations of toxicological significance were made at the low-dose (250 ppm).

Reproductive NOAEL = 14.1 mg/kg/day for both sexes (nontoxic)
Reproductive LOAEL = 114 mg/kg/day for both sexes based on decreased pup body weight and body weight gains, delayed sexual development, reductions in absolute and relative uterus and ovary weights, and histological changes in the uterus, vagina, and ovaries in the females.

5. **Determination of Susceptibility**

The HIARC determined that there is no evidence of increased susceptibility in rat or rabbit fetuses following *in utero* exposure or following pre/post-natal exposure to PT807-HCl.

6. **Recommendation for a Developmental Neurotoxicity Study**

The HIARC recommended that a developmental neurotoxicity study in rats be **required** based on evidence of neurotoxicity seen following gavage administration in the acute and subchronic neurotoxicity, developmental toxicity (rat), and two-generation reproduction toxicity studies.

7. **Recommendation for the FQPA Safety Factor Committee**

Based only on the hazard assessment (i.e., no consideration of exposure), the HIARC recommended that the FQPA safety factor be removed because the toxicology data base is complete, and there is no evidence of increased susceptibility in the prenatal and pre/postnatal studies.

The requirement of a prenatal developmental neurotoxicity study (DNT) does not warrant

an FQPA safety factor in this case because this requirement is based on the fact that this chemical is a neurotoxicant only in adult animals following oral (gavage) administration, and is not based on the criteria generally used for requiring a DNT study and an FQPA safety factor (e.g., neuropathy in adult animals; CNS malformations following prenatal exposure; brain weight or sexual maturation changes in offspring; and/or functional changes in offspring).

V. HAZARD CHARACTERIZATION

The data base adequately characterizes PT807-HCl as having low acute oral, dermal, and inhalation toxicity. It is Toxicity Category IV for acute dermal toxicity, acute inhalation toxicity, and primary dermal irritation; Toxicity Category III for acute oral and primary eye irritation; and it is not a dermal sensitizer.

There is no evidence of cumulative toxicity. The oral LD_{50} in rats (531 mg/kg) is not markedly greater than the oral subchronic rat LOAEL (300 mg/kg/day). Similarly, a comparison of subchronic and chronic LOAELs reveals no evidence of cumulation in the rat (300 mg/kg/day v 213/308, M/F) and dog (211/233 mg/kg/day v >135.7/141.5 mg/kg/day, HDT). This is because rats rapidly excrete PT807-HCl, primarily in the urine and secondarily in the feces, with very little remaining in the tissues after 7 days (≤0.34%). There may also be some adaptation due to enzyme induction.

Neurotoxicity was observed in several studies. Hyperactivity, hyperreflexivity, lack of coordination, tremors, convulsions, and ptyalism were observed at 300 mg/kg/day in the subchronic gavage study in rats. Rooting in the bedding and lethargy were observed at 250 mg/kg/day in the developmental toxicity study in rats. In the acute neurotoxicity study, the HIARC designated the LOAEL to be 200 mg/kg based on slight ataxia in 1 of 11 males. At a dose of 400 mg/kg, there was an increase in clinical signs in the functional observation battery, and decreases in motor activity. No toxicity was observed in the subchronic neurotoxicity study in rats at doses of 323 mg/kg/day in males and 386 mg/kg/day in females.

In the developmental toxicity study in rats, there was an increased incidence of enlarged lateral ventricles in pups at 500 mg/kg/day. The incidences were within historical limits, however, and occurred at a dose far in excess of the maternal NOAEL of 50 mg/kg/day. No developmental effects were seen in rabbit pups at 200 mg/kg/day, whereas the maternal NOAEL was 10 mg/kg/day. In the rat reproductive toxicity study, the systemic and reproductive LOAELs were both 114 mg/kg/day at which dose the parents exhibited decreased body weight and body weight gains, and the pups had decreased body weight and body weight gains, delayed sexual development, reductions in absolute and relative uterus and ovary weights, and histological changes in the uterus, vagina, and ovaries in the females.

No toxicity or tumors were observed in the chronic dog study or the mouse carcinogenicity study. The high-dose in the mouse study exceeded the limit dose (1000 mg/kg/day). In the chronic toxicity/carcinogenicity study in rats, survival was markedly increased in the high-dose (213/308 mg/kg/day, M/F) compared to the controls. The HIARC considers this dose to be excessive based on decreases in body weight and body weight gain. No other toxicity was seen. Although there was an increased incidence of hepatocellular adenomas and carcinomas in the high-dose males, the

HIARC attributes this to increased survival; that is, these rats lived long enough to develop more tumors. PT807-HCl was clastogenic with or without metabolic activation in Chinese hamster ovary cells cultured *in vitro*, but all other mutagenicity studies were negative. Thus, there is no evidence of clastogenic potential in whole animals. Based on these findings, the HIARC classified PT807-HCl as a "not likely human carcinogen."

VI. DATA GAPS

There are no data gaps. The HIARC has, however, requested a developmental neurotoxicity study.

VII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

EXPOSURE SCENARIO	DOSE (mg/kg/day)	UF	ENDPOINT	STUDY
Acute Dietary	NOAEL = 50 mg/kg/day	100	Acute RfD = 0.5 mg/kg/day	Acute Neurotoxicity in Rats
Chronic Dietary	NOAEL = 14 mg/kg/day	100	Chronic RfD = 0.14 mg/kg/day	Reproductive Toxicity in Rats
Dermal (all time intervals)	This risk assessment is not required because no systemic toxicity was seen at the limit dose in a 21-day dermal toxicity study.			
Inhalation (all time intervals)	Oral NOAEL = 30 mg/kg/day*	MOE = 100	Based on neurotoxic signs.	90-Day Toxicity in Rats

*Since an oral NOAEL was selected, and oral/inhalation absorption ratio of 1 is used in risk assessments.

Attachment 2

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

013792

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

October 15, 1999

MEMORANDUM

SUBJECT: ***PT807 HCl (Ecolyst®)*** - Report of the FQPA Safety Factor Committee

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Richard Loranger, Branch Senior Scientist
Registration Action Branch 2
Health Effects Division (7509C)

PC Code: 069089

The FQPA Safety Factor Committee met on October 4, 1999 to evaluate the hazard and exposure data for PT807 HCl (*Ecolyst®*) and recommended that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) be removed (1x) in assessing the risk posed by this chemical.

I. HAZARD ASSESSMENT

(*Correspondence:* J. Whalen to B. Tarplee dated September 24, 1999)

A. Adequacy of the Toxicology Database

The toxicology database for PT807 HCl is adequate, however, the HIARC concluded that a developmental neurotoxicity study is required based on the fact that this chemical is a neurotoxicant in adult animals following oral (gavage) administration.

B. Determination of Susceptibility

The toxicity data provided no indication of increased susceptibility for rats or rabbits to *in utero* and/or postnatal exposure to PT807 HCl. In the prenatal developmental toxicity studies in rats and rabbits and the 2-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity. Additionally, these effects were not considered to be qualitatively more serious than the effects observed in the parents.

II. EXPOSURE ASSESSMENTS

A. Dietary (Food) Exposure Considerations

(*Memorandum:* Y. Donovan to B. Tarplee dated September 28, 1999)

PT807 HCl is a new chemical for which tolerances are proposed on oranges. Tolerances will be established in terms of parent compound only. Tolerances for meat, milk, poultry, and eggs are not required for the proposed use on oranges.

PT807-HCl is most likely systemic. No monitoring data or percent crop treated (%CT) information are available for this new chemical. However, crop field trial data for oranges are available and indicate that residues were less than the limit of quantification (LOQ; 0.01 ppm) in all samples.

The HED Dietary Exposure Evaluation Model (DEEM) will be used to assess the risk from acute and chronic dietary exposure to residues of PT807 HCl in food. At the time of this meeting, these analyses were not complete. Since there are no monitoring data or percent crop treated (%CT) information, it is expected that these analyses will be unrefined (Tier 1) resulting in an overestimate of the dietary (food) exposure resulting from the use of PT807 HCl.

B. Dietary (Drinking Water) Exposure Considerations

(*Correspondence:* L. Libelo to B. Tarplee and Y. Donovan dated September 30, 1999)

The environmental fate database for PT807 HCl is incomplete. EFED reports that only two acceptable studies related to persistence and one acceptable study of mobility have been submitted and concludes that with such limited data, the characterization of drinking water exposure is qualitative, at best.

Based on the existing environmental fate data available, this compound appears to be very soluble in water and stable in the environment and therefore, it is likely that this chemical will move to surface and groundwater. Additionally, based on the existing data, concentrations in surface water are expected to accumulate in the environment with time and the continued use of the compound.

No monitoring data are available for this new chemical. Estimated Environmental Concentrations (EEC) values for the drinking water risk assessment for PT807 HCl were calculated using the PRZM/Exams model simulation of an application to citrus trees in Oceola County, Florida. There is concern for uncertainty associated with the values obtained since model inputs are based on limited data.

The FQPA Safety Factor Committee concluded that worst-case parameters and/or assumptions must be used to ensure that the drinking water exposure resulting from the use of PT807 HCl is not underestimated.

C. Non-Occupational (Residential) Exposure Considerations

(*Correspondence:* M. Collantes to Y. Donovan and B. Tarplee dated September 27, 1999)

Non-occupational exposure resulting from the use of PT807 HCl is not expected.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

A. Recommendation of the Factor

The Committee recommended that the FQPA safety factor for protection of infants and children (as required by FQPA) be **removed (1x).**

B. Rationale for Removing the FQPA Safety Factor

The Committee concluded that the safety factor could be removed because:

1. The toxicology database is complete for the assessment of the effects following *in utero* and/or postnatal exposure to PT807 HCl;

2. The toxicity data provided no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure;

3. the requirement of a developmental neurotoxicity study is not based on the criteria reflecting some special concern which are generally used for requiring a DNT study and an FQPA safety factor (e.g.: neuropathy in adult animals; CNS malformations following prenatal exposure; brain

weight or sexual maturation changes in offspring; and/or functional changes in offspring)[1] and therefore does not warrant an FQPA safety factor; and

4. The exposure assessments will not underestimate the potential dietary (food and water) exposures for infants and children from the use of PT807 HCl (currently no residential exposure is expected).

[1]This is an interim step towards accordance with the proposed 'OPP POLICY ON DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTOR(S) FOR USE IN THE TOLERANCE-SETTING PROCESS' which was presented to the FIFRA SAP meeting in May, 1999 and placed in the Docket for Public Comment (64FR37001; 7/8/99; Docket No. 37001).

FQPA SAFETY FACTOR COMMITTEE MEETING

40CT1999

PT807-HCl (Ecolyst™)

Name	Division/Branch
[signature]	Hed. SAB
[illegible]	HED/RRBY
Jon Flenchaus	OGC
[signature]	HED/RRBY
John Whalan	HED RAB2
Laurence Libelo	EFED/ERB IV
Yan Donovan	HED / RAB2
Debbie McCall	RD
Rick Keigwin	RD
[signature]	HED
[signature] Tarplee	HED / SAB
[signature]	EFED

Note: E. Zager not present (attending another meeting) - B. Turman presiding.

Attachment 3

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 10/27/99

Subject: Dietary Exposure Analysis for PT807-HCl.

DP Barcode: D259992
Chemical#: 069089

To: Yan Donovan, Chemist
Registration Action Branch 2
Health Effects Division (7509C)

From: William Cutchin, Chemist
Registration Action Branch 2
Health Effects Division (7509C)

THRU: Jennifer Rowell
Richard Griffin
Dietary Exposure SAC Reviewers

Richard Loranger, Branch Senior Scientist
Registration Action Branch 2
Health Effects Division (7509C)

Action Requested

Perform a dietary exposure assessment for PT807-HCl at 0.01 ppm in/on oranges as a result of a Section 3 request (PP#8F4998).

Executive Summary

The risk from acute and chronic dietary exposure to PT807-HCl, as represented by the %aPAD and%cPAD, respectively, is below HED's level of concern for the general U.S. population and all population subgroups.

Toxicological Endpoints

Summary Toxicological Endpoints Selected by HIARC (9/16/99).			
Parameter		Dose mg/kg/day	Remarks/Endpoint
Dietary	Acute	0.5 (aRfD[a], aPAD[b])	Rat acute neurotoxicity NOAEL of 50 mg/kg/day. With an UF of 100, the RfD is 0.5 mg/kg/day.
	Chronic	0.14 (RfD[a], cPAD[b])	Rat systemic NOAEL of 14.1 mg/kg/day from the rat reproductive toxicity study. With an UF of 100, the RfD is 0.14 mg/kg/day
Cancer		None	Classified - 'not likely'
FQPA Safety Factor		Remove 10X	Remove for acute and chronic (FQPA, 10/4/99)

[a] RfD=NOAEL/UF

[b] PAD(acute or chronic)=RfD(acute or chronic)/FQPA Safety Factor

Residue Information

No tolerances for PT807-HCl are published in the 40 CFR. For the acute and chronic analyses, tolerance level residues and 100% crop treated (%CT) were used. Based on the residue data for processed orange commodities (see Y. Donovan memo, pp#8F4998, DP Barcode: D250965), the adjustment factor for orange juice was set at 1.00. The DEEM default ratio of 3.72 was retained for residues potentially increasing from juice into concentrate. A summary of the residue information considered in the analyses is listed in Attachment 1.

Results

Acute Exposure Analysis

The Dietary Exposure Evaluation Model (DEEM™) acute dietary risk analysis estimates the distribution of single-day exposures for the overall U.S. population and certain subgroups. The analysis evaluates individual food consumption as reported by respondents in the USDA 1989-92 Continuing Survey of Food Intake by Individuals (CSFII) and accumulates exposure to the chemical for each commodity. Each analysis assumes uniform distribution of PT807-HCl in the commodity supply.

The resulting analysis is presented below as a percent of the acute PAD (%aPAD) at the 95th exposure percentile. The acute dietary risk estimate should be viewed as conservative. The acute exposure for the proposed PT807-HCl commodities are based on tolerance level residues and 100% CT (Attachment 2). Therefore, any additional refinements could reduce risk estimates significantly. In making a safety determination for these requested tolerances, HED is taking into account this conservative exposure assessment. HED is generally concerned with acute exposures that exceed 100% of the aPAD.

Acute exposure at 95th percentile:

Subgroup	Exposure (mg/kg/day)	%aPAD
U.S. Population	0.000068	<1
Non-nursing infants (<1 yr)	0.000134	<1
Children (1-6 years)	0.000175	<1
Females (13+/nursing)	0.000083	<1
Males (13-19 years)	0.000062	<1

Chronic Exposure Analysis

The DEEM analysis evaluates individual food consumption as reported by respondents in the USDA 1989-91 Continuing Survey of Food Intake by Individuals (CSFII) and accumulates exposure to the chemical for each commodity.

A DEEM chronic exposure analysis was performed using tolerance level residues and 100% CT to estimate the Theoretical Maximum Residue Concentration (TMRC) for the general population and subgroups of interest. Summaries of the TMRCs and their representations as percentages of cPAD are included as Attachment 3. HED's level of concern is for chronic exposure which exceed100% of the cPAD.

Subgroup	TMRC (mg/kg/day)	%cPAD
U.S. Population	0.000012	<1
Non-nursing infants	0.000013	<1
Children 1-6 yrs	0.000034	<1
Females 13+ (nursing)	0.000015	<1
Males 13-19 yrs	0.000012	<1

Conclusions

The acute and chronic analyses for PT807-HCl are conservative (Tier 1) estimates of dietary exposure using tolerance level residues and 100% CT. Even without additional refinements, the risks from acute and chronic dietary exposure to PT807-HCl, as represented by the %aPAD and %cPAD respectively, are below HED's level of concern for all the general U.S. population and the population subgroups.

Attachments: 1, 2, 3

cc: W. Cutchin, RAB2 Reading File, PP#8F4998, L. Richardson
RDI:BSS(R. Loranger):10/27/99

Attachment 1

Filename: D:\working\pt807\069089.R96
Chemical name: PT807-HCL
RfD(Chronic): .14 mg/kg bw/day NOEL(Chronic): 0 mg/kg bw/day
RfD(Acute): .5 mg/kg bw/day NOEL(Acute): 0 mg/kg bw/day
Date created/last modified: /8 Program ver. 6.77
Comment: FQPA 1x

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	RDF #	Adj.Factors #1	#2	Comment
36	10	Oranges-juice	0.010000	0	1.000	1.000	
33	10	Oranges-juice-concentrate	0.010000	0	3.720	1.000	
35	10	Oranges-peel	0.010000	0	1.000	1.000	
34	10	Oranges-peeled fruit	0.010000	0	1.000	1.000	

Attachment 2

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for PT807-HCL (1989-92 data)
Residue file: 069089.r96 Adjustment factor #2 NOT used.
Analysis Date: 10-07-1999/14:22:37 Residue file dated: 10-07-1999/14:09:09/8
Acute Reference Dose (aRfD) = 0.500000 mg/kg body-wt/day
Run Comment: FQPA 1x

Summary calculations:

	5th Percentile		1st Percentile		0.1st Percentile	
	Exposure	% aRfD	Exposure	% aRfD	Exposure	% aRfD
U.S. pop - all seasons:	0.000068	0.01	0.000153	0.03	0.000334	0.07
All infants (<1 year):	0.000095	0.02	0.000209	0.04	0.000843	0.17
Nursing infants (<1 year):	0.000000	0.00	0.000066	0.01	0.001518	0.30
Non-nursing infants (<1 yr):	0.000134	0.03	0.000217	0.04	0.000340	0.07
Children (1-6 years):	0.000175	0.04	0.000310	0.06	0.000517	0.10
Children (7-12 years):	0.000097	0.02	0.000204	0.04	0.000361	0.07
Females (13+/preg/not nsg):	0.000061	0.01	0.000094	0.02	0.000135	0.03
Females (13+/nursing):	0.000083	0.02	0.000111	0.02	0.000171	0.03
Females (13-19 yrs/np/nn):	0.000061	0.01	0.000108	0.02	0.000222	0.04
Females (20+ years/np/nn):	0.000047	0.01	0.000089	0.02	0.000154	0.03
Females (13-50 years):	0.000053	0.01	0.000102	0.02	0.000173	0.03
Males (13-19 years):	0.000062	0.01	0.000107	0.02	0.000169	0.03
Males (20+ years):	0.000041	0.01	0.000075	0.02	0.000153	0.03

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for PT807-HCL (1989-92 data)
Residue file: 069089.r96 Adjustment factor #2 NOT used.
Analysis Date: 10-07-1999/14:22:36 Residue file dated: 10-07-1999/14:09:09/8
Acute Reference Dose (aRfD) = 0.500000 mg/kg body-wt/day
Run Comment: FQPA 1x

U.S. pop - all seasons

	Daily Exposure Analysis 1/ (mg/kg body-weight/day) per Capita	per User
Mean	0.000012	0.000045
Standard Deviation	0.000033	0.000050
Standard Error	0.000000	0.000001
Percent of aRfD	0.00	0.01

Percent of Person-Days that are User-Days = 27.28%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000005	0.00	10.00	0.000094	0.02
80.00	0.000016	0.00	5.00	0.000132	0.03
70.00	0.000021	0.00	2.50	0.000172	0.03
60.00	0.000027	0.01	1.00	0.000235	0.05
50.00	0.000033	0.01	0.50	0.000301	0.06
40.00	0.000039	0.01	0.25	0.000363	0.07
30.00	0.000047	0.01	0.10	0.000435	0.09
20.00	0.000062	0.01			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000000	0.00	10.00	0.000042	0.01
80.00	0.000000	0.00	5.00	0.000068	0.01
70.00	0.000000	0.00	2.50	0.000101	0.02
60.00	0.000000	0.00	1.00	0.000153	0.03
50.00	0.000000	0.00	0.50	0.000200	0.04
40.00	0.000000	0.00	0.25	0.000246	0.05
30.00	0.000000	0.00	0.10	0.000334	0.07
20.00	0.000019	0.00			

1/ Analysis based on all three-day participant records in CSFII 1989-92 survey.

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for PT807-HCL (1989-92 data)
Residue file: 069089.r96 Adjustment factor #2 NOT used.
Analysis Date: 10-07-1999/14:22:36 Residue file dated: 10-07-1999/14:09:09/8
Acute Reference Dose (aRfD) = 0.500000 mg/kg body-wt/day

All infants (<1 year)

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000012	0.000137
Standard Deviation	0.000080	0.000231
Standard Error	0.000003	0.000029
Percent of aRfD	0.00	0.03

Percent of Person-Days that are User-Days = 9.02%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000009	0.00	10.00	0.000214	0.04
80.00	0.000020	0.00	5.00	0.000281	0.06
70.00	0.000030	0.01	2.50	0.000370	0.07
60.00	0.000082	0.02	1.00	0.000881	0.18
50.00	0.000109	0.02	0.50	0.001392	0.28
40.00	0.000138	0.03	0.25	0.001647	0.33
30.00	0.000156	0.03	0.10	0.001801	0.36
20.00	0.000169	0.03			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000000	0.00	10.00	0.000000	0.00
80.00	0.000000	0.00	5.00	0.000095	0.02
70.00	0.000000	0.00	2.50	0.000159	0.03
60.00	0.000000	0.00	1.00	0.000209	0.04
50.00	0.000000	0.00	0.50	0.000274	0.05
40.00	0.000000	0.00	0.25	0.000360	0.07
30.00	0.000000	0.00	0.10	0.000843	0.17
20.00	0.000000	0.00			

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for PT807-HCL (1989-92 data)
Residue file: 069089.r96 Adjustment factor #2 NOT used.
Analysis Date: 10-07-1999/14:22:36 Residue file dated: 10-07-1999/14:09:09/8
Acute Reference Dose (aRfD) = 0.500000 mg/kg body-wt/day

Nursing infants (<1 year)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000010	0.000624
Standard Deviation	0.000128	0.000808
Standard Error	0.000010	0.000305
Percent of aRfD	0.00	0.12

Percent of Person-Days that are User-Days = 1.59%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000008	0.00	10.00	0.001291	0.26
80.00	0.000016	0.00	5.00	0.001597	0.32
70.00	0.000041	0.01	2.50	0.001750	0.35
60.00	0.000076	0.02	1.00	0.001842	0.37
50.00	0.000111	0.02	0.50	0.001872	0.37
40.00	0.000147	0.03	0.25	0.001887	0.38
30.00	0.000182	0.04	0.10	0.001897	0.38
20.00	0.000679	0.14			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000000	0.00	10.00	0.000000	0.00
80.00	0.000000	0.00	5.00	0.000000	0.00
70.00	0.000000	0.00	2.50	0.000000	0.00
60.00	0.000000	0.00	1.00	0.000066	0.01
50.00	0.000000	0.00	0.50	0.000177	0.04
40.00	0.000000	0.00	0.25	0.000941	0.19
30.00	0.000000	0.00	0.10	0.001518	0.30
20.00	0.000000	0.00			

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for PT807-HCL (1989-92 data)
Residue file: 069089.r96 Adjustment factor #2 NOT used.
Analysis Date: 10-07-1999/14:22:37 Residue file dated: 10-07-1999/14:09:09/8
Acute Reference Dose (aRfD) = 0.500000 mg/kg body-wt/day

Non-nursing infants (<1 yr)

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000013	0.000110
Standard Deviation	0.000047	0.000085
Standard Error	0.000002	0.000012
Percent of aRfD	0.00	0.02

Percent of Person-Days that are User-Days = 12.14%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000008	0.00	10.00	0.000204	0.04
80.00	0.000019	0.00	5.00	0.000239	0.05
70.00	0.000030	0.01	2.50	0.000293	0.06
60.00	0.000084	0.02	1.00	0.000335	0.07
50.00	0.000114	0.02	0.50	0.000349	0.07
40.00	0.000137	0.03	0.25	0.000356	0.07
30.00	0.000148	0.03	0.10	0.000360	0.07
20.00	0.000158	0.03			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000000	0.00	10.00	0.000016	0.00
80.00	0.000000	0.00	5.00	0.000134	0.03
70.00	0.000000	0.00	2.50	0.000157	0.03
60.00	0.000000	0.00	1.00	0.000217	0.04
50.00	0.000000	0.00	0.50	0.000258	0.05
40.00	0.000000	0.00	0.25	0.000306	0.06
30.00	0.000000	0.00	0.10	0.000340	0.07
20.00	0.000000	0.00			

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for PT807-HCL (1989-92 data)
Residue file: 069089.r96 Adjustment factor #2 NOT used.
Analysis Date: 10-07-1999/14:22:37 Residue file dated: 10-07-1999/14:09:09/8
Acute Reference Dose (aRfD) = 0.500000 mg/kg body-wt/day

Children (1-6 years)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000034	0.000102
Standard Deviation	0.000068	0.000083
Standard Error	0.000001	0.000002
Percent of aRfD	0.01	0.02

Percent of Person-Days that are User-Days = 33.82%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000009	0.00	10.00	0.000199	0.04
80.00	0.000023	0.00	5.00	0.000256	0.05
70.00	0.000058	0.01	2.50	0.000322	0.06
60.00	0.000077	0.02	1.00	0.000400	0.08
50.00	0.000092	0.02	0.50	0.000475	0.10
40.00	0.000107	0.02	0.25	0.000527	0.11
30.00	0.000128	0.03	0.10	0.000550	0.11
20.00	0.000150	0.03			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000000	0.00	10.00	0.000129	0.03
80.00	0.000000	0.00	5.00	0.000175	0.04
70.00	0.000000	0.00	2.50	0.000228	0.05
60.00	0.000000	0.00	1.00	0.000310	0.06
50.00	0.000000	0.00	0.50	0.000375	0.08
40.00	0.000000	0.00	0.25	0.000439	0.09
30.00	0.000011	0.00	0.10	0.000517	0.10
20.00	0.000078	0.02			

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for PT807-HCL (1989-92 data)
Residue file: 069089.r96 Adjustment factor #2 NOT used.
Analysis Date: 10-07-1999/14:22:37 Residue file dated: 10-07-1999/14:09:09/8
Acute Reference Dose (aRfD) = 0.500000 mg/kg body-wt/day

Children (7-12 years)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000020	0.000058
Standard Deviation	0.000041	0.000053
Standard Error	0.000001	0.000002
Percent of aRfD	0.00	0.01

Percent of Person-Days that are User-Days = 33.56%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000005	0.00	10.00	0.000109	0.02
80.00	0.000011	0.00	5.00	0.000160	0.03
70.00	0.000029	0.01	2.50	0.000215	0.04
60.00	0.000042	0.01	1.00	0.000273	0.05
50.00	0.000051	0.01	0.50	0.000306	0.06
40.00	0.000061	0.01	0.25	0.000374	0.07
30.00	0.000071	0.01	0.10	0.000406	0.08
20.00	0.000084	0.02			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000000	0.00	10.00	0.000072	0.01
80.00	0.000000	0.00	5.00	0.000097	0.02
70.00	0.000000	0.00	2.50	0.000135	0.03
60.00	0.000000	0.00	1.00	0.000204	0.04
50.00	0.000000	0.00	0.50	0.000254	0.05
40.00	0.000000	0.00	0.25	0.000290	0.06
30.00	0.000005	0.00	0.10	0.000361	0.07
20.00	0.000043	0.01			

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for PT807-HCL (1989-92 data)
Residue file: 069089.r96 Adjustment factor #2 NOT used.
Analysis Date: 10-07-1999/14:22:37 Residue file dated: 10-07-1999/14:09:09/8
Acute Reference Dose (aRfD) = 0.500000 mg/kg body-wt/day

Females (13+/preg/not nsg)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000012	0.000034
Standard Deviation	0.000022	0.000025
Standard Error	0.000001	0.000002
Percent of aRfD	0.00	0.01

Percent of Person-Days that are User-Days = 35.46%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000003	0.00	10.00	0.000070	0.01
80.00	0.000007	0.00	5.00	0.000085	0.02
70.00	0.000022	0.00	2.50	0.000095	0.02
60.00	0.000029	0.01	1.00	0.000119	0.02
50.00	0.000035	0.01	0.50	0.000131	0.03
40.00	0.000039	0.01	0.25	0.000136	0.03
30.00	0.000042	0.01	0.10	0.000158	0.03
20.00	0.000048	0.01			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000000	0.00	10.00	0.000043	0.01
80.00	0.000000	0.00	5.00	0.000061	0.01
70.00	0.000000	0.00	2.50	0.000079	0.02
60.00	0.000000	0.00	1.00	0.000094	0.02
50.00	0.000000	0.00	0.50	0.000113	0.02
40.00	0.000000	0.00	0.25	0.000126	0.03
30.00	0.000005	0.00	0.10	0.000135	0.03
20.00	0.000031	0.01			

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for PT807-HCL (1989-92 data)
Residue file: 069089.r96 Adjustment factor #2 NOT used.
Analysis Date: 10-07-1999/14:22:37 Residue file dated: 10-07-1999/14:09:09/8
Acute Reference Dose (aRfD) = 0.500000 mg/kg body-wt/day

Females (13+/nursing)

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000015	0.000048
Standard Deviation	0.000028	0.000031
Standard Error	0.000002	0.000004
Percent of aRfD	0.00	0.01

Percent of Person-Days that are User-Days = 32.11%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000023	0.00	10.00	0.000095	0.02
80.00	0.000027	0.01	5.00	0.000104	0.02
70.00	0.000031	0.01	2.50	0.000113	0.02
60.00	0.000034	0.01	1.00	0.000139	0.03
50.00	0.000040	0.01	0.50	0.000162	0.03
40.00	0.000045	0.01	0.25	0.000174	0.03
30.00	0.000056	0.01	0.10	0.000181	0.04
20.00	0.000073	0.01			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000000	0.00	10.00	0.000055	0.01
80.00	0.000000	0.00	5.00	0.000083	0.02
70.00	0.000000	0.00	2.50	0.000099	0.02
60.00	0.000000	0.00	1.00	0.000111	0.02
50.00	0.000000	0.00	0.50	0.000129	0.03
40.00	0.000000	0.00	0.25	0.000149	0.03
30.00	0.000015	0.00	0.10	0.000171	0.03
20.00	0.000033	0.01			

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for PT807-HCL (1989-92 data)
Residue file: 069089.r96 Adjustment factor #2 NOT used.
Analysis Date: 10-07-1999/14:22:37 Residue file dated: 10-07-1999/14:09:09/8
Acute Reference Dose (aRfD) = 0.500000 mg/kg body-wt/day

Females (13-19 yrs/np/nn)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000011	0.000042
Standard Deviation	0.000025	0.000033
Standard Error	0.000001	0.000002
Percent of aRfD	0.00	0.01

Percent of Person-Days that are User-Days = 27.04%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000004	0.00	10.00	0.000082	0.02
80.00	0.000017	0.00	5.00	0.000099	0.02
70.00	0.000024	0.00	2.50	0.000117	0.02
60.00	0.000034	0.01	1.00	0.000154	0.03
50.00	0.000040	0.01	0.50	0.000179	0.04
40.00	0.000045	0.01	0.25	0.000261	0.05
30.00	0.000050	0.01	0.10	0.000271	0.05
20.00	0.000058	0.01			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000000	0.00	10.00	0.000047	0.01
80.00	0.000000	0.00	5.00	0.000061	0.01
70.00	0.000000	0.00	2.50	0.000084	0.02
60.00	0.000000	0.00	1.00	0.000108	0.02
50.00	0.000000	0.00	0.50	0.000133	0.03
40.00	0.000000	0.00	0.25	0.000158	0.03
30.00	0.000000	0.00	0.10	0.000222	0.04
20.00	0.000021	0.00			

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for PT807-HCL (1989-92 data)
Residue file: 069089.r96 Adjustment factor #2 NOT used.
Analysis Date: 10-07-1999/14:22:37 Residue file dated: 10-07-1999/14:09:09/8
Acute Reference Dose (aRfD) = 0.500000 mg/kg body-wt/day

Females (20+ years/np/nn)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000009	0.000033
Standard Deviation	0.000020	0.000025
Standard Error	0.000000	0.000000
Percent of aRfD	0.00	0.01

Percent of Person-Days that are User-Days = 26.47%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000006	0.00	10.00	0.000058	0.01
80.00	0.000016	0.00	5.00	0.000079	0.02
70.00	0.000021	0.00	2.50	0.000100	0.02
60.00	0.000024	0.00	1.00	0.000133	0.03
50.00	0.000029	0.01	0.50	0.000147	0.03
40.00	0.000034	0.01	0.25	0.000161	0.03
30.00	0.000040	0.01	0.10	0.000201	0.04
20.00	0.000046	0.01			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000000	0.00	10.00	0.000035	0.01
80.00	0.000000	0.00	5.00	0.000047	0.01
70.00	0.000000	0.00	2.50	0.000060	0.01
60.00	0.000000	0.00	1.00	0.000089	0.02
50.00	0.000000	0.00	0.50	0.000114	0.02
40.00	0.000000	0.00	0.25	0.000135	0.03
30.00	0.000000	0.00	0.10	0.000154	0.03
20.00	0.000018	0.00			

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for PT807-HCL (1989-92 data)
Residue file: 069089.r96 Adjustment factor #2 NOT used.
Analysis Date: 10-07-1999/14:22:37 Residue file dated: 10-07-1999/14:09:09/8
Acute Reference Dose (aRfD) = 0.500000 mg/kg body-wt/day

Females (13-50 years)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000009	0.000038
Standard Deviation	0.000022	0.000030
Standard Error	0.000000	0.000001
Percent of aRfD	0.00	0.01

Percent of Person-Days that are User-Days = 24.31%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000005	0.00	10.00	0.000075	0.01
80.00	0.000017	0.00	5.00	0.000096	0.02
70.00	0.000022	0.00	2.50	0.000114	0.02
60.00	0.000028	0.01	1.00	0.000145	0.03
50.00	0.000034	0.01	0.50	0.000161	0.03
40.00	0.000040	0.01	0.25	0.000196	0.04
30.00	0.000046	0.01	0.10	0.000284	0.06
20.00	0.000053	0.01			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000000	0.00	10.00	0.000039	0.01
80.00	0.000000	0.00	5.00	0.000053	0.01
70.00	0.000000	0.00	2.50	0.000074	0.01
60.00	0.000000	0.00	1.00	0.000102	0.02
50.00	0.000000	0.00	0.50	0.000123	0.02
40.00	0.000000	0.00	0.25	0.000144	0.03
30.00	0.000000	0.00	0.10	0.000173	0.03
20.00	0.000014	0.00			

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for PT807-HCL (1989-92 data)
Residue file: 069089.r96 Adjustment factor #2 NOT used.
Analysis Date: 10-07-1999/14:22:37 Residue file dated: 10-07-1999/14:09:09/8
Acute Reference Dose (aRfD) = 0.500000 mg/kg body-wt/day

Males (13-19 years)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000012	0.000038
Standard Deviation	0.000024	0.000030
Standard Error	0.000001	0.000001
Percent of aRfD	0.00	0.01

Percent of Person-Days that are User-Days = 31.87%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000004	0.00	10.00	0.000074	0.01
80.00	0.000011	0.00	5.00	0.000095	0.02
70.00	0.000024	0.00	2.50	0.000112	0.02
60.00	0.000032	0.01	1.00	0.000155	0.03
50.00	0.000036	0.01	0.50	0.000165	0.03
40.00	0.000042	0.01	0.25	0.000171	0.03
30.00	0.000046	0.01	0.10	0.000174	0.03
20.00	0.000052	0.01			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000000	0.00	10.00	0.000045	0.01
80.00	0.000000	0.00	5.00	0.000062	0.01
70.00	0.000000	0.00	2.50	0.000083	0.02
60.00	0.000000	0.00	1.00	0.000107	0.02
50.00	0.000000	0.00	0.50	0.000138	0.03
40.00	0.000000	0.00	0.25	0.000159	0.03
30.00	0.000002	0.00	0.10	0.000169	0.03
20.00	0.000030	0.01			

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for PT807-HCL (1989-92 data)
Residue file: 069089.r96 Adjustment factor #2 NOT used.
Analysis Date: 10-07-1999/14:22:37 Residue file dated: 10-07-1999/14:09:09/8
Acute Reference Dose (aRfD) = 0.500000 mg/kg body-wt/day

Males (20+ years)

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000007	0.000030
Standard Deviation	0.000017	0.000024
Standard Error	0.000000	0.000000
Percent of aRfD	0.00	0.01

Percent of Person-Days that are User-Days = 24.45%

Estimated percentile of user-days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000005	0.00	10.00	0.000057	0.01
80.00	0.000014	0.00	5.00	0.000069	0.01
70.00	0.000018	0.00	2.50	0.000085	0.02
60.00	0.000023	0.00	1.00	0.000117	0.02
50.00	0.000027	0.01	0.50	0.000145	0.03
40.00	0.000031	0.01	0.25	0.000167	0.03
30.00	0.000035	0.01	0.10	0.000247	0.05
20.00	0.000041	0.01			

Estimated percentile of per-capita days exceeding calculated exposure in mg/kg body-wt/day and corresponding percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
90.00	0.000000	0.00	10.00	0.000031	0.01
80.00	0.000000	0.00	5.00	0.000041	0.01
70.00	0.000000	0.00	2.50	0.000056	0.01
60.00	0.000000	0.00	1.00	0.000075	0.02
50.00	0.000000	0.00	0.50	0.000095	0.02
40.00	0.000000	0.00	0.25	0.000117	0.02
30.00	0.000000	0.00	0.10	0.000153	0.03
20.00	0.000013	0.00			

Attachment 3

U.S. Environmental Protection Agency Ver. 6.76
DEEM Chronic analysis for PT807-HCL (1989-92 data)
Residue file name: D:\working\pt807\069089.r96 Adjustment factor #2 NOT used.
Analysis Date 10-07-1999/14:10:29 Residue file dated: 10-07-1999/14:09:09/8
Reference dose (RfD, CHRONIC) = .14 mg/kg bw/day
COMMENT 1: FQPA 1x

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of Rfd
U.S. Population (total)	0.000012	0.0%
U.S. Population (spring season)	0.000012	0.0%
U.S. Population (summer season)	0.000012	0.0%
U.S. Population (autumn season)	0.000012	0.0%
U.S. Population (winter season)	0.000013	0.0%
Northeast region	0.000014	0.0%
Midwest region	0.000011	0.0%
Southern region	0.000011	0.0%
Western region	0.000014	0.0%
Hispanics	0.000017	0.0%
Non-hispanic whites	0.000011	0.0%
Non-hispanic blacks	0.000014	0.0%
Non-hisp/non-white/non-black)	0.000020	0.0%
All infants (< 1 year)	0.000012	0.0%
Nursing infants	0.000010	0.0%
Non-nursing infants	0.000013	0.0%
Children 1-6 yrs	0.000034	0.0%
Children 7-12 yrs	0.000020	0.0%
Females 13-19(not preg or nursing)	0.000011	0.0%
Females 20+ (not preg or nursing)	0.000009	0.0%
Females 13-50 yrs	0.000009	0.0%
Females 13+ (preg/not nursing)	0.000012	0.0%
Females 13+ (nursing)	0.000015	0.0%
Males 13-19 yrs	0.000012	0.0%
Males 20+ yrs	0.000007	0.0%
Seniors 55+	0.000009	0.0%
Pacific Region	0.000015	0.0%

Attachment 4

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

PC Code: 289087
DP Bar Code: D258699

DATE: September 23, 1999

MEMORANDUM

SUBJECT: Tier II Estimated Surface Water and Tier I Estimated Groundwater Environmental Concentrations for N,N-diethyl-2(4-methylbenzyloxy) ethylamine hydrochloride (PT807-HCl, Ecolyst)

FROM: E. Laurence Libelo, Ph.D., Environmental Engineer
Environmental Risk Branch IV
Environmental Fate and Effects Division (7507C)

THROUGH: Mah T. Shamim, Ph.D., Chief
Environmental Risk Branch IV, EFED (7507C)

TO: Cynthia Giles-Parker, Product Manager
Rose Kearns, PM Team Reviewer

This memo presents the Tier II surface water Estimated Environmental Concentrations (EECs) and Tier I groundwater EECs for N,N-diethyl-2(4-methylbenzyloxy) ethylamine hydrochloride (PT807-HCl or Ecolyst) used on citrus trees in Florida. These values were calculated using PRZM/EXAMS (surface water) and SCI-GROW (groundwater) for use in ecological and human health risk assessment.

This chemical is very soluble in water and stable in the environment. Based on it's chemical properties it is likely that this chemical will move to surface water and groundwater, and it may accumulate in the environment. According to information included in the proposed Ecolyst label, the maximum application rate for this chemical is 0.013 lb a.i./acre/year. The surface water acute EEC is **4.0 ppb.** The surface water chronic EEC is also **3.9 ppb**. These values represent the 1-in-10 year peak surface water concentration and 1-in-10 year mean yearly concentration. The calculated concentration in surface water increases over time as the compound builds up in the environment, and continued use will result in increasing concentration over time.

The groundwater screening concentration, Calculated using SCI-GROW is **0.02 ppb**. However, the properties of this compound are outside the range of values used to develop SCI-

GROW. Because of it's stability in the environment this chemical can be expect to accumulate in groundwater and the actual concentrations may be much higher.

PRZM/EXAMS:

To calculate simulated surface water EECs a simulated application at the maximum rate onto a ten hectare citrus field draining into a one hectare static pond, two meters deep with no outlet was used. A field located in Oceola County, Florida was used in the simulation. The soil in this area is Adamsville sand, a hyperthermic, uncoated Aquic Quartzipsamment in MLRA 156A. The Adamsville sand is a somewhat poorly drained, rapidly permeable soil that formed in thick sandy marine sediments occurring in Central and Southern Florida on slopes of 0-5 percent. The soil is typical of soils used for citrus production. Adamsville sand ranges from a Hydrologic Group A soil to a Hydrologic Group C soil, depending on the water table. For the purpose of this modeling, EFED used the curve numbers from the PIC of the Adamsville sand as a Group C soil. The weather and agricultural practices were simulated over 36 years so that the ten year excedence probability at the site could be estimated. The EEC's generated in this analysis were calculated using PRZM 3.12 (Pesticide Root Zone Model) for simulating runoff and erosion from the agricultural field and EXAMS 2.97.5 (Exposure Analysis Modeling System) for estimating environmental fate and transport in surface water. A list of input parameters for PRZM/EXAMS are presented in Table 1 and 2.

There are a number of factors which may limit the accuracy and precision of the PRZM/EXAMS modeling. These may include the selection of the exposure scenarios, the quality of the input data, the ability of the models to represent the real world and the number of years that were modeled. Also, for this chemical, data on microbial degradation is lacking. Only one measured value of degradation half-life for aerobic soil metabolism has been submitted. This greatly increases the uncertainty in the calculated EEC values.

SCI-GROW:

SCI-GROW provides a groundwater screening exposure value to be used in determining the potential risk to human health from drinking water contaminated with the pesticide. In this case, the chemical properties of the compound are outside the range of values for which SCI-GROW was developed. SCI-GROW calculates EEC values only for a single season and so is not useful in estimating EEC values for stable compounds that may persist in the environment. The EEC value calculated using SCI-GROW should therefore be used with caution since it probably significantly underestimates possible groundwater concentrations. SCI-GROW input parameters are shown in Table 3.

Modeling Inputs and Results:

Figure 1 shows the surface water EEC values as a function of time. The input values for PRZM, EXAMS and SCI-GROW are listed in Tables 1-3. Table 4 contains the estimated

concentrations for the maximum label use. Attached to this memo are copies of the original input file for PRZM and printouts of the SCI-GROW runs.

Figure 1: Calculated PT(807) Surface Water Concentration

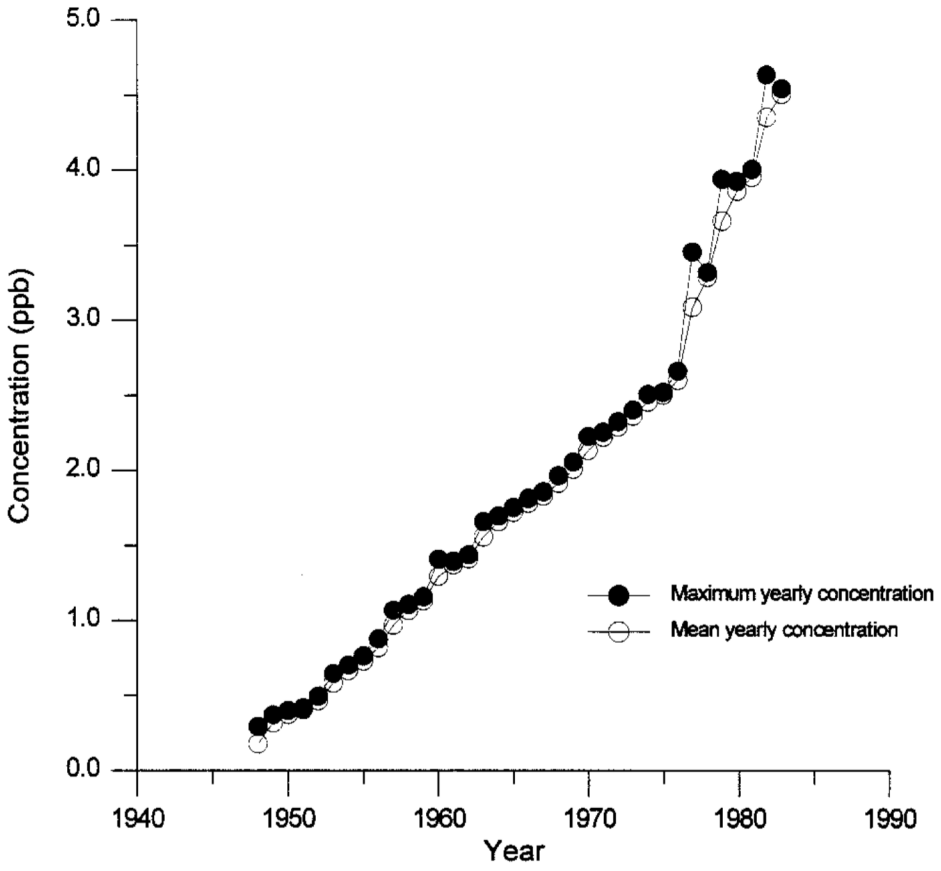


Table 1: Input Parameters for PRZM (version 3.12)

Variable (units)	Variable Description	Input Value	Source of Info/Reference
DWRATE(1)1 (day-1)	Dissolved phase pesticide decay rate in surface horizon	DWRATE(1) = DSRATE(1) = 7 x 10^{-4}/day	Aerobic soil metabolism half-life x3 (335 days x 3 =1005) MRID # 44354535
DSRATE(1)1 (day-1)	Adsorbed phase pesticide decay rate in surface horizon	7 x 10^{-4}/day	Aerobic soil metabolism half-life x3 (335 days x 3 =1005) MRID # 44354535
DWRATE(2) (day-1) DWRATE(3) (day-1)	Dissolved phase pesticide decay rate in 1st, and 2nd subsurface horizon	DWRATE(2) = DSRATE(2) = 3 x 10^{-4}/day DWRATE(3) = DSRATE(3) = 3 x 10^{-4}/day	No data submitted
DSRATE(2) (day-1) DSRATE(3) (day-1)	Adsorbed phase pesticide decay rate in 1st and 2nd subsurface horizon	3 x 10^{-4}/day	No data submitted
KD(1) KD(2) KD(3) (cm3 gm-1 or mL g-1 or L kg-1)	Pesticide partition or distribution coefficients for each horizon	K_d = 2.65	Mobility - Adsorption/Desorption study (GLN 163-1) value for sand MRID 44354536
TAPP (kg ha-1)	Application rate	0.013 lb a.i./acre	Proposed label
APPEFF (decimal)	Application efficiency	0.95	Standard Input
DRFT	Spray drift fraction	0.014 for ground spray	Standard Input

Table 2: Input Parameters for EXAMS (Version 2.97.5)

Variable (units)	Variable Description	Input Value	Source of Info/Reference
HENRY (atm-m3mole-1)	Henry's law constant	no input, let EXAMS computes	
KBACW1 (cfu/mL)-1 hour-1	Bacterial biolysis in water column	0.0	No data submitted
KBACS1 (cfu/mL)-1 hour-1	Bacterial biolysis in benthic sediment	0.0	No data submitted
KDP (hour-1)	Direct photolysis	0.0	No data submitted
KBH (mole-1 hour-1) KNH (hour-1) KAH (mole-1 hour-1)	Base hydrolysis Neutral hydrolysis Acid hydrolysis	0.0 0.0 0.0	MRID 44354534
KOC (mL g-1 O.C.)	Partition coefficient for organic carbon	285	MRID # 44354536
MWT (g mole-1)	Molecular weight	257.8	Product chemistry
SOL (mg L-1)	Aqueous solubility	1×10^{6}	Product chemistry
QUANT	Reaction quantum yield for direct hydrolysis	0.5	Standard Input
VAPR (torr)	Vapor pressure	1×10^{-7}	Product chemistry

Table 3: SCI-GROW Modeling Input Parameters

Chemical	**diethyl-2(4-methylbenzyloxy) ethylamine hydrochloride (PT807-HCl)**
PC Code	289087
Application Rate	0.013 lb a.i./acre
Maximum Number of Applications per year	1
Aerobic Soil Metabolism	$T_{1/2}$ = 335
Soil-Water Partitioning (K_{oc})	285 L/kg (Sand value)

Table 4: Modeling Results for N,N-diethyl-2(4-methylbenzyloxy) ethylamine hydrochloride (PT807-HCl) Use on Citrus

Application Method	**Application Rate (lbs a/i/acre)**	**Application Frequency**	**1 in 10 year Maximum Surface Water Concentration (ppb)**	**1 in 10 year Annual Mean Concentration**	**SCI-GROW Concentration (ppb)**
Ground Air-Blast	**0.013**	**one per season**	**4.0**	**3.9**	**0.02**

PRZM Input File:

```
***PRZM 3.1 Input Data File, created from PRZM 2.3***
*** FLCITRS1.INP Created 12/24/97***
*** Modified for PT807 - N,N-diethyl-2(4-methylbenzyloxy) ethylamine hydrochloride ***
*** on September 9, 1999 by L. Libelo ***
*** Citrus Blooning date from FL Ag Extension Service, Desoto Co 941-993-4846 ***
*** Assume sparse grass underneath the trees for heating***
*** Assume sparse grass within channels leading to surface waters***
*** Osceola County, Florida ***
ECOLYST
Adamsville Sand; MLRA U-156A, Osceola County, FL
*** Record 3
  0.770  0.150      0  25.00      1      1
*** Record 6
      4
*** Record 7
   0.10   0.13   1.00   10.00  6.20      3   4.00   354.0
*** Record 8
      1
*** Record 9
      1   0.10  100.00   80.00      3  94  84  89            0.00    500
*** Record 9a
      1      3
*** Record 9b, c, d
0101 0105 0108
0.30 0.30 0.30
0.04 0.04 0.04
*** Record 10
     36
 110548  170748  010848      1
 110549  170749  010849      1
 110550  170750  010850      1
 110551  170751  010851      1
 110552  170752  010852      1
 110553  170753  010853      1
 110554  170754  010854      1
 110555  170755  010855      1
 110556  170756  010856      1
 110557  170757  010857      1
 110558  170758  010858      1
 110559  170759  010859      1
 110560  170760  010860      1
 110561  170761  010861      1
 110562  170762  010862      1
 110563  170763  010863      1
 110564  170764  010864      1
 110565  170765  010865      1
 110566  170766  010866      1
 110567  170767  010867      1
 110568  170768  010868      1
 110569  170769  010869      1
```

110570 170770 010870 1
110571 170771 010871 1
110572 170772 010872 1
110573 170773 010873 1
110574 170774 010874 1
110575 170775 010875 1
110576 170776 010876 1
110577 170777 010877 1
110578 170778 010878 1
110579 170779 010879 1
110580 170780 010880 1
110581 170781 010881 1
110582 170782 010882 1
110583 170783 010883 1
*** Record 12
Application schedule: 1 ground spray/air blast @ 0.013 lb a.i/acre, 95% appl eff, 1.4% spray drift
*** Record 13 ***
36 1 0
*** Record 15
PT807: Kd = 2.65 ASM: T1/2 = 1005 days; AnSM: T1/2 days
*** Record 16
150448 0 2 0.00 0.01 0.95 0.05
150449 0 2 0.00 0.01 0.95 0.05
150450 0 2 0.00 0.01 0.95 0.05
150451 0 2 0.00 0.01 0.95 0.05
150452 0 2 0.00 0.01 0.95 0.05
150453 0 2 0.00 0.01 0.95 0.05
150454 0 2 0.00 0.01 0.95 0.05
150455 0 2 0.00 0.01 0.95 0.05
150456 0 2 0.00 0.01 0.95 0.05
150457 0 2 0.00 0.01 0.95 0.05
150458 0 2 0.00 0.01 0.95 0.05
150459 0 2 0.00 0.01 0.95 0.05
150460 0 2 0.00 0.01 0.95 0.05
150461 0 2 0.00 0.01 0.95 0.05
150462 0 2 0.00 0.01 0.95 0.05
150463 0 2 0.00 0.01 0.95 0.05
150464 0 2 0.00 0.01 0.95 0.05
150465 0 2 0.00 0.01 0.95 0.05
150466 0 2 0.00 0.01 0.95 0.05
150467 0 2 0.00 0.01 0.95 0.05
150468 0 2 0.00 0.01 0.95 0.05
150469 0 2 0.00 0.01 0.95 0.05
150470 0 2 0.00 0.01 0.95 0.05
150471 0 2 0.00 0.01 0.95 0.05
150472 0 2 0.00 0.01 0.95 0.05
150473 0 2 0.00 0.01 0.95 0.05
150474 0 2 0.00 0.01 0.95 0.05
150475 0 2 0.00 0.01 0.95 0.05
150476 0 2 0.00 0.01 0.95 0.05
150477 0 2 0.00 0.01 0.95 0.05

```
 150478  0 2 0.00  0.01 0.95 0.05
 150479  0 2 0.00  0.01 0.95 0.05
 150480  0 2 0.00  0.01 0.95 0.05
 150481  0 2 0.00  0.01 0.95 0.05
 150482  0 2 0.00  0.01 0.95 0.05
 150483  0 2 0.00  0.01 0.95 0.05
*** Record 17
   0.0      3    0.0
*** Record 18
   0.0   0.00    0.5
*** Record 19
Adamsville Sand; Hydrologic Group C;
*** Record 20
 100.00         0  0  0  0  0  0  0  0  0  0
*** Record 26
   0.0   0.00   0.00
*** Record 33
     3
*** Record 34, 36, 37
     1  10.00  1.440  0.086  0.000  0.000   0.00
        .0007  .0007 0.000
          0.1  0.086  0.036  0.580   2.65
     2  10.00  1.440  0.086  0.000  0.000   0.00
        .0003  .0003 0.000
          1.0  0.086  0.036  0.580   2.65
     3  80.00  1.580  0.030  0.000  0.000   0.00
        .0003  .0003 0.000
          5.0  0.030  0.023  0.116   2.65
     0
        YEAR     5        YEAR     5        YEAR     5  1
     1
     1 _____
     6  YEAR
   PRCP   TCUM  0  0
   RUNF   TCUM  0  0
   ESLS   TCUM  0  0  1.0E3
   RFLX   TCUM  0  0  1.0E5
   EFLX   TCUM  0  0  1.0E5
   RXFX   TCUM  0  0  1.0E5
```

SCI-GROW Output for Ecolyst on FL Citrus

INPUT VALUES

APPL (#/AC) RATE	APPL. NO.	URATE (#/AC/YR)	SOIL KOC	SOIL AEROBIC METABOLISM (DAYS)
.013	1	.013	285.0	335.0

GROUND-WATER SCREENING CONCENTRATIONS IN PPB

.017185

A= 330.000 B= 290.000 C= 2.519 D= 2.462 RILP= 3.872 F= .121 G= 1.322 URATE= .013 GWSC= .017185

Attachment 5 YAN DONOVAN

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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: **October 29, 1999**

SUBJECT: **Occupational and Residential Exposure Assessment For the Use of PT807-HCL (Ecolyst) on Citrus (PP# 8F04998)**

DP Barcode:	D259538	Submission:	S551488
PC Code:	069089	Case:	290274
Trade Name:	Ecolyst	Class:	Plant Growth Regulator

TO: Yan Donovan
Registration Action Branch 2
Health Effects Division (7509C)

FROM: Margarita Collantes, Biologist
Registration Action Branch 2
Health Effects Division (7509C)

THRU PEER REVIEW: Shih-Chi Wang, Biologist
Registration Action Branch 2
Health Effects Division (7509C)

THRU: Richard Loranger, Branch Senior Scientist
Registration Action Branch 2
Health Effects Division (7509C)

I. EXECUTIVE SUMMARY

A Section 3 registration is being requested for an end-use product containing the new plant growth regulator PT807-HCL, N, N-diethyl-2-{4-methylbenzyloxy} ethylamine hydrochloride, the sole active ingredient. The technical PT807-HCL and the product Ecolyst are both aqueous solutions. The concentration of the technical is 50% and Ecolyst contains 1.0 grams active ingredient/fluid ounce, or 3%. Ecolyst will be used as a plant growth regulator on oranges. This memordandum addresses risk from occupational and residential exposure to Ecolyst only.

The proposed agricultural use is to apply Ecolyst to citrus trees by ground air-blast spray equipment during spring bloom. Ecolyst will be applied at a rate of 0.0124 lb (6 grams) active ingredient (a.i.) per acre, once per season. The label proposes a restricted-entry interval (REI) of 12-hours.

Since no chemical-specific data for assessing human exposures during pesticide handling activities were submitted to the Agency in support of the registration of Ecolyst, HED used data from the Pesticide Handlers Exposure Data Base (PHED) Version 1.1 to assess handler exposures for this regulatory action. Defaults established by the Health Effects Division (HED) Science Advisory Council for Exposure were used for acres treated per day, body weight, the level for personal protective equipment worn by handlers and life expectancy. The Hazard Identification Assessment Review Committee (HIARC) identified an inhalation absorption factor of 100% and a short and intermediate-term inhalation endpoint of 30 mg/kg/day.

All inhalation MOEs were above 100. For workers, MOEs equal to or greater than 100 do not exceed HED's level of concern.

Although the potential for postapplication (dermal) exposure does exist, no systemic toxicity was observed in the 21-day dermal toxicity study in rats at the limit does of 1000 mg/kg/day. Therefore neither short- nor intermediate-term dermal endpoints were selected by the HIARC and a postapplication exposure assessment is not required.

Ecolyst currently has no registered residential uses (REFS 10/99) and none are proposed in the present action. Therefore a residential exposure assessment is not required at this time.

II. HAZARD CHARACTERIZATION

A. Hazard Profile

Acute Toxicity: The data base adequately characterizes PT807-HCl as having low acute oral, dermal, and inhalation toxicity. It is Toxicity Category IV for acute dermal toxicity, acute inhalation toxicity, and primary dermal irritation; Toxicity Category III for acute oral and primary eye irritation; and it is not a dermal sensitizer.

Cumulative Toxicity: There is no evidence of cumulative toxicity. The oral LD_{50} in rats (531 mg/kg) is not markedly greater than the oral subchronic rat LOAEL (300 mg/kg/day). Similarly, a comparison of subchronic and chronic LOAELs reveals no evidence of cumulation in the rat and dog. This is because rats rapidly excrete PT807-HCl, primarily in the urine and secondarily in the feces, with very little remaining in the tissues after 7 days (≤0.34%). There may also be some adaptation due to enzyme induction.

Neurotoxicity: Neurotoxicity was observed in several studies. Hyperactivity, hyperreflexivity, lack of coordination, tremors, convulsions, and ptyalism were observed at 300 mg/kg/day in the subchronic gavage study in rats. Rooting in the bedding and lethargy were observed at 250 mg/kg/day in the developmental toxicity study in rats. In the acute neurotoxicity study, the HIARC designated the LOAEL to be 200 mg/kg based on slight ataxia in 1 of 11 males. At a dose of 400 mg/kg, there was an increase in clinical signs in the functional observation battery, and decreases in motor activity. No toxicity was observed in the subchronic neurotoxicity study in rats at doses of 323 mg/kg/day in males and 386 mg/kg/day in females.

Developmental and Reproductive Toxicity: In the developmental toxicity study in rats, there was an increased incidence of enlarged lateral ventricles in pups at 500 mg/kg/day. The incidences were within historical limits, however, and occurred at a dose far in excess of the maternal NOAEL of 50 mg/kg/day. No developmental effects were seen in rabbit pups at 200 mg/kg/day, whereas the maternal NOAEL was 10 mg/kg/day. In the rat reproductive toxicity study, the systemic and reproductive LOAELs were both 114 mg/kg/day at which dose the parents exhibited decreased body weight and body weight gains, and the pups had decreased body weight and body weight gains, delayed sexual development, reductions in absolute and relative uterus and ovary weights, and histological changes in the uterus, vagina, and ovaries in the females.

Chronic/Carcinogenicity and Mutagenicity Studies: No toxicity or tumors were observed in the chronic dog study or the mouse carcinogenicity study. The high-dose in the mouse study exceeded the limit dose (1000 mg/kg/day). In the chronic toxicity/carcinogenicity study in rats, survival was markedly increased in the high-dose compared to the controls. The HIARC considers this dose to be excessive based on decreases in body weight and body weight gain. No other toxicity was seen. Although there was an increased incidence of hepatocellular adenomas and carcinomas in the high-dose males, the HIARC attributes this to increased survival; that is, these rats lived long enough to develop more tumors. PT807-HCl was clastogenic with or without metabolic activation in Chinese hamster ovary cells cultured *in vitro*, but all other mutagenicity studies were negative. Thus, there is no evidence of clastogenic potential in whole animals. Based on these findings, the HIARC concluded that PT807-HCl is **not likely** to be a human carcinogen.

B. FQPA Considerations

The FQPA Safety Factor Committee met on October 4, 1999 and recommended that the FQPA safety factor for protection of infants and children (as required by FQPA) be **removed (1x)** because:

1. The toxicology database is complete for the assessment of the effects following *in utero* and/or postnatal exposure to PT807 Hcl;

2. The toxicity data provided no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure;

3. the requirement of a developmental neurotoxicity study is not based on the criteria reflecting some special concern which are generally used for requiring a DNT study and an FQPA safety factor (e.g.: neuropathy in adult animals; CNS malformations following prenatal exposure; brain weight or sexual maturation changes in offspring; and/or functional changes in offspring)[1] and therefore does not warrant an FQPA safety factor; and

4. The exposure assessments will not underestimate the potential dietary (food and water) exposures for infants and children from the use of PT807 HCl (currently no residential exposure is expected).

C. Dose Response Assessment

PT807-HCl is a plant growth regulator which has been shown to be effective at shortening the time to maturation of citrus when applied during the Spring bloom. It will be applied to trees as a single foliar application at a rate of 6 grams a.i./A in 100 gallons of finished spray using an airblast sprayer.

On September 16, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of PT807-HCl, the active ingredient in Ecolyst®. The HIARC selected toxicology endpoints for oral and inhalation exposure risk assessments, dismissed carcinogenicity concerns, and addressed the potential enhanced sensitivity of infants and children from exposure to PT807-HCl as required by the Food Quality Protection Act (FQPA) of 1996.

Below in **Table 1** is a summary of the toxicological endpoints selected for Ecolyst.

---

[1]This is an interim step towards accordance with the proposed 'OPP POLICY ON DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTOR(S) FOR USE IN THE TOLERANCE-SETTING PROCESS' which was presented to the FIFRA SAP meeting in May, 1999 and placed in the Docket for Public Comment (64FR37001; 7/8/99; Docket No. 37001).

TABLE 1 : SUMMARY OF TOXICOLOGY ENDPOINT SELECTION				
EXPOSURE SCENARIO	**DOSE (mg/kg/day)**	**UF***	**ENDPOINT**	**STUDY**
Acute Dietary	50 mg/kg/day	100	Slight ataxia This risk assessment is required.	Acute Neurotoxicity in Rats
	Acute RfD = 0.5 mg/kg/day (Protective of females 13-50 years.)			
Chronic Dietary	14 mg/kg/day	100	Decreased pup body weight and body weight gains, delayed sexual development, reductions in uterus and ovary weights, and changes in female reproduction organs. This risk assessment is required.	Reproductive Toxicity in Rats
	RfD = 0.14 mg/kg/day (Protective of females 13-50 years.)			
Short-Term Dermal	This risk assessment is not required.			
Intermediate-Term Dermal	This risk assessment is not required.			
Long-Term Dermal	This risk assessment is not required.			
Inhalation (All times)	30 mg/kg/day (gavage)	100	Increased mortality; hyperactivity, hyperreflexivity, lack of coordination, tremors, convulsions, and increased salivation. This risk assessment is required	90-Day Toxicity in Rats

* An MOE generally exceeds HED's level of concern if it is less than the Uncertainty Factor (UF).

III. OCCUPATIONAL EXPOSURE ASSESSMENT

Workers may be exposed to Ecolyst during mixing, loading, application and postapplication activities. Based on the proposed use patterns, short and intermediate-term exposures may occur. Chronic exposures (6 months of continuous exposure) are not expected.

TABLE 2: USE PATTERNS AND FORMULATION FOR ECOLYST				
FORMULATION	**METHOD OF APPLICATION**	**USE SITES**	**APPLICATION RATES**	**TIMING OF APPLICATION**
Liquid Formulation (3.3% ai)	By ground air-blast sprayer equipment.	oranges	0.0124 lbs ai/A	Apply during spring bloom. Do not apply more than 1 application per season.

Handlers

Since no chemical-specific data for assessing human exposures during pesticide handling activities were submitted to the Agency in support of the registration of Ecolyst, it is the policy of HED to use data from the Pesticide Handlers Exposure Data Base (PHED) Version 1.1 to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure, Policy .007, "Use of Values from the PHED Surrogate Table and Chemical-Specific Data." Health Effects Division, Office of Pesticide Programs, January 1999.)

The unit exposure values calculated by PHED generally range from the geometric mean to the median of the selected data set. To add consistency and quality control to the values produced from this system, the PHED Task Force has evaluated all data within the system and has developed a set of grading criteria to characterize the quality of the original study data. The assessment of data quality is based on the number of observations and the available quality control data. These evaluation criteria and the caveats specific to each exposure scenario are summarized in **Table 3.** While data from PHED provide the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. HED has developed a series of tables of standard unit exposure values for many occupational scenarios that can be utilized to ensure consistency in exposure assessments (PHED Surrogate Exposure Guide. Health Effects Division, Office of Pesticide Program, August 1998).

Defaults established by the HED Science Advisory Council for Exposure were used for body weight, and the level of personal protective equipment worn by handlers. A short- and intermediate-term inhalation NOAEL of **30** mg/kg/day and **100%** inhalation absorption factor were established by the HIARC (9/16/99) for estimating risk from inhalation exposure. The HIARC did not select a dermal endpoint and determined that a risk assessment was **not** required for dermal exposure.

A summary of the exposure and risk estimates for handlers are included as **Table 3.** All MOEs are above 100. The inhalation MOEs ranged from 2,000,000 for mixer/loader to 500,000 for applicators. For workers, MOEs equal to or greater than 100 do not exceed HED's level of concern.

Per the Worker Protection Standard (WPS), the minimum level of PPE for handlers is based on the acute toxicity of the end-use product. RD is responsible for ensuring that PPE listed on the label is in compliance with WPS.

Postapplication

Although the potential for postapplication (dermal) exposure does exist, no systemic toxicity was observed in the 21-day dermal toxicity study in rats at the limit dose of 1000 mg/kg/day. Therefore neither short- nor intermediate-term dermal endpoints were selected by the HIARC and a postapplication exposure risk assessment is not required.

Restricted Entry Interval (REI). The REI is based on the acute toxicity of the technical material, which is classified in acute toxicity category III/IV (HIARC, 9/99). Acute toxicity category III and IV chemicals require a 12-hour REI. Thus, the 12-hour REI that appears on the PT807-HCL label is adequate.

IV. RESIDENTIAL (NON-OCCUPATIONAL) EXPOSURE

Ecolyst currently has no registered residential uses (REFS 10/99) and none are proposed in the present action. Therefore a residential exposure risk assessment is **not** required at this time.

Table 3: OCCUPATIONAL HANDLER INHALATION EXPOSURE RISK TO ECOLYST											
PHED Scenario [1]	Personal Protective Equipment [2]	Route of Exposure [3]	PHED Unit Exposure [4] (mg/lb ai)	PHED Data Conf [5]	AR [6] (lb ai/acre)	% AF [7]	Acres Treated [8] (A/day)	BW [9] (kg)	Daily Dose [10] (mg/kg/day)	Inhalation Short- and Intermediate-term	
										NOAEL [11] (mg/kg/day)	MOE [12]
Mixer/ Loader Exposure											
Mixing/Loading Liquid Formulation for Airblast Spray	Long Sleeves, Long Pants, Gloves	inhalation	0.0012	high	0.0124	1 (100%)	74	70	1.5 x 10-5	30	2,000,000
Applicator Exposure											
Applying Sprays to Orchard with Airblast (open-cab)	Long Sleeves, long Pants, Gloves	inhalation	0.0045	high	0.0124	1 (100%)	74	70	5.9 x 10-5	30	500,000

Footnotes:

1. Pesticide Handler Exposure Database (PHED) scenarios - Self-explanatory.
2. Personal Protective Equipment - Based on the acute toxicity of the end-use product.
3. Self-explanatory
4. Unit Exposure (UE) is from Pesticide Handlers Exposure Database (PHED) version 1.1, 8/98.
5. Unit exposure data quality is based on Subdivision U Guidelines
6. Application rate (AR) is from the label for Ecolyst Plant Growth Regulator
7. % Absorption Factor (AF) determined by HIARC 9/99
8. Acres treated per day are based on US Agriucltural Census.
9. Body weight for an adult male = 70 kg.
10. Daily Dose (DD) = [(lb ai/A) x (A/day) x UE (mg/lb ai handled) x AF] ÷ Body Weight (kg)
11. Short and Intermediate-term Inhalation NOAEL = 30 mg/kg/day established by HIARC based on 90-day gavage study in rats.
12. MOE = NOAEL/ Daily Dose

cc **WITH** Attachments: RAB2 Reading File, PP# 8F04998, M. Collantes