UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Date: 22 August 2007

Subject: **Pendimethalin. Human Health Risk Assessment for the Proposed Food Uses of the Herbicide on Artichoke, Globe; Asparagus; *Brassica* Head and Stem Vegetables, Subgroup 5A; and Grape (PP#6E7129).**

PC Code:	108501
DP Number:	334062
Regulatory Citation:	40CFR §180.361
Chemical Class:	Dinitroaniline Herbicide
Trade Names:	Prowl® 3.3 EC, Prowl® H_2O

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1.0 Executive Summary

A human health risk assessment has been conducted to support the proposed Section 3 registrations and associated tolerances for food uses of the herbicide pendimethalin on artichoke, globe; asparagus; *Brassica* head and stem vegetables, subgroup 5A; and grapes. The end-use products (EPs) proposed for use on these crops include an emulsifiable concentrate (EC) formulation and an aqueous capsule suspension (CS) formulation. Pendimethalin is a selective herbicide registered for control of broadleaf weeds and grassy weed species on a variety of agricultural crops, turf, and ornamentals. It acts as a microtubule disruptor by inhibiting cell division and cell elongation in plants, and is generally applied early in the growing season. Because a risk assessment reviewing requests for the use of pendimethalin on beans and peas has recently been completed (DP Num: 334766, 332747, W.Drew, 23/MAR/2007 and DP Num: 325176, M. Collantes, 03/MAR/2006), this current risk assessment document reviews and addresses changes in the dietary (food and drinking water), aggregate (residential plus dietary), and occupational exposures to pendimethalin arising from the proposed new uses. In most cases, information or conclusions which remain unchanged from the previous risk assessment are not reiterated; instead, a reference to the previous document is listed.

Toxicology

The toxicology database is adequate to support the proposed uses for pendimethalin. The scientific quality of the database for pendimethalin is relatively high, and the toxicity profile can be characterized for a wide range of effects, including potential developmental, reproductive, and neurotoxic effects.

No appropriate endpoint attributable to a single exposure was identified from the oral toxicity studies and developmental toxicity studies in rats and rabbits. Therefore, an acute point of departure (aPOD) was not established. Three studies (a 92-day thyroid function study in rats, a 56-day thyroid function study in rats, and a 14-day intra-thyroid metabolism study in rats) were considered together to select the dose and endpoint for establishing the chronic population adjusted dose (cPAD) of 0.03 mg/kg/day. The cPAD is derived from the NOAEL of 10 mg/kg/day for thyroid effects, and a combined uncertainty factor of 300.

The same three studies conducted in rats were used for dose and endpoint selection for all durations of dermal and inhalation exposure. A dermal absorption factor of 3%, and an inhalation absorption factor of 100% were used. Since both dermal and inhalation endpoints were based on the same toxicological effects, these route-specific margins of exposure (MOEs) were combined into a total MOE.

(For more detailed information, refer to DP Num: 325176, M. Collantes, 03/MAR/2006.)

Residue Chemistry

The nature of the residue in plants, livestock, and rotational crops is adequately understood. However, HED has previously requested a limited field accumulation study (OPPTS 860.1900) to determine the amount of pesticide residue uptake into rotational crops. The limited field trials should reflect the maximum label use rate on rotatable crops of 4.0 lb ai/A, and should be conducted on a representative crop (as defined in 40CFR §180.41), at two trial sites per crop, for the following three crop groups:

(1) root and tuber vegetables,

(2) leafy vegetables, and
(3) small grains (wheat, barley, oats, rye),

for a total of six trials. The six trials should be conducted on crops which the petitioner intends to have as rotational crops on the label. Samples should be analyzed for pendimethalin and its 3,5-dinitrobenzyl alcohol metabolite.

The residues of concern in plants (for both tolerance expression and risk assessment purposes) are the parent, pendimethalin, and its 3,5-dinitrobenzyl alcohol metabolite (CL202,347); in peanut hulls, the residues of concern also include the 2,4-dinitrobenzyl alcohol metabolite. The residue of concern in drinking water is pendimethalin, *per se*. ARIA has determined that there is no reasonable expectation of finite pendimethalin residues in animal commodities (40CFR §180.6[a][3]). Tolerances for pendimethalin residues in animal commodities are therefore not needed at this time.

Adequate field trials, storage stability data, and analytical methods are available to support the proposed new uses. In addition, adequate enforcement methods are available. However, the grape processing study was not adequate and must be submitted at an exaggerated application rate (>5X) to adequately address the guideline 860.1520 Processed Food and Feed as it pertains to the proposed use on grapes. In general, residue data indicate that pendimethalin and metabolite residues are low or non-detectable in food or feed crops.

Dietary Exposure
A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™), which uses food consumption data from the USDA's *Continuing Surveys of Food Intakes by Individuals* (CSFII) from 1994 to 1996, and 1998. Tolerance-level residues were assumed for all food commodities with current and proposed pendimethalin tolerances, and it was assumed that all of the crops included in the analysis were treated (100% crop treated). The estimated drinking water concentration (EDWC) of 0.006 ppm was directly entered into the exposure model to assess the contributions from drinking water. Acute dietary exposure estimates were not generated, because of the lack of an acute dietary endpoint and dose for risk assessment.

The most highly exposed population subgroup is children 1-2 years old. The chronic exposure estimate of 0.004749 mg/kg/day corresponds to approximately 16% of the cPAD. Risk estimates for the general US population and all other population subgroups are lower.

Residential (Non-Occupational) Exposure
The level of concern for oral, dermal and inhalation exposure is an MOE of less than 300. The previous residential exposure estimate for adults (consisting of dermal exposure only) results in a total MOE of 740, and is therefore not of concern. The residential exposure for children results in a total MOE (dermal + oral) of 410 at an application rate of 2 lb ai/acre, and an MOE of 400 for an application rate of 3 lb ai/acre. Residential aggregate exposure is not of concern.

With regard to the proposed new uses, ARIA determined that there is no potential for residential exposure to pendimethalin. Therefore, residential exposure/risk (associated with the proposed new

uses) was not assessed for pendimethalin.

Aggregate Risk Estimate
ARIA has combined chronic dietary (food and water) and non-dietary (residential) sources of exposure to pendimethalin. The resulting MOEs are all greater than 300 and, therefore, indicate that risk estimates for all population subgroups do not exceed ARIA's level of concern.

Occupational Handler Exposure
Occupational handler exposure risk estimates were calculated for total (combined dermal and inhalation) short- and intermediate-term exposures. A MOE of 30 is adequate to protect occupational pesticide handlers from exposures to pendimethalin. Provided mixer/loaders wear protective gloves as directed on the labels, all MOEs are > 30 and therefore do not exceed ARIA's level of concern.

Occupational Post-Application Exposure
Estimated occupational post-application risks, as calculated per ARIA default values, indicate that the risks from dermal exposure are not of concern (MOEs are above the level of concern of 30) on the day of treatment for all post-application tasks assessed. All pendimethalin proposed labels currently indicate a re-entry interval (REI) of 24 hours, and should therefore be adequate.

Environmental Justice Considerations:
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research:

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies (listed in Appendix D) have been determined to require a review of their ethical conduct, and have received that review.

Regulatory Recommendations and Proposed Tolerances

Pending the resolution of the following deficiencies, ARIA recommends that 40CFR §180.361 be revised to include tolerances for residues of pendimethalin (CAS name N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine and CAS number 40487-42-1) and its metabolite (4-[(1-ethylpropyl)amino]-2- methyl-3,5-dinitrobenzyl alcohol) in or on the commodities listed in Table 1.0, below.

Table 1.0 Tolerance Summary for Pendimethalin.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)
Brassica, head and stem, subgroup 5A	0.05	0.1
Artichoke, globe	0.05	0.1
Asparagus	0.1	0.15
Grape	0.05	0.1
Grape, raisin	---	0.50
Grape, juice	---	0.15

Residue Chemistry Deficiencies

860.1200 Directions for Use

1. The product label should be amended to restrict use to a single application for each of the proposed crops.

2. As previously requested by HED (DP Num: 329627, W. Drew, 12/JUL/2006), ARIA concludes that the registrant should impose PBIs of 90-days for rotated cereal grain crops, and 270-days for all other rotated crops, until limited field rotational crop studies (OPPTS 860.1900) have been conducted in order to determine if tolerances for residues of pendimethalin in rotational crops are needed.

860.1500 Crop Field Trials

Section F of the petition should be revised to reflect the recommended tolerance levels and correct commodity definitions listed in Table 1.0.

860.1520 Processed Food and Feed

The submitted grape processing study is not adequate. A new study must be submitted using 5X the application rate or the petitioner must submit evidence of crop phytotoxicity at the 5X rate. ARIA recommends for tolerances to be set at 0.50 ppm for raisins and 0.15 ppm for grape juice. Once adequate studies have been received, these tolerances may be revised or withdrawn.

860.1900 Field Accumulation in Rotational Crops

HED has previously requested a limited field accumulation study (OPPTS 860.1900) to determine the

amount of pesticide residue uptake into rotational crops. The limited field trials should reflect the maximum label use rate on rotatable crops of 4.0 lb ai/A, and should be conducted on a representative crop (as defined in 40CFR §180.41), at two trial sites per crop, for the following three crop groups:

(1) root and tuber vegetables,
(2) leafy vegetables, and
(3) small grains (wheat, barley, oats, rye),

for a total of six trials. The six trials should be conducted on crops which the petitioner intends to have as rotational crops on the label. Samples should be analyzed for pendimethalin and its 3,5-dinitrobenzyl alcohol metabolite.

2.0 Ingredient Profile

Pendimethalin is a selective dinitroaniline herbicide which acts as a microtubule disruptor by inhibiting cell division and cell elongation in plants. IR-4 is proposing new uses of pendimethalin on artichoke, globe; asparagus; *Brassica* head and stem vegetables, subgroup 5A; and grapes (PP#6E7129). The EP, Prowl® 3.3 EC Herbicide (EPA Reg. No. 241-337), is an EC formulation containing 37.4% ai (equivalent to 3.3 lb ai/gal), and Prowl® H_2O Herbicide (EPA Reg. No. 241-418) is a CS formulation containing 38.7% ai (equivalent to 3.8 lb ai/gal). Both have been proposed for use on the following crops, with the proposed maximum seasonal rates and preharvest intervals (PHIs) in parentheses:

(1) artichoke, globe (4.0 lb ai/A, 200 day PHI),
(2) asparagus (4.0 lb ai/A, 14 day PHI),
(3) *Brassica* head and stem vegetables, subgroup 5A (1.0 lb ai/A, 60 day PHI for broccoli, 70 day PHI for cabbage),
(4) grape (6.0 lb ai/A, 90 day PHI).

Both formulations can be applied as pre-emergence or post-emergence broadcast sprays directed to the soil surface using ground equipment.

2.1 Summary of Proposed Uses

Table 2.1. Summary of Directions for Use of Pendimethalin.

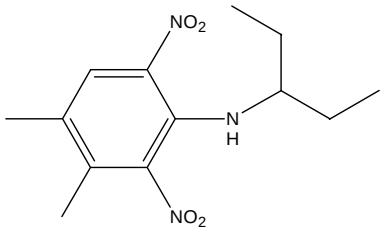
Applic. Timing, Type, and Equip.	Formulation (EPA Reg. No.)	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI[1] (days)	Use Directions and Limitations
Artichoke						
Apply as a broadcast spray directed to the soil surface 1-2 days prior to transplanting.	Prowl® 3.3 EC (241-377)	9.7 pints/A (4.0 lb ai/A)	1	9.7 pints/A (4.0 lb ai/A)	200	Do not feed forage or graze livestock in treated fields. Most effective when incorporated in the weed germination zone by rainfall or irrigation with 7 days of application.

Table 2.1. Summary of Directions for Use of Pendimethalin.						
Applic. Timing, Type, and Equip.	Formulation (EPA Reg. No.)	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI[1] (days)	Use Directions and Limitations
Apply as a broadcast spray directed to the soil surface 1-2 days prior to transplanting.	Prowl® H_20 (241-418)	8.2 pints/A (4.0 lb ai/A)	1	8.2 pints/A (4.0 lb ai/A)	200	Do not feed forage or graze livestock in treated fields. Most effective when incorporated in the weed germination zone by rainfall or irrigation with 7 days of application.
Asparagus						
Apply as soil directed broadcast spray at least 14 days before harvest, prior to spear emergence.	Prowl® 3.3 EC (241-377)	9.7 pints/A (4.0 lb ai/A)	1	9.7 pints/A (4.0 lb ai/A)	14	Do not feed forage or graze livestock in treated fields. Most effective when incorporated in the weed germination zone by rainfall or irrigation with 7 days of application.
Apply as soil directed broadcast spray at least 14 days before harvest, prior to spear emergence.	Prowl® H_20 (241-418)	8.2 pints/A (4.0 lb ai/A)	1	8.2 pints/A (4.0 lb ai/A)	14	Do not feed forage or graze livestock in treated fields. Most effective when incorporated in the weed germination zone by rainfall or irrigation with 7 days of application.
***Brassica* Head and Stem Vegetables**						
Apply as broadcast foliar spray to 2-4 leaf vegetable transplants at 1 to 3 days after transplanting or of dierect seeded plants.	Prowl® 3.3 EC (241-377)	2.4 pints/A (1.0 lb ai/A)	1	2.4 pints/A (1.0 lb ai/A)	60 broccoli, 70 cabbage	Do not feed forage or graze livestock in treated fields. Most effective when incorporated in the weed germination zone by rainfall or irrigation with 7 days of application.
Apply as broadcast foliar spray to 2-4 leaf vegetable transplants at 1 to 3 days after transplanting or of dierect seeded plants.	Prowl® H_20 (241-418)	2.1 pints/A (1.0 lb ai/A)	1	2.1 pints/A (1.0 lb ai/A)	60 broccoli, 70 cabbage	Do not feed forage or graze livestock in treated fields. Most effective when incorporated in the weed germination zone by rainfall or irrigation with 7 days of application.
Grape						
Apply as a soil directed broadcast spray underneath the canopy of grape vines at least 90 days before the	Prowl® 3.3 EC (241-377)	14.5 pints/A (6.0 lb ai/A)	1	14.5 pints/A (6.0 lb ai/A)	90	Do not feed forage or graze livestock in treated fields. Most effective when

Table 2.1. Summary of Directions for Use of Pendimethalin.						
Applic. Timing, Type, and Equip.	Formulation (EPA Reg. No.)	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI[1] (days)	Use Directions and Limitations
harvest.						incorporated in the weed germination zone by rainfall or irrigation with 7 days of application.
Apply as a soil directed broadcast spray underneath the canopy of grape vines at least 90 days before the harvest.	Prowl® H_20 (241-418)	12.3 pints/A (6.0 lb ai/A)	1	12.3 pints/A (6.0 lb ai/A)	90	Do not feed forage or graze livestock in treated fields. Most effective when incorporated in the weed germination zone by rainfall or irrigation with 7 days of application.

[1] PHI = Pre-harvest Interval

2.2 Structure and Nomenclature

TABLE 2.2. Test Compound Nomenclature	
Common name	Pendimethalin
Chemical Class	Dinitroaniline Herbicides
IUPAC name	*N*-(1-ethylpropyl)-2,6-dinitro-3,4-xylidine
CAS name	*N*-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine
CAS #	40487-42-1
End-use product/EP	Prowl® 3.3EC Herbicide (EPA Reg. No. 241-337), Prowl® H_2O Herbicide (EPA Reg. No. 241-418)
Chemical Structure	

2.3 Physical and Chemical Properties

Pendimethalin is an orange-yellow crystalline solid with a melting point of 54-58ºC. It is soluble in chlorinated hydrocarbons and aromatic solvents such as methylene chloride, acetone, and xylene, but

relatively insoluble in water (<0.5 ppm) at 20ºC. Pendimethalin is stable under acidic and alkaline conditions.

TABLE 2.3. Physicochemical Properties of the Technical Grade Test Compound	
Parameter	*Value*[a]
Molecular Weight	281.3
Melting point	57.7 - 58ºC
Boiling point	330ºC
Vapor pressure	1.94 x 10^{-3} Pa @ 25°C
Henry's Law Constant	2.728 x 10^{-3} KPa x m^3/mol
Density	0.85 g/cm^3 @ 25°C
Vapor pressure	1.2x 10^{-5} Pa @ 25°C
$Log_{10} K_{OW}$ (Log P)	5.2 @ pH 7
Solubility	0.54 mg/L @ 20°C in water (pH 4) 0.33 mg/L @ 20°C in water (pH 7) 0.44 mg/L @ 20°C in water (pH 10) 48.9 g/L @ 20°C in *n*-hexane 66.08 mg/L @ 20°C in n-octanol >800 g/L @ 20°C in ethyl acetate >800 g/L @ 20°C in xylene >800 g/L @ 20°C in acetone >800 g/L @ 20°C in dichloromethane
Dissociation Constant	pKa = 2.8

[a]European Commission Health & Consumer Protection Directorate-General, Directorate E – Pendimethalin 7477/ VI/98-final, 13 January 2000 (http://ec.europa.eu/food/plant/protection/evaluation/existactive/list1-35_en.pdf)

3.0 Hazard Characterization/Assessment

For detailed information, please refer to DP Num: 325176; M. Collantes; 03/MAR/2006.

Table 3.A Summary of Levels of Concern for Risk Assessment.			
Route of Exposure	Duration of Exposure		
	Short-Term (1 - 30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	30	30	30
Inhalation	30	30	30
Residential Exposure			

Dermal	300	300	300
Inhalation	300	300	300
Incidental Oral	300	300	---

TABLE 3.B Toxicological Doses and Endpoints for Pendimethalin Human Health Risk Assessments.				
Exposure Scenario	**Point of Departure**	**Dose Used in Risk Assessment, UF**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
		Dietary Exposure		
Acute Dietary (Females 13-49) (General US Pop.)	NA	NA	NA	No appropriate acute endpoint identified for these groups. There were no toxic effects attributable to a single dose.
Chronic Dietary (all populations)	NOAEL = 10 mg/kg/day Chronic RfD= 0.03 mg/kg/day	UF = 10X (intraspecies) 3X (interspecies) 10X (database UF) Total UF = 300X	Chronic RfD= 0.03 mg/kg/day cPAD = Chronic RfD cPAD = 0.03 mg/kg/day	92-day thyroid function study in rats; 56-day thyroid study in rats; 14-day intra thyroid metabolism study in rats. LOAEL= 31 mg/kg/day based on hormonal and histopathological changes in the thyroid.
Incidental Oral Exposure				
Incidental Oral Short-Term (1 - 30 days) Intermediate-Term (1 - 6 months)	NOAEL = 10 mg/kg/day	UF = 10X (intraspecies) 3X (interspecies) 10X (database UF) Total UF = 300X	Residential LOC = 300 Occupational LOC = 30	92-day thyroid function study in rats; 56-day thyroid study in rats; 14-day intra thyroid metabolism study in rats. LOAEL= 31 mg/kg/day based on hormonal and histopathological changes in the thyroid.
Dermal Exposure				
Dermal Short-Term (1 - 30 days) Intermediate-Term (1 - 6 months) Long-Term (> 6 months)	NOAEL = 10 mg/kg/day	UF = 10X (intraspecies) 3X (interspecies) 10X (database UF) Total UF = 300X Dermal Absorption = 3%	Residential LOC = 300 Occupational LOC = 30	92-day thyroid function study in rats; 56-day thyroid study in rats; 14-day intra thyroid metabolism study in rats. LOAEL= 31 mg/kg/day based on hormonal and histopathological changes in the thyroid.
Inhalation Exposure				

TABLE 3.B Toxicological Doses and Endpoints for Pendimethalin Human Health Risk Assessments.				
Exposure Scenario	**Point of Departure**	**Dose Used in Risk Assessment, UF**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Inhalation Short-Term (1 - 30 days) Intermediate-Term (1 - 6 months) Long-Term (> 6 months)	NOAEL = 10 mg/kg/day	UF = 10X (intraspecies) 3X (interspecies) 10X (database UF) Total UF = 300X Inhalation Absorption = 100%	Residential LOC = 300 Occupational LOC = 30	92-day thyroid function study in rats; 56-day thyroid study in rats; 14-day intra thyroid metabolism study in rats. LOAEL= 31 mg/kg/day based on hormonal and histopathological changes in the thyroid.
Cancer				
Cancer (oral, dermal, inhalation)	Pendimethalin is considered to be a possible human carcinogen; quantitative estimate of cancer risk is not required.			2-year chronic/carcinogenicity study in rats.

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

3.1 FQPA Hazard Considerations

3.1.1 Adequacy of the Toxicity Data Base

The toxicology database for pendimethalin is adequate for purposes of risk assessment. However, based on the hormonal changes (alterations in thyroid weights and histopathological lesions) observed in several studies following oral administration of pendimethalin, it is likely that pendimethalin may cause disruption in the endocrine system. There is concern that perturbation of thyroid homeostasis may lead to hypothyroidism, and possibly result in adverse effects on the developing nervous system. Consequently, HED recommends that a developmental thyroid assay be required to evaluate the impact of pendimethalin on thyroid hormones, structure, and/or thyroid hormone homeostasis during development. Furthermore, HED has recommended that the 10X database uncertainty factor (UF_{DB}) be retained pending receipt of the developmental thyroid study.

3.1.2 Evidence of Neurotoxicity

There were no neurotoxicity studies available for pendimethalin. Furthermore, there was no evidence of neurotoxic clinical signs, changes in brain weight, or histopathology of the nervous system in any study with pendimethalin. Neurotoxicity studies for pendimethalin are not required based on the chemical characteristics.

3.1.3 Developmental Toxicity Studies

In the rat, the pendimethalin NOAELs for developmental and maternal toxicity are both 500 mg/kg/day (highest dose tested). There were no maternal or developmental effects noted at any dose level tested. However, the study is considered adequate, and a new study is not required because in other rat studies, thyroid toxicity was seen at significantly lower doses (31 mg/kg/day) than the highest dose tested in this study, and because if thyroid parameters had been measured, maternal toxicity would likely have been demonstrated.

A rabbit toxicity study with pendimethalin did not demonstrate maternal toxicity at doses up to 60 mg/kg/day (highest dose tested). The NOAEL for developmental toxicity was 60 mg/kg/day (HDT). Since neither maternal nor developmental toxicity was seen at the highest dose tested, potential for increased sensitivity of the offspring could not be determined.

3.1.4 Reproductive Toxicity Study

A 2-generation reproduction study (MRID# 41725203) with pendimethalin was reviewed by HED. The pendimethalin RED and the Data Evaluation Report (DER), concluded that the parental systemic NOAEL was 172 mg/kg/day [M] and 216 mg/kg/day [F] (**2500 ppm**), based on decreased body weight gain and food consumption at the LOAEL of 346 mg/kg/day [M] and 436 mg/kg/day [F] (**5000 ppm**). The reproductive/offspring NOAEL was 172 mg/kg/day [M] and 216 mg/kg/day [F] (**2500 ppm**), based on decreased pup weight at the LOAEL of 346 mg/kg/day [M] and 436 mg/kg/day [F] (**5000 ppm**). The mg/kg/day were calculated from actual intake of chemical specific data in the DER.

Conclusions for the same 2-generation reproduction study (MRID# 41725203) with pendimethalin in the HIARC (4/18/2000) indicated that the parental systemic NOAEL was 25 mg/kg/day (**500 ppm**), based on decreased body weight gain and food consumption at the LOAEL of 125 mg/kg/day (**2500 ppm**). The reproductive/offspring NOAEL is 25 mg/kg/day (**500 ppm**), based on decreases in the number of pups born and pup weight at the LOAEL of 125 mg/kg/day (**2500 ppm**). Parental and reproductive NOAELs and LOAELs were based on a generic ratio (1:20) of dietary intake of chemical.

3.1.5 Additional Information from Literature Sources

There was no additional information available from the literature.

3.1.6 Pre-and/or Postnatal Toxicity

HED has concluded there is potential for pre- and/or postnatal toxicity (thyroid) in developing offspring resulting from exposure to pendimethalin.

3.1.6.1 Determination of Susceptibility

There was no indication of pre-/or postnatal qualitative or quantitative increased susceptibility in the developmental studies in rats and rabbits or the 2-generation reproduction studies in rats. However, because developmental LOAELs could not be determined in the developmental studies, HED has

requested developmental thyroid toxicity data, in order to determine potential thyroid toxicity following pre- and/or post-natal exposure to pendimethalin.

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

HED performed a Degree of Concern Analysis because the developmental studies were not adequate to fully address the potential for susceptibility. The purpose of the Degree of Concern analysis is (1) to determine the level of concern for the effects observed when considered in the context of all available toxicity data; and (2) identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment.

If residual uncertainties are identified, then HED determines whether these residual uncertainties can be addressed by a special FQPA safety factor and, if so, the size of the factor needed.

In the case of pendimethalin, the developmental studies in rats and rabbits were acceptable but not adequate to determine the potential for thyroid toxicity during development. Consequently, there is concern for potential increased sensitivity or susceptibility in offspring regarding thyroid effects. A developmental thyroid toxicity study has been required, and the registrant has met with the Agency to discuss the conduct of the ongoing study. Pending receipt of the study, a 10X database uncertainty factor (UF_{DB}) has been retained. The 10X special FQPA Factor has been reduced to 1X, however, since thyroid effects serve as the basis for endpoints for risk assessment for pendimethalin, since there were no developmental effects observed in the rat and rabbit developmental toxicity studies, and since the 10X UF_{DB} has been retained for the lack of data in the developing thyroid.

4.0 Public Health and Pesticide Epidemiology Data

Please refer to DP Num: 325176; M. Collantes; 03/MAR/2006.

5.0 Metabolism Assessment

Please refer to D325176; M. Collantes; 3/MAR/2006.

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

6.1.1 Drinking Water Residue Profile

The drinking water residues used in this chronic dietary risk assessment were provided by the EFED in a memorandum (DP Num: 334061, J. Breithaupt; 08/MAY/2007), and incorporated directly into the dietary assessment. Water residues were entered into the DEEM-FCID input file under the food categories “water, direct, all sources” and “water, indirect, all sources.”

It was determined that the parent, pendimethalin, is the only significant non-volatile residue, therefore, the EDWCs were calculated for pendimethalin only. For surface water sources of drinking water, the acute (peak) water concentration is 77.7 ppb (0.0777 ppm), 6.0 ppb (0.006 ppm) for chronic (non-cancer) and 4.8 ppb (0.0048 ppm) for cancer. The groundwater screening concentration for non-cancer chronic exposure ranged from 0.006 to 0.036 ppb. The EDWC of 0.006 ppm ((the 1 in 10 year annual

mean concentration in surface water, as calculated by PRZM-EXAMS modeling) was directly entered into the exposure model to assess the contributions from drinking water. This EDWC (resulting from a single application of pendimethalin to grapes (NY) at the rate of 6.0 lb ai/A) was the highest chronic modeling result calculated for either surface or groundwater sources of drinking water, and is therefore conservative.

Table 6.1.1 Summary of Estimated Surface Water and Groundwater Concentrations for Pendimethalin.

	[Chemical]	
	Surface Water Conc., ppb [a]	Groundwater Conc., ppb [b]
Acute	77.7	0.036[c]
Chronic (non-cancer)	6.0	0.036[c]
Chronic (cancer)	4.8	0.036[c]

[a] From the Tier II PRZM-EXAMS - Index Reservoir model. Input parameters are based on ...
[b] From the SCI-GROW model assuming a maximum seasonal use rate of 6.0 lb ai/A, a K_{oc} of 15,000, and a half-life of 172 days.
[c] EFED does not expect residue concentrations to exceed this level.

6.1.2 Food Residue Profile

As of July 1, 2007, tolerances are currently established (40CFR §180.361) for the combined residues of the herbicide pendimethalin and its metabolite in or on the following raw agricultural commodities (RACs):

Commodity	Parts per million
Alfalfa, Forage	3.0
Alfalfa, Hay	4.0
Alfalfa, Seed	0.10
Almond, hulls	0.4
Apple, wet pomace	0.20
Bean, lima, seed	0.1
Bean, lima, succulent	0.1
Bean, forage	0.1
Bean, hay	0.1
Carrots	0.5
Citrus, oil	0.5
Corn, field, forage	0.1
Corn, field, grain	0.1
Corn, field, stover	0.1
Corn, pop, grain	0.1
Corn, sweet, forage	0.1
Corn, sweet, kernel plus cob with husks removed	0.1
Corn, sweet, stover	0.1

Cotton, undelinted seed	0.1
Fruit, citrus, group 10	0.1
Fruit, pome, group 11	0.10
Fruit, stone, group 12	0.10
Garlic	0.1
Juneberry	0.10
Leek	0.20
Nut, tree, group 14	0.1
Onion, dry bulb	0.1
Onion, green	0.20
Onion, welsh	0.20
Pea, succulent	0.1
Peanut	0.1
Peanut, hay	0.1
Peppermint, oil	1.0
Peppermint, tops	0.2
Pistachio	0.1
Pomegranate	0.10
Potato	0.1
Rice, grain	0.1
Rice, straw	0.1
Shallot	0.2
Sorghum, forage	0.1
Sorghum, grain, grain	0.1
Sorghum, grain, stover	0.1
Soybean, forage	0.1
Soybean, hay	0.1
Soybean, seed	0.1
Spearmint, oil	1.0
Spearmint, tops	0.2
Strawberry	0.10
Sugarcane, cane	0.1
Sunflower, seed	0.1
Vegetable, fruiting, group 8	0.10
Wheat, grain	0.10
Wheat, forage	3.0
Wheat, hay	0.60
Wheat, straw	0.30

The residue chemistry data submitted to support the proposed uses (and associated tolerances) on artichoke, globe; asparagus; *Brassica* head and stem vegetables, subgroup 5A; and grapes are adequate with respect to field trials, analytical methods, and storage stability data. The grape processing study was not adequate (2x application rate) and therefore ARIA recommends in favor of establishing tolerances for pendimethalin in/on grape, juice and grape, raisin. ARIA also recommends in favor of

establishing tolerances for pendimethalin in/on these commodities, however the previously requested limited field accumulation study (DP Num: 271502, W. Drew, 12/JUL/2006) has yet to be submitted for review. In general, residue data indicate combined residues of parent pendimethalin and its metabolite are very low or non-detectable in food or feed items. However, residues concentrate in some processed commodities, most significantly citrus oil and mint oil.

6.1.3 International Residue Limits

There are currently no Canadian , Mexico or Codex maximum residue limits (MRLs) for pendimethalin on the proposed commodities. See the residue chemistry chapter (DP Num: 340343, D. Rate, 02/AUG/2007) for the International Residue Limit Status sheet.

6.2 Dietary Exposure and Risk

6.2.1 Acute Dietary Exposure/Risk

Due to a lack of an acute dietary endpoint and dose for risk assessment, an acute dietary risk assessment was not generated and is not required for this chemical.

6.2.2 Chronic Dietary Exposure/Risk

A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03) which uses food consumption data from the US Department of Agriculture's *Continuing Surveys of Food Intakes by Individuals* (CSFII) from 1994 to 1996, and 1998. The analysis was performed to support Section 3 registration requests from IR-4 proposing tolerances for pendimethalin in/on artichoke, globe; asparagus; *Brassica* head and stem vegetables, subgroup 5A; and grape. Acute and cancer dietary risk assessments are not required for this chemical.

The chronic dietary exposure analysis was based on the following assumptions:

(1) Tolerance-level residues of pendimethalin in/on all current RACs (e-CFR 40 §180.361, Updated July 1, 2007) and proposed RACs.
(2) Empirical processing factors obtained from processing studies (when available; including citrus commodities). Grape processing studies were not adequate, and tolerances for grape commodities (grape, raisin and grape, juice) were recommended and no processing factor was used in the dietary analysis.
(3) A processing factor of 8 for the processed commodities of wheat bran and wheat germ and 1.4 for wheat flour.
(4) DEEM 7.81 default processing factors were used for the remaining processed commodities.
(5) 100% crop treated (CT), and
(6) 0.006 ppm pendimethalin estimated drinking water concentration (EDWC).

These assumptions result in conservative estimates of dietary exposure and risk. In calculating dietary risk estimates, ARIA has compared the cPAD to the estimated dietary exposure. Typically, ARIA has concerns regarding dietary risk when the exposure estimates exceed 100% of the cPAD. Even with the conservative assumptions noted above, risk estimates associated with chronic dietary exposure to pendimethalin are significantly below ARIA's level of concern.

In the chronic dietary assessment, the most highly exposed population subgroup is children 1-2 years old. The chronic exposure estimate, 0.004749 mg/kg/day, corresponds to approximately 16% of the cPAD. Risks for the general US population were 5% of the cPAD.

6.2.3 Cancer Dietary Risk

The HED Cancer Peer Review Committee classified pendimethalin as a "Group C" (possible human) carcinogen, based on thyroid follicular cell adenomas in rats. The committee recommended a non-quantitative approach (non-linear, RfD approach). The chronic dietary risk assessment is considered to be protective of any cancer effects; therefore, a separate quantitative cancer dietary risk assessment is not required.

TABLE 6.2.3 Summary of Chronic Dietary Exposure and Risk Estimates for Pendimethalin.

Population Subgroup* [Years of Age]	DEEM Chronic Dietary Analysis		
	cPAD (mg/kg/day)	Exposure Estimate (mg/kg/day)	% cPAD
General US Population	0.03	0.001548	5
All Infants [<1]	0.03	0.003081	10
Children [1-2]	**0.03**	**0.004749**	**16**
Children [3-5]	0.03	0.003819	13
Children [6-12]	0.03	0.002304	8
Youths [13-19]	0.03	0.001417	5
Adults [20-49]	0.03	0.001166	4
Adults [50+]	0.03	0.001065	4
Females [13-49]	0.03	0.001164	4

***** Values for the population with the highest risk are in **bold** type.

7.0 Residential (Non-Occupational) Exposure/Risk Characterization

7.1 Residential Handler Exposure

As there are no new residential exposures as a result of the newly proposed uses, please refer to previously reviewed residential exposure in memorandum DP Num: 325176; M. Collantes; 03/MAR/2006. With regard to residential pendimethalin uses previously reviewed, HED combined all non-dietary sources of handler and post-application exposure to obtain an estimate of potential aggregate exposure. The scenarios used were short-term in duration and consisted of dermal (for adults and children) and oral (hand-to-mouth, object-to-mouth, and soil ingestion, for children only) exposure. HED combined risk values resulting from separate exposure scenarios when it was likely they could occur simultaneously, based on the use-pattern and the behavior associated with the exposed population.

The level of concern for oral, dermal and inhalation exposure is an MOE of less than 300. The residential exposure estimate for adults (consisting of dermal exposure only) results in a total MOE of 740, and is therefore not of concern. The residential exposure for children results in a total MOE (dermal + oral) of 410 at an application rate of 2 lb ai/acre, and an MOE of 400 for an application rate of 3 lb ai/acre. Residential aggregate exposure is not of concern.

With regard to the proposed new uses, ARIA has determined that there no potential for residential exposure to pendimethalin. However, proposed label instructions specify that pendimethalin be applied (pre- or early transplant) directly to the soil surface14 to 90 days before harvest. Based upon these factors, residential exposure during pick-your-own strawberry activities was determined to be unlikely to occur and, therefore, residential exposure/risk (associated with the proposed new uses) was not assessed for pendimethalin.

TABLE 7.1 Aggregate Risk Resulting from Residential Exposure to Pendimethalin (Tier 1).

Exposure Scenario	Popu-lation	TTR [1] (µg/cm^2)	Dermal Dose (mg/kg/day)		Total Oral Dose [3] (mg/kg/day)	Oral MOE [4]	Total Dose	Total MOE [5]
Turf Grass	Adults	1.1	0.0136	740	NA	NA	0.0136	740
	Children		0.0228	440	0.0015	6800	0.0243	410
					0.0022	4600	0.0250	400

[1] TTR values are based on Pendulum WDG TTR study (MRID #44969901).
[2] Dermal MOE = average of dermal MOEs for adults and children (calculated from TTR data in CA, PA, and FL).
[3] Oral Dose = hand-to-mouth dose + object-to-mouth dose + soil ingestion dose.
[4] Oral MOE = 1/(hand-to-mouth MOE + object-to-mouth MOE + soil ingestion MOE).
[5] Total MOE = 1/[(1/dermal MOE) + (1/oral MOE)]

7.2 Other (Spray Drift, etc.)

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

It is noted that the 3.0 lb ai/acre application rate for turf was modeled to estimate postapplication residential exposure of toddlers. As this rate is equal to or higher than many of agricultural application rates, this scenario is protective of any exposure of farm children via spray drift from agricultural pendimethalin applications.

8.0 Aggregate Risk Assessments and Risk Characterization

In an aggregate assessment, exposures from relevant sources are combined, and compared to quantitative estimates of hazard (such as a NOAEL or PAD). When aggregating exposures and risks from various sources, ARIA considers both the route and duration of exposure.

In evaluating the proposed uses of pendimethalin, ARIA has combined dietary (food and drinking water) and non-dietary (turf grass) sources of exposure to obtain an estimate of potential aggregate exposure. The non-dietary scenarios in the aggregate assessment include dermal exposure for adults

and children, as well as incidental oral exposures (hand- and object-to-mouth transfer of residues and ingestion of soil) for children only.

ARIA acknowledges that the aggregate exposure and risk estimates for children are likely to overestimate actual exposures since our estimates assume simultaneous, constant exposures from dietary and non-dietary sources. An assessment that takes into account the timing of source-specific exposures and the likelihood of their co-occurring would be expected to produce more realistic and lower exposure and risk estimates.

8.1 Acute Aggregate Risk

No toxic effects attributable to a single dose were identified for pendimethalin. Therefore, an acute risk assessment is not warranted for this chemical.

8.2 Short-Term Aggregate Risk

In estimating short-term aggregate risk, ARIA combines the chronic dietary (food and drinking water) exposure estimate and the total non-dietary (residential) exposure estimate for adults and children. The chronic dietary exposure estimate reflects average dietary exposure, and serves as an estimate of dietary exposure that co-occurs with potential short-term non-dietary exposure to adults and children. Short-term aggregate risk estimates for pendimethalin are summarized in Table 8.2, below. The level of concern for oral, dermal, and inhalation exposure is an MOE of less than 300. The short-term aggregate exposure estimate for adult males results in an aggregate MOE of 650, while the short-term aggregate exposure estimate for adult females results in an aggregate MOE of 580. The aggregate exposure estimate for children results in a total MOE of 410 at an application rate (to residential turf) of 2 lb ai/acre, and a total MOE of 390 for an application rate of 3 lb ai/acre. Aggregate exposure is therefore not of concern for any of the population subgroups.

TABLE 8.2 Short-Term Aggregate Risk Calculations.

Population	Short-Term Scenario				
	NOAEL (mg/kg/day)	Target MOE [1]	Average Dietary Exposure Estimate [2] (mg/kg/day)	Residential Exposure Estimate [3] (mg/kg/day)	Aggregate MOE [4] (Dietary and Residential)
Adult Male (US Population)	10	300	0.0015	0.014	650
Adult Female (Females 13+)	10	300	0.0012	0.016	580
Child (Children 1-2 yrs)	10	300	0.0050	0.024 [5]	410
				0.025 [6]	390

1. Target MOE = 300, based on a total UF of 100 (10X intraspecies, 3X interspecies, 10X Database).
2. Dietary exposure = [food exposure + drinking water exposure].
3. Residential exposure = [oral exposure + dermal exposure + inhalation exposure].
4. Aggregate MOE = [NOAEL ÷ (average dietary exposure + residential exposure)].
5. Based on an application rate of 2 lb ai/A.
6. Based on an application rate of 3 lb ai/A.

8.3 Intermediate-Term Aggregate Risk

Based on the currently requested uses, there are no scenarios that are likely to result in intermediate-

term exposure (30 to 180 days, continuous). Therefore, ARIA has not conducted an intermediate-term risk assessment for pendimethalin.

8.4 Long-Term Aggregate Risk

The dietary exposure (food and drinking water) pathway is the only source of exposure to pendimethalin that is expected to be of long term (180 to 365 days). Therefore, the long-term aggregate exposure and risk estimates are equivalent to the chronic dietary exposure and risk estimates discussed in Section 6.1.3, and do not exceed ARIA's level of concern.

8.5 Cancer Aggregate Risk

The HED Cancer Peer Review Committee classified pendimethalin (18/MAR/1992 and re-affirmed 01/NOV/1999) as a "Group C" (possible human) carcinogen based on a statistically significant increased trend and pair-wise comparison between the high dose group and controls for thyroid follicular cell adenomas in male and female rats. The committee recommended a non-quantitative approach (non-linear, RfD approach) since mode of action studies are available that demonstrate that the thyroid tumors are due to a thyroid-pituitary imbalance, and also since pendimethalin was shown to be non-mutagenic in mammalian somatic cells and germ cells. The chronic risk assessment is considered to be protective of any cancer effects; therefore, a separate quantitative cancer aggregate risk assessment is not required.

9.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to pendimethalin and any other substances and pendimethalin does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that pendimethalin has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

10.0 Occupational Exposure/Risk Pathway

For detailed information, please refer to DP Num: 334174; M. Dow; 09/JAN/2007.

10.1 Occupational Pesticide Handler Exposure

HED ExpoSAC SOP Number 12 (29 March 2000)

ARIA has determined that exposure to pesticide handlers is likely during the occupational use of pendimethalin. Based upon the proposed use patterns, applications are likely only to be made by ground-boom sprayers. For the proposed new uses, the most highly exposed occupational pesticide handlers will be mixer/loaders using open-pour loading of liquid formulations and applicators using open-cab, ground-boom sprayers. The agricultural products, Prowl® 3.3 EC and Prowl® H_2O, have been assessed for occupational exposures associated with the proposed new uses.

Since there is only one application/season and the treatment blocks (i.e., areas treated) are relatively small for the proposed new crop uses (as compared to typical field crops such as cotton, corn, soybeans or wheat), ARIA believes pesticide handlers will be exposed to short-term duration (1 - 30 days) exposures but not to intermediate-term (1 - 6 months) duration exposures. In other words, it is unlikely that pesticide handlers would be exposed continuously for 30 days or more. Estimates of intermediate-term exposures are, however, presented.

No chemical specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline" that is, for workers wearing a single layer of work clothing consisting of a long sleeved shirt, long pants, shoes plus socks and no protective gloves as well as for "baseline" and the use of protective gloves or other PPE as might be necessary. The PPE to be used with these two products includes long-sleeved shirt, long pants, shoes plus socks and chemical resistant gloves.

On 7 March 2005, the Agency issued a memorandum which contains toxicological endpoints for use in risk assessment (DP Num: 278047, C. Swartz, 07/MAR/2005). The Agency identified short-term (1 - 30 days), intermediate-term (1 - 6 months) and long-term (> 60 months) dermal and inhalation toxicological endpoints from a 56 - day thyroid study in the rat, a 14 day intra thyroid metabolism study in the rat and a 92 - day thyroid function study in the rat. The effects seen were hormonal and histopathological changes in the thyroid. The No Observable Adverse Effects Level (NOAEL) for each exposure duration of dermal and inhalation exposure is 10.0 mg ai/kg bw/day. The Agency identified a 10.0 % dermal absorption factor for use in exposure estimates. ARIA assumes 100 % absorption via the inhalation route of exposure.

Since the dermal and inhalation toxicological endpoints are the same and are identified from the same studies, the dermal and inhalation exposures are summed then divided into the NOAEL to derive the Margin of Exposure.

Subsequent to the 7 March 2005 hazard memorandum (DP Num: 278047, C. Swartz, 07/MAR/2005), the Agency conducted the two most recent risk assessments for assorted new uses of pendimethalin (DP Num: 325176; M. Collantes; 03/MAR/2006 and DP Num: 329627; W. Drew; 12/JUL/2006). The March and July assessments used the same dermal and inhalation toxicological endpoints (*i.e.* 10 mg ai/kg bw/day) however modifications were made to the dermal absorption factor and to the uncertainty factors. The dermal absorption factor was adjusted to 3.0 %. Regarding the uncertainty factors the Agency stated: HED has recommended retaining a 10X UF_{DB} (database uncertainty factor) for pendimethalin to account for the lack of a developmental thyroid toxicity study. The standard 10X intraspecies uncertainty factor and a 3X interspecies factor are applicable to pendimethalin risk assessments. The interspecies uncertainty factor of 10X is reduced to 3X due to the greater sensitivity of the adult rat thyroid effects compared to adult humans. Therefore, the level of concern (target MOE) for occupational exposure is 30X. See Table 10.1 for a summary of estimated exposures and risks to occupational pesticide handlers.

Table 10.1 Summary of Exposure & Risk for Occupational Handlers Applying Pendimethalin				
Unit Exposure[1]	**Applic. Rate[2]**	**Units**	**Avg. Daily Exposure[4]**	**MOE[5]**

mg ai/lb handled	lb ai/unit	**Treated**[3]	mg ai/kg bw/day	
Mixer/Loader Using Open Pour of Liquid Formulations				
Dermal: SLNoGlove 2.9 HC SLWithGlove 0.023 HC Inhal. 0.0012 HC	6.0 lb ai/A	200 A/day	Dermal: SLNoGlove 1.49 SLWithGlove 0.012 Inhal. 0.021	SLNoGlove 7 SLWithGlove 303
Applicator Using Open-Cab Ground-boom Sprayer				
Dermal: SLNoGlove 0.014 HC SLWithGlove 0.014 MC Inhal. 0.00074 HC	6.0 lb ai/A	200 A/day	Dermal: SLNoGlove 0.0072 SLWithGlove 0.0072 Inhal. 0.013	SLNoGlove 495 SLWithGlove 495

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. Inhal. = Inhalation. Units = mg a.i./pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence. Dermal SLNoglove = dermal exposure with a single layer of work clothing (long pants, long sleeved shirt and shoes + socks) and NO protective gloves; Dermal SLWithGlove = dermal exposure with a single layer of work clothing AND the use of protective gloves. Inhal. = inhalation exposure.
2. Applic. Rate. = Taken from the
3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; SOP No. 9.1. Science Advisory Council for Exposure; Revised 5 July 2000;
4. Average Daily Dose (ADD) = Unit Exposure * Applic. Rate * Units Treated * absorption factor (3.0 % dermal, 100 % inhalation) ÷ Body Weight (70 kg)
5. MOE = Margin of Exposure = No Observable Adverse Effect Level (NOAEL) (10 mg ai/kg bw/day) ÷ ADD. ADD = dermal exposure + inhalation exposure.

Occupational handler exposure risk estimates were calculated for total (combined dermal and inhalation) short- and intermediate-term exposures. MOEs are above the LOC of 30 for all exposure scenarios at single-layer (with gloves) level of risk mitigation, and are, therefore, not of concern to ARIA, as long as there is a label requirement for the use of PPE.

10.2 Occupational Post-Application Exposure

It is possible for agricultural workers to have post-application exposure to pesticide residues during the course of typical agricultural activities. HED in conjunction with the Agricultural Re-entry Task Force (ARTF) has identified a number of post-application agricultural activities that may occur and which may result in post-application exposures to pesticide residues. HED has also identified transfer coefficients (TC) (cm^2/hr) relative to the various activities which express the amount of foliar contact over time, during each of the activities identified (ExpoSAC SOP 3.1, Agricultural Transfer Coefficients, Rev. 7 Aug. 2000).

With the exception of broccoli and cabbage, applications for the proposed new uses are to be applied to the soil and incorporated with rainfall, irrigation or light mechanical incorporation. For broccoli and cabbage, applications are to be broadcast foliar, at the 2 - 4 leaf stage of crop development. Under the circumstances of the proposed new use pattern and according to the SOP 3.1, the uses with the highest TCs are broccoli and cabbage with a TC of 2,000 cm^2/hr for hand weeding in minimal foliage development.

Therefore, as a screening level assessment, ARIA uses the maximum rate of application (1.0 lb ai/A) for broccoli and cabbage and a TC of 2,000 cm^2/hr to assess postapplication exposure to agricultural workers. A screening level assessment is considered to be conservative *i.e.*, protective.

A MOE of 30 is adequate to protect agricultural workers from post-application exposures to pendimethalin applied as described above. The calculated MOE is 666. Since the calculated MOE is

> 30, the proposed uses do not exceed ARIA's level of concern.

10.3 Restricted Entry Interval (REI)

In the Agency's 3 March 2006 risk assessment (DP Num: 325176, M. Collantes, 03/MAR/2006), the Agency classified pendimethalin in Toxicity Category IV for acute dermal, acute inhalation toxicity and primary dermal irritation. It is classified in Toxicity Category III for primary eye irritation and it is not a dermal sensitizer. Except for broccoli and cabbage, all proposed applications are to be made directly to the soil. The current pendimethalin labels list a REI of 24 hours which is adequate to protect agricultural workers from post-application exposures.

11.0 Data Needs and Label Requirements

11.1 Toxicology

HED has previously requested the submission of developmental thyroid toxicity data for adult rats and young rats following pre- and post-natal exposure to pendimethalin. This study is still required.

11.2 Residue Chemistry

Please refer to the Residue Chemistry Deficiencies portion of the Executive Summary (Section 1.0).

11.3 Occupational and Residential Exposure

ARIA reiterates the label requirement for PPE.

REFERENCES

Endpoint Selection Document
*Pendimethalin: **REVISED** HED Human Health Risk Assessment to Support Section 3 Registration for use on Carrots, Mint, Citrus, and Tree Nuts. PC Code: 108501*; DP Num: 325176; M. Collantes; 03/MAR/2006.

***Pendimethalin. Addendum to Human Health Risk Assessment (D329627) of 7/12/2006: Inadvertently Omitted Tolerances (on Various Beans and Peas), Review of BASF's Proposal for Reduction of Citrus Fruit Pre-Harvest Interval, and Revision of the Chronic Toxicity Profile;* DP Num: 334766; W. Drew; 27/MAR/2007.**

Dietary Exposure Memorandum
Pendimethalin: Chronic Dietary (Food and Drinking Water) Analysis and Risk Assessment to Support the Section 3 Registration for New Food Uses of the Herbicide on Artichoke, Asparagus, Brassica Head and Stem Vegetables, Subgroup 5A, and Grape; DP Num: 334173; D. Rate; 02/AUG/2007.

Drinking Water Memorandum
Drinking Water Assessment for Pendimethalin for Cabbage, Asparague, Bearing Grapes, and Artichoke; DP Num: 334061, J. Breithaupt; 08/MAY/2007.

Product Chemistry Memorandum

European Commission Health & Consumer Protection Directorate-General, Directorate E – Pendimethalin 7477/ VI/98-final, 13 January 2000
(http://ec.europa.eu/food/plant/protection/evaluation/existactive/list1-35_en.pdf

Residue Chemistry Data Reviews
Pendimethalin. Tolerance Petition Requesting Section 3 Registration for Food/Feed Use of the Herbicide on Alfalfa. Summary of Analytical Chemistry and Residue Data. PP#5F6961.; DP Num: 319412; W. Drew; 12/JUL/2006.

Pendimethalin. Petitions for Tolerances on Brassica Head and Stem Vegetables, Subgroup 5A, Asparagus, Grape and Articoke. Summary of Analytical Chemistry and Residue Data. Petition Number 6E7129.; DP Num: 340343; D. Rate; 02/AUG/2007.

Occupational and Residential Exposure Memorandum
PENDIMETHALIN *- Human Non-Dietary Risk Assessment for the Proposed Use of Pendimethalin on Artichoke, Asparagus, Broccoli, Cabbage and Grape; DP Num: 334174*; M. Dow; 09/JAN/2007.

Re-registration Eligibility Document
Pendimethalin Re-registration Eligibility Document; DP Num: 221532; J. Leahy; 20/FEB/1996.

APPENDICES

APPENDIX A: TOXICOLOGY DATA REQUIREMENTS

HED has requested the submission of developmental thyroid toxicity data for adult rats and young rats following pre- and post-natal exposure to pendimethalin.

Table A.1 Acute Toxicity Profile - Pendimethalin

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral [Rat]	00026657	LD_{50}=1250 mg/kg (m) =1050 mg/kg (f)	III
870.1200	Acute dermal [Rabbit]	00026657	LD_{50} = > 5000 mg/kg	IV
870.1300	Acute inhalation [Rat]	00073342	LC_{50} = 32 mg/L	IV
870.2400	Acute eye irritation [Rabbit]	00026657	slight conjunctival irritation	III
870.2500	Acute dermal irritation [Rabbit]	00026657	no dermal irritation	IV
870.2600	Skin sensitization [Guinea pig]	00153767	non-sensitizer	-

Table A.2 Subchronic, Chronic and Other Toxicity Profile for Pendimethalin.

Guideline No.	Study Type	MRID No./ Classification	Dose Levels	Results
870.3100	Subchronic oral rat (30-day)	000106754 Supplementary	ppm = 0, 800, 1600, 3200 mg/kg/day = 0, 80, 160, 320	NOAEL = 160 mg/kg/day LOAEL = 320 mg/kg/day based on increased liver weight.
870.3100	Subchronic oral rat (13-week)	00156081	ppm = 0, 100, 500, 5000 mg/kg/day = 0, 10, 50, 500	NOAEL = 50 mg/kg/day LOAEL = 500 mg/kg/day based on decreased body weight gain and food consumption, decreased hematocrit and hemoglobin w/ increases in platelets in males, increased liver weight, red thyroids, and hypertrophy of the liver.
870.3100	Subchronic oral rat (13-week)	00059468 Supplementary	ppm = 0, 25, 50, 100, 500, 2500 mg/kg/day = 0, 2.5, 5, 10, 50, 250	NOAEL = 250 mg/kg/day LOAEL was not determined
870.3100	Subchronic oral rat (13 week)	00059469 Supplementary	ppm = 0, 2500 mg/kg/day = 0, 250	NOAEL = 250 mg/kg/day LOAEL was not determined

Table A.2 Subchronic, Chronic and Other Toxicity Profile for Pendimethalin.				
Guideline No.	**Study Type**	**MRID No./ Classification**	**Dose Levels**	**Results**
870.3100	Subchronic oral rat (92-day)	42054601	ppm = 0, 100, 5000 mg/kg/day = 0, 4.98, 245.4	NOAEL = 4.98 mg/kg/day LOAEL = 245.4 mg/kg/day based on thyroid effects
870.3100	Subchronic oral rat (56-day)	43135001	ppm = 0, 500, 5000 mg/kg/day = 0, 31, 292	NOAEL was not determined LOAEL = 31 mg/kg/day based on thyroid effects
870.3100	Subchronic oral rat (14-day)	43135003	ppm = 0, 100, 500 mg/kg/day = 0, 10, 500	NOAEL = 10 mg/kg/day LOAEL = 500 mg/kg/day based on thyroid effects
870.3100	Subchronic oral dog (90-day)	00026672 Supplementary	mg/kg/day = 0, 62.5, 250, 1000	NOAEL = 62.5 mg/kg/day LOAEL = 250 mg/kg/day based on body weight loss
870.3150	Subchronic oral mouse (30-day)	000106754 Supplementary	ppm = 0, 500, 1000, 2000 mg/kg/day = 0, 75, 150, 300	NOAEL = 300 mg/kg/day LOAEL was not determined
870.3200	21-Day dermal toxicity (rat)	00026663	mg/kg/day = 0, 250, 500, 1000	NOAEL = 1000 mg/kg/day LOAEL was not determined
870.3700a	Prenatal Developmental Toxicity (Rat)	00025752 Supplementary; but satisfactory when considered w/ rabbit developmental	mg/kg/day = 0, 125, 250, 500	**Maternal NOAEL** = 500 mg/kg/day (highest dose tested) **Maternal LOAEL** was not determined **Developmental NOAEL** = 500 mg/kg/day (highest dose tested) **Developmental LOAEL** was not determined
870.3700b	Prenatal Developmental Toxicity (Rabbit)	00117444 Supplementary; Upgradeable	mg/kg/day = 0, 15, 30, 60	**Maternal NOAEL** = 60 mg/kg/day (highest dose tested) **Maternal LOAEL** was not determined **Developmental NOAEL** = 60 mg/kg/day (highest dose tested) **Developmental LOAEL** was not determined **Note:** range finding study indicated doses ≥125 mg/kg/day associated with increased mortality

Table A.2 Subchronic, Chronic and Other Toxicity Profile for Pendimethalin.				
Guideline No.	**Study Type**	**MRID No./ Classification**	**Dose Levels**	**Results**
870.3800	Reproduction and fertility effects (2-Generation Reproduction in Rats)	41725203	ppm = 0, 500, 2500, 5000 mg/kg/day (M/F) = 0, 34/43, 172/216, 346/436 HED RED mg/kg/day = 0, 25, 125, 250 HIARC Document **Note:** Doses were obtained from a HED pendimethalin RED and a HIARC document (4/18/2000) which resulted in different dose calculations for mg/kg/day. Consequently, doses are given as a range, based on calculations from actual chemical intake and a generic ratio (1:20) of dietary intake.	**Parental/Systemic NOAEL** = 25-34/43 (M/F) mg/kg/day (500 ppm) **Parental /Systemic LOAEL** = 125-172/216 (M/F) mg/kg/day (2500 ppm) based on decreased body weight gain and food consumption. **Reproductive/Offspring NOAEL** = 25-34/43 (M/F) mg/kg/day (500 ppm) **Reproductive/Offspring LOAEL** = 125-172/216 (M/F) mg/kg/day (2500 ppm) based on decreases in the number of pups born and pup weights.
870.3800	Reproduction and fertility effects 3-Generation Reproduction in Rats	00026671, 0040304, 00059470	ppm = 0, 500, 5000 mg/kg/day = 0, 25, 250	**Parental/Systemic NOAEL** = 25 mg/kg/day. **Parental/Systemic LOAEL** = 250 mg/kg/day based on decreased body weight. **Reproductive/Offspring NOAEL** = 25 mg/kg/day **Reproductive/Offspring LOAEL** = 250 mg/kg/day based on decreased pup body weight gain and possible decreased pups born alive and pup survival.

Table A.2 Subchronic, Chronic and Other Toxicity Profile for Pendimethalin.				
Guideline No.	**Study Type**	**MRID No./ Classification**	**Dose Levels**	**Results**
870.4100a	Chronic toxicity (Mouse)	40909901	ppm = 0, 100, 500, 5000 mg/kg/day (M/F) = 0, 12.3/15.6, 62.3/78.3, 622.1/806.9	NOAEL = 62.3/78.3 mg/kg/day LOAEL = 622.1/806.99 mg/kg/day based on mortality, body weight decrease, organ weight changes and amyloidosis.
870.4100b	Chronic toxicity (2-year Oral Dog)	00058657	mg/kg/day = 0, 12.5, 50, 200	NOAEL = 200 mg/kg/day LOAEL was not established. [2]
870.4200	Chronic Toxicity/Carcino-genicity (2-year Oral Rat)	40174401	ppm = 0, 100, 500, 5000 mg/kg/day = 0, 5, 25, 250	NOAEL = 25 mg/kg/day LOAEL = 250 mg/kg/day based on decreased survival, body weight gain and decreased food consumption, increased gamma glutamyl transferase, cholesterol and liver weights and thyroid effects.
870.4200	Chronic Toxicity (2-year Oral Rat)	42027802	ppm = 0, 1250, 2500, 3750, 5000 mg/kg/day = 0, 51, 103, 154, 213	NOAEL was not determined LOAEL = 51 mg/kg/day based on non-neoplastic thyroid follicular cell changes.
870.4300	Carcinogenicity (18-month Oral Mouse)	40909901	ppm = 0, 100, 500, 5000 mg/kg/day (M/F) = 0, 12.3/15.6, 62.3/78.3, 622.1/806.9	NOAEL = 62.3/78.3 mg/kg/day LOAEL = 622./806.9 mg/kg/day based on mortality, body weight decrease, organ weight changes and amyloidosis.
870.5100	Reverse Gene Mutation Assay in Bacteria strains of S. typhimurium	00153768	50, 158, 500, 1581, 5000 µg/plate	**Positive** Evidence of a 2-fold increase in number of induced mutant colonies over background at all doses from 50 to 5000 µg/plate
870.5100	Reverse Gene Mutation Assay in Escherichia coli WP2	43177801	25, 50, 100, 250, 500, 750 µg/plate	**Negative**
870.5100	Reverse Gene Mutation Assay in Escherichia coli WP2	43135005	50, 158, 500, 1581, 5000 µg/plate or 1000 µg/paper disk/plate	**Negative**

Table A.2 Subchronic, Chronic and Other Toxicity Profile for Pendimethalin.				
Guideline No.	**Study Type**	**MRID No./ Classification**	**Dose Levels**	**Results**
870.5100	Reverse Gene Mutation Assay in Escherichia coli WP2	43135006	50, 100, 250, 500, 750 µg/plate	**Negative**
870.5300	Mammalian Cell Gene Mutation in Chinese hamster ovary	43177802	1, 5, 7.5, 10, 20, 30, 40, 50 µg/ml (-S9) 10, 25, 50, 75, 100, 125, 150, 175 µg/ml (+S9)	**Negative**
870.5375	Chromosomal Aberration (CHO)	00153770	Doses ranging from 5-50 µg/ml	**Negative**
870.5395	Mouse Micronucleus Study	42027801	313, 625, 1250 mg/kg	**Negative**
870.5550	Alkaline Elution Assay in Rats	43135007	1250, 2500, 5000 mg/kg/bw	**Negative**
870.7485	Metabolism and pharmacokinetics in Rat	00046275	n/a	Pendimethalin is eliminated from body with 70% being excreted in feces primarily parent compound and 20% in urine within 24 hours.

Some of the LOAELs/NOAELS in Table 4.1b were previously denoted as LOELs/NOELS in Data Evaluation Records (DERs), the language was updated to comply with current standards without re-examining effects. As new uses for pendimethalin are submitted, DERs will be re-reviewed and updated.

APPENDIX B: METABOLISM CONSIDERATION

The nature of the residue in plants, livestock and rotational crops is adequately understood.

Metabolism studies identified and discussed in the 13/MAY/1996 RED chapter support the currently proposed uses. Rotational crop tolerances are not needed, provided labels specify rotational crop PBIs of 90-days for cereal grains, and 270 days for all other crops.

As a result of the proposed increase in seasonal application rate (pursuant to the alfalfa petition) which may be applied to rotatable food/feed crops (from 2.0 lb ai/A to 4.0 lb ai/A), HED is requesting a limited field accumulation study (OPPTS 860.1900) to determine the amount of pesticide residue uptake into rotational crops. HED concludes that the registrant should impose PBIs of 90-days for rotated cereal grain crops, and 270-days for all other rotated crops, until the limited field rotational crop study has been conducted.

APPENDIX C: TOLERANCE ASSESSMENT SUMMARY AND TABLE
(DP Num: 334173; D. Rate; 02/AUG/2007)

The Residue Chemistry Chapter for the Pendimethalin RED concluded that the residues of concern in plants are pendimethalin [N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine] and its metabolite, 4-[(1-ethylpropyl)amino]-2-methyl-3,5-dinitrobenzyl alcohol (CL202,347). The chemical names and structures of pendimethalin and CL202,347 are depicted in Appendix I. The proposed tolerance expression is consistent with 40CFR §180.361.

A summary of tolerance assessments, following ARIA's review of submitted field and processing studies, is presented in Table 7. ARIA recommends tolerances of 0.10 ppm for the commodities listed in Table 7 which were not entered in a Tolerance/MRL Harmonization Spreadsheet (all proposed commodities except asparagus), because all of the samples treated at the proposed 1X application rate bore residues below the method LLMV (or LOQ) (<0.050 ppm) for each analyte. Following application at 1X, the combined residues were <0.1 ppm in all samples of artichoke (n = 6 samples), broccoli (n = 12), cabbage (n = 7) and grape (n = 18). The residues observed in all but two samples of asparagus (n = 12) treated at 1X were also <0.050 ppm for each analyte. The proposed tolerance for asparagus was calculated using the maximum limit estimator (MLE) and the maximum residue limit (MRL) spreadsheet. Without ignoring lognormality, a value of 0.15 ppm was recommended for asparagus using the 95th percentile of EU method I.

There are currently no Canadian , Mexico or Codex maximum residue limits (MRLs) for pendimethalin on the proposed commodities. An International Residue Limit Status sheet is appended at the end of this document in Appendix II.

Pendimethalin tolerances are not required for milk, meat, poultry, nor eggs for the purpose of evaluating the subject IR-4 petition.

Pending submission of a revised Section F to reflect appropriate tolerance levels, there are adequate residue data to support the establishment of pendimethalin tolerances on artichoke, globe; asparagus; *Brassica* head and stem vegetables, subgroup 5A; and grape.

Table C.1 Tolerance Summary for Pendimethalin.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments[1]; *Correct Commodity Definition*
Brassica, head and stem, subgroup 5A	0.05	0.1	Adequate field trial data are available. All combined residues were <0.1 ppm.
Artichoke, globe	0.05	0.1	Adequate field trial data are available. All combined residues were <0.1 ppm.
Asparagus	0.1	0.15	Adequate asparagus field trial data are available and the tolerance was calculated using the MLE and MRL spreadsheets.
Grape	0.05	0.1	Adequate grape field trial data are

			available. All residues in the field studies were below the combined residue LLMV (<0.1 ppm).
Grape, juice	--	0.15	Adequate grape processing studies were not provided. The study must use an application rate of at least 5X or the petitioner may show that the exaggerated rate is phytotoxic to the crop. Once adequate studies have been reviewed, the tolerance may be revised or withdrawn.
Grape, raisin	--	0.50	

[1] MLE = Maximum Limit Estimater; MRL = Maximum Residue Limit

APPENDIX D: REVIEW OF HUMAN RESEARCH

No MRID - PHED Surrogate Exposure Guide