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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: 9/23/2005

MEMORANDUM

SUBJECT: Amendment to HED Human Health Risk Assessment: Pyridaben in/on Hops (PP#1E06226), Tropical Fruit (PP#3E06460), Strawberries (PP#0E06068), Stone Fruit (PP#2E06303), and Tomatoes (PP#1E06303).

DP Barcode:	D323441	Decision No.:	305467
Chemical No.:	129105	Class:	Insecticide
Trade Name:	Oracle	EPA Reg No.:	7969-125
40 CFR:	§180.494		

Regulatory Action: Section 3 Registration
Risk Assessment Type: Single Chemical Aggregate

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Dr. K.W. Dorschner, IR-4 Project Coordinator, Interregional Research Project Number 4 (IR-4), State Agricultural Experimental Station, Rutgers University, New Brunswick, New Jersey, on behalf of the IR-4 project, has submitted petitions for the establishment of permanent tolerances for residues of the miticide/insecticide pyridaben in/on hops at 10.0 ppm, tropical fruit (including: papaya, star apple, black sapote, mango, sapodilla, mamey sapote, and canistel) at 0.10 ppm, strawberries at 2.5 ppm, stone fruit (group 12) at 2.5 ppm, and greenhouse-grown tomatoes at 0.15 ppm. The petitioner also proposes to delete the existing pyridaben tolerances for residues in/on peach, nectarine, apricot, cherry, plum, and prune.

On May 12, 2005, HED issued a human health risk assessment covering uses of the insecticide Pyridaben on hops, tropical fruit, strawberries, stone fruit, and greenhouse-grown tomatoes (W. Wassell *et al.*, DP Barcode D316833, 5/12/05). That assessment includes an acute dietary risk assessment which utilized a FQPA database uncertainty factor of 10x for lack of a developmental neurotoxicity study (DNT). Further evaluation of the toxicity database and the entire weight of evidence has lead to the conclusion that the FQPA Safety Factor be reduced to 1X and a

NOV 14 2005

developmental neurotoxicity study not be required. The human health risk assessment associated with the petitions cited above has been re-examined and the acute aggregate risks have been amended accordingly. Other modifications to the amended risk assessment include revision of the recommended tolerance for greenhouse tomatoes from 2.0 ppm to 1.5 ppm, and BEAD validation of percent crop treated (PCT) inputs to dietary exposure estimates.

Recommendation for Tolerances

This human health risk assessment supports the establishment of permanent tolerances for residues of pyridaben in conjunction with a conditional registration in or on the following commodities at the indicated levels:

Hop, Dried Cones	10.0 ppm
Papaya	0.10 ppm
Star Apple	0.10 ppm
Black Sapote	0.10 ppm
Mango	0.10 ppm
Sapodilla	0.10 ppm
Mamey Sapote	0.10 ppm
Canistel	0.10 ppm
Stone Fruit, Group 12	2.5 ppm
Strawberry	2.5 ppm
Tomato	0.15 ppm

Additionally, tolerances for residues of pyridaben in/on peach, nectarine, apricot, cherry, plum, and prune should be deleted.

Additional data requirements are listed in Section 10.0 (Data Needs/Label Requirements) of this memorandum.

Table of Contents

1.0	Executive Summary	6
2.0	Ingredient Profile	8
2.1	Summary of Registered/Proposed Uses	8
2.2	Structure and Nomenclature	10
2.3	Physical and Chemical Properties	12
3.0	Metabolism Assessment	12
3.1	Comparative Metabolic Profile	12
3.2	Nature of the Residue in Foods	13
3.2.1	Description of Primary Crop Metabolism	13
3.2.2	Description of Livestock Metabolism	15
3.3	Environmental Degradation	16
3.4	Tabular Summary of Metabolites and Degradates	18
3.5	Toxicity Profile of Major Metabolites and Degradates	25
3.6	Summary of Residues for Tolerance Expression and Risk Assessment	25
3.6.1	Tabular Summary	25
3.6.2	Rationale for Inclusion of Metabolites and Degradates	25
4.0	Hazard Characterization/Assessment	26
4.1	Hazard Characterization	27
4.2	FQPA Hazard Considerations	32
4.2.1	Adequacy of the Toxicity Data Base	32
4.2.2	Evidence of Neurotoxicity	32
4.2.4	Reproductive Toxicity Study	35
4.2.5	Additional Information from Literature Sources	36
4.2.6	Pre-and/or Postnatal Toxicity	36
4.3	Recommendation for a Developmental Neurotoxicity Study	36
4.3.1	Evidence that supports requiring a Developmental Neurotoxicity study	37
4.3.2	Evidence that supports not requiring a Developmental Neurotoxicity study	37
4.4	Hazard Identification and Toxicity Endpoint Selection	38
4.4.1	Acute Reference Dose (aRfD) - Females age 13-49	38
4.4.2	Acute Reference Dose (aRfD) - General Population	39
4.4.3	Chronic Reference Dose (cRfD)	39
4.4.4	Incidental Oral Exposure (Short and Intermediate Term)	40
4.4.5	Dermal Absorption	41
4.4.6	Dermal Exposure (Short, Intermediate and Long Term)	42
4.4.7	Inhalation Exposure (Short, Intermediate and Long Term)	43
4.4.8	Margins of Exposure	44

4.4.9	Recommendation for Aggregate Exposure Risk Assessments	45
4.4.10	Classification of Carcinogenic Potential	45
4.5	Endocrine disruption	50
5.0	Public Health Data	51
5.1	Incident Reports	51
6.0	Exposure Characterization/Assessment	51
6.1	Dietary-Exposure/Risk Pathway	51
6.1.1	Residue Profile	51
6.1.2	Acute and Chronic Dietary-exposure and Risk	55
6.1.3	Percent Crop Treated (PCT) Information	58
6.2	Water Exposure/Risk Pathway	59
6.3	Residential (Non-Occupational) Exposure/Risk Pathway	60
6.3.1	Home Uses	60
6.3.2	Recreational Uses	60
6.3.3	Other (Spray Drift, etc.)	60
7.0	Aggregate Risk Assessments and Risk Characterization	62
7.1	Acute Aggregate Risk	62
7.2	Short-Term Aggregate Risk	63
7.3	Intermediate-Term Aggregate Risk	64
7.4	Chronic-Term (Non-Cancer) Aggregate Risk	64
7.5	Cancer Risk	65
8.0	Cumulative Risk Characterization/Assessment	65
9.0	Occupational Exposure/Risk Pathway	66
9.1	Short/Intermediate/Long-Term Handler Risk	66
9.2	Short/Intermediate/Long-Term Postapplication Risk	69
10.0	Data Needs and Label Requirements	72
10.1	Toxicology	72
10.2	Residue Chemistry	72
10.3	Occupational and Residential Exposure	72
References:		72
Appendices		74
	Residue Chemistry Data Summary:	76
	Summary of Metabolism Data - Oranges, Apples, and Eggplant	78

Summary of Metabolism Data - Livestock	93
Metabolism in Confined Rotational Crops - (MRID No. 44939702	102
Summary of Analytical Methods	107
Summary of Magnitude of the Residue Studies – Livestock	107
Rat Metabolism	108
Environmental Fate	108
Environmental Persistence	109
Expected Mobility	109
Environmental Metabolites	109

1.0 Executive Summary

Pyridaben [2-*tert*-butyl-5-(4-*tert*-butylbenzylthio)-4-chloropyridazin-3(2*H*)-one] is a selective contact miticide/insecticide that controls various types of phytophagous mites and insects in orchards and vineyards. Pyridaben is currently registered for use on tree nuts, pistachio, apple, pear, citrus fruits, grape, apricot, cherry, nectarine, peach, plum, prune, and cranberry. In the subject petitions, IR-4 has proposed the establishment of uses for pyridaben on hops, tropical fruit (including: papaya, star apple, black sapote, mango, sapodilla, mamey sapote, and canistel), strawberry, and greenhouse-grown tomatoes. Additionally, IR-4 proposes to modify the currently registered use for pyridaben on cherry and apricot, such that a group tolerance for residues in/on stone fruits could be established. Residential uses are not proposed or registered for pyridaben. Pyridaben belongs to the pyridazinone class of pesticides. Other active ingredients that belong to this class of pesticides include pyrazon and norflurazon.

Permanent tolerances are established (40 CFR§180.494(a)) for residues of pyridaben in or on various plant commodities at levels ranging from 0.05 ppm (for tree nuts) to 10.0 ppm (for citrus oil), and for residues of pyridaben and its metabolites PB-7 [2-*tert*-butyl-5-[4-(1-carboxy-1-methylethyl) benzylthio]-4-chloropyridazin-3(2*H*)-one] and PB-9 [2-*tert*-butyl-5-[4-(1,1-dimethyl-2-hydroxyethyl) benzylthio]-4-chloropyridazin-3(2*H*)-one] in or on various livestock commodities including milk at 0.01 ppm and other ruminant commodities at 0.05 ppm. A tolerance with regional registration is established (40 CFR§180.494(b)) for residues of pyridaben in or on cranberries at 0.5 ppm.

The toxicology data base for pyridaben is complete. The data base supports the establishment of permanent tolerances for residues of pyridaben in/on the proposed crops resulting from the currently proposed uses. In general, the acute toxicology studies conducted on pyridaben demonstrate that pyridaben has moderate to mild toxic effects at relatively high doses. The most common toxicity endpoint across the various studies and tested species was decreased body weight/weight gain followed by decreased feed consumption and/or feed efficiency. There is no quantitative or qualitative evidence of increased susceptibility of rat and rabbit fetuses to in utero exposure to pyridaben in developmental studies. There is no quantitative or qualitative evidence of increased susceptibility of rat and rabbit fetuses to in utero exposure to pyridaben in developmental studies. There is no quantitative or qualitative evidence of increased susceptibility to pyridaben following pre-/postnatal exposure in a 2-generation reproduction study incorporating neurotoxicity measurements. There is no concern for developmental neurotoxicity resulting from exposure to pyridaben. Since there was no observed evidence of potential developmental neurotoxicity in short and long-term toxicity studies in rats, mice, and dogs, a developmental neurotoxicity (DNT) study is not required and the FQPA Safety Factor is reduced to 1X. Pyridaben has been classified as a "Group E" chemical (*i.e.*, evidence of non-carcinogenicity for humans) based on the lack of evidence of carcinogenicity in male and female rats as well as in male and female mice.

Acute Dietary Endpoint: An acute dietary endpoint for all population subgroups was identified. An acute oral neurotoxicity study in rats was used to select the dose and endpoint for establishing the acute reference-dose (aRfD) of 0.44 mg/kg bw/day. The lowest-observable-adverse-effect-

level (LOAEL) of 80 mg/kg bw/day was based on an increase in the incidence of piloerection, hypoactivity, tremors, partially closed eyes, and decreases in body weight gain and food consumption in both sexes. The no-observable-adverse-effect-level (NOAEL) is 44 mg/kg bw. A 100-fold uncertainty factor (UF) is required. Since the special FQPA SF has been reduced to 1X, the acute population-adjusted-dose or aPAD is equal to the aRfD.

Short-Term (1-30 days) and Intermediate-Term (1-6 months) Dermal Endpoint: A 21-day dermal toxicity study with rats was used to select the dose and endpoint for assessing risk due to dermal exposure to pyridaben. For this study, the NOAEL is 100 mg/kg bw/day based on decreased body weight gain in females at the LOAEL of 300 mg/kg bw/day. For occupational exposure, a margin-of-exposure or MOE of greater than or equal to 100 is required.

Inhalation Endpoint (all durations): A 30-day inhalation toxicity study in rats was used to select the dose and endpoint for assessing inhalation exposure for all durations. The LOAEL of 0.003 mg/L (0.783 mg/kg bw/day) is based on an increased incidence of dried red nasal discharge, decreased body weight gain, and decreased albumin levels. The NOAEL is 0.00087 mg/L (0.261 mg/kg bw/day). For occupational exposure, an MOE of greater than or equal to 100 is required.

Chronic Dietary Endpoint: A chronic toxicity study with dogs was used to select the dose and endpoint for establishing the chronic RfD of 0.005 mg/kg bw/day. The LOAEL for systemic toxicity in males and females is 0.5 mg/kg bw/day based on an increased incidence of ptyalism, emesis, soft stools, and decreased body weight gain in females. The NOAEL for systemic toxicity is 0.5 mg/kg bw/day. This RfD is applicable to all population subgroups. A 100-fold UF is required. Since the special FQPA SF has been reduced to 1X, the chronic PAD or cPAD is equal to the cRfD.

Although there are some minor residue chemistry deficiencies, the data base is adequate for conditional registration, provided revised Sections B (proposed label) and F (proposed tolerances) are submitted. The residues of concern in plants for tolerance setting purposes are pyridaben, while the residues of concern for risk assessment are pyridaben and all metabolites containing the pyridazinone ring. The residues of concern for tolerance setting and risk assessment in livestock are pyridaben and its metabolites PB-7 and PB-9. The residues of concern in drinking water are pyridaben.

Acute and chronic dietary exposure assessments were completed using DEEM-FCID™. The acute assessment is highly-refined, while the chronic assessment is partially-refined. Modeled drinking water levels for residues of pyridaben were provided by EFED. The acute and chronic dietary risks for all population subgroups are below HED's level of concern. Since there are no residential uses registered or proposed for pyridaben, the dietary risk estimates also represent the aggregate risk estimates. Occupational risks are also below HED's level of concern.

Recommendations for Tolerances

This human health risk assessment supports the establishment of permanent tolerances for residues of pyridaben in or on the following commodities at the indicated levels:

Hop, Dried Cones	10.0 ppm
Papaya	0.10 ppm
Star Apple	0.10 ppm
Black Sapote	0.10 ppm
Mango	0.10 ppm
Sapodilla	0.10 ppm
Mamey Sapote	0.10 ppm
Canistel	0.10 ppm
Stone Fruit, Group 12	2.5 ppm
Strawberry	2.5 ppm
Tomato	0.15 ppm

Additionally, tolerances for residues of pyridaben in/on peach, nectarine, apricot, cherry, plum, and prune should be deleted.

Additional data requirements are listed in Section 8.0 (Data Needs/Label Requirements) of this memorandum.

2.0 Ingredient Profile

Pyridaben is a selective contact miticide/insecticide that controls various types of phytophagous mites and insects in orchards and vineyards. This active ingredient (ai) is a contact acaricide with prolonged residual effects and no known systemic or translaminar activities. There has been no resistance or cross-resistance demonstrated in test pest populations. Pyridaben is currently registered for use on tree nuts, pistachio, apple, pear, citrus fruits, grape, apricot, cherry, nectarine, peach, plum, prune, and cranberry. Pyridaben is not registered or proposed for use in residential settings. Pyridaben belongs to the pyridazinone class of pesticides. Other active ingredients that belong to this class of pesticides include pyrazon and norflurazon.

In conjunction with the subject petitions, IR-4 has proposed the establishment of uses for pyridaben on hops, tropical fruit (including: papaya, star apple, black sapote, mango, sapodilla, mamey sapote, and canistel), strawberry, and greenhouse-grown tomatoes. Additionally, IR-4 proposes to modify the currently registered use for pyridaben on cherry and apricot, such that a group tolerance for residues in/on stone fruits could be established.

Pyridaben is formulated as Pyramite™ Miticide/Insecticide (EPA Reg. No. 7969-125) and Nexter® Miticide/Insecticide (EPA Reg No.7969-106). These products have been proposed for use on hops, tropical fruit, stone fruit, tomatoes, and strawberries. These products contain 60% (Pyramite™) or 75% (Nexter®) by weight pyridaben. These products are formulated as wettable powders in water soluble packaging.

2.1 Summary of Registered/Proposed Uses

Table 2.1. Summary of Directions for Use of Pyridaben.							
Crops	Trade Name	Application, Timing, and Equipment Type	Application Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI ¹ (days)	Use Directions and Limitations
Stone Fruit Citrus Pears Pistachio Tree Nuts	Pyramite ² Nexter ³	Broadcast, foliar, by ground equipment w/ 30-days between applications	0.5	2	1.0	7	Do not apply by air. Do not make more than 2 applications per year. Do not apply through any type of irrigation equipment.
Strawberry	Pyramite Nexter		0.25 to 0.50	2	1.0	1	
Hops Tropical Fruits	Pyramite Nexter		0.50	2	1.0	21	
Apples	Pyramite Nexter		0.50	2	1.0	25	
Tomato Greenhouse only	Pyramite		0.19	2	0.38	2	For use on fresh-market tomatoes grown in the greenhouse. Not for use on field grown tomatoes. Do not make more than 2 applications per year.
Cranberry	Pyramite		0.50	2	1.0	21	Do not apply by air. Do not make more than 2 applications per year. Do not apply through any type of irrigation equipment. Use limited to the States of MA, NJ, RI, ME, NY, CT, NH, VT, and DE.

¹PHI = Pre-harvest interval.

²Pyramite (EPA Reg. No. 7969-125) contains 60% pyridaben formulated as a wettable powder in water-soluble bags.

³Nexter (EPA Reg. No. 7969-106) contains 75% pyridaben formulated as a wettable powder in water-soluble bags.

Pyridaben is not registered or proposed for use in residential settings. Pyridaben belongs to the pyridazinone class of pesticides.

2.2 Structure and Nomenclature

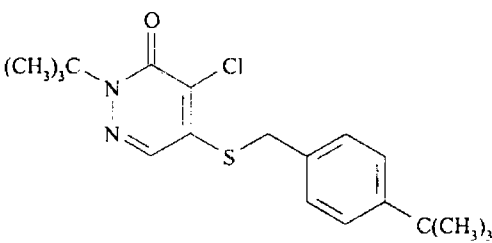
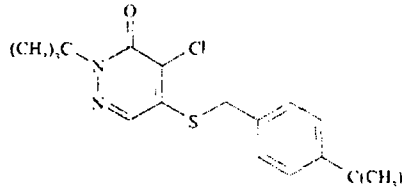
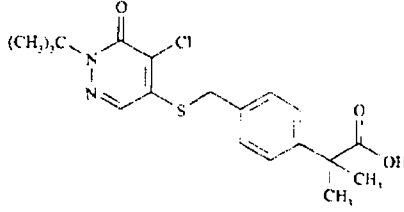
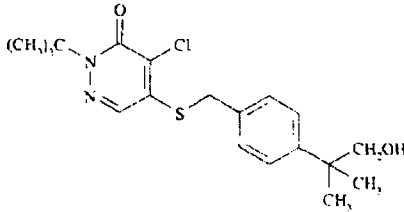
Table 2.2.a Identification of Active Ingredient.	
Compound	Chemical Structure 
Common name	Pyridaben (ANSI approved)
Company experimental name	BAS 300
IUPAC name	2- <i>tert</i> -butyl-5-(4- <i>tert</i> -butylbenzylthio)-4-chloropyridazin-3(2 <i>H</i>)-one
CAS name	4-chloro-2-(1,1-dimethylethyl)-5-[[[4-(1,1-dimethylethyl)phenyl]methyl]thio]-3(2 <i>H</i>)-pyridazinone
CAS #	96489-71-3
Chemical Class	pyridazinone class of pesticides
PC Code	129105
Empirical Formula	C ₁₉ H ₂₅ ClN ₂ OS
Molecular Weight	364.9
Registrant	BASF Corporation
End-use product/EP	Pyramite™ Miticide/Insecticide (EPA Reg. No. 7969-124) Nexter™ Miticide/Insecticide (EPA Reg. No. 7969-106)
Known Impurities of Concern	None

Table 2.2.b Pyridaben Residues of Concern for Tolerance Setting Purposes.		
Company Name/ Code	CAS Name	Structure
Pyridaben	4-chloro-2-(1,1-dimethylethyl)-5-[[[4-(1,1-dimethylethyl)phenyl]methyl]thio]-3(2 <i>H</i>)-pyridazinone	
PB-7	2- <i>tert</i> -butyl-5-[4-(1-carboxy-1-methylethyl)benzylthio]-4-chloropyridazin-3(2 <i>H</i>)-one	
PB-9	2- <i>tert</i> -butyl-5-[4-(1,1-dimethyl-2-hydroxyethyl)benzylthio]-4-chloropyridazin-3(2 <i>H</i>)-one	

2.3 Physical and Chemical Properties

Table 2.3 Physicochemical Properties of Pyridaben.	
Parameter	Value
Appearance	White crystalline powder
Melting Range	111 - 112°C
pH	6.81 in a solution containing 90.1 mg/L
Water solubility (25°C)	0.012 µg/mL
Solvent solubility (g/L at 20°C)	57 g/L in ethanol 10 g/L in hexane 390 g/L in xylene 320 g/L in cyclohexane 110 g/L in benzene 63 g/L in n-octanol 460 g/L in acetone
Vapor pressure at 20°C	0.25 mPa
Dissociation constant (pK _a)	N/A
Octanol/water partition coefficient Log(K _{ow})	log K _{OW} = 6.37 (at 23°C)
Half-Lives	Stable (hydrolysis at pH 5, 7, and 9) Stable (soil photolysis) 2 hours (aqueous photolysis) 258 days (aerobic soil metabolism) 518 days (aerobic aquatic metabolism) Stable (anaerobic aquatic metabolism)

3.0 Metabolism Assessment

3.1 Comparative Metabolic Profile

Rat Metabolism: Absorption of an oral dose of NC-129 was fairly rapid but incomplete at all dose levels. The presence of a significant percentage of excreted radioactivity in bile at the high dose (20-30%) indicates that some of the absorbed test material was excreted by this route and/or reabsorbed from the intestinal tract for subsequent biliary elimination. The gastrointestinal tract was a major site for distribution of NC-129 derived radioactivity, and the Bz-labeled test material showed higher tissue levels for many sites vs the Pz-labeled material at 72 and 168 hours post-dose. Repeated low oral dosing resulted in increased distribution to the eye of female rats only, while at the high dose, significant amounts of radioactivity were observed in fat for both labels at 168 hours post-dose in relation to other tissues. Feces was the major route for elimination of NC-129 derived radioactivity for both labels, representing 80-97% of the administered dose across all dose groups for both labels. For Bz-labeled test material, urinary elimination was slightly higher than for Pz-labeled test material. Plasma levels following a single low oral dose peaked at 2-3 hours post-dose for both labels, while at the high dose, peak levels were not achieved until approximately 24 hours post-dose. Decline in blood levels was more rapid for Bz-labeled test material than for Pz-labeled test material.

Urinary, fecal and liver metabolites of 14 were isolated and identified by 2-dimensional TLC, HPLC, and mass spectroscopy. At the low dose, the main urinary component from administration of Pz-labeled test material was the P-9 metabolite, or mercapturic acid conjugate of the pyridazinone moiety. The B-11 and B-15 metabolites were the main components in urine after administration of Bz-labeled test material. In feces, the main component observed after administration of both the Pz- and Bz-labels test material and representing approximately 20% of the dose, was unmetabolized parent compound. Some evidence of glucuronide conjugates of NC-129 was observed for biliary metabolites, but no definitive characterization could be performed. The liver contained several metabolites from administration of either Pz- or Bz-labeled test material, but these comprised 1.6% or less of the dose.

Plant Metabolism: The submitted plant metabolism studies indicate that pyridaben is highly metabolized, although the only major residue identified in primary crops was pyridaben *per se*. Several minor metabolites containing either the pyridazinone or phenyl ring were identified. These metabolites generally sum up to >10% of the total radioactive residues (TRR). Residues primarily remained on the surface of the fruit. The principal metabolic pathway apparently involves the photo-induced rearrangement of the parent, in which the phenyl group is substituted for the chlorine on the pyridazinone ring to form a thioalcohol. The other metabolic pathways involve the oxidation of the tertiary butyl groups or the hydrolytic cleavage and subsequent oxidation of the phenyl and pyridazinone moieties.

Rotational Crops: The submitted confined rotational crop study indicates that pyridaben is highly metabolized and the uptake into rotated crops was limited. Solvent extractable ¹⁴C-residues were comprised mainly of polar unknowns (described as multi-component fractions, with each component contributing <10% TRR), and minor amounts of the parent compound. Parent compound was identified in several commodities at levels less than 0.001 ppm.

Livestock Metabolism: The submitted livestock metabolism studies indicate that pyridaben is highly metabolized. The goat metabolism study indicated that parent is the only major residue in liver, while metabolites PB-7 and PB-9 are minor metabolites. No specific residue was firmly identified in other tissues or in milk. The metabolism study using laying hens indicated that PB-7 is the major metabolite (in liver) and parent was not found. The petitioner has proposed that the metabolism of pyridaben in goats and hens involves the hydroxylation of one or both of the tertiary butyl groups followed by oxidation of the hydroxyl group(s) to an acid. Data from urine and feces also suggests that some cleavage of the molecule occurs.

3.2 Nature of the Residue in Foods

3.2.1 Description of Primary Crop Metabolism

Plant metabolism data for pyridaben in/on eggplant were submitted in conjunction with PP#0E06068. Previously, metabolism data for pyridaben in/on apples and oranges were submitted in conjunction with PP#4E4370. These studies are briefly summarized below.

The results of pyridaben metabolism studies using oranges, apples, and eggplants were discussed in a meeting on 1/14/2004 (see Appendix 3.0 for additional information). At this meeting, it was concluded that the residues of concern in primary crops for tolerance setting purposes are pyridaben. Additionally, it was concluded that the residues of concern for risk assessment are pyridaben and all metabolites containing the pyridazinone ring. It was further concluded that for the proposed uses, no additional metabolism studies are required. If uses are proposed for grain crops and/or leafy vegetables, additional metabolism data using either a grain crop or leafy vegetable will be required.

Metabolism in Oranges (MRID No. 43258902):

BASF Corporation submitted data from a [^{14}C]pyridaben metabolism study on oranges. [^{14}C]Pyridaben was labeled in either the phenyl [^{14}C -Bz] or pyridazinone [^{14}C -Pz] ring. In this study, Hamlin and Valencia oranges were individually sprayed twice with [^{14}C -Pz] or [^{14}C -Bz]pyridaben at rates of 0.51 or 4.25 lb ai/A/application. For the low dose samples that were analyzed for metabolite identification, the total radioactive residues (TRR) in whole fruit were 0.048-0.122 ppm. For the high dose samples that were analyzed for metabolite identification, the TRR in the whole fruit were 0.368-0.966 ppm. For oranges collected from 0 to 14 days after the second low or high dose application, the majority of the TRR was recovered in the surface wash (57-95 % TRR) and the peel extract (0.7-24% TRR) with very little recovered in the pulp and juice (<7% TRR). The data indicate that the parent is the major residue in oranges. All other isolated metabolites accounted for <10% TRR and <0.010 ppm.

Based upon this study, the petitioner has proposed that the metabolism of pyridaben is similar in oranges and apples (see below) involving primarily photochemical, hydrolytic, and oxidative reactions. The principal metabolic pathway apparently involves the photo-induced rearrangement of the parent, in which the phenyl group is substituted for the chlorine on the pyridazinone ring to form a thioalcohol. The other metabolic pathways involve the oxidation of the tertiary butyl groups or the hydrolytic cleavage and subsequent oxidation of the phenyl and pyridazinone moieties.

Metabolism in Apple (MRID No. 43287601):

BASF Corporation submitted data from a [^{14}C]pyridaben metabolism study with apples. Metabolism studies were conducted in which apples received three spray treatments of [benzyl- ^{14}C]pyridaben at 1x the proposed rate and fruit were harvested 25 days later. Individual fruit were also treated by painting with either [benzyl- ^{14}C]pyridaben ([^{14}C -Bz]) or [pyridazinone-3,6- ^{14}C]pyridaben ([^{14}C -Pz]) at 40x the proposed rate and harvested after 40 days. TRR were 0.138 ppm in whole fruit from the 1x spray treatment and 5.310 and 5.411 ppm, respectively, from the fruit "painted" at 40x with [^{14}C -Bz] or [^{14}C -Pz]pyridaben. The majority of the radioactivity remained on the peel (80% of the TRR in the 1x treated apples and 95% in the samples from the 40x treatments). The parent compound was the major residue, accounting for 21% of the TRR (0.028 ppm) in the 1x treated apples and 50% of the TRR (2.6 to 2.8 ppm) in apples from both 40x treatments. All other isolated metabolites accounted for <10% TRR and <0.010 ppm.

Based upon this study, the petitioner has proposed that the metabolism of pyridaben in apples involves primarily photochemical, hydrolytic, and oxidative reactions. The principal metabolic pathway apparently involves the photo-induced rearrangement of the parent, in which the benzyl group is substituted for the chlorine on the pyridazinone ring to form a thioalcohol. The petitioner theorizes that exposure to sunlight causes formation of a delocalized $n-\pi^*$ excited state di-radical and a partial carbon-to-carbon bond that weakens the carbon-chloride and carbon-sulfur bonds. The photo-rearrangement product (PB-15) then forms after collapse of the proposed transition state and is either reduced to PB-17 or further oxidized to the D-1 dimer, PB-14, and PB-22. The other metabolic pathways involve the oxidation of the tertiary butyl groups or the hydrolytic cleavage and subsequent oxidation of the phenyl and pyridazinone moieties.

Metabolism in Eggplant (MRID No. 44939703):

The petitioner has submitted data concerning the metabolism of pyridaben in eggplants. In this study, the absorption, translocation, and metabolism of [^{14}C]pyridaben were studied with eggplants grown under greenhouse conditions.

Absorption and translocation study from leaves of eggplant seedlings: The absorption and translocation study was conducted by topically applying 100 μL of pyridaben (200 ppm solution) to a newly developed leaf. In another study, a leaf in the middle of the shoot (fourth leaf) was treated with 200 μL of pyridaben (200 ppm). Five and twelve days following application of [^{14}C]pyridaben to eggplant seedlings (leaf surface), a large majority of the radioactivity (84% to 103%) remained in/on the treated leaves. Only 0.2 to 1.1% of the radioactivity was translocated to other parts of the plant. The results indicate that translocation of pyridaben in eggplant seedlings is almost negligible.

Absorption, translocation, and metabolism study by mature eggplants: In this study, eggplants with fruits were treated with a 200 ppm solution of the test substance with the use of a brush. In a separate study, the fruits were covered with polyethylene bags and the remaining foliar portion (stems and leaves) were treated in a similar manner in order to determine if translocation to the fruits occurs. A large majority of the residue (> 80% of the TRR) was recovered in surface rinses of the fruit. The TRR concentrations of the surface rinses decreased gradually with increased pre-harvest intervals, while those in the methanol extract did not vary significantly with time. Bound residue levels increased over time, however, the concentrations were very low. For the plants with covered fruit, the TRR levels at a PHI of 14 days were low in the fruits (0.007 ppm and 0.006 ppm for Bz- and Pz-labels respectively). Thus, translocation from the stems and leaves of the plant to fruit was low.

Only the surface rinses of the leaves and fruit and the ethyl acetate phase of the methanol extracts were subjected to TLC analysis. The major identified residue was that of the parent compound which accounted for approximately 72 to 88% of the TRR. Residues of D-1 were low (0.004 to 0.008 ppm, <0.6% of the TRR).

3.2.2 Description of Livestock Metabolism

BASF has previously submitted metabolism studies for lactating goats and laying hens. Poultry feed items are not associated with the registered or proposed uses of pyridaben. Thus, the data concerning the metabolism of pyridaben in poultry are informational. Ruminant feed items are associated with citrus, apples, and almonds. Thus, the metabolism of pyridaben in ruminants is of concern. The results of pyridaben goat and laying hen metabolism studies were discussed at a meeting on 1/14/2004 (see Appendix 3.0 for additional information). At this meeting, it was concluded that residues of concern for tolerance setting and risk assessment in livestock are pyridaben and its metabolites PB-7 and PB-9.

Metabolism in Lactating Goats:

BASF Corporation submitted data depicting the metabolism of [^{14}C]pyridaben in lactating goats. Goats were dosed with [^{14}C]pyridaben radiolabeled either uniformly in the phenyl ring (^{14}C -Bz) or at the 3 and 6 positions of the pyridazinone ring (^{14}C -Pz). Four goats were orally dosed for 5 consecutive days with either [^{14}C -Pz]pyridaben or [^{14}C -Bz]pyridaben at a low (0.2 mg/day) or high (20 mg/day) dose. Based upon this study, the petitioner has proposed that the metabolism of pyridaben in goats involves the hydroxylation of one or both of the tertiary butyl groups followed by oxidation of the hydroxyl group(s) to an acid. Data from urine and feces also suggests that some cleavage of the molecule occurs.

Metabolism in Laying Hens:

BASF Corporation submitted data from a preliminary study and a final study depicting the metabolism of [^{14}C]pyridaben in laying hens. In both studies, hens were dosed with [^{14}C]pyridaben radiolabeled either uniformly in the phenyl ring (^{14}C -Bz) or at the C-3 and C-6 positions of the pyridazinone ring (^{14}C -Pz). In the preliminary study, four pairs of laying hens were orally dosed for 8 consecutive days with either [^{14}C -Pz]pyridaben or [^{14}C -Bz]pyridaben at a low (12.5 $\mu\text{g/day}$) or high (1 mg/day) dose.

Based upon these studies, the petitioner proposed that the metabolism of pyridaben in hens is similar to the metabolism in goats and involves the hydroxylation of one or both of the tertiary butyl groups followed by oxidation of the hydroxyl group(s) to an acid. Data from excreta suggests that some cleavage of the molecule also occurs in the GI tract.

3.2.3 Description of Rotational Crop Metabolism

Metabolism in Confined Rotational Crops - (MRID No. 44939702)

The petitioner has submitted data concerning the accumulation of [pyridazinone-3,6- ^{14}C]pyridaben in confined rotational crops planted 30 or 240 days following the last application of [^{14}C]pyridaben to the soil. In this study, solvent extractable ^{14}C -residues were comprised mainly of polar unknowns (described as multi-component fractions, with each component contributing <10% TRR), and minor amounts of the parent compound. Parent compound was identified in several commodities at levels less than 0.001 ppm.

3.3 Environmental Degradation

Pyridaben may be available in the soils during the first few weeks after application. Due to its low solubility (12 ppb) and high level of binding ($K_{ads}=108-6600$) it appears that pyridaben would remain bound to the soils during run-off events. Therefore, it would reach adjacent bodies of water when the run-off events are accompanied by erosion.

Pyridaben would remain bound to the soils and would be released slowly into the water. Once the chemical is dissolved, it may photolyze in clear, shallow waters. An Outdoor Aquatic Microcosms study and a Confined Aquatic Field Dissipation study seem to confirm that pyridaben will not persist under aquatic conditions.

Because of its relative immobility, pyridaben is not likely to reach subsurface soil environments (lower microbial activity) or ground water at significant concentrations.

The major routes of degradation/dissipation of pyridaben are aqueous photolysis (half-life 5 to 40 minutes) and soil photolysis (11 days). Hydrolysis (stable), aerobic (86 days) and anaerobic soil metabolism did not appear to play an important role in the degradation of pyridaben.

The body of evidence (four terrestrial field dissipation studies and a confined [^{14}C] terrestrial field dissipation study) indicates that pyridaben degradates are unlikely to leach: the degradates remain in the upper 0-6" (0-3" for the confined study) soil level.

3.4 Tabular Summary of Metabolites and Degradates

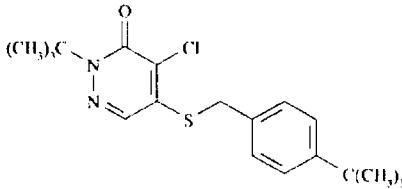
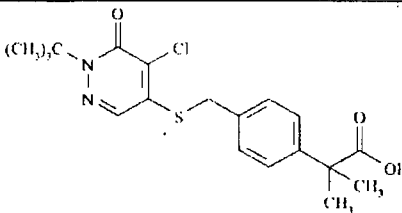
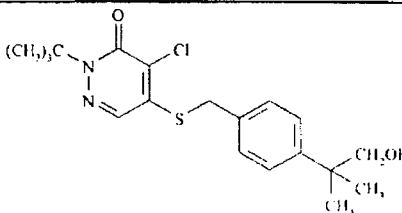
Table 3.4. Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM) ¹		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
Pyridaben (PB-1, NC-129) 2- <i>tert</i> -butyl-5-(4- <i>tert</i> -butylbenzylthio)-4-chloropyridazin-3(2 <i>H</i>)-one	Orange	36.3 (0.26)		
	Apple	51.5 (2.789)		
	Eggplant	88.3 (1.69)		
	Rotational Crops		1.5 (<0.001)	
	Ruminant	17.6 (0.025 - liver)	NF (all other tissues)	
	Poultry		NF (all tissues)	
	Rat	Yes		
	Water	Yes		
PB-7 2- <i>tert</i> -butyl-5-[4-(1-carboxy-1-methylethyl)benzylthio]-4-chloropyridazin-3(2 <i>H</i>)-one	Orange		NF	
	Apple		NF	
	Eggplant		NF	
	Rotational Crops		NF	
	Ruminant		7.9 (0.005 - liver only)	
	Poultry	31.5 (0.028 - liver)	NF (all other tissues)	
	Rat		Yes	
	Water		Yes	
PB-9 2- <i>tert</i> -butyl-5-[4-(1,1-dimethyl-2-hydroxyethyl)benzylthio]-4-chloropyridazin-3(2 <i>H</i>)-one	Orange	NF		
	Apple	NF		
	Eggplant	NF		
	Rotational Crops	NF		
	Ruminant		5.1 (0.007 - liver only)	

Table 3.4. Tabular Summary of Metabolites and Degradates

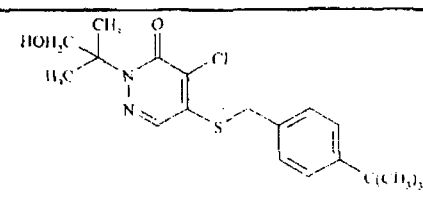
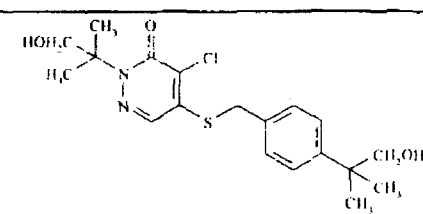
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM) ¹		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
	Poultry		1.8 (0.002 - liver only)	
	Rat		Yes	
	Water		Yes	
PB-11 5-(4- <i>tert</i> -butylbenzylthio)-4-chloro-2-(1,1-dimethyl-2-hydroxyethyl)pyridazin-3(2 <i>H</i>)-one	Orange		4.1 (0.002)	
	Apple		NF	
	Eggplant		NF	
	Rotational Crops		NF	
	Ruminant		58.1 (0.020 - kidney only)	
	Poultry		21.8 (0.006 - fat only)	
	Rat		Yes	
	Water		Yes	
PB-13 4-chloro-2-(1,1-dimethyl-2-hydroxy-ethyl)-5-[4-(1,1-dimethyl-2-hydroxy-ethyl)benzylthio]-pyridazin-3(2 <i>H</i>)-one	Orange		NF	
	Apple		NF	
	Eggplant		NF	
	Rotational Crops		NF	
	Ruminant		NF	
	Poultry	13.2 (0.001 - muscle only)		
	Rat		NF	
	Water		Yes	

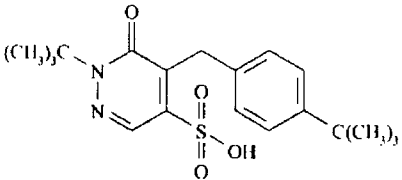
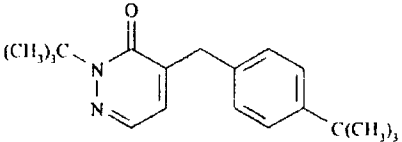
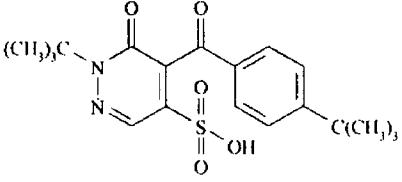
Table 3.4. Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM) ¹		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
PB-14 2- <i>tert</i> -butyl-4-(4- <i>tert</i> -butylbenzyl)pyridazin-3(2 <i>H</i>)-one-5-sulfonic acid	Orange		4.6 (0.004)	
	Apple		2.3 (0.123)	
	Eggplant		NF	
	Rotational Crops		NF	
	Ruminant		NF	
	Poultry		NF	
	Rat		NF	
	Water		Yes	
PB-17 2- <i>tert</i> -butyl-4-(4- <i>tert</i> -butylbenzyl)-pyridazin-3(2 <i>H</i>)-one	Orange		NF	
	Apple		1.4 (0.002)	
	Eggplant		NF	
	Rotational Crops		NF	
	Ruminant		NF	
	Poultry		NF	
	Rat		NF	
	Water		NF	
PB-22 2- <i>tert</i> -butyl-4-(4- <i>tert</i> -butylbenzoyl)pyridazin-3(2 <i>H</i>)-one-5-sulfonic acid	Orange		1.4 (0.001)	
	Apple		3.1 (0.004)	
	Eggplant		NF	
	Rotational Crops		NF	
	Ruminant		NF	
	Poultry		NF	
	Rat		NF	
	Water		NF	

Table 3.4. Tabular Summary of Metabolites and Degradates

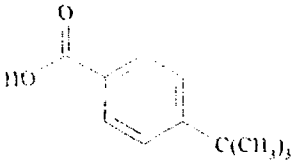
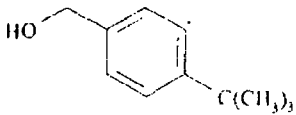
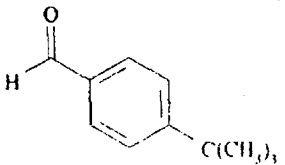
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM) ¹		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
B-1 4- <i>tert</i> -butyl-benzoic acid	Orange		Yes	
	Apple		6.0 (0.008)	
	Eggplant		NF	
	Rotational Crops		NF	
	Ruminant		NF	
	Poultry		NF	
	Rat		Yes	
	Water		Yes	
B-3 4- <i>tert</i> -butylbenzylalcohol	Orange		0.6 (0.001)	
	Apple		Yes	
	Eggplant		NF	
	Rotational Crops		NF	
	Ruminant		NF	
	Poultry		NF	
	Rat		Yes	
	Water		Yes	
B-5 4- <i>tert</i> -butylbenzaldehyde	Orange		NF	
	Apple		2.72 (0.144)	
	Eggplant		NF	
	Rotational Crops		NF	
	Ruminant		NF	
	Poultry		NF	
	Rat		NF	
	Water		NF	

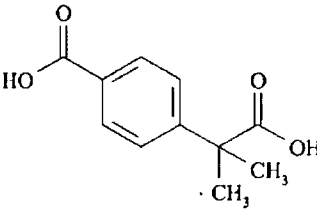
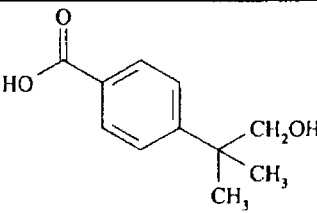
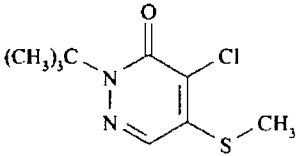
Table 3.4. Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM) ¹		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
B-7 2-(4-carboxyphenyl)-2-methylpropionic acid	Orange		NF	
	Apple		NF	
	Eggplant		NF	
	Rotational Crops		NF	
	Ruminant		NF	
	Poultry		NF	
	Rat		Yes	
	Water		Yes	
B-11 2-(4-carboxyphenyl)-2-methyl-1-propanol	Orange		2.7 (0.002)	
	Apple		NF	
	Eggplant		NF	
	Rotational Crops		NF	
	Ruminant		NF	
	Poultry		NF	
	Rat		Yes	
	Water		NF	
P-2 2-tert-butyl-4-chloro-5-methylthiopyridazin-3(2H)-one	Orange		NF	
	Apple		1.6 (0.087)	
	Eggplant		NF	
	Rotational Crops		NF	
	Ruminant		NF	
	Poultry		NF	
	Rat		NF	
	Water		NF	

Table 3.4. Tabular Summary of Metabolites and Degradates

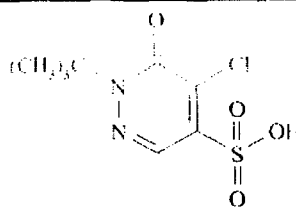
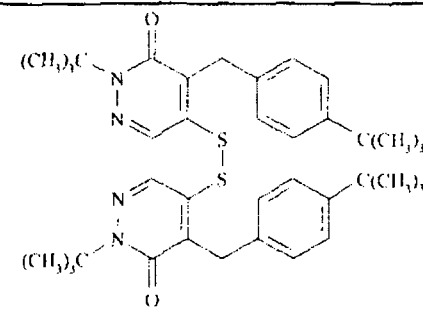
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM) ¹		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
P-14 2- <i>tert</i> -butyl-4-chloropyridazin-3(2 <i>H</i>)-one-sulfonic acid	Orange		3.6 (0.004)	
	Apple		NF	
	Eggplant		NF	
	Rotational Crops		NF	
	Ruminant		NF	
	Poultry		NF	
	Rat		NF	
	Water		NF	
D-1 Di[2- <i>tert</i> -butyl-4-(4- <i>tert</i> -butylbenzyl)-pyridazin-3(2 <i>H</i>)-one-5-yl]disulfide	Orange		NF	
	Apple		0.8 (0.039)	
	Eggplant		0.6 (0.007)	
	Rotational Crops		NF	
	Ruminant		NF	
	Poultry		NF	
	Rat		NF	
	Water		NF	

Table 3.4. Tabular Summary of Metabolites and Degradates

Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM) ¹		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
<p>Oranges: MRID No. 43258902; application rate: 2 x 4.25 lb ai/A/application (8.5x rate) or 2 x 0.51 lb ai/A/application (1x rate); 7-day PHI.</p> <p>Apples: MRID No. 43287601; application rate: 3 x 300 g ai/ha (1x rate); ~ 30 days between applications, 25-day PHI; painted w/ ¹⁴C-pyridaben at 1 mg/apple; 40-day PHI.</p> <p>Eggplant: MRID No. 44939703 100µL of pyridaben (200 ppm solution) to a newly developed leaf; a middle leaf treated with 200 µl. of pyridaben (200 ppm solution); 5- & 12- day PHIs.</p> <p>Ruminant: MRID No. 432589-18; dosed for 5 days at 0.2 mg/day (7.8 ppm) or 20 mg/day (6.9 ppm) dose; the 7.8 ppm dose represents an exaggerated feeding level of 4.4x and 6.2x for beef and dairy cattle, respectively.</p> <p>Poultry: MRID No. 432589-03; dosed for 8 days at a low (12.5 µg/day) or high (1 mg/day) dose. Based upon feed consumption data, the doses were equivalent to pyridaben dietary levels of approximately 0.1 ppm for the low dose and 7.5 to 7.9 ppm for the high dose. Dietary-exposure of poultry to pyridaben residues is not expected as a result of the proposed uses.</p> <p>Rotational Crops; MRID No. 44939702; 2 applications directed to the soil with 35 days between applications at a rate of 0.66 lbs ai/A for a total of 1.32 lbs ai/A (1.1x rate); mustard greens, radish, and winter wheat were planted 30 days final application and radishes, Swiss chard, and sorghum were planted 240 days post treatment.</p> <p>Rat: MRID No. 43258901; dosing level:3 mg/kg or 30 mg/kg for 14 days.</p>				

3.5 Toxicity Profile of Major Metabolites and Degradates

There are several minor metabolites containing either the pyridazinone or phenyl ring. These metabolites generally sum up to >10% of the TRR. HED believes that the metabolites containing the pyridazinone ring share similar toxicity to the parent based on their structural similarity to the parent (i.e., possessing the pyridazinone ring). Metabolites containing only the phenyl moiety are anticipated to be significantly less toxic than the parent.

3.6 Summary of Residues for Tolerance Expression and Risk Assessment

3.6.1 Tabular Summary

Table 3.6 Residues of Concern in Crops, Livestock, Rotational Crops, and Water		
Matrix	Tolerance Expression	Residues for Risk Assessment
Crops	Pyridaben only.	Pyridaben plus all metabolites containing the pyridazinone ring.
Livestock	Pyridaben and its metabolites PB-7 and PB-9.	Pyridaben and its metabolites PB-7 and PB-9.
Rotational Crops	Pyridaben only.	Pyridaben only.
Water	N/A	Pyridaben only.

3.6.2 Rationale for Inclusion of Metabolites and Degradates

Plants: Plant metabolism studies using oranges, apples, and eggplant indicated that parent is the only major residue (>10% TRR). There are several minor metabolites containing either pyridazinone ring or the phenyl ring. These metabolites generally sum up to >10% of the TRR. HED believes that the metabolites containing the pyridazinone ring share similar toxicity to the parent, based on their structural similarity to the parent (i.e., possessing the pyridazinone ring). Metabolites containing only the phenyl moiety are anticipated to be significantly less toxic than the parent. For risk assessment purposes, parent and all metabolites containing the pyridazinone ring are the residues of concern. For the tolerance expression, pyridaben is the residue of concern since it is the most abundant residue and can serve as a measure of misuse.

HED has calculated a ratio of residues containing the pyridazinone ring to pyridaben based upon the low-dose pyridaben apple and orange metabolism studies. The low-dose studies were conducted to mimic the proposed use of pyridaben on oranges and apples. The ratio has been determined to be 1.47.

HED concludes for **chronic dietary-exposure analysis** tolerance levels should be multiplied by the ratio of pyridaben plus pyridazinone ring containing metabolites to pyridaben in order to account for all of the residues of concern for risk assessment. For the **acute dietary-exposure analysis**, residue values from crop field trials should be multiplied by the ratio of pyridaben plus pyridazinone ring containing metabolites to pyridaben in order to account for all of the residues

of concern for risk-assessment. These values were used to construct residue distribution files for the acute probabilistic dietary-exposure assessment.

Livestock: The goat metabolism study indicated that parent is the only major residue in liver, while metabolites PB-7 and PB-9 are minor metabolites (3.8 to 7.9% TRR). No specific residue was firmly identified in other tissues or in milk. The metabolism study using laying hens indicated that PB-7 is the major metabolite (in liver) and parent was not found. HED considers PB-7 and PB-9 to have similar toxicity to the parent based on their structural similarity to the parent and concluded that the residues of concern for risk assessment and the tolerance expression are pyridaben, PB-7 and PB-9. All three compounds are determined by the livestock method. Parent and PB-7 were found in milk and tissues (liver, fat), respectively, in the cattle feeding study.

Rotational Crops: The confined rotational crop study found that the ^{14}C -residues were comprised mainly of polar unknowns (described as multi-component fractions, with each component contributing <10% TRR), and minor amounts of pyridaben. Pyridaben was identified in several commodities at levels less than 0.001 ppm. HED concludes that parent only is the residue of concern for rotational crops.

Drinking Water: Environmental fate studies indicated that pyridaben is stable, has low water solubility (12 ppb), and a high level of binding to soil ($K_{\text{ads}}=108\text{-}6600$). It appears that pyridaben would remain bound to the soils during run-off events. Because of its relative immobility, pyridaben is not likely to reach subsurface soil environments (lower microbial activity) or ground water at significant concentrations. Lab studies indicated that the major routes of degradation/dissipation of pyridaben are aqueous photolysis (half-life 5 to 40 minutes) and soil photolysis (11 days). Based on the use pattern and the stability of pyridaben, aqueous photolysis and soil photolysis are likely to occur after the application of pyridaben. The only major degradate identified in any fate study was B-3 (27% of the applied dose) in aqueous photolysis. Based on the structure, HED believes that B-3 is likely to be significantly less toxic than the parent. B-3 is also not likely to be persistent in drinking water due to its potential to be oxidized to the benzoic acid degradate in the environment. HED has concluded that B-3 can be excluded as a residue of concern. Among all the minor degradates, HED believes that none of them will likely be significantly more toxic than the parent. Thus, HED concludes that pyridaben is the residue of concern to be included in the drinking water assessment.

4.0 Hazard Characterization/Assessment

On June 17, 2003, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the database for pyridaben with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to pyridaben was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document. This section is an update of the prior decision. RAB3 in consultation with HED's Hazard Scientific Policy Council (HaSPoC) reevaluated the database for the value of the 10x database

uncertainty factor (May 24, 2004). RAB3 also met with the registrant on September 1, 2004 to discuss the status of the DNT study. It was concluded, based on the available toxicology evidence, that pyridaben is not a neurotoxicant and that there is no datagap for the Developmental Neurotoxicity study. Therefore, the 10X database uncertainty factor is not needed.

4.1 Hazard Characterization

Acute toxicology studies conducted on pyridaben demonstrate that pyridaben has moderate to mild toxic effects at relatively high doses. Pyridaben was classified as Toxicity Category III based upon the acute oral, dermal, inhalation, and eye irritation studies. Pyridaben is a slight ocular irritant, and is not a dermal irritant (Toxicity Category IV) or sensitizer. However, severe dermal irritation was observed after multiple dermal exposures of technical pyridaben in the dermal developmental toxicity study in rabbits.

There are guideline acute and subchronic neurotoxicity studies as well as developmental toxicity studies in rats and rabbits (by the oral or dermal routes) and a multi-generation reproduction study in rats. The developmental and reproduction studies show no effects on reproduction and no increased susceptibility of rats or rabbits to *in utero* and/or *postnatal* exposure to pyridaben as demonstrated by higher lowest-observable-adverse-effect-levels (LOAELs) than those needed to produce maternal toxicity. In the acute and subchronic neurotoxicity studies, moderate clinical signs were seen only at relatively high doses; the effects were suggestive of neurotoxicity, but there were no supportive neuropathological (gross pathology including brain weights or histopathology) effects.

In a 90-day rat feeding study, plasma cholinesterase inhibition (ChEI) was reported in females only at the highest dose tested. Pyridaben may have some flexibility and charge characteristics which would allow it to interact with the cholinesterase receptor in some tissues, but this response is not indicative of a neurotoxic mode of action. In the subchronic and chronic dog studies, ptialism, emesis, soft stools and decreases in body weight gain were observed.

The most common toxicity endpoint across the various studies and tested species was decreased body weight/weight gain followed by decreased feed consumption and/or feed efficiency. There is no evidence of increased susceptibility of fetuses or pups in any of these endpoints.

In a rat metabolism study, pyridaben seems to be rapidly metabolized and metabolism is complex with several pathways of biotransformation. The gastrointestinal tract was the major site for distribution and elimination. The highest residues were found in liver, pancreas, spleen, kidney, lymph node, and fat. Several metabolites (totaling up to 20-30 metabolites) were identified in urine and feces.

There was lack of evidence of carcinogenicity in the acceptable studies in male and female rats and mice and pyridaben was classified as a "not likely" human carcinogen (Group E). Also, there was no evidence that pyridaben is mutagenic based on acceptable *in vitro* and *in vivo* mutagenicity studies.

Table 4.1a Acute Toxicity Profile - Pyridaben				
Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
870.1100 (81-1)	Acute Oral	42680119	LD ₅₀ (M/F) = 1100/570 mg/kg	III
870.1200 (81-2)	Acute Dermal	42680121	LD ₅₀ = >2000 mg/kg	III
870.1300 (81-3)	Acute Inhalation	42680122	LC ₅₀ (M/F) = 0.66/0.64 mg/L	III
870.2400 (81-4)	Primary Eye Irritation	42680123	Slight ocular irritant in rabbits.	III
870.2500 (81-5)	Primary Skin Irritation	42680124	Not a dermal irritant in rabbits.	IV
870.2600 (81-6)	Dermal Sensitization	42680125	Not a dermal sensitizer in guinea pigs.	NA

Table 4.1b Subchronic, Chronic and Other Toxicity Profile for Pyridaben

Guideline No. / Study Type	MRID No. / (Year)	Results
870.3100 (82-1-a) 13- Week Subchronic-Feeding-Rat	42680126 (1988)	NOAEL in males = 65 ppm (4.94 mg/kg/day). NOAEL in females = 30 ppm (2.64 mg/kg/day). Decreased body weight gain, food consumption, food efficiency and altered clinical pathology parameters in males observed at the LOAEL of 155 ppm (11.55 mg/kg/day) . Decreased body weight gain and food efficiency in females observed at the LOAEL of 65 ppm (5.53 mg/kg/day) .
870.3100 (82-1-a) 13 - Week Subchronic-Feeding-Mouse	43064101 (1988)	NOAEL = 30 ppm (males: 4.07 & females 4.92 mg/kg/day). Decreased body weight gain observed at the LOAEL of 90 ppm (males: 13.02 & females: 14.65 mg/kg/day) .
870.3150 (82-1-b) 13 Week Subchronic-Feeding - Dog	42680127 (1989)	NOAEL = 1.0 mg/kg/day. Increased incidence of clinical signs and decreased body weight gain in both sexes observed at the LOAEL of 4.0 mg/kg/day.
870.3150 (82-1-b) 13 Week Subchronic-Oral Dog (Supplement)	42680128 (1989)	NOAEL = < 2.4 mg/kg/day. Increased incidence of clinical signs and depletion of fat in all treated animals observed at the LOAEL of ≤ 2.4 mg/kg/day.
870.3465 (82-4) 30-Day Inhalation Toxicity - Rat	42680131 (1989)	NOAEL = 0.001 mg/L. Increased incidence of clinical signs and clinical chemistry changes in both sexes and decreased body weight gain in females observed at the LOAEL of 0.003 mg/L.
870.3200 (82-2) 21-Day Dermal Toxicity - Rat	42680130 (1992)	NOAEL = 100 mg/kg/day. Decreased body weight gain observed in females at the LOAEL of 300 mg/kg/day. Dermal irritation NOAEL = 1000 mg/kg/day.
870.3700 (83-3-a) Developmental Oral Toxicity - Rat	42680139 (1988)	Maternal NOAEL = 4.7 mg/kg/day. Decreased body weight, body weight gain and food consumption observed at the Maternal LOAEL of 13 mg/kg/day. Developmental NOAEL = 13 mg/kg/day. Decreased fetal body weight and incomplete ossification of bones was observed at the Developmental LOAEL of 30 mg/kg/day.
870.3700 (83-3-b) Developmental Dermal Toxicity - Rabbit	42680416 (1995)	Maternal NOAEL = 70 mg/kg/day. Decreased body weight loss and food consumption at the Maternal LOAEL of 170 mg/kg/day. Developmental NOAEL = 170 mg/kg/day. Increased incidence of fetuses with retarded growth (incompletely ossified skull) was observed at the Developmental LOAEL of 450 mg/kg/day.
870.3700 (83-3-b) Developmental Oral Toxicity - Rabbit	42680141 42680142 (1988)	Maternal NOAEL = Not established. Decreased body weight gain, and food consumption at the Maternal LOAEL of 1.5 mg/kg/day. Developmental NOAEL = 15 mg/kg/day (HDT). No toxicity was observed at any dose, therefore, the NOAEL is equal to or greater than highest dose tested.

Guideline No. / Study Type	MRID No. / (Year)	Results
870.3800 (83-4) 2 - Generation Reproductive Toxicity Study - Rat	42680144 (1990)	Parental NOAEL = 28 ppm (males: 2.20 & females: 2.41 mg/kg/day). Decreased body weight, body weight gains, and food efficiency observed at the Parental LOAEL of 80 ppm (males: 6.31 & 7.82 mg/kg/day). Offspring NOAEL = 28 ppm (2.2 mg/kg bw/day). Decreased pup body weights from PND 7-25 and decreased pup body weight gains throughout lactation at the Offspring Toxicity LOAEL of 80 ppm (6.3 mg/kg bw/day). Reproductive NOAEL = 80 ppm (males: 6.31 & 7.82 mg/kg/day). Reproductive LOAEL = >80 ppm (males: 6.31 & 7.82 mg/kg/day).
870.4100 (83-1-b) 1 Year Chronic Feeding - Dog	42680134 (1990)	NOAEL = Not established. Increased clinical signs of toxicity in both sexes and decreased body weight gain in females observed at the LOAEL of 1.0 mg/kg/day.
870.4100 (83-1-b) 1 Year Chronic - Feeding- Dog	42680135 (1991)	NOAEL = Not established. Increased clinical signs of toxicity in both sexes and decreased body weight gain in females observed at the LOAEL of 0.5 mg/kg/day.
870.4200 Carcinogenicity - 78-week - Mouse	42680137 (1990)	NOAEL = 25 ppm (males & females 2.78 mg/kg/day). Decreased body weight gain, decreased food efficiency and changes in organ weights and histopathology (males) observed at the LOAEL of 80 ppm (MTD) (males: 8.88 & females: 9.74 mg/kg/day).
870.4300 (83-5) Chronic Toxicity / Carcinogenicity - 2 Yr - Rat	42680132 (1990)	NOAEL = 28 ppm (males: 1.13 & females: 1.46 mg/kg/day). Decreased body weight and body weight gain observed in males and females, and decreased ALT in males at the LOAEL of 120 ppm (males: 5 & females: 6.52 mg/kg/day). There was no evidence of carcinogenicity.
870.5100 (84-2-a) Gene Mutation - <i>Salmonella</i>	43680145 (1986)	Negative
870.5300 (84-2-a) Gene Mutation in Chinese Hamster Cultured V-79	43680147 43680417 (1995) 42680149 (1989)	Negative
870.5385 (84-2-b) Mutagenic - Structural Chromosome Aberration - Micronucleus - mouse	42680147 (1988)	Negative
870.5500 (84-2-b) Mutagenic- Structural Chromosome Aberration -In vitro Cytogenetics - Chinese Hamster	43680148 (1989)	Negative

Guideline No. / Study Type	MRID No. / (Year)	Results
84-4 Mutagenic- DNA Damage/Repair- E. Coli	42680146 (1986)	Negative
870.6200 (81-8) Acute Oral Neurotoxicity - Rat	43680412 (1995)	NOAEL = 50mg/kg (both sexes). Clinical signs of toxicity, decreased food consumption and body weight gain in both sexes observed at the LOAEL of 100. No neuropathological effects were observed.
870.6200 (82-7) Oral 13 week Neurotoxicity - Rat	43680413 (1995)	NOAEL = 100 ppm (males: 8.5 & females: 9.3 mg/kg/day). Decreased body weight, body weight gain, food consumption and food efficiency in both sexes observed at the LOAEL of 350 ppm (MTD) (males: 28.8 & females: 31.1 mg/kg/day). No neuropathological effects were observed.
870.7485 (85-1) Metabolism - Rat	43258901 (1994)	Rapidly metabolized. Gastrointestinal tract was the major site for distribution, and elimination. Highest residues were found in liver, pancreas, spleen, kidney, lymph node and fat. Parent compound was metabolized to 20 -30 metabolites and were resolved in urine and feces.

4.2 FQPA Hazard Considerations

On June 17, 2003, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the database for pyridaben and evaluated the potential for increased susceptibility of infants and children from exposure to pyridaben as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document. The HIARC concluded that a developmental neurotoxicity (DNT) study was required for pyridaben hazard characterization and recommended that the 10x FQPA Safety Factor (UF_{DB} for lack of a DNT) be retained when assessing acute dietary exposure scenarios and be removed for chronic dietary exposure scenarios.

On September 1, 2004, BASF provided HED with an overview of developmental, reproductive and neurotoxicity test results and a discussion on the need for the 10x database uncertainty factor.

The RAB3 Risk Assessment Team and HED's Hazard Scientific Policy Council reevaluated the toxicity database for pyridaben, and concluded that the available toxicology database is adequate for an FQPA determination and that a DNT is not required. The available toxicity data do not indicate that pyridaben is a neurotoxicant. It was concluded, based on the available toxicology evidence, that pyridaben is not a neurotoxicant and that there is no datagap for the Developmental Neurotoxicity study. Therefore, the 10X database uncertainty factor is not needed.

4.2.1 Adequacy of the Toxicity Data Base

The toxicology data base for pyridaben is adequate to evaluate the potential increased susceptibility of infants and children. Relevant studies include prenatal developmental toxicity studies in the rat and rabbit, a 2-generation reproduction study in rats with neurotoxicity parameters, and acute and subchronic neurotoxicity studies in the rat.

4.2.2 Evidence of Neurotoxicity

No neurobehavioral alterations or evidence of neuropathological effects were observed in the available guideline studies with rats, dogs, and mice. Pyridaben has a weak neurotoxicity signs as demonstrated in the acute neurotoxicity study in rats. Piloerection, hypoactivity, tremors, and partially closed eyes were observed in animals in the 100 mg/kg bw group. There was inhibition of plasma cholinesterase activity at the highest dose (27.7 mg/kg bw/day) in females in the 90 day rat feeding study. There were transient (appearing at Week 8, but not at Weeks 4 or 13), poorly coordinated righting reflex in high dose males (28.8 mg/kg bw/day) observed in the absence of other neurotoxicity or neuropathology in the subchronic neurotoxicity study.

Rat Acute Neurotoxicity (MRID No. 43680412): In an acute neurotoxicity study (MRID 43680412), 10 CD rats/sex/group received NC-129 [pyridaben] (98.0% purity, Lot/Batch No. 129 T 8605) in a 1% aqueous carboxymethylcellulose at dose levels of 0, 50, 100 or 200 mg/kg bw (a.i. equivalents: 0, 44.3, 79.6, and 190 mg/kg bw for males and 0, 44.5, 99.7 and 190 mg/kg bw

for females, respectively). Observations were made for clinical signs of toxicity and mortality for 14 days. Additional observations included: body weight and body weight gain, food consumption, neurobehavioral evaluations (FOB, motor activity) and microscopic examination of the central and peripheral nervous system.

Survival and microscopic examination of the central and peripheral nervous system were unaffected by treatment with NC-129. A dose-dependent increase in clinical signs of toxicity (piloerection, hypoactivity, tremors and partially closed eyes) was observed in males and females (piloerection only) in the 100 and 200 mg/kg bw groups. Hypoactivity, tremors and partially closed eyes were observed in females in the 200 mg/kg bw group. These clinical signs were absent by day 4. Body weight gain was decreased in males and females in the 100 (83 and 64% of controls, respectively) and 200 (26% of controls; females lost 4 g) mg/kg bw groups from day 0-5. On the day of dosing, food consumption was decreased in males and females in the 50, 100 and 200 mg/kg bw groups (59, 57 and 27% of controls for males, 70, 55 and 50% of controls for females). Reduced body temperature was observed in males in the 200 mg/kg bw group within 6 hours of dosing (peak time of effect). Reduced motor activity (rearing and cage floor activity) ($\geq 44\%$) was observed in males in the 200 mg/kg bw group on day 1.

The LOAEL is 80 mg/kg bw based on an increase in the incidence of piloerection, hypoactivity, tremors and partially closed eyes, decreases in body weight gain and food consumption in both sexes. The NOAEL is 44 mg/kg bw.

Rat Subchronic Neurotoxicity (MRID No. 43680413): In a subchronic neurotoxicity study (MRID 43680413), 10 CD rats/sex/group received NC-129 (98.0% purity, Lot/Batch No. 129 T 8605) at dietary levels of 0, 30, 100 or 350 ppm (0, 2.5, 8.5 and 28.8 mg/kg bw/day in males; 0, 2.8, 9.3 and 31.1 mg/kg bw/day in females) for 13 weeks. Observations were made for clinical signs of toxicity and mortality. Additional observations included: body weight and body weight gain, food consumption, neurobehavioral evaluations (FOB, motor activity) and microscopic examination of the brain, spinal cord, eyes and optic nerve, pituitary and sciatic and tibial nerves of 5 rats/sex from the control and 350 ppm groups. Brain and pituitary weights were determined.

No deaths occurred. Clinical signs of toxicity (piloerection and hunched posture) were observed in several male and a few females in the 350 ppm group. Body weight gain was decrease in male (59% of controls) and in females (62% of controls) in the 350 ppm group over 13 weeks. Food consumption was decreased in males (76% of controls) and in females (79% of controls) over 13 weeks. Food efficiency was also decreased in males and females in the 350 ppm group over 13 weeks. Exophthalmos was observed in males in the 350 ppm group. Piloerection was observed in females in the 100 and 350 ppm groups. The righting reflex was impaired in males in the 350 ppm group.

The LOAEL is 350 ppm (28.8 mg/kg bw/day in males and 31.1 mg/kg bw/day in females based on decrease in body weight gain food consumption, food efficiency and impairment of the righting reflex in males. The NOAEL is 100 ppm (8.5 mg/kg bw/day in males and 9.3 mg/kg bw/day in females.

4.2.3 Developmental Toxicity Studies

Rat Oral Developmental Toxicity (MRID No. 42680139): In a prenatal developmental toxicity study (MRID 42680139), 22 Sprague Dawley female rats/group received NC-129 [pyridaben](98.0% purity, Lot/Batch No. 129 T 8605) by gavage at dose levels of 0, 2.5, 5.7, 13.0 or 30.0 mg/kg bw/day (equivalent to 0, 1.8, 4.7, 12.5 or 26.7 mg/kg bw/day, respectively, based on mean concentrations of 0, 72%, 82%, 96% and 89% for solutions making up the 0, 2.5, 5.7, 13.0 and 30.0 mg/kg bw/day targeted doses, respectively) from gestation days [GDs] 6 through 15. Observations were made for clinical signs of toxicity, mortality, body weight and body weight gain, food consumption, placental weights, number of corpora lutea, implantation sites, resorptions (early and late), live and dead fetuses, fetal sex and weight, external, visceral and skeletal examination of fetuses. Maternal survival was unaffected by treatment with NC-129. Maternal body weight gain was significantly decreased in the 13.0 and 30.0 mg/kg bw/day groups (86% and 54% of controls, respectively) during the dosing period (from GDs 6-15) and in the 30 mg/kg bw/day group (83% of controls) from GD 6-20. Compensatory weight gain was increased in the 30.0 mg/kg bw/day group (116% of controls) from GDs 16-20. Food consumption was significantly decreased in dams in the 13.0 and 30.0 mg/kg bw/day groups during the dosing period, GDs 6-15, (88% and 73% of controls, respectively). **The maternal LOAEL is 12.5 mg/kg bw/day based on decreases in body weight gain. The maternal NOAEL is 4.7 mg/kg bw/day.** Developmental toxicity was observed at 30.0 mg/kg bw/day and consisted of significantly decreased fetal body weights (94% of controls) and incomplete ossification. **The developmental LOAEL is 26.7 mg/kg bw/day based on decreased fetal body weights and incomplete ossification. The developmental NOAEL is 12.5 mg/kg bw/day.**

Rabbit Oral Developmental Toxicity (MRID No. 42680142): In a prenatal developmental toxicity study (MRID 42680142), 19 or 20 female New Zealand white rabbits/group received NC-129 [pyridaben](98.0% purity, Lot/Batch No. 129 T 8605) by gavage at dose levels of 0, 1.5, 5 or 15 mg/kg bw/day from gestation days [GDs] 6 through 19. Observations were made for clinical signs of toxicity, mortality, body weight and body weight gain, food consumption, placental weights, number of corpora lutea, implantation sites, resorptions (early and late), live and dead fetuses, fetal sex and weight, external, visceral and skeletal examination of fetuses. Maternal survival was unaffected by treatment with NC-129. Maternal body weight gain was significantly decreased in the 15 mg/kg/day groups (9% of controls) and decreased (non-significantly) in the 5 mg/kg bw/day group (48% of controls) during the dosing period (GDs 6-12). Food consumption was significantly decreased in does in the 15 mg/kg bw/day group during the dosing period, GDs 6-19 (60% of controls) and decreased (non-significantly) in the 5 mg/kg/day group (77% of controls). There was an increase in the incidence of abortion in does in the 15 mg/kg bw/day group. **The maternal LOAEL is 15 mg/kg bw/day based on decreases in body weight, body weight gain and food consumption, and abortions. The maternal NOAEL is 5 mg/kg bw/day.**

There was an increase in abortions and an increase in the "12/13" and "13/13" ribs in fetuses in the 15 mg/kg bw/day group. **The developmental LOAEL is 15 mg/kg bw/day based on an**

increase in abortions and an increase in the "12/13" and "13/13" ribs. The developmental NOAEL is 5 mg/kg bw/day.

Note: It should be noted that 2 abortions occurred in the high dose group at days 19 and 25, also, that the increase in 12/13 and 13/13 ribs is a variation not associated with any change in function.

Rabbit Dermal Developmental Toxicity (MRID No. 43680416): In a prenatal developmental toxicity study (MRID 43680416), 14 or 15 female New Zealand white rabbits/group received NC-129 [pyridaben](99.7% purity, Lot/Batch No. 900304) by dermal application at dose levels of 0, 70, 170 or 450 mg/kg bw/day from gestation days [GDs] 6 through 19. Observations were made for clinical signs of toxicity, mortality, body weight and body weight gain, food consumption, placental weights, number of corpora lutea, implantation sites, resorptions (early and late), live and dead fetuses, fetal sex and weight, external, visceral and skeletal examination of fetuses. Maternal survival was unaffected by treatment with NC-129. Moderate to severe skin reactions (erythema, edema and/or eschar formation) was observed at all dose levels. The skin reactions increased in severity with increasing dose. Mean maternal body weight loss of 23 and 14 g was observed in the 170 and 450 mg/kg bw/day groups, respectively, during the dosing period (GDs 6-19). Food consumption was significantly decreased in does in the 170 (76% of controls) and 450 mg/kg bw/day (68% of controls) groups during the dosing period (GDs 6-19). **The maternal systemic LOAEL is 170 mg/kg bw/day based on decreases in body weight and food consumption. The maternal systemic NOAEL is 70 mg/kg bw/day.**

There was an increase in incomplete ossification of the skull in fetuses in the 450 mg/kg bw/day group. **The developmental LOAEL is 450 mg/kg bw/day based on growth retardation. The developmental NOAEL is 170 mg/kg bw/day.**

4.2.4 Reproductive Toxicity Study

Rat 2-Generation Reproduction Study (MRID No. 42680144): In a 2-generation reproduction study (MRID 42680144), CD rats of Sprague-Dawley origin from Charles River U.K. (25 rats/sex/group) received NC-129 [pyridaben](98.0% purity, Lot/Batch No. 129 T 8605) at dietary concentrations of 0, 10, 28, or 80 ppm in the diet (equivalent to 0, 0.78, 2.20, 6.31 mg/kg bw/day for males and 0, 0.94, 2.41, 7.82 mg/kg bw/day for females, respectively). The protocol was a standard reproduction study with litters culled to 4 animals per sex on post partum day 4. In addition, physical development was assessed on a litter basis by recording the day of onset and completion of pinna unfolding, hair growth, tooth eruption and eye opening. Further, auditory and visual function were assessed using the startle response and examination of pupil closure and assessment of the visual placing response.

Parental (systemic) toxicity was noted in the form of decreased body weights (86-90% of controls), body weight gains (85-88% of controls) and food efficiency (89-95% of controls) in the high dose males. The high dose females showed an occasional similar effect although not as pronounced. The high dose females showed slightly decreased body weights (93-96% of controls) and body weight gains (93-97% of controls) during gestation with an apparent rebound

in body weight gains noted during the lactation period. **The LOAEL for parental (systemic) toxicity is 80 ppm (6.3 mg/kg bw/day for males; 7.8 mg/kg bw/day for females) based on decreased body weights, body weight gains and food efficiency. The NOAEL for parental systemic toxicity is 28 ppm (2.2 mg/kg bw/day for males; 2.4 mg/kg bw/day for females).**

Fetuses in the high dose group had decreased body weights from post natal days (PNDs) 7-25. The high dose litters gained less weight than control (85-86% of controls) throughout the lactation period. **The LOAEL for offspring toxicity is 80 ppm (6.3 mg/kg bw/day) based on decreased pup body weights from PND 7-25 and decreased pup body weight gains throughout lactation. The NOAEL for offspring toxicity is 28 ppm (2.2 mg/kg bw/day).**

There was no effect on reproductive parameters at the dose levels tested in this study. **The LOAEL for reproductive toxicity is greater than 80 ppm (> 6.3 mg/kg bw/day [HDT]). The NOAEL is equal to or greater than 80 ppm \geq 6.3 mg/kg bw/day [HDT]).**

4.2.5 Additional Information from Literature Sources

Open literature searches identified no relevant additional information concerning the toxicity of pyridaben.

4.2.6 Pre-and/or Postnatal Toxicity

There is no concern for pre- and/or postnatal toxicity resulting from exposure to pyridaben.

4.2.6.1 Determination of Susceptibility

HED concluded that there is no quantitative and/or qualitative evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to pyridaben. There is no evidence of increased quantitative and/or qualitative susceptibility to pyridaben following pre-natal exposure in a 2-generation reproduction study(s) in the rat.

4.2.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre and/or Post-natal Susceptibility

HED concluded that there are no concerns or residual uncertainties for pre-/post-natal toxicity.

4.3 Recommendation for a Developmental Neurotoxicity Study

Pyridaben elicited weak clinical signs (piloerection, hypoactivity, tremors) in an acute neurotoxicity study and a transient effect on the righting reflex in a subchronic feeding study. These signs were initially judged to be evidence of neurotoxicity and a DNT study was required (HLARC, June 17, 2003). However, further evaluation of the entire weight of evidence has led to the conclusion that these signs are non-specific in nature and not indicative of a direct effect on the nervous system.

4.3.1 Evidence that supports requiring a Developmental Neurotoxicity study

Pyridaben has a weak neurotoxicity signs as demonstrated in the acute neurotoxicity study in rats. Piloerection, hypoactivity, tremors, and partially closed eyes were observed in animals in the 100 mg/kg bw group. In the subchronic neurotoxicity study, transient poorly coordinated righting reflex was observed in high dose males (28.8 mg/kg bw/day) in the absence of other neurotoxicity or neuropathology in the subchronic neurotoxicity study. Inhibition of plasma cholinesterase activity at the highest dose (27.7 mg/kg bw/day) in females in the 90 day rat feeding study.

4.3.2 Evidence that supports not requiring a Developmental Neurotoxicity study

- The lack of evidence for abnormalities in the development of the fetal nervous system including the prenatal developmental toxicity studies in either rats (oral gavage up to 1000 mg/kg/day) or rabbits (oral greater than 15 mg/kg/day and dermal up to 450 mg/kg/day) and the 2-generation reproduction study in rats (up to 6.31 mg/kg/day).
- The levels at which effects occurred in the acute and subchronic neurotoxicity studies were the highest doses tested where significant toxicity, other than neurotoxic signs were noted. Transient piloerection and hypoactivity were noted in the mid dose males (100 mg/kg/day) and piloerection, hypoactivity, tremors and partially closed eyes were observed in animals in the 200 mg/kg bw group (highest dose tested) in the acute neurotoxicity study in rats. There was also transient (only one week), poorly coordinated righting reflex in highest dose tested (28.8 mg/kg/day) in males only in the subchronic neurotoxicity study. No neuropathology was noted in either study.
- Inhibition of plasma (butyryl and acetyl) cholinesterase activity at the highest dose tested (31.1 mg/kg/day, females) in the standard 90 day rat feeding study, this was not seen in the reversibility phase of the study. Pyridaben may have some flexibility and charge characteristics which would allow it to interact with the cholinesterase receptor in some tissues, but this response is not indicative of a neurotoxic mode of action.
- Only transient (appearing at only Week 8, but not at Weeks 4 or 13), poorly coordinated righting reflex in high dose males (28.8 mg/kg bw/day) observed in the absence of neurotoxicity in the subchronic neurotoxicity study.
- No other study of any duration showed evidence of neurotoxic effects (clinical signs, organ weights, histopathology) and the studies were tested high enough to elicit frank toxicity (other than neurotoxicity).
- The 2-generation reproduction study in rats included developmental and neurotoxicity assessments. The observations included a comprehensive evaluation of clinical signs, onset and completion of pinna (ear) unfolding, hair growth, tooth eruption, eye opening, auditory and visual

function assessed using the startle response and examination of pupil closure along with assessment of the visual placement response. No effects were noted up to and including the highest dose tested (6.31 mg/kg/day). No effects were noted on reproductive parameters. The observed effects in the 2-generation reproduction study were minimal in nature involving only body weight and food consumption.

4.3.2.2 Adequacy of the Exposure Database

The dietary exposure scenarios includes metabolites and/or degradates of concern and the dietary food exposure assessment is refined for acute food exposure and partially refined for chronic food exposure. Although refined, the assessments are based on reliable data and will not underestimate exposure/risk. The dietary drinking water assessment (Tier 2 estimates) utilizes values generated by models and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations. There is no potential for residential exposure.

4.3.2.3 Safety Factor for Infants and Children

There is a complete toxicity database for pyridaben and exposure data are complete. There is no evidence of susceptibility following in utero exposure in the developmental toxicity studies in rats or rabbits, and in the 2- generation rat reproduction study. There are no residual uncertainties concerning pre- and postnatal toxicity and no neurotoxicity concerns. Dietary food exposure assessments are refined, and the assessments are based on reliable data and will not underestimate exposure/risk. There is no potential for residential exposure. Based on these data the Agency has reduced the FQPA Safety Factor to 1X and a developmental neurotoxicity study will not be required.

4.4 Hazard Identification and Toxicity Endpoint Selection

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

No study was identified that indicated a hazard attributable to a single oral dose. Originally the HIARC selected the developmental toxicity study in the rabbit for this exposure scenario. The increase in abortions and the increase in 12/13, and 13/13 ribs were described as presumed to occur following a single exposure (dose); however, the abortions occurred only in the high dose at gestation days 19 and 25 which are more than one dose of the chemical and the litter based increase in 12/13, and 13/13 ribs is not that great and this variation has no functional consequences and as such are not relevant for this risk assessment for this subpopulation (i.e., females of child bearing age) and the developing fetuses. The following aRfD will be protective of all populations and the endpoint is of the correct duration.

4.4.2 Acute Reference Dose (aRfD) - General Population, Infants and Children

Study Selected: Acute Oral Neurotoxicity Study in Rats § OPPTS 870.6200

MRID. No.: 43680412

Executive Summary: See Section 4.2.2

Dose and Endpoint for Establishing an (aRfD): NOAEL = 44 mg/kg based on an increase in the incidence of piloerection, hypoactivity, tremors and partially closed eyes, decreases in body weight gain and food consumption observed in both sexes at 80 mg/kg (LOAEL).

Uncertainty Factor (UF): 100X (10X for inter-species extrapolation, 10X for intra-species variability).

Comments about Study/Endpoint and Uncertainty Factor: The endpoint selected is appropriate for this risk assessment since systemic toxicity occurred following a single oral exposure (dose). As mentioned above, this endpoint will be protective of all populations.

$$\text{Acute RfD} = \frac{44 \text{ mg/kg}}{100 \text{ (UF)}} = 0.44 \text{ mg/kg}$$

4.4.3 Chronic Reference Dose (cRfD)

Study Selected: Chronic Toxicity-Dogs § OPPTS 870.4100

MRID Nos.: 42680134 and 42680135

Executive Summary¹: In two chronic toxicity studies (MRID 42680134 and 42680135), four beagle dogs/sex/group (one control group/study) received NC-129 [pyridaben](98.0% purity, Lot/Batch No. 129 T 8605) by gelatin capsule dosages of 0, 0.5, 1.0, 4.0, 16.0 or 32.0 mg/kg bw/day for 1 year. Observations were made for clinical signs of toxicity, mortality, body weight and body weight gain, food consumption and food efficiency, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, macroscopic and microscopic examination, and organ weights.

All of the animals survived until the end of the study. The number and incidence of clinical signs of toxicity were increased in all the treated groups as compared to the controls. The most commonly observed effects included thinness, dehydration, diarrhea, food-like emesis, frothy emesis, soft stool, ptialism and relaxed winking reflex. Ptyalism was observed in males and females at all dose levels. The greatest response was in the highest 3 dose levels. Survival, food consumption, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, macroscopic and microscopic examination, and organ weights were unaffected by treatment with NC-129. Although not dose-related, decreases in mean body weight gain were seen in the 4.0,

¹This combines both Executive Summaries of the specified MRIDs 42680134 and 42680135.

16.0, and 32.0 mg/kg bw/day group males and all the treated females. Body weight gain was decreased in males and females in the 1.0 (77%/71% of controls), 4.0 (60%/42% of controls), 16.0 (50%/46% of controls) and 32.0 mg/kg bw/day (50%/25% of controls) groups, respectively. Weekly mean food consumption measurements showed wide variations, however decreases in the treated animals could not account for the decreases in body weight gain. On gross necropsy, one female in the 32 mg/kg bw/day group was pale and emaciated. On microscopic examination, this animal had mild hepatocellular hypertrophy, mild atrophy of skeletal muscle and thymus and mild hypocellularity of the femoral and sternal bone marrow. **The LOAEL for systemic toxicity in males and females is 0.5 mg/kg bw/day based on an increased incidence of ptialism, emesis and soft stools, and decreased body weight gain in females. The NOAEL for systemic toxicity \leq 0.5 mg/kg bw/day.**

(The second RfD/Peer Review Committee Report dated February 15, 1996 concluded that "the 0.5 mg/kg/day dose level should be considered a threshold LOAEL for clinical signs of toxicity. A NOAEL for body weight gain reduction was considered to be 0.5 mg/kg bw/day". The % decrease in BWG for the 0.5 group is 42% in females (males were unaffected) at 90 days. At the meeting of June 17, 2003 the HIARC concluded, that the effects at 0.5 mg/kg bw/day were minimal and that the 0.5 mg/kg bw/day group should be used in calculating the RfD.)

Dose and Endpoint for Establishing a (cRfD): LOAEL = 0.5 mg/kg bw/day (increased incidence of ptialism, emesis and soft stools, and decreased body weight gain in females).

Uncertainty Factor (UF): 100 (10x for inter-species extrapolation and 10 x for intra-species variability).

Comments about Study/Endpoint and Uncertainty Factor: Although a LOAEL was used for establishing the RfD, the HIARC determined that no additional uncertainty factor is required (i.e., for the lack of a NOAEL) because, the effects of concern (clinical signs and decrease in body weights in females) seen at this dose were minimal when compared to the responses seen at the higher doses and in a subchronic study conducted to select doses for the chronic study, the NOAEL was 1.0 mg/kg/day and the LOAEL was 4.0 mg/kg/day, based on the same endpoints of concern (MRID 42680135, 1991).

$$\text{Chronic RfD} = \frac{0.5 \text{ mg/kg/day (LOAEL)}}{100 \text{ (UF)}} = 0.005 \text{ mg/kg/day}$$

4.4.4 Incidental Oral Exposure (Short and Intermediate Term)

Incidental Oral Exposure: Short-Term (1-30 days)

Study Selected: Prenatal Developmental Toxicity - Rabbit § OPPTS 870.3700b

MRID. No.: 42680142

Executive Summary: See II. 1. Acute Dietary (aRfD) - [Females 13-50 years old].

Dermal Exposure: Long-Term (> 6 Months)**Study Selected:** Chronic Feeding-Dog § 870.4100**MRID No.:** 42680139**Executive Summary:** See II. 3. Chronic Reference Dose (cRfD).**Dose and Endpoint for Risk Assessment:** LOAEL = 0.5 mg/kg bw/day (increased incidence of ptialism, emesis and soft stools, and decreased body weight gain in females).**Comments about Study/Endpoint:** This study/dose/endpoint was also used to establish the chronic RfD.**4.4.7 Inhalation Exposure (Short, Intermediate and Long Term)****Study Selected:** 30-Day Inhalation Toxicity Study in Rats § 82-4**MRID No.:** 42680131**Executive Summary:** In a 4-week subchronic inhalation toxicity study (MRID 42680131), 10 Sprague-Dawley (CD) rats/sex in the control and high-dose groups were exposed to atmospheric concentrations of 0 or 0.010 mg/L of NC-129 [pyridaben](92.6% purity, Lot/Batch No. 610704) for 6 hours/day, 5 days/week. Two additional groups of 5 Sprague-Dawley (CD) rats/sex received 0.00087 or 0.003 mg/L of NC-129 under similar exposure conditions. [These were analytically measured concentrations.] Observations were made for clinical signs of toxicity, mortality, body weight and body weight gain, food consumption, hematology, clinical chemistry, macroscopic and microscopic examination, and organ weights.

There was no mortality, no biologically significant changes in hematology or organ weights. In addition, the results of the macroscopic and microscopic examinations were negative or inconclusive. Clinical signs of toxicity observed were dried red nasal discharge in the 0.003 and 0.010 mg/L groups, and increased yellow ano-genital staining in the 0.010 mg/L group. Body weight and body weight gain of females in the 0.003 and 0.010 mg/L group were decreased (92 and 74% of controls, respectively). Albumin was significantly decreased in females in the 0.003 and 0.010 mg/L group (91 and 87% of controls, respectively). Both sexes of the 0.003 and 0.010 mg/L groups had significant decreases in SGPT at Week 4 but not at Week 6.

The LOAEL is 0.003 mg/L (0.783 mg/kg bw/day) based on an increased incidence of dried red nasal discharge, decreased body weight gain and decreased albumin levels. The NOAEL is 0.00087 mg/L (0.261 mg/kg bw/day).

Dose and Endpoint for Risk Assessment: NOAEL = 0.261 mg/kg bw/day (0.00087 mg/L) based on an increased incidence of dried red nasal discharge, decreased body weight gain and decreased albumin levels at 0.783 mg/kg bw/day (0.003 mg/L, LOAEL).

Comments about Study/Endpoint: Since no other inhalation toxicity studies are available, the HIARC (see memorandum dated June 22, 1998) recommended that this study/endpoint should be used for the short-, intermediate-, and long-term exposure risk assessments.

4.4.8 Margins of Exposure

Summary of target Margins of Exposure (MOEs) for risk assessment.

Route Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	300
Residential (Non-Dietary) Exposure			
Oral	100	100	NA
Dermal	100	100	100
Inhalation	100	100	300

For **occupational short-, intermediate-, and long-term dermal and short- and intermediate-term inhalation** exposure risk assessments a MOE of 100 is adequate. This is based on the conventional 100X which includes the 10X for intra-species extrapolation and 10X for inter-species variation.

For **residential incidental oral and dermal (short- and intermediate-terms)** exposure risk assessments a MOE of 100 is adequate.

For **residential long-term dermal** risk assessment, and **short- and intermediate-term inhalation** risk assessments, a MOE of 100 is adequate.

For **occupational and residential long-term inhalation** exposure risk assessments, a MOE of 300 is required. This includes the conventional 100X and an additional 3X for the use of a short-term study for long-term risk assessment. It was determined that a 3X (as opposed to a 10X) is adequate since there was only a 2-3 fold difference between the NOAEL/LOAELs in the oral subchronic (NOAEL/LOAEL = 2.64/5.53 mg/kg/day) and chronic (1.09/3.18 mg/kg/day) studies in rats.

Dose and Endpoint for Risk Assessment: Maternal NOAEL = 5.0 mg/kg/day based on decreases in body weight, body weight gain and food consumption, and abortions observed at 15.0 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The decreases in body weight, body weight gain and food consumption are relevant for the duration, exposure route and population of concern for this risk assessment.

Incidental Oral Exposure: Intermediate-Term (1 - 6 Months)

Study Selected: 90-Day Oral Toxicity-Dog § 870.3150

MRID No.: 42680127

Executive Summary: In a 90-day oral toxicity study (MRID 42680127), 4 beagle dogs/sex/group received NC-129 [pyridaben](98.0% purity, Lot/Batch No. 129 T 8605) by capsule at dose levels of 0, 0.5, 1.0, 4.0 or 16.0 mg/kg bw/day for 13 weeks. Observations were made for clinical signs of toxicity, mortality, body weight and body weight gain, food consumption and food efficiency, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, macroscopic and microscopic examination, and organ weights.

Survival, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, macroscopic and microscopic examination, and organ weights were unaffected by treatment with NC-129. Ptyalism was observed in all males and the majority of females in the 4.0 and 16.0 mg/kg bw/day groups. Body weight gains were decreased in males in the 4.0 and 16.0 mg/kg bw/day groups (46 and 31% of controls, respectively) and in females in the 4.0 and 16.0 mg/kg bw/day groups (89 and 78% of controls, respectively).

The LOAEL is 4.0 mg/kg bw/day based on an increased incidence of ptyalism and decreases in body weight gain. The NOAEL is 1.0 mg/kg bw/day.

Dose and Endpoint for Risk Assessment: NOAEL = 1.0 mg/kg bw/day based on an increased incidence of ptyalism and decreases in body weight gain observed at 4.0 mg/kg bw/day (LOAEL).

Comments about Study/Endpoint: The study duration and endpoint selected are appropriate for this risk assessment.

4.4.5 Dermal Absorption

Dermal Absorption Factor: 5%

The HIARC estimated a dermal absorption rate based on a comparison of the LOAELs established from similar endpoints observed in an oral developmental study and a 21-day dermal toxicity study in the same species (rats).

In the oral developmental toxicity study in rats, the maternal NOAEL 4.7 mg/kg/day and the LOAEL was 13 mg/kg/day based on decreased body weight/weight gain and feed consumption (MRID 42680139).

In the 21-day dermal toxicity study, the systemic toxicity NOAEL was 100 mg/kg/day and the LOAEL was 300 mg/kg/day based on decreased body weight in the females (MRID 42680130).

A ratio of the LOAELs from the oral and dermal studies, indicated an approximate dermal absorption rate of 5% (oral LOAEL of 13 mg/kg/day ÷ dermal LOAEL of 300 x 100= 4.4%).

4.4.6 Dermal Exposure (Short, Intermediate and Long Term)

Dermal Exposure: Short-(1 - 30 days) and Intermediate-(1-6 Months) Term

Study Selected: 21-Day Dermal Toxicity Study in Rats § OPPTS 870.3200

MRID No.: 42680130

Executive Summary: In a 21-day dermal toxicity study (MRID 42680130), 5 Sprague-Dawley (CD) [Cd:CrI:CD (SD) BR] rats/sex/group received repeated dermal applications of NC-129 [pyridaben](98.0% purity, Lot/Batch No. 129 T 8605) at dose levels of 0, 30, 100, 300 or 1000 mg/kg bw/day for 21 days. Observations were made for clinical signs of toxicity, mortality, body weight and body weight gain, food consumption, hematology, clinical chemistry, urinalysis, macroscopic and microscopic examination, and organ weights.

There was no mortality or clinical signs of toxicity observed. Body weights were decreased in males in the 1000 mg/kg bw/day group (86% of controls). Body weight gain was decreased in males in the 1000 mg/kg bw/day group (49% of controls) and in females in the 300 and 1000 mg/kg bw/day groups (54 and 45% of controls, respectively). Food consumption was decreased in males and females in the 1000 mg/kg bw/day group at week 1 (80 and 50% of controls, respectively). Squamous cell hyperplasia and desquamation of the epithelial cells of the skin were observed in males and females in the 100, 300 and 1000 mg/kg bw/day groups.

The LOAEL (systemic) is 300 mg/kg bw/day based on decreased body weight gain in females. The NOAEL (systemic) is 100 mg/kg bw/day in females. The LOAEL (dermal) is 100 mg/kg bw/day based on squamous cell hyperplasia and desquamation of the epithelial cells of the skin. The NOAEL (dermal) is 30 mg/kg bw/day.

Dose and Endpoint for Risk Assessment: NOAEL = 100 mg/kg/day based on decreased body weight gain in females at 300 mg/kg/day (LOAEL).

Comments about Study/Endpoint: This dose and endpoint are appropriate for this risk assessment since the route of exposure in this study is relevant to the route (dermal) of exposure of concern for this exposure scenario. This endpoint may be on the conservative side since the body weight gain decrement may be due to the skin irritation rather than true systemic toxicity.

4.4.9 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated as follows:

For short-, intermediate- and long-term aggregate risk assessments, the oral, dermal and inhalation exposures can be combined due to the presence of a common toxicity endpoint (decreased body weight, body weight gain or food consumption/food efficiency).

4.4.10 Classification of Carcinogenic Potential

On March 17, 1994, The HED RfD/Peer Review Committee, considered the high dose levels tested in the rat and mouse studies adequate for carcinogenicity testing and classified pyridaben as a "Group E" (not likely human carcinogen) chemical based on the lack of evidence of carcinogenicity in male and female rats as well as in male and female mice [HLARC (see memorandum dated June 22, 1998)].

1. Combined Chronic Toxicity/Carcinogenicity Study-Rats

MRID No.:

42680132

§ OPPTS 870.4300

Executive Summary: In a combined chronic/carcinogenicity study (MRID 42680132), CD rats of Sprague-Dawley origin from Charles River U.K. received NC-129 [pyridaben](>98.0% purity, Lot/Batch No. 129 T 8605) at dietary concentrations of 0, 4, 10, 28, 80 or 120 ppm (equivalent to 0, 0.16, 0.39, 1.09 or 3.18 mg/kg/day for males and 0, 0.2, 0.51, 1.47 or 4.23 mg/kg/day for females, respectively) for 53 (80 ppm group) to 104 weeks. The protocol used 35 animal/sex/group in the 104 week toxicity phase (no 80 ppm group) with 12 animals/sex/group being sacrificed at 53 weeks, and 50 animals/sex/group in the 104 week carcinogenicity phase. Observations were made for clinical signs of toxicity, mortality, body weight and body weight gain, food consumption and food efficiency, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, macroscopic and microscopic examination, and organ weights.

In both the chronic toxicity and carcinogenicity sub-groups, there were no clinical signs of toxicity observed. Survival, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, macroscopic and microscopic examination, and organ weights were unaffected by treatment with NC-129. Body weights were decreased in males (81-88% of controls at 52 weeks) and in females (87-91% of controls at 52 weeks) in the 120 ppm groups beginning at 13 weeks. Body weight gains were similarly decreased in males (77-87% of controls) and females (81-87% of controls) in the 120 ppm groups. Food consumption was marginally decreased in males (87-94% of controls) and females (92-94% of controls) in the 120 ppm group.

The LOAEL is 120 ppm (3.18 mg/kg/day in males, and 4.23 mg/kg/day in females) based on decreased body weight and body weight gain. The NOAEL is 80 ppm (1.09 mg/kg/day in males and 1.47 mg/kg/day in females).

Discussion of Tumor Data: There was no evidence of carcinogenicity.

Adequacy of the Dose Levels Tested: The doses tested were 0, 4, 10, 28, and 80 ppm for assessment of carcinogenicity and 0, 4, 10, 28, and 120 ppm for assessment of chronic toxicity. At the highest tested dose in both the carcinogenicity sub-group (80 ppm), and the chronic toxicity sub-group (120 ppm, LOAEL), the only observed significant treatment-related effect was decreased body weight and body weight gain of >10% for both sexes. The NOAEL was 28 ppm (M/F = 1.1/1.5 mg/kg/day). Male rats in the chronic toxicity sub-group at the 120 ppm dose level also had decreased serum ALT whose relevance to the clinical state is questionable. No other significant treatment-related effects were seen. The RfD/Peer Review Committee considered the high dose levels tested in rats adequate for carcinogenicity testing (see memorandum dated May 11, 1994).

2. **Carcinogenicity Study-Mice**

MRID No.: 42680137

§ OPPTS 870.4200

Executive Summary: In a carcinogenicity study (MRID 42680137), CD-1 mice received NC-129 [pyridaben](98.0% purity, Lot/Batch No. 129 T 8605) at dietary concentrations of 0, 2.5, 8.0, 28 or 80 ppm in the diet (equivalent to 0, 0.27, 0.81, 2.78 or 8.58 mg/kg bw/day for males and 0, 0.29, 0.91, 2.78 or 9.74 mg/kg bw/day for females, respectively) for 78 weeks. The protocol used 12 animal/sex/group in the 52 week interim phase, and 52 animals/sex/group in the 78 week carcinogenicity phase. Observations were made for clinical signs of toxicity, mortality, body weight and body weight gain, food consumption and food efficiency, hematology, macroscopic and microscopic examination, and organ weights.

In both the chronic toxicity and carcinogenicity sub-groups, there were no clinical signs of toxicity observed. Survival, food consumption, hematology, macroscopic and microscopic examination, and organ weights were unaffected by treatment with NC-129. Body weight gain was significantly decreased in males (66-80% of controls at various time intervals) and in females (61-89% of controls at various time intervals) in the 80 ppm groups. Food efficiency was decreased in males (80-86% of controls) in the 80 ppm group.

The LOAEL is 80 ppm (8.88 mg/kg bw/day in males, and 9.74 mg/kg bw/day in females) based on decreased body weight gain (both sexes) and feed efficiency in males. The NOAEL is 25 ppm (2.78 mg/kg bw/day in males and females).

Discussion of Tumor Data: There was no evidence of carcinogenicity at either the interim (52 weeks) or terminal (78 weeks) sacrifice.

Adequacy of the Dose Levels Tested: The doses tested were 0, 2.5, 8.0, 25, or 80 ppm (equivalent to 0, 0.27, 0.81, 2.78, or 8.88 mg/kg/day in males and 0, 0.29, 0.91, 2.78, or 9.74 mg/kg/day in females, respectively). The NOAEL was 25 ppm (2.78 mg/kg/day) based on decreased body weight gain and food efficiency, and on changes in the relative organ weights at 80 ppm (LOAEL and MTD). The RfD/Peer Review Committee considered the high dose levels tested in mice adequate for carcinogenicity testing (see memorandum dated May 11, 1994).

MUTAGENICITY

The HIARC concluded that there is not a concern for mutagenicity resulting from exposure to pyridaben.

MUTAGENICITY SUMMARY FOR PYRIDABEN

- **Bacterial Reverse Mutation (Ames) Test (1986, MRID 43680145)**

Executive Summary: In two independent bacterial/mammalian microsome reverse mutation assays, NC-129 technical [pyridaben](98% a.i.) was tested in *S. typhimurium* strains TA1535, TA1537, TA98 and TA100 and *E. coli* strain WP2 uvrA (initial assay only) at dose levels up to 5000 µg/plate in the presence or absence of S9 metabolic activation. NC-129 technical was negative for mutagenicity in these assays.

- ***In vitro* Mammalian Gene Mutation Test Using Chinese Hamster V79 Cells (1995, MRID 43680149)**

Executive Summary: NC-129 technical [pyridaben](98% a.i.) was tested up to the limit of solubility (50 µg/mL) in the presence or absence of S9 metabolic activation in cultured *in vitro* mammalian gene mutation assay using Chinese hamster V79 cells. NC-129 technical was negative for mutagenicity at the TK locus in this assay. [However, there was concern that the dose level tested was inadequate and the study was deemed to be unacceptable, unless it could "clearly" be demonstrated that 50 µg/mL is the solubility limit.]

- ***In vitro* Mammalian Chromosome Aberration Test Using Chinese Hamster Lung Cells (1989, MRID 43680148)**

Executive Summary: NC-129 technical [pyridaben](98% a.i.) was tested up to 50 µg/mL in the presence or absence of S9 metabolic activation in *an in vitro* mammalian chromosome aberration test using Chinese hamster lung cells for 6 hours followed by an 18 hour recovery period. NC-129 technical did not induce structural chromosomal aberrations when cells were continuously exposed to nonactivated doses up to 100 µg/mL for 24 hours or 10 µg/mL for 48 hours. Clear evidence of cytotoxicity (i.e. greater than or equal to 50% reduction in the mitotic index) was demonstrated at 50 µg/mL +/-S9 (6 hour treatment, 18 hour recovery), and all doses (0.1-10 µg/mL -S9) in the 48 hour treatment.

● **Mammalian Erythrocyte Micronucleus Test (1988, MRID 42680147)**

Executive Summary: NC-129 technical [pyridaben](98% a.i.) was administered by gavage at dose levels up to 140 mg/kg to male and female ICR mice a mammalian erythrocyte micronucleus test. Mortality was observed. There was no production of micro nuclei in the bone marrow of ICR mice at 24, 48 or 72 hours post-dosing.

● **Bacterial DNA Damage or Repair Test Using *E. Coli* (1986, MRID 42680146)**

Executive Summary: No induction of primary DNA damage occurred in a bacterial DNA damage or repair test using *E. Coli* repair deficient strains WP67 or CM871 recovered 2 or 18 hours post-exposure to NC-129 [pyridaben] concentrations up to 10,000 µg/mL +/-S9 activation. Cytotoxicity was not demonstrated for the DNA competent strain (WP2) or the DNA deficient strains at any dose.

Table 4.4. Summary of Toxicological Doses and Endpoints for Pyridaben for Use in Human Risk Assessments			
Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age)			No study applicable to a single oral exposure
Acute Dietary (General population including infants and children)	NOAEL = 44 mg/kg/day UF = 100 Acute RfD = 0.44 mg/kg/day	FQPA SF = 1X aPAD = <u>acute RfD</u> FQPA SF = 0.44 mg/kg/day	Acute Neurotoxicity-Rat LOAEL = 80 mg/kg/day based on an increased incidence of piloerection, hypoactivity, tremors and partially closed eyes, decreased body weight gain and food consumption.
Chronic Dietary (All populations)	LOAEL = 0.5 mg/kg/day UF = 100 Chronic RfD = 0.005 mg/kg/day	FQPA SF = 1X cPAD = <u>chronic RfD</u> FQPA SF = 0.005 mg/kg/day	Chronic Feeding-Dog LOAEL = 0.5 mg/kg/day based on an increased incidence of ptyalism, emesis and soft stools, and decreased body weight gain in females.
Short-Term Incidental Oral (1-30 days)	NOAEL = 5 mg/kg/day	Residential LOC for MOE = 100 Occupational = NA	Developmental-Rabbit Maternal LOAEL = 15 mg/kg/day based on decreases in maternal body weight, body weight gain and food consumption, and abortions.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Intermediate-Term Incidental Oral (1- 6 months)	NOAEL= 1.0 mg/kg/day	Residential LOC for MOE = 100 Occupational = NA	90-Day Feeding-Dog LOAEL = 4.0 mg/kg/day based on an increased incidence of ptyalism and decreased body wt. gain.
Short-Term Dermal (1 to 30 days)	Dermal NOAEL= 100 mg/kg/day	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	21-Day Dermal-Rat LOAEL = 300 mg/kg/day based on decreased body weight gain in females.
Intermediate-Term Dermal (1 to 6 months)	Dermal NOAEL= 100 mg/kg/day	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	21-Day Dermal-Rat LOAEL = 300 mg/kg/day based on decreased body weight gain in females.
Long-Term Dermal (>6 months)	Oral LOAEL = 0.5 mg/kg/day	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	Chronic Feeding-Dog LOAEL = 0.5 mg/kg/day based on an increased incidence of ptyalism, emesis and soft stools, and decreased body weight gain in females.
Short-Term Inhalation (1 to 30 days)	Inhalation NOAEL = 0.261 mg/kg/day	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	30-Day Inhalation-Rat LOAEL = 0.783 mg/kg/day based on an increased incidence of dried red nasal discharge, decreased body weight gain and decreased albumin levels.
Intermediate-Term Inhalation (1 to 6 months)	Inhalation NOAEL = 0.261 mg/kg/day	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	30-Day Inhalation-Rat LOAEL = 0.783 mg/kg/day based on an increased incidence of dried red nasal discharge, decreased body weight gain and decreased albumin levels.
Long-Term Inhalation (>6 months)	Inhalation NOAEL = 0.261 mg/kg/day	Residential LOC for MOE = 300 Occupational LOC for MOE = 300	30-Day Inhalation-Rat LOAEL = 0.783 mg/kg/day based on an increased incidence of dried red nasal discharge, decreased body weight gain and decreased albumin levels.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Cancer (oral)	"Group E" chemical based on the lack of evidence of carcinogenicity in male and female rats as well as in male and female mice [HIARC (see memorandum dated June 22, 1998)].		

UF = uncertainty factor, UF_{DB} = uncertainty factor in the data base, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

4.5 Endocrine disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). In the available toxicity studies on pyridaben, there was no estrogen, androgen, and/or thyroid mediated toxicity. When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, pyridaben may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Public Health Data

5.1 Incident Reports

There are a total of 6 incident reports for pyridaben. There is some indication that pyridaben may be an eye irritant. However, there are too few incidents reported for pyridaben to draw conclusions on adverse effects.

6.0 Exposure Characterization/Assessment

6.1 Dietary-Exposure/Risk Pathway

References:

PP#1E06226: Pyridaben (Pyramite™ Miticide/Insecticide) in/on Hops. Evaluation of Analytical Methodology and Residue Data and Submission of 1/17/2001; W. D. Wassell; 1/28/04; D271838 and D276072.

PP#2E06460: Pyridaben (Pyramite™ Miticide/Insecticide) in/on Tropical Fruit Group (Including: Papaya, Star Apple, Black Sapote, Mango, Sapodilla, Mamey Sapote, and Canistel). Evaluation of Analytical Methodology and Residue Data. (Memo, 1/28/2004, W.D. Wassell, D285562).

PP#0E6068: Pyridaben (Pyramite™ Miticide/Insecticide) in/on Strawberries. Evaluation of Analytical Methodology and Residue Data for Strawberries and Confined Rotational Crops; W. D. Wassell; 2/18/04; D260466.

PP#2E6457: Pyridaben; Petition for the Establishment of a Permanent Tolerance for Residues in/on Stone Fruit. Summary of Analytical Chemistry and Residue Data; W. D. Wassell; 2/23/04; D285553.

PP#1E6303: Pyridaben; Petition for the Establishment of a Permanent Tolerance for Residues in/on Greenhouse-grown Tomato. Summary of Residue Data and a Waiver Request; W. D. Wassell; 2/23/04; D278766.

PP#1E6303: Pyridaben; Petition for the Establishment of a Permanent Tolerance for Residues in/on Greenhouse-grown Tomato. Reevaluation of crop field trial data; W. D. Wassell; 8/24/05; D320915.

6.1.1 Residue Profile

Pyridaben is a selective contact miticide/insecticide that controls various types of phytophagous mites and insects in orchards and vineyards. This active ingredient is a contact acaricide with prolonged residual effects and no known systemic or translaminar activities. There has been no resistance or cross-resistance demonstrated in test pest populations. Pyridaben is currently registered for use on tree nuts, pistachio, apple, pear, citrus fruits, grape, apricot, cherry, nectarine, peach, plum, prune, and cranberry. Pyridaben is not registered or proposed for use in residential settings. Detectable residues in plant commodities are predominantly parent residues. However, there are several minor metabolites containing either the pyridazinone or phenyl ring. These metabolites generally sum up to >10% of the TRR. Residue transfer to ruminant tissues from the consumption of pyridaben treated feed items is expected. As pyridaben is not registered for use on poultry feed items, secondary residues of pyridaben and its metabolites are not expected. Environmental fate studies indicated that pyridaben is stable, has low water solubility, and a high level of binding to soil. It appears that pyridaben would remain bound to the soils during run-off events. Because of its relative immobility, pyridaben is not likely to reach subsurface soil environments or ground water at significant concentrations.

Nature of the Residue in Plants, Livestock and Rotational Crops

The nature of the residue in plants and livestock is adequately understood based on acceptable metabolism studies conducted on lactating goats, laying hens, oranges, apples, eggplant, and confined rotational crops.

The submitted plant metabolism studies indicate that pyridaben is the only major residue identified in primary crops. However, there are several minor metabolites containing either the pyridazinone or phenyl ring. These metabolites generally sum up to >10% of the TRR. There are several minor metabolites containing either the pyridazinone or phenyl ring. These metabolites generally sum up to >10% of the TRR. The submitted goat metabolism study indicated that pyridaben is the only major residue in liver, while metabolites PB-7 and PB-9 are minor metabolites. No specific residue was firmly identified in other tissues or in milk. The metabolism study using laying hens indicated that PB-7 is the major metabolite (in liver) and parent was not found. The confined rotational crop study found that the radioactive residues were comprised mainly of polar unknowns (described as multi-component fractions, with each component contributing <10% TRR), and minor amounts of the parent compound. Parent compound was identified in several commodities at levels less than 0.001 ppm.

The results of pyridaben metabolism studies using oranges, apples, eggplants, rotational crops, and livestock were discussed in a meeting on 1/14/2004. In conjunction with this meeting the following conclusions were made:

Primary Crops: The residue of concern for tolerance setting purposes is the parent compound, pyridaben. Additionally, the residues of concern for risk assessment are pyridaben and all metabolites containing the pyridazinone ring.

Livestock: The residues of concern for tolerance setting purposes and risk assessment purposes are pyridaben and its metabolites PB-7 and PB-9.

Rotational Crops: The residue of concern for tolerance setting purposes and risk assessment purposes is pyridaben.

Residue Analytical Methods

Two parent-specific GC/ECD methods were developed for the conduct of the residue trials and for enforcement purposes. These methods are designated as BASF Methods D9312 and D9309B. The former was used for analysis of apples, pears, cranberries, peaches, grapes, plums, and plum processed fractions; the latter was utilized for analysis of pecans.

BASF Method D9312 (apples, pears, cranberries, peaches, grapes, tomatoes, strawberries, hops, tropical fruit, stone fruit - MRID No. 442062-01):

Briefly, residues are extracted into acetone:water [80:20, v/v], macerated, and concentrated by vacuum filtration. The acetone extract was mixed with an equal volume of water, cleaned up on

a mini-C₁₈ column and analyzed by GC/ECD. The limit of quantification (LOQ) was validated to be 0.05 ppm for residues of pyridaben in all matrices. A successful independent laboratory validation (ILV) of this method has been conducted using apples. Additionally, this method has been successfully validated by ACB/BEAD for use with apples and almond nutmeat. HED concludes this method is adequate for enforcement purposes with apples, pears, cranberries, peaches, grapes, tomatoes, strawberries, hops, tropical fruit, and stone fruit.

BASF Method D9309B (citrus fruit, tree nuts - MRID No. 442601-01):

Briefly, residues are extracted from homogenized samples into acetone/water, macerated, concentrated by vacuum filtration, washed with acetone, and diluted. The acetone/water extract is concentrated, 10% aqueous NaCl is added, and the mixture extracted dichloromethane (DCM). The DCM extract is evaporated, and the residues dissolved in DCM/hexane, and applied to a mini-silica gel column. The eluate is collected and analyzed by GC/ECD. The LOQ was validated to be 0.05 ppm for residues of pyridaben in pecans. A successful ILV has been conducted using orange and orange processed commodities. Additionally, this method has been successfully validated by ACB/BEAD for use with oranges. HED concludes this method is adequate for enforcement purposes with citrus fruit and tree nuts.

BASF Method D9405 (livestock -MRID No. 442601-01):

BASF Method D9405 determines residues of pyridaben and its metabolites PB-7 and PB-9. Each analyte is determined independently. Briefly, residues are extracted by macerating livestock tissue with acetone/water and milk with acetone. A portion of the extract is methylated with diazomethane. The methylated sample is cleaned on a octadecylsilane column. The sample extract is analyzed by GC/ECD. This method has been independently validated for use with milk and liver commodities. This method has been successfully validated by ACL/BEAD. HED concludes this method is adequate for enforcement purposes with ruminant commodities.

Multiresidue Methods (MRM)

The petitioner submitted data concerning the recovery of residues of pyridaben and its metabolites PB-7 and PB-9 using FDA multiresidue method protocols (PAM Vol. I). Pyridaben, PB-7 and PB-9 were not adequately recovered by these methods. These data have been submitted to FDA for evaluation.

Magnitude of Residues in Plants

Hops: The petitioner has submitted crop field trial data for pyridaben in/on hops. Residues of pyridaben in/on dried hop cones varied from 4.4 to 8.5 ppm. HED concludes the submitted residue data support a tolerance level of 10.0 ppm for residues of pyridaben in/on dried hop cones. **A revised Section F is required to revise the commodity designation to "hop, dried cones".**

Tropical Fruit: The petitioner has submitted crop field trial data for pyridaben in/on papaya to support the proposed tolerances for residues in/on tropical fruit (including papaya, star apple, black sapote, mango, sapodilla, mamey sapote, and canistel). Residues of pyridaben varied from <0.05 to 0.09 ppm in/on papaya. HED concludes the submitted residue data support a tolerance level of 0.10 ppm for residues of pyridaben in/on tropical fruits.

Strawberry: The petitioner has submitted data concerning the magnitude of the residue in strawberries following applications of pyridaben as per the proposed use directions. The residue data for pyridaben in/on strawberry are summarized below.

Table 6.1.1. Summary of Residue Data from Strawberry Field Trials with Pyridaben.

Commodity	Total Applic. Rate, lb ai/A	PHI (days)	Analyte	Residue Levels (ppm)					
				n	Min.	Max.	HAFT ¹	Mean	Std. Dev.
Strawberries	1.2	1	Pyridaben	14	0.33	1.28	1.18	0.67	0.26
	1.0	1	Pyridaben	16	0.19	2.26	2.19	1.22	0.54

¹ HAFT = Highest Average Field Trial.

HED concludes the submitted residue data support a tolerance level of 2.5 ppm for residues of pyridaben in/on strawberry.

Stone Fruit: Residue data for the use of pyridaben on peaches and plums were previously submitted, while data concerning the use on cherries were submitted in conjunction with the current petition.

Cherry: IR-4 has submitted field trial data depicting the magnitude of the residue of pyridaben in/on cherry. Residues of pyridaben in/on cherries ranged from <0.05 to 1.28 ppm at PHIs of 6-8 days.

Peach: Crop field trial data for pyridaben in/on peaches were previously submitted. Pyridaben residue levels ranged from <0.05 to 2.4 ppm (at the proposed 7-day PHI) in the submitted crop field trials.

Plums: Crop field trial data for pyridaben in/on plums were previously submitted. Pyridaben residue levels ranged from <0.05 to 0.68 ppm (at the proposed 7-day PHI) in the submitted crop field trials.

HED concludes the submitted residue data for pyridaben in/on peaches, plums, and cherries support the proposed tolerance of 2.5 ppm for residues of pyridaben in/on stone fruit (group 12).

Tomato: IR-4 has submitted field trial data depicting the magnitude of the residue of pyridaben in/on greenhouse-grown tomatoes. Residues of pyridaben in/on tomatoes ranged from 0.058 to 0.15 ppm at a PHI of 2 days. Using the rounding procedure as outlined in the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data SOP*, HED concludes the submitted residue data for pyridaben in/on greenhouse-grown tomatoes indicate the appropriate tolerance for residues of pyridaben in/on tomatoes is 0.15 ppm.

Magnitude of Residues in Livestock

Cattle: The petitioner has submitted the results of a cow feeding study. In this study, 12 lactating cows were administered pyridaben for 29 days at dose levels of 2.5, 7.5 or 25 ppm. For dairy cattle, the dose levels of the feeding study translate to an exaggerated feeding level of 0.71x, 2.1x, and 7.1x, respectively, and for beef cattle, the exaggeration rate is 0.96x, 2.9x, and 9.6x, respectively. Samples were analyzed for residues of pyridaben and its metabolites PB-7 and PB-9. The results of this study are presented in Table 6.1.1b.

Table 6.1.1b. Maximum Residues of Pyridaben and Its Metabolites PB-7 and PB-9 Found in Lactating Cows.

Dose Level (ppm):	2.5	7.5	25
Sample			
Milk	<0.01	<0.01	0.03 ¹
Liver	<0.05	0.05 ²	0.15 ²
Muscle	<0.05	<0.05	<0.05
Kidney	<0.05	<0.05	<0.05
Fat	<0.05	<0.05	0.081

¹ Pyridaben² PB-7

Poultry: A poultry feeding study has not been submitted.

International Tolerance Harmonization

There are no Codex, Canadian, or Mexican tolerances for pyridaben on hops, tomatoes, and tropical fruit. Thus, no compatibility questions exist with respect to Codex, Canada, and Mexico for hops, tomatoes and tropical fruit. For stone fruit and strawberry, there are no Codex or Mexican tolerances. However, there are Canadian tolerances for pyridaben in/on strawberry at 2.0 ppm, peaches and nectarines at 1.5 ppm. Therefore, no compatibility questions exist with respect to Codex and Mexico, but there are compatibility issues with Canada for these crops.

6.1.2 Acute and Chronic Dietary-exposure and Risk

Reference: **Pyridaben;** Acute and Chronic (Non-Cancer) Dietary-exposure Assessments for the Section 3, Registration Actions (PP#1E06226 - Hops, PP#2E06460 - Tropical Fruits, PP#2E06068 - Strawberries, PP#1E06303 - Tomatoes, and PP#2E06457 - Stone Fruit); (Memo, W.D. Wassell, 05/12/2005, DP Barcode: 316834).

NOTE: The dietary exposure/risk analysis (Memo, W.D. Wassell, 05/12/2005, DP Barcode: 316834) will be revised to reflect the analysis presented in Table 6.1 which utilizes an aPAD of 0.44 mg/kg/day rather than an aPAD of 0.044 mg/kg/day. As stated in Section 4.0 above, the hazard and exposure databases are adequate to support the removal of the 10x FQPA Safety Factor, including a database uncertainty factor for lack of a DNT.

Tier 3 acute (probabilistic) and Tier 2 chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.00-2.02), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analyses were performed to support Section 3 registration requests for the use of pyridaben on hops, tropical fruit, strawberries, and stone fruit.

HED has determined the tolerance expression for plant commodities will include residues of pyridaben *per se*. It was further concluded that residues of pyridaben and all metabolites containing the pyridazinone ring are the residues of concern for risk-assessment. HED has calculated a ratio of residues containing the pyridazinone ring to pyridaben based upon the low-dose pyridaben apple and orange metabolism studies. The low-dose studies were conducted to mimic the proposed use of pyridaben on oranges and apples. A summary of the data utilized for this calculation is presented below.

Ratio of Organosoluble Residues to Pyridaben in Apples and Oranges.

Matrix:	Apples	Oranges (Hamlin)	Oranges (Hamlin)	Oranges (Valencia)	Oranges (Valencia)
Label ¹	phenyl	phenyl	pyridazinone	phenyl	pyridazinone
Table ²	8 (8)	5 (5)	5 (5)	5 (5)	5 (5)
TRR ³	0.138 ppm	0.093 ppm	0.116 ppm	0.048 ppm	0.046 ppm
Pyridaben ⁴	20.8%	23.2%	12.6%	13.5%	23.2%
pyridazinone ring ⁴	8.7%	7.9%	10.5%	6.4%	6.3%
Total ⁵	29.5%	31.1%	23.1%	19.9%	29.5%
Ratio ⁶	1.42	1.34	1.83	1.47	1.27
Average Ratio	1.47				

¹ Radiolabel of parent compound in the corresponding low-dose study.

² Table and page number for data from the Report of the MARC for pyridaben.

³ Total radioactive residues.

⁴ Percentage of pyridaben or pyridazinone ring containing metabolites.

⁵ Total of pyridaben plus pyridazinone ring containing metabolites.

⁶ Ratio of pyridaben plus pyridazinone ring containing metabolites to pyridaben.

HED concludes for **chronic dietary-exposure analysis** tolerance levels should be multiplied by the ratio of pyridaben plus pyridazinone ring containing metabolites to pyridaben in order to account for all of the residues of concern for risk assessment. For the **acute dietary-exposure analysis**, residue values from crop field trials should be multiplied by the ratio of pyridaben plus pyridazinone ring containing metabolites to pyridaben in order to account for all of the residues of concern for risk-assessment. These values were used to construct residue distribution files for the acute probabilistic dietary-exposure assessment.

Acute Dietary-exposure Results and Characterization: A Tier 3, acute dietary-exposure assessment (probabilistic) was conducted for pyridaben. The assumptions of this dietary-exposure assessment are as follows: (1) probabilistic assessment based upon residue distribution

6.1.3 Percent Crop Treated (PCT) Information

Percent Crop Treated (PCT) data provided by BEAD included a Screening Level Usage Analysis (SLUA) dated 1/3/04 for existing crops and a projected PCT analysis dated 4/18/05 for proposed crops. PCT data were incorporated into the acute and chronic dietary exposure assessments as follows:

Crop ^a	Average PCT (Chronic)	Maximum PCT (Acute)
Almonds	<2.5	4
Apples	10	20
Cherries	<2.5	4
Grapefruit	15	35
Grapes	5	10
Lemons	<2.5	4
Nectarines (CA only)	9	15
Olives (CA only)	<1	1
Oranges	5	8
Peaches	5	8
Pears	15	22
Pistachios (CA only)	<1	1
Prunes & Plums	5	8
Sugar Beets (CA only)	<1	1
Tangelos (CA only)	13	20
Tangerines	15	25
Walnuts	<2.5	4
Greenhouse Tomatoes ^a	4	8
Strawberries ^a	19	46
Apricots ^a	34	67
Hops ^a	–	–
Tropical Fruit ^a	–	–
Cranberry	10	10

^aProjected PCT

files or anticipated-residue estimates derived from crop field trial data were utilized for most commodities; (2) processing factors from processing studies were utilized for most processed commodities; and (3) percent crop-treated estimates and projected market-share estimates were utilized for most crops.

For the acute analysis, the most highly-exposed population subgroup is children 1 to 2 years old. The acute exposure at the 99.9th percentile for children 1 to 2 years old is 0.0275 mg/kg bw/day, which utilizes 6% of the acute population-adjusted-dose (aPAD) for pyridaben. The acute dietary-exposure at the 99.9th percentile for the U.S. Population is 0.0110 mg/kg bw/day, which utilizes 3% of the aPAD for pyridaben. This assessment is considered to be highly-refined.

Chronic Dietary-exposure Results and Characterization: A Tier 2, partially-refined, chronic dietary-exposure assessment was conducted for pyridaben. The assumptions of this dietary-exposure assessment are as follows: (1) anticipated-residue estimates to account for the residues of concern for risk assessment derived from proposed and established tolerance levels; and (2) percent crop-treated estimates and projected market-share estimates were utilized for most crops.

For the chronic analysis, the most highly-exposed population subgroup is children 1 to 2 years old. The chronic exposure for children 1 to 2 years old is 0.00233 mg/kg bw/day, which utilizes 47% of the chronic population-adjusted-dose (cPAD) for pyridaben. The chronic dietary-exposure for the U.S. Population is 0.000672 mg/kg bw/day, which utilizes 13% of the cPAD for pyridaben. This assessment is considered to be partially-refined.

Table 6.1 Summary of Dietary-exposure and Risk (Food Only) for Pyridaben.						
Population Subgroup *	Acute Dietary (99.9th Percentile)			Chronic Dietary		
	aPAD, mg/kg	Exposure, mg/kg bw/day ^b	% aPAD	cPAD, mg/kg bw/day	Exposure, mg/kg bw/day ^b	% cPAD
General U.S. Population	0.44	0.0110	3%	0.005	0.000672	13
All Infants (< 1 year old)	0.44	0.0187	4%	0.005	0.00144	29
Children 1-2 years old	0.44	0.0275	6%	0.005	0.00233	47
Children 3-5 years old	0.44	0.0206	5%	0.005	0.00165	33
Children 6-12 years old	0.44	0.0142	3%	0.005	0.000861	17
Youths 13-19 years old	0.44	0.00864	2%	0.005	0.000408	8.2
Adults 20-49 years old	0.44	0.00994	2%	0.005	0.000552	11
Adults 50+ years old	0.44	0.00744	2%	0.005	0.000483	9.7
Females 13-49 years old	0.44	0.00917	2%	0.005	0.000450	9.0

^a The values for the population with the highest risk for each type of risk assessment are bolded.

^b Reported to 3 significant figures.

6.2 Water Exposure/Risk Pathway

Reference: *Drinking Water Exposure Screening Assessment for Proposed Uses of Pyridaben on Strawberries, Hops, Tropical Fruit, and Stone Fruit.* (Memo, 2/10/2004, K. Costello).

Risk Assessment for Proposed Uses of Pyridaben on Strawberries, Hops, Tropical Fruit and Stone Fruit. (Memo, 7/8/2004, Todd Phillips, et. Al., D285563)

Residues of concern in water: In the meeting of 1/14/2004, HED concluded the residues of concern in water are pyridaben only (see Appendix 3.0).

Surface water: Monitoring data for pyridaben are not available. For this reason, the Agency has decided to base our estimates on simulated values using the US EPA PRZM and EXAMS programs. Tier II drinking water estimates for pyridaben in surface water are estimated using the linked US EPA PRZM and EXAMS environmental fate and transport simulation models. The modeling is performed using the use patterns for hops, apple, and strawberry, maximum number of applications (4 or 2), and maximum application rates of 0.3 or 0.5 lbs ai/A permitted by the pesticide label. The combination of this permitted application rate for apples and the weather and soil conditions simulated, produce the highest EDWC values of any crop listed on the label.

A Tier II Estimated Drinking Water Concentration (EDWC) for a particular crop or use is based on a single index reservoir site that represents a high exposure scenario for the crop or use. The scenarios are indexed to a vulnerable former drinking water reservoir located in Oregon (for hops), Florida (for strawberry), and Pennsylvania (for apple). Weather and agricultural practices are simulated at an appropriate site for 30 years to estimate the probability of exceeding a given concentration (maximum concentration or average concentration) in a single year. Maximum EDWCs are calculated so that there is a 10% probability that the maximum concentration in a given year will exceed the EDWC at the site. This can also be expressed as an expectation that water concentrations will exceed EDWCs once every 10 years.

Ground water: Monitoring information are not available for pyridaben. Therefore, conservative, upper-level ground water concentrations for this assessment have be calculated with the SCI-GROW model. Table 6.2 presents the estimated drinking water concentrations for pyridaben.

Table 6.2. Summary of Estimated Surface and Ground Water Concentrations for Pyridaben.			
Crop	Surface Water (µg/L or ppb)		Ground Water (µg/L or ppb)
	Acute	Chronic	Acute and Chronic
Hops	5.5	1.4	0.006
Strawberry	1.7	0.5	0.007
Apple	12	2.2	0.006

6.3 Residential (Non-Occupational) Exposure/Risk Pathway

6.3.1 Home Uses

There are no residential uses currently registered or proposed for pyridaben. Consequently no exposure from residential uses is expected and no residential exposure assessment was performed.

6.3.2 Recreational Uses

Recreational exposures are not expected for pyridaben.

6.3.3 Other (Spray Drift, etc.)

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

7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (*e.g.*, a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. For pyridaben, potential exposures from acute- and chronic-term food and drinking water scenarios were aggregated as pyridaben is not registered or proposed for use in residential settings. Furthermore, pyridaben is considered not likely to be carcinogenic to humans, and therefore, an aggregate cancer assessment was not conducted.

In order to determine if aggregate risks are of concern, HED calculates drinking-water-levels-of-comparison, or DWLOCs. The DWLOC is the maximum amount of a pesticide in drinking water that would be acceptable in light of combined exposure from the food and residential pathways. The calculated DWLOCs are then compared to the EDWCs provided by EFED. To

calculate DWLOCs, the dietary food estimates (from DEEM-FCID™) were subtracted from the PAD value to obtain the maximum water exposure level. DWLOCs were then calculated using the standard body weights and drinking water consumption figures: 70 kg/2 L (for US population; adults 20-49 years old; adults 50+ years), 60 kg/2 L (for youths 13-19 years old, females 13-49 years old), and 10 kg/1 L (for infants and children). EDWCs can be based on water monitoring data or model-derived. Water monitoring data are not available for pyridaben; therefore, models have been used to estimate pyridaben residues in drinking water. If the model-derived EDWCs exceed the DWLOCs for surface or ground water, there may be a concern for dietary-exposure to residues in drinking water, and refinement or mitigation may be required.

7.1 Acute Aggregate Risk

There is potential acute exposure to pyridaben via the dietary (food and water) pathway. A Tier 3 acute dietary-exposure assessment (probabilistic) was conducted for pyridaben. The assumptions of this dietary-exposure assessment are summarized in Section 6.1.2 of this document. The EDWCs were determined using PRZM/EXAMS (for surface water) and SCI-GROW (for ground water) and are summarized in Section 6.2 of this document.

The dietary-exposure analyses in this assessment for pyridaben result in dietary risk (food only) estimates that are below the Agency's level of concern for acute dietary (food only) exposure. For the acute analysis, the most highly-exposed population subgroup is children 1 to 2 years old. The acute exposure at the 99.9th percentile for children 1 to 2 years old is 0.0275 mg/kg bw/day, which utilizes 6% of the acute population-adjusted-dose (aPAD) for pyridaben. The acute dietary exposure at the 99.9th percentile for the U.S. Population is 0.0110 mg/kg bw/day, which utilizes 3% of the aPAD for pyridaben. This dietary-exposure assessment is considered to be highly-refined.

The EDWCs generated by EFED are less than HED's calculated DWLOCs for acute exposure to pyridaben in drinking water. At the 99.9th percentile of exposure for the subgroup children 1 to 2 years old, the highest EDWC for acute exposure (12 ppb) is less than the DWLOC (4100 ppb). For the U.S. population, the EDWC for acute exposure (12 ppb) is less than the DWLOC (15000 ppb). **Thus, the acute aggregate exposure and risk estimates do not exceed HED's level of concern.** Acute pyridaben aggregate exposures and risk (food plus water) are summarized in Table 7.1.

Table 7.1 Aggregate Risk Assessment for Acute Dietary-exposure to Pyridaben.						
Population Subgroup¹	Acute Exposure Scenario					
	aPAD mg/kg bw	Acute Food Exp mg/kg bw	Max Acute Water Exp mg/kg bw	Ground Water EDWC (ppb)³	Surface Water EDWC (ppb)³	Acute DWLOC (ppb)⁴
U.S. Population	0.44	0.0110	0.429	0.007	12	15000
All Infants (<1 year old)	0.44	0.0187	0.4213			4200
Children 1-2 years old	0.44	0.0275	0.4125			4100
Children 3-5 years old	0.44	0.0206	0.4194			4200
Children 6-12 years old	0.44	0.0142	0.4258			4300
Youths 13-19 years old	0.44	0.00864	0.43136			12900
Adults 20-49 years old	0.44	0.00994	0.43006			15000
Adults 50+ years old	0.44	0.007435	0.432565			15000
Females 13-49 years old	0.44	0.00917	0.43083			12900

¹Data are summarized for the total U.S. Population and population subgroups which are specified in HED Hot Sheet # 20 (10/1/2002). HED default body weights are: 70 kg for the U.S. population, adults 20 to 49 years old, and adults 50+ years old; 60 kg for youths 13 to 19 years old, and females 13 to 49 years old; and 10 kg for subgroups that are exclusive to infants and children. HED default daily drinking rates are 2 L/day for adults and youths; and 1 L/day for children.

²Maximum acute water exposure (mg/kg bw/day) = [(aPAD (mg/kg bw/day) - acute food exposure (mg/kg bw/day))]

³EDWCs were generated using PRZM/EXAMS (for surface water) and SCI-GROW (for ground water) using the parameters of the maximum registered use rate for apples (2 applications at 0.5 lbs ai/A).

⁴Acute DWLOC($\mu\text{g/L}$) = $\frac{\text{maximum acute water exposure (mg/kg bw/day)} \times \text{body weight (kg)}}{[\text{water consumption (L)} \times 10^{-3} \text{ mg}/\mu\text{g}]}$

7.2 Short-Term Aggregate Risk

There are no residential uses currently registered or proposed for pyridaben and residential and/or recreational exposures to pyridaben are not expected. **Thus, a short-term aggregate risk assessment is not required at this time for pyridaben.**

7.3 Intermediate-Term Aggregate Risk

There are no residential uses currently registered or proposed for pyridaben and residential and/or recreational exposures to pyridaben are not expected. **Thus, an intermediate-term aggregate risk assessment is not required at this time for pyridaben.**

7.4 Chronic-Term (Non-Cancer) Aggregate Risk

There is potential chronic-term exposure to pyridaben via the dietary (food and water) pathway. A Tier 2 chronic dietary-exposure assessment was conducted for pyridaben. The assumptions of this dietary-exposure assessment are summarized in Section 6.1.2 of this document. The EDWCs were determined using PRZM/EXAMS (for surface water) and SCI-GROW (for ground water) and are summarized in Section 6.2 of this document.

The dietary-exposure analyses in this assessment for pyridaben result in dietary risk (food only) estimates that are below the Agency's level of concern for chronic dietary (food only) exposure. For the chronic analysis, the most highly-exposed population subgroup is children 1 to 2 years old. The chronic exposure for children 1 to 2 years old is 0.00233 mg/kg bw/day, which utilizes 47% of the chronic population-adjusted-dose (cPAD) for pyridaben. The chronic dietary exposure for the U.S. Population is 0.000672 mg/kg bw/day, which utilizes 13% of the cPAD for pyridaben. This assessment is considered to be partially-refined.

The EDWCs generated by EFED are less than HED's calculated DWLOCs for chronic exposure to pyridaben in drinking water. For the subgroup children 1 to 2 years old, the highest EDWC for chronic exposure (2.2 ppb) is less than the DWLOC (27 ppb). For the U.S. population, the highest EDWC for chronic exposure (2.2 ppb) is less than the DWLOC (150 ppb). **Thus, chronic-term (non-cancer) aggregate exposure to pyridaben does not exceed HED's level of concern.** Chronic (non-cancer) pyridaben aggregate exposures and risk (food plus water) are summarized in Table 7.4.

Table 7.4. Aggregate Risk Assessment for Chronic (Non-Cancer) Exposure to Pyridaben.

Population Subgroup ¹	Chronic Exposure Scenario					
	cPAD mg/kg bw/day	Chronic Food Exp mg/kg bw/day	Max Chronic Water Exp mg/kg bw/day ²	Ground Water EDWC (ppb) ³	Surface Water EDWC (ppb) ³	Chronic DWLOC (ppb)
U.S. Population	0.005	0.000672	0.004328	0.007	2.2	150
All Infants (<1 year old)	0.005	0.00144	0.00356			40
Children 1-2 years old	0.005	0.00233	0.00267			27
Children 3-5 years old	0.005	0.00165	0.00335			34
Children 6-12 years old	0.005	0.000861	0.004139			41
Youths 13-19 years old	0.005	0.000408	0.004592			140
Adults 20-49 years old	0.005	0.000552	0.004448			160
Females 13+ years old	0.005	0.000483	0.004517			140
Adults 50+ years old	0.005	0.000450	0.00455			160

¹Data are summarized for the total U.S. Population and population subgroups which are specified in HED Hot Sheet # 20 (10/1/2002). HED default body weights are: 70 kg for the U.S. population, adults 20 to 49 years old, and adults 50+ years old; 60 kg for youths 13 to 19 years old, and females 13 to 49 years old; and 10 kg for subgroups that are exclusive to infants and children. HED default daily drinking rates are 2 L/day for adults and youths; and 1 L/day for children.

²Maximum Chronic Water Exposure (mg/kg bw/day) = [Chronic PAD (mg/kg bw/day) - Chronic Dietary-exposure (mg/kg bw/day)]

³EDWCs were generated using PRZM/EXAMS (for surface water) and SCI-GROW (for ground water) using the parameters of the maximum registered use rate for apples (2 applications at 0.5 lbs ai/A).

⁴Chronic DWLOC($\mu\text{g/L}$) = $\frac{\text{maximum chronic water exposure (mg/kg bw/day)} \times \text{body weight (kg)}}{[\text{water consumption (L)} \times 10^{-3} \text{ mg}/\mu\text{g}]}$

7.5 Cancer Risk

Pyridaben is classified as a Group E chemical (*i.e.* evidence of non-carcinogenicity for humans) based on the lack of evidence of carcinogenicity in male and female rats as well as in male and female mice [HIARC (see memorandum dated June 22, 1998)]. **Thus, a cancer risk assessment for pyridaben is not required.**

8.0 Cumulative Risk Characterization/Assessment

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

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

9.0 Occupational Exposure/Risk Pathway

Reference: *Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration of the Pyridaben on Stone Fruits (Crop Group 12). Hops, Strawberries, Tropical Fruit and Greenhouse Tomatoes.* (Memo, 9/11/2003, J. Arthur, D261499).

9.1 Short/Intermediate/Long-Term Handler Risk

Using endpoints selected by the HIARC, potential exposure/risk to handlers of pyridaben was estimated for the following scenarios: (1) mixing/loading: wettable powder (WP) in water-soluble bags to support high-pressure handwand; (2) mixing/loading WP in water-soluble bags to support airblast sprayer; (3) mixing/loading WP in water-soluble bags to support groundboom sprayer; (4) application by high-pressure handwand; (5) application by air-blast sprayer, and; (6) application by groundboom sprayer.

No chemical-specific handler exposure data were submitted in support of this Section 3 registration. In accordance with HED's Exposure Science Advisory Council (SAC) policy, exposure data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) was used with other HED default values for acres treated per day, body weight, and the level of personal protective equipment to assess handler exposures. It should be noted that the PHED has values for a handler who mixes, loads and applies liquids using a high-pressure handwand. Even though this scenario may exist for handlers treating greenhouse tomatoes, it was not used. The PHED values are for liquids, while the pyridaben product is packaged in water-soluble bags. Using the combined activity unit exposure values from PHED for liquids might lead to an unreasonably conservative risk estimate, and would not allow for a determination of which tasks contributed the most exposure, and therefore, may be in need of additional PPE and clothing.

The unit exposure values from PHED are considered to be central tendency, while other inputs used in this assessment, such as maximum labeled application rates, are upper percentile values. Overall, the potential exposures estimated in this assessment are characterized as central to high-end.

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

Exposure and risk estimates for occupational handlers are summarized in Table 9.1.

Handlers who mix and load pyridaben were assessed at the maximum application rate, wearing long pants, long-sleeved shirt, shoes plus socks and gloves, and using the product in the marketed water-soluble bags. Handlers who apply pyridaben were assessed at the maximum application rate, in the above clothing (except for the gloves), and using open cab tractors. **Total MOEs (i.e., from combined dermal and inhalation routes) are 100 for all handler scenarios and do not exceed HED's level of concern.**

Table 9.1. Exposure and Risk Assessment for Occupational Handlers

PHED Scenario for Pyridaben Uses	PHED Unit Exposure ¹	Data Confidence	Max. Application Rate (lb ai/acre)	Area Treated (acres/day)	Daily Dose ² (mg/kg bw/day)	Short/Intermediate Term Risk (MOE) ³	Total Risk (MOE) ⁴
(1) Mix/load : WP for High-pressure Handwand ⁵ (Water-soluble bags; gloves)	Dermal 0.0098 (mg/lb ai)	Low	0.19 (per 100 gallons)	1000 (gallons)	0.00027	380,000	36,000
	Inhalation 0.24 (ug/lb ai)	Low			0.0000065	40,000	
(2) Mix/load : WP for Airblast sprayer (Water-soluble bags; gloves)	Dermal 0.0098 (mg/lb ai)	Low	0.5	40	0.0028	36,000	3400
	Inhalation 0.24 (ug/lb ai)	Low			0.000069	3800	
(3) Mix/load : WP for Ground-boom sprayer (Water-soluble bags; gloves)	Dermal 0.0098 (mg/lb ai)	Low	0.5	80	0.0056	18,000	1700
	Inhalation 0.24 (ug/lb ai)	Low			0.00014	1900	
(4) Application High-pressure Handwand	Dermal 1.8 (mg/lb ai)	Low	0.19 (per 100 gallons)	1000 (gallons)	0.049	2000	110
	Inhalation 79 (ug/lb ai)	Low			0.0021	120	
(5) Application Airblast Sprayer (Open Cab)	Dermal 0.36 (mg/lb ai)	High	0.5	40	0.103	970	170
	Inhalation 4.5 (ug/lb ai)	High			0.0013	200	
(6) Application Groundboom Sprayer (Open Cab)	Dermal 0.014 (mg/lb ai)	High	0.5	80	0.008	12,500	600
	Inhalation 0.74 (ug/lb ai)	High			0.00042	620	

¹ Unless otherwise specified, unit exposure values are for workers wearing baseline clothing (i.e., long-sleeved shirt, long pants, shoes and socks).

² Daily Dose = [Application Rate (lb ai/A) x Acres Treated (A/day) x Unit Exposure (mg/lb ai handled)] / Body Weight (70 kg).

³ MOE = NOAEL / Daily Dose. Short- and Intermediate-term Dermal NOAEL = 100 mg/kg bw/day. Short- and Intermediate-term Inhalation NOAEL = 0.261 mg/kg bw/day.

⁴ Total Risk MOE = 1 ÷ (1/MOE_{dermal} + 1/MOE_{inhalation}).

⁵ PHED unit exposure for "high-pressure handwand" most closely matches the "hand-gun" scenario for pyridaben application on greenhouse tomatoes, and is therefore used here.

9.2 Short/Intermediate/Long-Term Postapplication Risk

This Section 3 action on pyridaben involves foliar applications. Therefore, there is a potential for short- and intermediate-term postapplication exposure to workers entering pyridaben-treated areas to perform a variety of agricultural tasks, and a risk assessment for these exposure are required. Long-term exposure is not expected (even for greenhouse tomatoes, where only 2 applications per growing season are separated by a 30-day treatment interval).

Inhalation exposure is expected to be negligible for most postapplication scenarios. However, due to the enclosed nature of greenhouses, the airborne concentration of volatile or semi-volatile pesticides may result in concerns for greenhouse workers following application of such pesticides. In a greenhouse worker study, where malathion was used to treat carnations², the highest daily potential inhalation exposure was 50 ug/day (0.00071 mg/kg bw/day), which was within a couple of orders-of-magnitude of the potential dermal exposure found in the same study. The fact that the vapor pressure of malathion (4×10^{-5} mm Hg) is very similar to that of pyridaben (8.21×10^{-5} mm Hg), indicates that the postapplication presence of pyridaben might also be expected. However, because an estimate of inhalation exposure (0.0021 mg/kg bw/day) to greenhouse applicators (an activity which is expected to result in the highest airborne levels of pyridaben) did not result in concern for HED, the potential postapplication exposure to any residual airborne concentration of pyridaben also is not considered to be of concern.

As an additional check, an estimate of potential airborne levels of pyridaben following the treatment of greenhouse tomatoes was made using the latex paint module of the Consumer Exposure Model (CEM) found in the OPPTS website for the Exposure, Fate Assessment Screening Tool (E-FAST) at <http://www.epa.gov/opptintr/exposure/docs/efast.htm>. Using this conservative, screening level assessment tool resulted in a peak estimate of worker inhalation exposure to pyridaben following the treatment of greenhouse tomatoes on the order of 1×10^{-5} mg/kg bw/day, which does not exceed HED's level of concern. This model is designed to predict airborne levels of commercial products used in residential houses. It was modified to account for greenhouses by assuming that the product was confined to one very large room in a house. This modification may detract from the predictive capability of the model; however, use of the model is still worthwhile for comparing outputs to those from HED's standard methodology.

The transfer coefficients used in this assessment are from an interim transfer coefficient policy developed by HED's Science Advisory Council for Exposure SOP 3.1), using proprietary data from the Agricultural Re-entry Task Force (ARTF) data base.

Two dislodgeable foliar residue (DFR) studies were available for use in estimating postapplication risks to pyridaben. One study was conducted on almond trees in California (MRID No. 440292-03). The other study (MRID No. 436804-25) was conducted on orange trees in California, Florida and Texas. Existing reviews of these studies indicated that, while there

² CalDPR. *Pesticide Exposure of Workers in Greenhouses*. California Department of Pesticide Regulation. Health and Safety Report. HS-1835. November 19, 2002.

were certain weaknesses with parts of the studies (field recoveries, in particular), they were sufficiently compliant with EPA's Pesticide Testing Guidelines for use in the risk assessment.

The DFR study conducted on orange trees in California, Florida and Texas (MRID No. 436804-25) was used for estimating postapplication exposures for the crops subject to this petition. In this study, two applications of pyridaben (75% WP) were applied 30 days apart by airblast sprayer at a rate of 0.495 lb ai/acre. Following the second application, leaf punch samples were collected periodically for 70 days. While field recoveries for this study were low (average field recover for Texas: 62%; Florida: 63.5 %; and, California: 68%), the field recovery data were able to be used to correct the reported DFR data. Estimated residue levels on the day of treatment (day 0) were highest for the California site. The California estimates were used in the assessment as a screen.

Using the short-/intermediate-term dermal toxicity endpoints and data from the DFR study with pyridaben use on California citrus, the MOEs for all major postapplication activities reach **an MOE of 100 on the day of treatment (i.e., day 0) for all crops, and therefore, do not exceed HED's level of concern.** A summary of the postapplication exposure and risk assessment is seen in Table 9.2.

The technical material has a Toxicity Category III for Acute Dermal and Primary Eye Irritation, and Category IV for Primary Skin Irritation. Per the WPS, a 12-hr REI is required for chemicals classified under Toxicity Categories III and IV. Therefore, the interim REI of 12 hours appearing on the pyridaben labels should be retained.

Table 9.2 Exposure and Risk Assessment for Occupational Postapplication Activities

Crop Group ¹	Application Rate (lb ai/A)	Dermal Transfer Coefficient (cm ² /hr)	Dislodgeable Foliar Residue ² (ug/cm ²)	Postapplication Day (t)	Daily Dose ³ (mg/kg bw/day)	Short-/Intermed. Term Dermal MOE ⁴
Trees, fruit, deciduous (Stone fruits): * apricots * cherries * nectarines * peaches * plums * plumcots * prunes	0.5	100: propping	1.11 (Calif.)	0	0.013	7900
		1000: irrigation, scouting, weeding (central value from ARF023)			0.127	790
		1500: harvesting, pruning, training, tying (central value)			0.19	530
		3000: thinning (central value)			0.38	260
Bunch/bundle: * hops		100: irrigation, hand weeding, scouting immature/low foliage plants (central value)	1.11 (Calif.)	0	0.013	7900
		1300: irrigation, scouting mature plants (Low-end value from ARF024)			0.165	600
		2000: hand harvesting, stripping, training, thinning, topping, mechanical hop harvest. (High-end value from ARF024)			0.254	390
Berry, low * strawberries	0.5	400: irrigation, scouting, weeding, pruning, thinning (low end value)	1.11 (Calif.)	0	0.051	2000
		1500: harvesting, hand pruning, pinching, training (high end value)			0.190	530
Trees, fruit, evergreen (Tropical fruits): * papaya * star apple * black sapote * mango * sapodilla * manney sapote * canistel	0.5	100: propping	1.11 (Calif.)	0	0.013	7900
		1000: irrigation, scouting, hand weeding (central value from ARF023)			0.127	790
		1500: harvesting, pruning, training, tying, thinning (central value)			0.19	530
		3000: thinning, pollination, tying, staking, topping, training (central value)			0.38	260
Vegetable, fruiting: * tomatoes (greenhouse)	0.19	500: irrigation, scouting, thinning, weeding immature plants (low end value from ARF021)	1.11 (Calif.)	0	0.063	1600
		700: irrigation, scouting mature plants (central value)			0.088	1100
		1000: hand harvesting, pruning, staking, tying (central value)			0.127	790

¹ All crops are represented by data from a DFR study on citrus trees (MRID 436804-25).² The estimated "day 0" residue value from California site is the highest of the three sites studied and is used as a screen for estimated day "0" values.³ Daily Dose = (Dislodgeable Foliar Residue x 0.001 mg/ug x Dermal Transfer Coefficient x Exposure Time (8 hrs.))/Body weight (70 kg)⁴ MOE = NOAEL/Daily Dose. Short-/Intermediate-Term Dermal NOAEL = 100 mg/kg bw/day. For short- and intermediate-term dermal risk assessment, the dermal absorption factor of 100% was applied because the endpoint chosen for this risk assessment was derived from a dermal toxicity study.

10.0 Data Needs and Label Requirements

10.1 Toxicology

No additional toxicology data are required at this time.

10.2 Residue Chemistry

HED concludes the number and distribution of the hop residue field trials are adequate for tolerance setting purposes as per the Residue Chemistry Test Guidelines (860.1500). HED further concludes the submitted residue data support a tolerance level of 10.0 ppm for residues of pyridaben in/on dried hop cones. **A revised Section F is required to revise the commodity designation to "hop cones, dried".**

Pyramite™ Miticide/Insecticide (EPA Reg. No. 7969-125) has been proposed for use on strawberries. HED concludes the proposed directions for use of pyridaben on strawberries are not adequate. **The petitioner should add the following restriction to the label: Fields treated with pyridaben may be rotated to other crops 30 days following the final application of pyridaben.**

HED concludes the proposed directions for use of Nexter and Pyramite on stone fruit are not adequate. A restriction against the grazing of livestock in treated orchards should be added to the labels.

HED concludes the petitioner should submit the final report for field trial data for greenhouse-grown tomatoes which includes information on the conditions and length of sample storage prior to extraction and analysis.

10.3 Occupational and Residential Exposure

There are no outstanding occupational or residential data for pyridaben.

References:

PYRIDABEN - 3rd Report of the Hazard Identification Assessment Review Committee (Memo, 11/6/03, W.B. Greear, TXR No. 0052217).

Report of the Hazard Identification Assessment Review Committee. (Memo, 7/22/98, G.A. Dannan and J. Rowland, TXR No. 012730).

Report of the Hazard Identification Assessment Review Committee. (Memo, 11/8/99, W.M. Tehseen and W. Greear, TXR No. 0013829).

PP#1E06226; Pyridaben (Pyramite™ Miticide/Insecticide) in/on Hops. Evaluation of Analytical Methodology and Residue Data and Submission of 1/17/2001. (Memo, 1/28/2004, W.D. Wassell, D271838).

PP#2E06460; Pyridaben (Pyramite™ Miticide/Insecticide) in/on Tropical Fruit Group (Including: Papaya, Star Apple, Black Sapote, Mango, Sapodilla, Mamey Sapote, and Canistel). Evaluation of Analytical Methodology and Residue Data. (Memo, 1/28/2004, W.D. Wassell, D285562).

PP#0E6068; Pyridaben (Pyramite™ Miticide/Insecticide) in/on Strawberries. Evaluation of Analytical Methodology and Residue Data for Strawberries and Confined Rotational Crops. (Memo, 2/18/2004, W.D. Wassell, D260466).

PP#2E6457. Pyridaben; Petition for the Establishment of a Permanent Tolerance for Residues in/on Stone Fruit. Summary of Analytical Chemistry and Residue Data. (Memo, 2/23/2004, W.D. Wassell, D285553).

PP#1E6303. Pyridaben; Petition for the Establishment of a Permanent Tolerance for Residues in/on Greenhouse-grown Tomato. Summary of Residue Data and a Waiver Request. (Memo, 2/23/2004, W.D. Wassell, D278766).

PP#1E6303. Pyridaben; Petition for the Establishment of a Permanent Tolerance for Residues in/on Greenhouse-grown Tomato. Reevaluation of crop field trial data. (Memo, 8/24/2005, W. D. Wassell, D320915).

Pyridaben Acute and Chronic (Non-Cancer) Dietary Exposure Assessments for the Section 3, Registration Actions (PP#1E06226 - Hops, PP#2E06460 - Tropical Fruits, PP#2E06068 - Strawberries, PP#1E06303 - Tomatoes. and PP#2E06457 - Stone Fruit). (Memo, W.D. Wassell, 05/12/2005, DP Barcode: 316834)..

Drinking Water Exposure Screening Assessment for Proposed Uses of Pyridaben on Strawberries, Hops, Tropical Fruit, and Stone Fruit. (Memo, 2/10/2004, K. Costello).

Risk Assessment for Proposed Uses of Pyridaben on Strawberries, Hops, Tropical Fruit and Stone Fruit. (Memo, 7/8/2004, Todd Phillips, et. Al., D285563).

Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration of the Pyridaben on Stone Fruits (Crop Group 12), Hops, Strawberries, Tropical Fruit and Greenhouse Tomatoes. (Memo, 9/11/2003, J. Arthur, D261499).

Summary of Usage Analyses Provided by BEAD for Pyridaben and Suggested FR Language. (Memo, 9/21/05, R. Prieto).

Appendices

1.0 TOXICOLOGY DATA REQUIREMENTS

The requirements (40 CFR 158.340) for food uses for pyridaben are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	no	NA
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	NA
870.3465 90-Day Inhalation	yes	yes
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5385 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.55500 Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	NA
870.6100b 90-Day Neurotoxicity (hen)	no	NA
870.6200a Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b 90 Day Neuro. Screening Battery (rat)	yes	yes
870.6300 Develop. Neurotox.	no	NA
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	NA
Special Studies for Ocular Effects		
Acute Oral (rat)	no	NA
Subchronic Oral (rat)	no	NA
Six-month Oral (dog)	no	NA

2.0 METABOLISM CONSIDERATIONS

A meeting to discuss the metabolism of pyridaben was conducted on 1/14/2004. The following Agency scientists were in attendance at this meeting: Abdallah Khasawinah, Rick Loranger, Yan Donovan, Leung Cheng, John Doherty, Thuy Nguyen, PV Shah, William Wassell, Leonard Keifer, Christine Olinger, George Kramer, Steve Dapson, Kevin Costello, William Greear, Chuck Stafford, and Yaonong Qian. The following issues were discussed at this meeting:

Does the Committee agree with the previous determination by the HED Metabolism Committee that the residue of concern for tolerance setting purposes in/on plant commodities is pyridaben and that the residues of concern for risk assessment are all organosoluble residues?

Does the Committee agree with the previous determination by the HED Metabolism Committee that the residue of concern for tolerance setting purposes in/on livestock commodities is pyridaben and its metabolites PB-7 and PB-9 and that the residues of concern for risk assessment is all organosoluble residues?

What is the residue of concern for rotational crops?

What is the residue of concern for drinking water?

Are additional plant metabolism data required for pyridaben?

The following table summarizes the findings of this meeting.

Table 1. Residues of Concern in Crops, Livestock, Rotational Crops, and Water		
Matrix	Tolerance Expression	Residues for Risk Assessment
Crops	Pyridaben only.	Pyridaben plus all metabolites containing the pyridazinone ring.
Livestock	Pyridaben and its metabolites PB-7 and PB-9.	Pyridaben and its metabolites PB-7 and PB-9.
Rotational Crops	Pyridaben only.	Pyridaben only.
Water	N/A	Pyridaben only.

Decision Rationale:

Plants: Plant metabolism studies using oranges, apples, and eggplant indicated that parent is the only major residue (>10% total radioactive residues or TRR). There are several minor metabolites containing either the pyridazinone or phenyl ring. These metabolites generally sum up to >10% of the TRR. HED believes that the metabolites containing the pyridazinone ring share similar toxicity to the parent based on their structural similarity to the parent (*i.e.*, possessing the pyridazinone ring). Metabolites containing only the phenyl moiety are anticipated

to be significantly less toxic than the parent. For risk assessment purposes, parent and all metabolites containing the pyridazinone ring are the residues of concern. For the tolerance expression, parent only is the residue of concern since it is the most abundant residue and can serve as a measure of misuse.

Livestock: The goat metabolism study indicated that parent is the only major residue in liver, while metabolites PB-7 and PB-9 are minor metabolites (3.8 - 7.9% TRR). No specific residue was firmly identified in other tissues or in milk. The metabolism study using laying hens indicated that PB-7 is the major metabolite (in liver) and parent was not found. HED considers PB-7 and PB-9 to have similar toxicity to the parent based on their structural similarity to the parent and concluded that the residues of concern for risk assessment and the tolerance expression are parent, PB-7 and PB-9. All three compounds are determined by the livestock method. Parent and PB-7 were found in milk and tissues (liver, fat), respectively, in the cattle feeding study.

Rotational Crops: The confined rotational crop study found that the ^{14}C -residues were comprised mainly of polar unknowns (described as multi-component fractions, with each component contributing <10% TRR) and minor amounts of the parent compound. Parent compound was identified in several commodities at levels less than 0.001 ppm. HED concluded that parent only is the residue of concern for rotational crops.

Drinking Water: Environmental fate studies indicated that parent is stable, has low water solubility (12 ppb), and a high level of binding to soil ($K_{\text{ads}}=108\text{-}6600$). It appears that pyridaben would remain bound to the soils during run-off events. Because of its relative immobility, pyridaben is not likely to reach subsurface soil environments (lower microbial activity) or ground water at significant concentrations. Lab studies indicated that the major routes of degradation/dissipation of pyridaben are aqueous photolysis (half-life of 5 to 40 minutes) and soil photolysis (half-life of 11 days). Based on the use pattern and the stability of pyridaben, aqueous photolysis and soil photolysis are likely to occur after the application of pyridaben. The only major degradate identified in any fate study was B-3 (27% of the applied dose) in aqueous photolysis. Based on the structure, HED believes that B-3 is likely to be significantly less toxic than the parent. B-3 is also not likely to be persistent in drinking water due to its potential to be oxidized to the benzoic acid degradate in the environment. HED concluded that B-3 can be excluded as a residue of concern for water. Among all the minor degradates, HED believes that none of them will likely be significantly more toxic than the parent. Thus, HED concluded that parent only is the residue of concern to be included in the drinking water assessment.

Need for Additional Metabolism Data: HED concluded that for the currently registered uses and the current proposed uses (hops, strawberries, tropical fruits, stone fruits, and tomatoes), no additional metabolism studies are required. If uses are proposed for grain crops and/or leafy vegetables, additional metabolism data using either a grain crop or leafy vegetable will be required.

Residue Chemistry Data Summary:

Use Information: Pyridaben is currently registered for use on tree nuts, pistachio, apple, pear, citrus fruits, grape, apricot, cherry, nectarine, peach, plum, prune, and cranberry. In the subject petitions, IR-4 has proposed the establishment of uses for pyridaben on hops, tropical fruit (including: papaya, star apple, black sapote, mango, sapodilla, mamey sapote, and canistel), strawberry, and greenhouse-grown tomatoes. Additionally, IR-4 proposes to modify the currently registered use for pyridaben on cherry and apricot, such that a group tolerance for residues in/on stone fruits could be established.

Summary of Metabolism Data - Oranges, Apples, and Eggplant:

Plant metabolism data for pyridaben in/on eggplant were submitted in conjunction with PP#0E06068. Previously, metabolism data for pyridaben in/on apples and oranges were submitted in conjunction with PP#4E4370. These studies are briefly summarized below.

Previous Metabolism Committee Conclusions:

The results of the apple and orange metabolism studies were presented to the HED Metabolism Committee on 10/7/96. In conjunction with this meeting, HED concluded that the nature of the residue in apples and oranges is adequately understood. Additionally, it was concluded that the tolerance expression for plant commodities will include pyridaben only. It was further concluded that all organosoluble residues may be presumed to be of comparable toxicity to the parent. Thus, the risk assessment for human dietary consumption of pyridaben treated plant commodities will include all organosoluble residues.

Metabolism in Oranges (MRID No. 43258902):

BASF Corporation submitted data from a [¹⁴C]pyridaben metabolism study on oranges. [¹⁴C]Pyridaben was labeled in either the phenyl [¹⁴C-Bz] or pyridazinone [¹⁴C-Pz] ring. Hamlin and Valencia oranges were treated twice at a high (4.25 lb ai/A/application) or low (0.51 lb ai/A/application) rate with each of the labeled pyridaben test substances formulated as a 20% WP. The high rate represents an 8.5x exaggerated rate and the low rate represents a 1x rate. Oranges were collected at various post treatment intervals following the first and second applications.

Table 2. Summary of identified and characterized residues in Hamlin and Valencia oranges treated with two applications of [¹⁴C]pyridaben at the low dose (0.51 lb ai/A/application, 1x rate) and harvested at a 7-day PHI.

Metabolite/ Component	Hamlin [¹⁴ C-Bz] (0.093 ppm)		Valencia [¹⁴ C-Bz] (0.048 ppm)		Hamlin [¹⁴ C-Pz] (0.116 ppm)		Valencia [¹⁴ C-Pz] (0.046 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Pyridaben	23.2	0.022	13.5	0.007	12.6	0.015	23.2	0.010
PB-11	-	-	-	-	0.4	<0.001	4.1	0.002
PB-14	4.6	0.004	1.8	0.001	4.2	0.005	1.5	0.001
PB-22	1.4	0.001	0.5	<0.001	2.3	0.003	0.4	<0.001
B-1 + PB-11	1.9	0.002	4.1	0.002	-	-	-	-
B-3 + Unknown 3	0.6	0.001	-	-	-	-	-	-
B-11	2.7	0.002	0.7	<0.001	-	-	-	-
P-14	-	-	-	-	3.6	0.004	0.3	<0.001
Total Identified	34.4	0.032	20.6	0.012	23.1	0.028	29.5	0.015
Unknown(s) ^a	9.7 (7, ≤4.2)	0.010 (7, ≤0.004)	8.0 (5, ≤2.6)	0.005 (5, ≤0.001)	10.1 (7, ≤4.8)	0.013 (7, ≤0.006)	7.9 (6, ≤3.2)	0.006 (6, ≤0.001)
Organosoluble unknowns ^b	12.5	0.011	4.8	0.002	5.7	0.007	4.0	0.002
Intermediate polar	1.4	0.001	0.2	<0.001	0.5	0.001	0.7	<0.001
Polar	4.7	0.004	0.8	<0.001	1.1	0.003	0.6	<0.001
Aqueous soluble	3.5	0.003	2.1	0.001	6.8	0.008	2.4	0.001
Solids ^a	17.6 (2, ≤10.8)	0.016 (2, ≤0.010)	39.2 (2, ≤20.4)	0.019 (2, ≤0.010)	21.0 (2, ≤10.7)	0.024 (2, ≤0.012)	44.0 (2, ≤28.8)	0.020 (2, ≤0.013)
MeOH:H ₂ O extract of pulp combined with juice and pulp solids	1.0	0.001	0.4	<0.001	1.6	0.002	1.2	0.001
Total characterized/ identified	65.5	0.060	65.0	0.034	51.4	0.061	78.7	0.038

^a For the values listed parenthetically, the number on the left is the total number of fractions and the number on the right is the %TRR or ppm of the highest fraction.

^b The total radioactive residue in organosoluble unknowns is shown in this row. Radioactivity in unknown TLC spots isolated in the intermediate polar and polar regions of the plate is indicated in the two successive rows.

Table 3. Summary of identified and characterized residues in Hamlin and Valencia oranges treated with two applications of [¹⁴C]pyridaben at the high dose (4.25 lb ai/A/application) and harvested at a 7-day PHI.

Metabolite/ Component	Hamlin [¹⁴ C-Bz] (0.721 ppm)		Valencia [¹⁴ C-Bz] (0.490 ppm)		Hamlin [¹⁴ C-Pz] (0.966 ppm)		Valencia [¹⁴ C-Pz] (0.368 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Pyridaben	36.3	0.263	28.0	0.139	27.2	0.264	24.6	0.092
PB-11	--	--	--	--	1.1	0.010	0.9	0.003
PB-14	1.0	0.007	1.0	0.005	1.9	0.018	0.8	0.003
PB-22	0.4	0.003	0.2	0.001	0.7	0.007	0.3	0.001
B-1 + PB-11	1.0	0.007	1.3	0.007	--	--	--	--
B-3 + Unknown 3	0.2	0.001	0.4	0.002	--	--	--	--
B-11	1.1	0.008	0.9	0.004	--	--	--	--
P-14	--	--	--	--	2.4	0.023	0.3	0.001
PB-7	--	--	--	--	--	--	* d	--
Total Identified	40.0	0.289	31.8	0.158	33.3	0.322	26.9	0.100
Unknown(s) ^a	4.3 (3, ≤2.9)	0.031 (3, ≤0.021)	5.5 (5, ≤1.9)	0.028 (5, ≤0.010)	4.4 (6, ≤1.7)	0.044 (6, ≤0.017)	8.4 (7, ≤3.3)	0.031 (7, ≤0.012)
Organosoluble unknowns ^b :	5.7	0.042	4.6	0.021	5.4	0.058	4.1	0.015
Non-polar	-	-	-	-	0.3	0.003	0.1	<0.001
Intermediate polar	0.2	0.002	0.2	0.001	1.1	0.012	0.8	0.003
Polar	3.6	0.027	1.9	0.009	2.3	0.025	1.8	0.007
Aqueous soluble	3.8	0.028	3.8	0.018	3.0	0.032	2.7	0.010
Peel extract (soxhlet)	3.2	0.023	2.8	0.013	3.1	0.032	4.3	0.015
Peel extract (MeOH/HCl)	1.8	0.013	1.9	0.009	1.8	0.019	4.3	0.016
Solids ^a	7.7	0.056	21.0 (2, ≤13.4)	0.103 (2, ≤0.064)	15.9 (2, ≤8.3)	0.162 (2, ≤0.088)	28.6 ^c	0.104
MeOH:H ₂ O extract of pulp combined with juice and pulp solids	2.2	0.016	0.4	0.002	6.4	0.068	0.4	0.002
Total characterized/ identified	68.7	0.498	71.8	0.352	73.6	0.740	79.8	0.294

^a For the values listed parenthetically, the number on the left is the total number of fractions and the number on the right is the %TRR or ppm of the highest fraction.

^b The total radioactive residue in organosoluble unknowns is shown in this row. Radioactivity in unknown TLC spots isolated in the non-polar, intermediate polar, and polar regions of the plate is indicated in the two successive rows.

^c These solids are comprised of the surface wash particulate (13.5% TRR) and the peel solids (15.1% TRR). The peel solids were extracted with NaOH at ambient temperature, and twice solvent partitioned with EtOAc. The organic fractions contained a total of 7.1% TRR. The metabolites PB-7, PB-14, P-14, and P-16 were identified in this fraction by 2D-TLC.

^d PB-7 tentatively identified by 2D-TLC. No quantitative data presented.

The petitioner has proposed that the metabolism of pyridaben is similar in oranges and apples (see below) involving primarily photochemical, hydrolytic, and oxidative reactions. The principal metabolic pathway apparently involves the photo-induced rearrangement of the parent, in which the phenyl group is substituted for the chlorine on the pyridazinone ring to form a thioalcohol. The other metabolic pathways involve the oxidation of the tertiary butyl groups or

the hydrolytic cleavage and subsequent oxidation of the phenyl and pyridazinone moieties. Metabolites identified in oranges are shown in Figure 1.

Metabolism in Apple (MRID No. 43287601):

BASF Corporation submitted data from a [^{14}C]pyridaben metabolism study with apples. [^{14}C]Pyridaben was labeled in either the phenyl [^{14}C -Bz] or pyridazinone [^{14}C -Pz] ring. Apple trees were sprayed three times at intervals of 28 and 34 days with [Bz-U- ^{14}C]pyridaben at 300 g ai/ha (1x the proposed rate) and apples were collected 25 days following the final application. To obtain residue levels high enough for metabolite identification, individual apples were also painted with a solution of [Bz-U- ^{14}C] or [Pz-3,6- ^{14}C]pyridaben at 1 mg/apple, approximately 40x the proposed rate, and collected after 40 days.

Total Radioactive Residues (TRR)

The total radioactive residues in peel, pulp, and whole apples are presented in Table 4.

Table 4. Total radioactive residues in peel and pulp of [^{14}C]pyridaben-treated apples and TRR calculated in whole fruit.

Treatment/Sample	TRR (expressed as ppm in matrix)	TRR (expressed as ppm in whole fruit)
Three foliar applications at 1x (300 g ai/ha) with [^{14}C-Bz]pyridaben; 25-day PHI		
Peel	0.810	0.111
Pulp	0.031	0.027
Whole fruit *	--	0.138
Fruit painted with [^{14}C-Bz]pyridaben at 1 mg ai/apple; 40-day PHI		
Peel	34.088	5.079
Pulp	0.272	0.231
Whole fruit *	--	5.310
Fruit painted with [^{14}C-Pz]pyridaben at 1 mg ai/apple; 40-day PHI		
Peel	32.055	5.097
Pulp	0.373	0.314
Whole fruit *	--	5.411

Values for whole fruit were calculated by the petitioner from peel and pulp data.

A summary of the ^{14}C -residues identified and characterized in apple fruit is presented in Table 5; total amounts of each component in whole fruit were obtained by adding the respective peel and pulp values.

Table 5. Summary of ^{14}C -residues identified and characterized in apples treated with [^{14}C]Pyridaben.

Metabolite/ Component	Treatment					
	Spray 1x [^{14}C -Bz] (0.138 ppm)		Painted [^{14}C -Bz] (5.310 ppm)		Painted [^{14}C -Pz] (5.411 ppm)	
	% TRR ^a	ppm ^b	% TRR ^a	ppm ^b	% TRR ^a	ppm ^b
Pyridaben	20.8	0.028	48.6	2.58	51.54	2.789
PB-14	ND ^c	ND	ND	ND	2.28	0.123
PB-17	1.4	0.002	0.9	0.045	0.8	0.044
PB-22	3.1	0.004	1.04	0.055	1.44	0.078
PB-14/B-3	4.2	0.006	2.07	0.110	N/A ^d	N/A
B-1	6.0	0.008	1.12	0.059	N/A	N/A
B-5	ND	ND	2.72	0.144	N/A	N/A
P-2	N/A	N/A	N/A	N/A	1.6	0.087
D-1	ND	ND	0.8	0.039	ND	ND
Identified	35.5	0.048	57.25	3.040	57.76	3.120
Unknown HPLC Peaks						
Non-polar	0.06	<0.001	3.3	0.175	2.1	0.114
Intermediate polarity	4.52	0.006	9.48	0.503	7.54	0.407
Highly polar	18.54	0.026	10.28	0.546	7.76	0.420
Natural constituents						
Starch	8.3	0.012	NA	-- ^e	1.5	0.081
Cellulose	3.9	0.005	NA	--	1.0	0.054
Lignin	4.3	0.006	NA	--	15.7	0.850
Protein	ND	ND	NA	--	0.13	0.007
Total characterized	39.62	0.055	23.06	1.224	35.73	1.929
Insoluble	13.5	0.019	19.1	1.014	9.9	0.536
Volatiles	--	--	0.5	0.027	2.2	0.119
Aqueous, not analyzed	1.1	0.002	2.1	0.112	2.0	0.108
Other	9.1	0.013	0.5	0.028	0.5	0.027
Total	98.82	0.137	102.51	5.443	108.09	5.849

^a Percent of TRR for whole fruit calculated by reviewer from data on peel and pulp.^b Concentrations (ppm) of radioactivity were calculated by reviewer by multiplying the whole fruit % of TRR by the whole fruit TRR.^c ND = Not detected.^d N/A = Not applicable to this test owing to position of radiolabel.^e -- = Not analyzed in this study.

The petitioner has proposed that the metabolism of pyridaben in apples involves primarily photochemical, hydrolytic, and oxidative reactions. The principal metabolic pathway apparently involves the photo-induced rearrangement of the parent, in which the benzyl group is substituted for the chlorine on the pyridazinone ring to form a thioalcohol. The petitioner theorizes that exposure to sunlight causes formation of a delocalized $n-\pi^*$ excited state diradical and a partial carbon-to-carbon bond that weakens the carbon-chloride and carbon-sulfur bonds. The photo-rearrangement product (PB-15) then forms after collapse of the proposed transition state and is either reduced to PB-17 or further oxidized to the D-1 dimer, PB-14, and PB-22. The other metabolic pathways involve the oxidation of the tertiary butyl groups or the hydrolytic cleavage and subsequent oxidation of the phenyl and pyridazinone moieties. Metabolites identified in apples are shown in Figure 1.

Metabolism in Eggplant (MRID No. 44939703):

The petitioner has submitted data concerning the metabolism of pyridaben in eggplants. In this study, the absorption, translocation, and metabolism of [^{14}C]pyridaben were studied with eggplants grown under greenhouse conditions. The test substances used in this study were pyridaben that was uniformly labeled in the phenyl ring (referred to as ^{14}C -[Bz]-pyridaben) with a specific activity of 28.4 mCi/mmol and one that was labeled in the C-3 and C-6 positions of the pyridazone ring (referred to as ^{14}C -[Pz]-pyridaben) with a specific activity of 25.6 mCi/mmol. For the absorption and translocation portion of the study, eggplant seedlings in plastic pots were utilized. For the absorption, translocation and metabolism study, eggplants with fruits in plastic pot were utilized.

The absorption and translocation study was conducted by topically applying 100 μL of pyridaben (200 ppm solution) to a newly developed leaf. In another study, a leaf in the middle of the shoot (fourth leaf) was treated with 200 μL of pyridaben (200 ppm solution). Five and twelve days after treatment, two or three plants were pulled from the soil. The roots were washed with tap water to remove adhering soil. The plants were divided into treated leaf, other aerial parts, and root samples. The samples were air-dried. The levels of radioactivity were determined by combustion of the plant material followed by liquid scintillation counting. Additionally, five days after treatment a whole plant was subjected to autoradiography. The distribution of radioactivity in eggplant seedlings after topical application of pyridaben is summarized in Table 6.

Table 6. Distribution of Radioactivity in/on Eggplants Treated with [^{14}C]Pyridaben.

Compound	Plant Parts	Percent of Radioactivity			
		5-Day Samples		12-Day Samples	
		7L ¹	4L ²	7L	4L
^{14}C -[Bz]-pyridaben	Shoots				
	Upper Parts	0.2	0.1	0.4	0.1
	Treated Leaf	92.8	93.1	89	94.1
	Lower Parts	0.1	0	0.3	0.1
	Roots	0.1	0.1	0.1	0
	Total	93.2	93.3	89.8	94.3
^{14}C -[Pz]-pyridaben	Shoots				
	Upper Parts	0.1	0	0.6	0.2
	Treated Leaf	102.7	91.8	95.5	84.2
	Lower Parts	0.1	0	0.4	0.1
	Roots	0	0	0.1	0
	Total	102.9	91.8	96.6	84.5

¹7L = seventh leaf.

²4L = fourth leaf.

For the absorption, translocation, and metabolism study, eggplants with fruits were treated with a 200 ppm solution of the test substance with the use of a brush. In a separate study, the fruits were covered with polyethylene bags and the remaining foliar portion (stems and leaves) were treated in a similar manner in order to determine if translocation to the fruits occurs. On days one, seven, and fourteen following application to the whole plants, three fruits were harvested. These fruits were rinsed with acetone and aliquots of the acetone surface rinse were analyzed. Fourteen days following treatment, fruits were collected from the plant with the covered fruits.

The fruits were extracted twice via homogenization with methanol. The methanol extracts were filtered and combined. The solvent was exchanged to water and the aqueous phase was extracted twice with ethyl acetate. The solvent was exchanged to acetone prior to chromatographic analysis. Aliquots of the extracts and solids were analyzed to determine radioactivity levels. Total radioactive residue levels in eggplant samples and extracts are summarized in Tables 7 and 8, respectively.

Table 7. Total Radioactive Residues Found in/on Eggplant Fruits Treated with [¹⁴C]Pyridaben.

Samples	Total Radioactive Residues ¹ (ppm)
1-Day Bz ²	1.88
7-Day Bz	1.2
14-Day Bz	1.13
14-Day Covered (Bz)	0.007
1-Day Pz ³	1.91
7-Day Pz	1.8
14-Day Pz	1.6
14-Day Covered (Pz)	0.006

¹ Total radioactive residues are reported as pyridaben equivalents.

² Bz refers to the phenyl labeled compound.

³ Pz refers to the pyridazinone labeled compound.

Table 8. Distribution of Radioactive Residues in Various Extracts from [¹⁴C]Pyridaben Treated Eggplant Fruits.

Fraction	Total Radioactive Residue Levels and Percent of Total Recovered Radioactivity			
	Uncovered			Covered
	1-Day Sample ppm ¹ - %	7-Day Sample ppm - %	14-Day Sample ppm - %	14-Day Sample ppm - %
Bz Treated Eggplant Samples²				
Surface Rinse	1.697 - 90.2	0.98 - 82.1	0.887 - 78.2	-----
Methanol extracts	0.162 - 8.6	0.151 - 13.0	0.165 - 14.6	0.006 - 84.8
Ethyl acetate phase	0.119 - 6.3	0.112 - 9.8	0.123 - 10.8	-----
Aqueous Phase	0.043 - 2.3	0.039 - 3.3	0.042 - 3.8	-----
Bound Residues	0.023 - 1.3	0.058 - 4.8	0.077 - 7.2	0.001 - 15.2
Total	1.882 - 100	1.196 - 100	1.129 - 100	0.007 - 100
Pz Treated Eggplant Samples³				
Surface Rinse	1.799 - 94.2	1.545 - 85.9	1.304 - 81.6	-----
Methanol extracts	0.101 - 5.1	0.198 - 11.0	0.182 - 11.3	0.005 - 78.2
Ethyl acetate phase	0.079 - 4.0	0.146 - 8.2	0.138 - 8.6	-----
Aqueous Phase	0.022 - 1.1	0.052 - 2.9	0.044 - 2.7	-----
Bound Residues	0.014 - 0.8	0.054 - 3.0	0.110 - 7.0	0.0001 - 21.8
Total	1.914 - 100	1.796 - 100	1.569 - 100	0.006 - 100

¹ Residue levels are reported as pyridaben equivalents.² Bz refers to the phenyl labeled compound.³ Pz refers to the pyridazinone labeled compound.

Residues identified in the surface rinse and ethyl acetate extracts are summarized in Table 9 and 10, respectively.

Table 9. Summary of Identified Residues in the Surface Rinse of [¹⁴C]Pyridaben Treated Eggplant Fruits.

TLC Fraction	Identification	Radioactive Residue Levels and Percent of Total Recovered Radioactivity		
		Uncovered		
		1-Day Sample ppm ¹ - %	7-Day Sample ppm - %	14-Day Sample ppm - %
Bz treated samples¹				
ER-1	unknown	0.005 - 0.3	0.003 - 0.2	0.003 - 0.3
ER-2	D-1	0.005 - 0.3	0.004 - 0.4	0.007 - 0.6
ER-3	unknown	0.011 - 0.6	0.006 - 0.5	0.007 - 0.6
ER-4	pyridaben	1.573 - 83.6	0.916 - 76.2	0.812 - 71.6
ER-5	unknown	0.066 - 3.5	0.032 - 2.7	0.032 - 2.8
ER-6	origin - unknown	0.037 - 2.0	0.025 - 2.1	0.027 - 2.3
Total	-----	1.697 - 90.2	0.987 - 82.1	0.887 - 78.2
Pz treated samples²				
ER-1	unknown	0.005 - 0.3	0.003 - 0.2	0.003 - 0.2
ER-2	D-1	0.004 - 0.2	0.005 - 0.3	0.008 - 0.5
ER-3	unknown	0.011 - 0.6	0.010 - 0.6	0.009 - 0.6
ER-4	pyridaben	1.686 - 88.3	1.459 - 81.1	1.207 - 75.5
ER-5	unknown	0.058 - 3.0	0.035 - 1.9	0.038 - 2.4
ER-6	origin - unknown	0.036 - 1.9	0.032 - 1.8	0.038 - 2.4
Total	-----	1.779 - 94.2	1.545 - 85.9	1.304 - 81.6

¹ Residue levels are reported as pyridaben equivalents.

² Bz refers to the phenyl labeled compound.

³ Pz refers to the pyridazinone labeled compound.

Table 10. Summary of Identified Residues in the Ethyl Acetate Phase from Methanol Extracts of [¹⁴C]Pyridaben Treated Eggplant Fruits.

TLC Fraction	Identification	Radioactive Residue Levels and Percent of Total Recovered Radioactivity		
		Uncovered		
		1-Day Sample ppm ¹ - %	7-Day Sample ppm - %	14-Day Sample ppm - %
Bz treated samples¹				
EE-1	unknown	0.002 - 0.1	0.002 - 0.2	0.004 - 0.3
EE-2	pyridaben	0.075 - 4.0	0.060 - 5.4	0.006 - 5.7
EE-3	unknown	0.008 - 0.4	0.007 - 0.6	0.005 - 0.5
EE-4	unknown	0.004 - 0.2	0.002 - 0.2	0.003 - 0.3
EE-5	unknown	0.001 - 0.0	0.001 - 0.1	0.001 - 0.1
EE-6	unknown	0.011 - 0.6	0.009 - 0.8	0.009 - 0.8
EE-7	unknown	0.002 - 0.1	0.003 - 0.2	0.003 - 0.3
EE-8	origin - unknown	0.016 - 0.8	0.028 - 2.3	0.032 - 2.8
Total	—	0.119 - 6.3	0.112 - 9.8	0.123 - 10.8
Pz treated samples²				
EE-1	unknown	0.001 - 0.1	0.003 - 0.2	0.004 - 0.2
EE-2	pyridaben	0.057 - 2.9	0.093 - 5.2	0.087 - 5.5
EE-3	unknown	0.005 - 0.2	0.009 - 0.5	0.006 - 0.4
EE-4	unknown	0.003 - 0.1	0.003 - 0.2	0.003 - 0.2
EE-5	unknown	0.0 - 0.0	0.001 - 0.0	0.001 - 0.1
EE-6	unknown	0.005 - 0.2	0.008 - 0.4	0.007 - 0.4
EE-7	unknown	0.001 - 0.0	0.002 - 0.1	0.002 - 0.1
EE-8	origin - unknown	0.007 - 0.3	0.027 - 1.5	0.028 - 1.7
Total	—	0.079 - 4.0	0.146 - 8.2	0.138 - 8.6

¹ Residue levels are reported as pyridaben equivalents.² Bz refers to the phenyl labeled compound.³ Pz refers to the pyridazinone labeled compound.**Conclusions:**

Absorption and translocation study from leaves of eggplant seedlings: Five and twelve days following application of [¹⁴C]pyridaben to eggplant seedlings (leaf surface), a large majority of the radioactivity (84% to 103%) remained in/on the treated leaves. Only 0.2 to 1.1% of the

radioactivity was translocated to other parts of the plant. The results indicate that translocation of pyridaben in eggplant seedlings is almost negligible.

Absorption, translocation, and metabolism study by mature eggplants: Following applications of [^{14}C]pyridaben to eggplant (whole plant application and with the fruit covered), total radioactive residues in fruits from the whole plant application were 1.88 ppm for Bz-labeled pyridaben and 1.91 ppm for Pz- labeled pyridaben at a harvest interval of one day and decreased to 1.20 ppm (Bz-label) and 1.80 ppm (Pz- label) at 7-days following the application. A large majority of the residue (> 80% of the TRR) was recovered in surface rinses of the fruit. Fourteen days following the application TRRs were 1.13 ppm (Bz-label) and 1.60 ppm (Pz-label). The TRR concentrations of the surface rinses decreased gradually with increased pre-harvest intervals, while those in the methanol extract did not vary significantly with time. Bound residue levels increased over time, however, the concentrations were low (up to 0.11 ppm, 7% TRR).

For the plants with covered fruit, the TRR levels at a PHI of 14 days were low in the fruits (0.007 ppm and 0.006 ppm for Bz- and Pz-labels respectively). Thus, translocation from the stems and leaves of the plant to fruit was low.

Only the surface rinses of the leaves and fruit and the ethyl acetate phase of the methanol extracts were subjected to TLC analysis. For the surface rinses, the residues on the TLC plate were separated into fractions ER-1 through ER-6. Fraction ER-6 was characterized as polar unknowns, while fractions ER-4 and ER-2 were identified, by one method only, as pyridaben and metabolite D-1, respectively. The major identified residue was that of the parent compound which accounted for approximately 72 to 88% of the TRR. Residues of D-1 were low (0.004 to 0.008 ppm, <0.6% of the TRR). Residues in the ethyl acetate fraction of the methanol extract were separated by TLC analysis into fraction EE-1 through EE-8. Fraction EE-8 was characterized as polar unknowns (up to 0.032 ppm, 2.8% TRR), while fraction EE-2 was identified as pyridaben at up to 0.093 ppm (5.2% TRR).

Figure 1. Pyridaben and its metabolites in plants and livestock.

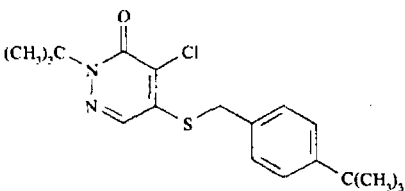
Common Name Chemical Name	Structure	Substrate
Pyridaben (PB-1) 2-tert-butyl-5-(4-tert-butylbenzylthio)-4-chloropyridazin-3(2H)-one		Apple Orange Eggplant Goat liver Poultry fat, skin, and excreta

Figure 1. Continued.

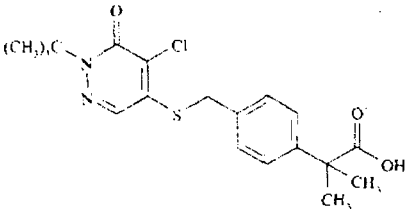
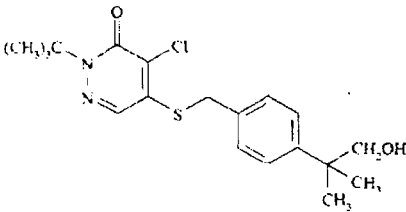
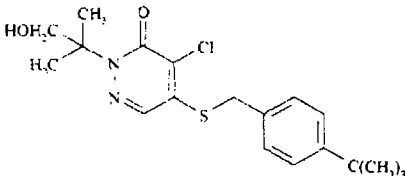
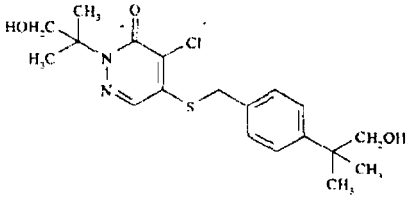
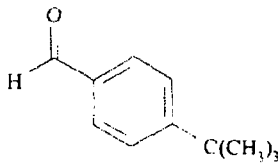
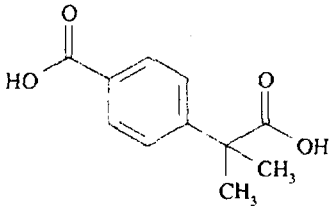
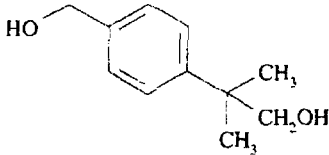
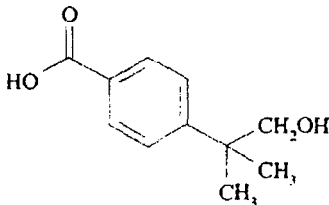
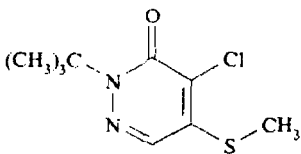
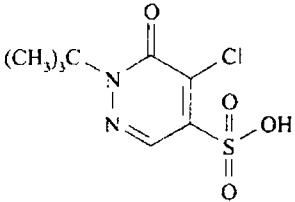
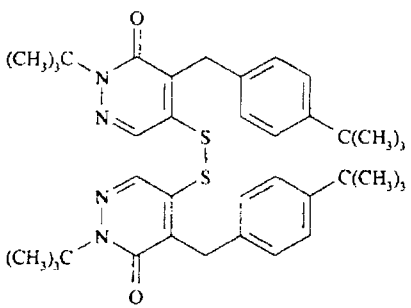
Common Name Chemical Name	Structure	Substrate
PB-7 2- <i>tert</i> -butyl-5-[4-(1-carboxy-1-methylethyl)benzylthio]-4-chloropyridazin-3(2 <i>H</i>)-one		Orange (tentative) Goat liver Poultry liver, fat, and skin
PB-9 2- <i>tert</i> -butyl-5-[4-(1,1-dimethyl-2-hydroxyethyl)-benzylthio]-4-chloropyridazin-3(2 <i>H</i>)-one		Goat liver Poultry liver, fat, and skin
PB-11 5-(4- <i>tert</i> -butylbenzylthio)-4-chloro-2-(1,1-dimethyl-2-hydroxyethyl)pyridazin-3(2 <i>H</i>)-one		Orange Poultry fat (tentative)
PB-13 4-chloro-2-(1,1-dimethyl-2-hydroxyethyl)-5-[4-(1,1-dimethyl-2-hydroxyethyl)benzylthio]-pyridazin-3(2 <i>H</i>)-one		Poultry muscle and excreta (tentative)

Figure 1. Continued.

Common Name Chemical Name	Structure	Substrate
PB-14 2- <i>tert</i> -butyl-4-(4- <i>tert</i> -butylbenzyl)pyridazin-3(2 <i>H</i>)-one-5-sulfonic acid		Apple Orange
PB-17 2- <i>tert</i> -butyl-4-(4- <i>tert</i> -butylbenzyl)pyridazin-3(2 <i>H</i>)-one		Apple
PB-22 2- <i>tert</i> -butyl-4-(4- <i>tert</i> -butylbenzoyl)pyridazin-3(2 <i>H</i>)-one-5-sulfonic acid		Apple Orange
B-1 4- <i>tert</i> -butylbenzoic acid		Apple Orange (tentative)
B-3 4- <i>tert</i> -butylbenzylalcohol		Apple Orange (tentative)

Figure 1. Continued.

Common Name Chemical Name	Structure	Substrate
B-5 4- <i>tert</i> -butylbenzaldehyde		Apple
B-7 2-(4-carboxyphenyl)-2-methylpropionic acid		Poultry excreta
B-8 2-(4-hydroxymethylphenyl)-2-methyl-1-propanol		
B-11 2-(4-carboxyphenyl)-2-methyl-1-propanol		Orange Poultry excreta (tentative)
P-2 2- <i>tert</i> -butyl-4-chloro-5-methylthiopyridazin-3(2 <i>H</i>)-one		Apple

Common Name Chemical Name	Structure	Substrate
P-14 2- <i>tert</i> -butyl-4-chloropyridazin-3(2 <i>H</i>)-one-sulfonic acid		Orange
D-1 Di[2- <i>tert</i> -butyl-4-(4- <i>tert</i> -butylbenzyl)-pyridazin-3(2 <i>H</i>)-one-5-yl]disulfide		Apple Eggplant

Summary of Metabolism Data - Livestock

BASF has previously submitted metabolism studies for lactating goats and laying hens. Poultry feed items are not associated with the registered or proposed uses of pyridaben. Thus, the data concerning the metabolism of pyridaben in poultry are informational. Ruminant feed items are associated with citrus, apples, and almonds. Thus, the metabolism of pyridaben in ruminants is of concern.

The results of the livestock metabolism studies were presented to the HED Metabolism Committee on 10/7/96. In conjunction with this meeting, HED concluded that the nature of residue in livestock is adequately understood. Additionally, it was concluded that the tolerance expression for ruminant commodities will include pyridaben and its metabolites PB-7 and PB-9. It was further concluded that all organosoluble residues may be presumed to be of comparable toxicity to the parent. The risk assessment for human consumption of ruminant commodities will also include all organosoluble residues. For liver HED will calculate a ratio of pyridaben, PB-7 and PB-9 residues to organosoluble residues based upon the ruminant metabolism study. For milk and other tissues best estimates of residues of concern for risk assessment may need to be based on total organosoluble residues in the goat metabolism study.

Metabolism in Lactating Goats:

BASF Corporation submitted data depicting the metabolism of [^{14}C]pyridaben in lactating goats. Goats were dosed with [^{14}C]pyridaben radiolabeled either uniformly in the phenyl ring (^{14}C -Bz)

or at the 3 and 6 positions of the pyridazinone ring (^{14}C -Pz). Four goats were orally dosed for 5 consecutive days with either [^{14}C -Pz]pyridaben or [^{14}C -Bz]pyridaben at a low (0.2 mg/day) or high (20 mg/day) dose. Based upon actual feed consumption, the administered doses were equivalent to average dietary levels of 0.20 ppm for both low dose goats and 7.8 and 6.9 ppm for the high dose goats fed [^{14}C -Pz]pyridaben and [^{14}C -Bz]pyridaben, respectively. Based upon a diet consisting of wet apple pomace, dried citrus pulp and almond hulls, the calculated maximum theoretical dietary exposure of beef and dairy cattle to pyridaben residues would be 1.8 and 1.3 ppm, respectively. The high dose (7.8 ppm) represents an exaggerated feeding level of 4.4x and 6.2x for beef and dairy cattle, respectively.

Total radioactive residues, expressed in [^{14}C]pyridaben equivalents, in milk and tissues are presented in Table 12.

Table 12.. Total Radioactive Residues (TRR) in Milk and Tissues from Lactating Goats Dosed with [^{14}C]Pyridaben at 0.2 ppm and 6.9-7.8 ppm for 5 Consecutive Days.

Matrix	Total Radioactive Residue (ppm ^a)			
	[^{14}C -Pz]pyridaben		[^{14}C -Bz]pyridaben	
	Low dose (0.2 ppm)	High dose (7.8 ppm)	Low dose (0.2 ppm)	High dose (6.9 ppm)
Liver	0.004	0.139	0.002	0.106
Kidney	0.001	0.034	0.001	0.019
Fat ^b	0.007-0.012	0.059	<0.001	0.026
Muscle ^b	<0.001-0.002	0.009	<0.001	0.005
Milk	1pm	0.0008	0.0007	0.0014
	am	0.0008	0.0005	0.0018
	2pm	0.0011	0.0007	0.0029
	am	0.001	0.0007	0.0019
	3pm	0.0012	0.0006	0.0023
	am	0.001	0.0006	0.002
	4pm	0.0013	0.0006	0.0028
	am	0.0008	0.0005	0.0019
	5pm	0.0011	0.0007	0.0023
	am	0.001	0.0005	-

^a Residues expressed as [^{14}C]pyridaben equivalents; values are the mean of duplicate analyses.

^b For low dose goats, data are from the duplicate analysis of each type of fat and muscle tissue; for the high dose goats, single composited muscle and fat samples were analyzed in duplicate.

^c Residues in milk are expressed as μg equivalents/mL.

A summary of the identification/characterization of ^{14}C -residues is presented in Table 13.

Table 13. summary of Characterization/identification of Radioactive Residues (TRR) in Milk and Tissues of a Lactating Goat Dosed with [^{14}C -Pz] and [^{14}C -Bz]pyridaben at ~7-8 Ppm for 5 Consecutive Days.

Metabolite/ Fraction	Milk ^a		Liver		Kidney		Muscle		Fat	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
[^{14}C-Pz]pyridaben										
Pyridaben	-	-	17.6	0.025	-	-	-	-	-	-
PB-7	-	-	3.8	0.005	-	-	-	-	-	-
PB-9	-	-	5.1	0.007	-	-	-	-	***	-
PB-11	-	-	*** ^c	-	58.1 ^b	0.020	-	-	-	-
PB-12	-	-	-	-	-	-	-	-	*** ^c	-
PB-13	-	-	*** ^c	-	-	-	-	-	-	-
Total Identified	-	-	26.5	0.037	58.1	0.020	-	-	-	-
Organosoluble unknowns	-	-	18.9 (6) ^d	0.026	18.2 (4)	0.006	83.0 (3)	0.007	39.0 (5)	0.023
Organosoluble	65.9	0.003	15.3 ^e	0.022	-	-	-	-	-	-
Aqueous soluble	34.1	0.002	28.5 ^f	0.039	8.3	0.003	8.5	0.001	8.5	0.005
Total Characterized/ Identified	100	0.005	89.2	0.124	84.6	0.029	91.5	0.008	47.5	0.028
Non-extractable	-	-	2.0	0.003	15.4	0.005	8.5	0.001	52.5	0.031
[^{14}C-Bz]Pyridaben										
Pyridaben	-	-	6.5	0.007	-	-	-	-	-	-
PB-7	-	-	7.9	0.008	-	-	-	-	-	-
PB-9	-	-	*** ^c	-	-	-	-	-	-	-
PB-11	-	-	*** ^c	-	-	-	-	-	-	-
PB-13	-	-	*** ^c	-	-	-	-	-	-	-
B-7	-	-	-	-	*** ^c	-	-	-	-	-
Total Identified	-	-	14.4	0.015	-	-	-	-	-	-
Organosoluble unknowns	-	-	25.6 (5)	0.027	78.1 (3)	0.015	77.4 (4)	0.004	56.1 (6)	0.015
Organosoluble	81.4	0.002	10.2 ^e	0.011	-	-	-	-	-	-
Aqueous soluble	18.6	<0.001	42.1 ^f	0.044	16.7	0.003	17.6	0.001	5.9	0.002
Total Characterized/ Identified	100	0.002	92.3	0.096	94.8	0.018	95.0	0.005	62.0	0.017
Non-extractable	-	-	9.2	0.003	5.2	0.001	5.0	<0.001	37.9	0.01

^a Milk sample from Day-5.

^b Tentatively identified by 1D-TLC.

^c Components tentatively identified by 1D-TLC but not quantified.

^d Number in parentheses indicate the minimum number of unknowns isolated by TLC or HPLC.

^e This fraction represents radioactivity remaining at the origin following TLC analysis of EtOAc-soluble ^{14}C -residues from the base hydrolysis of the aqueous soluble liver ^{14}C -residues.

^f Composed of several fractions of aqueous soluble liver ^{14}C -residues remaining following base hydrolysis of the initial aqueous fraction and enzyme hydrolysis of the solvent-extracted solids.

For the goat treated with [^{14}C -Pz]pyridaben at 6.9 ppm, pyridaben (17.6% TRR), PB-9 (5.1% TRR), and PB-7 (3.8% TRR) were identified in the organosoluble liver extract by HPLC and confirmed by TLC. The metabolites PB-1 and PB-13 were also tentatively identified in liver by TLC. TLC analysis of kidney detected PB-11 (58.1% TRR), but its identity was not confirmed.

TLC analysis of organosoluble residues from muscle did not identify any metabolite and each isolated component accounted for ≤ 0.005 ppm. In fat, TLC analysis tentatively identified PB-9 and PB-12, but their identities were also not confirmed. Due to low TRR levels in milk, residues were characterized as organosoluble (64.9%, 0.003 ppm) or aqueous soluble (34.1%, 0.002 ppm), but were not identified.

For the [^{14}C -Bz]pyridaben treated goat, HPLC analysis of organosoluble liver ^{14}C -residues identified pyridaben (6.5% TRR) and PB-7 (7.9% TRR). Their identities were confirmed by TLC analysis, which also detected the presence of PB-9. Other metabolites that were tentatively identified by TLC analyses included PB-11 and PB-13 in liver and B-7 in kidney. No metabolites were identified in either muscle or fat, and each isolated component contained <0.01 ppm of radioactivity. Due to low TRR levels in milk, residues were characterized as organosoluble (81.4%, 0.002 ppm) or aqueous soluble (18.6%, <0.001 ppm), but were not identified.

Although 1D-TLC analyses of organosoluble ^{14}C -residues in urine were inconclusive, 2D-TLC analyses identified PB-7 in urine of the Pz-treated goat and B-7, B-8 and B-11 in urine of the Bz-treated goat. 2D-TLC analyses of feces from both ^{14}C -Pz and ^{14}C -Bz treated goats indicated that pyridaben was the major component of the organosoluble residues in feces. In addition, 2D-TLC identified PB-7, PB-9, and PB-13 in feces from the Pz-treated goat, and PB-7 and PB-9 in feces from the Bz-treated goat.

Based upon these data, the petitioner has proposed that the metabolism of pyridaben in goats involves the hydroxylation of one or both of the tertiary butyl groups followed by oxidation of the hydroxyl group(s) to an acid. Data from urine and feces also suggests that some cleavage of the molecule occurs. Metabolites identified in goat matrices are shown in Figure 1.

Metabolism in Laying Hens:

BASF Corporation submitted data from a preliminary study and a final study depicting the metabolism of [^{14}C]pyridaben in laying hens. In both studies, hens were dosed with [^{14}C]pyridaben radiolabeled either uniformly in the phenyl ring (^{14}C -Bz) or at the C-3 and C-6 positions of the pyridazinone ring (^{14}C -Pz). In the preliminary study, four pairs of laying hens were orally dosed for 8 consecutive days with either [^{14}C -Pz]pyridaben or [^{14}C -Bz]pyridaben at a low (12.5 $\mu\text{g/day}$) or high (1 mg/day) dose. The dose level was not reported in terms of dietary exposure ($\mu\text{g/g}$ feed or ppm) and feed consumption data were not reported.

In the final study, four groups consisting of ten hens per group were orally dosed for 8 consecutive days with either [^{14}C -Pz]pyridaben or [^{14}C -Bz]pyridaben at a low (12.5 $\mu\text{g/day}$) or high (1 mg/day) dose. A fifth group of ten hens was used as a control. Doses were administered by capsule daily. Based upon feed consumption data, the doses were equivalent to pyridaben dietary levels of approximately 0.1 ppm for the low dose and 7.5-7.9 ppm for the high dose. Dietary exposure of poultry to pyridaben residues is not expected as a result of the proposed uses.

Total radioactive residues, expressed in [¹⁴C]pyridaben equivalents, in eggs and tissues from the preliminary and final poultry metabolism studies are presented in Tables 14 and 15, respectively.

Table 14. Total Radioactive Residues (TRR) in Eggs and Tissues from Laying Hens Dosed with [¹⁴C]Pyridaben at 12.5 mg/day and 1 mg/day for Eight Consecutive Days; Preliminary Poultry Metabolism Study.

Matrix	Total Radioactive Residue (ppm ^a)			
	[¹⁴ C-Pz]pyridaben		[¹⁴ C-Bz]pyridaben	
	Low dose (12.5 µg/day)	High dose (1 mg/day)	Low dose (12.5 µg/day)	High dose (1 mg/day)
Liver	ND ^b , ND	0.135, 0.105	ND, ND	0.195, 0.150
Kidney	0.002, ND	0.221, 0.213	ND, ND	0.255, 0.235
Lung	0.003, 0.003	0.196, 0.077	0.002, ND	0.187, 0.148
Muscle breast thigh	ND, ND	0.015, 0.007	ND, ND	0.018, 0.012
	ND, ND	0.020, 0.011	ND, ND	0.033, 0.020
Fat abdominal skin	ND, ND	0.041, 0.037	ND, ND	0.040, 0.021
	ND, ND	0.044, 0.021	ND, ND	0.031, 0.021
Skin	ND, ND	0.077, 0.041	ND, ND	0.086, 0.050
Eggs Day-1	<0.001, NS ^c	NS, NS	NS, ND	0.014, 0.001
	NS, ND	NS, NS	ND, ND	0.008, 0.003
	ND, NS	<0.001, 0.005	ND, ND	0.013, 0.006
	<0.001, ND	0.011, 0.002	ND, NS	0.019, NS
	ND, NS	NS, 0.005	ND, ND	NS, 0.009
	NS, NS	NS, NS	0.013, <0.001	0.022, 0.013
	<0.001, <0.001	NS, 0.006	NS, ND	0.025, NS
	<0.001, NS	0.027, NS	0.002, ND	NS, 0.046

^a Residues expressed as [¹⁴C]pyridaben equivalents; values are the mean of duplicate analyses.

^b ND = not detected.

^c NS = no sample.

Table 15. Total Radioactive Residues (TRR) in Eggs and Tissues of Laying Hens Dosed with [¹⁴C]Pyridaben at 12.5 mg/day (~0.1 ppm) and 1 mg/day (~8 ppm) for Eight Consecutive Days; Final Poultry Metabolism Study.

Matrix	Total Radioactive Residue (ppm ^a)			
	[¹⁴ C-Pz]pyridaben		[¹⁴ C-Bz]pyridaben	
	0.1 ppm	7.9 ppm	0.1 ppm	7.5 ppm
Liver	ND ^b -0.002 (<0.001) ^c	0.081-0.287 (0.119)	ND	0.050-0.195 (0.089)
Muscle (breast)	ND-0.001 (<0.001)	0.005-0.018 (0.009)	ND	0.006-0.015 (0.010)
Muscle (thigh)	ND	0.007-0.020 (0.010)	ND	0.008-0.025 (0.015)
Fat (abdominal)	ND	0.015-0.070 (0.028)	ND	0.012-0.041 (0.027)
Fat (skin)	ND	0.017-0.056 (0.028)	ND	0.012-0.045 (0.031)
Skin	ND-0.001 (<0.001)	0.034-0.089 (0.056)	ND	0.027-0.062 (0.042)
Eggs ^d	Day 1	ND	ND	ND-0.002 (<0.001)
	Day 2	ND	ND	0.001-0.006 (0.003)
	Day 3	ND	ND	0.003-0.012 (0.005)
	Day 4	ND	ND	0.004-0.016 (0.009)
	Day 5	ND	ND	0.006-0.022 (0.011)
	Day 6	ND	ND-0.001 (<0.001)	0.009-0.026 (0.015)
	Day 7	ND	ND-0.001 (<0.001)	0.011-0.027 (0.017)
	Day 8	ND	ND-0.001 (<0.001)	0.013-0.029 (0.019)

^a Residues expressed as [¹⁴C]pyridaben equivalents; data are the mean of duplicate analyses of samples from each hen.

^b ND = not detected.

^c Mean values for the ten hens are in parentheses.

^d Whites and yolks combined.

A summary of the identification/characterization of ¹⁴C-residues in laying hens is presented in Table 16.

Table 16. Summary of Characterization/Identification of Radioactive Residues in Eggs and Tissues of Laying Hens Dosed with [^{14}C -Pz] and [^{14}C -Bz]Pyridaben at 8 ppm for 8 Consecutive Days.

Metabolite/ Fraction	Eggs ^a		Liver		Breast Muscle		Thigh Muscle		Fat		Skin	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
[^{14}C-Pz]pyridaben												
PB-7	-	-	18.3	0.022	-	-	-	-	-	-	-	-
PB-9	-	-	1.8	0.002	-	-	-	-	-	-	-	-
PB-13 ^b	-	-	-	-	-	-	13.2	0.001	-	-	-	-
Total Identified	-	-	20.1	0.024	-	-	13.2	0.001	-	-	-	-
Organosoluble unknowns	4.7 (4) ^c	0.001	23.3 (7)	0.027	55.5 (4)	0.005	23.1 (2)	0.003	44.7 (6)	0.013	15.1 (8)	0.008
Aqueous soluble	4.3	0.001	14.6	0.017	3.9	<0.001	19.1	0.002	22.8	0.006	28.2	0.016
Total Characterized/ Identified	9.0	0.002	58.0	0.068	59.4	0.005	55.4	0.006	67.5	0.019	43.3	0.024
Non-extractable	91.0	0.013	38.9	0.046	40.7	0.004	44.6	0.004	32.5	0.009	56.7	0.032
[^{14}C-Bz]Pyridaben												
Pyridaben	-	-	-	-	-	-	-	-	** ^d	-	**	-
PB-7	-	-	31.5	0.028	-	-	-	-	**	-	**	-
PB-9	-	-	**	-	-	-	-	-	**	-	**	-
PB-11 ^b	-	-	-	-	-	-	-	-	21.8	0.006	-	-
Total Identified	-	-	31.5	0.028	-	-	-	-	21.8	0.006	-	-
Organosoluble unknowns	7.1 (6)	0.001	34.9 (3)	0.029	59.5 (3)	0.006	49.8 (5)	0.007	14.6 (4)	0.004	40.8 (7)	0.017
Aqueous soluble	6.6	0.001	9.2	0.008	13.0	0.001	22.8	0.003	16.4	0.004	7.8	0.003
Total Characterized/ Identified	13.7	0.002	75.6	0.066	72.5	0.007	72.6	0.010	52.8	0.014	48.6	0.020
Non-extractable	86.3	0.016	23.6	0.021	27.4	0.003	27.4	0.004	47.2	0.013	51.4	0.022

^a Egg samples from Day-8.

^b Tentatively identified by 1D-TLC.

^c Number in parentheses indicate the minimum number of components separated by TLC or HPLC.

^d Metabolites designated by "***" were detected by 2D-TLC analyses but not quantified.

For the [^{14}C -Pz]pyridaben treated hens, TLC analyses of organosoluble residues from breast muscle, fat, skin and eggs did not identify any possible metabolites and each isolated unknown component amounted to ≤ 0.006 ppm. In thigh muscle, a dihydroxy metabolite, PB-13, was tentatively identified at a level of 0.001 ppm. HPLC analysis of organosoluble ^{14}C -residues in ^{14}C -Pz liver identified the acid metabolite PB-7 (18.3% TRR; 0.022 ppm) as the principal residue in liver and minor amounts of a hydroxy metabolite, PB-9 (1.8% TRR; 0.002 ppm), were also detected. The identities of PB-7 and PB-9 were confirmed by TLC analysis.

For the [^{14}C -Bz]pyridaben treated hens, TLC analyses of organosoluble residues from muscle, fat, skin, and eggs did not identify any component amounting to >0.01 ppm. The metabolite PB-11 (21.8% TRR; 0.006 ppm) was tentatively identified in fat by 1D-TLC analysis, and pyridaben, PB-7 and PB-9 were detected but not quantified in fat and skin by 2D-TLC analysis. In liver, the acid metabolite PB-7 (31.5% TRR; 0.028 ppm) was identified by HPLC analysis and confirmed by TLC analysis. The metabolite PB-9 was also detected in liver by 2D-TLC analysis, but was not quantified.

Although no quantitative data were presented, 2D-TLC analyses of excreta from both ^{14}C -Pz and ^{14}C -Bz treated hens indicate that pyridaben was the major component of the organosoluble residues in excreta. These analyses also detected PB-7, PB-9, and PB-13 in excreta from ^{14}C -Pz treated hens and PB-7, B-7, B-11, and B-15 in excreta from ^{14}C -Bz treated hens.

Based upon the above data, the petitioner proposed that the metabolism of pyridaben in hens is similar to the metabolism in goats and involves the hydroxylation of one or both of the tertiary butyl groups followed by oxidation of the hydroxyl group(s) to an acid. Data from excreta suggests that some cleavage of the molecule also occurs in the GI tract.

Metabolism in Confined Rotational Crops - (MRID No. 44939702)

BASF Corporation has submitted data concerning the accumulation of ^{14}C -residues in confined rotational crops (mustard greens, radish, and winter wheat) planted 30 days following the last application of [^{14}C]pyridaben to the soil. Additionally, radishes, Swiss chard, and sorghum were planted 240 days following the application (DAT). The test substance, [pyridazinone-3,6- ^{14}C]pyridaben, having a specific activity of 1.63×10^5 dpm/ μg . The ^{14}C -pyridaben was mixed with unlabeled pyridaben to produce 500 mL of application solution. The specific activity of the application solution was 121049 dpm/ μg . The plot was constructed by digging a hole 4 ft wide x 3 ft deep x 8 feet long and inserting a 4 ft x 4 ft x 8 ft bottomless aluminum casket into the hole. The hole was filled with a sandy loam soil (1.9% organic material) obtained by a commercial supplier. The application solution was applied twice to the test plot (directed to the soil) with 35 days between applications at a rate of 0.66 lbs ai/A for a total of 1.32 lbs ai/A (1.1x the maximum proposed rate for strawberries).

Rotational crops (mustard green, radish, and winter wheat) were planted 30 days following the final application (DAFT) and grown to maturity. Additional crops (radish, Swiss chard, and sorghum) were planted at 240 DAFT. The crops planted at 240 DAFT were harvested as early maturity radishes and Swiss chard, and early sorghum forage. The plot was irrigated to supplement natural rainfall in order to maintain plant health and vigor.

Treated samples of rotational crop RACs were harvested at the sampling intervals specified in Table 17. At harvest, the samples were placed in coolers containing dry ice and were held in frozen storage ($< -20^\circ\text{C}$) when not actively in use. The TRRs in/on treated plant commodities are presented in Table 17.

Table 17. Total Radioactive Residues Found In/on Rotational Crop Matrices Grown in a Sandy Loam Soil Treated with [¹⁴C]Pyridaben at 1.32 lbs ai/A (1.1x the Maximum Proposed Seasonal Rate).

Crop	Commodity	Plant-back Interval ^a (days) - DAT	Harvest Interval ^a (days) - DAP	Total Radioactive Residues ^b (ppm)
Radish	Roots	30	40	0.013
	Leaves	30	49	0.05
Mustard Greens	Leaves	30	61	0.019
Wheat	Forage	30	201	0.011
	Hay	30	209	0.044
	Straw	30	244	0.045
	Grain	30	244	0.009
Radish	Leaves	240	32	0.049
	Roots	240	32	0.022
Chard	Immature Leaves	240	34	0.078
	Leaves	240	72	0.044
Sorghum	Forage	240	32	0.024

^a Crop sampling intervals are expressed in terms of days after soil treatment (DAT) and days after crop planting (DAP).

^b Residues are expressed as [¹⁴C]pyridaben equivalents and are the average of the analyses of 5 aliquots.

Radioactive residues were >0.01 ppm in rotational crop RACs at both PBIs with the exception of wheat grain (30 DAT sample). All 30 and 240 DAT samples with TRR levels >0.01 ppm were extracted for identification purposes.

Table 18. Fractionation of ¹⁴C-Residues in 30 DAT RACs Harvested From Crops Grown in Soil Treated with [¹⁴C]Pyridaben at Approximately 1.32 lbs ai/A (1.1x Maximum Seasonal Rate).

Fraction	Radish Root (0.013 ppm) ^a		Radish Leaves (0.050 ppm)		Mustard Greens (0.019 ppm)		Wheat Forage (0.011 ppm)		Wheat Hay (0.044 ppm)		Wheat Straw (0.045 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Aqueous	61.7	0	51.6	0.03	76	0.01	72.8	0	64.8	0.03	54.7	0.03
Combined Aqueous/Acetone	16.9	0	21.7	0.01	8.9	0	ND ^b	ND	22.3	0.01	ND	ND
Hydrolysis	13.5 ^c	0.002 ^c	24.2 ^d	0.012 ^d	9.0 ^c	0.002 ^c	ND	ND	ND	ND	ND	ND
Total Extractable Residue	92.1	0.01	97.5	0.05	93.9	0.02	72.8	0	87.1	0.04	54.7	0.03
Solids (PES) ^e	13.9	0	5.4	0	7.05	0	31.8	0	27	0.01	45.3	0.02
Recovery	106	0.01	103	0.05	101	0.02	105	0.01	114	0.05	100	0.05

^a TRR for each RAC is listed in parentheses; all ppm values are expressed as [¹⁴C]pyridaben equivalents.

^b ND = Not determined.

^c Acid hydrolysis only.

^d Sum of acid and base hydrolyses.

^e PES = post extraction solids.

Table 19. Fractionation of ^{14}C -Residues in 240 DAT RACs Harvested from Crops Grown in Soil Treated with [^{14}C]Pyridaben at Approximately 1.32 lbs ai/A (1.1x Maximum Seasonal Rate).

Fraction	Radish Root (0.022 ppm) ^a		Radish Leaves (0.049 ppm)		Swiss Chard (0.044 ppm)		Sorghum Forage (0.024 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Aqueous	55.5	0.012	66.2	0.032	59.7	0.026	47	0.011
Combined Aqueous/Acetone	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis	ND	ND	ND	ND	ND	ND	ND	ND
Total Extractable Residue	55.5	0.012	66.2	0.032	59.7	0.026	47	0.011
Solids (PES) ^b	44.5 ^c	0.010 ^c	33.8 ^c	0.017 ^c	40.3 ^c	0.018 ^c	53.0 ^c	0.013 ^c
Recovery	100	0.022	100	0.049	100	0.044	100	0.011

^a TRR for each RAC is listed in parentheses; all ppm values are expressed as [^{14}C]pyridaben equivalents.

^b PES = post extraction solids.

^c Calculated value, based upon TRR percent extracted.

Table 20. Summary of Characterization and Identification of Radioactive Residues in Rotational Crop Commodities
Grown In Soil Treated with ¹⁴C-Pyridaben at 1.33 lb ai/A.

Planting Interval/ Crop	Total Radioactive Residues (ppm)	Residues				
		Pyridaben		Metabolites		
		% TRR	ppm	% TRR	ppm	Comments
30-DAT Radish Roots	0.013	1.5	<0.001	76.5	0.0095	At least 8 individual regions, largest region 20.5% TRR (0.003 ppm) resolved into at least 3 components, all <10% TRR.
30-DAT Radish Leaves	0.05	<1	<0.001	79.5	0.041	Greater than 12 unknowns, all <10% TRR (<0.005 ppm).
30-DAT Mustard Greens	0.019	<1	<0.001	82.6	0.016	At least 11 unknowns, all <16% TRR (0.003 ppm).
30-DAT Wheat Forage	0.011	ND ^a	--	48.5	0.005	Two main polar peaks. Largest peak approximately 14% TRR (0.0015 ppm).
30-DAT Wheat Hay	0.041	ND	--	66.5	0.029	Two main polar peaks. Largest peak approximately 14% TRR (0.0062 ppm).
30-DAT Wheat Straw	0.045	ND	--	41.2	0.019	Approximately 9 unknown, all <10% TRR, (<0.0045 ppm).
30-DAT Wheat Grain	0.009	NA ^b	NA	NA	NA	Sample not analyzed.
240-DAT Radish Roots	0.049	ND	--	51.9	0.011	One main polar peak, ~ 30% TRR (0.0066 ppm).
240-DAT Radish Leaves	0.022	ND	--	40.4	0.02	One main polar unknown, ~ 11% TRR (0.005 ppm). Remainder consists of approximately 7 unknown, all <10% TRR (<0.005 ppm).
240-DAT Swiss Chard	0.044	ND	--	53	0.0023	Largest peak approximately 15% TRR (0.007 ppm). Remainder consists of approximately 12 unknowns, all <10% TRR (<0.004 ppm).
240-DAT Sorghum Forage	0.024	ND	--	36.1	0.009	Approximately 15 peaks, largest of which is ~7% TRR, 0.002 ppm).

^a ND = Not detected.

^b NA = Sample not analyzed.

Solvent extractable ^{14}C -residues were comprised mainly of polar unknowns (described as multi-component fractions, with each component contributing <10% TRR), and minor amounts of the parent compound. Parent compound was identified in several commodities at levels less than 0.001 ppm.

Summary of Analytical Methods

Two parent-specific GC/ECD methods were developed for the conduct of the residue trials and for enforcement purposes. These methods are designated as BASF Methods D9312 and D9309B. The former was used for analysis of apples, pears, cranberries, peaches, grapes, plums, and plum processed fractions; the latter was utilized for analysis of pecans.

BASF Method D9405 determines residues of pyridaben and its metabolites PB-7 and PB-9. Each analyte is determined independently.

Summary of Magnitude of the Residue Studies - Plants

Magnitude of residue data have been submitted for a variety of commodities including: almonds (MRID No. 440083-03), apples (MRID No. 437800-03 and -04), oranges, lemons, grapefruit (MRID Nos. 435189-01 through -04, 442296-01), cranberries (448260-01), peaches (MRID Nos. 442530-02 and 446636-01), plums (MRID No. 442530-01), pecans (MRID No. 443453-01), grapes (MRID No. 443253-02), cherry (MRID No. 45680501) and pears (MRID No. 440396-02). For all commodities except tree nuts (almonds and pecans), tolerances are based upon detectable residues of pyridaben. Tolerances for residues in tree nuts are based upon non-detectable residues in the nutmeats (<0.05 ppm).

Summary of Magnitude of the Residue Studies – Livestock

Cattle: The petitioner has submitted the results of a cow feeding study. In this study, 12 lactating cows were administered pyridaben for 29 days at dose levels of 2.5, 7.5 or 25 ppm. For dairy cattle, the dose levels of the feeding study translate to an exaggerated feeding level of 0.71x, 2.1x, and 7.1x, respectively, and for beef cattle, the exaggeration rate is 0.96x, 2.9x, and 9.6x, respectively. Samples were analyzed for residues of pyridaben and its metabolites PB-7 and PB-9. The results of this study are presented in Table 21.

Table 21. Maximum Residues of Pyridaben and Its Metabolites PB-7 and PB-9 Found in Lactating Cows.

Dose Level (ppm):	2.5	7.5	25
Sample			
Milk	<0.01	<0.01	0.03 ¹
Liver	<0.05	0.05 ²	0.15 ²
Muscle	<0.05	<0.05	<0.05
Kidney	<0.05	<0.05	<0.05
Fat	<0.05	<0.05	0.081

¹ Pyridaben² PB-7

Poultry: A poultry feeding study has not been submitted.

Rat Metabolism

In a rat metabolism study (MRID 43258901) by the oral route, pyridaben was mainly eliminated in feces where 80-97% of the administered dose was excreted regardless of dose or site of label (pyridazinone or phenyl ring). Nearly 20% of the excreted label in the feces was unmetabolized parent compound and there was some evidence of glucuronide conjugate(s) in the bile. The plasma levels following a single low oral dose (3 mg/kg) peaked at 2-3 hours while peak levels at the high dose (30 mg/kg) were at approximately 24 hours post-dose due, at least in part, to enterohepatic circulation where nearly 22-30% of an administered radioactive dose is excreted in bile within a period of 24 hours. Though the label site and dosing regimen (high vs. low or single vs. repeated) played some role in tissue distribution and persistence, residual radioactivity was at or near background levels for most tissues by 72 to 168 hours. Generally, there seemed to be increased distribution to fat over time and, compared to other tissues, fat seemed to have relatively more residual radioactivity. Several metabolites, totaling up to 20-30, were resolved in urine and feces and some were structurally identified. The metabolism of pyridaben seems to be complex with several pathways of biotransformation.

Environmental Fate

The following was distilled from the June 29, 2000 memo, "EFED Risk Assessment for IR4 Tolerance Petition for use of Pyridaben on Cranberries; New Uses on Vineyards, Orchards, and Tree Nut Groves."

The current new uses for pyridaben under consideration are on hops, strawberry, stone fruit and tropical fruit.

Pyridaben may be available in the soils during the first few weeks after application. Due to its low solubility (12 ppb) and high level of binding ($K_{ads}=108-6600$), it appears that pyridaben

would remain bound to the soils during run-off events. Therefore, it would reach adjacent bodies of water when the run-off events are accompanied by erosion.

Pyridaben would remain bound to the soils and would be released slowly into the water. Once the chemical is dissolved, it may photolyze in clear, shallow waters. An Outdoor Aquatic Microcosms study and a Confined Aquatic Field Dissipation study seem to confirm that pyridaben will not persist under aquatic conditions.

Because of its relative immobility, pyridaben is not likely to reach subsurface soil environments (lower microbial activity) or ground water at significant concentrations.

Environmental Persistence

The major routes of degradation/dissipation of pyridaben are aqueous photolysis (half-life of 5 to 40 minutes) and soil photolysis (half-life of 11 days). Hydrolysis (stable), aerobic (half-life of 86 days) and anaerobic soil metabolism did not appear to play an important role in the degradation of pyridaben.

Expected Mobility

Based on batch equilibrium experiments, pyridaben shows low mobility in sand, sandy loam, two silt loams, and a clay loam soil. Freundlich K_{ads} values were ≥ 108 , and K_{oc} values were $\geq 34,900$.

Soil type	Freundlich K_{ads}	K_{oc}	Freundlich K_{des}
sand	445	64,600	NA
sandy loam	108	34,900	115
low-CEC silt loam	220	87,900	611
high-CEC silt loam	330	78,700	373
clay loam	6660	2,150,000	380

Environmental Metabolites

An aged pyridaben study indicates that only the degradate P-14 is likely to be present and leach substantially. Based on batch equilibrium studies, P-14 is very mobile in four soil types. The K_d and K_{oc} values observed are as follows:

Soil type	K_d	K_{oc}
clay	0	0
loam	0.04	1.7
sand	0.05	54.9

loamy sand	0.06	14.8
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However, P-14 remained in the upper soil levels in all the terrestrial field dissipation studies. Furthermore, the degradate P-14 was formed only in small amounts throughout the field studies and in the aerobic soil metabolism study.

The body of evidence (four terrestrial field dissipation studies, and a confined [^{14}C] terrestrial field dissipation study) indicates that pyridaben degradates are unlikely to leach: the degradates remain in the upper 0-6" (0-3" for the confined study) soil level.

Table 22. Summary of Degradates in Environmental Fate Studies for Pyridaben							
Degradate ¹ (name and structure)	Maximum Degradate Concentration (% of applied) and Time (days) to Maximum Concentration in Study:					Degradates Analyzed in Study:	
	Soil Photo.	Aerobic Soil	Aquatic Photo.	Anaer. Soil	Aerobic Aquatic	Field Diss.	Ground Water
B-1				<8%			
B-3	no		27%	<8%		not anal.	
B-7				<8%			
unidentified			16 - 28%				
D-1			5%				
PB-4		<4.2%		<8%			
PB-5				<8%			
PB-7		<4.2%					
PB-9				<8%			
PB-11				<8%			
PB-14		<4.2%		<8%			

¹For degradate structures see Figure 1. However, the structures of PB-4 and P-16 are not included in Figure 1. PB-4 is 2-*tert*-butyl-5-(4-*tert*-butylbenzylsulfinyl)-4-chloropyridazin-3(2*H*)-one, while P-16 is 4-chloropyridazin-3(2*H*)-one-5-sulfonic acid