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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: **Environmental Fate and Effects Division Risk Assessment for the Section 3 New Chemical Registration of Flubendiamide**

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Please find the attached Environmental Fate and Effects Division's (EFED) environmental risk assessment for the proposed new chemical registration of flubendiamide. The proposed formulations are NNI-0001 480 SC (EPA Reg. 264-XXX) and NNI-0001 24 WG (EPA Reg. 264-XXX). Application of the flubendiamide formulation 480 SC is proposed for corn, cotton, tobacco, grapes, pome fruit, stone fruit, and tree nut crops. 24 WG is proposed for use on cucurbit vegetables, fruiting vegetables, leafy vegetables, and brassica (cole) leafy vegetables. The maximum proposed single foliar application rate is 0.156 lb a.i./A with annual maximum of 0.468 lb a.i./A for use on pome fruit.

A screening-level (Level I) risk assessment suggests that both flubendiamide and its des-iodo degradate will accumulate to concentrations in aquatic environment that will pose risks to freshwater benthic invertebrates. The available mesocosm data does not provide evidence to refute these conclusions. No degradation pathway was identified for the des-iodo degradate. Flubendiamide's technical product is not acutely toxic at its water solubility limit (29.9 µg/L) to freshwater or estuarine/marine organisms. The formulated products 480 SC and 24 WG do result in direct acute and chronic risk to freshwater invertebrates. Based on the potential direct effects to these taxa, there may be potential indirect effects to species of concern that depend on these taxa as a source of food and pollination. The screening assessment suggests that there is no potential risk to freshwater fish, marine fish and invertebrates, marine crustaceans, marine mollusks, and aquatic plants at the limit of solubility for parent flubendiamide. There is no potential acute risk or reproductive effects to birds and mammals for all of the proposed uses. In addition, there is no potential risk to earthworms, beneficial insects including bees and natural Lepidoptera predators, and terrestrial plants. There is some potential for risk to adult ladybird beetles due to ingestion of food items (aphids and pollen) containing flubendiamide residues. In addition, there is a potential direct risk to non-target Lepidoptera species, including endangered species.

Listed Species

Aquatic and terrestrial invertebrates (non-target Lepidoptera species and beetles) were identified as being of potential concern for direct effects for listed species for the proposed uses (**Table 1**). There is potential for flubendiamide to exert indirect effects upon the listed organisms by, for example, perturbing forage or prey availability, altering pollination and/or dispersal, etc. With additional refinement, such as exploring more detailed use patterns and species biology (*e.g.*, geographic location, specific feeding habits, time of year likely to utilize crop fields), it may be determined that some (or all) listed species may not be affected.

Table 1. Listed species risks associated with direct or indirect effects due to applications of flubendiamide

Listed Taxonomy	Direct Effects	Indirect Effects
Terrestrial and semi-aquatic plants – monocots	No	Yes[a]
Terrestrial and semi-aquatic plants – dicots	No	Yes[a]
Terrestrial invertebrates	Yes[a]	No
Birds (surrogate for terrestrial-phase amphibians and reptiles)	No	Yes [a]
Mammals	No	Yes[a]
Aquatic vascular plants	No	No
Aquatic non-vascular plants [a]	No	No
Freshwater fish (surrogate for aquatic-phase amphibians)	No	Yes[b]
Freshwater Invertebrates	Yes – due to exposure to formulations [b]	Yes[b]
Freshwater Benthic Invertebrates	Yes – due to exposure to both flubendiamide and the des-iodo degradate [c]	Yes[b]
Estuarine/Marine Fish	No	No
Estuarine/Marine Crustaceans	No	No
Estuarine/Marine Mollusks	No	No

[a] Potential risk to non-target insects (Lepidoptera) and adult ladybird beetles due to ingestion of food items (aphids and pollen) containing flubendiamide residues

[b] Acute and Chronic LOC exceeded for daphnids exposed to the formulations

[c] Potential risk to benthic invertebrates exposed to the des-iodo degradate

Key Uncertainties and Information Gaps

The following uncertainties, limitations, and assumptions were identified in this environmental risk assessment:

- The 480 SC and 24 WG proposed labels restrict use per season; however, there are crops, such as brassica leafy vegetables, that often have more that one season in a year. In this risk assessment, RQs are based on one season per year and risk is underestimated for crops that have more than one growing season per year.

- Registrant-submitted toxicity testing shows that both the SC and WG flubendiamide formulations to be more toxic to freshwater invertebrates than the parent compound on an acute and chronic basis. While on the surface, these observed differences in toxicity might constitute a source of uncertainty in risk conclusions, the risk assessment, in accordance with Overview Document methods performs a separate assessment for formulations difting directly to surface waters. Therefore, the risk assessment team is not recommending any further toxicity studies and feels the current assessment methods adequately address this issue.

- Two 28-day chronic toxicity studies indicate that flubendiamide and its des-iodo degradate are toxic to the midge, *Chironomus riparius*, in an overlying-water spiked system. It is evident that there is a potential for direct effects to benthic invertebrates exposed to the parent and degradate. Neither of the two chronic toxicity midge studies followed sediment toxicity guidelines which require the sediment to be spiked as opposed to the overlying water. Regardless of the route of administration in the studies, there were measured pore water concentrations and these combined with available mesocosm data suggest that there is sufficient information to reach a risk conclusion for bethic invertebrates.

- Data gaps in the environmental fate database for flubendiamide and NNI-0001-des-iodo exist. In order to refine the ecological risk assessment for flubendiamide and NNI-0001-des-iodo, EFED recommends submitting the following guideline and non-guideline studies:

  Flubendiamide

  (Non-guideline) **Small-scale Runoff/Vegetative buffer strip Study** – The runoff study is requested to determine the magnitude of the parent, flubendiamide, retained in buffer strips of various widths. EFED believes that the efficacy of buffers for flubendiamide use are uncertain. It appears that a program of monitoring receiving waters and storm water conveyances under varying conditions of use would greatly benefit any evaluation of potential utility of buffers to reduce flubendiamide loadings to receiving waters. Additionally, EFED has provided the registrant with a description of a framework for an acceptable runoff monitoring protocol as well as comments on proposed monitoring protocols (Memorandum from Sidney Abel, 5/15/01; Memorandum from Hetrick, Odenkirchen, Evans, and Abel, 5/6/02 (D282366 and D281864).

Des-iodo Degradate

(161-1) **Hydrolysis** – The hydrolysis study is requested to establish the significance of chemical hydrolysis as a route of degradation for NNI-0001-des-iodo and to identify, if possible, the hydrolytic products formed which may adversely affect non-target organisms.

(161-2) **Photodegradation in Water** – Pesticides introduced into aqueous systems in the environment can undergo photolytic transformation by sunlight. Data on rates of photolysis are needed to establish the importance of this transformation process and the persistence characteristics of the photoproducts formed.

162-3) **Anaerobic Aquatic Metabolism** – The anaerobic aquatic metabolism is needed to assess the effects the nature and extent of formation of NNI-0001-des-iodo residues in water and in hydrosoil since anaerobic conditions are more likely to exist in aquatic environments.

(162-4) **Aerobic Aquatic Metabolism** – The requested study is needed to determine the effects on NNI-0001-des-iodo to aerobic conditions in water and sediments during the period of dispersal of NNI-0001-des-iodo throughout the aquatic environment and to compare rates and formation of metabolites. The data from this study would provide the aerobic aquatic input parameter for PRZM/EXAMS reducing modeling uncertainty.

(164-1) **Terrestrial Field Dissipation Studies** – NNI-0001-des-iodo is persistent and moderately mobile which increases the likelihood for run-off and leaching. No definitive studies on the field dissipation and degradation properties of the major degradate have been submitted to the Agency.

Labeling Recommendations

According to the Label Review Manual, the following label statements are recommended:

Environmental Hazards

This pesticide is toxic to aquatic invertebrates. Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or other waters unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the EPA.

Surface Water and Ground Water Advisory

Flubendiamide and its degradate NNI-0001-des-iodo have properties and characteristics associated with chemicals detected in ground water. This chemical may leach into ground water if used in areas where soils are permeable, particularly where the water table is shallow.

Flubendiamide and its degradate may also impact surface water quality due to runoff of rain water. This is especially true for poorly draining soils and soils with shallow ground water. These chemicals are classified as having a medium potential for reaching both surface water and aquatic sediment via runoff several months or more after application. A level, well-maintained vegetative buffer strip between areas to which this product is applied and surface water features such as ponds, streams, and springs will reduce the potential loading of flubendiamide and its degradate NNI-0001-des-iodo from runoff water and sediment. Runoff of this product will be reduced by avoiding applications when rainfall is forecasted to occur within 48 hours.

SECTION 3 NEW CHEMICAL REGISTRATION

ENVIRONMENTAL FATE AND EFFECTS SCIENCE CHAPTER

Environmental Fate and Ecological Risk Assessment

for

Flubendiamide (027602)

3-iodo-*N'*-(2-mesyl-1,1-dimethylethyl)-*N*-{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-*o*-tolyl}phthalamide

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TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 4
 1.1 Nature of Chemical Stressor 4
 1.2 Potential Risks to Non-target Organisms 4
 1.3 Conclusions: Exposure Characterization 7
 1.4 Conclusions: Effects Characterization 8
 1.5 Uncertainties and Data Gaps 10
2 PROBLEM FORMULATION 12
 2.1 Nature of Regulatory Action 12
  2.1.1 Nature of the Chemical Stressor 12
  2.1.2 Overview of Pesticide Usage 14
 2.2 Receptors 15
  2.2.1 Aquatic and Terrestrial Effects 15
  2.2.2 Ecosystems Potentially at Risk 15
  2.2.3 Ecological Effects 16
 2.3 Conceptual Model 17
  2.3.1 Risk Hypotheses 17
  2.3.2 Conceptual Diagram 17
 2.4 Analysis Plan 19
  2.4.1 Conclusions from Previous Risk Assessments 19
  2.4.2 Preliminary Identification of Data Gaps and Analysis Plan 19
  2.4.3 Measures of Effect and Exposure 20
3 ANALYSIS 22
 3.1 Use Characterization 22
 3.2 Exposure Characterization 24
  3.2.1 Environmental Fate and Transport Characterization 24
  3.2.2 Measures of Aquatic Exposure 29
  3.2.3 Terrestrial Wildlife Exposures 35
  3.2.4 Terrestrial and Semi-Aquatic Plant Exposures 37
 3.3 Ecological Effects Characterization 38
  3.3.1 Aquatic Effects Characterization 42
  3.3.2 Terrestrial Effects Characterization 46
  3.3.3 Review of Incident Data 50
  3.3.4 Review of ECOTOX Data 50
4 RISK CHARACTERIZATION 52
 4.1 Risk Estimation: Integration of Exposure and Effects Data 52
  4.1.1 Non-target Aquatic Animals, Invertebrates, and Plants 52
  4.1.2 Non-target Terrestrial Animals and Plants 61
  4.1.3 Terrestrial and Semi-aquatic Plant Risk 65
 4.2 Risk Description 66
  4.2.1 Risks to Aquatic Organisms 66
  4.2.2 Risks to Terrestrial Organisms 69
  4.2.3 Endocrine Disruption Assessment 70
 4.3 Threatened and Endangered Species Concern 71
  4.3.1 Action Area 71

4.3.2 Taxonomic Groups Potentially at Risk: Direct Effects 72
4.3.3 Use of Probit Slope Response Relationship to Provide Information on the Endangered Species Levels of Concern 73
4.3.4 Indirect Effects Analysis 75
4.3.5 Critical Habitat for Listed Species 75
5 Description of Assumptions, Uncertainties, Strengths, and Limitations 77
5.1 Assumptions and Limitations Related to Exposure for All Taxa 77
5.2 Assumptions and Limitations Related to Exposure for Aquatic Species.. 77
5.3 Assumptions and Limitations Related to Exposure for Terrestrial Species 77
5.4 Assumptions and Limitations Related to Effects Assessment 80
6 LITERATURE CITED 82
APPENDIX A: Status of Fate and Ecological Effects Data Requirements 84
APPENDIX B: PRZM/ EXAMS Modeling Crop Application Scenarios and EECs 87
APPENDIX C: PRZM EXAMS Example Output File – MS Corn (aerial) 95
APPENDIX D. TERR-PLANT Model Runs for Flubendiamide 98
APPENDIX E: T-REX Example Run for Birds and Mammals- Pome Fruit 99
APPENDIX F: Ecological Toxicity Tables 102
APPENDIX G: ECOTOX Papers 118
APPENDIX H: Environmental Fate and Transport DER Summaries 121

1 EXECUTIVE SUMMARY

This environmental risk assessment addresses the new chemical registration request (Section 3) from the registrant, Bayer CropScience LP. The registrant submitted the labels NNI-0001 480 SC (hereafter denoted 480 SC), which is a white liquid suspension containing *ca.* 490 g ai/L or 39.0% ai, and NNI-0001 24 WG (hereafter denoted 24 WG), which is a formulation containing 24.0% ai. 480 SC is a suspension concentration formulation proposed for aerial and/or ground application to corn, cotton, tobacco, pome fruit, stone fruit, tree nuts, and grapes. 24 WG is a water-dispersible granule (applied as a liquid) proposed for aerial/ground applications to cucurbit vegetables, fruiting vegetables, leafy vegetables, and brassica leafy vegetables.

1.1 Nature of Chemical Stressor

Flubendiamide *(N^2-[1,1-Dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-[2-methyl-4-[1,2,2,2- tetrafluoro-1-(trifluoromethyl)ethyl]phenyl]-1,2-benzenedicarboxamide)* belongs to the novel phthalic acid diamide class of insecticides for control of adult and larval lepidoptera. It acts through a new biochemical mode of action, specifically by targeting the ryanodine cell receptor and interfering with the calcium release channel, which is involved in muscle contraction. It is known to stabilize insect ryanodine receptors in an open state in a species-specific manner and to desensitize the calcium dependence of channel activity. Continuous stimulation of muscle contraction by "locking" the calcium channel in an "open" state, leads to muscle paralysis and eventual death of the organism. Whole organism symptoms may include feeding cessation, lethargy, paralysis, and death (Lahm *et al* 2005).

1.2 Potential Risks to Non-target Organisms

There is a potential risk to benthic invertebrates exposed to flubendiamide and its des-iodo degradate. EFED has compared the body of toxicological data for the parent compound and the des-iodo degradate. With the possible exception of chronic testing with chironomid midges, there is no apparent difference in toxicity evident from the available data. In the case of the chironomid data, conversion of effect endpoints to pore water units results in an estimated NOAEC for the parent compound of approximately 1 µg/L. The corresponding NOAEC for the des-iodo degradate is 0.28 µg/L. Because of the estimated nature of the parent compound NOAEC (the value is estimated form the relationship between nominal and pore water measurements at other dose levels because actual measurements of pore water concentrations were not made at the NOAEC level) and because NOAEC comparisons are usually confounded by the dose selections at study design onset, EFED concluded that there was insufficient data to demonstrate a significant difference in toxicity between the parent and degradate. However, for the purposes of this risk assessment and in consideration of the use of data as prescribed in the Agency's Risk Assessment Overview Document, risk calculations will be based on the chronic endpoints established for each chemical specifically.

Using these NOAEC values, RQs for flubendiamide would range from 0.94 to 21.3, while RQs for the des-iodo degradate would be 1607 (450 μg/L/0.28 μg/L) for all scenarios provided flubendiamide were used for sufficient time for the degradate concentration to build up to its limit of solubility (450 μg/L). Considering only the accumulation within the first 30 years of use for all of the scenarios, RQs for the degradate would range from 0.03 to 6.9 in the 1st year, 2.9 to 64 by the 10th year, 4.9 to 127 in the 20th year , and 12 to 190 in the 30th year.

Registrant-submitted toxicity test results indicate that both the 480 SC and 24 WG formulations are more toxic than the technical-grade active ingredient (TGAI) on an acute basis to freshwater invertebrates. A screening-level (Level I) risk assessment, based on proposed uses, suggests that flubendiamide technical is not acutely toxic at its water solubility limit (29.9 μg/L) to freshwater or estuarine/marine organisms. Estimated environmental concentrations (EECs) for the degradate exceed the NOAEC in a 28-day chronic toxicity chironomid study in an overlying-water spiked system. In addition, the formulated products 480 SC and 24 WG do result in direct acute and chronic risk to freshwater invertebrates. The Acute Endangered Levels of Concern (LOCs) (0.05) and the Acute Restricted Use LOCs (0.1) are exceeded based on the 480 SC formulation EECs for one aerial application to corn and cotton (RQ = 0.10). The Acute Endangered LOC is exceeded based on the 24 WG formulation EECs for one aerial application to the proposed vegetables (RQs = 0.056– 0.084). Based on the potential for direct effects to these taxa, there may be potential indirect effects to species of concern that depend on these taxa as a source of food and pollination.

The probit dose response relationship was used to determine the probability of an individual mortality occurrence for freshwater invertebrates exposed to the formulations based on the slopes observed in the toxicity tests. The estimated chance of an individual acute mortality to the freshwater invertebrates exposed to the 480 SC formulation at the LOC of 0.05 is 1 in 331 (with respective upper and lower bounds of 1 in 63 to 1 in 2,540). The estimated chance of an individual acute mortality to the freshwater invertebrates exposed to the 24 WG formulation at the LOC of 0.05 is 1 in 129 (with respective upper and lower bounds of 1 in 23 to 1 in 1,120). There is a relatively high probability of an individual mortality occurrence due to the steep slopes of the mortality tests; therefore, flubendiamide is likely to adversely affect listed freshwater invertebrates exposed to the formulations.

The screening assessment suggests that there is no potential risk to freshwater and marine fish, marine crustaceans, marine mollusks, and aquatic plants at the limit of solubility for parent flubendiamide. There is no potential acute risk or reproductive effects to birds and mammals for all of the proposed uses. In addition, there is no potential risk to earthworms, beneficial insects including bees and natural Lepidoptera predators, and terrestrial plants. There is some potential for risk to adult ladybird beetles due to ingestion of food items (aphids and pollen) containing flubendiamide residues. In addition, there is a potential direct risk to non-target Lepidoptera species, including endangered species. Lepidoptera may occur in areas adjacent to treated fields (where they may be exposed to spray drift) and will likely move through treated fields. Additionally, the larvae of some lepidopteran species are aquatic (Merrit and Cummins, 1984) and, therefore, may be exposed to both the parent, formulations, and des-iodo degradate.

Listed Species

Aquatic and terrestrial invertebrates (non-target Lepidoptera species) were identified as being of potential concern for direct effects for listed species for the proposed uses (**Table 1**). There is potential for flubendiamide to exert indirect effects upon the listed organisms by, for example, perturbing forage or prey availability, altering pollination and/or dispersal, *etc.* With additional refinement, such as exploring more detailed use patterns and species biology (*e.g.*, geographic location, specific feeding habits, time of year the listed species are likely to utilize crop fields), it may be determined that some (or all) listed species may not be affected.

Table 1. Listed species risks associated with direct or indirect effects due to applications of flubendiamide

Listed Taxonomy	Direct Effects	Indirect Effects
Terrestrial and semi-aquatic plants – monocots	No	Yes[a]
Terrestrial and semi-aquatic plants – dicots	No	Yes[a]
Terrestrial invertebrates	Yes[a]	No
Birds (surrogate for terrestrial-phase amphibians and reptiles)	No	Yes [a]
Mammals	No	Yes[a]
Aquatic vascular plants	No	No
Aquatic non-vascular plants [a]	No	No
Freshwater fish (surrogate for aquatic-phase amphibians)	No	Yes[b]
Freshwater Invertebrates	Yes – due to exposure to formulations [b]	Yes[b]
Freshwater Benthic Invertebrates	Yes – due to exposure to des-iodo degradate [c]	Yes[b]
Estuarine/Marine Fish	No	No
Estuarine/Marine Crustaceans	No	No
Estuarine/Marine Mollusks	No	No

[a] Potential risk to non-target insects (Lepidoptera) and adult ladybird beetles due to ingestion of food items (aphids and pollen) containing flubendiamide residues

[b] Acute and Chronic LOC exceeded for daphnids exposed to the formulations

[c] Potential risk to benthic invertebrates exposed to the des-iodo degradate

1.3 Conclusions: Exposure Characterization

Environmental fate and transport data indicate that flubendiamide is stable to hydrolysis, aerobic and anaerobic soil metabolism, and aerobic aquatic metabolism. Photolysis and anaerobic aquatic metabolism appear to be the main routes of degradation for flubendiamide. Flubendiamide degrades to NNI-0001-des-iodo (hereafter des-iodo) under anaerobic aquatic conditions ($T_{½}$ = 364 days) and direct aqueous photolysis ($T_{½}$ = 11.58 day) and by soil photolysis ($T_{½}$ = 35.3 days). Volatilization from soil and water surfaces is not expected to be an important process since flubendiamide has a relatively low vapor pressure (7.5×10^{-7} mm Hg) and Henry's Law constant (8.9×10^{-11} atm·m^3/mol). Flubendiamide and des-iodo have potential to contaminate surface water through run-off due to their persistence in soil. Flubendiamide and des-iodo also have the potential for groundwater contamination in vulnerable soils with low organic carbon content, after very heavy rainfall, and/or the presence of shallow groundwater. Flubendiamide and its degradate's overall stability/persistence suggests that they will accumulate in soils, water column, and sediments with each successive application.

1.4 Conclusions: Effects Characterization

Aquatic Organisms

In general, flubendiamide is not acutely toxic at its water solubility limit (29.9 µg/L) to freshwater or estuarine/marine organisms. However, the degradate and the formulated products 480 SC and 24 WG do result in toxicity to aquatic freshwater invertebrates.

Flubendiamide is not toxic at its water solubility limit (29.9 µg/L) to freshwater or estuarine/marine fish as either the technical material or the 480 SC formulated product. A freshwater fish early life-stage study on fathead minnow (*Pimephales promales)* with flubendiamide technical resulted in no treatment-related effects on embryo survival, time to hatch, hatching success, post-hatch survival or growth in juvenile fathead minnows (NOAEC = 60.5 µg a.i./L).

Acute freshwater toxicity tests using *Daphnia magna* indicate that flubendiamide is not toxic at its limit of solubility, yielding an LC_{50} value of >54.8 µg a.i./L. Similarly, the des-iodo metabolite was also not toxic at its limit of solubility (450 µg/L), with an LC_{50} value of >881 µg/L. However, acute testing with *Daphnia magna* indicated that both formulations were very highly toxic, with EC_{50} values of 1.5 µg a.i./L (24 WG formulation) and 2.6 µg a.i./L (480 SC formulation). In a freshwater invertebrate life cycle toxicity tests using *Daphnia magna* exposed to technical-grade flubendiamide, there were reproductive effects observed (NOAEC = 41.1 µg a.i./L). In the life cycle test with 480 SC formulation, parental mortality, sub-lethal effects, and an inhibition in time to first offspring emergence were observed. The NOAEC and LOAEC values were 0.38 and 1.18 µg a.i./L, respectively.

Based on nominal water column concentrations, the des-iodo degradate appears to be more toxic than the flubendiamide parent to benthic invertebrates. A chronic toxicity midge study with flubendiamide technical in an overlying-water spiked system resulted in NOAEC and LOAEC values of 40 µg a.i./L (nominal) and 80 µg a.i./L (nominal, 69 µg a.i./L initial water column measurement) based on emergence inhibition. A chronic toxicity midge study with the des-iodo degradate resulted in a reduction in the percent emergence (NOAEC = 3.2 µg metabolite/L). However, based on pore water concentrations (a more appropriate method for assessing toxicity to benthic organisms), the parent and degradate appear to be roughly equally toxic (NOAEC = 1 µg/L for flubendiamide, see Section 4.1.1.5, and NOAEC = 0.28 for the des-iodo degradate) to a benthic midge species (*Chironomus riparius*). Acute testing with the freshwater benthic organism, midge (*C. riparius*) indicated that the 480 SC formulation is moderately toxic with an LC_{50} value of 1650 µg a.i./L, and the 24 WG formulation is highly toxic with an LC_{50} value of 130 µg a.i./L.

Flubendiamide technical is not acutely toxic at its limit of solubility (30 µg/L) to mysid shrimp (LC_{50} >28 µg a.i./L) or the eastern oyster (EC_{50} >49 µg a.i./L). In addition, a full life-cycle toxicity test indicated that technical-grade flubendiamide yielded no chronic toxic effects on the mysid shrimp (NOAEC = 20 µg a.i./L).

There was no toxicity observed at the highest concentration of the technical grade flubendiamide tested, at its limit of solubility, in the non-vascular (*Selenastrum capricornutum*, EC_{50} >69.3 µg a.i./L) and vascular (*Lemna gibba*, EC_{50} >54.6 µg a.i./L) aquatic plant tests. In addition, there was no toxicity observed at the highest concentration of the 480 SC formulation tested, in the non-vascular (*Pseudokirchneriella subcapitata,* EC_{50} >50,500 µg a.i./L) aquatic plant test.

In the mesocosm study with 480 SC formulation, based on the observed effects on *Daphnia longispina* as the most sensitive species, the NOAEC for this zooplankter was 1.0 µg/L.

Terrestrial Organisms

Flubendiamide technical is practically non-toxic to birds on an acute oral and subacute dietary basis. In addition, the 480 SC formulation is practically non-toxic to birds on an acute oral basis. No treatment related mortality was observed. Two chronic avian studies were submitted using flubendiamide technical. For chronic risks to the mallard duck, reproductive effects were observed at the 289 and 960 mg a.i./kg diet treatment levels, therefore the NOAEC = 98 mg a.i./kg diet. For bobwhite quail, no treatment related effects were observed and the NOAEC is 1059 mg a.i./kg diet.

Three acute oral mammalian studies showed flubendiamide to be practically non-toxic. In a mouse study, the LD_{50} is 2000 mg a.i./kg-bwt. In two studies using laboratory rats, the LD_{50}'s were estimated to be >5,000 mg/kg-BW. Observed chronic effects in the two-generation rat reproduction study (MRID 46817239) were parental and offspring effects including increases in absolute and relative liver, kidney, and thyroid weights in both sexes. The resulting NOAEC is 200 mg/kg-diet. There were no reproductive effects observed.

Acute and chronic earthworm toxicity studies showed no toxic effects for flubendiamide technical, formulation 480 SC, and the des-iodo degradate. In the formulation 24 WG chronic test, there was a significant reduction in the number of juveniles produced, resulting in a NOAEC of 562 mg a.i./kg-dw soil.

Flubendiamide technical and 480 SC formulation were classified as practically non-toxic based on the acute contact honey bee study (LD_{50} > 200 µg/bee). In addition, significant side effects to bumblebees and honey bees were not observed following application of both formulations at the proposed application rates.

Flubendiamide was tested against several natural predators of Lepidopterous insects including the parasitoid wasp (*Aphidius rhopalosiphi*), predatory mite (*Typhlodromas pyri*), and ladybird beetle (*Coccinella septempunctata*). In the parasitoid wasp test with 24 WG formulation, significant reductions in survival and reproduction were observed (NOAEC = 0.17 lb a.i./A). In the parasitoid wasp test with 480 SC formulation, reproduction was not inhibited; however, survival was affected (NOAEC values were

<0.2 and 0.39 lb a.i./A; LD_{50} were 0.423 and 0.60 lb a.i./A). In the predatory mite test with the 24 WG formulation, significant reductions in survival and reproduction were observed (NOAEC = 0.31 lb a.i./A, LD_{50} > 0.55 lb a.i./A). Three extended laboratory experiments were conducted exposing the ladybird beetle to the 480 SC formulation. There were no significant adverse effects to ladybird beetles observed due to contact with residues; however, adult survival was affected due to ingestion of food items (aphids and pollen) containing flubendiamide residues yielding LD_{50}, NOAEC, and LOAEC values of 0.089, 0.04, and 0.079 lb a.i./A, respectively. There were no effects to larval survival or reproduction.

In four Tier I studies assessing the effects of the 24 WG and 480 SC formulations on the seedling emergence and vegetative vigor of monocot and dicot terrestrial plant species, none of the species tested exhibited reductions of ≥25% in survival or dry weight, except the sunflower in which a 33% reduction in percent emergence was observed. In the Tier II seedling emergence study in which the sunflower was exposed to the 24 WG formulation, percent emergence was not inhibited by more than 5% at the highest treatment level (0.16 lbs a.i./A). Additionally, percent survival, dry weight, and plant height were not inhibited by more than 5% at any treatment level.

1.5 Uncertainties and Data Gaps

The following uncertainties, limitations, and assumptions were identified in this environmental risk assessment:

- The 480 SC and 24 WG proposed labels restrict use per season; however, there are crops, such as brassica leafy vegetables, that often have more that one season in a year. In this risk assessment, RQs are based on one season per year and risk is underestimated for crops that have more than one growing season per year.

- Registrant-submitted toxicity testing shows that both the SC and WG flubendiamide formulations to be more toxic to freshwater invertebrates than the parent compound on an acute and chronic basis. While on the surface, these observed differences in toxicity might constitute a source of uncertainty in risk conclusions, the risk assessment, in accordance with Overview Document methods performs a separate assessment for formulations drifting directly to surface waters. Therefore, the risk assessment team is not recommending any further toxicity studies and feels the current assessment methods adequately address this issue.

- Two 28-day chronic toxicity studies indicate that flubendiamide and its des-iodo degradate are toxic to the midge, *Chironomus riparius*, in an overlying-water spiked system. It is evident that there is a potential for direct effects to benthic invertebrates exposed to the parent and degradate. Neither of the two chronic toxicity midge studies followed sediment toxicity guidelines which require the sediment to be spiked as opposed to the overlying water. Regardless of the route of administration in the studies, there were measured pore water concentrations and these combined with available mesocosm data suggest that there is sufficient information to reach a risk conclusion for benthic invertebrates.

- Data gaps in the environmental fate database for flubendiamide and NNI-0001-des-iodo exist. In order to refine the ecological risk assessment for flubendiamide and NNI-0001-des-iodo, EFED recommends submitting the following guideline and non-guideline studies:

  Flubendiamide

  (Non-guideline) **Small-scale Runoff/Vegetative buffer strip Study** – The runoff study is requested to determine the magnitude of the parent, flubendiamide, retained in buffer strips of various widths. EFED believes that the efficacy of buffers for flubendiamide use are uncertain. It appears that a program of monitoring receiving waters and storm water conveyances under varying conditions of use would greatly benefit any evaluation of potential utility of buffers to reduce flubendiamide loadings to receiving waters.

  Des-iodo Degradate

  (161-1) **Hydrolysis** – The hydrolysis study is requested to establish the significance of chemical hydrolysis as a route of degradation for NNI-0001-des-iodo and to identify, if possible, the hydrolytic products formed which may adversely affect non-target organisms.

  (161-2) **Photodegradation in Water** – Pesticides introduced into aqueous systems in the environment can undergo photolytic transformation by sunlight. Data on rates of photolysis are needed to establish the importance of this transformation process and the persistence characteristics of the photoproducts formed.

  162-3) **Anaerobic Aquatic Metabolism** – The anaerobic aquatic metabolism is needed to assess the effects the nature and extent of formation of NNI-0001-des-iodo residues in water and in hydrosoil since anaerobic conditions are more likely to exist in aquatic environments.

  (162-4) **Aerobic Aquatic Metabolism** – The requested study is needed to determine the effects on NNI-0001-des-iodo to aerobic conditions in water and sediments during the period of dispersal of NNI-0001-des-iodo throughout the aquatic environment and to compare rates and formation of metabolites. The data from this study would provide the aerobic aquatic input parameter for PRZM/EXAMS reducing modeling uncertainty.

  (164-1) **Terrestrial Field Dissipation Studies** – NNI-0001-des-iodo is persistent and moderately mobile which increases the likelihood for run-off and leaching. No definitive studies on the field dissipation and degradation properties of the major degradate have been submitted to the Agency.

2 PROBLEM FORMULATION

The purpose of this problem formulation is to provide the foundation for the ecological risk assessment being conducted for the insecticide, flubendiamide. As such, it articulates the purpose and objectives of the risk assessment, evaluates the nature of the problem, and provides a plan for analyzing the data and characterizing the risk (U.S. EPA 1998).

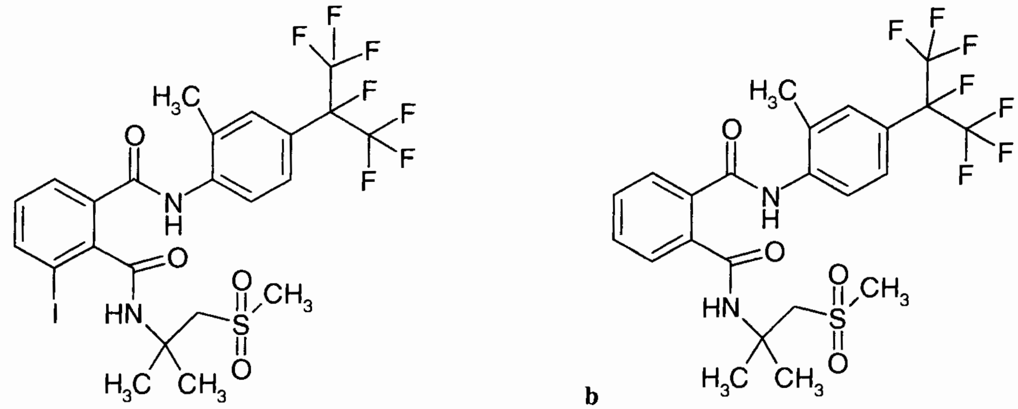
2.1 Nature of Regulatory Action

The proposed registration is for new chemical use (Section 3) of NNI-0001 480 SC (EPA Reg. 264-XXX) and NNI-0001 24 WG (EPA Reg. 264-XXX) flubendiamide formulations. Application of the flubendiamide formulation 480 SC is proposed for corn, cotton, tobacco, grapes, pome fruit, stone fruit, and tree nut crops. The 24 WG formulation is proposed for use on cucurbit vegetables, fruiting vegetables, leafy vegetables, and brassica (cole) leafy vegetables.

2.1.1 Nature of the Chemical Stressor

Flubendiamide, a systemic insecticide, belongs to the novel phthalic acid diamide class of insecticides for control of both adult and larval Lepidoptera (including armyworms, corn borers, loopers, bollworms, cutworms, fruitworms, and diamondback moths). It acts through a new biochemical mode of action, specifically by targeting the ryanodine cell receptor and interfering with the calcium release channel, which is involved in muscle contraction. It is active through ingestion and results in the rapid cessation of feeding and extended residual control. Moreover, flubendiamide as a systemic insecticide is quickly absorbed into plant tissue and can move up, but not down, in the plant (Bayer CropScience, 2006).

Environmental fate and transport data and reported physical-chemical properties indicate that flubendiamide is expected to be persistent in soil and aquatic environments. Volatilization from soil and water surfaces is not expected to be an important process since flubendiamide has a relatively low vapor pressure (7.5×10^{-7} mm Hg) and Henry's Law constant (8.9×10^{-11} atm·m^3/mol). Physical and chemical properties of flubendiamide can be found in **Table 2.** Flubendiamide is stable under laboratory hydrolysis, aerobic metabolism, and aerobic and anaerobic soil metabolism conditions. Under field conditions, flubendiamide also degrades very slowly ($T_{½}$ = 210-770.2 days). However, flubendiamide degrades to des-iodo under laboratory aquatic and soil photolysis ($T_{½}$ = 11.59 to 35.3 days) as well as anaerobic aquatic conditions ($T_{½}$ = 364 days). **Figure 1** shows the molecular structure of flubendiamide, and its major degradate, NNI-0001-des-iodo.



a b

Figure 1. Chemical structure of flubendiamide (a) and its major metabolite NNI-0001-des-iodo (b).

Although des-iodo was only detected in minor amounts (<3.4% of the applied) at the 0-15 cm soil depth at three sites in the field, under anaerobic aquatic conditions in the laboratory, 60.4% of the applied (total system) was identified as des-iodo at study termination (365 days). Flubendiamide is expected to be slightly to hardly mobile (K_{Foc}= 1076 to 3318 mL/g) in the environment, and its main transformation product, des-iodo, is expected to be moderately mobile (K_{Foc}= 234 to 581 mL/g). The octanol-water partition coefficients (log K_{ow}) of flubendiamide are 3.36 to 4.2 (4.1 at pH 7), which suggests it has low potential for bioaccumulation. Flubendiamide and des-iodo have the potential to contaminate surface water through runoff due to their persistence in the soil. Flubendiamide may also reach surface water via spray drift. The overall stability of the compound suggests that flubendiamide will tend to accumulate in the soil and its degradate in sediments with successive applications year to year.

Table 2. Physical-chemical properties of flubendiamide

Parameter	Value	Reference
Chemical Name	3-Iodo-*N'*-(2-mesyl-1,1-dimethylethyl)-*N*-{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-*o*-tolyl}phthalamide (IUPAC) N^2-[1,1-dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-[2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl]-1,2-benzenedicarboxamide (CAS)	
Chemical Class	Insecticide	
CAS Number	272451-65-7	
Synonyms	NNI-0001; R-41576; K-1155; AMSI 0085; M22919; AS-96576	
PC Code	027602	
Empirical Formula	$C_{23}H_{22}F_7IN_2O_4S$	Product Chemistry
Molecular Weight	682.4 g/mole	Product Chemistry
Melting Point	217.5-220.7°C	Product Chemistry
Octanol-Water Partition Coefficient (log K_{ow}, 25°C)	3.4-4.2 at pH 4 through 9	MRID 46816915
Vapor pressure (20/25°C)	7.5×10^{-7} mm Hg	Product Chemistry
Water Solubility (pH 6, 20°C)	29.9 µg/L	Product Chemistry
Henry's law constant (K_H)	8.9×10^{-11} atm·m^3/mole	MRID 96816915

Flubendiamide's major transformation product, NNI-0001-des-iodo, has the potential to contaminate groundwater. NNI-0001-des-iodo is persistent (stable in an aerobic soil environment), and is expected to be moderately mobile (K_{Foc} values were approximately 234 to 581 mL/g). **Table 3** summarizes the physical and chemical properties of NNI-0001-des-iodo.

Table 3. Physical-chemical properties of NNI-0001-des-iodo

Parameter	Value	Reference
Molecular weight	556.50 g/mole	
Molecular formula	$C_{23}H_{23}F_7N_2O_4S$	
Water Solubility	<1 mg/L <1 mg/L 390 µg/L (method = Banerjee's hypothesis) 450 µg/L (method = Irmann's procedure) 310 µg/L (method = WSKOW v1.41) 11 µg/L (method = Fragments)	MRID # 46816911 MRID # 46816920 MRID # 46816933 MRID # 46816933 EPI Suite EPI Suite
Vapor Pressure/Volatility	1.59×10^{-14} mm Hg, 25 deg C	EPI Suite
Henry's Law Constant	9.18×10^{-14} atm m^3/mole	EPI Suite
Octanol-water partition coefficient (log K_{ow})	3.40 ± 0.01	MRID # 46816911
Log K_{oa}	14.936	EPI Suite
Freundlich K_{oc}	8.365, 3.514, 2.574, 1.379, and 6.400 in treated soils	MRID # 46816906
Aerobic Soil Metabolism $t_{½}$	[^{14}C]Des-iodo was relatively stable in the treated soils, decreasing by ≤2% in the sand, sandy loam and silt soils and by 6-8% in the loamy sand soil during 212 days of incubation. In all soils, the measured concentrations were variable over time. Reviewer-calculated first-order linear half-lives were >6 years and are of uncertain value since they are extrapolated well beyond the duration of the study and assume that the pattern of degradation remains linear, and because the r^2 values are very low.	MRID # 46816911
Anaerobic Aquatic Metabolism	Desiodo-NNI-0001 was detected at maximums (individual samples) of 22.6%, 37.8% and 60.4% of the applied in the water, sediment and total system, respectively, at 365 days. 360 days	MRID # 46816914 EPI Suite
Pka	No dissociation between pH 2-11	MRID # 46816911
Stability of compound at room temperature, if provided	Stable in stock solution	MRID # 46816911

2.1.2 Overview of Pesticide Usage

Flubendiamide (trade name Belt®) is a broad-spectrum lepidopterous insecticide proposed for use of 480 SC formulation (a white liquid suspension containing *ca.* 490 g ai/L or 40.0% ai) on corn, cotton, tobacco, pome fruit (including apple, crabapple, loquat, mayhaw, pear, oriental pear, and quince), stone fruit (including apricot, cherry, nectarine, peach, plum, prune, and plum cot), tree nuts, and grapes (including American bunch grape, Muscadine grape, and Vinifera grape). In addition, the use of 24WG (formulation containing 24.0% ai) is proposed for new aerial and ground spray use on cucurbit vegetables, fruiting vegetables, leafy vegetables, and brassica (cole) leafy vegetables.

2.2 Receptors

2.2.1 Aquatic and Terrestrial Effects

The receptor is the biological entity that is exposed to the stressor (U.S. EPA 1998). Consistent with the process described in the Overview Document (U.S. EPA 2004), this risk assessment uses a surrogate species approach in its evaluation of flubendiamide. Toxicological data generated from surrogate test species, which are intended to be representative of broad taxonomic groups, are used to extrapolate to potential effects on a variety of species (receptors) included under these taxonomic groupings.

Acute and chronic toxicity data from studies submitted by pesticide registrants along with the available open literature are used to evaluate the potential direct effects of flubendiamide to the aquatic and terrestrial receptors identified in this section. This includes toxicity data on the technical grade active ingredient, degradates, and when available, formulated products (*e.g.* "Six-Pack" studies). The open literature studies are identified through U.S. EPA's ECOTOX database (http://cfpub.epa.gov/ecotox/), which employs a literature search engine for locating chemical toxicity data for aquatic life, terrestrial plants, and wildlife. The evaluation of both sources of data can also provide insight into the direct and indirect effects of flubendiamide on biotic communities from loss of species that are sensitive to the chemical and from changes in structure and functional characteristics of the affected communities.

2.2.2 Ecosystems Potentially at Risk

An ecosystem may be defined as a functional unit made up of all living organisms (animals, plants, and microbes) in a designated area, and all the non-living physical and chemical factors of their environment, linked together through nutrient cycling and energy flow. Moreover, an ecosystem can be of any size, *i.e.*, a log, pond, field, forest, or the earth's biosphere, but it always functions as a whole unit. Ecosystems are commonly described according to the major type of vegetation, for example, forest ecosystem, old-growth ecosystem, or range ecosystem.

Ecosystems potentially at risk are expressed in terms of the selected assessment endpoints. The typical assessment endpoints for screening-level pesticide ecological risks are reduced survival, and reproductive and growth impairment for both aquatic and terrestrial animal species. Aquatic animal species of potential concern include freshwater fish and invertebrates, estuarine/marine fish and invertebrates, and amphibians. Terrestrial animal species of potential concern include birds, mammals, and beneficial insects. For both aquatic and terrestrial animal species, direct acute and direct chronic exposures are considered. In order to protect threatened and endangered species, all assessment endpoints are measured at the individual level. Although endpoints are measured at the individual level, they provide insight about risks at higher levels of biological organization (*e.g.*, populations and communities). For example, pesticide effects on individual survivorship have important implications for both population rates of increase and habitat carrying capacity.

For terrestrial and semi-aquatic plants, the screening assessment endpoint is the perpetuation of populations of non-target plant species (crops and non-crop species). Existing testing requirements have the capacity to evaluate emergence of seedlings and vegetative vigor. Although it is recognized that the endpoints of seedling emergence and vegetative vigor may not address all terrestrial and semi-aquatic plant life cycle components, it is assumed that impacts at emergence and in active growth have the potential to impact individual competitive ability and reproductive success.

For aquatic plants, the assessment endpoint is the maintenance and growth of standing crop or biomass. Measurement endpoints for this assessment endpoint focus on vascular plant (*i.e.*, duckweed) growth rates and biomass measurements.

The ecological relevance of selecting the above-mentioned assessment endpoints is as follows: 1) the identification of exposure pathways for these receptors; 2) the receptors may be potentially sensitive to pesticides in affected media and in residues on plants, seeds, and insects; and 3) the receptors could potentially inhabit areas where pesticides are applied, or areas where runoff and/or spray drift may impact the sites because suitable habitat is available.

Given the persistence of flubendiamide and its degradates in soil and water environments and the widespread distribution of the plant species with proposed uses, ecosystems at risk can be generally defined as any adjoining field or water body where flubendiamide is applied.

2.2.3 Ecological Effects

Each assessment endpoint requires one or more "measures of ecological effect," which are defined as changes in the attributes of an assessment endpoint itself or changes in a surrogate entity or attribute in response to exposure to a pesticide. Ecological measurement endpoints for this risk assessment are based on a suite of registrant-submitted toxicity studies performed on a limited number of organisms in the following broad groupings:

1. Birds (mallard duck and bobwhite quail), also used as a surrogate for terrestrial-phase amphibians and reptiles,
2. Mammals (laboratory rat and mouse),
3. Freshwater fish (rainbow trout), also used as a surrogate for aquatic-phase amphibians,
4. Freshwater invertebrates (daphnid, chironomid),
5. Estuarine/marine fish (sheepshead minnow),
6. Estuarine/marine invertebrates (Eastern oyster),
7. Terrestrial plants (monocots and dicots),

8. Aquatic plants (freshwater vascular plants, freshwater and estuarine/marine non-vascular plants),
9. Terrestrial invertebrates (earthworm, honeybee, natural lepidopteran predators)

Within each of these very broad taxonomic groups, an acute and chronic endpoint is selected from the available test data, as the data sets allow. Additional ecological effects data were available for other taxa and have been incorporated into the risk characterization as other lines of evidence, including acute contact and oral toxicity on honeybees.

2.3 Conceptual Model

For a pesticide to pose an ecological risk, it must reach ecological receptors in biologically significant concentrations. An exposure pathway is the means by which a pesticide moves in the environment from a source to an ecological receptor. For an ecological pathway to be complete, it must have a source, a release mechanism, an environmental transport medium, a point of exposure for ecological receptors, and a feasible route of exposure.

A conceptual model provides a written description and visual representation of the predicted relationships between flubendiamide, potential routes of exposure, and the predicted effects for the assessment endpoint. A conceptual model consists of two major components: risk hypotheses and a conceptual diagram (U.S. EPA 1998).

2.3.1 Risk Hypotheses

- Terrestrial and aquatic organisms are subject to adverse direct effects such as reduced survival, growth, and reproduction when exposed to flubendiamide/degradate residues as a result of labeled use of the pesticide.
- Non-target terrestrial, semi-aquatic, and aquatic plants are subject to adverse effects such as reductions in vegetative vigor and seedling emergence (terrestrial) or biomass and growth rate (aquatic) when exposed to flubendiamide/degradate residues as a result of labeled use of the pesticide
- Indirect effects, such as food web dynamics, perturbing forage or prey availability, and altering the extent and nature of nesting, will potentially occur if residue concentrations exceed levels of concern for acute or chronic exposure for terrestrial and/or aquatic species.
- Listed species are subject to adverse effects if calculated risk quotients exceed acute Listed or chronic levels of concern

2.3.2 Conceptual Diagram

In order for a chemical to pose an ecological risk, it must reach ecological receptors in biologically significant concentrations. An exposure pathway is the means by which a contaminant moves in the environment from a source to an ecological receptor. For an ecological exposure pathway to be complete, it must have a source, a release mechanism, an environmental transport medium, a point of exposure for ecological receptors, and a feasible route of exposure. In addition, the potential mechanisms of transformation (*i.e.*, which degradates may form in the environment, in which media, and how much) must be known, especially for a chemical whose metabolites/degradates are of greater toxicological concern. The assessment of ecological exposure pathways, therefore, includes an examination of the source and potential migration pathways for constituents, and the determination of potential exposure routes (*e.g.*, ingestion, inhalation, and dermal absorption).

Based on the labels submitted by the registrant, the source and mechanisms of release for flubendiamide are aerial and/or ground application in the form of suspension concentrate formulation and chemigation in the form of water dispersible granule formulation. The conceptual model and subsequent analysis of exposure and effects are all based on the parent flubendiamide and des-iodo degradate. Potential emission of volatile compounds is not considered as a viable release mechanism for flubendiamide, because vapor pressure information (7.5×10^{-7} mm Hg at 20°C) suggests that volatilization is not expected to be a significant route of dissipation for this chemical (indicated by dashed lines in the diagram). The conceptual model shown in **Figure 2** generically depicts the potential source of flubendiamide, release mechanisms, abiotic receiving media, and biological receptor types.

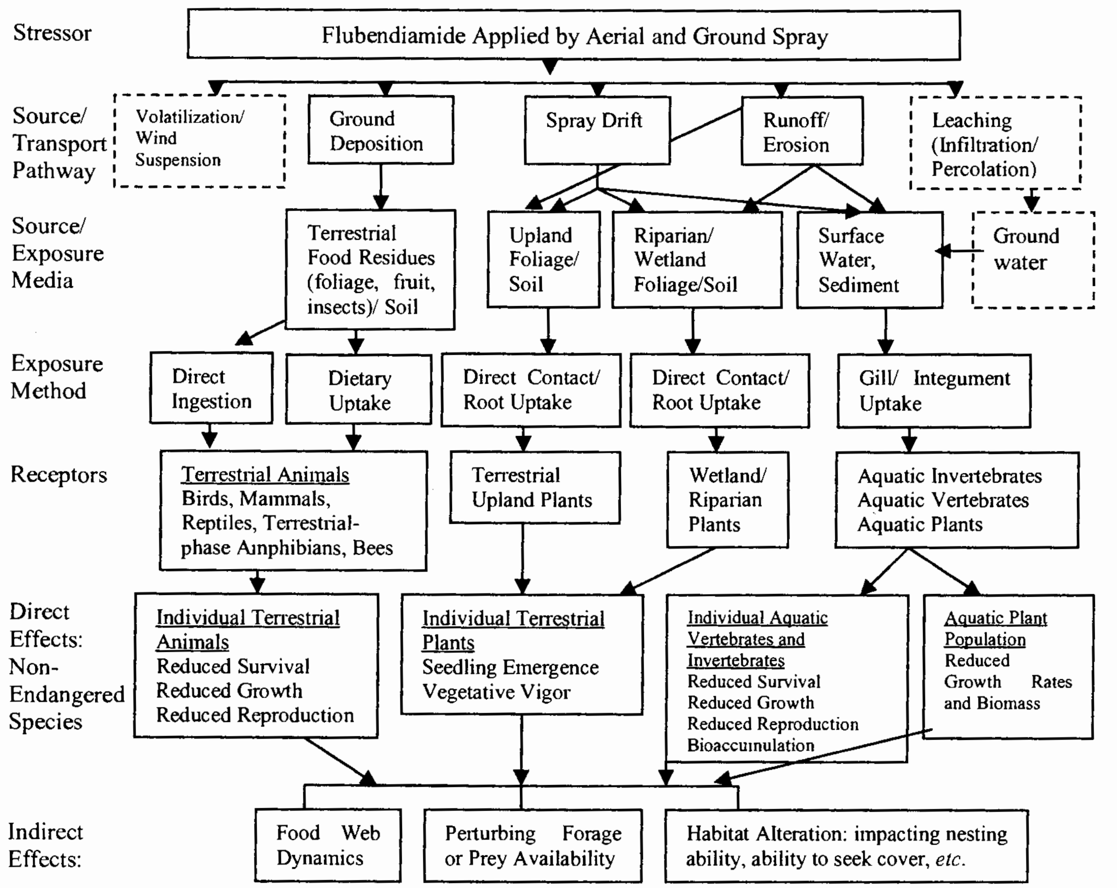


Figure 2. Conceptual model depicting ecological risk based on current flubendiamide applications.

2.4 Analysis Plan

2.4.1 Conclusions from Previous Risk Assessments

No previous risk assessments for flubendiamide have been performed.

2.4.2 Preliminary Identification of Data Gaps and Analysis Plan

A complete listing and classification of all flubendiamide environmental fate and ecotoxicity studies are provided in **Appendix A.**

Data gaps in the environmental fate database for flubendiamide and NNI-0001-des-iodo exist. In order to refine the ecological risk assessment for flubendiamide and NNI-0001-des-iodo, EFED recommends submitting the following guideline and non-guideline studies:

<u>Flubendiamide</u>

(Non-guideline) **Small-scale Runoff/Vegetative buffer strip Study** – The runoff study is requested to determine the magnitude of the parent, flubendiamide, retained in buffer strips of various widths. EFED believes that the efficacy of buffers for flubendiamide use are uncertain. It appears that a program of monitoring receiving waters and storm water conveyances under varying conditions of use would greatly benefit any evaluation of potential utility of buffers to reduce flubendiamide loadings to receiving waters. Additionally, EFED has provided the registrant with a description of a framework for an acceptable runoff monitoring protocol as well as comments on proposed monitoring protocols (Memorandum from Sidney Abel, 5/15/01; Memorandum from Hetrick, Odenkirchen, Evans, and Abel, 5/6/02 (D282366 and D281864).

Des-iodo Degradate

(161-1) **Hydrolysis** – The hydrolysis study is requested to establish the significance of chemical hydrolysis as a route of degradation for NNI-0001-des-iodo and to identify, if possible, the hydrolytic products formed which may adversely affect non-target organisms.

(161-2) **Photodegradation in Water** – Pesticides introduced into aqueous systems in the environment can undergo photolytic transformation by sunlight. Data on rates of photolysis are needed to establish the importance of this transformation process and the persistence characteristics of the photoproducts formed.

162-3) **Anaerobic Aquatic Metabolism** – The anaerobic aquatic metabolism is needed to assess the effects the nature and extent of formation of NNI-0001-des-iodo residues in water and in hydrosoil since anaerobic conditions are more likely to exist in aquatic environments.

(162-4) **Aerobic Aquatic Metabolism** – The requested study is needed to determine the effects on NNI-0001-des-iodo to aerobic conditions in water and sediments during the period of dispersal of NNI-0001-des-iodo throughout the aquatic environment and to compare rates and formation of metabolites. The data from this study would provide the aerobic aquatic input parameter for PRZM/EXAMS reducing modeling uncertainty.

(164-1) **Terrestrial Field Dissipation Studies** – NNI-0001-des-iodo is persistent and moderately mobile which increases the likelihood for run-off and leaching. No definitive studies on the field dissipation and degradation properties of the major degradate have been submitted to the Agency.

2.4.3 Measures of Effect and Exposure

Table 4 lists the measures of environmental exposure and ecological effects used to assess the potential risks of flubendiamide to non-target organisms (U.S. EPA 2004).

Table 4. Measures of environmental exposure and ecological effects used to assess the potential risks of flubendiamide to non-target organisms

Assessment Endpoint	Measures of Effect	Measures of Exposure

Table 4. Measures of environmental exposure and ecological effects used to assess the potential risks of flubendiamide to non-target organisms

Assessment Endpoint	Measures of Effect	Measures of Exposure
1. Abundance (*i.e.*, survival, reproduction, and growth) of individuals and populations of birds	1a. Bobwhite quail acute oral LD_{50} 1b. Bobwhite quail/ mallard duck sub-acute dietary LC_{50} 1c. Bobwhite quail/ mallard duck chronic reproduction NOAEC and LOAEC	Maximum residues on food items (foliar)
Abundance (*i.e.*, survival, reproduction, and growth) of individuals and populations of mammals	Laboratory rat acute oral LD_{50} Laboratory rat 1-generation NOAEC and LOAEC	
Survival and reproduction of individuals and communities of freshwater fish	Rainbow trout, carp, bluegill sunfish, fathead minnow LC_{50}	Peak EEC[4]
	Fathead minnow early-life NOAEC and LOAEC	60-day average EEC[4]
Survival and reproduction of individuals and communities of freshwater invertebrates	Daphnid EC_{50} Chironomid LC_{50}	Peak EEC[4]
	Daphnid life cycle NOAEC and LOAEC	21-day average EEC[4]
Survival of individuals and communities of estuarine/marine fish and invertebrates	Sheepshead minnow acute LC_{50} Eastern oyster EC_{50} Mysid shrimp LC_{50}	Peak EEC[4]
	Mysid shrimp NOAEC and LOAEC	21-day average EEC[4]
Survival of beneficial insect populations and natural Lepidoptera predators	5a. Honeybee, bumblebee acute contact LD_{50} 5b. Earthworm EC_{25} 5c. Parasitoid Wasp LD_{50} 5d. Predatory Mite LD_{50} 5e. Ladybird Beetle LD_{50} 5f. White springtail soil arthropod LD_{50} 5g. Green lacewing LD_{50}	Single Maximum application rate
6. Maintenance and growth of individuals and populations of terrestrial plants from standing crop or biomass	6a. Monocot EC_{25} values for seedling emergence and vegetative vigor (survival and growth rate) 6b. Dicot EC_{25} values for seedling emergence and vegetative vigor (survival and growth rate)	Estimates of runoff and spray drift to non-target areas
7. Maintenance and growth of individuals and populations of aquatic plants from standing crop or biomass	6a. Vascular plant (*i.e.*, Lemna) EC_{50} values for growth rate and biomass measurements 6b. Non-vascular plant (*i.e.*, green algae) EC_{50} values for growth rate and biomass measurements	Peak EEC[4]

[1] If species listed in this table represent most commonly encountered species from registrant-submitted studies, risk assessment guidance indicates most sensitive species tested within taxonomic group are to be used for baseline risk assessments.
[2] Birds represent surrogates for amphibians (terrestrial phase) and reptiles.
[3] Freshwater fish may be surrogates for amphibians (aquatic phase).
[4] One in 10-year return frequency.
[5] Four species of two families of monocots - one is corn, six species of at least four dicot families, of which one is soybeans. LD_{50} = Lethal dose to 50% of the test population; NOAEC = No observed adverse effect concentration; LOAEC = Lowest observed adverse effect concentration; LC_{50} = Lethal concentration to 50% of the test population; EC_{50}/EC_{25} = Effect concentration to 50%/25% of the test population.

3 ANALYSIS

3.1 Use Characterization

Flubendiamide, trade name Belt©, is a broad spectrum lepidopterous insecticide proposed for use on major crops in the United States, including corn, cotton, tobacco, pome fruits, and grapes. The two label formulations proposed for use are 480 SC (39% ai) and 24 WG (24% ai) and are applied by aerial and/or ground broadcast applications onto foliage of perennial and annual crops. Application of the flubendiamide formulation 480 SC is proposed for corn, cotton, tobacco, grapes, pome fruit, stone fruit, and tree nut crops. 24 WG is proposed for use on cucurbit vegetables, fruiting vegetables, leafy vegetables, and brassica (cole) leafy vegetables.

Many of these crops, including leafy vegetables, have multiple growing seasons per year and annual pesticide usage is addressed neither on the labels nor in this assessment. In these circumstances, annual pesticide usage may be under estimated. Complete seasonal maximum use rates and management practices for 480 SC and 24 WG by crop based on proposed labels is presented in **Table 5**.

Table 5. Flubendiamide crop application information for 480 SC and 24 WG formulations				
Crops	Max. Application Rate (lbs ai/A)	Max. # of Applications	Recommended Interval Between Apps. (days)	Max. Seasonal Use Rate (lbs ai)
Corn 480 SC Formulation	0.094	4	3	0.375
Cotton– 480 SC Formulation	0.094	3	5	0.282
Tobacco – 480 SC Formulation	0.094	4	5	0.375
Pome Fruit– 480 SC Formulation				
Apple/Crabapple/ Loquat/Mayhaw/ Pear/Oriental Pear/Quince	0.156	3	7	0.468
Stone Fruit– 480 SC Formulation				
Apricot/Cherry/Nectarine/Peach/Plum/ Plumcot/Prune	0.125	3	7	0.375
Tree Nut Crops– 480 SC Formulation				
Almond/Beech Nut/ Brazil Nut/Butter Nut/Cashew/Chestnut/ Chinquapin/Filbert/ Hickory Nut/Maca-damia Nut/Pecan Nut/Pistachio/ Walnut/	0.125	3	7	0.375
Grapes– 480 SC Formulation				
American Bunch Grape/Muscadine/ Vinifera	0.125	3	5-7	0.375
Cucurbit Vegetables- 24 WG Formulation				
Chayote/Chinese Waxgourd/Citron Melon/Cucumber/Gherkin/ Edible Gourds/Momordica spp./Muskmelon/Pumpkin/ Summer Squash/Winter Squash/Watermelon	0.045	5	7	0.225
Fruiting Vegetables- 24 WG Formulation				
Eggplant/Groundcherry/ Pepino/Peppers/Tomatillo/ Tomato	0.045	5	3	0.225
Leafy Vegetables- 24 WG Formulation				
Amaranth/Arugula/ Cardoon/Celery/Chinese Celery/Celtuce/Chervil/ Edible Garland Chrysan-themum/Corn Salad/ Upland and Garden Cress/ Dandelion/Dock/Endive/ Fennel/Head and Lead/Lettuce/Orach/Parsley/ Purslane/Radicchio/Rhubarb/Spinach/Swiss Chard	0.045	5	3	0.225
Brassica Leafy Vegetables- 24 WG Formulation				
Broccoli/Brussell Spouts/Cabbage/ Cauliflower/Collards/Kale/Kohirabi/Mizuna/ Mustard Greens/Mustard Spinach/Rape Greens	0.03	3	3	0.09

The recommended application timings of both formulations are to coincide with the early threshold level in a developing lepidoptera larval population. **Table 6** lists by crops targeted lepidoptera pests.

Table 6. Targeted Lepidoptera by crop

Crop	Pests to Control
Corn	Armyworms (including beet, fall, yellowstriped, and true), Black cutworm, Corn earworm, European corn bearer, Southwestern corn bearer, Western bean cutworm
Cotton	Armyworms (including beet, fall, yellowstriped, and true), Cotton leafworm, Cotton leaf perforator, Loopers (including cabbage and soybean), Saltmarsh caterpillar
Tobacco	Tobacco budworm, Tobacco hornworm
Pome Fruit	Codling moth, Eyespotted bud moth, Green fruitworm, Laconobia fruitworm, Leaf rollers (including oblique banded, pandemic, redbanded, and variegated).
Stone Fruit	Green fruitworm, Leaf rollers (including obliquebanded, pandemic, redbanded, and variegated)
Tree Nut Crops	Fall webworm, Hickoryshuck worm, Naval orange worm, Peach twig borer, Pecan nut case bearer, Walnut caterpillar
Grape	Cutworm, Grape leaf folder, Grape leaf skeltonizer, Omnivorous leaf roller, Orange tortrix
Cucurbit Vegetables	Cabbage looper, Melon worm, Pickleworm, Rindworm
Fruiting Vegetables	Armyworms (including beet fall, yellowstriped, and true), European corn bearer, Hornworms, Loopers, Tomato fruitworm
Leafy Vegetables	Armyworms (including beet fall, yellowstriped, and true), Diamond back moth, Imported cabbage worm, Loopers
Brassica Leafy Vegetables	Armyworms (including beet fall, yellowstriped, and true), Diamond back moth, Imported cabbage worm, Loopers

3.2 Exposure Characterization

3.2.1 Environmental Fate and Transport Characterization

Based on the submitted environmental fate data and reported physical-chemical properties, flubendiamide is expected to be persistent in the environment **(Table 6).** Detailed descriptions of the laboratory and terrestrial field fate studies as well as the major transformation products of the parent compound flubendiamide can be found in **Appendix H**. Volatilization from soil and water surfaces is not expected to be an important dissipation route since flubendiamide has a relatively low vapor pressure (7.5×10^{-7} mm Hg) and Henry's Law constant (8.9×10^{-11} atm·m^3/mol).

3.2.1.1 Degradation

Flubendiamide is stable to hydrolysis, aquatic aerobic metabolism, and aerobic and anaerobic soil metabolism under laboratory conditions. Flubendiamide degrades to des-iodo under laboratory soil photolysis ($T_{½}$ = 35.3 days) study. In laboratory aerobic soil studies, using four soils ranging from loamy sand to silt, flubendiamide was stable with <5% of the applied dissipating at 371 days post treatment. In field experiments, flubendiamide half-lives in three soils ranging from loamy sand to silt loam were 210-770.2 days, and in a sandy loam soil under outdoor conditions the half-life was 322 days.

Flubendiamide degrades by direct aqueous photolysis ($T_{½}$ = 11.56 day) and soil photolysis ($T_{½}$ = 35.3 days). Flubendiamide was stable to hydrolysis at pH's 4, 5, 7, and 9. In aerobic and anaerobic aqueous environments, flubendiamide is expected to dissipate somewhat faster than in aerobic soil, likely as a result of metabolism. Laboratory experiments using anaerobic and aerobic aquatic systems resulted in flubendiamide half-lives (water plus soil/sediment) of 127-364 days and 32.8-533.2 days, respectively. Under anaerobic aquatic conditions, 60.4% of applied radioactivity was identified as des-iodo (in the total system) at the time of study termination (365 days). **Table 7** summarizes the environmental fate and transport properties of flubendiamide.

Table 7. Environmental fate and transport properties of flubendiamide

Parameter	Value	Reference
Chemical Name	3-Iodo-*N'*-(2-mesyl-1,1-dimethylethyl)-*N*-{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-*o*-tolyl}phthalamide (IUPAC) N^2-[1,1-dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-[2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl]-1,2-benzenedicarboxamide (CAS)	
CAS Number	272451-65-7	
Synonyms	NNI-0001; R-41576; K-1155; AMSI 0085; M22919; AS-96576	
PC Code	027602	
Empirical Formula	$C_{23}H_{22}F_7IN_2O_4S$	Product Chemistry
Molecular Weight	682.4 g/mole	Product Chemistry
Appearance	Crystalline powder	Product Chemistry
Color	White	Product Chemistry
Melting Point	217.5-220.7°C	Product Chemistry
Octanol-Water Partition Coefficient (log K_{ow}, 25°C)	4.1 at pH 7	MRID 46816915
Vapor pressure (20/25°C)	7.5×10^{-7} mm Hg	Product Chemistry
Water Solubility (pH 6, 20°C)	0.04 mg/L	Product Chemistry
Henry's law constant (K_H)	8.9×10^{-11} atm·m^3/mole	MRID 96816915
Hydrolysis half-life (25°C)	Stable at pH 4,5,7 and 9	MRID 46816907
Aqueous photolysis half-life	11.58 days	MRID 46816908
Soil photolysis half-life (20°C, 75% of 1/3 bar)	35.3 days	MRID 46816909
Aerobic soil metabolism half-life (20°C, 75% of 1/3 bar)	Stable	MRID 46816910
Anaerobic soil metabolism half-life (20°C, 75% of 1/3 bar)	Stable (total system)	MRID 46816912
Aerobic aquatic metabolism half-life (20°C)	Stable	MRID 46816913
Anaerobic aquatic half-life	$t_{1/2}$ = 364 days (in sediment)	MRID 46816914
Freundlich adsorption coefficient (K_F)	18.3 (German silt) 23.5 (German sandy loam) 30.0 (Kansas silty clay) 17.3 (Washington loamy sand) 24.8 (Canadian loam)	MRID 46816905

Table 7. Environmental fate and transport properties of flubendiamide		
Parameter	**Value**	**Reference**
Freundlich coefficient normalized to organic carbon content (K_{Foc})	1076 (Canadian loam) 1172 (German silt) 1596 (German sandy loam) 2609 (Kansas silty clay) 3318 (Washington loamy sand)	MRID 46816905
Terrestrial field dissipation half-life (flowable suspension concentrate, 4.8% ai)	$t_{1/2}$ = 770.2 days; California sandy loam; detected below a depth of 30 cm at only one sampling event (3DAT, 30-45 cm). $t_{1/2}$ = 693.1 days; Mississippi silt loam; detected below a depth of 30 cm at three sampling events (547 DAT, 30-45 cm; 265, 547 DAT, 45-60 cm). $t_{1/2}$ = 210 days; Washington loamy sand; detected below a depth of 30 cm at only two sampling events (62DAT, 30-45 cm; 3DAT, 45-60 cm).	MRID 46816915

3.2.1.2 Degradates

The major transformation products (formed in amounts greater than or equal to 10% of applied radioactivity) resulting from the degradation of flubendiamide are: des-iodo (due to soil photolysis and anaerobic aquatic metabolism) and NNI-0001-oxalinic acid (soil photolysis). Flubendiamide degrades mainly to NNI-0001-des-iodo **(Table 8)**, which is formed in large amounts (total system basis maximums of 17.6% and 12.8% in soil photolysis and aqueous photolysis, respectively, and 60.4% in anaerobic aquatic metabolism). Des-iodo further degrades to NNI-0001-oxalinic acid (maximum of 10.8% of applied), CO_2 and bound soil residues in the soil photolysis study.

Table 8. Physical-chemical properties of NNI-0001-des-iodo:		
Parameter	**Value**	**Reference**
Molecular weight	556.50 g/mole	
Molecular formula	$C_{23}H_{23}F_7N_2O_4S$	
Water Solubility	<1 mg/L <1 mg/L	MRID # 46816911 MRID # 46816920
Vapor Pressure/Volatility	1.59E-014 mm Hg, 25 deg C	EPI Suite
Henry's Law Constant	9.18E-014 atm m^3/mole	EPI Suite
Octanol-water partition coefficient (log K_{ow})	3.40 ± 0.01	MRID # 46816911
Log Koa	14.936	EPI Suite
Freundlich K_{oc}	8.365, 3.514, 2.574, 1.379, and 6.400 in treated soils	MRID # 46816906
Aerobic Soil Metabolism $t_{½}$	[^{14}C]Des-iodo was relatively stable in the treated soils, decreasing by ≤2% in the sand, sandy loam and silt soils and by 6-8% in the loamy sand soil during 212 days of incubation. In all soils, the measured concentrations were variable over time. Reviewer-calculated first-order linear half-lives were >6 years and are of uncertain value since they are extrapolated well beyond the duration of the study and assume that the pattern of degradation remains linear, and because the r^2 values are very low.	MRID # 46816911
Anaerobic Aquatic Metabolism	Desiodo-NNI-0001 was detected at maximums (individual samples) of 22.6%, 37.8% and 60.4% of the applied in the water, sediment and total system, respectively, at 365 days. 360 days	MRID # 46816914 EPI Suite
Pka	No dissociation between pH 2-11	MRID # 46816911
Stability of compound at room temperature, if provided	Stable in stock solution	MRID # 46816911

Flubendiamide degrades to des-iodo by removal of the iodide on the phthalic acid ring. Theoretically, des-iodo can further degrade to des-iodo-alkylphthalimide by loss of the aniline ring. Des-iodo can also degrade to des-iodo-des-mesyl-carboxy and ultimately to trace metabolites, CO_2 and nonextractable residues. Flubendiamide can also degrade to NNI-0001-benzyl alcohol (a postulated intermediate), which is further degraded to NNI-0001-benzoic acid as the aniline methyl ortho-substituent is oxidized. Finally, flubendiamide can degrade to NNI-0001-3-OH with the replacement of the iodine atom with a hydroxyl substituent. Theoretically, flubendiamide is ultimately degraded to polar compounds.

3.2.1.3 Mobility and Transport

Flubendiamide is expected to be slightly to hardly mobile (K_{FOC} = 1076 to 3318 L/Kg) according to FAO classification (FAO 2000) in the environment, and its major transformation product, des-iodo, is expected to be moderately mobile (K_{FOC} = 234 to 581 L/kg). Since the exponents of the Freundlich isotherm (1/N) range from 0.9 to 1.1, the estimated K_Fs are assumed to be equal to K_Ds. The desorption K_Ds values ranged from 43.3 to 68.4 and the desorption K_{FOC} values ranged from 2061 to 13154. The main transformation product, des-iodo is more mobile than the parent. However, des-iodo was only detected in a small quantity (<3.4% of the applied) at the 0-15 cm soil depth at three sites in the terrestrial field studies.

Flubendiamide will enter surface water through spray drift when applied using a ground spray or aerial spray, through dissolution into runoff water, and through runoff of sediment bound residues (erosion) from agricultural fields. Des-iodo will also reach surface water in runoff. Although flubendiamide is not very mobile, and des-iodo is only moderately mobile, they are both persistent in the soil and flubendiamide has been detected below 30 cm at three sites in the terrestrial field studies. This indicates flubendiamide and des-iodo may reach ground water, particularly in vulnerable soils with lower organic carbon content. Concentrations of flubendiamide in ground water are anticipated to be higher in areas with high water tables (because there is less depth to travel before reaching ground water) and during times when heavy rainfall occurs, especially soon after application.

3.2.1.4 Field Studies

The major routes of dissipation of flubendiamide in soil, predicted from laboratory studies, appear to be consistent with the three terrestrial field dissipation studies (MRIDs 46816915, 46816916, and 46816917). These studies were conducted at three sites in the United States. The field data show that flubendiamide was persistent in the soil, dissipating from the top soil layer with half-lives of 210 to 770.2 days, and leaching to a depth of 30 to 60 cm. There were no significant degradates, however, des-iodo, NNI-0001-3-OH and NNI-0001-benzoic acid were detected in minor amounts in the top 0-15 cm soil depths. A non-guideline soil under outdoor conditions study (MRID 46816922) also indicated flubendiamide was persistent in the soil, dissipating with a half-life of 322 days. There were no significant degradates, however, des-iodo, NNI-0001-3-OH, NNI-0001-benzyl-alcohol, and NNI-0001-benzoic acid were detected in minor amounts.

The terrestrial field studies did not document to where and in what form flubendiamide residues dissipate. Based on laboratory experiments, flubendiamide residues are likely to degrade further to polar compounds, bind to soil particles and possibly be incorporated by soil microorganisms. Prior to binding, solubilized residues and polar compounds may move off site over the soil surface through runoff, downward through soil through leaching, or laterally with soil through subsurface flow. The small amounts of bound flubendiamide residues may dissipate through erosion or movement of wind-borne soil particles may occur. It is highly unlikely that volatilization is significant. With the exception of leaching, none of these dissipation routes were observed because run-off of bound or unbound residues, volatilization, and wind transport were not measured.

3.2.1.5 Bioaccumulation

Flubendiamide has a potential for bioaccumulation in fish due to flubendiamide being stable to hydrolysis and having a relatively high log K_{ow} (4.1 at pH 7). However in general, chemicals are a concern for bioaccumulation with BCF of 1000 or greater and log K_{ow} of 4.5 - 5.0 or greater. Flubendiamide residues in bluegill sunfish in the high dose study had a maximum mean fish bioconcentration factors (BCF) of 109.9X, 57.0X, and 206.3X for edible, non-edible, and whole fish tissue, respectively. After a 14-day depuration period, flubendiamide residues in the whole fish declined by a mean of 83% (low dose) and 86% (high dose). The residues depurated with a half-life of 4.6 and 4.8 days, from the low and high dose studies.

The des-iodo degradate is also not of concern for bioaccumulation in that it has a octanol-water partition coefficient of log K_{ow} 3.40 and calculated mean BCF values, based on total radioactive residues, of 12.6, 20.4, and 7.7 for whole fish, viscera, and edible tissues, respectively.

3.2.2 Measures of Aquatic Exposure

Aquatic EECs were calculated in several different ways in order to provide concentrations that are comparable and logically consistent with the toxicity study endpoints available for flubendiamide and it's degradate. EECs were calculated for aquatic exposure in the water column for the parent as TGAI and formulations and des-iodo degradate and benthic pore water for the parent as TGAI and des-iodo degradate.

3.2.2.1 Modeling Estimates

The estimated environmental concentrations in surface water were derived from Tier II PRZM (Pesticide Root Zone Model; Version 3.12.2, May 12, 2005) and EXAMS (Exposure Analysis Modeling System; Version 2.98.04.06, Apr. 25, 2005). PRZM simulated pesticide transport as a result of runoff, erosion, and off-target spray drift from an agricultural field. EXAMS estimates environmental fate and transport of pesticides in surface water. Additionally, a graphical interface shell, PE5.pl (dated 7/27/2007), was employed to facilitate an input of use-specific information in the PRZM input **(Table 9)** and the EXAMS chemical files.

Table 9. PRZM/EXAMS input parameters for proposed flubendiamide uses

Parameter	Input Value and Unit	Comment	Source
Chemical Application Method (CAM)	2	Foliar Application	Guidance
Hydrolysis ($t_{1/2}$)	0	Stable	MRID 46816907
Spray drift and application efficiency	Aerial: 0.05 Ground: 0.01	Efficiency – Aerial: 0.95 Ground: 0.99	Guidance
Aerobic soil metabolism ($t_{1/2}$)	0	Stable	MRID 46816910

Table 9. PRZM/EXAMS input parameters for proposed flubendiamide uses			
Parameter	**Input Value and Unit**	**Comment**	**Source**
Aerobic aquatic metabolism ($t_{1/2}$)	0	Stable	MRID 46816913
Anaerobic aquatic metabolism ($t_{1/2}$)	1092 days	364 days × 3[a]	MRID 46816914
Aquatic photolysis ($t_{1/2}$)	11.58 days	5.79 × 2[b]	MRID 46816909
Henry's Law constant (20 C)	8.9×10^{-11} atm·m^3/mole		MRID 96816915
Vapor pressure	7.5×10^{-7} mm Hg		Product Chemistry
Solubility in water (pH 7, 20 C)	0.3 mg/L	0.03 mg/L × 10[c]	
Molecular weight	682.4 g/mole		
Partition coefficient K_{FOC}	1954.2 mg/L	Average of 5 Soils	MRID 46816905
Foliar Extraction Rate (FEXTRC)	0.5	Default Value	Guidance

[a] Selected input parameters were multiplied by 3 according to Guidance for selecting input parameters in modeling for environmental fate and transport of pesticides. Version II February 28, 2002.
[b] Multiplied by 2 to model day/night cycle from continuous light study results.
[c] Water solubility was multiplied by 10 according to Guidance for selecting input parameters in modeling for environmental fate and transport of pesticides. Version II. February 28, 2002.

Linked crop-specific scenarios and meteorological data were used to estimate exposure as a result of flubendiamide uses on various crops. Simulations were done using the standard farm pond scenario in EXAMS, which is a surrogate for a permanent surface water aquatic environment. Weather and agricultural practices were simulated over 30 years to estimate the 1-in-10 year exceedance probability at the site.

The application rate used in each scenario is the recommended maximum label application rate for each use. Application dates were chosen to fall between typical emergence date and maturation date. The standard scenarios were developed by EFED to represent nationwide crop coverage and high-end vulnerability sites to runoff and erosion and, therefore, pesticide transport. The crop/region specificity of the scenarios may require that several regional scenarios be run for a given crop depending on the need to capture the most conservative set of results due to regional differences in precipitation and soil characteristics. Twenty-four EFED standard modeling scenarios are used for this modeling purpose. The application information for MS Corn and CA Tomatoes, the crop scenarios that produced the highest and lowest PRZM/EXAMS EECs, is provided in **Table 10** and the crop application information for all modeled crops is located in **Appendix B**.

Table 10. EFED aquatic modeling scenarios for proposed flubendiamide uses				
PRZM Crop Scenario	**First Application Date dd-mm**	**Max Number of Applications**	**Minimum Application Interval (days)**	**Maximum Single Application Rate (lb ai/A)**
Corn				
Mississippi Corn	01-05	4	3	0.094
Fruiting Vegetable				
California Tomato	15-04	5	3	0.045

Flubendiamide Parent Exposure

PRZM/EXAMS models were used to estimate flubendiamide parent concentrations in both the water column and benthic pore water. Water column EECs are used for comparison with toxicity endpoints for fish and invertebrates that live in the water column and are considered to be exposed to the active ingredient through spray drift, runoff, and erosion as to all components of the formulations (active ingredients and inerts) through spray drift alone. Benthic pore water EECs are used for comparison with toxicity endpoints for invertebrates that live in or on the sediment.

The high and low PRZM/EXAMS EECs for water column exposure to the active ingredient through spray drift, runoff, and erosion for all scenarios are presented in **Table 11.** The EECs for the modeled PRZM/Exams scenarios are located in **Appendix B**. Peak EEC values were used to determine acute risks to organisms associated with the water column. The 21-day average EEC values were used to determine chronic risks to aquatic invertebrates. The 60-day average EEC values were used to determine chronic risks to aquatic fish. A PRZM/EXAMS output file from the PE5 shell based on MS corn use is presented in **Appendix C.**

Table 11. Estimated water column concentrations of flubendiamide after aerial and ground application

Crop	Spray Application	Peak Conc. µg/L	21day Conc. µg/L	60 day Conc. µg/L
Corn (0.094 lbs ai/acre × 4 applications with 3 days interval)				
Mississippi Corn	Aerial	24.07	23.27	22.96
	Ground	23.29	22.39	21.98
Fruiting Vegetables (0.045 lbs ai/acre × 5 applications with 3 days interval)				
California Tomato	Aerial	2.25	2.13	2.03
	Ground	1.1	1.04	1.02

Toxicity data indicate that the flubendiamide formulations are more toxic to freshwater invertebrates tested than the technical grade flubendiamide. Formulations may contain chemicals that help to keep the active ingredient in suspension, or keep the active ingredient stable, *etc*. For example, emulsifiers, which keep chemicals of low solubility in suspension may also be disruptive to biological membranes and therefore exhibit toxicity.

To assess the risk of this additional toxicity of the formulations, it is assumed that the inert ingredient(s) degrade rapidly in the environment. Therefore, the inert ingredient(s) will not be transferred to aquatic environments through any pathways (runoff or erosion) other than spray drift. According to EFED policy, the spray drift fraction that falls on the standard PRZM/EXAMS pond is assumed to be 5% of the application rate for aerial applications and 1% for ground. The following equation was used to calculate EECs for comparison with the formulation toxicity endpoints (**Table 12**):

$$EEC = \frac{AppRate(\text{lbs./A}) \times 1.12 \frac{\text{kg/ha}}{\text{lbs./A}} \times SDFraction \times 10^{9}\ \mu\text{g/kg}}{2 \times 10^{7}\ \text{L/ha of Pond}}$$

Table 12. Estimated water column concentrations of flubendiamide formulations due to spray drift alone (no runoff or erosion contributions) after aerial and ground application						
	480 SC **Corn and Cotton**	**Tobacco**	**480 SC** **Pome Fruit**	**480 SC** **Stone Fruits, Tree Nuts, and Grapes**	**24 WG** **Fruiting, Leafy, and Cucurbit Vegetables**	**24 WG** **Brassica Leafy Vegetables**
Application Rate	0.094 lbs. ai/A	0.094 lbs. ai/A	0.156 lbs. ai/A	0.125 lbs. ai/A	0.045 lbs. ai/A	0.03 lbs. ai/A
Aerial	0.263 µg/L	N/A	N/A	N/A	0.126 µg/L	0.084 µg/L
Ground	0.053 µg/L	0.053 µg/L	0.087 µg/L	0.070 µg/L	0.025 µg/L	0.017 µg/L

In **Table 13**, the PRZM/EXAMS benthic pore water EECs are presented for the scenarios that produced the highest and lowest water column EECs. Other scenarios are expected to produce benthic pore water EECs within the range bounded by the aerial Mississippi Corn and the ground California tomato values.

Table 13. Estimated concentrations of flubendiamide in benthic pore water based on aerial and ground applications to Mississippi Corn and California Tomato scenarios			
Spray Application	**Peak Conc. (µg/L)**	**21day Conc. (µg/L)**	**60 day Conc. (µg/L)**
Mississippi Corn (0.094 lbs ai/acre × 3 applications with 3-day interval)			
Aerial	21.35	21.33	21.3
Ground	20.65	20.64	20.62
California Tomato (0.045 lbs ai/acre × 5 applications with 3-day interval)			
Aerial	1.82	1.81	1.81
Ground	0.94	0.94	0.94

Figure 3 presents the temporal variation in the accumulation of the des-iodo degradate over time in the standard EXAMS pond for both the lowest (CA tomato) and highest (MS corn) exposure scenarios for both the water column concentrations (**Figure 3a**) and pore water concentrations (**Figure 3b**). Examining the temporal trend of the high exposure scenario, it can be seen that flubendiamide concentrations rapidly accumulate for the first 20 years of application before leveling off over the last ten years of the simulation.

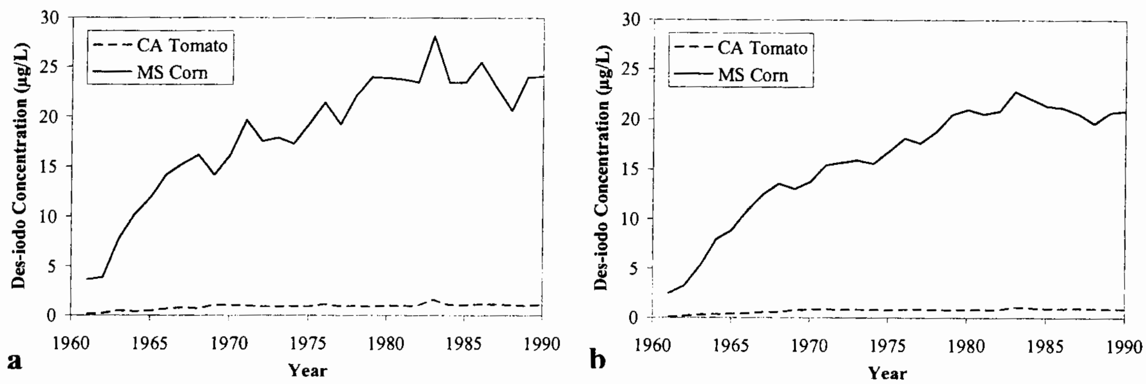


Figure 3. Accumulation of flubendiamide in water column (a) and pore water (b) of the PRZM/EXAMS standard pond under a low flubendiamide application rate, ground application to California tomatoes, and high application rate, air application to Mississippi corn.

Degradate EECs

The toxicity of the des-iodo degradate was tested with aquatic freshwater invertebrates (daphnid EC_{50} >881 µg metabolite/L and chironomid NOAEC = 1.0 µg metabolite/L). Because the chironomid NOAEC is less than the limit of solubility of the des-iodo degradate (450 µg/l), EECs for the des-iodo degradate were calculated to determine if the degradate poses risk to freshwater invertebrates.

The des-iodo degradate does not appear to degrade in aquatic environments. In the anaerobic aquatic metabolism study (MRID 46816914), the des-iodo degradate was the only degradate identified over this 365-day-long study. At the end of this study, 60.4% of applied radioactivity had been converted to the des-iodo degradate, while 39.7% remained as the parent compound.

In the aquatic photolysis study (MRID 46816908), 3 degradates were generated in this 7-day-long study. The degradates in the distilled-water aquatic photolysis experiments were the des-iodo degradate (11.9 and 21.6% of applied radioactivity in the phthalic- and aniline-labeled flubendiamide experiments, respectively, at study end), NNI-0001-3-OH (2.0 and 2.3% of applied in the phthalic- and aniline-labeled flubendiamide experiments, respectively, at study end), and dihydroxy-NNNI-0001 (8.2 and 11.6% of applied in the phthalic- and aniline-labeled flubendiamide experiments, respectively, at study end). At the end of these experiments, 51.7 and 35.4% of applied radioactivity remained as flubendiamide in the phthalic- and aniline-labeled flubendiamide experiments, respectively.

It appears that aquatic photolysis study indicates two separate degradation pathways. The first produces the des-iodo degradate directly from flubendiamide by substituting a hydrogen atom for iodine. The second produces the NNI-0001-3-OH degradate directly from flubendiamide by substituting a hydroxyl group for iodine and then produces dihydroxy-NNNI-0001 from NNI-0001-3-OH by substituting a second hydroxyl group for a fluorine atom.

In order to estimate the des-iodo degradate concentrations in both water column and pore water, PRZM/EXAMS simulations were performed using the chemical and fate properties of the des-iodo degradate (**Table 8**) using the same application dates, number of applications, and minimum re-treatment interval as the parent. To estimate an appropriate des-iodo application rate, the parent application rate was corrected for the difference in molecular weight of the degradate and multiplied by the highest conversion rate observed in any of the fate studies (60.4%; MRID 46816914).

Figure 3 presents the temporal variation in the accumulation of the des-iodo degradate over time in the standard EXAMS pond for both the lowest (CA tomato) and highest (MS corn) exposure scenarios for both the water column concentrations (**Figure 4a**) and pore water concentrations (**Figure 4b**). Examining the temporal trend of the high exposure scenario, it can be seen that des-iodo concentrations continuously accumulates over the 30 years of the simulation. Because the des-iodo degradate does not appear to degrade in the aquatic environment according to the registrant-submitted fate studies, this degradate is assumed to be persistent and, therefore, will continuously accumulate in aquatic environments.

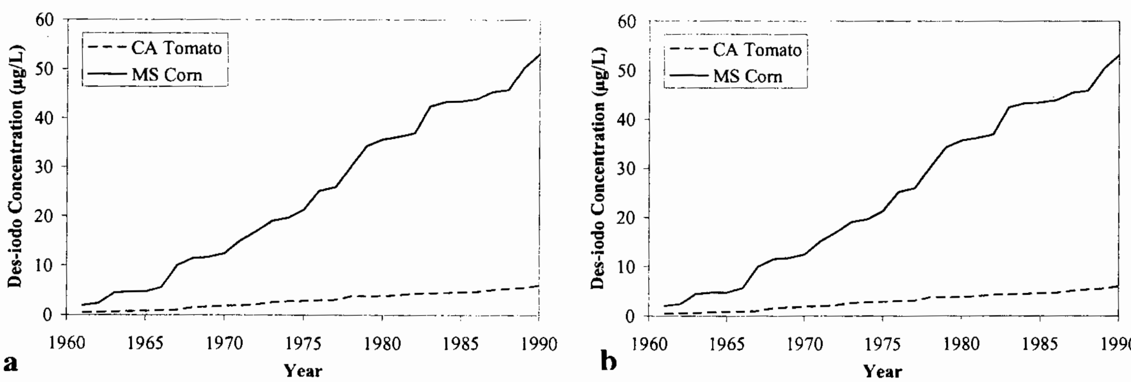


Figure 4. Accumulation of the flubendiamide des-iodo degradate in water column (a) and pore water (b) of the PRZM/EXAMS standard pond under a low flubendiamide application rate, ground application to California tomatoes, and high application rate, air application to Mississippi corn.

Typically EFED characterizes EECs in terms of 1-in-10-year concentrations. These 1-in-10-year concentrations would be used later in this document as a basis for calculating RQs. However, because the des-iodo concentrations continuously accumulate and never level off, the EEC or RQ value for a scenario will always continue to increase with time and cannot be adequately described with a single EEC or RQ value. Graphs of the benthic pore water concentrations for all scenarios appear in **Appendix Figure B1**.

3.2.2. Monitoring Data

Since flubendiamide is a new insecticide in the process of pesticide registration, there are no available monitoring data at this time for flubendiamide or its degradates.

3.2.3 Terrestrial Wildlife Exposures

Terrestrial wildlife exposure estimates are typically calculated for birds and mammals emphasizing a dietary exposure route for uptake of pesticide residues on vegetative matter and insects. These exposures are considered as surrogates for terrestrial-phase amphibians as well as reptiles. For exposure to terrestrial organisms, pesticide residues on food items are estimated based on the assumption that organisms are exposed to a single pesticide residue in a given exposure scenario. The residue estimates from spray applications are based on a nomogram by Hoerger and Kenaga (1972) as modified by Fletcher *et al.* (1994) that correlated residue levels, based on application rate, on various terrestrial items immediately following application in the field. The "maximum" residue concentration, an upper bound defined by Fletcher *et al.* (1994), for each food group was derived from literature and tolerance data.

Determination of residue dissipation over time on food items following single and multiple applications are predicted using a first-order residue degradation half-life with EFED's "T-REX_v1.3.1" model. The risk assessment uses a default foliar dissipation half-life estimate of 35 days. This half-life is used in lieu of representative foliar dissipation data for flubendiamide, because no foliar dissipation data were provided to EFED. The predicted maximum residues for application to a variety of crops as calculated by T-REX are provided in **Table 14.**

Table 14. Estimated environmental concentrations on avian and mammalian food items (ppm) at maximum application rates.

	Food Items			
Crop	**Short grass**	**Tall grass**	**Broadleaf/forage plants and small insects**	**Fruits, pods, seeds, and large insects**
Corn	82.73	37.92	46.53	5.17
Cotton	61.50	28.19	34.59	3.84
Tobacco	78.26	35.87	44.02	4.89
Pome Fruits	97.66	44.76	54.93	6.1
Stone fruits/tree nuts	78.85	36.14	44.35	4.93
Grapes	81.78	37.48	46.00	5.11
Fruiting Vegetables	48.12	22.05	27.07	3.01
Leafy Vegetables	29.3	13.42	16.47	1.83
Brassica Leafy Vegetables	20.38	9.34	11.46	1.27
Cucurbit Vegetable	41.72	19.12	23.46	2.61

The residues or EECs on food items may be compared directly with sub-acute dietary toxicity data or converted to an ingested whole-body dose (single oral dose, as the later is the case for small mammals and birds. Single-oral dose estimates represent, for many pesticides, an exposure scenario where absorption of the pesticide is maximized over a single ingestion event. Sub-acute dietary estimates provide for possible effects of the dietary matrix and more extended time of gut exposure to pesticide absorption across the gut. However, dietary exposure endpoints are limited in their utility because the current food ingestion estimates are uncertain and may not be directly comparable from laboratory conditions to field conditions. The EEC is converted to an oral dose by multiplying the EEC by the percentage of body weight consumed as estimated through allometric relationships. These consumption-weighted EECs (*i.e.,* EEC equivalent dose) are determined for each food source and body size for mammals (15, 35, and 1000 g) and birds (20, 100, and 1000 g). As an example, the EEC equivalent doses for birds and mammals based on application to pome fruits are given in **Tables 15 and 16**, respectively. The output from T-REX for all evaluated crops is included in **Appendix E**.

Table 15. Avian EEC equivalent dose adjusted for body weight for flubendiamide application to pome fruits.			
EEC Equivalent Dose [1] (mg/kg-body weight)	**Avian Classes and Body Weights**		
	Small	**Mid**	**Large**
	20 g	**100 g**	**1000 g**
Percent Body Weight Consumed	**114%**	**65%**	**29%**
Short Grass	112.08	63.91	28.61
Tall Grass	51.37	29.29	13.11
Broadleaf plants/small insects	63.04	35.95	16.10
Fruits/pods/large insects	7.00	3.99	1.79

[1] EEC equivalent dose = EEC (from Table 14) * (percent body weight consumed / 100)

Table 16. Mammalian EEC equivalent dose adjusted for body weight for flubendiamide application to pome fruits.						
	Mammalian Classes and Body weight					
EEC Equivalent Dose [1] (mg/kg-body weight)	**Herbivores/ Insectivores**			**Granivores**		
	15 g	**35 g**	**1000 g**	**15 g**	**35 g**	**1000 g**
Percent Body Weight Consumed	**95%**	**66%**	**15%**	**21%**	**15%**	**3%**
Short Grass	93.82	64.85	15.03			
Tall Grass	43.00	29.72	6.89			
Broadleaf plants/sm Insects	52.78	36.48	8.46			
Fruits/pods/seeds/lg insects	5.86	4.05	0.94	1.30	0.90	0.21

[1] EEC equivalent dose = EEC (from Table 14) * (percent body weight consumed / 100)

3.2.4 Terrestrial and Semi-Aquatic Plant Exposures

Terrestrial and semi-aquatic plants may be exposed to pesticides from runoff, spray drift, or volatilization. Semi-aquatic plants are those that inhabit low-laying wet areas that may be dry at certain times of the year. The runoff scenario in TERRPLANT 1.2.2 is: (1) based on a pesticide's water solubility and the amount of pesticide present on the soil surface and its top one centimeter, (2) characterized as "sheet runoff" (one treated acre to an adjacent acre) for dry areas, (3) characterized as "channel runoff" (10 acres to a distant low-lying acre) for semi-aquatic or wetland areas, and (4) based on percent runoff values of 0.01, 0.02, and 0.05% for water solubility values of <10, 10-100, and >100 ppm, respectively. Spray drift is assumed as (1) 1% for ground application, (2) 5% for aerial, airblast, forced air, and spray chemigation applications, and (3) 0% for granular applications. Currently, EFED derives plant exposure concentrations from a single maximum application rate only. Exposure through volatilization is not accounted for in this screening assessment, and based on the low vapor pressure it is not expected to be a significant route of exposure. EECs for pome fruit and corn are presented in **Table 17.** The TERRPLANT output for exposure due to use on pome fruits is provided in **Appendix E.**

Table 17. Flubendiamide estimated environmental concentrations for terrestrial and semi-aquatic plants for aerial and/or ground application to pome fruits and corn.		
Description	**Pome Fruits (0.156 lbs a.i./acre)**	**Corn (0.094 lbs a.i./acre)**
Runoff to dry areas	0.00156	0.00094
Runoff to semi-aquatic areas	0.0156	0.0094
Spray drift	0.0078	0.0047
Total for dry areas	0.0094	0.0056
Total for semi-aquatic areas	0.0234	0.0141

3.3 Ecological Effects Characterization

In screening-level ecological risk assessments, effects characterization describes the types of effects a pesticide can produce in an animal or plant. This characterization is based on registrant-submitted studies that describe acute and chronic effects toxicity information for various aquatic and terrestrial animals and plants.

Appendix E summarizes the results of all of the registrant-submitted toxicity studies for this risk assessment. Toxicity testing reported in this section does not represent all species of birds, mammals, or aquatic organisms. Only a few surrogate species for both freshwater fish and birds are used to represent all freshwater fish (2000+) and bird (680+) species in the United States. For mammals, toxicity studies are typically limited to the laboratory rat. Estuarine/marine testing is limited to a crustacean, a mollusk, and a fish. Also, neither reptiles nor amphibians are tested. The risk assessment assumes that avian and reptilian and terrestrial-phase amphibian toxicities are similar. The same assumption is used for fish and aquatic-phase amphibians. The most sensitive ecological toxicity endpoints for aquatic organisms, terrestrial organisms, and aquatic and terrestrial plants were used for risk characterization.

The most sensitive ecological toxicity endpoints for aquatic organisms (**Table 18**), aquatic and terrestrial plants (**Table 19**), terrestrial vertebrates (**Table 20**), and terrestrial invertebrates (**Table 21**) which were used for risk characterization of flubendiamide and the formulations are summarized below. **Table 22** summarizes the toxicity endpoints tested with the des-iodo degradate. Discussions of the effects of flubendiamide and the formulations on aquatic and terrestrial taxonomic groups are also presented below. In addition, a review of the Ecological Incident Information System (EIIS) and the ECOTOX database was conducted to further refine the characterization of potential ecological effects.

Table 18. Summary of acute aquatic toxicity data used for risk determination for flubendiamide applications.					
Species	**Acute Toxicity (LC/EC50 µg a.i./L)**			**Chronic Toxicity (NOAEC/LOAEC µg a.i./L)**	
	Technical	**Formulation 480 SC**	**Formulation 24 WG**	**Technical**	**Formulation 480 SC**
Freshwater Fish Rainbow trout(*Oncorhynchus mykiss*)	>65.1 Not Toxic at Limit of Solubility (468169-40)	>91.1 Not Toxic at Limit of Solubility (468169-43)	----	----	----
Freshwater Fish Bluegill sunfish (*Lepomis macrochirus*)	>67.7 Not Toxic at Limit of Solubility (468169-39)	>80.2 Not Toxic at Limit of Solubility (468169-42)	----	----	----
Freshwater Fish Fathead minnow *(Pimephales promales)*	>66.5 Not Toxic at Limit of Solubility (468169-37)	----	----	60.5/>60.5 No Effects (468169-47)	---
Freshwater Invertebrate Water flea *(Daphnia magna)*	>54.8 Not Toxic at Limit of Solubility (468169-30)	2.6 Very Highly Toxic (468169-31)	1.5 Very Highly Toxic (468169-32)	41.1/68.5 # of Aborted Eggs, # of Dead Neonates, Sub-Lethal·Effects of Neonates (468169-44)	0.38/1.18 Parental mortality, time to first brood (468169-45)
Estuarine/Marine Fish Sheepshead minnow	>29.8 Not Toxic at Limit of Solubility (468169-38)	----	----	----	----
Estuarine/Marine Invertebrate Mysid shrimp *Americampsis bahia*	>28 Not Toxic at Limit of Solubility (468169-36)	----	----	>20/>20 No Effects (468169-46)	----
Estuarine/Marine Mollusks Eastern oyster	>49 Not Toxic at Limit of Solubility (468169-35)			----	----
Freshwater Benthic Midge *Chironomus riparius*	LOAEC = 3 (pore water measured) Emergence Inhibition (468170-22)	1650 Mortality (468170-13)	130 Mortality (468170-14)	----	----

Table 19. Summary of aquatic and terrestrial plant toxicity data used for risk determination for flubendiamide application.			
Species	**Technical**	**Formulation 480 SC**	**Formulation 24 WG**
Vascular Plant Duckweed *Lemna gibba*	>54.6 No effects (468170-39)	----	----

Table 19. Summary of aquatic and terrestrial plant toxicity data used for risk determination for flubendiamide application.			
Species	**Technical**	**Formulation 480 SC**	**Formulation 24 WG**
Nonvascular Plant Green algae	>69.3 No effects *Selenastrum capricornutum* (468170-41)	>50,500 No effects *Pseudokirchneriella subcapitata* (468170-40)	----
Terrestrial Plants: Seedling Emergence	----	EC25 >0.363 lb a.i./A NOAEC =0.393 lb a.i./A (468170-36 (a))	EC25 >0.158 lb a.i./A NOAEC =0.158 lb a.i./A (468170-34) (468170-38)
Terrestrial Plants: Vegetative vigor	----	EC25 >0.426 lb a.i./A NOAEC =0.426 lb a.i./A (468170-36 (b))	EC25 >0.158 lb a.i./A NOAEC =0.158 lb a.i./A (468170-37)

Table 20. Summary of terrestrial acute and chronic toxicity data used for risk determination for flubendiamide application.						
	Acute Oral Toxicity (mg/kg bw)		**Subacute Toxicity (mg/kg diet)**		**Chronic Toxicity (mg/kg diet)**	
Species	**Technical**	**Formulation 480 SC**	**Technical**	**Formulation 480 SC**	**Technical**	**Affected Endpoints (MRID)**
Northern Bobwhite Quail *Colinus virginianus*	LD_{50}>2,000 Practically Non-Toxic (468170-03)	LD_{50}>2,000 Practically Non-Toxic (468170-04)	LC_{50}>5,199 Practically Non-Toxic (468170-06)	----	NOAEC= 1,059	No Effects (468170-08)
Mallard duck *Anas platyrhynchos*	----	----	LC_{50}>4,535 Practically Non-Toxic (468170-05)	----	NOAEC= 98	Hatchling Survivors/ Normal Hatchlings, Survivor weight (468170-07)
Laboratory rat	>5,000 Practically non-toxic (468171-43)	----	----	----	NOAEC= 50	Parental and offspring effects (468172-16)

Table 21. Summary of terrestrial invertebrate acute and chronic toxicity data used for risk determination for flubendiamide application.					
	Acute Toxicity			**Chronic Toxicity**	
Species	**Technical**	**Formulation 480 SC**	**Formulation 24 WG**	**Formulation 24 WG**	**Formulation 480 SC**
Earthworm (*Eisenia fetida*)	LD50>1000 mg a.i./kg (468170-28)	LD50>1000 mg a.i./kg (468170-29)	----	LD50>1000 mg a.i./kg NOAEC= 562 mg a.i./kg- reproduction effects (468170-32)	LD50>1000 mg a.i./kg (468170-31)
Honey bee (*Apis mellifera*)	LD50>200 µg a.i./bee (468170-09)	LD50>200 µg a.i./bee (468170-10)	----	----	----
Parasitoid Wasp (*Aphidius rhopalosiphi*)	----	Rate response test LD50>0.423 lb a.i./A (468170-21)	LD50>0.55 lb a.i./A (468170-20)	----	----
Predatory mite (*Typhlodromas pyri*)	----	----	LD50>0.55 lb a.i./A (468170-19)	----	----
Ladybird Beetle (*Coccinella septempunctata*)	----	----	----	----	45-day LD50=0.089 lb a.i./A NOAEC = 0.04 lb a.i./A (468170-15)
	----	----	----	----	47-day Life Cycle LD50=0.41 lb a.i./A NOAEC = 0.24 lb a.i./A (468170-17)
White springtail soil arthropod *(Folsomia candida)*	----	----	----	----	NOAEC = 31.6 mg a.s./kg (dw) LOAEC= 31.6 mg a.s./kg (dw) (468170-27)
Green lacewing (*Chrysoperla carnea*)	----	----	----	----	LD50=0.160 lb a.i./A (468170-18)

Table 22. Summary of toxicity data used for risk determination for flubendiamide degradate, des-iodo			
Species	**Degradate, des-iodo Acute Toxicity**	**Comment**	**MRID**
Freshwater Invertebrate Water flea *(Daphnia magna)*	EC50 >881 µg a.i./L	Not Toxic at Limit of Solubility (assuming solubility is the same as parent)	468169-33

Table 22. Summary of toxicity data used for risk determination for flubendiamide degradate, des-iodo			
Species	**Degradate, des-iodo Acute Toxicity**	**Comment**	**MRID**
Midge *Chironomus riparius*	NOAEC = 0.28 μg a.i./L (measured pore water concentration)	Supplemental	468170-23
Earthworm (*Eisenia fetida*) 14-day test	LD50 > 1000 mg a.i./kg	No effects on mortality or percent weight change	468170-30

3.3.1 Aquatic Effects Characterization

3.3.1.1 Toxicity to Freshwater Fish

Acute toxicity studies indicate flubendiamide was not toxic at the limit of its water solubility for both flubendiamide technical and the 480 SC formulated product. The LC_{50} values for studies conducted with technical product ranged from >65.1 μg a.i./L for the rainbow trout (MRID 468169-40), >67.7 μg a.i./L for the bluegill (MRID 468169-39), >66.5 μg a.i./L for the fathead minnow (MRID 468169-37), and >84.8 μg a.i./L for the common carp (MRID 468169-41). The LC_{50} values for studies conducted with the formulated product were >80.2 μg a.i./L for the bluegill sunfish (MRID 468169-42) and >91.1 μg a.i./L for the rainbow trout (MRID 468169-43).

A freshwater fish early life-stage study on fathead minnow (*Pimephales promales)* was used to evaluate the chronic toxicity of flubendiamide technical (MRID 468169-47). Flubendiamide had NOAEC and LOAEC values of 60.5 and >60.5 μg a.i./L, respectively. There were no treatment-related effects on embryo survival, time to hatch, hatching success, post-hatch survival, or growth in juvenile fathead minnows.

3.3.1.2 Toxicity to Freshwater Invertebrates

Acute freshwater toxicity tests using *Daphnia magna* indicate that flubendiamide is not toxic at its limit of solubility, yielding an LC_{50} value of >54.8 μg a.i./L (MRID 468169-30). Similarly, the des-iodo metabolite was also not toxic at its limit of solubility, with an LC_{50} value of >881 μg a.i./L (MRID 468169-33).

Acute testing with *Daphnia magna* indicated that both formulations were very highly toxic, with EC_{50} values of 1.5 μg a.i./L (24 WG formulation, MRID 468169-32) and 2.6 μg a.i./L (480 SC formulation, MRID 468169-31).

The acute toxicity of the 480 SC formulation was also evaluated when *Daphnia magna* were fed algal suspensions of varying density (MRID 46819-34). *Daphnia magna* fed an algal suspension of 10^6 cells/mL exhibited no toxic effects up to a concentration of 12.2 μg a.i./L, while *D. magna* fed algal suspensions of 10^2 and 10^4 cells/mL yielded EC_{50} values of 6.44 and 7.50 μg a.i./L, respectively. Unfed *D. magna* yielded EC_{50} values of 4.3 μg a.i./L. This test demonstrated that in the presence of an algal food source, the toxicity of the formulation was decreased by three times.

Two freshwater life cycle toxicity tests using *Daphnia magna* exposed to technical-grade flubendiamide (MRID 468169-44) or the 480 SC formulation (MRID 468169-45) were submitted. In the flubendiamide technical study, there was an increase in the number of aborted eggs, dead neonates and the presence of sub-lethal effects in neonates observed at 68.5 µg a.i./L. These effects were not observed at the other treatment levels (3.3 – 41.1 µg a.i./L). The NOAEC and LOAEC values were 41.1 and 68.5 µg a.i./L, respectively. In the 480 SC formulation study, parental mortality, sub-lethal effects, and an inhibition in time to first offspring emergence were observed. The NOAEC and LOAEC values were 0.38 and 1.18 µg a.i./L, respectively.

A 28-day chronic toxicity study with flubendiamide technical was submitted investigating the emergence and development rate of the midge, *Chironomus riparius*, in an overlying-water spiked system with nominal concentrations of 10 – 640 µg a.i./L (MRID 468170-22). Measured concentrations were only taken in the 10, 80, and 160 µg a.i./L nominal treatment groups. The NOAEC and LOAEC based on emergence was 40 µg a.i./L (nominal) and 80 µg a.i./L (nominal, 69 µg a.i./L 1-hr initial overlying water measurement). The pore water concentration at the NOAEC is unknown. The time-weighted average pore water concentration at the LOAEC is 3 µg a.i./L. This study was classified as supplemental because the sediment was not spiked and there was a significant effect on emergence in the solvent control as compared to the negative control. However, the study contained valuable information and it was clear that there were treatment effects at 80 µg a.i./L nominal treatment level given that the concentration of solvent was equal in all treatments.

A 28-day chronic toxicity study with the degradate des-iodo was submitted for the midge, *Chironomus riparius*, in an overlying-water spiked system with nominal concentrations of 0.25 - 32 µg metabolite/L (MRID 468170-23). Analytical results were only collected at the 0.25, 4.0, and 32 µg metabolite/L nominal treatment groups and time-weighted averages are <LOQ, 1.9 and 16 µg metabolite/L overlying water and <LOQ, 0.28 and 3.91 µg metabolite/L pore water. The percent emergence was adversely affected at 8.0, 16 and 32.0 µg metabolite/L, based on nominal overlying water concentrations. The NOAEC value was 1.9 µg metabolite/L (time-weighted measured overlying water) and 0.28 µg metabolite/L (time-weighted measured pore water) based on reductions in percent emergence. This study is classified as supplemental because the sediment was not spiked.

Acute testing with a freshwater benthic organism, midge (*Chironomus riparius*) indicated that the 480 SC formulation is moderately toxic with an LC_{50} value of 1650 µg a.i./L (MRID 468170-13), and the 24 WG formulation is highly toxic with an LC_{50} value of 130 µg a.i./L (MRID 468170-14).

3.3.1.3 Mesocosm Study

In a mesocosm study, the ecological effects of SC formulation were determined for different trophic levels including phytoplankton, zooplankton, aquatic macroinvertebrates, and emergent insects (no fish). The SC formulation was applied once onto the water surface in May 2003 and included five treatment levels 0.4, 1.0, 2.3, 5.3 and 12 µg a.i./L. There were two replicates of the 0.4 – 5.3 µg a.i./L groups and no replication of the 12 µg a.i./L treatment group. There were three control tanks. The mesocosms were observed two weeks before and 16 weeks after treatment.

Following application, a steady decline of flubendiamide was observed in the mesocosm water, with a mean DT_{50} of 59.4 days, and a mean DT_{50} of 66.1 days for the whole test system (water plus sediment). By study termination, *ca.* 30% of nominal concentrations were present in the water. Flubendiamide increased in the sediment until day 49, then remained more or less the same or declined slightly for the remainder of the study (day 112); the portion of flubendiamide in sediment did not exceed 15% of the total applied amount in any mesocosm. A small part of flubendiamide metabolized to des-iodo (metabolite A-1) in both water (≤0.21 µg/L at the 12 µg/L level) and sediment (≤3.65 µg/kg dw at the 12 µg/L level), and approximately 20% of the applied adsorbed to surfaces and particles (*e.g.*, macrophytes, periphyton or algae cells).

A significant number of taxa developed in the mesocosms: 36 zooplankton species, 21 macrozoobenthic organisms, 49 emerging insect species, and 7 classes of phytoplankton. Of these, the Cladocera *Daphnia longispina* was the most sensitive species. Consistent effects (including lower abundance) were observed in *D. longispina* at the 2.3 µg/L level during the first 7 days following application and at the 5.3 µg/L level until 4 weeks after application. At the 12 µg/L level, effects continued through 5 weeks after application, but a full recovery of this species was observed by 6 weeks after application. Further short-term adverse effects were observed on single dates for the freshwater crustaceans (Phyllopoda *Simocephalus vetulus*) (day 14) and the Copepod Nauplii (day 7). The Ostracoda development was postponed for 4 weeks at the 12 µg/L level compared to the control, but reached the control level by the end of the study. A faster than normal-trend decline of the Phyllopoda *Chydorus spaericus* was observed at the 12 µg/L level (no organisms present by day 14) and, while a statistically-significant effect at this level was not detected, a biologically-significant effect may have existed. Based on the observed effects on *Daphnia longispina* as the most sensitive species, the NOAEC on the population and community level for the zooplankton was 1.0 µg/L. Persistent effects were not observed for any taxon in the study up to the highest treatment level (12 µg/L), but there was no replication at this level. As a result, NOEAEC (no observed ecological adverse effect concentration, *i.e.*, no long-lasting effects) for this study is 5.3 µg/L for the zooplankton.

Regarding macroinvertebrates, the number of Tubificidae in the 12 µg/L treatment was significantly reduced from days 14 to 42 (NOAEC of 5.3 µg/L), but reached the control level within 7 weeks after application. The community analysis yielded a NOAEC of 5.3 µg/L on day 14 only. Similarly, the artificial substrate samplers did not indicate persistent effects for any taxon as well as for the macroinvertebrate community for all treatment levels.

No direct effects were observed on the phytoplankton. Following application, cell densities of Cryptophyceae were slightly lower at the 12 µg/L level for a short time as in the controls, caused by indirect food-web effects. The community NOAEC for phytoplankton and the NOEAEC was 5.3 µg/L (due to the missing replication at the highest treatment level).

No effects on the coverage of the ponds and the biomass of macrophytes and filamentous algae were observed at any treatment level throughout the study. No direct or indirect effects were observed on the emergence of insects. In addition, no direct or indirect effects of the application of 480 SC formulation to the physico-chemical parameters in the pond water (*e.g.*, temperature, oxygen level, pH, nitrogen compounds, phosphate, conductivity, hardness, COD) were observed at any test concentration.

The effects in this study were limited to short-term effects on a very few species and effects were not replicated at the highest test level, resulting in an overall NOEAEC of 5.3 µg/L.

Some deviations from guidance included a finfish population was not investigated; the 12 µg/L level was not replicated, and only two replicates were included for the remainder of treatment levels (excluding controls, where three replicate ponds were maintained); and flubendiamide levels in biota were not determined. This study is classified as supplemental.

3.3.1.4 Toxicity to Estuarine/Marine Fish

An estuarine/marine fish acute toxicity test with sheepshead minnow (*Cyprinodon variegates)* was conducted using flubendiamide (MRID # 468169-38). Flubendiamide is categorized as not toxic at its limit of solubility (LC_{50} >29.8 µg a.i./L) to estuarine/marine fish on an acute toxicity basis.

3.3.1.5 Toxicity to Estuarine/Marine Invertebrates

Results from an acute toxicity study with mysid shrimp (*Americamysis bahia*) show that technical-grade flubendiamide is not toxic at its limit of solubility (LC_{50} >28 µg a.i./L; MRID 468169-36).

In addition, a full life-cycle toxicity test indicated that technical-grade flubendiamide yielded no chronic toxic effects on the mysid shrimp, *Americamysis bahia* (MRID 468169-46). The NOAEC and LOAEC values were 20 and >20 µg a.i./L, respectively.

3.3.1.6 Toxicity to Estuarine/Marine Mollusks

The results from an estuarine/marine acute shell deposition toxicity test show technical-grade flubendiamide is not toxic at its limit of solubility (EC_{50} >49 µg a.i./L) to the eastern oyster, *Crassostrea virginica* (MRID 468169-35).

3.3.1.7 Aquatic Plant Toxicity

There was no toxicity observed at the highest concentration of the technical grade flubendiamide tested, at its limit of solubility, in the non-vascular (*Selenastrum capricornutum*) and vascular (*Lemna gibba*, EC_{50}>54.6 µg a.i./L) aquatic plant tests. In addition, there was no toxicity observed at the highest concentration of the 480 SC formulation tested, in the non-vascular (*Pseudokirchneriella subcapitata*) aquatic plant tests.

3.3.2 Terrestrial Effects Characterization

3.3.2.1 Acute (oral-gavage) Toxicity to Birds

Two acute oral-gavage studies were submitted for the northern bobwhite quail (*Colinus virginianus*, MRIDs # 468170-03 and 468170-04), one using the TGAI and one using 480 SC Formulation with 40% a.i. In both cases, the resulting LD_{50} values (LD_{50}>2,000 mg/kg-BW) for both studies show that flubendiamide is categorized as "Practically non-toxic" to avian receptors on an acute oral-gavage basis as no mortalities were reported in this study. These studies were classified as acceptable.

3.3.2.2 Sub-acute (dietary) Toxicity to Birds

One avian sub-acute dietary toxicity study analyzing the dietary effects flubendiamide may potentially pose to birds was submitted using the bobwhite quail and the TGAI of flubendiamide. Based on the resulting 8-day LC_{50} value for the sub-acute dietary toxicity study using the bobwhite quail (LC_{50}>5,199 mg/kg-diet), the TGAI of flubendiamide is categorized as "Practically non-toxic" to avian receptors on a sub-acute dietary toxicity basis due to no mortalities being reported in this study. The study was classified as acceptable.

3.3.2.3 Chronic Toxicity to Birds

Two chronic toxicity studies were submitted to the Agency, for northern bobwhite quail and mallard duck (MRID 468170-08 and 468170-07) both using the TGAI of flubendiamide. In the study using the Bobwhite Quail (MRID 468170-08), no adult or reproductive parameters were inhibited by exposure of bobwhite to flubendiamide during the avian reproduction study, resulting in NOAEC and LOAEC values of 1,059 and >1,059 mg a.i./kg diet, respectively. In the study using the Mallard duck (MRID 468170-07), there was a biologically significant reduction in the number of hatchling survivors/normal hatchlings (3 - 7%) at the 289 and 960 mg a.i./kg diet, yielding NOAEC and LOAEC values of 98 and 289 mg a.i./kg diet, respectively (MRID 468170-07). This mallard duck reproduction study was classified as supplemental because statistically significant effects (although slight) were observed at the lowest test concentration.

3.3.2.4 Acute Oral and Dermal Toxicity to Mammals

Wild mammal testing is required on a case-by-case basis, depending on the results of lower tier laboratory mammalian studies, intended use pattern, and pertinent environmental fate characteristics. In most cases, rat or mouse toxicity values obtained from the Agency's Registration Division (RD) and the Health Effects Division (HED) substitute for wild mammal testing.

Three acute oral mammalian studies were submitted to the Agency for review. In a mouse study, the LD_{50} >2000 mg a.i./kg-bwt (combined sexes - MRID 468171-42). In two other studies using the laboratory rats, the LD_{50}'s were estimated to be >5,000 mg/kg-BW (combined sexes) (MRID 468171-43).

Based on the acute studies provided for the formulation product, 24 WG, flubendiamide has a low acute dermal (LD50 >2000 mg/kg bw), and inhalation toxicity (LC50 >0.0685 mg/L air, the mean maximum attainable concentration) in male and female rats. 24 WG is a slight irritant to the eye, but is non-irritating to skin and it shows no skin sensitization potential under the conditions of the guinea pig maximization test.

3.3.2.5 Chronic Toxicity to Mammals

In a 2-generation reproduction study (MRID 46817216), flubendiamide was administered to 24 Wistar Hanover rats in the diet at target dose levels of 0, 50, 200, 2000, or 20,000 ppm. For parental effects, absolute and relative liver weights were increased in both sexes as well as increases in the kidney and thyroid weights of males and females. Moreover, absolute and relative pituitary weights were decreased in both males and females as well. Clinical signs of toxicity were limited to effects on the eyes. The NOAEC for parental toxicity is 50 ppm based on effects on the liver, thyroid, and kidneys.

For offspring effects, there were no effects of treatment on the number of implantations, number of pups delivered, sex ratio, or on the live birth, viability, or lactation indices. At 20,000 ppm, F1 pup body weights were decreased by an estimated 9% in both sexes compared to controls on PND 21. Sexual maturation was delayed in the males, as indicted by a dose-dependent increase ($p \leq 0.05$) in the mean number of days until preputial separation at 50 ppm (42.5 days), 2000 ppm (43.0 days), and 20,000 ppm (43.7 days) compared to controls (41.3 days). Additionally at 2000 and 20,000 ppm, the body weight at which preputial separation occurred was increased ($p \leq 0.05$) by 5-7% over controls. The NOAEC for offspring toxicity is 50 ppm based on effects on the liver and thyroid.

For reproductive effects, there was no evidence of any treatment-related effects or signs of reproductive impairment in males or females (the precoital interval; mating, fertility, or gestation indices; or gestation duration in either generation). Due to an apparent delay in balanopreputial separation in the first generation at 50 ppm and above, as well as, a finding of enlarged eyeballs, albeit poorly correlated to dose, the two-generation study was supplemented by a one-generation study (468172-39) in order to confirm or reject a relationship to treatment regarding these two endpoints. The one-generation reproduction supplemental study showed no effect on balanopreputial separation up through and including 200 ppm in males and females. An increase in the mean age of vaginal opening 20,000 ppm in males and females F1 offspring was also noted in the supplemental one-generation study, but was not reproduced in the two-generation study. The supplemental study also confirmed the treatment-related finding of enlarged eyeballs. The NOAEC for reproductive toxicity is 20,000 ppm in that no reproductive toxicity was observed.

3.3.2.6 Acute Toxicity to Non-target Insects

In two 48-hr acute contact tests, honey bees (*Apis millifera*) were exposed to technical-grade flubendiamide (MRID #468170-09) and to the 480 SC formulation (MRID 468170-10). The resulting LD_{50} values for both tests were >200 µg a.i./bee. No mortality was observed in either the control or the single test group of 200 µg a.i./bee. Flubendiamide and the formulation are categorized as practically non-toxic to honey-bees. This study is classified as acceptable.

The effects of the 480 SC formulation on the honey bee (*Apis mellifera*) were evaluated under semi-field conditions by exposing the honey bees to plots of lacy phacelia (*Phacelia tanacetifolia*) treated at application rates of 0.08 and 0.160 lb a.i./A; MRID 468170-11). No adverse effects were observed in mortality, flight intensity, or behavior during the test. Brood development was slightly reduced following initiation in the 0.160 lb a.i./A, but recovery was observed. The LD_{50} and NOAEC values were not determined.

The effects of the 24 WG formulation on the bumblebee (*Bombus terrestris*) was exposed for 27 days to plots of tomatoes (*Lycopersicon esculentum*) treated with the 24 WG formulation at 0.160 lb a.i./A in a greenhouse (MRID 468170-12). The test material did not yield any deleterious impacts on pollination activity, flight frequency, or hive condition.

Two extended laboratory studies were conducted by exposing the parasitoid wasp (*Aphidius rhopalosiphi*) to the 24 WG formulation (MRID 468170-20) and the 480 SC formulation (MRID 468170-21). In the 15-day exposure test with 24 WG formulation, significant reductions in survival and reproduction were observed with survival as the most sensitive endpoint, and yielding NOAEC and LOAEC values of 0.17 and 0.30 lb a.i./A, respectively. The LD_{50} > 0.55 lb a.i./A. The reproductive NOAEC is 0.30 lb a.i./A based on the number of mummies per female. In the 14-day rate response test with 480 SC formulation, reproduction was not inhibited; however, survival was affected in both tests (tested different range of concentrations, and the resulting NOAEC values were <0.2 and 0.39 lb a.i./A. The LD_{50} were 0.423 and 0.60 lb a.i./A. In the first test, significant morality was observed at all test concentrations resulting in NOAEC <0.2 lb a.i./A, however this effect was not observed in the second test at the same concentration, so there is uncertainties concerning mortality at this concentration.

A 14-day laboratory study was conducted by exposing the predatory mite (*Typhlodromas pyri*) to the 24 WG formulation (MRID 468170-19). Significant reductions in survival

(14%) and reproduction (24%) were observed yielding NOAEC and LOAEC values of 0.31 and 0.55 lb a.i./A, respectively. The LD_{50} > 0.55 lb a.i./A.

Three extended laboratory experiments were conducted exposing the ladybird beetle (*Coccinella septempunctata*) to the 480 SC formulation. The first test was conducted by placing ladybird beetle larvae on apple (*Malus domestica*) leaves treated with the test material at up to 0.60 lb a.i./A (MRID 468170-17). Reproduction was not affected; however, the LD_{50}, NOAEC, and LOAEC values for larval survival were 0.41, 0.24, and 0.60 lb a.i./A, respectively. In the second test, the ladybird beetles were exposed to apple leaves treated with the 480 SC formulation at up to 0.16 lb a.i./A; in addition, beetles were fed with aphids (*Acyrthosiphon pisum*) and pollen treated with corresponding application rates (MRID 468170-15). Larval survival and reproduction were not affected, while the LD_{50}, NOAEC, and LOAEC values for adult survival were 0.089, 0.040, and 0.079 lb a.i./A, respectively. The third toxicity study with the ladybird beetle consisted of two separate bioassays (MRID 468170-16). Beetles in the first bioassay were exposed to freshly-dried residues of the 480 SC formulation on vine (*Vicia faba*) plants treated at 0.17 lb a.i./A, and were fed aphids that were treated with the corresponding application rate. Beetles in the second bioassay were exposed to 14-day old residues of the 480 SC formulation on vine plants. Survival and reproduction remained unaffected during both assays, yielding LD_{50}, NOAEC, and LOAEC values of >0.17, 0.17, and >0.17 lb a.i./A, respectively.

An extended toxicity study was conducted with the green lacewing *Chrysoperla carnea* to determined the effect of applied to freshly dried 480 SC residues on *Phaseolus vulgaris* (beans) and treated food (eggs) on larval mortality and reproduction (MRID 468170-18). Based on a preliminary review of this study, there was no significant dose-response relationship for larval mortality (LD_{50}> 0.16 lb a.i./A), and there was no significant effect on reproduction (hatching rate and fertile eggs/female/day). EFED has not finalized the review of this study as this time.

Acute toxicity was assessed for earthworms (*Eisenia fetida*) exposed to technical-grade flubendiamide (MRID 468170-28), the 480 SC formulation (MRID 468170-29), and the des-iodo degradate (MRID 468170-30). Earthworms did not exhibit acute effects when treated under acute conditions with technical-grade flubendiamide, the 480 SC formulation, or the des-iodo degradate at concentrations of 1,000 mg a.i./kg, yielding LC_{50} and NOAEC values of >1,000 and 1,000 mg a.i./kg, respectively. Chronic toxicity was assessed for earthworms exposed to the 480 SC (MRID 468170-31) and 24 WG (MRID 468170-32) formulations. When treated with the 480 SC formulation, earthworms did not exhibit any effects based on survival or reproduction, yielding NOAEC and LOAEC values of 1,000 and >1,000 mg a.i./kg, respectively. Earthworms experienced a reduction in reproduction (number of juveniles) when treated with the 24 WG formulation, yielding NOAEC and LOAEC values of 562 and 1,000 mg a.i./kg, respectively.

A 28-day toxicity study was conducted with the soil arthropod Collembola species *Folsomia candida* (white springtail) to determined the effect of 480 SC on reproduction

(MRID 468170-27). Based on a preliminary review of this study, there was no dose-response relationship for adult mortality. There was a significant reduction of the number juveniles produced resulting in NOAEC and LOAEC values of 31.6 and 100 mg a.i./kg (dw).

3.3.2.7 Toxicity to Terrestrial Plants

Four Tier I studies were submitted to assess the effects of the 24 WG and 480 SC formulations on the seedling emergence and vegetative vigor of monocot and dicot terrestrial plant species. The effects of the 480 SC formulation on the seedling emergence and vegetative vigor of monocots and dicots were assessed by exposing the organisms to the maximum labeled rate of the formulation (0.468 lbs a.i./A) (MRID 468170-36(a) and (b)). No inhibitions of ≥25% were observed in percent survival, shoot height, or dry weight for any of the species tested.

Monocots (corn and oat) and dicots (cucumber, oilseed rape, soybean, and sunflower) were exposed to the maximum labeled rate of the 24 WG formulation (0.158 lbs a.i./A) to determine the effects on seedling emergence (MRID 468170-34). None of the species tested exhibited reductions of ≥25% in survival or dry weight; however, sunflower exhibited a 33% reduction in percent emergence at the single treatment level. Therefore, a Tier II seedling emergence study was required for sunflower exposed to the 24 WG formulation only, based on the 33% inhibition in percent emergence at the maximum labeled rate relative to the negative control group. The effects on the vegetative vigor following exposure to the maximum labeled rate of the 24 WG formulation (MRID 468170-37) was assessed using the same species from the seedling emergence test with an additional monocot (onion, *Allium cepa*) and an additional dicot (lettuce, *Lactuca sativa*). No species exhibited a reduction of ≥25% in survival or dry weight.

A Tier II seedling emergence study was conducted by exposing sunflower (*Helianthus annus*) to the 24 WG formulation (MRID 468170-38). In contrast to the Tier I study, percent emergence was not inhibited by more than 5% at the highest treatment level (0.16 lbs a.i./A) relative to the negative control group. Additionally, percent survival, dry weight and plant height were not inhibited by more than 5% at any treatment level.

3.3.3 Review of Incident Data

A review of the EIIS database for ecological incidents involving flubendiamide resulted in no reported incidents. This is expected with new pesticides because such chemicals have typically not been used widely in the environment. Although there were no reported incidences for this chemical, this does not rule out any existing risks that may potentially impact terrestrial and aquatic organisms.

3.3.4 Review of ECOTOX Data

A search of the ECOTOX database was completed on October 22, 2007 in which 3 papers were classified as "Acceptable" for ECOTOX and OPP standards (**Appendix G**).

These papers evaluate the insecticidal efficacy of flubendiamide against bollworms on cotton (Narayana 2006; Dhawan 2006; Tomar 2005). These papers will not be used in this risk assessment because they did not provide information about toxicity to non-target species.

4 RISK CHARACTERIZATION

Risk characterization is the integration of exposure and effects characterization to determine the ecological risk from the use of flubendiamide and the likelihood of effects on aquatic life, wildlife, and plants based on different pesticide-use scenarios. The risk characterization provides an estimation and description of the risk; articulates risk assessment assumptions, limitations, and uncertainties; synthesizes an overall conclusion; and provides the risk managers with information to make regulatory decisions.

4.1 Risk Estimation: Integration of Exposure and Effects Data

Results of the exposure and toxicity effects data are used to evaluate the likelihood of adverse ecological effects on non-target species. For the assessment of flubendiamide risks, the risk quotient (RQ) method is used to compare exposure and measured toxicity values:

$$RQ = EEC / \text{(Acute or Chronic Toxicity Values)}$$

where: *EEC* is the estimated environmental concentration generated by the exposure scenarios. The RQs are compared to the Agency's levels of concern (LOCs). These LOCs are the Agency's interpretive policy and are used to analyze potential risk to non-target organisms and the need to consider regulatory action. These criteria are used to indicate when a pesticide's use as directed on the label has the potential to cause adverse effects on non-target organisms. **Appendix G** of this document summarizes the LOCs used in this risk assessment.

4.1.1 Non-target Aquatic Animals, Invertebrates, and Plants

Surface water concentrations resulting from flubendiamide application were predicted for flubendiamide parent alone (1 – 24.07 μg a.i./L), des-iodo degradate (up to the limit of solubility for des-iodo, 450 μg/L) and formulation exposure which is only based on the spray drift fraction and does not include runoff or erosion contributions (0.017 – 0.437 μg a.i./L). Application scenarios were selected to represent the entire range of soil and environmental conditions of the proposed actions.

Peak EECs were compared to acute toxicity endpoints to derive acute risk quotients. The 21-day EECs were compared to chronic toxicity endpoints (NOAEC values) to derive chronic risk quotients for invertebrates. The 60-day EECs were compared to chronic toxicity endpoints (NOAEC values) to derive chronic risk quotients for fish.

4.1.1.1 Fish

For acute risk to freshwater and marine fish, there was no toxicity observed at the highest concentration of the technical grade flubendiamide tested, which was at the limit of solubility. Therefore, acute risk quotients were not calculated.

For chronic risk to freshwater fish, there was no toxicity observed at the highest concentration of the technical grade flubendiamide tested, which was at the limit of solubility, in the early life cycle fathead minnow test. Therefore, chronic risk quotients were not calculated.

In addition, for acute risk to freshwater fish exposed to the 480 SC formulation, there was no toxicity observed to rainbow trout and bluegill sunfish at the highest concentration tested, which was at the limit of solubility. Therefore, acute risk quotients were not calculated.

4.1.1.2 Freshwater Invertebrates

For acute risk to freshwater invertebrates, there was no toxicity observed at the highest concentration of the technical grade flubendiamide tested, which was at the limit of solubility. Therefore, acute risk quotients were not calculated.

The degradate, des-iodo, is not acutely toxic at the limit of its solubility to freshwater invertebrates (daphnid). Therefore, acute risk quotients were not calculated.

For chronic risk to freshwater invertebrates, there was an increase in the number of eggs aborted and the number of dead neonates observed at the highest concentration of the technical grade flubendiamide tested (68.5 µg a.i./L), which is above the limit of solubility, in the daphnid life cycle test. At the NOAEC (41.1 µg a.i./L), RQs do not exceed the chronic LOCs when compared to 21-day parent only EECs. Even when compared to long term concentrations, in which flubendiamide reaches its limit of solubility (29.9 µg/L), the RQ (0.73) is less than the chronic LOC (1.0).

The 480 SC formulation was very highly toxic to freshwater invertebrates (daphnids) on an acute basis. Using the EC_{50} (2.6 µg a.i./L), acute RQs exceed the Acute Endangered LOC (0.05) and the Acute Restricted Use LOC (0.1) when compared to the formulation EECs for one aerial application to corn and cotton (RQ = 0.10). LOCs are not exceeded based on ground application (**Table 23**).

Table 23. Risk Quotients for Daphnid based on formulation EECs following one application and formulation toxicity values

Crops	Formulation EEC (µg/L)		480 SC RQ EC_{50} = 2.6 µg/L	480 SC RQ NOAEC= 0.38 µg/L	24 WG RQ EC_{50} = 1.5 µg/L
Corn, Cotton	Aerial	0.263	**0.10****	0.69	NA
	Ground	0.053	0.02	0.14	NA
Tobacco	Ground	0.053	0.02	0.14	NA
Pome Fruits	Ground	0.087	0.03	0.23	NA
Stone Fruits, Grapes	Ground	0.070	0.03	0.18	NA
Fruiting, Leafy, and Cucurbit Vegetables	Aerial	0.126	NA	NA	**0.084***
	Ground	0.025	NA	NA	0.017
Brassica Leafy Vegetables	Aerial	0.084	NA	NA	**0.056***
	Ground	0.017	NA	NA	0.01

NA – Not applied to these crops
* Exceeds Acute Endangered Risk LOC (≥0.05)

** Exceeds Acute Endangered Risk LOC and Acute Restricted Use LOC (≥0.10)
+ Exceeds Chronic Risk LOC (≥1.0)

24 WG formulation was also very highly toxic to freshwater invertebrates (daphnids) on an acute basis. Using the EC_{50} (1.5 µg a.i./L), acute RQs exceed the Acute Endangered LOC when compared to the formulation EECs for one aerial application to all proposed vegetables (RQs = 0.056 – 0.084, **Table 23**).

4.1.1.3 Estuarine/Marine Invertebrates

For acute risk to marine crustaceans (mysid) and marine mollusks (oyster), there was no toxicity observed at the highest concentration of the technical grade flubendiamide tested, which was at the limit of solubility. Therefore, acute risk quotients were not calculated.

For chronic risk to marine crustaceans (mysid), there was no toxicity observed at the highest concentration of the technical grade flubendiamide tested, which was at the limit of solubility, in the mysid life cycle test. Therefore, chronic risk quotients were not calculated.

Due to risk for freshwater invertebrates exposed to the formulations, there is uncertainty regarding risk to marine invertebrates. This potential for risk cannot be excluded at this time.

4.1.1.4 Freshwater Benthic Invertebrates

Several freshwater benthic invertebrate studies produce multiple lines of evidence that flubendiamide and its des-iodo degradate will adversely affect benthic invertebrate populations. This evidence is presented in this section and the mesocosm study section (Section 4.1.1.5).

A 28-day chronic toxicity study with flubendiamide technical was submitted investigating the emergence and development rate of the midge, *Chironomus riparius*, in an overlying-water spiked system with nominal concentrations of 10 – 640 µg a.i./L (MRID 468170-22). The NOAEC and LOAEC based on emergence was 40 µg a.i./L (nominal) and 80 µg a.i./L (nominal, 69 µg a.i./L 1-hr initial water column measurement). Measured concentrations were only taken in the 10, 80, and 160 µg a.i./L treatment groups. Therefore, the pore water concentration at the NOAEC is unknown. The time-weighted average pore water concentration at the LOAEC is 3 µg a.i./L. Using the LOAEC as a NOAEC **(Table 24)**,

Table 24. Risk quotients for flubendiamide in benthic pore water based on aerial and ground applications to Mississippi Corn and California Tomato scenarios

Spray Application	21-day EEC in benthic Pore Water (µg/L)	MRID 468170-22 LOAEC = 3 µg a.i./L
Mississippi Corn (0.094 lbs ai/acre × 3 applications with 3-day interval)		
Aerial	21.33	**7.1**
Ground	20.64	**6.9**

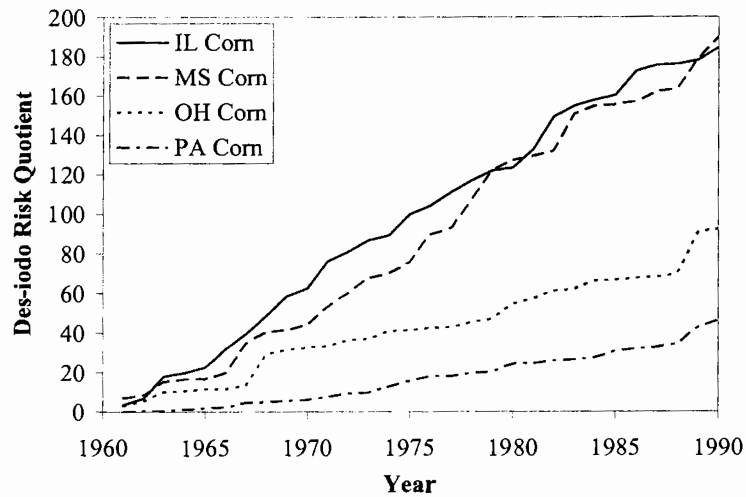
Table 24. Risk quotients for flubendiamide in benthic pore water based on aerial and ground applications to Mississippi Corn and California Tomato scenarios		
Spray Application	**21-day EEC in benthic Pore Water (µg/L)**	**MRID 468170-22 LOAEC = 3 µg a.i./L**
California Tomato (0.045 lbs ai/acre × 5 applications with 3-day interval)		
Aerial	1.81	0.60
Ground	0.94	0.31

In a 28-day chronic toxicity midge, *Chironomus riparius,* study with des-iodo degradate (MRID 468170-23), the percent emergence was adversely affected at 8.0, 16 and 32.0 µg metabolite/L, based on nominal overlying water concentrations. The NOAEC value was 1.9 µg metabolite/L (time-weighted measured overlying water) and 0.28 µg metabolite/L (time-weighted measured pore water) based on reductions in percent emergence (**Table 25**).

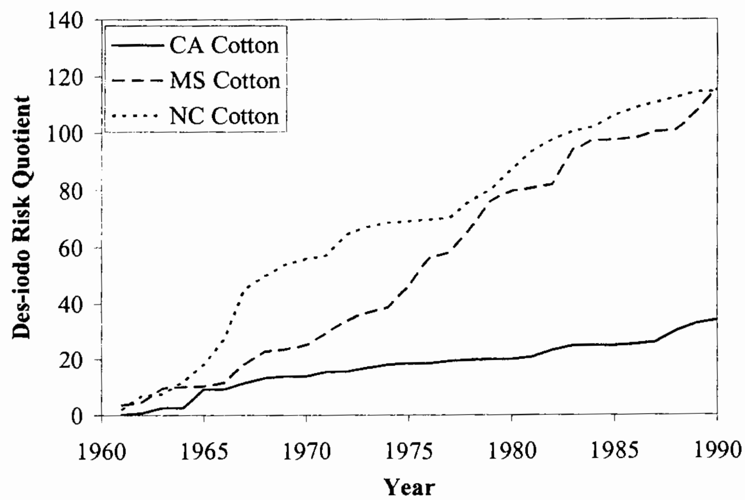
Table 25. Risk quotients for the des-iodo degradate based on benthic water column and pore water endpoint concentrations for aerial and ground applications to Mississippi Corn and California Tomato scenarios				
	Water Column Concentrations		**Pore Water Concentrations**	
Spray Application	**21-day EEC in Water Column (µg/L)**	**MRID 468170-23 NOAEC = 1.9 µg/L**	**21-day EEC in Benthic Pore Water (µg/L)**	**MRID 468170-23 NOAEC = 0.28 µg/L**
Mississippi Corn (0.094 lbs ai/acre × 3 applications with 3-day interval)				
Aerial	23.27	**12.2**	21.33	**76.2**
Ground	22.39	**11.8**	20.64	**73.7**
California Tomato (0.045 lbs ai/acre × 5 applications with 3-day interval)				
Aerial	2.13	**1.1**	1.81	**6.5**
Ground	1.04	0.54	0.94	**3.4**

Figure 5 depicts the change in risk to bethic invertebrates over time as the des-iodo degradate accumulates in the pore water of the standard EXAMS pond based on a NOAEC of 0.28 µg/L and the EECs depicted in **Appendix Figure B1**. A table of risk quotient values for 1, 10, 20, and 30 years is presented in **Appendix Table B4**.

Corn (0.094 lbs ai/acre x 4 applications with 3 days interval)



Cotton (0.094 lbs ai/acre x 3 applications with 5 days interval)



Tobacco (0.094 lbs ai/acre x 4 applications with 5 days interval)

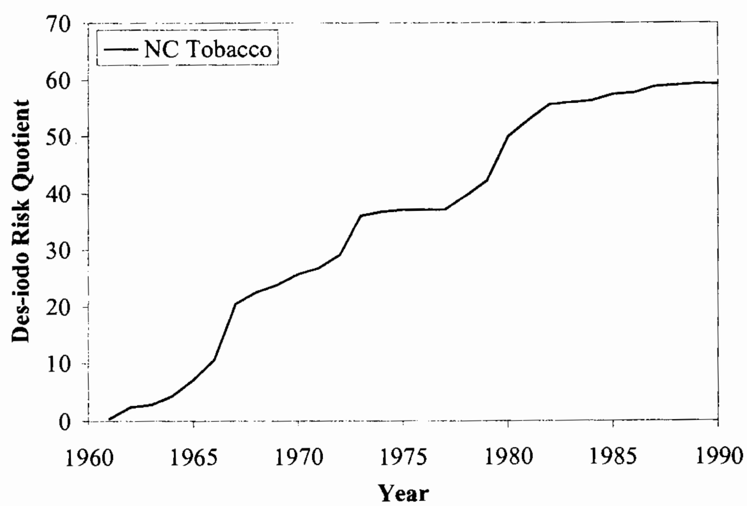


Figure 5. Variation of risk quotients over time as the des-iodo degradate accumulates in the standard EXAMS pond.

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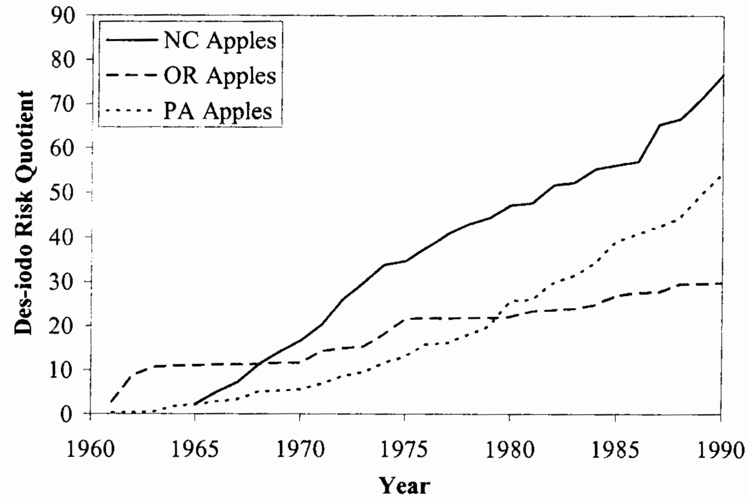
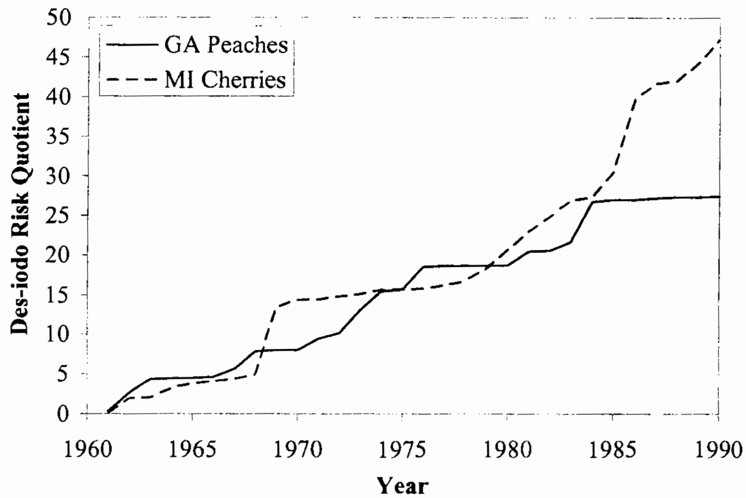
Pome Fruits (0.156 lbs ai/acre x 3 applications with 7 days interval)



Stone Fruits (0.125 lbs ai/acre x 3 applications with 7 days interval)



Tree Nuts (0.125 lbs ai/acre x 3 applications with 7 days interval)

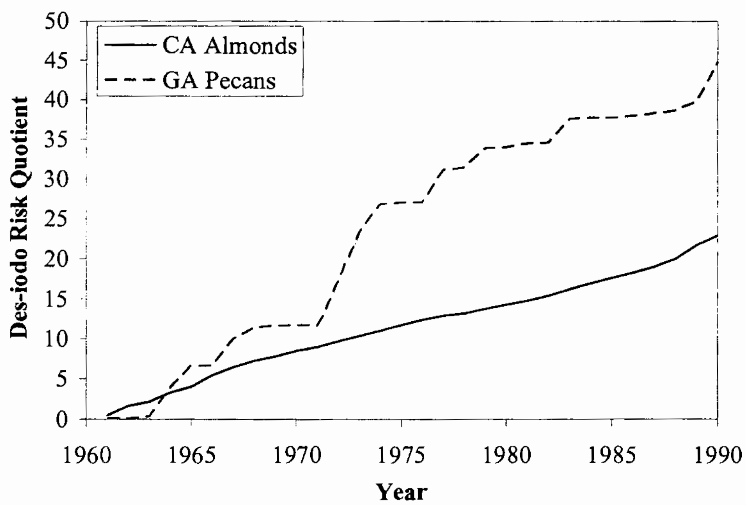
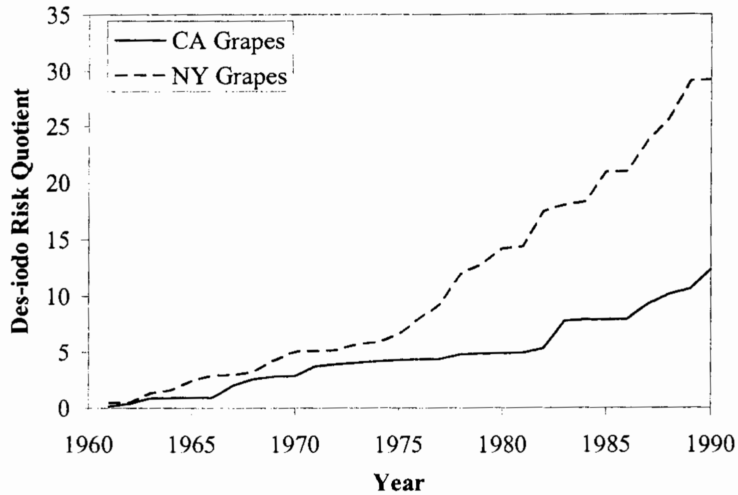
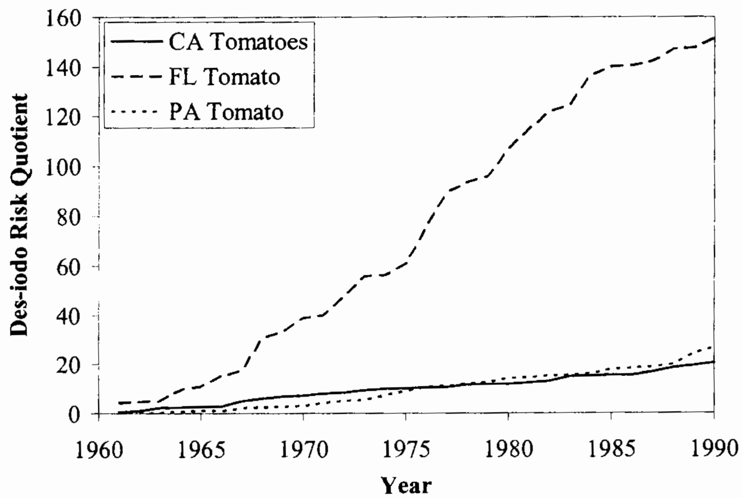


Figure 5. Continued.

Grapes (0.125 lbs ai/acre x 3 applications with 5 days interval)



Fruiting Vegetables (0.045 lbs ai/acre x 5 applications with 3 days interval)



Other Vegetables i
Leafy Vegetables (0.045 lbs ai/acre x 5 applications with 3 days interval – CA Lettuce)
Brassica Leafy Vegetables (0.03 lbs ai/acre x 3 applications with 3 days interval – FL Cabbage)
Cucurbit Vegetable (0.045 lbs ai/acre x 5 applications with 7 days interval – FL Cucumber)

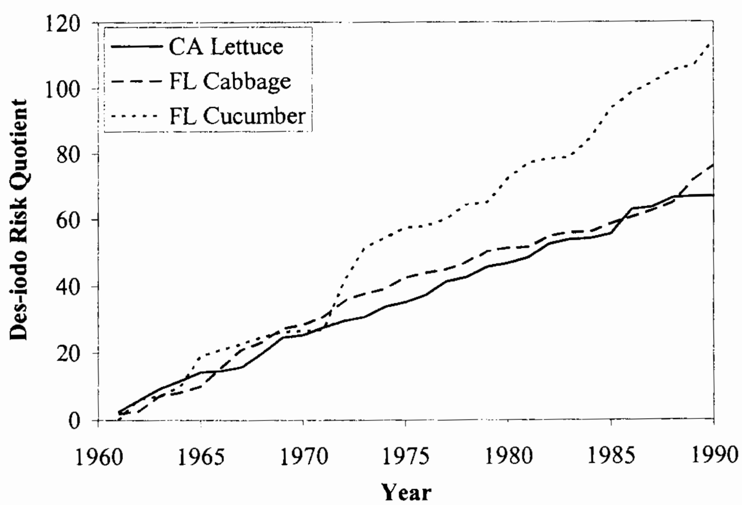


Figure 5. Continued.

Mortality was observed in acute testing with the 24 WG formulation (LC_{50} = 130 µg a.i./L) and the 480 SC formulation (LC_{50} = 1650 µg a.i./L). Acute LOCs are not exceeded when the toxicity values are compared to formulation EECs.

4.1.1.5 Mesocosm Study

The study designated as MRID 46817002 is a mesocosm study involving application of flubendiamide product 480 SC to the aqueous compartment. Initial evaluation of effects endpoints expressed the values in terms of nominal additions of the active ingredient per liter of overlying water. Reliance on overlying water concentration units for effects endpoints might be appropriate for organisms residing in the aqueous layer; it is not the optimal expression of effects endpoints for benthic and sediment-dwelling organisms.

Consideration of cladoceran effects data in comparison with the mesocosm results

The EFED risk assessment identifies an acute effects endpoint (EC_{50}) for the cladoceran, *Daphnia magna,* of 2.6 µg/L active ingredient when introduced to the test system as 480 SC formulation. The no observed adverse effect concentration (NOAEC) for this same study is 0.45 µg/L. The risk assessment also reports a chronic reproduction NOAEC of 0.38 and a lowest adverse effect concentration (LOAEC) of 1.18 µg a.i./L for the same formulation in the same cladoceran species. These endpoints can be compared to cladoceran endpoints from the mesocosm study, expressed as overlying water concentrations to determine if the two suggest similar effects levels.

Figure 27 from the mesocosm study presents the results of the cladoceran *D. longispina* at 0 through 112 days following administration of SC 480 to the overlying water. At the highest introduction rate, 12 µg a.i./L, the product produced marked decreases in the number of individuals through 35 days post treatment with indications of an upward recovery in the species occurring at 28 days post treatment. The following presents the corresponding measured water concentrations for this time period, from **Table 26** of the study.

Table 26. Estimates of bioavailable water column flubendiamide concentrations in the first 35 days of the mesocosm study

Day	Water Concentration µg a.i./L	Bioavailable Water Concentration µg a.i./L*
0	3.52	2.8
2	10.4	8.3
4	9.88	7.9
7	9.1	7.3
14	9.1	7.3
21	8.0	6.4
28	7.4	5.9
35**	6.2	5.0

* Assumes 80% dissolved fraction as per page 204 of the study

** Recovery potentially observed for *D. longispina*

From the above table it appears that daphnia show recovery as the concentration of the active ingredient falls below 6 µg a.i./L. This concentration falls between the NOAEC and the EC_{50} for single species water only testing of the other cladoceran *D. magna*. It is also remarkably close to the chronic LOAEC for *D. magna*. Taken as a whole, all these lines of evidence support effects endpoints somewhere in the vicinity of 0.4 to 6 µg a.i./L for some species of water column dwelling invertebrates both over the short term of a few days to multiple weeks of exposure (**Table 27**).

Table 27. Risk quotients for flubendiamide in the water column (MRID 46817002) based on aerial and ground applications to Mississippi Corn and California Tomato scenarios

Spray Application	21-day EEC in Water Column (µg/L)	Low Estimate of NOAEC = 0.4 µg a.i./L	High Estimate of NOAEC = 6 µg a.i./L
Mississippi Corn (0.094 lbs ai/acre × 3 applications with 3-day interval)			
Aerial	23.27	**58.2**	**3.9**
Ground	22.39	**56.0**	**3.7**
California Tomato (0.045 lbs ai/acre × 5 applications with 3-day interval)			
Aerial	2.13	**5.3**	0.36
Ground	1.04	**2.6**	0.17

Consideration of benthic fauna effects data in comparison with the mesocosm results

The EFED risk assessment reports a 28-day sediment toxicity test NOAEC of 40 µg a.i./L and a LOAEC of 80 mg a.i./L nominal in overlying water (MRID 46817022). However, the study does report measured time weighted average concentrations in pore water corresponding to some of these dose groups. For example the pore water concentration corresponding to the LOAEC is 2 µg a.i./L. while the pore water was not measured at the NOAEC, the relationship between overlying water nominal and pore water measured at the LOAEC, when applied to the NOAEC would yield an estimated pore water concentration of 1 µg/L. These pore water concentrations can be compared to benthic invertebrate results from the mesocosm study.

The mesocosm study does not present sediment concentrations in pore water units. However, the study does present total dry weight sediment concentrations and the data from the study suggest that there were no effects on chironomid numbers or general benthic invertebrate abundance at even the highest dose group of 12 µg a.i./L in overlying water. Measured sediment concentrations at this dose group ranged from 21 to 57 µg a.i./kg dry weight. Converting this range of sediment concentrations to a conservative estimate of a corresponding pore water concentration can be made using the following formula:

$$\text{Concentration in pore water} = \text{Concentration in bulk sediment}/(K_{oc} \times F_{oc})$$

where: Dry weight sediment is a conservative substitute for bulk sediment concentration
K_{oc} is 1954 for the active ingredient
F_{oc} is 0.039 as reported in the mesocosm study

This yields a range in estimated pore water concentrations of 0.27 to 0.74 µg a.i./L. It should be noted that these are likely overestimates of pore water concentrations as the water fraction of sediment is removed in the dry sediment measurements, thereby inflating the bulk sediment concentrations.

It can be seen from a comparison of estimated mesocosm pore water to chironomid chronic sediment NOAEC and LOAEC values, that the mesocosm study does not achieve sufficient pore water concentrations (0.27 to 0.74 µg a.i./L) to approach concentrations in single species sediment testing that elicit adverse effects (LOAEC = 2 µg a.i./L). Therefore there is insufficient information in the mesocosm study to refute the accuracy of effects concentrations achieved with a single species sediment toxicity study. In essence, the mesocosm study only confirms that pore water concentrations of 1 µg/a.i./l or lower are not likely to cause adverse effects on benthic invertebrates. **Table 28** provides RQs based on this estimation of the NOAEC (1 µg a.i./L).

Table 28. Risk quotients for flubendiamide in benthic pore water based on aerial and ground applications to Mississippi Corn and California Tomato scenarios

Spray Application	21-day EEC in benthic Pore Water (µg/L)	(Extrapolated from Multiple Studies) NOAEC = 1 µg a.i./L
Mississippi Corn (0.094 lbs ai/acre × 3 applications with 3-day interval)		
Aerial	21.33	**21.3**
Ground	20.64	**20.6**
California Tomato (0.045 lbs ai/acre × 5 applications with 3-day interval)		
Aerial	1.81	**1.8**
Ground	0.94	0.94

Although the available data for single species daphnid testing suggests the des-iodo degradate is more toxic than the parent, the toxicity of both compounds appears to be equivalent when expressed on a pore water basis.

4.1.1.6 Aquatic Plants

For risk to aquatic plants, there was no toxicity observed at the highest concentration of the technical grade flubendiamide tested, which was at the limit of solubility, in the non-vascular (*Selenastrum capricornutum*) and vascular (*Lemna gibba*) aquatic plant tests. Therefore, RQs were not calculated.

In addition, there was no toxicity observed at the highest concentration of the 480 SC formulation tested, in the non-vascular (*Pseudokirchneriella subcapitata*) aquatic plant tests. Therefore, risk quotients were not calculated.

4.1.2 Non-target Terrestrial Animals and Plants

4.1.2.1 Avian Risk

Since the LD_{50} and LC_{50} for birds were both non-definitive values of >2000 mg/kg bw and >4535 mg/kg diet, respectively, and no treatment related mortality was observed, risk quotients were not calculated. In addition, the LD_{50} >2000 for bobwhite quail exposed to the 480 SC formulation was non-definitive because no treatment related mortality was observed.

For chronic risks to the mallard duck, reproductive effects were observed at the 289 and 960 mg a.i./kg diet treatment levels, therefore the NOAEC = 98 mg a.i./kg diet. For bobwhite quail, no treatment related effects were observed and the NOAEC is 1059 mg a.i./kg diet. Using the mallard duck study results, the RQ is equal to the chronic LOCs (RQ = 1) for pome fruits for birds consuming short grass; however the chronic LOCs are not exceeded for the other proposed crops.

4.1.2.2 Mammalian Risk

Since the LD_{50} for mammals was non-definitive values of >2000 mg/kg bw and no treatment related mortality was observed, risk quotients were not calculated.

In a two-generation rat reproduction study, frank developmental and reproductive effects were not observed (MRID 46817216). The NOAEC for parental toxicity is 50 ppm based on effects on the liver, thyroid, and kidneys. For offspring effects, there were no effects of treatment on the number of implantations, number of pups delivered, sex ratio, or on the live birth, viability, or lactation indices. Sexual maturation was only slightly delayed in the males. The NOAEC for offspring toxicity is 50 ppm based on effects on the liver and thyroid. There was no evidence of any treatment-related effects or signs of reproductive impairment in males or females. Due to an apparent delay in balanopreputial separation in the first generation at 50 ppm and above, the two-generation study was supplemented by a one-generation study (MRID 468172-39). The one-generation reproduction supplemental study showed no effect on balanopreputial separation up through and including 200 ppm in males and females. An increase in the mean age of vaginal opening 20,000 ppm in males and females F1 offspring was also noted in the supplemental one-generation study, but was not reproduced in the two-generation study. The NOAEC for reproductive toxicity is 20,000 ppm in that no reproductive toxicity was observed. Risk Quotients were not calculated because of the lack of frank reproductive effects.

4.1.2.3 Terrestrial Invertebrates

Toxicity to Earthworms

The registrant submitted 14-day acute earthworm toxicity studies for flubendiamide technical, formulation 480 SC, and the degradate des-iodo. All three studies, resulted in LC_{50} >1000 mg a.i./kg-dw soil. There was no treatment effects on mortality or body weight observed. Two 28-day chronic earthworm studies were submitted using the flubendiamide formulation 480 SC and 24 WG. Both chronic tests resulted in LC_{50} >1000 mg a.i./kg-dw soil. In the 480 SC tested there we no treatment effects on mortality or body weight observed. In the 24 WG test, there was a significant reduction in the number of juveniles produced, resulting in a NOAEC of 562 mg a.i./kg-dw soil.

To evaluate the risk to earthworms, RQs were calculated using the bulk densities of the soils of the PRZM/EXAMS scenarios used in this assessment and the formula:

$$RQ = \frac{\left[\dfrac{application\,rate(mg\,/\,cm^2)}{soil\,incorporation\,depth(cm) \times bulk\,density(kg\,/\,cm^3)}\right]}{LC_{50}(mg\,ai\,/\,kg\,soil)}$$

The range of bulk densities in the PRZM EXAMS scenario soils was 0.37 to 1.8 g/cm^3 in the top 10 cm of soil, and a soil incorporation depth of 1 cm was assumed since this is not a soil incorporated product. Using the single maximum application rate of 0.156 lbs a.i./acre and a conservative LC_{50} of 1000 mg/kg soil, all calculated RQs were <0.01. Using the single maximum application rate of 0.156 lbs ai/acre and NOAEC of 562 mg/kg soil, all calculated RQs were <0.01. Based on these RQs, minimal risk to earthworms is assumed after a single application of flubendiamide at the proposed label rate. This screening assessment does not consider risks to earthworms from multiple applications of flubendiamide. Because flubendiamide is persistent and accumulates in the soil, there is uncertainty regarding risk to earthworms following multiple applications.

A 28-day toxicity study was conducted with the soil arthropod Collembola species *Folsomia candida* (white springtail) to determine the effect of 480 SC on reproduction (MRID 468170-27). There was a significant reduction of the number juveniles produced resulting in NOAEC and LOAEC values of 31.6 and 100 mg a.s./kg (dw). Using the same procedure described above at a single maximum application rate of 0.156 lbs a.i./acre and NOAEC of 31.6 mg/kg soil, the calculated RQ is 0.03. Minimal risk to soil arthropods is assumed after a single application of flubendiamide at the proposed label rate.

Toxicity to Bees - Beneficial Pollinators

EFED currently does not quantify risks to terrestrial non-target insects. Risk quotients are therefore not calculated for these organisms. Flubendiamide technical and 480 SC formulation were classified as practically non-toxic based on the acute contact honey bee study ($LD_{50} > 200$ µg/bee); therefore, there is no potential for flubendiamide to have acute contact adverse effects on bees and other beneficial pollinators.

The effects of the 480 SC formulation on the honey bee were also evaluated under semi-field conditions by exposing honey bees to plots of the wildflower, lacy phacelia (*Phacelia tanacetifolia*), treated at application rates of 0.08 and 0.16 lb ai/A. No adverse effects were observed in mortality, flight intensity, or behavior during the test. Brood development was slightly reduced following initiation in the 0.16 lb a.i./A, but recovery was observed. The effects of the 24 WG formulation on the bumblebee (*Bombus terrestris*) was exposed for 27 days to plots of tomatoes (*Lycopersicon esculentum*) treated with the 24 WG formulation at 0.160 lb ai/A in a greenhouse. The test material did not yield any deleterious impacts on pollination activity, flight frequency, or hive condition. The single maximum application rates of the proposed crops range from 0.03 – 0.156 lb a.i./A. Significant side effects to bumble bees and honey bees are not expected following application of both formulations to the proposed crops.

Toxicity to Natural Lepidoptera Predators

Flubendiamide is an insecticide to treat against Lepidoptera agricultural pests. It was also tested against several natural predators of Lepidopterous insects including the parasitoid wasp (*Aphidius rhopalosiphi*), predatory mite (*Typhlodromas pyri*), ladybird beetle (*Coccinella septempunctata*) and green lacewing (*Chrysoperla carnea*). This chemical was designed to be effective against several Lepidoptera pests, but safe for beneficial natural predators of Lepidoptera so it could be used in integrated pest management (IPM) programs (Tohnishi *et al* 2005).

Extended laboratory studies were conducted by exposing the parasitoid wasp (*Aphidius rhopalosiphi*) and predatory mite (*Typhlodromas pyri*) to the 24 WG and the 480 SC formulations. The WG formulation resulted in significant reductions in survival and reproduction for the wasp yielding NOAEC = 0.17 and LD_{50} >0.55 lb a.i./A. The results of the predatory mite study exposed to the 24 WG formulation were significant reductions in survival (14%) and reproduction (24%) were observed yielding NOAEC and LOAEC values of 0.31 and 0.55 lb a.i./A, respectively. The LD_{50} > 0.55 lb a.i./A. However, because the single maximum application rates to the proposed vegetables for the 24 WG formulation, which range from 0.03 – 0.045 lb a.i./A, are below the NOAEC; significant adverse effects to parasitoid wasps and predatory mite are not expected for WG formulation.

The SC formulation resulted in significant reductions in survival in the parasitoid wasp in two tests (different range of concentrations tested), and the resulting NOAEC values were <0.2 and 0.39 lb a.i./A. The LD_{50} were 0.423 and 0.60 lb a.i./A. In the first test, significant morality was observed at all test concentrations resulting in NOAEC <0.2 lb a.i./A. However this effect was not observed in the second test at the same concentration, so there is uncertainty concerning mortality at this concentration. Because the single maximum application rates to the proposed vegetables for the SC formulation, which range from 0.094 – 0.156 lb a.i./A, are generally below the LD_{50} (and the NOAEC for test #2); significant adverse effects to parasitoid wasps are not expected for the SC formulation.

Three extended laboratory experiments were conducted exposing the ladybird beetle (*Coccinella septempunctata*) to the 480 SC formulation. When the ladybird beetle larvae were placed on apple leaves (*Malus domestica*) treated with the test material, larval survival was affected yielding LD_{50}, NOAEC, and LOAEC values of 0.41, 0.24, and 0.60 lb a.i./A, respectively. Because the single maximum application rates to the proposed vegetables for the SC formulation, which range from 0.094 – 0.156 lb a.i./A, are generally below the NOAEC; significant adverse effects to ladybird beetles due to contact with residues are not expected for the SC formulation. When the beetles were exposed to freshly-dried and 14-day old residues on vine (*Vicia faba*) plants and fed treated aphids, survival and reproduction remained unaffected during both assays, yielding LD_{50}, NOAEC, and LOAEC values of >0.17, 0.17, and >0.17 lb a.i./A, respectively. However, there is a potential for adverse effects to adult ladybird beetles due to ingestion of food items (aphids and pollen) containing flubendiamide residues.

When the ladybird beetles were exposed to treated apple leaves and fed treated aphids (*Acyrthosiphon pisum*) and pollen, adult survival was affected yielding LD_{50}, NOAEC, and LOAEC values of 0.089, 0.04, and 0.079 lb a.i./A, respectively. There were no effects to larval survival or reproduction.

An extended toxicity study was conducted with the green lacewing *Chrysoperla carnea* to determine the effect of 480 SC on larval mortality and reproduction. There was no significant dose-response relationship for larval mortality (LD_{50}> 0.16 lb a.i./A). There was no significant effect on reproduction (hatching rate and fertile eggs/female/day). Because the single maximum application rates to the proposed vegetables for the SC formulation, which range from 0.094 – 0.156 lb a.i./A, are generally below the LD_{50}; significant adverse effects to green lacewings due to contact with residues are not expected for SC formulation.

4.1.3 Terrestrial and Semi-aquatic Plant Risk

Terrestrial and semi-aquatic plants may be exposed to pesticides from runoff, spray drift or volatilization. Semi-aquatic plants are those that inhabit low-lying wet areas that may be dry at certain times of the year. EECs for terrestrial and semi-aquatic plants are derived for areas adjacent to the treatment site. Acute RQs for terrestrial plants are derived by dividing the EEC by the EC_{25} from Tier II seedling emergence and vegetative vigor toxicity tests. Acute RQs for listed plant species are calculated by dividing the EEC by the NOAEC (if not available, an EC_{05} is used) value from Tier II toxicity tests as follows below:

Terrestrial Plants Inhabiting Areas Adjacent to Treatment Site:

Emergence RQ = Total Loading to Adjacent Area or EEC/Seedling Emergence EC25 or NOAEC

Drift RQ = Drift EEC/EC25 or NOAEC (most sensitive of veg vigor or seedling emerge)

Terrestrial Plants Inhabiting Semi-aquatic Areas Near Treatment Site:

Emergence RQ = Total Loading to Semi-aquatic Area or EEC/Seedling Emergence EC25 or NOAEC

Drift RQ = Drift EEC/EC25 or NOAEC (most sensitive of veg vigor or seedling emerge)

Terrestrial plant EECs and toxicity endpoints are provided in **Table 15**. EECs and RQs are calculated using TERRPLANT 1.2.2 (**Appendix D**) and summarized in **Table 29**. For a single application on pome fruits at the maximum rate, the LOC was not exceeded for all listed and non-listed non-target terrestrial plants for pome fruits. Thus, it can be assumed that for the remainder of the proposed crops, there will be no LOC exceedances.

Table 29. Risk quotient (RQ) values for plants in dry and semi-aquatic areas exposed to flubendiamide through runoff and/or spray drift*

Plant Type		Listed Status	Dry	Semi-Aquatic	Spray Drift
Maximum single application rate of 0.156 lbs ai/acre (pome fruits), aerial application					
	Monocot	non-listed	<<0.1	0.15	<<0.1
	Monocot	listed	<<0.1	0.15	<<0.1
	Dicot	non-listed	<<0.1	0.15	<<0.1
	Dicot	listed	<<0.1	0.15	<<0.1

*If RQ > 1.0, the LOC is exceeded, resulting in potential for risk to that plant group.

4.2 Risk Description

A screening-level (Level I) risk assessment, based on proposed uses of flubendiamide, suggests that levels of flubendiamide, and its des-iodo degradate in the environment, when compared with minimum toxicity values, may result in direct acute and chronic effects to freshwater invertebrates exposed to the TGAI, formulations and des-iodo degradate. In addition, there is no potential risk to earthworms, beneficial insects including bees and natural Lepidoptera predators, and terrestrial plants. However, there is a potential direct risk to non-target Lepidoptera species, including endangered species. Lepidoptera may occur in areas adjacent to treated fields (where they may be exposed to spray drift) and will likely move through treated fields. Additionally, the larvae of some lepidopteran species are aquatic (Merrit and Cummins, 1984) and, therefore, may be exposed to both the TGAI, formulations, and des-iodo degradate. Based on the potential for direct effects to these taxa, there may be potential indirect effects to species of concern that depend on these taxa as a source of food or pollination.

4.2.1 Risks to Aquatic Organisms

There is no potential for acute and chronic risk to freshwater and marine fish, marine crustaceans, marine mollusks, and aquatic plants exposed to technical grade flubendiamide at its limit of solubility. In addition, there is no acute risk to freshwater fish exposed to the 480 SC formulation.

There is no potential for acute and chronic risk to freshwater invertebrates (daphnid) exposed to technical grade flubendiamide at its limit of solubility. In addition, there is no acute risk to freshwater invertebrates exposed to the degradate, des-iodo, at its limit of solubility.

There is potential for acute risk to freshwater invertebrates (daphnid) exposed to the formulations 480 SC and 24 WG. The Acute Endangered (0.05) and the Acute Restricted Use LOCs (0.1) are exceeded based on the 480 SC formulation EECs for one aerial application to corn and cotton (RQ = 0.10). The Acute Endangered (0.05) is exceeded based on the 24 WG formulation EECs for one aerial application to the proposed vegetables (RQs = 0.056– 0.084).

Due to risk for freshwater invertebrates exposed to the formulations, there is uncertainty regarding risk to marine invertebrates. This potential for risk marine invertebrates exposed to the formation cannot be excluded at this time.

Flubendiamide and the des-iodo degradate should probably be considered roughly equally toxic to freshwater benthic invertebrates with a NOAEC of approximately 1 µg/L for flubendiamide and 0.28 µg/L for the des-iodo degradate. Using this NOAEC, RQs for flubendiamide would range from 0.94 to 21.3, while RQs for the des-iodo degradate would be 450 for all scenarios provided flubendiamide were used for sufficient time for the degradate concentration to build up to its limit of solubility (450 µg/L). Considering only the accumulation within the first 30 years of use for all of the scenarios, RQs for the degradate would range from 0.03 to 6.9 in the 1st year, 2.9 to 64 by the 10th year, 4.9 to 127 in the 20th year , and 12 to 190 in the 30th year (**Appendix Table B4**).

In the mesocosm study with 480 SC formulation, based on the observed effects on *Daphnia longispina* as the most sensitive species, the NOAEC for this zooplankter was 1.0 µg/L.

Does the mesocosm study change aquatic risk conclusions?

This EFED risk assessment suggests that formulations of flubendiamide are more toxic than the active ingredient. These conclusions are based in part on results from single species daphnid testing. This conclusion is supported by the results of the formulation-based mesocosm study results for daphnid species which show effects concentrations on par with single species testing endpoints for the same formulation.

The EFED risk assessment did not identify serious concerns for water column invertebrates from the introduction of the formulations directly to water via spray drift. Concentrations estimated in water from this exposure route ranged from 0.017 µg/L to 0.437 µg/L. In all cases these values are well below water concentrations shown to be associated with recovery of daphnids in the mesocosm study (5 to 6 µg/L). Therefore the mesocosm results tend to support the EFED risk conclusions for water column invertebrates exposed to drift of formulated products.

The registrant-submitted studies, on the basis of comparisons of estimated water concentrations of the active ingredient with overlying water nominal toxicity endpoints from single species sediment testing, do not indicate a concern for benthic invertebrates. However, the more technically appropriate comparison of bioavailable active ingredient exposure is a comparison based on a pore water concentration basis. The risk assessment provides a range of these estimated pore water concentrations of 0.94 to 21.35 µg a.i./L (**Table 13**). These values would be very near to, or above, pore water effects thresholds for single species chironomid testing. Moreover, these values would exceed the mesocosm NOAEC for benthic invertebrates in general. The conclusion is that flubendiamide levels in sediment pore water are sufficiently high to cause adverse effects in certain benthic invertebrate species and that the available mesocosm data, owing to its low range of tested pore water concentrations, is insufficient to refute this risk conclusion.

What are the implications for aquatic resources?

For this risk assessment, EFED has relied on acute and chronic endpoints based on chironomid toxicity data as the primary basis for conducting the freshwater invertebrate risk assessment. It is not surprising that aquatic insect larvae, such a chironomids, are sensitive to flubendiamide and its toxic degradates. After all, flubendiamide is an insecticide. However, it is notable that, compared to the other freshwater invertebrates tested, insect larvae may possibly be more sensitive than other tested freshwater invertebrate species The ecological implications of effects on chironomids specifically and for preduictions to aquatic invertebrates in general warrants discussion.

What is the significance of the order of Chironomidae in aquatic systems? Coffman and Ferrington (1996) provide some insight in their characterization of the family. They maintain that the Chironomidae family is an ecologically important group of aquatic insects that often is found in high densities. Densities of up to 50,000 larvae per square meter of benthic substrate have been reported. Aquatic systems exhibit a high diversity of chironomids as well. The number of chironomid species in most systems accounts for at least 50% of the total macroinvertebrates present. Natural lakes, ponds, and streams may exhibit 50, 100, or more chironomid species. The short life cycles of these organisms, coupled with the large larval biomass in aquatic systems indicates a significance in the overall energy flow through aquatic systems. Chironomids feed on a great variety of organic substrates including coarse leaf litter, medium and fine detrital particulate, algae, vascular plants, fungi, and animals. In turn, most aquatic predators feed extensively on chironomids (larvae, pupae, or adults) at some point in their life cycles. Pennak (1978) further states that, from and economic standpoint, chironomid larvae form an important item in the food of young and adult fishes.

Even more significant is the degree to which the disparate sensitivity among freshwater aquatic invertebrates is cause for concern that other potentially high sensitivity species may exist in aquatic taxonomic groups. There exists considerable uncertainty as to the potential for even more sensitive invertebrates, in particular other families of aquatic insects. Representative aquatic insect families may be found in 11 of the 30 to 35 orders of insects (Pennak, 1978).

Would spray drift buffers provide sufficient protection to surface water resources?

One potential measure for controlling pesticide exposures is to require buffers around surface water bodies (ponds, lakes, streams, *etc.*) where pesticides cannot be applied. Because reliable methods have not been developed to predict the attenuation of pesticide transport through runoff and erosion from such buffer areas, EFED can only estimate reductions of spray drift contributions to EECs. However, an analysis of flubendiamide spray drift contribution shows that most of the contributions to aquatic environments are from means other than spray drift (runoff and erosion).

In **Appendix Table B2**, the 1-in-10-year peak, 21-day, and 60 day EECs for each scenario are presented for aerial (if appropriate for that scenario), ground (if appropriate), and no drift assumptions. Aerial applications assume 5% spray drift contribution to EECs predicted for the standard EXAMS pond, while ground and no drift applications assume 1% and 0%, respectively. The scenario with the largest potential for EEC reduction through spray drift control is the California tomato scenario. Comparing the California tomato aerial and the CA tomato no drift scenarios indicate that an approximately 60% reduction in EECs could be obtained by controlling drift (from 2.25 to 0.89 μg/L). However, for the Florida and Pennsylvania tomato scenarios the potential to reduce EECs through spray drift control is only 14 and 9 per cent, respectively, and only if spray drift were controlled completely. Therefore, it appears unlikely that buffer areas would substantially reduce risk to aquatic invertebrates from flubendiamide and its des-iodo degradate.

4.2.2 Risks to Terrestrial Organisms

4.2.2.1 Birds and Mammals

The screening assessment for flubendiamide suggests that there is no potential acute risk to birds and mammals for all of the proposed uses; however, there is a potential for chronic risk to these species. In addition, there is no acute risk to birds exposed to the 480 SC formulation.

In the mallard duck toxicity test, significant reproductive effects were observed at the treatment levels 289 and 960 mg a.i./kg diet; therefore the NOAEC is 98 mg a.i./kg diet. In the bobwhite quail toxicity test, no treatment related effects were observed and the NOAEC is 1059 mg a.i./kg diet. Using the mallard duck study results, chronic LOCs were exceeded for pome fruits (RQ = 1.0). Chronic LOCs are not exceeded for the other proposed crops. Given that the RQ is at the LOC at the maximum Kenaga value and no other crops exceeded the LOC, the potential chronic risk to birds is minimal given that the RQ assumes 100% of the diet is short grass which is unlikely in wild bird populations.

In a two-generation rat reproduction study, frank developmental and reproductive effects were not observed (MRID 46817216). The NOAEC for parental toxicity is 50 ppm based on effects on the liver, thyroid, and kidneys. The NOAEC for offspring toxicity is 50 ppm based on effects on the liver and thyroid. There was no evidence of any treatment-related effects or signs of reproductive impairment in males or females. Due to an apparent delay in balanopreputial separation in the first generation at 50 ppm and above, the two-generation study was supplemented by a one-generation study (MRID 468172-39). The one-generation reproduction supplemental study showed no effect on balanopreputial separation up through and including 200 ppm in males and females. The NOAEC for reproductive toxicity is 20,000 ppm in that no reproductive toxicity was observed. Risk Quotients were not calculated because of the lack of frank reproductive effects.

Mammals do not appear to be as sensitive as insects to the mode of action. The selectivity is, in large part, explained by the different ryanodine receptor isoforms identified in mammals compared to only one form found in insects (HED Flubendiamide Report).

4.2.2.2 Non-target insects

Acute and chronic earthworm toxicity studies showed no toxic effects for flubendiamide technical, formulation 480 SC, and the degradate des-iodo. In the formulation 24 WG chronic test, there was a significant reduction in the number of juveniles produced, resulting in a NOAEC of 562 mg a.i./kg-dw soil. However, at the single maximum application rate of 0.156 lbs ai/acre, all calculated RQs were <0.01. There is minimal risk to earthworms and Collembola soil arthropod species after a single application of flubendiamide at the proposed label rate. This screening assessment does not consider risks to earthworms from multiple applications of flubendiamide. Because flubendiamide is persistent and accumulates in the soil, there is uncertainty regarding risk to earthworms following multiple applications.

EFED currently does not quantify risks to terrestrial non-target insects. Flubendiamide technical and 480 SC formulation were classified as practically non-toxic based on the acute contact honey bee study (LD_{50} >200 μg/bee); therefore, there is no potential for flubendiamide to have acute contact adverse effects on bees and other beneficial pollinators. In addition, significant side effects to bumblebees and honey bees are not expected following application of both formulations at the proposed application rates.

Flubendiamide is an insecticide proposed to control Lepidopteran agricultural pests. There is a potential for risk to non-target Lepidopteran species, including endangered species. Flubendiamide was tested against several natural predators of Lepidopterous insects including the parasitoid wasp (*Aphidius rhopalosiphi*), predatory mite (*Typhlodromas pyri*), and ladybird beetle (*Coccinella septempunctata*).

Extended laboratory studies were conducted by exposing the parasitoid wasp (*Aphidius rhopalosiphi*), predatory mite (*Typhlodromas pyri*), and green lacewing (*Chrysoperla carnea*) to the 24 WG and the 480 SC formulations. The 24 WG and 480 SC formulations resulted in significant reductions in survival and reproduction for the wasp and predatory mite, however, because the single maximum application rates are below the NOAEC; significant adverse effects are not expected. There were no significant effects to the green lacewing.

Three extended laboratory experiments were conducted exposing the ladybird beetle (*Coccinella septempunctata*) to the 480 SC formulation. Because the single maximum application rates to the proposed vegetables for the SC formulation, which range from 0.094 – 0.156 lb a.i./A, are generally below the NOAEC; significant adverse effects to ladybird beetles due to contact with residues are not expected. However, there is a potential for adverse effects to adult ladybird beetles due to ingestion of food items (aphids and pollen) containing flubendiamide residues. Adult survival was affected yielding LD_{50}, NOAEC, and LOAEC values of 0.089, 0.04, and 0.079 lb a.i./A, respectively. There were no effects to larval survival or reproduction.

4.2.2.3 Terrestrial plants

Terrestrial and semi-aquatic plants may be exposed to pesticides from runoff, spray drift or volatilization. Based on the maximum single application rate, (pome fruit), the LOC was not exceeded for all listed and non-listed non-target terrestrial plants. Thus, it can be assumed that for the remainder of the proposed crops there will be no LOC exceedances.

4.2.3 Endocrine Disruption Assessment

EPA is required under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act (FQPA), to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) *"may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate."* Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, flubendiamide may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

The potential for endocrine disruptor related effects was observed in mammalian and avian toxicity studies submitted to the Agency. Significant reproductive effects were observed in the mallard duck study (MRID 468170-07), however at the proposed application rates, there is minimal potential risk to birds.

At higher doses (20,000 ppm or limit dose), possible endocrine effects following exposure to flubendiamide were noted in the adrenal (increased adrenal weight and cortical cell hypertrophy in rats; cortical hypertrophy in dogs), ovary (interstitial cell vacuolation in rats), delay in balanopreputial separation compared to controls in the developmental neurotoxicity study and thyroid (increased thyroid weight and follicular cell hypertrophy in rats). The reversibility of histological thyroidal effects was demonstrated in subchronic female rats during a four-week recovery period. Thyroid follicular cell hypertrophy emerged as one major endpoint in all rat studies. Rats and mice are particularly sensitive to the decreased availability of thyroxine and triodothyronine and respond with hypertrophy and hyperplasia of follicular cells as evident in the flubendiamide toxicological database. However, there were no reproductive effects or signs of reproductive impairment in males or females observed in the two-generation test (468172-16).

4.3 Threatened and Endangered Species Concern

4.3.1 Action Area

For listed species assessment purposes, the action area is considered to be the area affected directly or indirectly by the Federal action and not merely the immediate area involved in the action. At the initial screening-level, the risk assessment considers broadly described taxonomic groups and so conservatively assumes that listed species within those broad groups are co-located with the pesticide treatment area. This means that terrestrial plants and wildlife are assumed to be located on or adjacent to the treated site and aquatic organisms are assumed to be located in a surface water body adjacent to the treated site. The assessment also assumes that listed species are located within an assumed area, which has the relatively highest potential exposure to the pesticide, and that exposures are likely to decrease with distance from the treatment area. This risk assessment presents the use of flubendiamide and establishes initial co-location of species with treatment areas.

If the assumptions associated with the screening-level action area result in RQs that are below the listed species LOCs, a "no effect" determination conclusion is made with respect to listed species in that taxa, and no further refinement of the action area is necessary. Furthermore, RQs below the listed species LOCs for a given taxonomic group indicate no concern for indirect effects upon listed species that depend upon the taxonomic group covered by the RQ as a resource. However, in situations where the screening assumptions lead to RQs in excess of the listed species LOCs for a given taxonomic group, a potential for a "may affect" conclusion exists and may be associated with direct effects on listed species belonging to that taxonomic group or may extend to indirect effects upon listed species that depend upon that taxonomic group as a resource. In such cases, additional information on the biology of listed species, the locations of these species, and the locations of use sites could be considered to determine the extent to which screening assumptions regarding an action area apply to a particular listed organism. These subsequent refinement steps could consider how this information would impact the action area for a particular listed organism and may potentially include areas of exposure that are downwind and downstream of the pesticide use site.

4.3.2 Taxonomic Groups Potentially at Risk: Direct Effects

Based on available screening level information, for the proposed uses of flubendiamide, there is a potential for direct effects to listed aquatic invertebrates and non-target Lepidopteran insects due to exposure to the formulations. There is a potential for direct effects to benthic invertebrates exposed to the parent and des-iodo degradate. In addition, there is a potential for adverse effects (mortality) to adult ladybird beetles due to ingestion of food items (aphids and pollen) containing flubendiamide residues. There were no effects to larval survival or reproduction.

Consequently, there is a potential concern for indirect effects upon the listed organisms by, for example, perturbing forage or prey availability. In conducting a screen for indirect effects, direct effect LOCs for each taxonomic group are used to make inferences concerning the potential for indirect effects upon listed species that rely upon non-endangered organisms in these taxonomic groups as resources critical to their life cycle. A summary of the risk conclusions and direct and indirect effects determinations is presented in **Table 30**.

Table 30. Listed species risks associated with direct or indirect effects due to applications of flubendiamide

Listed Taxonomy	Direct Effects	Indirect Effects

Table 30. Listed species risks associated with direct or indirect effects due to applications of flubendiamide		
Listed Taxonomy	**Direct Effects**	**Indirect Effects**
Terrestrial and semi-aquatic plants – monocots	No	Yes[a]
Terrestrial and semi-aquatic plants – dicots	No	Yes[a]
Terrestrial invertebrates	Yes[a]	No
Birds (surrogate for terrestrial-phase amphibians and reptiles)	No	Yes [a]
Mammals	No	Yes[a]
Aquatic vascular plants	No	No
Aquatic non-vascular plants [a]	No	No
Freshwater fish (surrogate for aquatic-phase amphibians)	No	Yes[b]
Freshwater Invertebrates	Yes – due to exposure to formulations [b]	Yes[b]
Freshwater Benthic Invertebrates	Yes – due to exposure to flubendiamide and the des-iodo degradate [c]	Yes[b]
Estuarine/Marine Fish	No	No
Estuarine/Marine Crustaceans	No	No
Estuarine/Marine Mollusks	No	No

[a] Potential risk to non-target insects (Lepidoptera) and adult ladybird beetles due to ingestion of food items (aphids and pollen) containing flubendiamide residues

[b] Acute and Chronic LOC exceeded for daphnids exposed to the formulations

[c] Potential risk to benthic invertebrates exposed to the des-iodo degradate

The LOCATES database (version 2.9.7) identifies those U.S. counties that grow corn, cotton, tobacco, grapes, pome fruit, stone fruit, cucurbit vegetables, fruiting vegetables, leafy vegetables, and brassica leafy vegetables and that have federally-listed endangered or threatened species that may be directly (aquatic and terrestrial invertebrates) or indirectly (terrestrial plants, birds, mammals, fish, and benthic invertebrates) affected. The list of affected species derived from LOCATES was not included in this assessment because the uses cover most of the United States and the direct and indirect effects includes most species. With additional refinement by exploring more detailed use patterns and species biology (*e.g.*, geographic location, specific feeding habits, time of year likely to utilize crop fields), some species listed may be determined to be not likely to be affected.

4.3.3 Use of Probit Slope Response Relationship to Provide Information on the Endangered Species Levels of Concern

The Agency uses the probit dose response relationship as a tool for providing additional information on the listed animal species acute levels of concern. The acute listed species LOCs of 0.1 and 0.05 are used for terrestrial and aquatic animals, respectively. As part of the risk characterization, an interpretation of acute LOCs for listed species is discussed. This interpretation is presented in terms of the chance of an individual event (*i.e.*, mortality or immobilization) should exposure at the estimated environmental concentration actually occur for a species with sensitivity to flubendiamide on par with the acute toxicity endpoint selected for RQ calculation. To accomplish this interpretation, the Agency uses the slope of the dose response relationship available from the toxicity study used to establish the acute toxicity measurement endpoints for each taxonomic group. The individual effects probability associated with the LOCs is based on the mean estimate of the slope and an assumption of a probit dose response relationship. In addition to a single effects probability estimate based on the mean, upper and lower estimates of the effects probability are also provided to account for variance in the slope. The upper and lower bounds of the effects probability are based on available information on the 95% confidence interval of the slope. A statement regarding the confidence in the applicability of the assumed probit dose response relationship for predicting individual event probabilities is also included. Studies with good probit fit characteristics (*i.e.*, statistically appropriate for the data set) are associated with a high degree of confidence. Conversely, a low degree of confidence is associated with data from studies that do not statistically support a probit dose response relationship. In addition, confidence in the data set may be reduced by high variance in the slope (*i.e.*, large 95% confidence intervals), despite good probit fit characteristics.

Individual effect probabilities are calculated based on an Excel spreadsheet tool IECV1.1 (Individual Effect Chance Model Version 1.1) developed by Ed Odenkirchen of the U.S. EPA, OPP, Environmental Fate and Effects Division (June 22, 2004). The model allows for such calculations by entering the mean slope estimate (and the 95% confidence bounds of that estimate) as the slope parameter for the spreadsheet. In addition, the LOC (0.1 for terrestrial animals and 0.05 for aquatic animals) is entered as the desired threshold.

The acute endangered species risk LOC (0.05) and Acute Restricted Use LOC (0.1) are exceeded for freshwater invertebrates exposed to the 480 SC formulation based on use on corn, cotton, tobacco, pome fruits, stone fruits, and grapes. The RQs range from 0.1 – 0.17. The acute toxicity test for the daphnid resulted in a LC_{50} = 2.6 μg a.i./L with a slope of 2.11 with 95% confidence limits of 1.65 and 2.58 (MRID 468169-31). The corresponding estimated chance of an individual acute mortality to the freshwater invertebrates at the LOC of 0.05 is 1 in 331 (with respective upper and lower bounds of 1 in 63 to 1 in 2,540).

The acute endangered species risk LOC (0.05) is exceeded for freshwater invertebrates exposed to the 24 WG formulation based on use on cucurbit vegetables, fruiting vegetables, leafy vegetables, and brassica leafy vegetables. The RQs range from 0.056 – 0.084. The acute toxicity test for the daphnid resulted in a LC_{50} = 1.5 μg a.i./L with a slope of 1.84 with 95% confidence limits of 1.32 and 2.40 (MRID 468169-32). The corresponding estimated chance of an individual acute mortality to the freshwater invertebrates at the LOC of 0.05 is 1 in 129 (with respective upper and lower bounds of 1 in 23 to 1 in 1,120).

There is a relatively high probability of an individual mortality occurrence due to the steep slopes of the mortality tests; therefore, flubendiamide is likely to adversely affect listed freshwater invertebrates exposed to the formulations.

4.3.4 Indirect Effects Analysis

The Agency acknowledges that pesticides have the potential to exert indirect effects upon the listed organisms by, for example, perturbing forage or prey availability, altering the extent of nesting habitat, *etc.* In conducting a screen for indirect effects, direct effect LOCs for each taxonomic group are used to make inferences concerning the potential for indirect effects upon listed species that rely upon non-endangered organisms in these taxonomic groups as resources critical to their life cycle.

Based on the acute and chronic risk to freshwater invertebrates exposed to the formulations, direct effects to benthic invertebrates exposed to the degradate, there may be potential indirect effects to aquatic and terrestrial species that depend on these organisms (including their surrogates) as a source of food or pollination.

4.3.5 Critical Habitat for Listed Species

In the evaluation of pesticide effects on designated critical habitat, consideration is given to the physical and biological features (primary constituent elements) of a critical habitat identified by the U.S Fish and Wildlife and National Marine Fisheries Services as essential to the conservation of a listed species and which may require special management considerations or protection. The evaluation of impacts for a screening level pesticide risk assessment focuses on the biological features that are primary constituent elements and is accomplished using the screening-level taxonomic analysis (RQs) and listed species' levels of concern (LOCs) that are used to evaluate direct and indirect effects to listed organisms.

The screening-level risk assessment for flubendiamide has identified potential concerns for direct effects on listed aquatic and terrestrial invertebrates (Lepidoptera species) and indirect effect to those organisms dependant upon them for food. In light of the potential for indirect effects, the next step for EPA and the Service(s) is to identify which listed species and critical habitat are potentially implicated.

Analytically, the identification of such species and critical habitat can occur in either of two ways. First, the agencies could determine whether the action area overlaps critical habitat or the occupied range of any listed species. If so, EPA would examine whether the pesticide's potential impacts on non-endangered species would affect the listed species indirectly or directly affect a primary constituent element of the critical habitat. Alternatively, the agencies could determine which listed species depend on biological resources, or have constituent elements that fall into the taxa that may be directly or indirectly impacted by a pesticide. Then EPA would determine whether or not use of the pesticide overlaps the critical habitat or the occupied range of those listed species. At present, the information reviewed by EPA is not sufficient to permit use of either analytical approach to make a definitive identification of species that are potentially impacted indirectly or critical habitats that are potentially impacted directly by the use of pesticides. EPA and the Service(s) are working together to conduct the necessary analysis.

This screening-level risk assessment for critical habitat provides a listing of potential biological features that, if they are primary constituent elements of one or more critical habitats, would be of potential concern. These correspond to the taxa identified above as being of potential concern for indirect effects and include birds, reptiles, terrestrial phase amphibians, mammals, terrestrial plants and aquatic organisms. This list should serve as an initial step in problem formulation for further assessment of critical habitat impacts outlined above, should additional work be necessary.

5 Description of Assumptions, Uncertainties, Strengths, and Limitations

5.1 Assumptions and Limitations Related to Exposure for All Taxa

There are a number of areas of uncertainty in the aquatic and terrestrial risk assessments. The toxicity assessment for terrestrial and aquatic animals is limited by the number of species tested in the available toxicity studies. Use of toxicity data on representative species does not provide information on the potential variability in susceptibility to acute and chronic exposures.

This screening-level risk assessment relies on labeled statements of the maximum rate of flubendiamide application, the maximum number of applications, and the shortest interval between applications. Together, these assumptions constitute a maximum use scenario. The frequency at which actual uses approach these maximums is dependant on resistance to the fungicide, timing of applications, and market forces.

The 480 SC and 24 WG proposed labels restrict use per season; however, there are crops, such as brassica leafy vegetables, that often have more that one season in a year. In this risk assessment, RQs are based on one season per year and risk is underestimated for crops that have more than one growing season per year.

5.2 Assumptions and Limitations Related to Exposure for Aquatic Species

The fate and transport database for flubendiamide was sufficient to conduct aquatic modeling for exposure assessment of aquatic species. No data gaps were identified. The following uncertainties have been identified in the environmental fate properties and exposure models for flubendiamide:

- Insufficient toxicological and environmental fate data provided on the degradates (other than the des-iodo degradate) that form from the parent flubendiamide. Even though quantities for the degradate products of flubendiamide were less than 10%, insufficient scientific data on these degradates was provided which limited the conclusion of the environmental fate and transport activities of these degradates as well as their overall toxicological effects on aquatic and terrestrial receptors.

5.3 Assumptions and Limitations Related to Exposure for Terrestrial Species

Variation in habitat and dietary requirements

For screening terrestrial risk assessments, a generic bird or mammal is assumed to occupy either the treated field or adjacent areas receiving pesticide at a rate commensurate with the treatment rate on the field. The habitat and feeding requirements of the modeled species and the wildlife species may be different. It is assumed that species occupy, exclusively and permanently, the treated area being modeled. This assumption leads to a maximum level of exposure in the risk assessment.

The acute studies have a fixed exposure period, not allowing for the differences in response of individuals to different durations of exposure. Further, for the acute oral study, flubendiamide is administered in a single dose which does not mimic wild birds' exposure through multiple feedings. Also, it does not account for the effect of different environmental matrices on the absorption rate of the chemical into the animal. Because exposure occurs over several days, both the accumulated dose and elimination of the chemical from the body for the duration of the exposure determine the exact exposure to wildlife, however they are not taken into account in the screening assessment. There was also no assumption of an effect of repeated doses that change the tolerance of an individual to successive doses.

Variation in diet composition

The risk assessment and calculated RQs assume 100% of the diet is relegated to single food types foraged only from treated fields. The assumption of 100% diet from a single food type may be realistic for acute exposures, but diets are likely to be more variable over longer periods of time. This assumption is likely to be conservative and will tend to overestimate potential risks for chronic exposure, especially for larger organisms that have larger home ranges. These large animals (*e.g.*, deer and geese) will tend to forage from a variety of areas and move on and off of treated fields. Small animals (*e.g.*, mice, voles, and small birds) may have home ranges smaller than the size of a treated field and will have little or no opportunity to obtain foodstuffs that have not been treated with flubendiamide. Even if their home range does cover area outside the treated field, flubendiamide may have runoff to areas adjacent to the treated field.

Exposure routes other than dietary

Only dietary and incidental ingestion of contaminated soils exposure is included in the exposure assessment. Other exposure routes are possible for animals in treated areas. These routes include ingestion of contaminated drinking water, dermal contact, inhalation, and preening. Because flubendiamide does not volatilize appreciably (vapor pressure 7.5×10^{-7} mm Hg), inhalation does not appear to be a significant contributor to the overall exposure. Given that flubendiamide is soluble in water, there exists the potential to dissolve in runoff and puddles on the treated field may contain the chemical. If toxicity is expected through any of these other routes of exposure, then the risks of a toxic response to flubendiamide is underestimated in this risk assessment.

Dietary Intake - The Differences between Laboratory and Field Conditions

There are several aspects of the dietary test that introduce uncertainty into calculation of the LC_{50} value (Mineau, *et al* 1994; ECOFRAM 1999). The endpoint of this test is reported as the concentration mixed with food that produces a response rather than as the dose ingested. Although food consumption sometimes allows for the estimate of a dose, calculations of the mg/kg/day are confounded by undocumented spillage of feed and how consumption is measured over the duration of the test. Usually, if measured at all, food consumption is estimated once at the end of the five-day exposure period. Further, group housing of birds undergoing testing only allows for a measure of the average consumption per day for a group; consumption estimates can be further confounded if birds die within a treatment group. The exponential growth of young birds also complicates the estimate of the dose; controls often nearly double in size over the duration of the test. Since weights are only taken at the initiation of the exposure period and at the end, the dose per unit body weight (*e.g.*, mg/kg) is difficult to estimate with any precision. The interpretation of this test is also confounded because the response of birds is not only a function of the intrinsic toxicity of the pesticide, but also the willingness of the birds to consume treated food.

Further, the acute and chronic characterization of risk rely on comparisons of wildlife dietary residues with LC_{50} or NOAEC values expressed in concentrations of pesticides in laboratory feed. These comparisons assume that ingestion of food items in the field occurs at rates commensurate with those in the laboratory. Although the screening assessment process adjusts dry-weight estimates of food intake to reflect the increased mass in fresh-weight wildlife food intake estimates, it does not allow for gross energy and assimilative efficiency differences between wildlife food items and laboratory feed. On gross energy content alone, direct comparison of a laboratory dietary concentration-based effects threshold to a fresh-weight pesticide residue estimate would result in an underestimation of field exposure by food consumption by a factor of 1.25 - 2.5 for most food items. Only for seeds would the direct comparison of dietary threshold to residue estimate lead to an overestimate of exposure.

Differences in assimilative efficiency between laboratory and wild diets suggest that current screening assessment methods do not account for a potentially important aspect of food requirements. Depending upon species and dietary matrix, bird assimilation of wild diet energy ranges from 23 - 80%, and mammal's assimilation ranges from 41 - 85% (U.S. EPA 1993). If it is assumed that laboratory chow is formulated to maximize assimilative efficiency (*e.g.*, a value of 85%), a potential for underestimation of exposure may exist by assuming that consumption of food in the wild is comparable with consumption during laboratory testing. In the screening process, exposure may be underestimated because metabolic rates are not related to food consumption.

Finally, the screening procedure does not account for situations where the feeding rate may be above or below requirements to meet free living metabolic requirements. Gorging behavior is a possibility under some specific wildlife scenarios (*e.g.*, bird migration) where the food intake rate may be greatly increased. Kirkwood (1983) has suggested that an upper-bound limit to this behavior might be the typical intake rate multiplied by a factor of 5. In contrast is the potential for avoidance, operationally defined as animals responding to the presence of noxious chemicals in their food by reducing consumption of treated dietary elements. This response is seen in nature where herbivores avoid plant secondary compounds.

In the absence of additional information, the acute oral LD_{50} test provides the best estimate of acute effects for chemicals where exposure can be considered to occur over relatively short feeding periods, such as the diurnal feeding peaks common to avian species (ECOFRAM 1999).

Incidental Pesticide Releases Associated with Use

This risk assessment is based on the assumption that the entire treatment area is subject to flubendiamide application at the rates specified on the label. In reality, there is the potential for uneven application of flubendiamide through such plausible incidents as changes in calibration of application equipment, spillage, and localized releases at specific areas of the treated field that are associated with specifics of the type of application equipment used (*e.g.*, increased application at turnabouts when using older application equipment).

5.4 Assumptions and Limitations Related to Effects Assessment

There is uncertainty as to the significance of the reproductive endpoint used for assessment purposes with respect to wild mammal populations because frank developmental and reproductive effects were not observed in the study. Observed chronic effects in the two-generation rat reproduction study (MRID 46817239) were parental effects including increases in absolute and relative liver, kidney, and thyroid weights in both sexes. Clinical signs of toxicity were limited to effects on the eyes. Sexual maturation was significantly delayed in both sexes. The only effect to offspring was an increase in absolute and relative liver weights in both males and females. At necropsy, incidences of dark-colored livers were increased (25.7-42.8%) compared to controls. The resulting NOAEC is 200 mg/kg-diet. There were no reproductive effects or signs of reproductive impairment in males or females.

Age class and sensitivity of effects thresholds

It is generally recognized that test organism age may have a significant impact on the observed sensitivity to a toxicant. The screening risk assessment acute toxicity data for fish are collected on juvenile fish between 0.1 and 5 grams. Aquatic invertebrate acute testing is performed on recommended immature age classes (*e.g.*, first instar for daphnids, second instar for amphipods, stoneflies and mayflies, and third instar for midges). Similarly, acute dietary testing with birds is also performed on juveniles, with mallard being 5-10 days old and quail 10-14 days old.

Testing of juveniles may overestimate toxicity of older age classes for pesticidal active ingredients, such as flubendiamide, that act directly (without metabolic transformation) because younger age classes may not have the enzymatic systems associated with detoxifying xenobiotics. The screening risk assessment has no current provisions for a generally applied method that accounts for this uncertainty. In so far as the available toxicity data may provide ranges of sensitivity information with respect to age class, the risk assessment uses the most sensitive life-stage information as the conservative screening endpoint.

Use of the Most Sensitive Species Tested

Although the screening risk assessment relies on a selected toxicity endpoint from the most sensitive species tested, it does not necessarily mean that the selected toxicity endpoint reflect sensitivity of the most sensitive species existing in a given environment. The relative position of the most sensitive species tested in the distribution of all possible species is a function of the overall variability among species to a particular chemical. In the case of listed species, there is uncertainty regarding the relationship of the listed species' sensitivity and the most sensitive species tested.

The Agency is not limited to a base set of surrogate toxicity information in establishing risk assessment conclusions. The Agency also considers toxicity data on non-standard test species when available.

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APPENDIX A: Status of Fate and Ecological Effects Data Requirements

Table A-1: Environmental Fate Data Requirements for Flubendiamide				
Guideline #		Data Requirement	MRID #s	Study Classification
161-1	835.212	Hydrolysis	46816907	Acceptable
161-2	835.224	Photodegradation in Water	46816908	Acceptable
161-3	835.241	Photodegradation on Soil	46816909	Acceptable
161-4	835.237	Photodegradation in Air	NA[1]	NA
162-1	835.41	Aerobic Soil Metabolism	Parent: 46816910 Degradate:46816911	Acceptable Acceptable
162-2	835.42	Anaerobic Soil Metabolism	46816912	Supplemental
162-3	835.44	Anaerobic Aquatic Metabolism	46816914	Acceptable
162-4	835.43	Aerobic Aquatic Metabolism	46816913	Acceptable
163-1	835.1240 835.1230	Leaching-Adsorption/Desorption	Parent: 46816905 Degradate: 46816906	Supplemental Supplemental
163-2	835.141	Laboratory Volatility	NA	NA
163-3	835.81	Field Volatility	NA	NA
164-1	835.61	Terrestrial Field Dissipation	46816915 46816916 46816917	Acceptable Acceptable Acceptable
165-4	850.173	Accumulation in Fish	46816949 46817001	Acceptable Acceptable
		Quantum Yield in Water	46816919	Supplemental

[1] Not Available.

Table A-2 : Ecological Effects Data Requirement Table for Flubendiamide					
Guideline #		Data Requirement	Formulation	MRID (Accession #)	Study Classification
71-1	850.2100	Avian Oral LD_{50}	Technical 480 SC	46817003 46817004	Acceptable Acceptable
71-2	850.2200	Avian Dietary LC_{50}	Technical Technical	46817005 46817006	Acceptable Acceptable
71-4	850.2300	Avian Reproduction	Technical Technical	46817007 46817008	Supplemental Acceptable
72-1	850.1075	Freshwater Fish LC_{50}	Technical Technical Technical Technical 480 SC 480 SC	46816937 46816939 46816940 46816941 46816942 46816943	Acceptable Acceptable Acceptable Acceptable Acceptable Acceptable
72-2	850.1010	Freshwater Invertebrate LC_{50}	Technical 24 WG 480 SC 480 SC Des-iodo	46816930 46816932 46816931 46816934 46816933	Acceptable Acceptable Acceptable Supplemental Acceptable
72-3(a)	850.1075	Estuarine/Marine Fish LC_{50}	Technical	46816938	Acceptable
72-3(b)	850.1025	Estuarine/Marine Mollusk EC_{50}	Technical	46816935	Acceptable
72-3(c)	850.1035 850.1045	Estuarine/Marine Shrimp LC_{50}	Technical	46816936	Acceptable
72-4(a)	850.1400	Freshwater Fish Early Life Stage	Technical	46816947	Acceptable
72-4(b)	850.1300 850.1350 850.1300	Aquatic Invertebrate Life-cycle	Technical Technical 480 SC	46816944 46816946 46816945	Supplemental Acceptable Acceptable
	850.1790	Benthic Organisms	Technical 24 WG 480 SC Des-iodo	46817022 46817014 46817013 46817023	Supplemental Acceptable Acceptable Supplemental
		Mesocosm Study	480 SC	46817002	Supplemental
72-5	850.1500	Freshwater Fish Life-Cycle	Technical	46816948	Unacceptable
122-1(a)	850.4100	Seed Germination/ Seedling Emergence Tier 1	24 WG 480 SC	46817034 46817036(a)	Acceptable Acceptable
		Herbicidal Toxicity Terrestrial plants Tier 2	480 SC	46817035	Supplemental, Non-guideline
122-1(b)	850.4150	Vegetative Vigor Tier 1	Technical 24 WG	46817036(b) 46817037	Acceptable Supplemental
122-2	850.4400	Aquatic Plant (Non-Vascular) Tier 1&II	Technical 480 SC	46817041 46817040	Acceptable Acceptable
122-2	850.4400	Aquatic Plant (Vascular) Tier 2	Technical	46817039	Acceptable
123-1(a)	850.4225	Seed Germination/ Seedling Emergence Tier 2	24 WG	46817038	Acceptable

Table A-2 : Ecological Effects Data Requirement Table for Flubendiamide					
Guideline #		Data Requirement	Formulation	MRID (Accession #)	Study Classification
141-1	850.3020	Honey Bee Acute Contact LD_{50}	Technical 480 SC 480 SC WG 40	46817009 46817010 46817011 46817012	Acceptable Acceptable Acceptable Supplemental, Non-guideline
	850.6200	Acute Toxicity to Earthworms	Technical 480 SC Des-iodo	46817028 46817029 46817030	Supplemental Supplemental Supplemental
	850.6200	Chronic Toxicity to Earthworms	480 SC 24 WG	46817031 46817032	Supplemental Supplemental
141-2	850.3030	Honey Bee Residue on Foliage	NA	NA	NA
		Parasitoid Wasp	WG 40	46817020	Supplemental, Non-guideline
		Predatory Mite	WG 40	46817019	Supplemental, Non-guideline
		Ladybird Beetle (45 day study)	480 SC	46817015	Supplemental, Non-guideline
		Ladybird Beetle (Extended Study)	480 SC	46817016	Supplemental, Non-guideline
		Ladybird Beetle (Life Cycle Test)	480 SC	46817017	Supplemental, Non-guideline
		Parasitic Wasp (Side Effects Tests)	480 SC	46817021	Supplemental, Non-guideline
		White springtail (Reproduction Test)	480 SC	46817027	Supplemental
		Green lacewing (Extended Study)	480 SC	46817018	Supplemental

APPENDIX B: PRZM/ EXAMS Modeling Crop Application Scenarios and EECs

Appendix Table B1. Standard EFED aquatic crop application scenarios for proposed flubendiamide uses				
PRZM Crop Scenario	**First Application Date dd-mm**	**Max Number of Applications**	**Minimum Application Interval (days)**	**Maximum Single Application Rate (lb ai/A)**
Corn				
Illinois Corn	01-07	4	3	0.094
Mississippi Corn	01-05	4	3	0.094
North Carolina Corn	08-06	4	3	0.094
Ohio Corn	17-05	4	3	0.094
Pennsylvania Corn	01-05	4	3	0.094
Cotton				
California Cotton	07-03	3	5	0.094
Mississippi Cotton	01-05	3	5	0.094
North Carolina Cotton	08-06	3	5	0.094
Tobacco				
North Carolina Tobacco	08-06	4	5	0.094
Pome Fruit				
North Carolina Apples	08-06	3	7	0.156
Oregon Apples	18-03	3	7	0.156
Pennsylvania Apples	01-05	3	7	0.156
Stone Fruit				
Georgia Peaches	14-05	3	7	0.125
Michigan Cherries	05-06	3	7	0.125
Tree Nuts				
California Almonds	15-04	3	7	0.125
Georgia Pecans	15-04	3	7	0.125
Grapes				
California Grapes	15-04	3	5	0.125
New York Grapes	21-03	3	5	0.125
Fruiting Vegetables				
California Tomato	15-04	5	3	0.045
Florida Tomato	20-05	5	3	0.045
Pennsylvania Tomato	01-05	5	3	
Leafy Vegetable				
California Lettuce	21-03	5	3	0.045
Brassica Leafy Vegetables				
Florida Cabbage	10-07	5	3	0.030
Cucurbit Vegetable				
Florida Cucumber	10-07	5	7	0.045

Appendix Table B2. Estimated water column concentrations of flubendiamide after aerial and ground application				
Crop	**Spray Application**	**Peak Conc. µg/L**	**21day Conc. µg/L**	**60 day Conc. µg/L**
Corn (0.094 lbs ai/acre x 4 applications with 3 days interval)				
Illinois Corn	Aerial	21.94	21.4	21.06
	Ground	20.43	20.0	19.6
	No Drift	20.07	19.63	19.23

Appendix Table B2. Estimated water column concentrations of flubendiamide after aerial and ground application				
Crop	**Spray Application**	**Peak Conc. µg/L**	**21day Conc. µg/L**	**60 day Conc. µg/L**
Mississippi Corn	Aerial	24.07	23.27	22.96
	Ground	23.29	22.39	21.98
	No Drift	23.11	22.20	21.84
North Carolina Corn	Aerial	16.19	15.37	14.47
	Ground	14.72	13.89	13.16
	No Drift	14.31	13.50	12.81
Ohio Corn	Aerial	18.08	17.17	16.55
	Ground	16.26	15.45	14.90
	No Drift	15.81	15.01	14.48
Pennsylvania Corn	Aerial	14.97	14.18	14.12
	Ground	13.16	12.73	12.29
	No Drift	12.74	12.30	11.86
Cotton (0.094 lbs ai/acre x 3 applications with 5 days interval)				
California Cotton	Aerial	3.8	3.49	3.28
	Ground	2.52	2.2	2.03
	No Drift	2.19	1.73	1.69
Mississippi Cotton	Aerial	15.3	14.71	14.53
	Ground	14.63	13.97	13.68
	No Drift	14.47	13.80	13.46
North Carolina Cotton	Aerial	19.13	18.61	17.99
	Ground	18.36	17.28	17.05
	No Drift	18.12	17.57	12.10
Tobacco (0.094 lbs ai/acre x 4 applications with 5 days interval)				
North Carolina Tobacco	Aerial	N/A	N/A	N/A
	Ground	7.0	6.63	6.42
	No Drift	6.54	6.19	5.99
Pome Fruits (0.156 lbs ai/acre x 3 applications with 7 days interval)				
North Carolina Apples	Aerial	N/A	N/A	N/A
	Ground	10.79	10.17	19.6
	No Drift	10.30	9.69	9.11
Oregon Apples	Aerial	N/A	N/A	N/A
	Ground	10.47	10.11	9.83
	No Drift	9.98	9.61	9.35
Pennsylvania Apples	Aerial	N/A	N/A	N/A
	Ground	11.64	11.09	10.74
	No Drift	11.14	10.59	10.22
Stone Fruits (0.125 lbs ai/acre x 3 applications with 7 days interval)				
Georgia Peaches	Aerial	N/A	N/A	N/A
	Ground	3.42	3	2.7
	No Drift	2.98	2.58	2.33
Michigan Cherries	Aerial	N/A	N/A	N/A
	Ground	11.35	11.11	10.79
	No Drift	10.75	10.51	10.24
Tree Nuts (0.125 lbs ai/acre x 3 applications with 7 days interval)				
California Almonds	Aerial	N/A	N/A	N/A
	Ground	2.86	2.77	2.72
	No Drift	2.54	2.40	2.30
Georgia Pecans	Aerial	N/A	N/A	N/A
	Ground	5.99	5.55	5.27
	No Drift	5.66	5.17	4.93

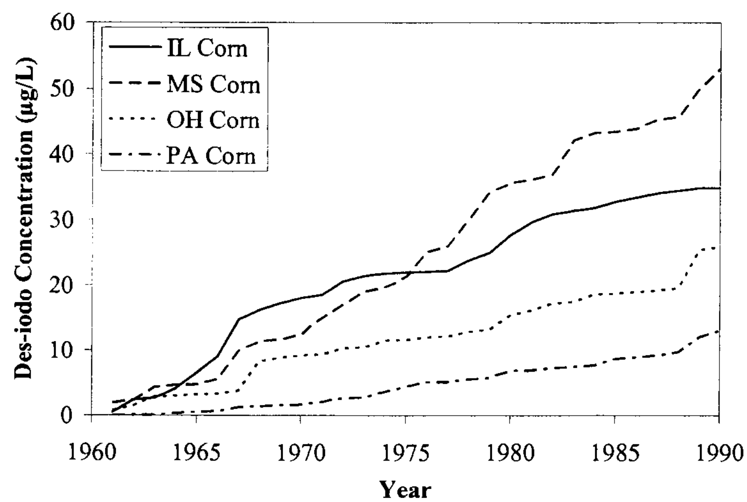
Appendix Table B2. Estimated water column concentrations of flubendiamide after aerial and ground application				
Crop	**Spray Application**	**Peak Conc. µg/L**	**21day Conc. µg/L**	**60 day Conc. µg/L**
Grapes (0.125 lbs ai/acre x 3 applications with 5 days interval)				
California Grapes	Aerial	N/A	N/A	N/A
	Ground	2.48	2.35	2.22
	No Drift	2.26	2.07	1.91
New York Grapes	Aerial	N/A	N/A	N/A
	Ground	10.12	9.55	9.15
	No Drift	9.74	9.24	8.78
Fruiting Vegetables (0.045 lbs ai/acre x 5 applications with 3 days interval)				
California Tomato	Aerial	2.25	2.13	2.03
	Ground	1.1	1.04	1.02
	No Drift	0.89	0.80	0.78
Florida Tomato	Aerial	4.93	4.63	4.49
	Ground	4.41	3.89	3.77
	No Drift	4.25	3.73	3.59
Pennsylvania Tomato	Aerial	7.67	7.25	6.96
	Ground	7.11	6.67	6.4
	No Drift	6.97	6.54	6.27
Leafy Vegetables (0.045 lbs ai/acre x 5 applications with 3 days interval)				
California Lettuce	Aerial	8.08	7.37	7.16
	Ground	7.59	6.85	6.5
	No Drift	7.46	6.72	6.36
Brassica Leafy Vegetables (0.03 lbs ai/acre x 3 applications with 3 days interval)				
Florida Cabbage	Aerial	3.19	3.05	2.95
	Ground	3.04	2.89	2.76
	No Drift	3.00	2.85	2.71
Cucurbit Vegetable (0.045 lbs ai/acre x 5 applications with 7 days interval)				
Florida Cucumber	Aerial	8.25	7.84	7.53
	Ground	7.87	7.40	7.05
	No Drift	7.78	7.28	6.94

Appendix Table B3. Estimated pore water concentrations (µg/L) of the des-iodo degradate over time				
Crop	**1-year**	**10-years**	**20-years**	**30-years**
Corn (0.094 lbs ai/acre x 4 applications with 3 days interval)				
Illinois Corn	0.97	17.56	34.56	51.68
Mississippi Corn	1.93	12.44	35.67	53.08
North Carolina Corn	0.53	18.02	27.68	34.93
Ohio Corn	0.84	9.2	15.36	25.84
Pennsylvania Corn	0.02	1.68	6.82	13.02
Cotton (0.094 lbs ai/acre x 3 applications with 5 days interval)				
California Cotton	0.02	3.92	5.6	9.53
Mississippi Cotton	1.01	7.02	22.32	32.37
North Carolina Cotton	0.56	15.63	24.39	32.11
Tobacco (0.094 lbs ai/acre x 4 applications with 5 days interval)				
North Carolina Tobacco	0.12	7.2	13.99	16.59
Pome Fruits (0.156 lbs ai/acre x 3 applications with 7 days interval)				
North Carolina Apples	0.64	9.48	15.49	21.47 (26 Years)[1]
Oregon Apples	0.74	3.27	6.24	8.36
Pennsylvania Apples	0.043	1.56	7.22	15.19

Appendix Table B3. Estimated pore water concentrations (µg/L) of the des-iodo degradate over time				
Crop	**1-year**	**10-years**	**20-years**	**30-years**
Stone Fruits (0.125 lbs ai/acre x 3 applications with 7 days interval)				
Georgia Peaches	0.072	2.25	5.24	7.69
Michigan Cherries	0.018	4.02	5.77	13.23
Tree Nuts (0.125 lbs ai/acre x 3 applications with 7 days interval)				
California Almonds	0.13	2.38	4.01	6.41
Georgia Pecans	0.028	3.28	9.55	12.55
Grapes (0.125 lbs ai/acre x 3 applications with 5 days interval)				
California Grapes	0.051	0.81	1.38	3.47
New York Grapes	0.14	1.43	3.98	8.17
Fruiting Vegetables (0.045 lbs ai/acre x 5 applications with 3 days interval)				
California Tomato	0.14	1.97	3.31	5.72
Florida Tomato	1.23	10.91	29.91	42.44
Pennsylvania Tomato	0.0086	0.81	3.98	7.43
Leafy Vegetables (0.045 lbs ai/acre x 5 applications with 3 days interval)				
California Lettuce	0.69	7.05	13.07	18.73
Brassica Leafy Vegetables (0.03 lbs ai/acre x 3 applications with 3 days interval)				
Florida Cabbage	0.55	7.91	.14.35	21.31
Cucurbit Vegetable (0.045 lbs ai/acre x 5 applications with 7 days interval)				
Florida Cucumber	0.035	7.41	20.25	31.99

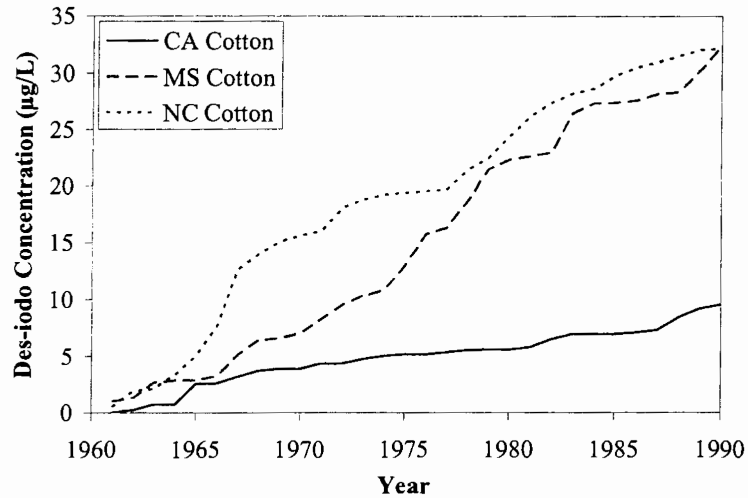
[1] The North Carolina Apple scenario only runs for 26 Years because there is only 26 years of data in the meteorological file associated with this scenario.

Corn (0.094 lbs ai/acre x 4 applications with 3 days interval)

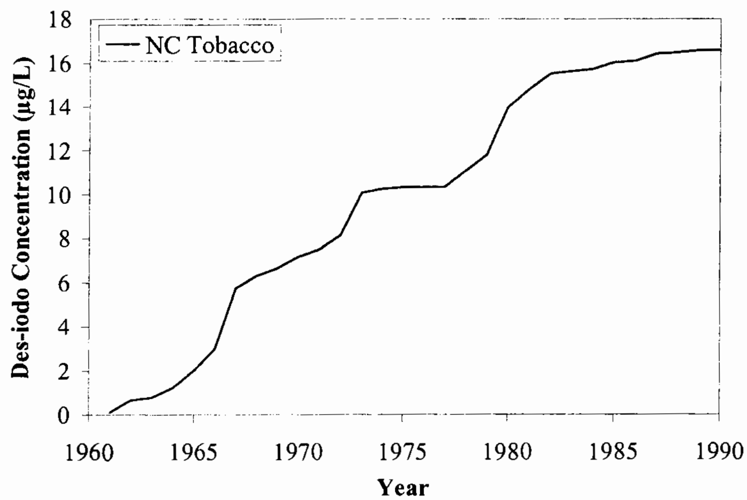


Appendix Figure B1. Accumulation of the des-iodo degradatein the standard EXAMS pond over time.

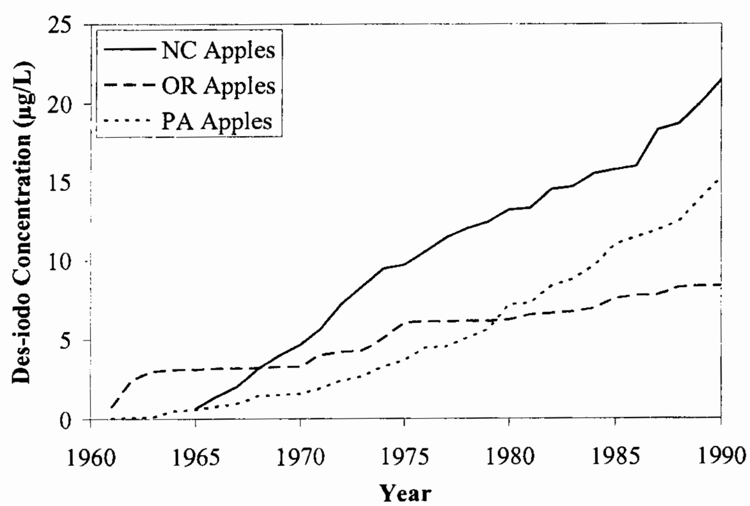
Cotton (0.094 lbs ai/acre x 3 applications with 5 days interval)



Tobacco (0.094 lbs ai/acre x 4 applications with 5 days interval)

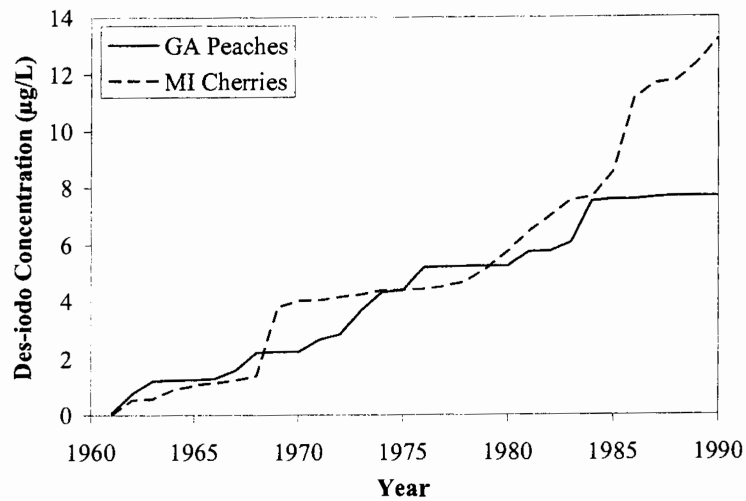


Pome Fruits (0.156 lbs ai/acre x 3 applications with 7 days interval)

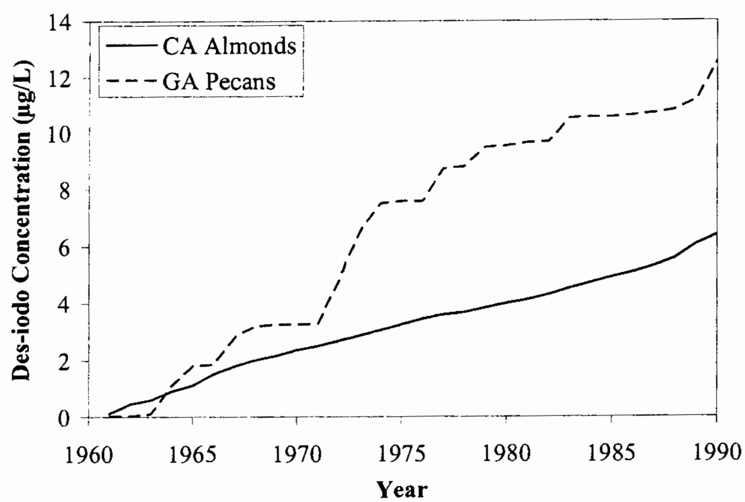


Appendix Figure B1. Continued.

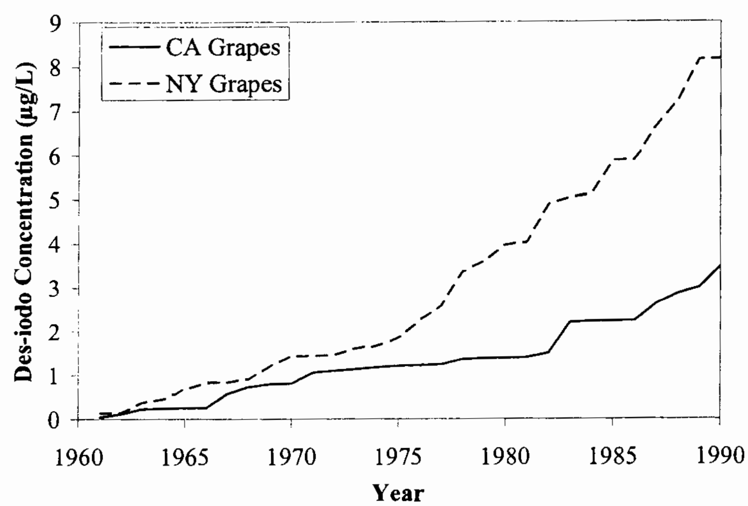
Stone Fruits (0.125 lbs ai/acre x 3 applications with 7 days interval)



Tree Nuts (0.125 lbs ai/acre x 3 applications with 7 days interval)

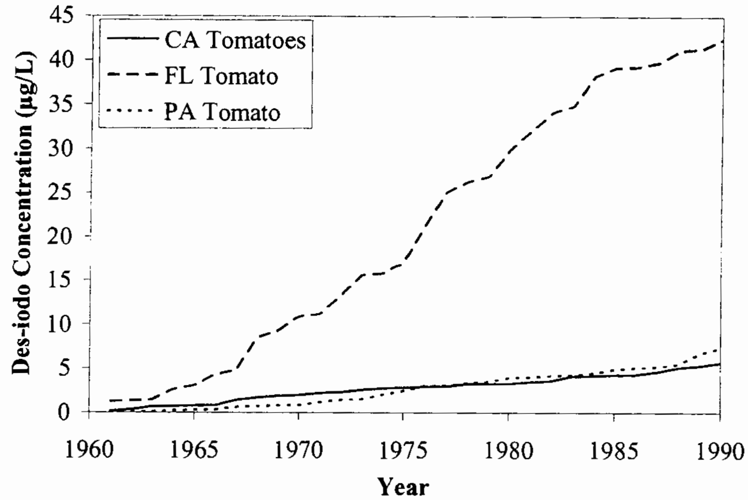


Grapes (0.125 lbs ai/acre x 3 applications with 5 days interval)

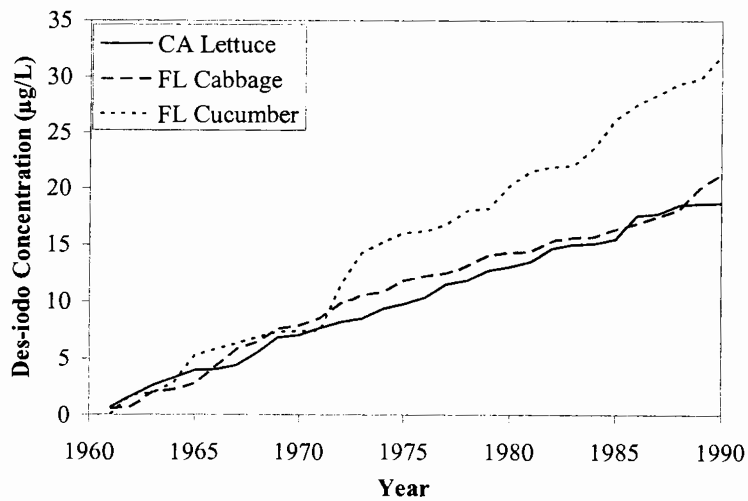


Appendix Figure B1. Continued.

Fruiting Vegetables (0.045 lbs ai/acre x 5 applications with 3 days interval)



Other Vegetables i
Leafy Vegetables (0.045 lbs ai/acre x 5 applications with 3 days interval – CA Lettuce)
Brassica Leafy Vegetables (0.03 lbs ai/acre x 3 applications with 3 days interval – FL Cabbage)
Cucurbit Vegetable (0.045 lbs ai/acre x 5 applications with 7 days interval – FL Cucumber)



Appendix Figure B1. Continued.

Appendix Table B4. Risk quotients based on the accumulation of the des-iodo degradate in benthic pore water over time.

Crop	1-year	10-years	20-years	30-years
Corn (0.094 lbs ai/acre x 4 applications with 3 days interval)				
Illinois Corn	3.46	62.71	123.43	184.57
Mississippi Corn	6.89	44.43	127.39	189.57
North Carolina Corn	1.89	64.36	98.86	124.75
Ohio Corn	3.00	32.86	54.86	92.29
Pennsylvania Corn	0.07	6.00	24.36	46.50
Cotton (0.094 lbs ai/acre x 3 applications with 5 days interval)				
California Cotton	0.07	14.00	20.00	34.04
Mississippi Cotton	3.61	25.07	79.71	115.61
North Carolina Cotton	2.00	55.82	87.11	114.68
Tobacco (0.094 lbs ai/acre x 4 applications with 5 days interval)				
North Carolina Tobacco	0.43	25.71	49.96	59.25
Pome Fruits (0.156 lbs ai/acre x 3 applications with 7 days interval)				

Appendix Table B4. Risk quotients based on the accumulation of the des-iodo degradate in benthic pore water over time.				
Crop	**1-year**	**10-years**	**20-years**	**30-years**
North Carolina Apples	2.29	33.86	55.32	76.68 (26 Years)[1]
Oregon Apples	2.64	11.68	22.29	29.86
Pennsylvania Apples	0.15	5.57	25.79	54.25
Stone Fruits (0.125 lbs ai/acre x 3 applications with 7 days interval)				
Georgia Peaches	0.26	8.04	18.71	27.46
Michigan Cherries	0.06	14.36	20.61	47.25
Tree Nuts (0.125 lbs ai/acre x 3 applications with 7 days interval)				
California Almonds	0.46	8.50	14.32	22.89
Georgia Pecans	0.10	11.71	34.11	44.82
Grapes (0.125 lbs ai/acre x 3 applications with 5 days interval)				
California Grapes	0.18	2.89	4.93	12.39
New York Grapes	0.50	5.11	14.21	29.18
Fruiting Vegetables (0.045 lbs ai/acre x 5 applications with 3 days interval)				
California Tomato	0.50	7.04	11.82	20.43
Florida Tomato	4.39	38.96	106.82	151.57
Pennsylvania Tomato	0.03	2.89	14.21	26.54
Leafy Vegetables (0.045 lbs ai/acre x 5 applications with 3 days interval)				
California Lettuce	2.46	25.18	46.68	66.89
Brassica Leafy Vegetables (0.03 lbs ai/acre x 3 applications with 3 days interval)				
Florida Cabbage	1.96	28.25	51.25	76.11
Cucurbit Vegetable (0.045 lbs ai/acre x 5 applications with 7 days interval)				
Florida Cucumber	0.13	26.46	72.32	114.25

[1] The North Carolina Apple scenario only runs for 26 Years because there is only 26 years of data in the meteorological file associated with this scenario.

APPENDIX C: PRZM EXAMS Example Output File – MS Corn (aerial)

```
stored as FLMSCOA.out
Chemical: Flubendiamide
PRZM environment: MScornSTD.txt     modified Tueday, 29 May 2007 at
11:57:40
EXAMS environment: pond298.exv      modified Thuday, 29 August 2002 at
15:33:30
Metfile: w03940.dvf     modified Wedday, 3 July 2002 at 08:05:46
Water segment concentrations (ppb)

Year  Peak  96 hr 21 Day      60 Day      90 Day      Yearly
1961  3.633 3.541 3.309 2.904 2.603 1.514
1962  3.857 3.814 3.539 3.45  3.405 3.227
1963  7.777 7.539 6.805 6.013 5.735 4.823
1964  10.27 10.04 9.327 8.701 8.724 7.343
1965  11.93 11.67 10.9  10.05 9.739 8.902
1966  14.26 14.11 13.42 12.31 12.03 10.89
1967  15.28 15.03 14.55 13.94 13.73 12.43
1968  16.21 16.01 15.68 14.96 14.6  13.49
1969  14.2  14.11 13.88 13.6  13.49 13.27
1970  16.16 15.96 15.55 14.97 14.76 13.83
1971  19.68 19.34 18.34 17.23 16.88 15.6
1972  17.58 17.48 17.15 16.69 16.45 15.9
1973  17.92 17.79 17.52 17.02 16.72 16.02
1974  17.33 17.21 16.82 16.51 16.34 16.09
1975  19.3  19.16 18.77 18.13 17.9  17.05
1976  21.42 21.14 20.69 19.97 19.65 18.18
1977  19.25 19.13 18.74 18.24 18.13 18.01
1978  22.11 21.86 21.34 20.51 20.11 18.78
1979  24.01 23.8  23.12 22.44 22.16 20.85
1980  23.93 23.73 23.27 22.44 22.11 21.06
1981  23.77 23.62 22.89 22.5  22.26 20.88
1982  23.47 23.25 22.66 22.3  22.08 21.13
1983  28.14 27.8  26.56 25.18 24.6  22.81
1984  23.45 23.34 23.22 22.98 22.84 22.48
1985  23.48 23.27 22.61 21.92 21.86 21.6
1986  25.5  25.18 24.34 23.28 22.88 21.48
1987  23    22.83 22.4  21.84 21.71 20.89
1988  20.67 20.58 20.38 20.16 20.08 19.83
1989  23.98 23.71 23.02 22.75 22.43 20.83
1990  24.08 23.84 23.19 22.44 22.02 20.93

Sorted results
Prob. Peak  96 hr 21 Day      60 Day      90 Day      Yearly
0.032258064516129 28.14 27.8  26.56 25.18 24.6  22.81
0.0645161290322581      25.5  25.18 24.34 23.28 22.88 22.48
0.0967741935483871      24.08 23.84 23.27 22.98 22.84 21.6
0.129032258064516 24.01 23.8  23.22 22.75 22.43 21.48
0.161290322580645 23.98 23.73 23.19 22.5  22.26 21.13
0.193548387096774 23.93 23.71 23.12 22.44 22.16 21.06
0.225806451612903 23.77 23.62 23.02 22.44 22.11 20.93
0.258064516129032 23.48 23.34 22.89 22.44 22.08 20.89
0.290322580645161 23.47 23.27 22.66 22.3  22.02 20.88
0.32258064516129  23.45 23.25 22.61 21.92 21.86 20.85
0.354838709677419 23    22.83 22.4  21.84 21.71 20.83
```

```
0.387096774193548 22.11 21.86 21.34 20.51 20.11 19.83
0.419354838709677 21.42 21.14 20.69 20.16 20.08 18.78
0.451612903225806 20.67 20.58 20.38 19.97 19.65 18.18
0.483870967741936 19.68 19.34 18.77 18.24 18.13 18.01
0.516129032258065 19.3  19.16 18.74 18.13 17.9  17.05
0.548387096774194 19.25 19.13 18.34 17.23 16.88 16.09
0.580645161290323 17.92 17.79 17.52 17.02 16.72 16.02
0.612903225806452 17.58 17.48 17.15 16.69 16.45 15.9
0.645161290322581 17.33 17.21 16.82 16.51 16.34 15.6
0.67741935483871  16.21 16.01 15.68 14.97 14.76 13.83
0.709677419354839 16.16 15.96 15.55 14.96 14.6  13.49
0.741935483870968 15.28 15.03 14.55 13.94 13.73 13.27
0.774193548387097 14.26 14.11 13.88 13.6  13.49 12.43
0.806451612903226 14.2  14.11 13.42 12.31 12.03 10.89
0.838709677419355 11.93 11.67 10.9  10.05 9.739 8.902
0.870967741935484 10.27 10.04 9.327 8.701 8.724 7.343
0.903225806451613 7.777 7.539 6.805 6.013 5.735 4.823
0.935483870967742 3.857 3.814 3.539 3.45  3.405 3.227
0.967741935483871 3.633 3.541 3.309 2.904 2.603 1.514

0.1    24.073      23.836      23.265      22.957      22.799
       21.588
                               Average of yearly averages:
       16.0039666666667

Inputs generated by pe5.pl - Novemeber 2006

Data used for this run:
Output File: FLMSCOA
Metfile:    w03940.dvf
PRZM scenario:    MScornSTD.txt
EXAMS environment file: pond298.exv
Chemical Name:    Flubendiamide
Description Variable Name     Value Units Comments
Molecular weight  mwt   682.4 g/mol
Henry's Law Const.      henry 8.9e-11     atm-m^3/mol
Vapor Pressure    vapr  7.5e-7      torr
Solubility  sol   0.4   mg/L
Kd    Kd          mg/L
Koc   Koc   1954.2      mg/L
Photolysis half-life    kdp   11.58 days  Half-life
Aerobic Aquatic Metabolism    kbacw 0     days  Halfife
Anaerobic Aquatic Metabolism  kbacs 1092  days  Halfife
Aerobic Soil Metabolism asm   0     days  Halfife
Hydrolysis: pH 7        days  Half-life
Method:     CAM   2     integer     See PRZM manual
Incorporation Depth:    DEPI  0     cm
Application Rate: TAPP  0.11  kg/ha
Application Efficiency: APPEFF      0.95  fraction
Spray Drift DRFT  0.05  fraction of application rate applied to pond
Application Date  Date  01-05 dd/mm or dd/mmm or dd-mm or dd-mmm
Interval 1  interval    3     days  Set to 0 or delete line for single
app.
app. rate 1 apprate           kg/ha
Interval 2  interval    3     days  Set to 0 or delete line for single
app.
app. rate 2 apprate           kg/ha
```

```
Interval 3  interval    3     days  Set to 0 or delete line for single
app.
app. rate 3 apprate           kg/ha
Record 17:  FILTRA
      IPSCND      1
      UPTKF
Record 18:  PLVKRT
      PLDKRT
      FEXTRC      0.5
Flag for Index Res. Run IR    EPA Pond
Flag for runoff calc.   RUNOFF      none  none, monthly or
total(average of entire run)
```

APPENDIX D. TERR-PLANT Model Runs for Flubendiamide

TerrPlant v. 1.2.2
Green values signify user inputs (Tables 1, 2 and 4).
Input and output guidance is in popups indicated by red arrows.

Table 1. Chemical Identity.	
Chemical Name	flubendiamide
PC code	27602
Use	pome fruit
Application Method	foliar
Application Form	aerial spray
Solubility in Water (ppm)	0.04

Table 2. Input parameters used to derive EECs.			
Input Parameter	**Symbol**	**Value**	**Units**
Application Rate	A	**0.156**	y
Incorporation	I	**1**	none
Runoff Fraction	R	**0.01**	none
Drift Fraction	D	**0.05**	none

Table 3. EECs for flubendiamide. Units in y.		
Description	**Equation**	**EEC**
Runoff to dry areas	(A/I)*R	0.00156
Runoff to semi-aquatic areas	(A/I)*R*10	0.0156
Spray drift	**A*D**	**0.0078**
Total for dry areas	**((A/I)*R)+(A*D)**	**0.00936**
Total for semi-aquatic areas	**((A/I)*R*10)+(A*D)**	**0.0234**

Table 4. Plant survival and growth data used for RQ derivation. Units are in y.				
	Seedling Emergence		**Vegetative Vigor**	
Plant type	**EC25**	**NOAEC**	**EC25**	**NOAEC**
Monocot	**0.158**	**0.158**	**0.158**	**0.158**
Dicot	**0.158**	**0.158**	**0.158**	**0.158**

Table 5. RQ values for plants in dry and semi-aquatic areas exposed to flubendiamide through runoff and/or spray drift.*				
Plant Type	**Listed Status**	**Dry**	**Semi-Aquatic**	**Spray Drift**
Monocot	non-listed	<0.1	0.15	<0.1
Monocot	listed	<0.1	0.15	<0.1
Dicot	non-listed	<0.1	0.15	<0.1
Dicot	listed	<0.1	0.15	<0.1
*If RQ > 1.0, the LOC is exceeded, resulting in potential for risk to that plant group.				

APPENDIX E: T-REX Example Run for Birds and Mammals- Pome Fruit

Upper Bound Kenaga Residues For RQ Calculation		
Chemical Name:	flubendiamide	
Use	pome fruit	
Formulation	0	
Application Rate	0.156	lbs a.i./acre
Half-life	35	days
Application Interval	7	days
Maximum # Apps./Year	3	
Length of Simulation	1	year

Endpoints			
Avian	Bobwhite quail	LD50 (mg/kg-bw)	2000.00
	Mallard duck)	LC50 (mg/kg-diet)	4535.00
	0	NOAEL(mg/kg-bw)	0.00
	Mallard duck	NOAEC (mg/kg-diet)	98.00
Mammals		LD50 (mg/kg-bw)	2000.00
		LC50 (mg/kg-diet)	0.00
		NOAEL (mg/kg-bw)	10.00
		NOAEC (mg/kg-diet)	200.00

Dietary-based EECs (ppm)	Kenaga Values
Short Grass	98.41
Tall Grass	45.10
Broadleaf plants/sm Insects	55.35
Fruits/pods/seeds/lg insects	6.15

Avian Class	Body Weight (g)	Ingestion (Fdry) (g bw/day)	Ingestion (Fwet) (g/day)	% body wgt consumed	FI (kg-diet/day)
Small	20	5	23	114	2.28E-02
Mid	100	13	65	65	6.49E-02
Large	1000	58	291	29	2.91E-01

Avian Body Weight (g)	Adjusted LD50 (mg/kg-bw)
20	1440.86
100	1834.29
1000	2591.00

Dose-based EECs (mg/kg-bw)	Avian Classes and Body Weights		
	small 20 g	mid 100 g	large 1000 g
Short Grass	112.08	63.91	28.61
Tall Grass	51.37	29.29	13.11
Broadleaf plants/sm Insects	63.04	35.95	16.10
Fruits/pods/seeds/lg insects	7.00	3.99	1.79

Dose-based RQs (Dose-based EEC/adjusted LD50)	Avian Acute RQs		
	20 g	100 g	1000 g
Short Grass	0.08	0.03	0.01
Tall Grass	0.04	0.02	0.01
Broadleaf plants/sm insects	0.04	0.02	0.01
Fruits/pods/seeds/lg insects	0.00	0.00	0.00

Dietary-based RQs (Dietary-based EEC/LC50 or NOAEC)	RQs	
	Acute	Chronic
Short Grass	0.02	1.00
Tall Grass	0.01	0.46
Broadleaf plants/sm Insects	0.01	0.56
Fruits/pods/seeds/lg insects	0.00	0.06

Mammalian Class	Body Weight	Ingestion (Fdry) (g bwt/day)	Ingestion (Fwet) (g/day)	% body wgt consumed	FI (kg-diet/day)
Herbivores/ insectivores	15	3	14	95	1.43E-02
	35	5	23	66	2.31E-02
	1000	31	153	15	1.53E-01
Granivores	15	3	3	21	3.18E-03
	35	5	5	15	5.13E-03
	1000	31	34	3	3.40E-02

Mammalian Class	Body Weight	Adjusted LD50	Adjusted NOAEL
Herbivores/ insectivores	15	4395.66	21.98
	35	3556.56	17.78
	1000	1538.32	7.69
Granivores	15	4395.66	21.98
	35	3556.56	17.78
	1000	1538.32	7.69

Dose-Based EECs (mg/kg-bw)	Mammalian Classes and Body weight					
	Herbivores/ insectivores			Granivores		
	15 g	35 g	1000 g	15 g	35 g	1000 g
Short Grass	93.82	64.85	15.03			
Tall Grass	43.00	29.72	6.89			
Broadleaf plants/sm Insects	52.78	36.48	8.46			
Fruits/pods/seeds/lg insects	5.86	4.05	0.94	1.30	0.90	0.21

Dose-based RQs (Dose-based EEC/LD50 or NOAEL)	15 g mammal		35 g mammal		1000 g mammal	
	Acute	Chronic	Acute	Chronic	Acute	Chronic
Short Grass	0.02	4.27	0.02	3.65	0.01	1.95
Tall Grass	0.01	1.96	0.01	1.67	0.00	0.90
Broadleaf plants/sm insects	0.01	2.40	0.01	2.05	0.01	1.10
Fruits/pods/lg insects	0.00	0.27	0.00	0.23	0.00	0.12
Seeds (granivore)	0.00	0.06	0.00	0.05	0.00	0.03

Dietary-based RQs (Dietary-based EEC/LC50 or NOAEC)	Mammal RQs	
	Acute	Chronic
Short Grass	#DIV/0!	0.49
Tall Grass	#DIV/0!	0.23
Broadleaf plants/sm insects	#DIV/0!	0.28
Fruits/pods/seeds/lg insects	#DIV/0!	0.03

APPENDIX F: Ecological Toxicity Tables

Table 1: Acute Toxicity of Flubendiamide to Freshwater Fish							
Species	% a.i.	96-hr LC_{50}, µg/L (confid. int.)	NOAEC (µg/L)	Study Properties[a]	Toxicity Classification	MRID/Acc #, Author, Year	Status
EPA PC Code: 027602- Flubendiamide Technical							
Rainbow trout	97	>65.1	65.1	M, S	Not toxic at limit of solubility	468169-40, Dorgerloh, 2003	Acceptable
Carp	96.7	>84.8	84.8	M, Static Renewal	Not toxic at limit of solubility	468169-41, Yamakazi, 2003	Acceptable
Bluegill sunfish	97	>67.7	67.7	M, S	Not toxic at limit of solubility	468169-39, Dorgerloh, 2003	Acceptable
Fathead Minnow	96.6	>66.5	66.5	M, S	Not toxic at limit of solubility	468169-37, Kern, 2004	Acceptable
Flubendiamide Formulation 480 SC							
Rainbow trout	40	>91.1	91.1	M, S	Not toxic at limit of solubility	468169-43, Dorgerloh, 2003	Acceptable
Bluegill sunfish	40	>80.2	80.2	M, S	Not toxic at limit of solubility	468169-42, Dorgerloh, 2003	Acceptable

[a] M=mean-measured chemical concentrations, N=nominal chemical concentrations; F-T=flow-through; S=static.

Table 2: Acute Toxicity of Flubendiamide to Freshwater Invertebrates							
Species	% a.i.	48-hr EC_{50}, µg/L (confid. int.)	NOAEC (µg/L)	Study Properties[a]	Toxicity Classification	MRID, Author, Year	Status
EPA PC Code: 027602- Flubendiamide Technical							
Daphnia magna	97	>54.8	54.8	M, S	Not toxic at limit of solubility	469189-30, Dorgerloh, 2003	Acceptable
Flubendiamide Formulation – 24 WG							
Daphnia magna	24	1.5 (0.97 – 2.3) Slope = 1.84 +/- 0.255	<1.21 based on sublethal effects	M, S	Very Highly Toxic	468169-32, Dorgerloh, 2005	Acceptable
Flubendiamide Formulation – 480 SC							
Daphnia magna	494.8 g/L	2.6 (2.0 – 3.3) Slope = 2.11	0.45 based on sublethal effects	M, S	Very Highly Toxic	468169-31, Dorgerloh, 2005	Acceptable
Daphnia magna	482.16 g/L	Unfed- 4.3	<1.25	M, S	Very Highly Toxic	468169-34, Dorgerloh, 2005	Supplemental
		10^2 cells/mL- 6.44	1.25				
		10^4 cells/mL- 7.5	<1.25				
		10^6 cells/mL- >12.2	12.2				
Flubendiamide degradate – des-iodo							
Daphnia magna	99.3	> 881	881	M, S	Not toxic at limit of solubility	468169-33 Dorgerloh, 2004	Acceptable

[a] M=mean-measured chemical concentrations, N=nominal chemical concentrations; F-T=flow-through; S=static

Table 3: Acute Toxicity of Flubendiamide to Estuarine/Marine Invertebrates							
Species	% a.i.	96-hr EC_{50}, µg/L (confid. int.)	NOAEC (µg/L)	Study Properties[a]	Toxicity Classification	MRID, Author, Year	Status
EPA PC Code: 027602- Flubendiamide Technical							
Mysidopsis bahia Mysid Shrimp	96.28	>28	28	M, S	Not toxic at limit of solubility	468169-36 Dionne, 2004	Acceptable
EPA PC Code: 027602- Flubendiamide Technical							
Crassostrea virginica Eastern Oyster	97	>49	49	M, S	Not toxic at limit of solubility	468169-35 Dionne, 2004	Acceptable

[a] M=mean-measured chemical concentrations, N=nominal chemical concentrations; F-T=flow-through; S=static

Table 4: Acute Toxicity of Flubendiamide to Estuarine Fish							
Species	% a.i.	96-hr LC_{50} µg/L (confid. int.)	NOAEC (µg/L)	Study Properties[a]	Toxicity Classification	MRID, Author, Year	Status
EPA PC Code: 027602- Flubendiamide Technical							
Sheepshead minnow	97.3	>29.8	29.8	M,S	Not toxic at limit of solubility	468169-38 Banman, 2004	Acceptable

[a] M=mean-measured chemical concentrations, N=nominal chemical concentrations; F-T=flow-through; S=static

Table 5: Chronic (Early-life) Toxicity of Flubendiamide to Fish							
Species	% a.i.	NOAEC (µg/L)	LOAEC (µg/L)	Study Properties[a]	Most sensitive parameter	MRID, Author, Year	Status
EPA PC Code: 027602- Flubendiamide Technical							
Fathead minnow	97.3	60.5	> 60.5	M, F-T	No treatment related effects	468169-47, Kern, 2004	Acceptable

[a] M=mean-measured chemical concentrations, N=nominal chemical concentrations; F-T=flow-through; S=static.

Table 6: Chronic (Full Life Cycle) Toxicity of Flubendiamide to Fish							
Species	% a.i.	NOAEC (µg/L)	LOAEC (µg/L)	Study Properties[a]	Most sensitive parameter	MRID, Author, Year	Status
EPA PC Code: 027602- Flubendiamide Technical							
Fathead minnow	97.1	<4.3	4.3	M, F-T	Growth (length and weight)	468169-48, Kern, 2004	Unacceptable (Significant reproductive effects in solvent control compared to neg. control)

[a] M=mean-measured chemical concentrations, N=nominal chemical concentrations; F-T=flow-through; S=static.

Table 7: Chronic (Life-cycle) Toxicity of Flubendiamide to Aquatic Invertebrates							
Species	% ai	NOAEC (µg a.i./L)	LOAEC (µg ai/L)	Study Properties[a]	Most sensitive parameter	MRID, Author, Year	Status
EPA PC Code: 122101 - Flubendiamide Technical							
Daphnia magna	97	41.1	68.5	M, Static Renewal	Number of eggs aborted, number of dead neonate	468169-44, Dorgerloh 2003	Supplemental, uncertainties regarding analytical stability
Mysid-opsis bahia	98.1	> 20	>20	M, F-T	No treatment effects	468169-46. Putt, 2005	Acceptable
Flubendiamide Formulation 480 SC							
Daphnia magna	494.8 g ai/L	0.38	1.18	M, Static Renewal	Parental mortality, sublethal effects, time to first brood	468169-45, Dorgerloh 2003	Acceptable

[a] M=mean-measured chemical concentrations, N=nominal chemical concentrations; F-T=flow-through; S=static

Table 8: Acute Toxicity of Flubendiamide to Aquatic Plants							
Species	%a.i.	EC_{50} (µg ai/L)	NOAEC /EC_{05} (µg/L) a.i.	Most sensitive parameter	Initial/mean measured concentrations	MRID, Author, Year	Status
EPA PC Code: 027602- Flubendiamide Technical							
Vascular Plant Duckweed (*Lemna gibba*) Tier II	96.6	7-day test > 54.6	54.6	Frond number	mean	468170-39 Kern, 2004	Acceptable
Non-Vascular Plant Green algae (*Selenastrum capricornutum*) Tier I	96.7	96-hr test >69.3 (2% inhibition)	69.3	Cell density, growth rate, area under the growth curve	mean	468170-41 Yamazaki, 2003	Acceptable
Flubendiamide Formulation 480 SC							
Non-Vascular Plant Green algae (*Pseudokirchneriella subcapitata*) Tier II	489.54 g/L	72- hour test > 50,500	50,500	Cell density, growth rate	mean	468170-40 Dorgerloh, 2005	Acceptable OECD 3-day studies accepted for review as Tier I screen only

Table 8: Acute Toxicity of Flubendiamide to Benthic Organisms						
Species	%a.i.	EC_{50} (µg ai/L)	NOAEC/ (µg/L) a.i.	Most sensitive parameter	MRID, Author, Year	Status
EPA PC Code: 027602- Flubendiamide Technical						
Chironomid (*Chironomus riparius*)	97.4	28-day test	NOAEC= 40 µg a.i./L (nominal) LOAEC= 80 µg a.i./L (nominal, 69 µg a.i./L 1-hr initial water column measured)	Percent emergence	468170-22 Dorgerloh, 2003	Supplemental Sediment not analyzed for a.i. Emergence success sign. Lower in solvent control
Flubendiamide Formulation 24 WG						
Chironomid (*Chironomus riparius*)	24	48- hr test 130 (95- 178) Slope = 2.05	36	Mortality	468170-14 Dorgerloh, 2005	Acceptable
Flubendiamide Formulation 480 SC						
Chironomid (*Chironomus riparius*)	24	48- hr test 1650 (1180- 2310) Slope = 1.64	380	Mortality	468170-13 Dorgerloh, 2005	Acceptable
Flubendiamide Degradate, des-iodo						
Chironomid (*Chironomus riparius*)	99.3% des-iodo	28-day test	NOAEC= 3.2 µg a.i./L (initial measured) LOAEC= 8.0 µg a.i./L (nominal)	Reduction in percent emergence and male and female development rates	468170-23	Supplemental

Table 9: Mesocosm Study						
Species	%a.i.	LC_{50}, (µg ai/L)	NOAEC/ EC_{05} (µg/L) a.i.	Most sensitive parameter	MRID, Author, Year	Status
Flubendiamide Formulation 480 SC						
Zooplankton, phytoplankton, benthos,	478.5 g/L	Not determined Concentration tested 0.4, 1.0, 2.3, 5.3 ppb (two ponds per level) 12 ppb – one pond per level		Daphnia was the most sensitive species	468170-02 Heimbach *et al* 2006	Supplemental (nsufficient number of replicate ponds were tested for each level, finfish not included)

Table 10: Acute Toxicity to Flubendiamide to Birds (oral administration)							
Species	Purity	LD_{50}, mg/kg-bw (conf. interval)	NOAEL, mg/kg-bw	Effects	Toxicity Classification (based on a.i.)	MRID, Author, Year	Status
EPA PC Code: 027602- Flubendiamide Technical							
Bobwhite quail	97%	>2000	2000	One mortality in 250 mg/kg group	Slightly toxic	468170-03 Barfknecht 2004	Acceptable
Flubendiamide Formulation 480 SC							
Bobwhite quail	489.54 g/L	> 2000	1000	Enlarged gall bladder, whitish pancreas, no mortality	Practically non-toxic	468170-04 Barfknecht 2004	Acceptable

Table 11: Acute Toxicity to Flubendiamide to Birds (dietary administration)							
Species	% a.i.	LC_{50}, mg/kg-diet	NOAEC, mg/kg-diet	Effects	Toxicity Classification	MRID, Author, Year	Status
EPA PC Code: 027602- Flubendiamide Technical							
Bobwhite quail	97	>5199	5199	No treatment effects	Practically non-toxic	468170-06 Barfknecht, 2003	Acceptable
Mallard duck	96.62	>4535	4535	No treatment effects	Practically non-toxic	468170-05 Bowers, 2005	Acceptable

Table 12: Avian Developmental and Chronic Toxicity to Flubendiamide						
Test Type	% a.i.	NOAEC (mg ai/kg-diet)	LOAEC (mg ai/kg-diet)	Effects	MRID #, Author, Year	Status
EPA PC Code: 027602- Flubendiamide Technical						
One-generation reproductive Mallard duck	97.3	98	298	The ratio of viable embryos to eggs set was significantly reduced (6%) from control at the lowest treatment level, dose-dependent response for hatchling survival of number hatched. Percent reductions in this endpoint were slight (1, 3, and 7%, respectively) with increasing test levels, but did follow a dose-dependent pattern. Survivor weights were adversely affected at the 289 mg ai/kg diet level and numerous reproductive parameters, including eggs set of eggs laid, viable embryos, live embryos, hatchling survivors, and egg shell quality (strength and thickness) were adversely affected at the 960 mg ai/kg diet level.	468170-07, Sabbert, 2006	Supplemental (statistically significant effects observed at the lowest test level)
One-generation reproductive - Bobwhite quail	97	1059	>1059	No treatment related effects were observed at any test level	468170-08, Bowers, 2005	Acceptable

Table 13: Mammalian Acute Oral Toxicity to Flubendiamide					
Species	% a.i.	LD_{50} (mg a.i./kg-bw)	Toxicity Classification	MRID #, Author, Year	Status[a]
EPA PC Code: 027602- Flubendiamide Technical					
laboratory mouse	N/A	>2000 Combined sexes	Practically non-toxic	468171-42	Acceptable
laboratory rat *(Rattus norvegicus)*	N/A	>5000 Combined sexes	Practically non-toxic	468171-43	Acceptable

N/A: Not Available

Table 14: Mammalian Developmental and Chronic Toxicity to Flubendiamide						
Test Type	% a.i.	NOAEL (mg ai/kg-diet)	LOAEL (mg ai/kg-diet)	Effects	MRID #	Status[a]
EPA PC Code: 027602- Flubendiamide Technical						
2-generation reproduction study (rats)	N/A	Parental 50	2000	Effects on liver, thyroid, and kidneys	468172-16	Acceptable
		Offspring 50	2000	Effects on liver and thyroid		
		Reproduction 20,000	>20,000	No reproductive effects observed		
		Eye Effect 50	2000	Eyeball enlargement and liver hypertrophy		
1-generation reproduction study (rats)	N/A	200 ppm – parental	2000 ppm	Effects on liver, thyroid, and kidneys At 20,000 ppm, F1 pup body weights were decreased by an estimated 9% in both sexes compared to controls on PND 21. Absolute and relative (to body weight) anogenital distances were increased by in the ≥2000 ppm male pups on PND 4. These parameters were comparable to controls in the treated females. Sexual maturation was significantly delayed in both sexes.	468172-39	Supplemental
		200 ppm – offspring	2000 ppm	At ≥2000 ppm, absolute and relative liver weights were increased ($p \leq 0.001$) in both males and females. At necropsy, incidences of dark-colored livers were increased at ≥2000 ppm (25.7-42.8%) compared to 0 controls.		
		20,000 ppm - reproductive	>20,000 ppm	no evidence of any-treatment-related effects or signs of reproductive impairment in males or females		
		Eye Effect 200	2000	Microscopic effects on the eyes		

N/A: Not Available

[a] Status (acceptability) based on HEDs guidelines.

Table 15: Toxicity of Flubendiamide to Terrestrial Plants (Seedling Emergence - Tier 1)						
Species	% a.i.	EC_{25}, (lbs ai/acre)	$NOAEC/EC_{05}$ (lbs ai/acre)	Most sensitive parameter, % Inhibition	MRID, Author, Year	Status
Flubendiamide Formulation 24 WG						
Monocots:	24%				468170-34 Nguyen, 2005	Acceptable
Oat		>0.158	0.158	N/A		
Corn		>0.158	0.158	N/A		
Dicots:						
Soybean		>0.158	0.158	N/A		
Oilseed rape		>0.158	0.158	N/A		
Cucumber		>0.158	0.158	Survival- 19%		
Sunflower		<0.158	<0.158	Percent Emergence- 33%		
Flubendiamide Formulation 480 SC						
Monocots:						
Oat	40.5%	>0.393	0.393	N/A	468170-36(a) Nguyen, 2005	Acceptable
Corn		>0.393	0.393	N/A		
Ryegrass		>0.393	0.393	N/A		
Dicots:						
Soybean		>0.393	0.393	N/A		
Cabbage		>0.393	0.393	Dry Weight, 14%		
Cucumber		>0.393	0.393	Dry Weight, 14%		
Tomato		>0.393	0.393	N/A		
Lettuce		>0.393	0.393	N/A		
Turnip		>0.393	0.393	N/A		

Table 16: Toxicity of Flubendiamide to Terrestrial Plants Vegetative Vigor - Tier 1						
Species	% a.i.	EC_{25}, (lbs ai/acre)	NOAEC/EC_{05} (lbs ai/acre)	Most sensitive parameter % Inhibition	MRID, Author, Year	Status
Flubendiamide Formulation 24 WG						
Monocots	24				468170-37 Nguyen, 2005	Supplemental (non-GLP lab, low number of reps)
Onion, corn, oat		>0.158	0.158	N/A		
Dicots						
Soybean		>0.158	<0.158	Dry Weight, 22%		
Oilseed rape, lettuce, cucumber, sunflower		>0.158	0.158	N/A		
Flubendiamide Formulation 480 SC						
Monocots					468170-36(b) Christ, 2005	Acceptable
Onion, corn, oat, ryegrass		>4.26	4.26	N/A		
Dicots						
Cabbage, cucumber, lettuce soybean, tomato, turnip		>4.26	4.26	N/A		

Table 17: Toxicity of Flubendiamide to Terrestrial Plants (Seedling Emergence - Tier 2)						
Species	% a.i.	EC_{25}, (lbs ai/acre)	NOAEC/EC_{05} (lbs ai/acre)	Most sensitive parameter	MRID, Author, Year	Status
Flubendiamide Formulation WG24						
Dicot: Sunflower	23.33	>0.16	0.16	n/a	468170-38 Christ 2006	Acceptable

Measured application rates tested – 0, 0.0098, 0.017, 0.037, 0.0881, and 0.16 lb a.i./A

Table 18: Herbicidal Toxicity of Flubendiamide to Terrestrial Plants (Seedling Emergence - Tier 2)					
Species	% a.i.	Pre-Emergence Treatment 21-day	Post Emergence Treatment 17-day	MRID, Author, Year	Status
Flubendiamide Formulation 480 SC					
5 monocots	494.8 g/L	No phytotoxic effects up to 0.22 lb ai.A	No phytotoxic effects up to 0.22 lb ai.A	468170-35 Lechelt-Kunze 2002	Supplemental (non-guideline)
6 dicots					

Table 19: Acute Toxicity of Flubendiamide to Earthworms						
Species	% a.i.	LC_{50}	NOAEC	Most sensitive parameter	MRID, Author, Year	Status
EPA PC Code: 027602- Flubendiamide Technical						
Earthworm (*Eisenia fetida*) 14-day test	97%	> 1000 mg a.i./kg	> 1000 mg a.i./kg	No effects on mortality or percent weight change	468170-28, Lechelt Kunze, 2002	Supplemental (non-guideline)
Flubendiamide Formulation 480 SC						
Earthworm (*Eisenia fetida*) 14-day test	480 g/L	> 1000 mg a.i./kg	> 1000 mg a.i./kg	No effects on mortality or percent weight change	468170-29, Lechelt Kunze, 2004	Supplemental (non-guideline)
Flubendiamide Degradate, des-iodo						
Earthworm (*Eisenia fetida*) 14-day test	99.3%	> 1000 mg a.i./kg	> 1000 mg a.i./kg	No effects on mortality or percent weight change	468170-30, Lechelt Kunze, 2004	Supplemental (non-guideline)

Table 20: Chronic Toxicity of Flubendiamide to Earthworms and Collembola species.						
Species	% a.i.	EC_{25}, (lbs ai/acre)	$NOAEC/EC_{05}$ (lbs ai/acre)	Most sensitive parameter	MRID, Author, Year	Status
Flubendiamide Formulation 480 SC						
Earthworm (*Eisenia fetida*) 28-day test	494.8 g/L	> 1000 mg a.i./kg	> 1000 mg a.i./kg	No effects on mortality or percent weight change	468170-31, Luhrs, 2002	Supplemental (significant guideline deviations)
White springtail soil arthropod (*Folsomia candida*)	482.16 g/L	--	NOAEC = 31.6 mg a.s./kg (dw) LOAEC= 31.6 mg a.s./kg (dw)	Number of juveniles produced	468170-27 Frommholz, 2005	Supplemental
Flubendiamide Formulation 24 WG						
Earthworm (*Eisenia fetida*) 28-day test	494.8 g/L	> 1000 mg a.i./kg	562 mg a.i./kg	No effects on mortality or body weight, Significant reduction of number of juveniles produced	468170-32, Lechelt Kunze, 2005	Supplemental

Table 21: Acute Toxicity of Flubendiamide to Bees						
Species	% a.i.	EC_{25}	$NOAEC/EC_{05}$	Most sensitive parameter	MRID, Author, Year	Status
EPA PC Code: 027602- Flubendiamide Technical						
Acute Contact 48-hrs Honey bee (*Apis mellifera*)	97%	> 200 µg ai/bee	200 µg ai/bee	Mortality, same results for oral and contact tests	468170-09, Barth, 2002	Acceptable
Flubendiamide Formulation 480 SC						
Acute Contact 48-hrs Honey bee (*Apis mellifera*)	480 g/L	> 200 µg ai/bee	200 µg ai/bee	Mortality, same results for oral and contact tests	468170-10, Barth, 2002	Acceptable

Table 21: Acute Toxicity of Flubendiamide to Bees						
Species	% a.i.	EC_{25}	NOAEC/EC_{05}	Most sensitive parameter	MRID, Author, Year	Status
Side Effects 15-days Honey bee (*Apis mellifera*)	39.2%	Not determined, some brood development effects at 0.16 lb ai./A but showed recovery		No adverse effects on mortality, flight intensity, and behavior	468170-11, Schur, 2006	Acceptable
Flubendiamide Formulation WG24						
Bumblebee (*Bombus terrestris*) 27 day test Greenhouse test	24%	Not determined		No adverse effects on pollination activity, flight frequency, or final hive evaluation data	468170-12, Nguyen, 2005	Supplemental Non-guideline

Table 22: Acute Toxicity of Flubendiamide to Non-target Arthropods						
Species	% a.i.	LD_{50}	NOAEC	Most sensitive parameter	MRID, Author, Year	Status
Flubendiamide Formulation WG24						
Parasitoid Wasp (*Aphidius rhopalosiphi*) 15-day test	24.2 %	> 0.55 lb a.i./A	0.17 lb a.i./A	Survival and reproduction were adversely affected	468170-20, Waltersdorfer, 2005	Supplemental non-guideline
Predatory mite (*Typhlodromas pyri*) 14-day test	485.9 g/L	> 0.55 lb a.i./A	0.31 lb ai/A	Mortality (14%), Reproduction (24%)	468170-19, Waltersdorfer, 2005	Supplemental non-guideline
Flubendiamide Formulation 480 SC						
45-day test Ladybird beetle (*Coccinella septempunctata*) Coleoptera	485.9 g/L	LD50= 0.089 lb a.i./A	0.04 lb a.i./A	Adult survival, no effect on larval survival or reproduction	468170-15, Waltersdorfer, 2004	Supplemental non-guideline
Extended laboratory study aged residue test Ladybird beetle (*Coccinella septempunctata*)	482.2 g/L	LD50 > 0.17 lb a.i./A	0.17 lb a.i./A	No reduction of survival or reproduction	468170-16, Moll, 2005	Supplemental non-guideline
Life cycle Test 47 days Ladybird beetle (*Coccinella septempunctata*)	494.8 g/L	LD50 = 0.41 lb a.i./A	0.24 lb a.i./A	Larval survival	468170-17, Maus, 2002	Supplemental non-guideline
Rate-response test 14-days Parasitic wasp (*Aphidius rhopalosiphi*) Side Effects Test	494.8 g/L	Test 1: LD50 = 0.423 lb a.i./A	< 0.2 lb a.i./A	Survival	468170-21 Fussell, 2002	Supplemental non-guideline
		Test 2: LD50 > 0.6 lb a.i./A	0.39 lb a.i./A			
Green lacewing (*Chrysoperla carnea*)	478.5 3 g/L	LD50 > 0.16 lb a.i./A	--	Measured mortality and reproduction	468170-18 Waltersdorfer, 2004	Supplemental

APPENDIX G: ECOTOX Papers

Acceptable for ECOTOX and OPP

1. Dhawan, A.K., Singh,K., Singh R., and Kumar, T. (2006). Field Evaluation of Flubendiamide (NNI 0001 480 SC) Against Bollworms Complex on Upland Cotton. J. *Cotton Res.Dev.* 20:232-235.

   EcoReference No.: 92630
   Chemical of Concern: FDB,ES; Habitat: T; Effect Codes: POP; Rejection Code: LITE EVAL CODED(FBD).

2. Narayana, S.L. and Rajasri, M. (2006). Flubendiamide 20 WDG (RIL-038) – a new Molecule for the Management of the American Bollworm Helicoverpa armigera on Cottor. *Pestology* 30: 16-18

   EcoReference No.: 92813
   Chemical of Concern: SS,IDC,FBD; Habitat: T; Effect Codes: POP,GRO; Rejection Code: LITE EVAL CODED(FBD).

3. Tomar, S.P.S, Choudhary, R.K., and Shrivastava, V.K (2005). Evaluation of Bioefficacy of Flubendiamide 20 WDG (Ril 038) Against Bollworms on Cotton. J. *Cotton Res.Dev.* 19: 231-233.

   EcoReference No.: 92816
   Chemical of Concern: LCYT,SS,IDC,FBD; Habitat: T; Effect Codes: POP;GRO Rejection Code: LITE EVAL CODED(FBD).

Acceptable for ECOTOX, but not OPP

1. Tohnishi, M., Nakao, H. Furuya, T., Seo, A., Kodama, H., Tsubata, K., Fujioka,S., A., Kodama, H., Hirooka, T., and Nishimatsu, T. (2005). Flubendiamide, a Novel Insecticide Highly Active Against Lepidopterous Insect Pests. *J.Pesitic.Sci.* 30:354-360.

   EcoReference No.: 92541
   Chemical of Concern: FBD,MOM,CYH,EMMBCFP; Habitat: T; Effect Codes: PHY,MOR; Rejection Code: NO ENDPOINT(FBD,MOM).

FLUBENDIAMIDE
Papers that Were Excluded from ECOTOX

1. Ebbinghaus-Kintscher, Ulrich, Luemmen, Peter, Lobitz, Nicole, Schulte, Thomas, Funke, Christian, Fischer, Rudiger, Masaki, Takao, Yasokawa, Noriaki, and Tohnishi, Masanori (2006). Phthalic acid diamides activate ryanodine-sensitive Ca2+ release channels in insects. *Cell Calcium* 39: 21-33.

   Chemical of Concern: FBD; Habitat: T

2. Javaregowda and Naik, L. K. (2005). Bio-efficacy of Flubendiamide 20 WDG (RIL-038) Against Paddy Pests and Their Natural Enemies. *Pestology* 29: 58-60.

   Chemical of Concern: FBD; Habitat: T; Rejection Code: NO SOURCE(FBD).

3. Luemmen, Peter, Ebbinghaus-Kintscher, Ulrich, Funke, Christian, Fischer, Ruediger, Masaki, Takao, Yasokawa, Noriaki, and Tohnishi, Masanori (2007). Phthalic acid diamides activate insect ryanodine receptors. *ACS Symposium Series, Synthesis and Chemistry of Agrochemicals VII* 948: 235-248.

   Chemical of Concern: FBD; Habitat: T

4. Lummen, Peter. Ebbinghaus-Kintscher, Ulrich, Lobitz, Nicole, Schulte, Thomas, Funke, Christian, and Fischer, Rudiger (2005). Phthalic acid diamides activate ryanodine-sensitive calcium release channels in insects. *Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005* AGRO-025.

   Chemical of Concern: FBD; Habitat: T

5. Masaki, T., Yasokawa, N., Tohnishi, M., Nishimatsu, T., Tsubata, K., Inoue, K., Motoba, K., and Hirooka, T. (2006). Flubendiamide, a Novel Ca2+ Channel Modulator, Reveals Evidence for Functional Cooperation Between Ca2+ Pumps and Ca2+ Release. *Mol.Pharmacol.* 69: 1733-1739.

   Chemical of Concern: FBD; Habitat: T; Rejection Code: NO IN VITRO(FBD).

6. Masaki, Takao, Yasokawa, Noriaki, Tohnishi, Masanori, Nishimatsu, Tetsuyoshi, Tsubata, Kenji, Inoue, Kazuyoshi, Motoba, Kazuhiko, and Hirooka, Takashi (2006). Flubendiamide, a novel Ca2+ channel modulator, reveals evidence for functional cooperation between Ca2+ pumps and Ca2+ release. *Molecular Pharmacology* 69: 1733-1739.

   Chemical of Concern: FBD; Habitat: T

7. Nauen, R. (2006). Insecticide Mode of Action: Return of the Ryanodine Receptor. *Pest Manag.Sci.* 62: 690-692.

   Chemical of Concern: FBD; Habitat: T; Rejection Code: NO REVIEW(FBD).

8. Nishimatsu, T., Hirooka, T., Kodama, H., Tohnishi, M., and Seo, A (2005). Flubendiamide - a new insecticide for controlling lepidopterous pests. *BCPC International Congress: Crop Science & Technology, Congress Proceedings, Glasgow, United Kingdom, Oct. 31-Nov. 2, 2005* 1: 57-64.

   Chemical of Concern: FBD; Habitat: T

9. Tohnishi, Masanori, Nakao, Hayami, Furuya, Takashi, Seo, Akira, Kodama, Hiroki, Tsubata, Kenji, Fujioka, Shinsuke, Kodama, Hiroshi, Hirooka, Takashi, and Nishimatsu, Tetsuyoshi (2005). Novel class insecticide, flubendiamide: Synthesis and biological activity. *Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005* AGRO-009.

Chemical of Concern: FBD; Habitat: T

APPENDIX H: Environmental Fate and Transport DER Summaries

Hydrolysis

[^{14}C]Flubendiamide was stable at pH 4, 5 and 7; half-lives were not calculated. Overall recoveries of [^{14}C] residues averaged 99.4 ± 2.0% of the applied (range 95.6-102.9%) from the pH 4 buffer solution, 99.6 ± 2.9% (range 95.5-106.3%) from the pH 5 buffer solution, 98.7 ± 2.3% of the applied (range 93.1-103.6%) from the pH 7 buffer solution and 99.6 ± 1.6% (range 97.7-102.5%) from the pH 9 buffer solution. There was no pattern of loss of material over time from any of the buffer solutions.

This study was conducted in accordance with JMAFF Test Guidelines for supporting registration of chemical pesticides (12 Nousan No. 8147; November 2000), OECD Guidelines for the testing of chemicals "111, Hydrolysis as function of pH" (1981), EU European Communities Directive 91/414/EEC (1991) as amended by directive 94/37/EC (1994) and EPA Pesticide Assessment Guidelines, Subdivision N, Chemistry: Environmental Fate, Section 161-1 (1982; p. 13). No significant deviations from the objectives of subdivision N guidelines were noted (MRID 46816907).

Photodegradation in Water

Based on a first-order linear regression analysis [^{14}C] flubendiamide (combined radiolabels) degraded with a half-lives of 5.79, 4,20, and 6.44 days in distilled water, natural water, and distilled water containing 1% acetone, respectively. Because flubendiamide was stable in dark controls, the actual **phototransformation half-lives** were doubled to the half-lives observed of the continuously irradiated samples to be based on a 12 hour light/dark cycle. The **phototransformation half-lives** of [^{14}]C flubendiamide (combined radiolabels) are 11.58, 8.40, and 12.88 days based on a 12 hour light/dark cycle in distilled water, natural water, and distilled water containing 1% acetone respectively. The **phototransformation half-lives** of [phthalic-U-^{14}C]flubendiamide are 7.0, 4.2 and 5.9 days based on the continuous irradiation used in the study, or 14.0, 8.4 and 11.8 days based on a 12-hour light/12-hour dark cycle in distilled water, natural water and distilled water containing 1% acetone, respectively. The **phototransformation half-lives** of [aniline-U-^{14}C]flubendiamide are 4.9 and 7.1 based on the continuous irradiation used in the study, or 9.8 and 14.2 days based on a 12-hour light/12-hour dark cycle in distilled water and distilled water containing 1% acetone, respectively (MRID 46816908).

Photodegradation on Soil

Based on first-order linear regression analysis [^{14}C]flubendiamide (combined radiolabels), flubendiamide degraded with a half-life of 11.25 days in the irradiated samples. Since flubendiamide was stable in the dark controls, the phototransformation half-life is equivalent to the half-life observed in the irradiated samples. The phototransformation half-lives of [phthalic-U-^{14}C] and [aniline-U-^{14}C]flubendiamide are 11.49 days and 11.04 days, respectively, based on the continuous irradiation used in the study, or 22.98 days and 22.08 days based on a 12-hour light/12-hour dark cycle, respectively. Based on solar intensity representative of average conditions in the 48 contiguous states in the United States for all seasons, 1 day of artificial light was reported to be equivalent to 3.07 solar days. Therefore, the predicted environmental photolytic half-lives for [phthalic-U-^{14}C] and [aniline-U-^{14}C]flubendiamide were 35.3 and 33.9 days, respectively (MRID 46816909).

Aerobic Soil Metabolism

No major transformation products were isolated from any soils [^{14}C]Flubendiamide was relatively stable in the treated soils, decreasing by <3% of the applied in the sandy loam, silt loam, silt, and [aniline ring -^{14}C]flubendiamide-treated loamy sand soil during 120 days of incubation. In the [phthalic ring-^{14}C]flubendiamide-treated loamy sand soil, [^{14}C]flubendiamide averaged 87.7% of the applied at time 0, 82.6% at 120 days posttreatment, and 83.4% at 371 days, a decrease of 4.3% over the course of the experiment. In all soils, the measured concentrations were variable over time. Reviewer-calculated first-order linear half-lives were >5 years and are of uncertain value since they are extrapolated well beyond the duration of the study and assume that the pattern of degradation remains linear, and because the r^2 values are very low (MRID 46816910).

No major transformation products were isolated from any soils. Four minor transformation products were identified: •

- Des-iodo [A-1; N^2-(1,1-dimethyl-2-methylsulfonylethyl)-N^1-{2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoro-methyl)ethyl]phenyl} phthalamide],
- NNI-0001-3-OH [A-2; N^2-(1,1-dimethyl-2-methylsulfonylethyl)-3-hydroxy-N^1-{2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl] phenyl}phthalamide],
- NNI-0001-benzoic acid [A-18; 2-[[2-{[(1,1-dimethyl-2-methylsulfonylethyl)amino]carbonyl}-3-iodophenyl)carbonyl]amino}-5-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl] benzonic acid], and
- Des-iodo-alkylphthalimide[A-27; N-(1,1-dimethyl-2-methylsulfonylethyl)phthalimide].

In the <u>sandy loam soil</u> (120-day experiment), A-1 and A-18 averaged maximums of 2.7% and 0.9% of the applied. In addition, a discrete area of radioactivity (ROI 1) averaged a maximum of 0.8% of the applied; this region did not correspond to any reference standards and was not analyzed further. Unidentified [^{14}C]residues averaged a maximum of 3.6% of the applied. In the <u>silt loam soil</u> (120-day experiment), A-1 and A-18 averaged maximums of 1.5% and 0.7% of the applied. The unknown ROI 1 averaged a maximum of 1.1% of the applied, and unidentified [^{14}C]residues averaged 3.5%. In the <u>silt soil</u> (120-day experiment), A-1 and A-18 averaged maximums of 7.2% and 1.6% of the applied. The unknown ROI 1 averaged a maximum of 0.6% of the applied, and unidentified [^{14}C] residues averaged 3.6%.

In the <u>loamy sand soil treated with [phthalic acid ring-UL-^{14}C]flubendiamide</u> (371-day experiment), A-1, A-2, A-18, and A-27 and A-18 each averaged maximums of ≤1.8% of the applied. The unknown ROI 1 averaged a maximum of 1.8% of the applied, and unidentified [^{14}C]residues averaged 2.8%. In the loamy sand soil treated with [aniline ring-UL-^{14}C]flubendiamide (120-day experiment), A-1 and A-2 averaged maximums of 1.7% and 0.8% of the applied. The unknown ROI 1 averaged a maximum of 1.0% of the applied, and unidentified [^{14}C]residues averaged 4.4%.

Concentrations of extractable and nonextractable [^{14}C]residues varied over time in the four soils, with no clear pattern of either decline or formation. Extractable [^{14}C]residues ranged from 84.4-96.5% of the applied, and nonextractable [^{14}C]residues ranged from 3.5-7.1%. The duration of the experiment (120 vs 371 days) did not affect the minimum and maximum observed concentrations of extractable and nonextractable residues. In the four soils at study termination, $^{14}CO_2$ totaled ≤0.4% of the applied and volatile [^{14}C] organics were <0.1%.

The study author provided a transformation pathway for flubendiamide. Flubendiamide is ultimately degraded to CO_2 and bound residues via three pathways. Flubendiamide degrades to Des-iodo (A-1), which is further degraded to Des-iodo-alkylphtalimide (A-27) by loss of the aniline ring. Flubendiamide degrades to NNI-0001-benzylalcohol (A-16; a postulated intermediate not detected in this study), which is further degraded to NNI-0001-benzoic acid (A-18) as the aniline methyl ortho-substituent is oxidized. Flubendiamide degrades to NNI-0001-3-OH (A-2) with the replacement of the iodine atom with a hydroxyl substituent.

Anaerobic Soil Metabolism

Flubendiamide was primarily stable under the conditions of this study, with some gradual formation of bound soil residues. Regression half-lives were not calculated due to lack of flubendiamide degradation. No major nonvolatile transformation products were detected and no consistent formation of any minor nonvolatile products was apparent. Total unidentified [^{14}C]residues were ≤5.1% of the applied at any interval. At study termination, extractable soil plus water layer [^{14}C]residues comprised 82.2-91.6% of the applied, while nonextractable [^{14}C]residues totaled 11.7-12.2%. Formation of $^{14}CO_2$ and volatile [^{14}C]organic compounds was not significant totaling ≤0.3% of the applied at any sampling interval.

For both labels, overall recovery of material balance averaged 97.3 ± 4.5% (range 86.6-103.6%) of the applied, with no consistent pattern of decline in recoveries for either label. Low recoveries of 86.6-87.8% of the applied at 56-days post-flooding appear to have been due to procedural errors, with recoveries at all other sampling intervals ≥93.9%. Partitioning of [^{14}C] residues between the soil and water layer could not be determined because water layers were combined with the soil extracts prior to analysis. There was no apparent degradation of flubendiamide during the 120-day post-flood incubation; however, any possible dissipation of flubendiamide from the treated soil to the water layer could not be assessed.

The study was considered supplemental because the soil extracts were combined with the water layers prior to LSC and TLC analysis. Therefore, the possible movement of flubendiamide from the soil layer into the water was not addressed (MRID 46816912).

Anaerobic Aquatic Metabolism

Given the rapid partitioning of parent flubendiamide from the water phase to the sediment, the day 0 water results were assigned the interval of 2 hours post treatment (sample processing time) for the purposes of determining a secondary dissipation half-life (*i.e.*, regression analysis intervals 2 hours to 365 days) of flubendiamide in the water layer, with the initial dissipation half-life then an observed DT_{50} of <2 hours.

Observed DT50 values of flubendiamide were 2 hours in the water layer, ca. ≥ 365 days in the sediment and 269-365 days in the total system. In the water, sediment and total system, calculated linear half-lives (r2 = 0.8293-0.9743) were 127 (secondary dissipation), 364 and 292 days, respectively, with nonlinear half-lives (r^2 = 0.8489-0.9775) of 57 (secondary dissipation), 385 and 289 days, respectively. One major transformation product,

- N-[1,1-dimethyl-2-(methylsulfonyl)ethyl]-N'-[2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl]-1,2-benzenedicarboxamide (desiodo-NNI-0001);

averaged maximums of 22.0%, 36.9% and 58.8% of the applied in the water, sediment and total system, respectively, at study termination. No minor products were detected (MRID 46816914).

Aerobic Aquatic Metabolism

Calculated dissipation half-lives for flubendiamide in the both sediments and the total sand system were not determined due to variable data and insufficient degradation; the linear half-life for flubendiamide in the total pond water-loam system was 533 days (r^2 = 0.8389). For both systems, observed DT50 values were *ca.* 2 hours-3 days in the water layers and >125 days in the sediments and total systems. No major transformation products were detected (MRID 4681913).

Mobility Studies

Leaching Adsorption/Desorption

After 24 hours of equilibration, 45.1-48.0%, 41.9-47.5%, 50.6-57.0%, 33.9-39.9%, and 54.0-59.6% of the applied [^{14}C]flubendiamide was adsorbed to the Hoefchen silt, Laacher Hof AXXa sandy loam, Stanley silty clay, Ephrata loamy sand, and Saskatoon loam soils, respectively. Registrant-calculated Freundlich adsorption K values were 18.3, 23.5, 30.0, 17.3, and 24.8 for the Hoefchen silt, Laacher Hof AXXa sandy loam, Stanley silty clay, Ephrata loamy sand, and Saskatoon loam soils, respectively; corresponding Freundlich

K_{oc} values were 1172, 1596, 2609, 3318, and 1076. Registrant-calculated adsorption K and K_{oc} values were not reported. At the end of the first desorption step (three desorption steps for high dose; one desorption step for all other doses), 45.6-53.0%, 44.7-66.3%, 40.1-46.5%, 51.6-72.2%, and 39.2-42.8% of the applied [^{14}C]flubendiamide desorbed from the Hoefchen silt, Laacher Hof AXXa sandy loam, Stanley silty clay, Ephrata loamy sand, and Saskatoon loam soils, respectively. Following the third desorption step (high dose soils only), the percent of [^{14}C]flubendiamide desorbed from the test soils, as percent of the radioactivity adsorbed, was 32.5% for the Hoefchen silt, 38.6% for the Laacher Hof AXXa sandy loam, 34.7% for the Stanley silty clay, 33.3% for the Ephrata loamy sand, and 31.7% for the Saskatoon loam soils. Registrant-calculated Freundlich desorption K values were 44.3, 76.1, 51.8, 68.4, and 47.4 for the Hoefchen silt, Laacher Hof AXXa sandy loam, Stanley silty clay, Ephrata loamy sand, and Saskatoon loam soils, respectively; corresponding Freundlich desorption K_{oc} values were 2838, 5176, 4502, 13154, and 2061. Registrant-calculated desorption K and K_{oc} values were not reported.

Dissipation Studies

Terrestrial Field Dissipation

In three separate dissipation reports, the major route of dissipation of NNI-0001 480SC under field conditions was transformation. In the first study, MRID 46816915, NNI-0001 480SC was applied to bare sandy loam in Fresno, California. The flubendiamide had a reviewer-calculated half-life of 770.2 days in soil (r^2 = 0.5183; based on all available replicate data, using linear regression and the equation $t½ = \ln 2/k$, where k is the rate constant). Based on nonlinear regression analysis (SigmaPlot vers. 9.0), the half-life was 693.1 days (r^2 = 0.9802). However, these half-lives extend beyond the scope of the study and are of limited value. The observed half-life of flubendiamide was >538 days (MRID 46816915).

In the second study, MRID 4681916, flubendiamide was applied under field conditions in Leland, Mississippi in bare silt loam soil. Flubendiamide had a reviewer-calculated half-life of 693.1 days in soil (r^2 = 0.351; based on all available replicate data, using linear regression and the equation $t_{½} = ln\ 2/k$, where k is the rate constant). Based on nonlinear regression analysis (SigmaPlot vers. 9.0), the half-life was 495.1 days (r^2 = 0.937). The observed half-life of flubendiamide was 15-547 days.

In the final study (MRID 46816917) NNI-0001 480SC was applied to bare loamy sand in Ephrata, Washington. Under field conditions in the bare loamy sand soil, flubendiamide had a reviewer-calculated half-life of 210 days in soil (r^2 = 0.699; based on all available replicate data, using linear regression and the equation $t_{½} = ln\ 2/k$, where k is the rate constant). Based on nonlinear regression analysis (SigmaPlot vers. 9.0), the half-life was 315.1 days (r^2 = 0.9570). The observed half-life of flubendiamide was 272-366 days.

Accumulation Studies

Bioaccumulation in Fish

In the fish tissue samples, [^{14}C]flubendiamide residues reached steady state at 10-28 days of exposure (mean whole body concentrations of 52 µg/kg and 47.1 µg/kg at nominal concentrations of 0.5 µg/L and 5.0 µg/L, respectively, according to the study authors). For the low-dose study, maximum mean [^{14}C]flubendiamide residues were 57.5 µg/kg in whole fish, 107.1 µg/kg in viscera, and 28.5 µg/kg in edible tissue, each on exposure day 28. Reviewer-calculated maximum mean BCF values were 119.0 for whole fish, 58.9 for edible tissue, and 221.8 for inedible tissue (28 days exposure). In edible and inedible tissue samples, [^{14}C]flubendiamide residues ranged from 22.5-28.5 µg/kg and 76.5-107.1 µg/kg at 10-28 days, respectively. For the high-dose study, maximum mean [^{14}C]flubendiamide residues were 521.3 µg/kg in whole fish, 978.4 µg/kg in viscera, and 270.3 µg/kg in edible tissue, each on exposure day 14. Reviewer-calculated maximum mean BCF values were 109.9 for whole fish, 57.0 for edible tissue, and 206.3 for inedible tissue (14 days exposure). In edible and inedible tissue samples, [^{14}C]flubendiamide residues ranged from 234.9-270.3 µg/kg and 749.0-978.4 µg/kg at 10-28 days, respectively. The mean lipid content in the whole fish was 6.63%. The lipid-normalized BCF for total [^{14}C]flubendiamide residues in whole fish was 66.

Following 14 days of depuration, [^{14}C]flubendiamide residues in the whole fish decreased by a mean of 83% (low dose) and 86% (high dose). The residues depurated with a half-life of 4.6 and 4.8 days, from the low- and high-dose studies, respectively. Mean lipid content in the whole fish after 14 days of depuration was 80.9 g/kg. The depuration rate constant (K_2), based on the predicted curve from the Origin™ non-linear kinetic modeling program, was calculated to be 0.150 ± 0 day^{-1} for the low-dose study and 0.146 ± 0.01 day^{-1} for the high-dose study. The kinetic bioconcentration factor (BCF_K) was calculated as 108 for the low-dose (0.5 µg/L) study and 99.4 for the high-dose (5.0 µg/L flubendiamide) study (46816949).

For the des-iodo degradate, the octanol-water partition coefficient is log Kow 3.40 and the calculated mean BCF values, based on total radioactive residues, of 12.6, 20.4, and 7.7 for whole fish, viscera, and edible tissues, respectively.

Non Subdivision N Guideline Studies

Quantum Yield in Water

The UV-VIS absorption spectra of flubendiamide per litre buffered aqueous solution pH 4, pH 7, and pH 9/acetonitrile (1:1, v:v) showed comparable absorption properties. Based on these results, the study author concluded that the absorption properties of flubendiamide indicated the possibility of direct interactions between flubendiamide in aqueous solution with sunlight in the troposphere.

This study is classified as supplemental. It provides supplemental information on the phototransformation of flubendiamide (NNI-0001) in water. The study was considered supplemental because the sterility check and pH measurements were not preformed and the mass balances were not determined. This study does not follow the EPA Subdivision N Guidelines (MRID 46816919).

NNI-0001-Desi-iodo (transformation product of flubendiamide)

Degradation Studies

Aerobic Soil Metabolism

[^{14}C]Des-iodo was relatively stable in the treated soils, decreasing by ≤2% in the sand, sandy loam and silt soils and by 6-8% in the loamy sand soil during 212 days of incubation. In all soils, the measured concentrations were variable over time. Reviewer-calculated first-order linear half-lives were >6 years and are of uncertain value since they are extrapolated well beyond the duration of the study and assume that the pattern of degradation remains linear, and because the r^2 values are very low (MRID 46816911).

Metabolism Studies

Leaching Adsorption/Desorption

Mass balances for soils at the end of the adsorption phase were not reported. Mean mass balances for soils at the end of the desorption phase were 98.4 ± 4.3% (range 93.2-120.6%), 98.5 ± 5.4% (range 90.5-105.1%), 97.8 ± 2.7% (range 94.6-100.1%), 94.8 ± 2.9% (range 90.6-97.7%), and 96.5 ± 4.5% (range 90.1-100.7%) of the applied for the Höfchen silt loam, Laacher Hof AXXa sandy loam, Laacher Hof AIIIa silt loam, Ephrata loamy sand, and Stanley clay loam soils, respectively.

After 24 hours of equilibration, 52.6-57.1%, 43.5-50.4%, 36.6-44.9%, 22.8-31.2%, and 46.9-55.1% of the applied [^{14}C]Des-iodo was adsorbed to the Höfchen silt loam, Laacher Hof AXXa sandy loam, Laacher Hof AIIIa silt loam, Ephrata loamy sand, and Stanley clay loam soils, respectively. Registrant-calculated adsorption K and K_{oc} values were not reported. Registrant-calculated Freundlich adsorption K values were 8.365, 3.514, 2.574, 1.379, and 6.400 for the Höfchen silt loam, Laacher Hof AXXa sandy loam, Laacher Hof AIIIa silt loam, Ephrata loamy sand, and Stanley clay loam soils, respectively; corresponding Freundlich K_{oc} values were 319, 270, 234, 265, and 581. Following the first desorption step (three desorption steps for high-dose; one desorption step for lower doses), the percent of [^{14}C]Des-iodo desorbed from the test soils, as percent of the radioactivity adsorbed, was 62.2-71.3%, 55.2-66.3%, 51.2-63.6%, 42.7-68.0%, and 61.5-

70.5% for the Höfchen silt loam, Laacher Hof AXXa sandy loam, Laacher Hof AIIIa silt loam, Ephrata loamy sand, and Stanley clay loam soils, respectively. For the high-dose soils, at the end of the third desorption step, 66.8%, 66.3%, 64.7%, 63.2%, and 77.7% of the applied [^{14}C]Des-iodo desorbed from the Höfchen silt loam, Laacher Hof AXXa sandy loam, Laacher Hof AIIIa silt loam, Ephrata loamy sand, and Stanley clay loam soils, respectively. Registrant-calculated desorption K and K_{oc} values were not reported. Registrant-calculated Freundlich desorption K values were 9.548, 4.356, 3.237, 1.254, and 8.495 for the Höfchen silt loam, Laacher Hof AXXa sandy loam, Laacher Hof AIIIa silt loam, Ephrata loamy sand, and Stanley clay loam soils, respectively; corresponding Freundlich desorption K_{oc} values were 364, 335, 294, 241, and 771.

This study is classified as supplemental. No significant deviations from good scientific practices were noted. However, the study was conducted using a transformation product of flubendiamide, rather than the parent compound. Furthermore, it could not be determined if the German test soils were comparable to soils found in typical use areas in the United States (MRID 46816906).

Non Subdivision N Guideline Studies

Quantum Yield in Water

Based on the data obtained from the arithmetic models, it was determined that environmental direct phototransformation half-lives of Des-iodo were more than 1 year for all seasons and locations assessed. It was also determined that direct phototransformation in water does not contribute to elimination of Des-iodo in the environment. However, this assessment does not consider any indirect mechanisms which may enhance the photodegradation in natural water.

This study is classified as scientifically valid. No significant deviations from good scientific practices were noted, however it does not follow the EPA Subdivision N Guidelines (MRID 46816920).