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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 10-JULY-2001

SUBJECT: HED Risk Assessment: Human Health Risk Assessment for Clethodim to Support Request for New Uses of Clethodim in/on Onion (green), Lettuce (leaf), Head/Stem *Brassica* Crop Subgroup 5-A (Broccoli and Cabbage), and Canola, Mustard, and Flax, Seed.

Submission#:	S590307	Caswell #:	N/A
Chemical #:	121011	Class:	Herbicide
DP Barcode:	D271747, D271248, D273651, D240302	Trade Name:	Select®
PRAT Case#:		EPA Reg. #:	59639-3, 59639-78
Petition #	PP# 1E06249 PP# 0E06202	40 CFR:	§180.458

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The Interregional Research Project No. 4 (IR-4) has submitted a petition for the establishment of permanent tolerances for residues of the herbicide clethodim (Select® Herbicide 0.94EC (also called Prism) and Select® 2EC Herbicide (EPA Reg. Nos 59639-78 and 59639-3)). The proposed tolerances for the combined residues of clethodim [(E)-(±)-2-[1-[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one] and its metabolites containing the 5-(2-(ethylthiopropyl)cyclohexene-3-one and 5-[2-(ethylthio)propyl]-

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5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones for the raw agricultural commodities are as follows:

Onion, green	2.0 ppm
Lettuce, leaf	2.0 ppm
Head/stem *Brassica*, crop subgroup 5-A	2.0 ppm
Flax	0.30 ppm
Mustard, seed	0.40 ppm
Canola, seed	0.50 ppm
Canola, meal	1.5 ppm

A summary of the findings and an assessment of human risk resulting from the proposed uses for the establishment of tolerances for the residues of clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones in/on green onion, leaf lettuce, the Head/stem *Brassica*, crop subgroup 5-A, canola, flax, and mustard, seed, are provided in this document.

The residue chemistry data review and the dietary exposure assessment were performed by Manying Xue, the occupational/residential assessment was performed by Mary Rust, the toxicology review was performed by Meta Bonner and the water exposure assessment was performed by Fred Jenkins and James Breithaupt of the Environmental Fate & Effects Division (EFED).

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1.0 EXECUTIVE SUMMARY

Clethodim (Select®) is a cyclohexenone herbicide used for control of annual and perennial grass weeds in broad leaf crops. Other chemicals with similar molecular structure include sethoxydim, tralkoxydim and cycloxydim.

Clethodim (Select® 2 EC, EPA Reg. No. 59639-3; Select® or Prism® Herbicide, EPA Reg. No. 59639-78; and Select Super® Herbicide, EPA Reg. No. 59639-102) is currently registered for post-emergence control of annual and perennial grasses in cotton, soybeans, sugar beets, dry bulb onions, garlic, shallots, tomatoes, alfalfa, peanuts, dry beans, potatoes, sweet potatoes, yams, sunflower, canola, cucumbers, peppers, ornamentals, conifer trees, non-bearing food crops, fallow land, non-crop or non-planted areas. The new uses proposed in this action include the head and stem *Brassica* subgroup (5-A), green onion, leaf lettuce, mustard, flax. and canola.

In November, 2000, HED completed a risk assessment for the proposed use of clethodim on crop groups tuberous and corm vegetables, fruiting vegetables, root vegetables, leaves of root and tuber vegetables, and leaf petioles, and the crops melons, squash/cucumbers, sugar beets, sunflower, canola, cranberry, strawberry, and clover. The November, 2000 risk assessment (Attachment 1), includes a detailed evaluation of the chemistry, toxicology and exposure databases. HED has high confidence in the quality of the toxicology, chemistry and exposure databases used to assess risk from clethodim. Attachment 1 should be used as a companion to the following risk assessment, which will focus upon the chemistry and exposure specific to the proposed new uses only.

Permanent tolerances have been established under 40 CFR §180.458(a)(1), (4), and (5) for the combined residues of the herbicide clethodim and its metabolites containing the 2-cyclohexen-1-one moiety in/on the fat, meat, and mbyp of cattle, goats, hogs, horses, poultry, and sheep at 0.20 ppm, milk at 0.05 ppm, eggs at 0.20 ppm, cottonseed at 1.0 ppm, potatoes at 0.5, soybeans at 10.0 ppm, potato flakes and granules at 1.0 ppm, cottonseed meal 2.0 ppm. In addition, permanent tolerances are established under 40 CFR §180.458(a)(3) and (6) for the combined residues of clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim, in/on dry bulb onions at 0.20 ppm, sugar beet roots at 0.20 ppm, sugar beet tops at 0.50 ppm, and sugar beet molasses at 2.0 ppm.

Time limited tolerances (set to expire on 4/30/01) are established under 40 CFR §180.458(a)(2) for the combined residues of clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim, in/on alfalfa forage at 6 ppm, alfalfa hay at 10 ppm, dry beans at 2 ppm, peanuts and peanut hay at 3 ppm, peanut meal at 5 ppm, tomatoes at 1 ppm, tomato paste at 3 ppm, and tomato puree at 2 ppm. Tolerances have also been proposed for residues in/on tuberous and corm vegetables, sunflowers, and canola

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(PP#7F4873).

Recently, tolerances have been established for the residues of clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones in/on the tuberous and corm vegetables crop subgroup 1c, fruiting vegetables crop group, root vegetables (except sugar beets) crop subgroup 1b, leaves of root and tuber vegetables (excluding sugar beets, crop group 2), sugar beet, tops and sugar beet, molasses at 1.0 ppm, leaf petioles crop subgroup 4b at 0.6 ppm, melon crop subgroup 9a at 2.0 ppm, squash/cucumber crop subgroup 9b and cranberry at 0.5 ppm, sugar beets, roots at 0.20 ppm, sunflower seed at 5.0 ppm, strawberry at 3.0 ppm, sunflower, meal and clover, forage at 10.0 ppm, and clover, hay at 20.0 ppm.

Overall, the quality of the toxicology data base for clethodim is good and the confidence in the hazard and dose-response assessments is high. The toxicology data base is complete and there are no data gaps. For more information about the toxicology of clethodim, please see the 11/30/00 risk assessment (Attachment 1) or the 10/24/97 HIARC Report (Attachment 2).

The Hazard Assessment Review Committee (HIARC) met on October 16, 1997 to evaluate the toxicology data base for clethodim. Endpoints were identified for chronic dietary (chronic reference dose), short-, intermediate- and long-term dermal and inhalation routes of exposure, and corresponding risk assessments for these routes were performed.

An endpoint for acute dietary exposure was not identified since no effects were observed in oral toxicity studies that could be attributable to a single dose. The chronic reference dose (RfD) of 0.01 mg/kg/day, is based on alterations in hematology and clinical chemistry parameters and increased and absolute and relative liver weights observed in a chronic dog study. The chronic population-adjusted dose (cPAD) is equal to the chronic RfD.

The endpoint chosen for short-term dermal and inhalation risk assessment is based on a developmental toxicity study in rats in which maternal effects (decreased body weight gain and clinical signs of toxicity) were observed. An oral NOAEL of 100 mg/kg/day was identified for short-term dermal and inhalation risk assessment. The endpoint chosen for intermediate-term dermal and inhalation risk assessment is based on increases in absolute and relative liver weights that were observed in a subchronic oral toxicity study in dogs. A NOAEL of 25 mg/kg/day was identified for intermediate-term dermal and inhalation risk assessment. The endpoint chosen for long-term dermal and inhalation risk assessment is from a chronic toxicity study in dogs in which alterations in hematology and clinical chemistry patterns as well as increases in absolute and relative liver weights were observed. An oral NOAEL of 1 mg/kg/day was identified for long-term dermal and inhalation risk assessment.

The HIARC determined that there is no evidence that clethodim is neurotoxic. HIARC did not recommend that a developmental neurotoxicity study be performed. Mutagenicity studies for clethodim, except for one positive in an *in vitro* mutagenicity

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chromosome aberration study, were negative.

Clethodim was negative for carcinogenicity in feeding studies in rats and mice and was classified as "not likely" to be a human carcinogen. Dermal absorption is 30% based on a dermal absorption study in rats.

The oral perinatal and prenatal data demonstrated no indication of increased sensitivity of rats or rabbits to *in utero* exposure to clethodim. The Food Quality Protection Act (FQPA) Safety Factor Committee evaluated the available hazard and exposure data for clethodim on July 31, 2000, and concluded that the safety factor could be removed for clethodim primarily because there is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure. For more information about the FQPA decision, see Attachment 3.

Clethodim is currently registered on a variety of agricultural food crops and non-crop areas, including ornamental plants. Exposure may occur to individuals who mix, load and apply clethodim, eat foods that have been treated with clethodim, drink water that may contain clethodim residues or otherwise come into contact with clethodim residues.

Recently revised clethodim labels do not include ornamentals as a use site. Therefore, exposure to homeowners, either directly or indirectly through commercial or homeowner application in a residential setting, is not expected. As an additional measure of protection, HED recommends that homeowner use of clethodim be explicitly prohibited on the label.

Dietary exposure assessments have been performed for both food- and water-source dietary residues and chronic aggregate dietary exposure (food plus water). Dermal and inhalation exposure assessments have also been performed for people who handle or work in fields treated with clethodim.

An acute dietary exposure analysis was not performed because an appropriate endpoint was not identified by HIARC.

The food-source chronic dietary exposure analysis was performed using tolerance level residues for all crops and livestock commodities. Percent of crop treated information was used for selected crops. The chronic dietary risk analysis (food only) results in an estimate of risk below HED's level of concern (less than 100% of the cPAD). Children aged 1-6 years were the most highly exposed population at 61% of the cPAD.

Surface and ground water contamination may occur from the sulfoxide and sulfone degradates of clethodim, as well as from parent clethodim. However, the risk of water contamination is primarily associated with clethodim sulfone and clethodim sulfoxide rather than parent clethodim based on greater persistence and mobility for the degradates.

Drinking water estimates provided by EFED were based on the results of the

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GENEEC and SCI-GROW models using the highest seasonal application rate. These estimates were used to assess chronic dietary aggregate risk. Back-calculated drinking water levels of comparison (DWLOCs) did not exceed EFED estimates for drinking water from either surface or ground water sources and therefore are not of concern.

HED thus concludes with reasonable certainty that residues ofclethodim in drinking water will not contribute significantly to the chronic aggregate human health risk and that the chronic aggregate exposure from clethodim residues in food and drinking water will not exceed the Agency's level of concern (100% of the Chronic PAD) for chronic dietary aggregate exposure by any population subgroup. EPA generally has no concern for exposures below 100% of the Acute or Chronic PAD, because it is a level at or below which daily aggregate dietary exposure will not pose appreciable risks to the health and safety of any population subgroup. These chronic exposure risk assessments are considered high confidence, very conservative, and very protective of human health.

Potential occupational exposure scenarios for clethodim handlers include mixing/loading liquids for groundboom and aerial applications, groundboom and aerial applications of liquid formulations and mixing/loading and applying with handheld equipment for spot treatment (professional applicators). Short- and intermediate-term occupational exposure estimates were calculated for these workers. MOE's for all scenarios and time periods were above the target of 100.

Workers performing post-application activities such as scouting, irrigating, harvesting, etc. may receive dermal exposure to clethodim residues. Dermal MOEs calculated on the day of application which represent the highest day of exposure were above the target of 100 for all occupational activities.

HED does not believe that aggregate exposure for any population subgroup will exceed our level of concern. Based on the highly conservative assumptions underlying this assessment, HED concludes the findings of this human health risk assessment support the granting of the use of clethodim on the use sites proposed in this action. HED recommends that tolerances be established for residues of clethodim in/on onion (green), lettuce (leaf), head/stem *Brassica* crop subgroup 5-A (broccoli and cabbage), mustard and flax seed at the levels stated below.

Draft copies of Select® and Select® 2EC labels have a 24-hour restricted entry interval (REI). The 24-hour REI does <u>not</u> comply with the Worker Protection Standard: as shown in Table 1, clethodim is categorized in Category I for primary dermal irritation. The appropriate REI that should be stated on the labels is **48 hours**.

HED has evaluated the residue chemistry data base, which is from residue field trials and processing studies. Provided a revised Section F is submitted and a revised Section B/label is submitted, HED concludes there are no residue chemistry data requirements that would preclude the establishment of permanent tolerances for the combined residues of clethodim [(E)-(±)-2-[1-

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[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one] and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim as follows:

Onion, green	2.0 ppm
Lettuce, leaf	2.0 ppm
Brassica, Head and Stem, Subgroup	3.0 ppm
Flax	0.50 ppm
Flax,meal	1.0 ppm
Mustard, seed	0.50 ppm
Canola	0.50 ppm
Canola, meal	1.0 ppm

However, the registration for the use of clethodim on leaf lettuce should be made conditional based upon the need for additional crop field trial data for clethodim on leaf lettuce. A permanent tolerance with time-limited registration for canola and flax should be established with continued registration conditional upon submission of the requested canola processing study.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Clethodim is a member of the cyclohexenone class of herbicides. Product chemistry data for clethodim were previously submitted and have been reviewed. No deficiencies and no toxicological concerns for any clethodim impurities were cited. Details about the product chemistry and the physical/chemical properties of clethodim are available in Attachment 1, HED Risk Assessment.

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

References: Attachment 1: *HED Risk Assessment: Human Health Risk Assessment for Clethodim to Support Request for New Uses of Clethodim on the Crop Groups Tuberous and Corm Vegetables, Fruiting Vegetables Crop Group, Root Vegetables, Leaves of Root and Tuber Vegetables, and Leaf Petioles, and the Crops Melons, Squash/Cucumbers, Sugar Beets, Sunflower, Canola, Cranberry, Strawberry, and Clover.* M. Rust. 11/30/00.

Attachment 2: *CLETHODIM: Report of the Hazard Identification Assessment Review Committee.* J. Rowland. 10/24/97.

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Table 1. Acute Toxicity of Clethodim Technical

Study Type	MRID	Dose	Results	Toxicity Category
Acute Oral (Rat)	40974507	2.5 g/kg tech. 83.3% a.i.	LD50: ♂: 1.63 g/kg ♀: 1.36 g/kg	III
Acute Dermal (Rabbit)	40974510	2.0 & 5.0 g/kg tech 83.3% a.i.	LD50 > 5.0 g/kg for ♂ and ♀	IV
Acute Inhalation (Rat)	40974512	3.9 mg/L, MMAD= 2.8 um	LC50: . 3.9 mg/L	III
Primary Eye Irritation (Rabbit)	40974514	0.1 ml tech 83.3% a.i.	mild ocular irritation	III
Primary Dermal Irritation (Rabbit)	40974516	0.5 ml tech 83.2% a.i.	severe erythema observed at 72 hours	I
Dermal Sensitization (Guinea Pig)	40974518	0.5 & 5.0% induction; 0.5% challenge	Not a dermal sensitizer	N/A

3.2 FQPA Considerations

Reference: Attachment 3: *CLETHODIM - Report of the FQPA Safety Factor Committee*, B. Tarplee, 08/31/00.

The FQPA Safety Factor Committee evaluated the available hazard and exposure data for clethodim on July 31, 2000 and concluded that the FQPA safety factor could be removed (*i.e.*, reduced to 1x) in assessing the risk posed by this chemical.

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

- There is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure;
- A developmental neurotoxicity study is **not** required; and
- The dietary (food and drinking water) and non-dietary (residential) exposure assessments will not underestimate the potential exposures for infants and children

3.3 Dose-Response Assessment

Reference: Attachment 2: *CLETHODIM: Report of the Hazard Identification Assessment Review Committee.* J. Rowland. 10/24/97.

On February 6, 1996, the Health Effects Division Toxicology Endpoint Selection Committee (TESC) considered the available toxicology data for clethodim. Toxicology endpoints

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and dose levels of concern were identified for use in dietary and non-dietary risk assessments. On October 16, 1997, the Health Effects Division's Hazard Identification Review committee met to evaluate the toxicology data base of clethodim with special reference to the reproductive, developmental and neurotoxicity data. The Committee also re-assessed the doses and endpoints selected for acute dietary, chronic dietary (RfD) as well as occupational and residential exposure risk assessments by the TESC in 1996. Endpoints and doses for use in risk assessment are reported in the table below.

Table 2. Toxicological Endpoints for Use in Risk Assessment

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Level of Concern (LOC) for Risk Assessment	Study and Toxicological Effects
Acute Dietary All Populations	N/A	N/A	None Selected. There were no effects observed in oral toxicity studies including developmental toxicity studies in rats and rabbits that could be attributable to a single dose (exposure). Therefore, a dose and endpoint were not selected for this risk assessment.
Chronic Dietary All populations	NOAEL= 1.0 mg/kg/day UF = 100 Chronic RfD = 0.01 mg/kg/day	FQPA SF = 1 cPAD = chronic RfD / FQPA SF = 0.01 mg/kg/day	Chronic Toxicity-Dog (1 year). Alterations in hematology and clinical chemistry parameters and increased absolute and relative liver weights observed at the LOAEL of 75 mg/kg/day.
Short-Term Dermal (1 to 7 days) (Residential)	Oral study Maternal NOAEL= 100 mg/kg/day (dermal absorption rate = 30%)	LOC for MOE = 100 (Residential)	Developmental Toxicity-Rat. LOAEL = 350 mg/kg/day based on decreased body weight gain and clinical signs of toxicity (salivation).
Intermediate-Term Dermal (1 week to several months) (Residential)	Oral study NOAEL= 25 mg/kg/day (dermal absorption rate = 30%)	LOC for MOE = 100 (Residential)	Subchronic Toxicity-Dog (90 days). LOAEL = 75 mg/kg/day based on increased absolute and relative liver weights.
Long-Term Dermal (several months to lifetime) (Residential)	Oral study NOAEL= 1.0 mg/kg/day (dermal absorption rate = 30%)	LOC for MOE =100 (Residential)	Chronic Toxicity-Dog (1 year). LOAEL = 75 mg/kg/day based on alterations in hematology and clinical chemistry parameters as well as increases in absolute and relative liver weights.
Short-Term Inhalation (1 to 7 days) (Residential)	Oral study Maternal NOAEL= 100 mg/kg/day (inhalation absorption rate = 100%)	LOC for MOE =100 (Residential)	Developmental-Rat LOAEL = 350 mg/kg/day based on decreased body weight gain and clinical signs of toxicity (salivation).

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Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Level of Concern (LOC) for Risk Assessment	Study and Toxicological Effects
Intermediate-Term Inhalation (1 week to several months) (Residential)	Oral study NOAEL = 25 mg/kg/day (inhalation absorption rate = 100%)	LOC for MOE = 100 (Residential)	Subchronic Toxicity-Dog (90 days). LOAEL = 75 mg/kg/day based on increased absolute and relative liver weights.
Long-Term Inhalation (several months to lifetime) (Residential)	Oral study NOAEL= 1.0 mg/kg/day (dermal absorption rate = 30%)	LOC for MOE =100 (Residential)	Chronic Toxicity-Dog (1 year). LOAEL = 75 mg/kg/day based on alterations in hematology and clinical chemistry parameters as well as increases in absolute and relative liver weights.
Cancer (oral, dermal, inhalation)	N/A	N/A	Clethodim is classified as a "Not Likely" carcinogen

[1]A dermal absorption factor of 30% is used for these risk assessments, based on the results of a dermal absorption study (MRID 41030202).

3.4 Endocrine Disruption

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

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

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Clethodim (Select®) is a cyclohexenone herbicide used for control of annual and

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perennial grass weeds in broad leaf crops. Existing uses include cotton, soybeans, sugar beets, dry bulb onions, garlic, shallots, tomatoes, alfalfa, peanuts, dry beans, potatoes, sweet potatoes, yams, sunflower, canola, cucumbers, peppers, ornamentals, conifer trees, non-bearing food crops, fallow land, non-crop or non-planted areas. The new uses proposed in this action include the head and stem *Brassica* subgroup, green onion, leaf lettuce, canola, flax, and mustard seed.

Two registered formulations of clethodim are proposed for use: (1) Select® 2 EC Herbicide (EPA Reg. No. 59639-3) is an emulsifiable concentrate containing 26.4% of active ingredient (ai). This formulation contains 2 pounds of ai per gallon. (2) Select® 0.94EC (EPA Reg. No. 59639-78) is an emulsifiable concentrate containing 12.6% of active ingredient (ai). The formulation contains 0.94 pounds of ai per gallon.

The registered labels state that applications may be made using ground or aerial equipment in a minimum of 5 or 3 gallons of water/A, respectively. Spot treatments may be made using hand sprayers or high-volume sprayers using hand guns with a ½-1% PRISM® Herbicide mix. The labels specify a maximum seasonal application rate of 0.5 lb ai/A (0.25 lb ai/A in Long Island, NY). The labels prohibit application of clethodim through any type of irrigation system, and specifies a 24-hour restricted entry interval (the REI should be changed to 48 hours based on acute toxicity). Rotational crop restrictions are not specified with the exception of uses on fallow land where a 30-day PBI is specified for crops without registered clethodim uses. The supplemental directions provided for each crop state that a crop oil concentrate containing at least 15% emulsifier should be used at 1% v/v of finished spray volume unless tank mix instructions indicate otherwise.

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

References: Attachment 4: *PP# 1E06249. Clethodim (ANSI) in/on Onion (green), Lettuce (leaf), Head/Stem Brassica Crop Subgroup 5-A (Broccoli and Cabbage). Evaluation of Analytical Method and Magnitude of the Residue Data.* M. Xue. 03/21/01.

Attachment 4A: *PP# 0E06202. Clethodim in/on Flax and Mustard, Seed. Evaluation of Analytical Method and Magnitude of the Residue Data.* M. Xue. 06/14/01.

Recommendations

Provided a revised Section F is submitted and a revised Section B/label is submitted (as specified in Attachment 4 above), HED concludes there are no residue chemistry data requirements that would preclude the establishment of permanent tolerances for the combined residues of clethodim [(E)-(±)-2-[1-[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one] and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim on onion (green) at 2.0 ppm, lettuce (leaf) at 2.0 ppm, and *Brassica*, Head and Stem, Subgroup at 3.0 ppm. The

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registration for the use of clethodim on leaf lettuce should be made conditional based upon the need for additional crop field trial data for clethodim on leaf lettuce.

Provided that a revised Section B/label and revised Section F are submitted, HED concludes there are no residue chemistry data requirements that would preclude the establishment of permanent tolerances for the combined residues of clethodim [(E)-(±)-2-[1-[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one] and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim on mustard, seed at 0.5 ppm.

Provided the petitioner submits a revised Section B/label and a revised Section F, there will be no residue chemistry data requirements that would preclude the establishment of a permanent tolerance with time-limited registration, with continued registration conditional upon submission of the requested canola processing study. The permanent tolerances should be proposed for the combined residues of the combined residues of clethodim [(E)-(±)-2-[1-[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one] and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim **on canola and flax, seed at 0.50 ppm, and canola and flax, meal at 1.0 ppm (based on residue data from a canola processing study).**

Metabolism in Plants

No new plant metabolism study has been submitted with this petition. Metabolism studies for clethodim in/on carrots, soybeans, and cotton were previously reviewed and are adequate for tolerance setting as proposed in this action. There are available metabolism studies on soybean, cotton, and carrots included soybean foliage, cotton foliage, and carrot leaves. The metabolism in soybean, cotton, and carrots, including soybean foliage, cotton foliage, and carrot leaves is similar. Metabolism data are adequate for canola, flax and mustard, seed; and the data for soybean foliage, cotton foliage, and carrot leaves can be translated to green onions, leaf lettuce, and the Head and Stem *Brassica* Crop Subgroup 5-A for this IR-4 petition. The residues of concern are clethodim and its metabolites containing the 5-(2-ethylthiopropyl) cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene -3-one moieties and their sulphoxides and sulphones.

Metabolism in Livestock

No new livestock metabolism study has been submitted with this petition. Metabolism studies of [propyl-1-^{14}C]-clethodim in a lactating goat and laying hens were previously reviewed. The nature of the residue in ruminants and poultry is adequately understood for the purposes of the subject petition. HED previously concluded that the residues of concern in livestock commodities are clethodim and its metabolites containing the 2-cyclohexen-1-one moiety.

Enforcement Method for Plants

Method RM-26A-1, a gas-liquid chromatographic (GLC) procedure, was validated

for the analyses of residues of clethodim sulfoxide and its metabolite (5-OH clethodim sulfone) in/on flax at fortification levels of 0.05 ppm and 0.5 ppm, and on canola at a fortification level of 0.2 ppm. Method RM-26A-1 is basically the same as the enforcement method for sethoxydim residues, which is published in PAM II (§180.412). Method RM-26A-1 can determine all clethodim metabolites retaining the cyclohex-1-one moiety (DME and DME-OH). The method RM-26A-1 for the determination of clethodim and its metabolites in mustard, seed and flax is acceptable for data collection.

Method RM-26B-2 was validated for the analyses of residues of clethodim sulfoxide and its metabolite (5-OH clethodim sulfone) in/on broccoli. The fortification levels for clethodim sulfoxide and 5-OH-clethodim sulfone were each 0.05 ppm, 1.0 ppm and 2.0 ppm. Recoveries of residues of clethodim sulfoxide in broccoli were within the acceptable range at the fortification level of 0.05 ppm. Recoveries of residues of 5-OH-clethodim sulfone in broccoli were within the acceptable range at fortification levels of 0.05, 1.0 and 2.0 ppm. Recoveries of residues of clethodim sulfoxide in broccoli were low at the fortification levels of 1.0 and 2.0 ppm. The method RM-26B-2 for the determination of clethodim and its metabolites in broccoli is acceptable for data collection and enforcement purposes.

Method RM-26B-3 (a modification of RM-26B-2) was validated for the analyses of residues of clethodim sulfoxide and its metabolite (5-OH clethodim sulfone) in/on green onions, leaf lettuce, and cabbage. The fortification levels for clethodim sulfoxide and 5-OH clethodim sulfone were 0.11 ppm-2.0 ppm for green onions, 0.11 ppm - 0.91 ppm for leaf lettuce, 0.11 ppm - 1.1 ppm for cabbage. Recoveries of residues of clethodim sulfoxide in green onions, leaf lettuce, and cabbage were within the acceptable range at all fortification levels tested. Recoveries of residues of 5-OH-clethodim sulfone were within the acceptable range except for low recoveries in green onions fortified at 2.0 ppm and cabbage fortified at 0.77 and 0.98 ppm. The method RM-26B-3 for the determination of clethodim and its metabolites in green onions, leaf lettuce, and cabbage is acceptable for data collection.

The common moiety method RM-26B-3 for the determination of clethodim and its metabolites is similar to the common moiety method RM-26B-2. The method RM-26B-2 has previously undergone a successful Petition Method Validation by the Agency. Method RM-26B-2 as an enforcement method and Method RM-26B-3 as a letter method have been forwarded to FDA for inclusion in PAM II.

Analytical Methods - Livestock

Livestock feed items are associated with canola and flax seed uses. The Agency has previously concluded that adequate analytical methodology is available to enforce tolerances for residues of clethodim in livestock commodities. The compound specific method, EPA-RM-26D-2, is suitable for enforcement of tolerances for total clethodim residues in crops and livestock tissues, and it has been forwarded to FDA for publication in the Pesticide Analytical Manual, Volume II (PAM II). The common moiety method, RM-26B-2, serves as the enforcement method for milk as RM-26D-2 is not quantitative for residues in milk.

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Multiresidue Methodology

The petitioner has previously submitted data describing the testing of clethodim and its metabolites through FDA Multiresidue Methods. These data, which have been forwarded to FDA for review, indicate that adequate recoveries of clethodim, clethodim sulfoxide, and 5-OH clethodim sulfone have been obtained under FDA's multiresidue protocols.

Freezer Storage Stability Data

The submitted storage stability data are adequate to support the residue field trials for green onions, leaf lettuce, broccoli and cabbage. The maximum field sample storage intervals were 1145 days for green onions, 331 days for leaf lettuce, 969 days for broccoli, and 881 days for cabbage. The storage stability data showed that residues of clethodim and its metabolites are stable under frozen storage for 1131 days (37 months) in green onions, 499 days (16 months) in leaf lettuce, and 943 days (31 months) in broccoli. Clethodim residues showed degradation in cabbage after 888 days (30 months) frozen storage. Correction of the crop field trial residue data for storage degradation is required for cabbage.

Adequate storage stability data are available on canola. The canola residue data will be used in lieu of residue data on flax and mustard, seed. Therefore, no additional storage stability data are needed for flax or mustard, seed.

Magnitude of the Residue in Green Onions

The submitted onion (green) field trial data and geographic representation are adequate to satisfy the requirements described in OPPTS 860.1500 for a tolerance. Three green onion field trials were conducted in regions X (1), III (1), and VI (1) [i.e., CA(1), FL (1), and TX (1)]. Green onion samples were harvested 14 days following the last of two applications of clethodim (0.94 lb/gal EC) at 0.25 lb ai/A/application, at 13-14 day retreatment intervals (RTI), for a total of 0.50 lb ai/A/season (1x the maximum proposed rate). Combined residues of clethodim and its metabolites ranged from <0.20 to <0.87 ppm. The proposed tolerance of 2.0 ppm for green onions is adequate. The proposed tolerance of 2.0 ppm for residues of clethodim and its metabolites containing the 5-(2-ethylthiopropyl) cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene -3-one moieties and their sulphoxides and sulphones. in/on green onions is adequate.

Magnitude of the Residue in Leaf Lettuce

The submitted lettuce (leaf) field trial data and geographic representation are **inadequate** to satisfy the requirements described in OPPTS 860.1500 for a permanent registration; however, the data are adequate for a conditional registration. The Guidelines indicate that eight lettuce (leaf) field trials are required and the eight field trials need to be conducted in regions X (6), III (1), and I (1) or II (1). However, only six leaf lettuce field trials were conducted in regions X (3), III (2), and II (1) [i.e., CA(3), FL (2), and NJ (1)]. Leaf lettuce samples from the six field trials were harvested 14 days following the last of two applications of clethodim (0.94 lb/gal EC) at 0.25 lb ai/A/application, at 13-15 day retreatment intervals (RTI), for a total of 0.50 lb ai/A/season (1x the maximum proposed rate). Combined residues of clethodim and its metabolites ranged from <0.25 to <1.10 ppm. However, two additional field

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trials must be conducted in region X. The proposed tolerance level of 2.0 ppm for residues of clethodim and its metabolites containing the 5-(2-ethylthiopropyl) cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene -3-one moieties and their sulphoxides and sulphones in/on leaf lettuce is adequate.

Magnitude of the Residue in Cabbage and Broccoli

The submitted broccoli and cabbage residue data and geographic representation for the head and stem *Brassica* crop subgroup 5-A are adequate to satisfy the requirements described in OPPTS 860.1500 for a tolerance. Six broccoli field trials were conducted in regions X (4), XII (1), and VI (1) [i.e., CA(4), OR (1), and TX (1)], and six cabbage field trials were conducted in regions X (1), III (1), II (1), I (1), V (1) and VI (1) [i.e., CA(1), FL (1), NC (1), NY (1), WI (1), and TX (1)]. Samples were harvested 30 days following the last of two applications at 0.25 lb ai/A/application, and at 13-14 day RTIs, for a total of 0.50 lb ai/A/season (1x the maximum proposed rate). The application rates in TX were slightly higher: 0.34 and 0.37 lb ai/A/application on broccoli and cabbage, respectively. Combined residues of clethodim and its metabolites were <0.1-1.20 ppm in/on broccoli, and <0.24-1.17 ppm in/on cabbage. HED recommends a tolerance of 3.0 ppm for residues of clethodim and its metabolites in/on the head and stem *Brassica* crop subgroup 5-A, due to low recoveries from concurrent method validation of broccoli and cabbage and the storage stability studies of cabbage in this submission. Therefore, a revised Section F must be submitted proposing a tolerance at 3.0 ppm for residues of clethodim and its metabolites in/on the Head and Stem *Brassica* Crop Subgroup 5-A.

Magnitude of the Residue in Mustard, Flax and Canola, Seed

No residue data for clethodim and its metabolites in/on mustard, seed were submitted. Provided a revised Section B/label is submitted, the submitted canola field trial data are adequate to be translated to mustard, seed for a tolerance petition. Six canola field trials were conducted in Saskatchewan (3), Manitoba (1), Alberta (1), and Ontario (1), Canada (EPA Regions VII and V). The six canola field trial data were previously submitted and reviewed. Based on canola residue data from <0.05 ppm to 0.35 ppm, HED concludes that a tolerance of 0.50 ppm for residues of clethodim and its metabolites in/on mustard, seed will be adequate provided that a 75-day PHI is established. **The petitioner must submit a revised Section F to propose a tolerance of 0.50 ppm for clethodim and its metabolites in/on mustard, seed.**

The submitted flax field trial data and geographic representation are inadequate to satisfy the requirements described in OPPTS 860.1500 for a tolerance petition. The Guidelines indicate that five field trials are required and the five field trials need to be conducted in regions V(2) and VII (3). Only two field trials were conducted in Manitoba and Alberta, Canada (EPA region VII). However, six canola field trial data were previously submitted and reviewed; and the residue data can be translated to flax. Clethodim residues from the six field trials ranged from <0.05 ppm to 0.35 ppm. The proposed 0.3 ppm tolerance for residues of clethodim and its metabolites in/on flax is too low. A tolerance of 0.50 ppm for residues of clethodim and its metabolites in/on flax will be adequate provided that a 75-day PHI is established. The petitioner must submit a revised Section F to propose a tolerance of 0.50 ppm for clethodim and its metabolites in/on flax.

The submitted field trial data and geographic representation for canola are inadequate to satisfy the data requirement described in OPPTS 860.1500. The petitioner has submitted canola/rapeseed field trial data which were conducted in Canada, France and Great Britain. Only six field trials from Canada are acceptable. The submitted field trial data from France and Great Britain are not acceptable. The analytical method RM-26A-1, which was used to analyze canola seeds and its processed commodities in this petition was not successfully validated; therefore, HED requires new canola field trials. According to OPPTS 860.1500, eight canola field trials should be conducted in Regions II (1), V (2), VII (2) XI (3); and the field trial data should reflect the proposed use including the PHI. **However, based on a meeting between HED and RD on 3/21/2001, HED proposes that, in the interim, the tolerance on canola be set at 0.50 ppm with a preharvest interval of 75 days (PP#7F04873, D240302 and D273651, M.Xue, 9/7/00 and 3/21/01).**

Processed Food/Feed

No new processing studies for canola and flax have been submitted with this petition. However, processing studies for canola were previously conducted and reviewed and the data can be translated to flax. The canola was treated at the rate of 0.19 - 0.21 lb ai/A (2.4-2.6 X) with a 67-75 day PHI. The residues concentrated 2.6X in canola meal. The HAFT from the current canola field trials, which are translated to flax, reflecting the maximum proposed use pattern is 0.32 ppm. Therefore, the expected residues should be 0.83 ppm in canola and flax meal. **The petitioner should submit a Section F proposing a tolerance of 1.0 ppm for residues of clethodim and its metabolites at 1.0 ppm in/on canola and flax meal for a conditional registration.** The tolerance for residues in/on canola and flax meal will be reevaluated upon submission of the canola processing study which was which was requested in PP#7F04873.

There are no other regulated processed food or feed items derived from the commodities associated with green onion, leaf lettuce, head/stem *Brassica* crop subgroup or mustard seed.

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Magnitude of the Residue in Meat, Milk, Poultry and Eggs

No feeding studies have been submitted with this petition. Canola and flax meal are the only feeding item associated with this petition. The established tolerances on meat and milk are adequate to cover the proposed use on canola and flax. As livestock feeds are not derived from green onions, leaf lettuce, broccoli, cabbage, and mustard seed a discussion concerning secondary residues in livestock commodities are not relevant to this petition.

Confined/Field Accumulation in Rotational Crops

A confined rotational crop study of [ring-4,6-^{14}C]-clethodim with carrots, lettuce, and wheat was conducted. Results indicated that there is no need for field rotational crop trials. A 1-month plantback interval for crops rotated with alfalfa was specified. The use directions submitted with the current petition do not specifically address rotational crops. The directions for use on fallow or nonproducing agricultural land state do not plant any crop for 30 days after application unless clethodim is registered for use on that crop.

The Section B/label must be revised to state "Do not plant any crop for 30 days after application unless clethodim is registered for use on that crop".

International Harmonization of Tolerances

There are no established Codex maximum residue limits (MRLs) for residues of clethodim in/on the commodities discussed in the subject petition; therefore, there are no questions with respect to Codex/U.S. tolerance compatibility. Codex MRLs are currently established on various crop and livestock commodities in terms of the sum of clethodim and its metabolites containing 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim. There are estabolished Canadian residue limits for clethodim residues and its metabolites containing the 2-cyclohex-1-enone moiety on mustard, seed at 0.4 ppm, on flax at 0.3 ppm and on canola at 0.5 ppm. However, based on the submitted residue data, HED can not harmonize the tolerances of flax and mustard, seed with canadian residue limits.

4.2.2 Acute Dietary

An endpoint was not identified for acute dietary exposure and risk assessment because no effects were observed in oral toxicity studies including developmental toxicity studies in rats or rabbits that could be attributable to a single dose (exposure). Therefore, an acute dietary exposure assessment was not performed.

4.2.3 Chronic Dietary

References: Attachment 5: *Chronic Dietary Exposure Analyses for Clethodim in/on Green Onions, Leaf Lettuce, and the Head/Stem Brassica Crop Subgroup 5-A. PC Code 121011, DP Barcode: D274747.* M. Xue, 06/06/01.

Attachment 5A: *Chronic Dietary Exposure Analyses for Clethodim in/on Canola, Flax and Mustard, Seed. PC Code 121011*, DP Barcode: D275543. M.Xue. 06/14/01.

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HED conducts dietary risk assessments using the Dietary Exposure Evaluation Model (DEEM™), which incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For this chronic dietary risk assessment, the three-day average of consumption for each sub-population is combined with residues to determine average exposure as mg/kg/day.

The chronic analysis used tolerance level residues for all crops and livestock commodities. The projected percent crop trated data (2% for lettuce, broccoli and cauliflower, 15% cabbage, 25% for onion, and 1% for brusseles sprouts), and the weighted average % crop treated data (3% for cotton, 8% for onions, 3% for peanuts 4% for soybeans, 15% for sugar beets, and 1% for tomatoes), and 100% crop treated (CT) data (for most crops) were used for the analyses.

The chronic dietary risk estimate associated with all registered and proposed uses does not exceed HED's level of concern (i.e. results are less than 100% of the cPAD). The chronic analysis estimates are 30% of the cPAD for U.S. Population. Children 1 - 6 years old were the most highly exposed population at 61% of the cPAD. Exposure estimates and associated risk, as percent of the cPAD, are shown below in Table 3 for selected population subgroups. This analysis should be viewed as somewhat refined since percent of crop treated information was used. Further refinements could be made by using anticipated residues, actual processing factors, or other criteria. A complete listing of chronic exposure estimates for all DEEM™ population subgroups is available (see Attachment 5).

Table 3. Chronic Dietary (Food Only) Tier 2 Exposure Estimates

Population Subgroup	Exposure, mg/kg/day	% cPAD
U.S. Population (total)	0.0030	30
All infants (< 1 year)	0.0043	43
Children 1-6 yrs	0.0061	61
Children 7-12 yrs	0.0042	42
Females 13-50 years	0.0023	23
Males 13-19 years	0.0030	30

1. This analysis is considered Tier 2 because percent of crop treated information was used.

4.2.4 Cancer Dietary

Clethodim has been classified as a group E carcinogen. Therefore, a cancer risk assessment is not required.

4.3 Water Exposure/Risk Pathway

Reference: Attachment 7: *IR-4 Use of Clethodim (PC # 121011)*. F. Jenkins and J. Breithaupt. 05/22/01.

Surface and ground water contamination may occur from the sulfoxide and sulfone degradates of clethodim, as well as from parent clethodim. However, the risk of water contamination is primarily associated with clethodim sulfone and clethodim sulfoxide rather than parent clethodim based on greater persistence and mobility for the degradates.

The only significant routes of dissipation of clethodim are microbial degradation in soil and movement by leaching or runoff. Parent clethodim is moderately persistent to hydrolysis at pH 5 with half-lives of 26-42 days and stable at pH 7 and 9 with half-lives of greater than 300 days. Even though acceptable water and soil photolysis studies show half-lives of 1.5 to 9.3 days, this may not be an important route of dissipation because of suspended sediment and shading. Photolysis is only an important route of dissipation in shallow, well-mixed surface water with no shading. The half-lives in aerobic soil are 2-3 days for parent clethodim, and 30-38 days for total toxic residues (parent + sulfoxide + sulfone). The sulfoxide and sulfone metabolites are more persistent than parent clethodim and are formed in significant quantities in soil. All residues of clethodim (parent and metabolites) are very mobile in soil with five out of six soil dissorption coefficients (K_d) less than one. The field dissipation studies show that parent clethodim was only found at levels at or near the quantitation limit of 0.02 ppm, which is consistent with the rapid degradation in soil. Clethodim sulfoxide had an apparent half-life of 2.5 to 3.7 days, indicating that movement from the treated field may have been an important route of dissipation

Surface water

Parent clethodim may move from the treated field to surface water or ground water through run-off or leaching which occurs shortly after application (e.g. rainfall). Also, the sulfoxide and sulfone degradates may migrate by runoff or leaching for longer periods of time since they are more persistent. All residues of clethodim (parent and degradates) are very mobile in soil. Tier 1 surface water concentrations (Table 2) for parent clethodim and total toxic residues (parent + sulfoxide + sulfone) were estimated using the Generic Estimated Environmental Concentration (GENEEC) model.

The peak GENEEC estimated environmental concentration (EEC) of clethodim and its degradates, sulphoxide and sulphone, in surface water is **24.2 ppb.** The chronic GENEEC EEC is **18.3 ppb**. HED policy allows for a three-fold reduction of GENEEC 56-day estimates, which result in a chronic value of **6.1 ppb**. This reduced value was used to compare to HED's calculated DWLOCs. These estimates are based on a maximum application rate of 0.5 lb ai/acre per year (2 applications). The GENEEC values represent upper-bound estimates of the concentrations that might be found in surface water due to clethodim use.

Groundwater

Parent clethodim is mobile, but has a short metabolic half-life in soil under aerobic conditions. Therefore, parent compound should not be a ground water concern in most environments. While EFED expects the parent to be transformed to sulfoxide or sulfoxone products fairly quickly by soil metabolism ($t_{½}$ = 1 - 3 days), it may be more persistent since it is leached below the more biologically active top soil. In such instances (i.e., leaching rainfall

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shortly after application) parent clethodim concentrations may be higher than estimated. In the event that parent clethodim did reach ground water, the available routes of disappearance would be dilution, some metabolism to persistent degradates, and slow hydrolysis with the rate depending on the pH of the ground water. The results of the screening level groundwater model, SCI-GROW2, for both parent clethodim and the total toxic clethodim (parent + sulfoxide + sulfoxone) are **0.49 ppb** for acute exposure and **0.08 ppb.**for chronic exposure.

4.4 Residential Exposure/Risk Pathway

Based on recently revised clethodim labels, there are no use sites through which homeowners or the public are likely to become exposed to clethodim residues, either directly through application or indirectly by contact with residues on treated surfaces. Therefore, non-occupation exposure assessment was not performed.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Acute aggregate risk was not considered because an acute dietary endpoint was not identified for acute dietary exposure by the HIARC. Short- and intermediate-term oral, dermal and inhalation aggregate risks were not calculated because postapplication exposure assessments for these routes of exposure were not performed (see Section 4.4).

Chronic dermal, inhalation and incidental oral aggregate risks were not calculated because, based on the current and proposed use patterns, exposure through these routes on a chronic basis is not expected. Chronic aggregate dietary risk from food and drinking water sources was performed. Clethodim has been classified as a "Not Likely" carcinogen. Therefore, a cancer risk assessment is not required.

5.1 Acute Risk

Acute aggregate risk was not considered because an acute dietary endpoint was not identified for acute dietary exposure by the HIARC.

5.2 Short-Term Risk

Short-term oral, dermal and inhalation aggregate risks are made up of exposure from these routes of exposure which are compared to the appropriate short-term endpoints. Dermal and incidental oral exposures were not calculated because postapplication exposure assessments for these routes of exposure are not expected and corresponding risk assessments were not performed (see Section 4.4).

5.3 Intermediate-Term Risk

Intermediate-term oral, dermal and inhalation aggregate risks are made up of exposures from these routes of exposure. Dermal and incidental oral exposures were not

calculated because postapplication exposure assessments for these routes of exposure are not expected and corresponding risk assessments were not performed (see Section 4.4).

5.4 Chronic Risk

Aggregate risks from chronic dermal, inhalation and incidental oral (from children eating grass and soil) exposures were not calculated because, based on the current and proposed use patterns, exposure through these routes is not expected. However, chronic dietary risk from food and drinking water sources was considered. Estimated chronic aggregate risks for clethodim based on food and drinking water sources are presented in Table 4 and 5 below.

Table 4. Chronic DWLOCs and Input Parameters

Population[1]	cPAD mg/kg/day	Food Exposure mg/kg/day	Maximum Water Exposure mg/kg/day[2]	Ground Water EEC (ppb)[3]	Surface Water EEC (ppb)[4]	DWLOC (ppb)
US Population	0.01	0.0030	0.0070	0.08	6.1	250
Children (1-6 years)	0.01	0.0061	0.0039	0.08	6.1	40
Females (13-50 years)	0.01	0.0023	0.0077	0.08	6.1	230
Males (13-19 years)	0.01	0.0030	0.0070	0.08	6.1	250

[1]Population subgroups chosen were the total US population, infant/child subgroups with the highest food exposure (10 kg. body weight assumed) and the female subgroup with the highest food exposure (60 kg. body weight assumed).

[2]Maximum Water Exposure (mg/kg/day) = PAD (mg/kg/day) - TMRC (theoretical maximum residue contribution, i.e. "food exposure") from DEEM (mg/kg/day)

[3] Based upon SCI-GROW modeling results.

[4]Based upon GENEEC Index Reservoir modeling results.

Table 5. Chronic Aggregate Risk for Clethodim

Population Subgroup	cPAD (mg/kg)	% cPAD (Food)	Surface Water EEC (ppb)	Ground Water EEC (ppb)	Chronic DWLOC (ppb)
US Population (total)	0.01	0.0030	6.1	0.08	250
Children 1-6 years	0.01	0.0061	6.1	0.08	40
Females 13-50 years	0.01	0.0023	6.1	0.08	230
Males 13-19 years	0.01	0.0030	6.1	0.08	250

Chronic DWLOCs for all population subgroups are above the estimated concentrations of clethodim and its metabolites in drinking water, and are therefore not of concern.

HED thus concludes with reasonable certainty that residues of clethodim in drinking water will not contribute significantly to the chronic aggregate human health risk and that the chronic aggregate exposure from clethodim residues in food and drinking water **will not exceed the Agency's level of concern** (100% of the Chronic PAD) for chronic dietary aggregate exposure by any population subgroup. EPA generally has no concern for exposures below 100% of the Chronic PAD, because it is a level at or below which daily aggregate dietary exposure will not pose appreciable risks to the health and safety of any population subgroup. This chronic exposure risk assessment is considered high confidence, very conservative, and very protective of human health.

5.5 Cancer Risk

Clethodim has been classified as a group E carcinogen. Therefore, a cancer risk assessment is not required, and an aggregate cancer risk assessment was not performed.

6.0 CUMULATIVE RISK

EPA does not have, at this time, available data to determine whether clethodim has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, EPA has not assumed that clethodim has a common mechanism of toxicity with other substances.

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether clethodim shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for clethodim need to be modified or revoked.

7.0 OCCUPATIONAL EXPOSURE

Reference:

Attachment 6: *Occupational and Residential Risk Assessment to Support Request for New Uses of Clethodim on Potatoes, Sugar Beets, Sunflower, Canola, Cucumbers, Bell Peppers and Non-Bell Peppers.* M. Rust. 10/04/00.

There is a potential for occupational exposure to clethodim during mixing, loading, application, and postapplication activities. Select® products are proposed for use by ground or aerial equipment. For occupational handlers and those involved in postapplication activities such as scouting, irrigation and hand harvesting, short-term or intermediate-term exposures may occur. Chronic exposures are not expected.

An occupational exposure assessment with a summary of exposure and risk estimates for workers was included in the most recent clethodim risk assessment (Attachment 1). The previous assessment can be used to estimate exposure to workers exposed to clethodim based on the new uses proposed in this action because the application methods and use rates are expected to be the same. All occupational handler MOEs are above 100. The lowest MOE, 230, was calculated for intermediate-term risk for professional applicators who mix, load and apply clethodim for spot treatment (wearing no gloves). For occupational handlers, MOEs of 100 or greater do not exceed HED's level of concern.

For postapplication exposure and risk, the potential postapplication exposure to workers for all crops proposed in this action except *Brassica* (broccoli and cabbage) are not expected to exceed those previously assessed (Attachment 6). For *Brassica*, the estimated postapplication exposure potential for hand harvesters is relatively high.and results in a higher dermal risk to workers. Transfer coefficient values were taken from those reported in the Exposure SAC Policy No. 3.1, "Agriculture Transfer Coefficients" (August, 2000). The postapplication exposure and risk for workers in broccoli crops are presented below.
Daily dermal absorbed doses (mg/kg/day) were calculated for post-application activities using the following equation:

$$\textbf{Daily dermal absorbed dose}_t = \frac{DFR_t\ (\mu g/cm^2) \times 1E\text{-}3\ mg/\mu g \times Tc\ (cm^2/hr) \times DA \times ET\ (hrs)}{BW\ (kg)}$$

Where,

DFR_t	=	dislodgeable foliage residue on day "t" (ug/cm^2)
Tc	=	transfer coefficient (cm^2/hr)
DA	=	dermal absorption factor (0.3; unitless)
ET	=	exposure time (8 hr/day)
BW	=	body weight (60 kg for short term; 70 for intermediate term)

Dislodgeable foliar residue values on the day of application were calculated using the following equation:

$\mathbf{DFR_t}$ (ug/cm^2) = Application Rate (lb ai/acre) x F x 4.54E8 μg/lb x 24.7E-9 acre/cm^2

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Where:

DFR_t = ... dislodgeable foliage residue on day "t" (ug/cm^2)
Rate = ... application rate (0.25 lb ai/acre)
F = ... fraction of ai retained on foliage (0.2; unitless)

The non-cancer risk or margin of exposure (MOE) for all time durations was calculated as follows:

$$\textbf{MOE} = \frac{\text{NOAEL (mg/kg/day)}}{\text{Daily Absorbed Dose (mg/kg/day)}}$$

Table 6. Occupational Postapplication Exposure and Risk

Postapplication Activities (highest exposure crop)	Transfer Coefficient (cm^2/hr)	Short-Term Daily Dermal Absorbed Dose (mg/kg/day)	Intermediate-Term Dermal Absorbed Dose (mg/kg/day)	Short-Term Day '0' MOE (day of treatment)	Intermediate-Term Day '0' MOE	Days to Reach Target MOE of at least 100
Hand Harvesting (broccoli and cabbage)	5000[1]	0.11	0.096	890	260	0

1. Transfer Coefficient is the central value taken from Agriculture reentry Task Force study ARF012.

As can be seen in Table 6 above, postapplication MOEs for workers hand harvesting broccoli are above the target of 100 on day zero and are not a concern.

For all other postapplication exposure and risk estimates, see Attachment 6. MOEs were calculated on the day of application which represents the highest day of exposure. All postapplication MOE's are above the target of 100 for all occupational activities on day zero.

Draft copies of Select® and Select® 2EC labels have a 24-hour restricted entry interval (REI). The 24-hour REI does not comply with the Worker Protection Standard: as shown in Table 1, clethodim is categorized in Category I for primary dermal irritation. The appropriate REI that should be stated on the labels is **48 hours**.

8.0 DATA NEEDS/LABEL REQUIREMENTS

Draft copies of Select® and Select® 2EC labels have a 24-hour restricted entry interval (REI). The 24-hour REI does not comply with the Worker Protection Standard: as shown in Table 1, clethodim is categorized in Category I for primary dermal irritation. The appropriate REI that should be stated on the labels is **48 hours**.

Recently revised clethodim labels do not include ornamentals as a use site. Therefore, no exposure to homeowners, either directly or indirectly through commercial or homeowner application, is expected. As an additional measure of protection, HED recommends that

homeowner use of clethodim be explicitly prohibited on the label.

Provided a revised Section F is submitted (as specified in Conclusion 9c of Attachment 4) and a revised Section B/label is submitted (as specified in Conclusion 12b of Attachment 4), HED concludes there are no residue chemistry data requirements that would preclude the establishment of permanent tolerances for the combined residues of clethodim and its metabolites and their sulphoxides and sulphones, expressed as clethodim on onion, green at 2.0 ppm, lettuce, leaf at 2.0 ppm, and *Brassica*, Head and Stem, Subgroup at 3.0 ppm. The registration for the use of clethodim on leaf lettuce should be made conditional based upon the need for additional crop field trial data for clethodim on leaf lettuce (as specified in Conclusion 9b of Attachment 4).

Provided that a revised Section B/label (Conclusions 2a & 2b of Attachment 4A) and revised Section F (Conclusion 9a of Attachment 4A) are submitted, HED concludes there are no residue chemistry data requirements that would preclude the establishment of permanent tolerances for the combined residues of clethodim and its metabolites and their sulphoxides and sulphones, expressed as clethodim on mustard, seed at 0.5 ppm.

Provided the petitioner submits a revised Section B/label (Conclusions 2a and 2b of Attachment 4A) and a revised Section F (Conclusions 9b and 10 of Attachment 4A), there will be no residue chemistry data requirements that would preclude the establishment of a permanent tolerance with time-limited registration, with continued registration conditional upon submission of the requested canola processing study (Conclusion 10 of Attachment 4A). The permanent tolerances should be proposed for the combined residues of the combined residues of clethodim and its metabolites and their sulphoxides and sulphones, expressed as clethodim on flax, seed at 0.50 ppm and flax, meal at 1.0 ppm.

Provided the petitioner submits a revised Section B/label and a revised Section F, the permanent tolerances, with continued registration conditional upon submission of the requested canola processing study (Conclusion 10 of Attachment 4A), should be proposed for the combined residues of the combined residues of clethodim and its metabolites and their sulphoxides and sulphones, expressed as clethodim on canola, seed at 0.50 ppm and canola, meal at 1.0 ppm.

Attachments:

1 *HED Risk Assessment: Human Health Risk Assessment for Clethodim to Support Request for New Uses of Clethodim on the Crop Groups Tuberous and Corm Vegetables, Fruiting Vegetables Crop Group, Root Vegetables, Leaves of Root and Tuber Vegetables, and Leaf Petioles, and the Crops Melons, Squash/Cucumbers, Sugar Beets, Sunflower, Canola, Cranberry, Strawberry, and Clover.* M. Rust. 11/30/00.

2 *CLETHODIM: Report of the Hazard Identification Assessment Review Committee.* J. Rowland. 10/24/97.

3 *CLETHODIM - Report of the FQPA Safety Factor Committee*, B. Tarplee, 08/31/00.

4 *PP# 1E06249. Clethodim (ANSI) in/on Onion (green), Lettuce (leaf), Head/Stem Brassica Crop Subgroup 5-A (Broccoli and Cabbage). Evaluation of Analytical Method and Magnitude of the Residue Data.* M. Xue. 03/21/01.

4A *PP# 0E06202. Clethodim in/on Flax and Mustard, Seed. Evaluation of Analytical Method and Magnitude of the Residue Data.* M. Xue. 06/14/01.

5 *Chronic Dietary Exposure Analyses for Clethodim in/on Green Onions, Leaf Lettuce, and the Head/Stem Brassica Crop Subgroup 5-A. PC Code 121011, DP Barcode: D274747.* M. Xue, 06/06/01.

5A *Chronic Dietary Exposure Analyses for Clethodim in/on Canola, Flax and Mustard, Seed. PC Code 121011*, DP Barcode: D275543. M.Xue. 06/14/01.

6 *Occupational and Residential Risk Assessment to Support Request for New Uses of Clethodim on Potatoes, Sugar Beets, Sunflower, Canola, Cucumbers, Bell Peppers and Non-Bell Peppers.* M. Rust. 10/04/00.

7 *IR-4 Use of Clethodim (PC # 121011).* F. Jenkins and J. Breithaupt. 05/22/01.

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