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Interregional Research Project (IR-4)

PP No. 8E7314 (Revised NOF to address Potato 9/08) [EPA-HQ-OPP-2008-0272]

EPA has received a pesticide petition (PP# 8E7314) from IR-4 Project Headquarters, 500 College Road East, Suite 201 W. Princeton, NJ 08540, proposing, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180.493, by establishing a tolerance for residues of dimethomorph, [(E,Z)4-[3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)-1-oxo-2-propenyl]-morpholine] in or on beans, lima at 0.6 parts per million (ppm); ginseng at 0.85 ppm; grape at 3.5 ppm; grape raisin at 6.0 ppm; and greens, turnip 20 ppm**. Additionally, it is proposed that the existing tolerance level for potato, wet peel be increased from 0.15 to 0.20 ppm and that a tolerance for potato at 0.05 ppm be re-established.** EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data support granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism*. Based upon the results of metabolism studies conducted on potato, grape, and lettuce, the nature of the residues in lima beans, ginseng, grape, raisin, and turnip greens is considered to be understood. The results of the potato metabolism study show only negligible residues in tubers, 0.01-0.02 parts per million (ppm) total radioactive residues (TRR). This is in contrast to the aerial portions of the plant, which were found to have up to 23.5 ppm TRR, thus demonstrating that translocation of dimethomorph downward within the plant was not significant. Almost all of the radioactive residue (97.8%) was extractable from the plant at harvest. In the aerial portion of the plant, approximately 70% of the TRR was identified as dimethomorph. No metabolites were identified that require regulation.

The results of the grape metabolism study showed that the TRR in/on grapes harvested 35 days following the last of four applications [0.8 lb active ingredient per acre (ai/A) per application for four consecutive weeks] for a total rate of 3.2 lb ai/A was 14.6 ppm. Unmetabolized dimethomorph accounted for 87.3% of the TRR (12.7 ppm). No metabolites were identified that require regulation.

The results of the lettuce metabolism study showed that the TRR in/on lettuce leaves harvested 4 days following the last of 4 applications [approximately 1.0 lb ai/A per application with a 9 to 11 day spray interval], for a total rate of 4.1 lb ai/A, was 102 ppm. Of this total residue, 98.5% was extractable and unmetabolized dimethomorph accounted for greater than 93% of the extractable TRR. No metabolites were identified that require regulation.

2. *Analytical method*. A reliable method for the determination of dimethomorph residues in lima beans, ginseng, grape, raisin and turnip greens exists; this method is the FDA Multi-Residue Method, Protocol D, as published in the Pesticide Analytical Manual I.

3. *Magnitude of residues*. The residue data for Ginseng submitted to support this tolerance petition were collected from 4 ginseng studies conducted in region 5 of the United States. Trials were conducted using multiple applications (7) of dimethomorph applied at 0.198 to 0.24 lb ai/A with a maximum seasonal rate of 1.4 to 1.7 lb ai/A (1.4 to 1.7X the proposed label rate). Dimethomorph residues observed in these field trials for ginseng ranged from 0.28 ppm to 0.62 ppm when harvested 13 to 15 days after the last application. Therefore, a tolerance of 0.85 ppm in or on Ginseng is proposed.

The residue data for Lima Bean submitted to support this tolerance petition were collected from 7 lima bean studies conducted in regions 2 and 5 of the United States. Trials were conducted using multiple applications (7 to 8) of dimethomorph applied at 0.2 lb ai/A with a maximum seasonal rate of 1.4 to 1.6 lb ai/A (1.4 to 1.6X the proposed label rate). Dimethomorph residues observed in these field trials for lima bean ranged from 0.03 ppm to 0.48 ppm when harvested 0 days after the last application. Therefore, a tolerance of 0.6 ppm in or on Lima Bean is proposed.

The residue data for Grape submitted to support this tolerance petition were previously submitted to establish the current import tolerance for grape and grape, raisin. The residue data for grape were collected from 27 grape studies conducted in Europe. Trials were conducted using multiple applications (4 to 11) of dimethomorph applied at 0.11 to 0.36 lb ai/A with a maximum seasonal rate of 0.55 to 3.57 lb ai/A (0.55 to 3.57X the proposed label rate). Dimethomorph residues observed in these field trials for grape ranged from 0.05 ppm to 2.6 ppm when harvested 0 to 90 days after the last application. Therefore, tolerances of 3.5 ppm in or on Grape and 6 ppm for Grape, Raisin are proposed.

The residue data for Turnip Greens submitted to support this tolerance petition were previously submitted to establish the current tolerance for brassica leafy greens at 20 ppm. The residue data for leafy brassica greens were collected from eight (8) mustard green studies conducted in mustard green producing regions of the United States. Trials were conducted using multiple applications (7) of dimethomorph applied at 0.2 lb ai/A with a maximum seasonal rate of 1.4 lb ai/A. This exceeds the proposed label rate for dimethomorph on turnip greens (1.0 lb ai/A). Dimethomorph residues observed in these field trials ranged from 0.65 to 18.1 ppm after last application on day of harvest. Therefore, a tolerance of 20.0 ppm in or on Turnip Greens is proposed.

In the Federal Register of March 26, 1997 (62 FR 14418)(FRL-5594-7), EPA issued a notice pursuant to section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(e) announcing the filing of a pesticide petition (PP 7F4816) for tolerance by American Cyanamid Company, Agricultural Products Division, P.O. Box 400, Princeton, NJ 08543-0400. The EPA subsequently established tolerances for residues of potato at 0.05 ppm in a Federal Register of October 13, 1998 (63 FR 54597)(FRL-6036-7). Since that time the

potato tolerance has been inadvertently removed from 40 CFR part 180.493. Therefore, a tolerance for potato at 0.05 ppm is proposed.

B. Toxicological Profile

1. *Acute toxicity*. i. Oral LD50 studies were conducted on dimethomorph technical:

a. An acute oral toxicity study in the Sprague-Dawley rat for dimethomorph technical with a LD_{50} of 4,300 milligrams/kilogram body weight (mg/kg b.w.) for males and 3,500 mg/kg b.w. for females. Based upon EPA toxicity criteria, the acute oral toxicity category for dimethomorph technical is Category III or slightly toxic.

b. An acute toxicity study in the CD-1 mouse for dimethomorph technical with a LD50 of greater than 5000 mg/kg b.w. for males and 3699 mg/kg/b.w. for females. Based on the EPA toxicity category criteria, the acute oral toxicity category for dimethomorph technical is Category III or slightly toxic.

ii. Oral LD_{50} studies were conducted on the two isomers (E and Z) alone:

a. An acute oral toxicity study in the Wistar rat for the E-isomer with a LD_{50} greater than 5,000 mg/kg b.w. for males and approximately 5,000 mg/kg b.w. for females.

b. An acute oral toxicity study in the Wistar rat for the Z-isomer with a LD_{50} greater than 5,000 mg/kg b.w. for both males and females.

iii. An acute dermal toxicity study in the Wistar rat for dimethomorph technical with a dermal LD_{50} greater than 5,000 mg/kg b.w. for both males and females. Based on the EPA toxicity category criteria, the acute dermal toxicity category for dimethomorph is Category IV or relatively non-toxic.

iv. A 4-hour inhalation study in Wistar rats for dimethomorph technical with a LC_{50} greater than 4.2 mg/L for both males and females. Based on the EPA toxicity category criteria, the acute inhalation toxicity category for dimethomorph technical is Category IV or relatively non-toxic.

v. A skin irritation study was performed using New Zealand White rabbits. Based on the EPA toxicity criteria, the skin irritation toxicity category for dimethomorph technical in this study is Category IV or non-to-slightly irritating.

vi. An eye irritation study using New Zealand White rabbits demonstrated dimethomorph technical produced moderate conjunctival redness, slight to moderate chemosis and slight discharge three hours after treatment. Based on the EPA toxicity criteria, the eye toxicity category for dimethomorph technical is Category III (slightly-to-moderately irritating)

2. *Genotoxicty*. i. Salmonella reverse gene mutation assays (2 studies) were negative up to a limit dose of 5,000 μg/plate. Chinese hamster lung V79 cells were negative for mutations at the HGPRT locus at up to toxic doses in two studies.

ii. Two Chinese hamster lung (V79 cells) structural chromosomal studies were reportedly positive for chromosomal aberrations at the highest dose tested (HDT) (160 μg/ml/-S9; 170 μg/ml/+S9). However, dimethomorph induced only a weak response in increasing chromosome aberrations in this test system. In addition, these results were not confirmed in two micronucleus tests under in vivo conditions.

iii. Structural Chromosomal Aberration studies were weakly positive in human lymphocytic cultures, but only in S9 activated cultures treated at 422 μg/ml, the highest dose tested (HDT), which was strongly cytotoxic. No increase in chromosomal aberrations was observed in the absence of S9 activation at all doses. Furthermore, the positive clastogenic response observed under the in vitro conditions was not confirmed in two in vivo micronucleus assays.

iv. Micronucleus assay (2 studies) indicated that dimethomorph was negative for inducing micronuclei in bone marrow cells of mice following i.p. administration of doses up to 200 mg/kg or oral doses up to the limit dose of 5,000 mg/kg. Thus, dimethomorph was found to be negative in these studies for causing cytogenic damage in vivo.

v. Dimethomorph was negative for inducing unscheduled DNA synthesis, in cultured rat liver cells, at doses up to 250 μg/ml, a weakly cytotoxic level.

Dimethomorph was negative for transformation in Syrian hamster embryo cells treated, in the presence and absence of activation, up to cytotoxic concentrations (265 μg/ml/+S9; 50 μg/ml/-S9).

3. *Reproductive and developmental toxicity*. i. A rat developmental toxicity study with a Lowest-Observed-Effect Level (LOEL) for maternal toxicity of 160 mg/kg/day and a No-Observed-Effect Level (NOEL) for maternal toxicity of 60 mg/kg/day. The NOEL for developmental toxicity is 60 mg/kg/day. Dimethomorph is not teratogenic in the Sprague-Dawley rat.

ii. A rabbit development toxicity study with a LOEL for maternal toxicity of 650 mg/kg/day and a NOEL for maternal toxicity of 300 mg/kg/day. The NOEL for developmental toxicity is 650 mg/kg/day, the highest dose tested. Dimethomorph is not teratogenic in the New Zealand white rabbit.

iii. A two-generation rat reproduction study with a LOEL for parental systemic toxicity of 1000 ppm, or approximately 80 mg/kg/day, and a NOEL for parental systemic toxicity of 300 ppm, or approximately 24 mg/kg/day. The NOEL for fertility and reproductive function was 1000 ppm, the highest concentration tested, or approximately 80 mg/kg b.w./day.

4. *Subchronic toxicity*. i. A 90-day dietary study in Sprague-Dawley rats with a NOEL of greater than or equal to 1000 ppm, the highest concentration tested, or approximately 73 mg/kg/day for males and 82 mg/kg/day for females.

ii. A 90-day dog dietary study with a NOEL of 450 ppm, or approximately 15 mg/kg/day, and a LOEL of 1350 ppm, or approximately 43 mg/kg/day.

5. *Chronic toxicity*. i. A 2-year chronic toxicity study in Sprague-Dawley rats with a NOEL of 200 ppm or approximately 9 mg/kg/day for males and 12 mg/kg/day for females. The LOEL for systemic toxicity is 750 ppm, or approximately 36 mg/kg/day for males and 58 mg/kg/day for females.

ii. A 1-year chronic toxicity study in dogs with a NOEL of 450 ppm, or approximately 14.7 mg/kg/day and a LOEL of 1350, or approximately 44.6 mg/kg/day.

iii. A 2-year oncogenicity study in Sprague-Dawley rats with a NOEL for systemic toxicity of 200 ppm, or approximately 9 mg/kg/day for males and 11 mg/kg/day for females.

The LOEL for systemic toxicity was 750 ppm, or approximately 34 mg/kg/day for males and 46 mg/kg/day for females. There was no evidence of increased incidence of neoplastic lesions in treated animals. The NOEL for oncogenicity is 2000 ppm, the highest concentration tested, or approximately 95 mg/kg/day for males and 132 mg/kg/day for females.

iv. A 2-year oncogenicity study in CD-1 mice with a NOEL for systemic toxicity of 100 mg/kg/day and a LOEL of 1,000 mg/kg/day. There was no evidence of increased incidence of neoplastic lesions in treated animals. The NOEL for oncogenicity is 1,000 mg/kg/day, the highest dose tested.

6. *Animal metabolism*. Results from the livestock and rat metabolism studies show that orally administered dimethomorph was rapidly excreted by the animals. The principal route of elimination is the feces.

7. *Metabolite toxicology*. There were no metabolites identified in plant or animal commodities which require regulation.

8. *Endocrine disruption*. Collective organ weights and histopathological findings from the two-generation reproduction study in rats, as well as from the subchronic and chronic toxicity studies in two or more animal species, demonstrate no apparent estrogenic effects or effects on the endocrine system. There is no information available that suggests that dimethomorph technical would be associated with endocrine effects.

C. Aggregate Exposure

1. *Dietary exposure*. An assessment was conducted to evaluate the potential risk due to chronic dietary exposure of the U.S. population and sub-populations to residues of dimethomorph. This analysis included all current tolerances listed in U.S. 40 CFR § 180.493 including potato peel and potato and the proposed tolerances for lima beans, ginseng, grape, grape raisin, and turnip greens.

i. *Food*. Acute Dietary Exposure Assessment

An acute assessment was not needed since the U.S. EPA Toxicological Endpoint Selection (TES) Committees had previously evaluated the dimethomorph toxicity data, including developmental and maternal toxicity in the developmental toxicity studies and determined there was no toxicological endpoints for acute dietary exposure and a quantitative acute dietary exposure and risk assessment were not required.

Chronic Dietary Exposure Assessment

A Tier 1 chronic dietary exposure assessment was conducted assuming tolerance level residues and 100% crop treated factors for all registered and proposed crops. The EPA Food Commodity Ingredient Database (FCID) was also used in Exponent's Dietary Exposure Evaluation Module (DEEM-FCID) software. Inadvertent residues in animal commodities (i.e. meat, meat byproducts, milk, eggs) were not considered as a result of grain forage since studies have shown

dimethomorph does not accumulate in animal tissues or milk and tolerance values for these commodities are not required by the EPA.

Dietary exposure estimates were compared against the established dimethomorph chronic Population Adjusted Dose (cPAD) of 0.11 mg/kg b.w./day for all populations. Results of the chronic dietary assessments are listed in the table below. The estimated chronic dietary exposure from crops (both established and proposed tolerances) was less than 16% of the cPAD for all subpopulations (Table 1). Additional refinements such as the use of anticipated residues would further reduce the estimated chronic dietary exposure. The results in the Table below demonstrate that there are no safety concerns for any subpopulation based on established and new uses, and that the results clearly meet the FQPA standard of reasonable certainty of no harm.

Table 1. Summary of Chronic Dietary Exposure Assessment considering crops with established and proposed tolerances for Dimethomorph.

Population sub-group	Chronic Exposure (mg/kg bw/day)	%cPAD
US Population	0.0075910	6.90
All infants (< 1 year)	0.0042140	3.83
Children 1-2	0.0168600	15.33
Children 3-5	0.0132540	12.05
Children 6-12	0.0078260	7.11
Youth 13-19	0.0058480	5.32
Adults 20-49	0.0071590	6.51
Adults 50+ yrs	0.0069390	6.31
Females 13 - 49 yrs	0.0067210	6.11

ii. *Drinking water*. The chronic drinking water values used in this analysis were the values proposed by EPA Federal Register Notice, September 29, 2003, Volume 68, No. 188. The chronic drinking water value used was 28.3 ug/L.

Table 1. Summary of Chronic Drinking Water Exposure Assessment Considering the Maximum Estimated Chronic Drinking Water Concentration for Dimethomorph.

Population sub-group	Chronic Exposure (mg/kg bw/day)	%cPAD
US Population	0.000506	0.46
All infants (< 1 year)	0.001658	1.51
Children 1-2	0.000751	0.68
Children 3-5	0.000703	0.64
Children 6-12	0.000485	0.44
Youth 13-19	0.000366	0.33
Adults 20-49	0.000472	0.43
Adults 50+ yrs	0.000497	0.45
Females 13 - 49 yrs	0.00047	0.43

Acute Aggregate Exposure and Risk (Food and water)

Since the U.S. EPA Toxicological Endpoint Selection (TES) Committees has evaluated the dimethomorph toxicity data and determined there was no toxicologic endpoints for acute dietary exposure, the determination of an acute aggregate exposure and risk evaluation was not required.

Chronic Aggregate Exposure and Risk (food and water)
The aggregate chronic risk includes residues of dimethomorph from food and water (Table 3). Exposures from residential uses are not included in the chronic aggregate assessment. The results demonstrate there are no safety concerns for any subpopulation based on established and new uses, and that the results clearly meet the FQPA standard of reasonable certainty of no harm.

Table 3. Estimated Chronic Aggregate Exposure and Risk for Dimethomorph.

Population Subgroup	cPAD (mg/kg/day)	Food Exposure (mg/kg/day)	Water Exposure (mg/kg/day)	Total Exposure (mg/kg/day)	% cPAD
U.S. Population	0.11	0.007591	0.000506	0.008097	7.36
All Infants (< 1 yr old)	0.11	0.004214	0.001658	0.005872	5.34
Children 1-2 years	0.11	0.01686	0.000751	0.017611	16.01
Children 3-5 years	0.11	0.013254	0.000703	0.013957	12.69
Children 6 – 12 years	0.11	0.007826	0.000485	0.008311	7.56
Youth 13-19 years	0.11	0.005848	0.000366	0.006214	5.65
Females 13-49 years	0.11	0.007159	0.000472	0.007631	6.94
Adults 20-49 years	0.11	0.006939	0.000497	0.007436	6.76
Adults + 50	0.11	0.006721	0.00047	0.007191	6.54

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2. *Non-dietary exposure*. Dimethomorph is not registered for use on any sites that would result in residential exposure. Therefore, a residential exposure and risk assessment was not conducted.

D. Cumulative Effects

There is no information to indicate that any toxic effects produced by dimethomorph would be cumulative with those of any other chemical. The fungicidal mode of action of dimethomorph is unique; dimethomorph inhibits cell wall formation only in Oomycete fungi. The result is lysis of the cell wall that kills growing cells and inhibits spore formation in mature hyphae. This unique mode of action and limited pest spectrum suggest that there is little or no potential for cumulative toxic effects in mammals. In addition, the toxicity studies submitted to support this petition do not indicate that dimethomorph is a particularly toxic compound. No toxic end-points of potential concern were identified.

E. Safety Determination

1. *U.S. population*. Based on this risk assessment, BASF concludes that there is a reasonable certainty that no harm will result to the general population from the aggregate exposure to dimethomorph residues.

2. *Infants and children*. Based on this risk assessment, BASF concludes that there is a reasonable certainty that no harm will result to infants or children from the aggregate exposure to dimethomorph residues.

F. International Tolerances

There are no Canadian, Mexican, or Codex MRLs established for dimethomorph for the commodities associated with this request; consequently, a discussion of international harmonization is not relevant.