ENVIRONMENTAL PROTECTION AGENCY

[PF–801; FRL–5781–9]

Notice of Filing of Pesticide Petitions

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This notice announces the initial filing of pesticide petitions proposing the establishment of regulations for residues of certain pesticide chemicals in or on various food commodities.

DATES: Comments, identified by the docket control number PF–801, must be received on or before May 15, 1998.

ADDRESSES: By mail submit written comments to: Public Information and Records Integrity Branch, Information Resources and Services Division (7502C), Office of Pesticides Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. In person bring comments to: Rm. 119FF, CM #2, 1921 Jefferson Davis Highway, Arlington, VA.

Comments and data may also be submitted electronically by following the instructions under ''SUPPLEMENTARY INFORMATION.'' No confidential business information should be submitted through e-mail.

Information submitted as a comment concerning this document may be claimed confidential by marking any part or all of that information as ''Confidential Business Information'' (CBI). CBI should not be submitted through e-mail. Information marked as CBI will not be disclosed except in accordance with procedures set forth in 40 CFR part 2. A copy of the comment that does not contain CBI must be submitted for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice. All written comments will be available for public inspection in Rm. 1132 at the address given above, from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays.

FOR FURTHER INFORMATION CONTACT: The product manager listed in the table below:

Product Manager	Office location/telephone number	Address
Sidney Jackson (PM 5)	Rm. 268, CM #2, 703–305–7610, e-mail:jackson.sidney@epamail.epa.gov.	1921 Jefferson Davis Hwy, Arlington, VA
Bipin Gandhi (PM 5)	Rm. 4W53, CS #2, 703–308–8380, e-mail: gandhi.bipin@epamail.epa.gov.	Do.

SUPPLEMENTARY INFORMATION: EPA has received pesticide petitions as follows proposing the establishment and/or amendment of regulations for residues of certain pesticide chemicals in or on various food commodities under section 408 of the Federal Food, Drug, and Comestic Act (FFDCA), 21 U.S.C. 346a. EPA has determined that these petitions contain data or information regarding the elements set forth in section 408(d)(2); 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.

The official record for this notice of filing, as well as the public version, has been established for this notice of filing under docket control number [PF–801] (including comments and data submitted electronically as described below). A public version of this record, including printed, paper versions of electronic comments, which does not include any information claimed as CBI, is available for inspection from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The official record is located at the address in ''ADDRESSES'' at the beginning of this document.

Electronic comments can be sent directly to EPA at:

opp-docket@epamail.epa.gov

Electronic comments must be submitted as an ASCII file avoiding the use of special characters and any form of encryption. Comment and data will also be accepted on disks in Wordperfect 5.1 file format or ASCII file format. All comments and data in electronic form must be identified by the docket number FRL–5781–9 and appropriate petition number. Electronic comments on notice may be filed online at many Federal Depository Libraries.

List of Subjects

Environmental protection, Agricultural commodities, Food additives, Feed additives, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: April 1, 1998

James Jones,

Director, Registration Division, Office of Pesticide Programs.

Summaries of Petitions

Petitioner summaries of the pesticide petitions are printed below as required by section 408(d)(3) of the FFDCA. The summaries of the petitions were prepared by the petitioners and represent the views of the petitioners. EPA is publishing the petition summaries verbatim without editing them in any way. The petition summary announces the availability of a description of the analytical methods available to EPA for the detection and measurement of the pesticide chemical residues or an explanation of why no such method is needed.

1. Interregional Research Project

PP 2E4101

EPA has received a pesticide petition (PP 2E4101) from the Interregional Research Project Number 4 (IR-4), proposing pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 346a(d), to amend 40 CFR part 180 by establishing a tolerance for residues of the insecticide cyfluthrin, [cyano[4-fluoro-3-phenoxyphenyl]-methyl-3-[2,2- dicloroethenyl]-2,2-dimethylcyclopropanecarboxylate] in or on the raw agricultural commodity dried hops at 20.0 parts per million (ppm) and to remove the established tolerance for fresh hops at 4.0 ppm. EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the Federal Food Drug and Cosmetic Act (FFDCA); however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the proposed tolerance. Additional data may be needed before EPA rules on the petition. This notice includes a summary of the petition prepared by Bayer Corporations (Bayer), the registrant.

A. Residue Chemistry

1. *Plant metabolism*. The metabolism of cyfluthrin in plants is adequately understood. Studies have been conducted to delineate the metabolism of radiolabeled cyfluthrin in various crops all showing similar results. The residue of concern is cyfluthrin.

2. *Analytical method*. Adequate analytical methodology (gas liquid chromatography with an electron capture detector) is available for enforcement purposes. The methodology was successfully validated by EPA's Beltsville laboratory in support of tolerances on cottonseed. The enforcement methodology has been submitted to the Food and Drug Administration for publication in the Pesticide Analytical Manual Vol. II (PAM II). Because of the long lead time for publication of the method in PAM II, the analytical methodology is being made available in the interim to anyone interested in pesticide enforcement when requested from Calvin Furlow, Public Response and Program Resource Branch, Field Operations Division (7502C), Office of Pesticide Programs, U.S. Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. Office location and telephone number: Rm. 119FF, CM #2, 1921 Jefferson-Davis Hwy., Arlington, VA 22202, (703) 305-5232.

The established tolerances for residues of cyfluthrin in/on eggs, milks, fat, meat and meat by-products of cattle, goats, hogs, horses, sheep and poultry are adequate to cover secondary residues resulting from the proposed use as delineated in 40 CFR 180.6(a)(2).

3. *Magnitude of residues*. Import tolerances for cyfluthrin are presently established on fresh hops at 4.0 ppm and on dried hops at 20.0 ppm. IR-4 has conducted field trials in Washington, Oregon and Idaho in order to support expansion of the tolerances to include the domestic production of hops in the United States.

The residue data submitted to the EPA by IR-4 consist of three trials, one each in Washington, Oregon and Idaho. In each trial, hops were planted in three plots, two treated and one untreated. Cyfluthrin (Baythroid 2) was applied by foliar (ground) application at a rate of 0.05 pounds(lb) active ingredient(ai)/acre(A) to one plot and 0.1 lb ai/A to another. Five separate applications were made with an interval of 7-days between the last application and harvest.

Residues of cyfluthrin were detected in all treated samples from each trial and no interferences were detected in samples from control plots. The residue data are consistent for each trial. Cyfluthrin applied at 0.05 lb ai/A was detected from 0.44 to 0.78 ppm on fresh hops and from 1.83 to 2.36 ppm on dried hops. At 0.10 lb ai/A, residues were detected at 1.10 to 2.70 ppm on fresh hops and 3.76 to 7.57 ppm on dried hops.

B. Toxicological Profile

The data base for cyfluthrin is essentially complete. Data lacking but desirable are an acute neurotoxicity study in rats and a 90-day neurotoxicity study in rats. Although these data are lacking, Bayer believes the available toxicity data are sufficient to support the proposed tolerance and these missing data will not significantly change its risk assessment. Bayer has committed to submit the acute neurotoxicity study and the 90-day neurotoxicity study.

1. *Acute toxicity*. Results of acute toxicity tests show an acute oral lethal dose (LD_{50}) grater than or equal to 16.2 milligram (mg)/ kilogram (kg), a dermal (LD_{50}) >5,000 mg/kg, inhalation lethal concentration (LC_{50} greater than or equal to 0.468 mg/liter(L), primary eye irritation and primary dermal irritation show toxicity categories III and IV, respectively. Dermal sensitization tests conducted show that cyfluthrin is not a dermal sensitizer.

2. *Genotoxicty*. Mutagenicity tests were conducted, including several gene mutation assays (reverse mutation and recombination assays in bacteria and a Chinese hamster ovary(CHO)/HGPRT assay); a structural chromosome aberration assay (CHO/sister chromatid exchange assay); and an unscheduled DNA synthesis assay in rat hepatocytes. All tests were negative for genotoxicity.

3. *Reproductive and developmental toxicity*. An oral developmental toxicity study in rats with a maternal and fetal no-observed effect level (NOEL) of 10 mg/kg/day (highest dose tested). An oral developmental toxicity study in rabbits with a maternal NOEL of 20 mg/kg/day and a maternal lowest effect level (LEL) of 60 mg/kg/day, based on decreased body weight gain and decreased food consumption during the dosing period. A fetal NOEL of 20 mg/kg/day and a fetal LEL of 60 mg/kg/day were also observed in this study. The LEL was based on increased resorptions and increased postimplantation loss.

A developmental toxicity study in rats by the inhalation route of administration with a maternal NOEL of 0.0011 mg/l and a LEL of 0.0047 mg/l, based on reduced mobility, dyspnea, piloerection, ungroomed coats and eye irritation. The fetal NOEL is 0.00059 mg/l and the fetal LEL is 0.0011 mg/l, based on sternal anomalies and increased incidence of runts. A second developmental toxicity study in rats by the inhalation route of administration has been submitted to the Agency. A 3-generation reproduction study in rats with a systemic NOEL of 2.5 mg/kg/day and a systemic LEL of 7.5 mg/kg/day due to decreased parent and pup body weights. The reproductive NOEL and LEL are 7.5 mg/kg/day and 22.5 mg/kg/day respectively.

4. *Subchronic toxicity*. In a 28-day oral toxicity study in rats, cyfluthrin demonstrated a NOEL of 20 mg/kg/day. The lowest-observed-effect level (LOEL) was 80 (40) mg/kg/day in both sexes based on clinical signs of nerve toxicity, decreases in body weight gain, and changes in liver and adrenal weights. The high dose was 80 mg/kg/day during the first and third weeks and 40 mg/kg/day during the second and fourth weeks.

In a six month dog feeding study established a NOEL at 5 mg/kg/day for male and females. The LOEL for this study was 15 mg/kg/day for both sexes, based on neurological effects (hindlimb abnormalities) and gastrointestinal disturbances.

A 21-day repeated dose dermal toxicity study, male and female rats were treated with cyfluthrin by dermal occlusion at target doses of 0, 100, 340, or 1,000 mg/kg/day for 6 hours/day (average actual dose levels were 0, 113, 376 or 1,077 mg/kg/day). No mortality was observed, and there were no treatment-related effects on body weight, ophthalmology, organ weights, clinical biochemistry, or hematology. The LOEL for dermal effects was 376 mg/kg/day for male and female Sprague-Dawley rats based on gross and histological skin lesions. The NOEL for dermal effects was 113 mg/kg/day. The LOEL for systemic effects was 1,077 mg/kg/day based on decreased food consumption, red nasal discharge and urine staining. The NOEL for systemic effects was 376 mg/kg/day.

5. *Chronic toxicity*. A 12-month chronic feeding study in dogs with a NOEL of 4 mg/kg/day. The LEL for this study is established at 16 mg/kg/day, based on slight ataxia, increased vomiting, diarrhea and decreased body weight.

A 24-month chronic feeding/carcinogenicity study in rats showed a NOEL of 2.5 mg/kg/day and LEL of 6.2 mg/kg/day, based on decreased body weights in males, decreased food consumption in males, and inflammatory foci in the kidneys in females.

6. *Carcinogenicity*. A 24-month carcinogenicity study in mice was conducted. There were no carcinogenic effects observed under the conditions of the study.

A 24-month chronic feeding/carcinogenicity study in rats was conducted. There were no carcinogenic effects observed under the conditions of the study.

Cyfluthrin has been classified as a Group E chemical (evidence of non-carcinogenicity for humans) by the Agency. The classification was based on a lack of convincing evidence of carcinogenicity in adequate studies with two animal species, rat and mouse.

7. *Animal metabolism*. A metabolism study in rats showed that cyfluthrin is rapidly absorbed and excreted, mostly as conjugated metabolites in the urine, within 48 hours. An enterohepatic circulation was observed.

8. *Ednocrine effects*. No special studies investigating potential estrogenic or endocrine effects of cyfluthrin have been conducted. However, the standard battery of required studies has been completed. These studies include an evaluation of the potential effects on reproduction and development, and an evaluation of the pathology of the endocrine organs following repeated or long-term exposure. According to Bayer no endocrine effects were noted in any of the studies.

C. Aggregate Exposure

1. *Dietary exposure*. In examining aggregate exposure, FFDCA section 408 requires that EPA take into account available and reliable information concerning exposure from the pesticide residue in the food in question, residues in other foods for which there are tolerances, residues in ground water or surface water that is consumed as drinking water, and other non-occupational exposures through pesticide use in gardens, lawns, or buildings (residential and other indoor uses). Dietary exposure to residues of a pesticide in a food commodity are estimated by multiplying the average daily consumption of the food forms of that commodity by the tolerance level or the anticipated pesticide residue level. The Theoretical Maximum Residue Contribution (TMRC) is an estimate of the level of residues consumed daily if each food item contained pesticide residues equal to the tolerance. In evaluating food exposures, EPA takes into account varying consumption patterns of major identifiable subgroups of consumers, including infants and children. The TMRC is a ''worst case'' estimate since it is based on the assumptions that food contains pesticide residues at the tolerance level and that 100% of the crop is treated by pesticides that have established tolerances. If the TMRC exceeds the Reference Dose (RfD) or poses a lifetime cancer risk that is greater than approximately one in a million, EPA attempts to derive a more accurate exposure estimate for the pesticide by evaluating additional types of information (anticipated residue data and/or percent of crop treated data) which show, generally, that pesticide residues in most foods when they are eaten are well below established tolerances.

2. *Food*. Under a petition to establish tolerances for cyfluthrin in or on citrus (PP 4F4313 and FAP 4H5687, the EPA has recently performed a chronic dietary exposure/risk assessment for cyfluthrin using a RfD of 0.025 mg/kg body weight(bwt)/day, based on a NOEL of 50 ppm (2.5 mg/kg bwt/day) and an uncertainty factor of 100. The NOEL was determined in a 2-year rat feeding study. The endpoint effects of concern were decreased body weights in males and inflammation of the kidneys in females at the LEL of 6.2 mg/kg/day. This dietary exposure/risk assessment estimated the current dietary exposure for the U.S. population resulting from established tolerances, including the current 4 ppm tolerance on fresh hops, is 0.002907 mg/kg/bwt day. This represents 11.6% of the RfD. The exposure to children (1-6 years old), the subgroup population exposed to the highest risk was 0.00662 mg/kg/bwt/day or 26.4% of the RfD. The current action will increase the exposure to 0.003266 mg/kg/bwt day or 13% of the RfD for the U.S. population and 0.006622 mg/kg/bwt day or 26.4% or the RfD for children (1-6 years old). Generally speaking, EPA has no cause for concern if the total dietary exposure from residues for uses for which there are published and proposed tolerances is less than the RfD. Therefore, Bayer concludes that the chronic dietary risk of cyfluthrin, as estimated by the dietary risk assessment, does not appear to be of concern.

3. *Drinking water*. Cyfluthrin is immobile in soil, therefore, will not leach into ground water. Additionally, due to the insolubility and lipophilic nature of cyfluthrin, any residues in surface water will rapidly and tightly bind to soil particles and remain with sediment, therefore, Bayer does not anticipate dietary exposures to cyfluthrin from drinking water.

4. *Non-dietary exposure*. Non-occupational exposure to cyfluthrin may occur as a result of inhalation or contact from indoor residential, indoor commercial, and outdoor residential uses. Reliable data to determine aggregate exposures from these sources are currently not available. However, determinations of worst case exposure from inhalation in indoor settings (continuous exposure at saturation vapor concentration) indicated that adequate margins of safety existed even under these conditions. Since this evaluation greatly overestimated exposure, the contribution to aggregate exposure from inhalation in normal uses would be expected to be negligible. Estimations of outdoor residential exposure have been required for cyfluthrin in a data call-in issued in 1995. These data are being generated by the Outdoor Residential Exposure Task Force (ORETF). However, available data show that the acute dermal toxicity of cyfluthrin is very low, with the LD_{50} being greater than 5,000 mg/kg, the highest dose tested. Sub-acute (21-day) dermal toxicity data showed only localized (skin) effects at higher level exposures (1,000 mg/kg/day and 340 mg/kg/day). Other than skin effects at these high exposure levels, no effects were observed at any exposure levels, the highest level tested being 1,000 mg/kg/day. The use rate for cyfluthrin on residential turf is 1 g (1,000 mg) active ingredient per 1,000 square feet which would indicate that potential exposures would be well below levels tested. In addition, the localized skin effects seen at the prolonged higher exposures in animal tests have not been reported for non-occupational exposures to cyfluthrin in currently accepted uses, indicating that exposures are below the threshold of any observable effects. Indoor uses are limited to areas with little or no contact, so exposures would be expected to be even less. Thus, the dermal route of exposure does not appear to be significant and the contribution to aggregate exposure from dermal contact would be expected to be negligible.

D. Cumulative Effects

In consideration of potential cumulative effects of cyfluthrin and other substances that have a common mechanism of toxicity, Bayer concludes that there are currently no available data or other reliable information indicating that any toxic effects produced by cyfluthrin would be cumulative with those of other chemical compounds; thus only the potential risks of cyfluthrin have been considered in this assessment of its aggregate exposure.

E. Safety Determination

1. *U.S. population*. Using the conservative exposure assumptions described above and based on the completeness and reliability of the toxicity data it can be concluded that total aggregate exposure to cyfluthrin from all current uses as well as the proposed tolerance will utilize little more than 13% of the RfD for the U.S. population. EPA generally has no concerns for exposures below 100% of

the RfD, because the RfD represents the level at or below which daily aggregate exposure over a lifetime will not pose appreciable risks to human health. Thus, it can be concluded that there is a reasonable certainty that no harm will result from aggregate exposure to cyfluthrin residues.

2. *Infants and children*. In assessing the potential for additional sensitivity of infants and children to residues of cyfluthrin, the data from developmental studies in both rat and rabbit and a 2-generation reproduction study in the rat can be considered. The developmental toxicity studies evaluate any potential adverse effects on the developing animal resulting from pesticide exposure of the mother during prenatal development. The reproduction study evaluates any effects from exposure to the pesticide on the reproductive capability of mating animals through 2-generations, as well as any observed systemic toxicity.

FFDCA section 408 provides that EPA may apply an additional safety factor for infants and children in the case of threshold effects to account for pre- and post- natal effects and the completeness of the toxicity database. Based on current toxicological data requirements, the toxicology database for cyfluthrin relative to pre- and post-natal effects is complete. The NOELs observed in the developmental and reproduction study are equivalent or higher than the NOEL from the 2-year rat feeding study, used with a 100 fold uncertainty factor to establish the reference dose. Therefore, Bayer believes that an additional uncertainty factor is not warranted and that the RfD at 0.025 mg/kg/day is appropriate for assessing aggregate risk to infants and children.

Using the conservative exposure assumptions described above, cyfluthrin residues resulting from established tolerances, including a tolerance of 20 ppm on dry hops, would utilize 26.4% of the RfD for children (1-6 years old), the subgroup population exposed to the highest risk. Generally, EPA has no cause for concern if the exposure is less than 100% of the RfD. Therefore, based on the completeness and the reliability of the toxicity data and the conservative exposure assessment, Bayer concludes that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the residues of cyfluthrin, including all anticipated dietary exposure and all other non-occupational exposures.

F. International Tolerances

A Codex maximum residue levels (MRLs) or 20 ppm has been established for residues of cyfluthrin on dried hops.

2. Interregional Research Project

PP Nos. 6E3404, 6E4685, 1E3966, 9E3697, and 5E4580

EPA has received pesticide petitions (PP Nos. 6E3404, 6E4685,1E3966, 9E3697, and 5E4580) from the Interregional Research Project Number 4 (IR-4), 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 tolerances for residues of esfenvalerate, (*S*)-cyano-(3-phenoxyphenyl)methyl (*S*)-4-chloro-alpha-(1-methylethyl) benzeneacetate in or on the raw agricultural commodities mustard greens at 5 ppm (PP 6E3404), kiwifruit at 0.5 ppm (PP 6E4685), globe artichoke at 1.0 ppm (PP 1E3966), cranberry at 0.2 ppm (PP 9E3697), and kohlrabi at 2.0 ppm (PP 5E4580). EPA has determined that these petitions contain 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 submitted data at this time or whether these data support granting the proposed tolerances. Additional data may be needed before EPA rules on the petitions. This notice contains a summary of the petitions submitted by DuPont Agricultural Products, the registrant.

A. Residue Chemistry

1. *Plant metabolism*. The metabolism and chemical nature of residues of fenvalerate in plants and animals are adequately understood. The fate of fenvalerate has been extensively studied using radioactive tracers in plant and animal metabolism/nature of the residue studies. These studies have demonstrated that the parent compound is the only residue of toxicological significance. EPA has concluded that the qualitative nature of the residue is the same for both fenvalerate and esfenvalerate.

2. *Analytical method*. There is a practical analytical method utilizing electron-capture gas chromatography with nitrogen phosphorous detection available for enforcement with a limit of detection that allows monitoring food with residues at or above tolerance levels. The limit of detection for updated method is the same as that of the current PAM II, which is 0.01 ppm.

3. *Magnitude of residues*. Fenvalerate is a racemic mixture of four isomers (about 25% each). Technical Asana (the S,S-isomer enriched formulation, esfenvalerate), has been the only fenvalerate formulation sold in the U.S. for agricultural use. Since the S,S-isomer is the insecticidally active isomer, the use rate for Asana® is 4 times lower than that for Pydrin®. A petition is pending (PP 4F4329), to convert tolerances (still to be expressed as the sum of all isomers) based on the use rates for Asana®. Bridging residue studies have shown Asana® residues to be 3-4 times lower than Pydrin® residues.

B. Toxicological Profile

1. *Acute toxicity*. A battery of acute toxicity studies places technical esfenvalerate in Toxicity Category II for acute oral toxicity (rat lethal dose LD_{50} 87.2 mg/kg, Category III for acute dermal (rabbit LD_{50} >2,000 mg/kg) and primary eye irritation (mild irritation in rabbits), and Category IV for primary skin irritation (minimal skin irritation in rabbits that reversed within 72 hours after treatment). Acute inhalation on technical grade active ingredient (a.i.) was waived due to negligible vapor pressure. A dermal sensitization test on esfenvalerate in guinea pigs showed no sensitization.

2. *Genotoxicity*. Esfenvalerate was not mutagenic in reverse mutation assays in *S. typhimurium* and *E. coli* and did not induce mutations Chinese hamster V79 cells or chromosome aberrations in Chinese hamster ovary cells. Esfenvalerate did not induce micronuclei in bone marrow of mice given up to 150 mg/kg intra peritoneally. Esfenvalerate did not induce unscheduled deoxyribonucleic acid (DNA) synthesis in HeLa cells. Other genetic toxicology studies submitted on racemic fenvalerate indicate that the mixture containing equal parts of the four stereoisomers is not mutagenic in bacteria. The racemic mixture was also negative in a mouse host mediated assay and in a mouse dominant lethal assay.

3. *Reproductive and developmental toxicity*. Esfenvalerate was administered to pregnant female rats by gavage in a pilot developmental study at doses of 0, 1, 2, 3, 4, 5, and 20 mg/kg/day and a main study at 0, 2.5, 5, 10, and 20 mg/kg/day. Maternal clinical signs (abnormal gait and mobility) were observed at 2.5 mg/kg/day and above. A maternal NOEL of 2 mg/kg/day was established for the pilot study. The developmental NOEL was >20 mg/kg/day.

Esfenvalerate was administered by gavage to pregnant female rabbits in a pilot developmental study at doses of 0, 2, 3, 4, 4.5, 5, and 20 mg/kg/day and a main study at doses of 0, 3, 10, and 20 mg/kg/day. Maternal clinical signs (excessive grooming) were observed at 3 mg/kg/day and above. A maternal NOEL of 2 mg/kg/day was established on the

pilot study. The developmental NOEL was > 20 mg/kg/day.

A 2-generation feeding study with esfenvalerate was conducted in the rat at dietary levels of 0,75, 100, and 300 ppm. Skin lesions and minimal (non biologically significant) parental body weight effects occurred at 75 ppm. The NOEL for reproductive toxicity was 75 ppm (4.2-7.5 mg/kg/day) based on decreased pup weights at 100 ppm.

4. *Subchronic toxicity*. Two 90-day feeding studies with esfenvalerate were conducted in rats - one at 50, 150, 300, and 500 ppm esfenvalerate, and a second at 0, 75, 100, 125, and 300 ppm to provide additional dose levels. The NOEL was 125 ppm (6.3 mg/kg/day) based on clinical signs (jerky leg movements) observed at 150 ppm (7.5 mg/kg/day) and above.

A 90-day feeding study in mice was conducted at 0, 50, 150, and 500 ppm esfenvalerate with a NOEL of 150 ppm (30.5 mg/kg) based on clinical signs of toxicity at 500 ppm (106 mg/kg).

A 3-month subchronic study in dogs was satisfied by a 1-year oral study in dogs, in which the NOEL was 200 ppm (5 mg/kg/day).

A 21-day dermal study in rabbits with fenvalerate conducted at 100, 300, and 1,000 mg/kg/day with a no-observed-adverse effect level (NOAEL) of 1,000 mg/kg/day.

5. *Chronic toxicity*. In a 1-year study, dogs were fed 0, 25, 50, or 200 ppm esfenvalerate with no treatment related effects at any dietary level. The NOEL was established at 200 ppm (5 mg/kg/day). An effect level for dietary administration of esfenvalerate for dogs of 300 ppm had been established earlier in a three week pilot study used to select dose levels for the chronic dog study.

One chronic study with esfenvalerate and three chronic studies with fenvalerate have been conducted in mice.

In an 18-month study, mice were fed 0, 35, 150, or 350 ppm esfenvalerate. Mice fed 350 ppm were sacrificed within the first 2 months of the study after excessive self-trauma related to skin stimulation and data collected were not used in the evaluation of the oncogenic potential of esfenvalerate. The NOEL was 35 ppm (4.29 and 5.75 mg/kg/day for males and females, respectively) based on lower body weight and body weight gain at 150 ppm. Esfenvalerate did not produce carcinogenicity.

In a 2-year feeding study, mice were administered 0, 10, 50, 250 or 1,250 ppm fenvalerate in the diet. The NOEL was 10 ppm (1.5 mg/kg/day) based on granulomatous changes (related to fenvalerate only, not esfenvalerate) at 50 ppm (7.5 mg/kg/day). Fenvalerate did not produce carcinogenicity.

In an 18-month feeding study, mice were fed 0, 100, 300, 1,000, or 3,000 ppm fenvalerate in the diet. The NOEL is 100 ppm (15.0 mg/kg/day) based on fenvalerate-related microgranulomatous changes at 300 ppm (45 mg/kg/day). No compound related carcinogenicity occurred.

Mice were fed 0, 10, 30, 100, or 300 ppm fenvalerate for 20-months. The NOEL was 30 ppm (3.5 mg/kg/day) based on red blood cell effects and granulomatous changes at 100 ppm (15 mg/kg/day). Fenvalerate was not carcinogenic at any concentration.

In a 2-year study, rats were fed 1, 5, 25, or 250 ppm fenvalerate. A 1,000 ppm group was added in a supplemental study to establish an effect level. The NOEL was 250 ppm (12.5 mg/kg/day). At 1,000 ppm (50 mg/kg/day), hind limb weakness, lower body weight, and higher organ-to-body weight ratios were observed. Fenvalerate was not carcinogenic at any concentration. (A conclusion that fenvalerate is associated with the production of spindle cell sarcomas at 1,000 ppm was retracted by EPA).

EPA has classified esfenvalerate in Group E - evidence of non-carcinogenicity for humans.

6. *Animal metabolism*. In animal studies, after oral dosing with radioactive fenvalerate, the majority of the administered radioactivity was eliminated in the initial 24-hours. The metabolic pathway involved cleavage of the ester linkage followed by hydroxylation, oxidation, and conjugation of the acid and alcohol moieties.

7. *Metabolite toxicology*. The parent molecule is the only moiety of toxicological significance appropriate for regulation in plant and animal commodities.

C. Aggregate Exposure

1. *Dietary exposure*. Tolerances have been established for the residues of fenvalerate/esfenvalerate, in or on a variety of agricultural commodities. In addition, pending tolerance petitions exist for use of esfenvalerate on sugar beets, sorghum, head lettuce, celery, pistachios, and a number of other minor use commodities. For purposes of assessing dietary exposure, chronic and acute dietary assessments have been conducted using all existing and pending tolerances for esfenvalerate. EPA recently (August 2, 1997) reviewed the existing toxicology data base for esfenvalerate and selected the following toxicological endpoints. For acute toxicity, EPA established a NOEL of 2.0 mg/kg/day from rat and rabbit developmental studies based on maternal clinical signs at higher concentrations. An MOE of 100 was required. For chronic toxicity. EPA established the Reference Dose (RfD) for esfenvalerate at 0.02 mg/kg/day. This RfD was also based on a NOEL of 2.0 mg/kg/day in the rat developmental study with an uncertainty factor of 100. Esfenvalerate is classified as a Group E carcinogen - no evidence of carcinogenicity in either rats or mice. Therefore, a carcinogenicity risk analysis for humans is not required.

2. *Food*. A chronic dietary exposure assessment was conducted using Novigen's DEEM (Dietary Exposure Estimate Model). Anticipated residues and adjustment for percent crop treated were used in the chronic dietary risk assessment. The percentages of the RfD utilized by the most sensitive sub-population, children 1-6 years, was 4.6% based on a daily dietary exposure of 0.000911 mg/kg/day. Chronic exposure for the overall US population was 1.9% of the RfD based on a dietary exposure of 0.000376 mg/kg/day. This assessment has been approved by EPA and included pending tolerances (including mustard greens, kiwifruit, globe artichoke, cranberry, and kohlrabi) and all food tolerances for incidental residues from use in food handling establishments. EPA has no concern for exposures below 100% of the RfD because the RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health.

Potential acute exposures from food commodities were estimated using a Tier 3 (Monte Carlo) Analysis and appropriate processing factors for processed food and distribution analysis. This analysis used field trial data to estimate exposure and federal and market survey information to derive the percent of crop treated. These data are considered reliable and used the upper end estimate of percent crop treated in order to not underestimate any significant subpopulation. Regional consumption information was taken into account. The MOEs for the most sensitive sub-population (children 1-6 years) were 202 and 103 at the 99th, and 99.9th percentile of exposure, respectively, based on daily exposures of 0.009908 and 0.019445 mg/kg/day. The MOEs for the general population are 355 and 171 at the 99th and 99.9th percentile of exposure, respectively, based on daily exposure estimates of 0.005635 and 0.011717 mg/kg/day. The EPA has stated there is no cause for concern if total acute exposure

calculated for the 99.9th percentile yields an MOE of 100 or larger. This acute dietary exposure estimate is considered conservative and EPA considered the MOEs adequate in a recent final rule published in the **Federal Register** at 62 FR 63019 (November 26, 1997) (FRL-5781-1).

3. *Drinking water*. Esfenvalerate is immobile in soil and will not leach into groundwater. Due to the insolubility and lipophilic nature of esfenvalerate, any residues in surface water will rapidly and tightly bind to soil particles and remain with sediment, therefore not contributing to potential dietary exposure from drinking water.

A screening evaluation of leaching potential of a typical pyrethroid was conducted using EPA's Pesticide Root Zone Model (PRZM). Based on this screening assessment, the potential concentrations of a pyrethroid in ground water at depths of 1 and 2 meters are essentially zero (much less than 0.001 parts per billion (ppb).

Surface water concentrations for pyrethroids were estimated using PRZM3 and Exposure Analysis Modeling System (EXAMS) using Standard EPA cotton runoff and Mississippi pond scenarios. The maximum concentration predicted in the simulated pond was 0.052 ppb. Concentrations in actual drinking water would be much lower than the levels predicted in the hypothetical, small, stagnant farm pond model since drinking water derived from surface water would be treated before consumption.

Chronic drinking water exposure was estimated to be 0.000001 mg/kg/day for both the U.S. general population and for non-nursing infants. Less than 0.1% of the RfD was occupied by both population groups.

Using these values, the contribution of water to the acute dietary risk estimate was estimated for the U.S. population to be 0.000019 mg/kg/day at the 99th percentile and 0.000039 mg/kg/day at the 99.9th percentile resulting in MOEs of 105,874 and 51,757, respectively. For the most sensitive subpopulation, non-nursing infants less than 1-year old, the exposure is 0.000050 mg/kg/day and 0.000074 mg/kg/day at the 99th and 99.9th percentile, respectively, resulting in MOEs of 39,652, and 27,042, respectively.

Therefore, DuPont believes that there is reasonable certainty of no harm from drinking water.

4. *Non-dietary exposure*. Esfenvalerate is registered for non-crop uses including spray treatments in and around commercial and residential areas, treatments for control of ectoparasites on pets, home care products including foggers, pressurized sprays, crack and crevice treatments, lawn and garden sprays, and pet and pet bedding sprays. For the non-agricultural products, the very low amounts of active ingredient they contain, combined with the low vapor pressure (1.5 x 10^{-9} mm Mercury at 25° C.) and low dermal penetration, would result in minimal inhalation and dermal exposure.

To assess risk from (nonfood) short and intermediate term exposure, EPA has recently selected a toxicological endpoint of 2.0 mg/kg/day, the NOEL from the rat and rabbit developmental studies. For dermal penetration/absorption, EPA selected 25% dermal absorption based on the weight-of-evidence available for structurally related pyrethroids. For inhalation exposure, EPA used the oral NOEL of 2.0 mg/kg/day and assumed 100% absorption by inhalation.

Individual non-dietary risk exposure analyses were conducted using a flea infestation scenario that included pet spray, carpet and room treatment, and lawn care, respectively. The total potential short- and intermediate-tern aggregate non-dietary exposure including lawn, carpet, and pet uses are: 0.000023 mg/kg/day for adults, 0.00129 mg/kg/day for children 1-6 years and 0.00138 mg/kg/day for infants less than 1-year old.

EPA concluded in the final rule published in the **Federal Register** at 62 FR 63019 (November 26, 1997) that the potential non-dietary exposure for esfenvalerate are associated with substantial margins of safety.

5. *Aggregate exposure dietary and non dietary*. EPA has concluded that aggregate chronic exposure to esfenvalerate from food and drinking water will utilize 1.9% of the RfD for the U.S. population based on a dietary exposure of 0.000377 mg/kg/day. The major identifiable subgroup with the highest aggregate exposure are children 1-6 years old. EPA generally has no concern for exposures below 100% of the RfD because the RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health.

The acute aggregate risk assessment takes into account exposure from food and drinking water. The potential acute exposure from food and drinking water to the overall U.S. population provides an acute dietary exposure of 0.011756 mg/kg/day with an MOE of 170. This acute dietary exposure estimate is considered conservative, using anticipated residue values and percent crop-treated data in conjunction with Monte Carlo analysis.

Short- and intermediate-term aggregate exposure takes into account chronic dietary food and water (considered to be a background exposure level) plus indoor and outdoor residential exposure. The potential short- and intermediate-term aggregate risk for the U.S. population is an exposure of 0.0082 mg/kg/day with an MOE of 244.

It is important to acknowledge that these MOEs are likely to significantly underestimate the actual MOEs due to a variety of conservative assumptions and biases inherent in the exposure assessment methods used for their derivation. Therefore, it can be concluded that the potential non-dietary and dietary aggregate exposures for esfenvalerate are associated with a substantial degree of safety. EPA has previously determined in the final rule published in the **Federal Register** at 62 FR 63019 (November 26, 1997) that there was reasonable certainty that no harm will result from aggregate exposure to esfenvalerate residues. Head lettuce was included in that risk assessment.

D. Cumulative Effects

Section 408 (b) (2) (D) (v) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider ''available information'' concerning the cumulative effects of a particular pesticide's residues and ''other substances that have a common mechanism of toxicity''. In a recent final rule on esfenvalerate published in the **Federal Register** at 62 FR 63019 (November 26, 1997) EPA concluded, available information in this context might include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodologies to resolve the complex scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will increase the Agency's scientific understanding of this question such that EPA will be able to develop and apply scientific principles for better

determining which chemicals have a common mechanism of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions on specific classes of chemicals will be heavily dependent on chemical specific data, much of which may not be presently available.

Although at present the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments, there are pesticides as to which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed). Although esfenvalerate is similar to other members of the synthetic pyrethroid class of insecticides, EPA does not have, at this time, available data to determine whether esfenvalerate has a common method of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, esfenvalerate 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 esfenvalerate has a common mechanism of toxicity with other substances.

E. Safety Determination

1. *U.S. population*. A chronic dietary exposure assessment using anticipated residues, monitoring information, and percent crop treated indicated the percentage of the RfD utilized by the General Population to be 1.9%. There is generally no concern for exposures below 100% of the RfD because the RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health.

For acute exposure, a MOE of greater than 100 is considered an adequate MOE. A Tier 3 acute dietary exposure assessment found the General Population to have MOE's of 355 and 171 at the 99th and 99.9th percentile of exposure, respectively. These values were generated using actual field trial residues and market share data for percentage of crop treated. These results depict an accurate exposure pattern at an exaggerated daily dietary exposure rate.

Short- and intermediate-term aggregate exposure risk from chronic dietary food and water plus indoor and outdoor residential exposure for the U.S. population is an exposure of 0.0082 mg/kg/day with an MOE of 244.

Therefore, there is a reasonable certainty that no harm will result from chronic dietary, acute dietary, non-dietary, or aggregate exposure to esfenvalerate residues.

2. *Infants and children*. FFDCA section 408 provides that EPA shall apply an additional tenfold margin of safety for infants and children unless EPA determines that a different margin of safety will be safe for infants and children. EPA has stated that reliable data support using the standard MOE and uncertainty factor (100 for combined inter- and intra-species variability) and not the additional tenfold MOE/uncertainty factor when EPA has a complete data base under existing guidelines and when the severity of the effect in infants or children or the potency or unusual toxic properties of a compound do not raise concerns regarding the adequacy of the standard MOE/safety factor. In a recent final rule published in the **Federal Register** at 62 FR 63019 (November 26 1997), EPA concluded that reliable data support use of the standard 100-fold uncertainty factor for esfenvalerate, and that an additional uncertainty factor is not needed to protect the safety of infants and children. This decision was based on, no evidence of developmental toxicity at a doses up to 20 mg/kg/day (ten times the maternal NOEL) in prenatal developmental toxicity studies in both rats and rabbits; offspring toxicity only at dietary levels which were also found to be toxic to parental animals in the 2-generation reproduction study; and no evidence of additional sensitivity to young rats or rabbits following pre- or postnatal exposure to esfenvalerate.

A chronic dietary exposure assessment found the percentages of the RfD utilized by the most sensitive sub-population to be 4.6% for children 1-6 years based on a dietary exposure of 0.000912 mg/kg/day. The % RfD for nursing and non-nursing infants was 1.1% and 2.7%, respectively. The Agency has no cause for concern if RfD are below 100%.

The most sensitive sub-population, children 1-6 years, had acute dietary MOEs of 202 and 103 at the 99th and 99.9th percentile of exposure, respectively. Nursing infants had MOEs of 195 and 146 at the 99th and 99.9th percentile of exposure, respectively. Non-nursing infants had MOEs of 304 and 158 at the 99th and 99.9th percentile of exposure, respectively. The Agency has no cause for concern if total acute exposure calculated for the 99.9th percentile yields a MOE of 100 or larger.

EPA has recently concluded that the potential short- or intermediate-term aggregate exposure of esfenvalerate from chronic dietary food and water plus indoor and outdoor residential exposure to children (1-6 years old) is 0.0113 mg/kg/day with an MOE of 177. For infants (less than 1-year old) the exposure is 0.0098 mg/kg/day with an MOE of 204. Thus, there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to esfenvalerate residues published in the **Federal Register** at 62 FR 63019 (November 26, 1997) (FRL-5754-6).

F. International Tolerances

Codex maximum residue levels (MRL's) have been established for residues of fenvalerate on a number of crops that also have U.S. tolerances. There are some minimal differences between the section 408 tolerances and certain Codex MRL values for specific commodities. These differences could be caused by differences in methods to establish tolerances, calculate animal feed, dietary exposure, and as a result of different agricultural practices. Therefore, some harmonization of these maximum residue levels may be required.

3. Novartis Crop Protection, Inc.

PP 7E4920

EPA has received a pesticide petition (PP 7E4920) from Novartis Crop Protection, Inc., P.O. Box 18300, Greensboro, NC 27419, proposing pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 346a(d), to amend 40 CFR part 180 by establishing inert tolerances for residues of cloqiontocet-mexyl (acteic acid, [5-chloro-8-quinolinyl)oxy]-,1-methylhexylester; CGA–185072) in or on the raw agricultural commodities wheat grain at 0.02 ppm and wheat straw at 0.05 ppm. The proposed analytical method involves homogenization, filtration, partition, and cleanup with analysis by high performance liquid chromotography using UV detection. 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 supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism*. The metabolism of CGA–185072 in wheat has been investigated. Total residues in all crop samples are low. Metabolism involves primarily rapid hydrolysis of the parent to the resulting acid followed by conjugation.

2. *Analytical method*. Novartis has submitted practical analytical methods for the determination of CGA–185072 and its major plant metabolite CGA–153433 in wheat raw agricultural commodities (RACs). CGA–185072 is extracted from crops with acetonitrile, cleaned up by solvent partition and solid phase extraction and determined by column switching HPLC with UV detection. CGA–153433 is extracted from crops with an acetone-buffer (pH=3) solution, cleaned up by solvent partition and solid phase extraction, and determined by HPLC with UV detection. The limits of quantification (LOQ) for the methods are 0.02 ppm for CGA–185072 in forage and grain, 0.05 ppm for CGA–185072 in straw, and 0.05 ppm for CGA–153433 in forage, straw and grain.

3. *Magnitude of residues*. Twelve residue trials were conducted from 1989–1992 in the major spring wheat growing areas of Manitoba, Alberta and Saskatchewan, which share compatible crop zones with the major spring wheat growing areas of the U.S. (MT, ND, SD, MN). Nine trials were conducted in 1989-91 with a tank mix of CGA–184927 (a.i.) and the CGA–185072 safener as separate EC formulations and three trials in 1992 were conducted with CGA–184927 and the CGA–185072 safener as a pre-pack EC formulation. All trials had a single post-emergence application of CGA–185072 at a rate of 20 g a.i./Ha. At PHIs of 55-97 days, no detectable residues of CGA-185072 or its metabolite CGA–153433 were found in mature grain or straw from these trials. Separate decline studies (3) on green forage showed no detectable residues of CGA–185072 or CGA–153433 at 3 days after application. Freezer storage stability studies indicated reasonable stability of both analytes for a period of one year, with CGA–185072 declining to 83% in grain and 67% in straw after two years, while CGA–153433 was stable for at least two years.

B. Toxicological Profile

1. *Acute toxicity*. The acute oral and dermal LD_{50} values for cloquintocet-mexyl are greater than 2,000 mg/kg for rats of both sexes, respectively. Its acute inhalation LC_{50} in the rat is greater than 0.94 mg/liter , the highest attainable concentration. Cloquintocet-mexyl is slightly irritating to the eyes, minimally irritating to the skin of rabbits, but was found to be sensitizing to the skin of the guinea pig. This technical would carry the EPA signal word ''Caution''.

2. *Genotoxicty*. The mutagenic potential of cloquintocet-mexyl was investigated in six independent studies covering different end points in eukaryotes and prokaryotes *in vivo* and *in vitro*. These tests included: Ames reverse mutation with *Salmonella typhimurium* and Chinese hamster V79 cells; chromosomal aberrations using human lymphocytes and the mouse micronucleus test; and DNA repair using rat hepatocytes and human fibroblasts. Cloquintocet-mexyl was found to be negative in all these tests and, therefore, is considered devoid of any genotoxic potential at the levels of specific genes, chromosomes or DNA primary structure.

3. *Reproductive and developmental toxicity*. Dietary administration of cloquintocet-mexyl over two generations at levels as high as 10,000 ppm did not affect mating performance, fertility, or litter sizes, but a slightly reduced body weight development of adults and pups was noted at this level. The target organ was kidney in adults and pups. The treatment had no effect on reproductive organs. The developmental and reproductive NOEL was 5,000 ppm, corresponding to a mean daily intake of 350 mg/kg cloquintocet-mexyl.

In a developmental toxicity study in rats, the highest dose level of 400 mg/kg resulted in reduced body weight gain of the dams and signs of retarded fetal development. No teratogenic activity of the test article was detected. The NOEL for dams and fetuses was 100 mg/kg/day.

In a developmental toxicity study in rabbits, mortality was observed in dams at dose levels of 300 mg/kg. No teratogenic effects were noted. Fetuses showed signs of slightly retarded development. The NOEL for both dams and fetuses was 60 mg/kg/day.

4. *Subchronic toxicity*. In a 90-day study, rats fed 6,000 ppm exhibited reduced body weight gain and one male died with acute nephritis and inflamed urinary bladder. Reduced liver and kidney weights were observed in males fed 1,000 and 6,000 and in females fed 6,000 ppm. Target organs were identified to be kidney and urinary bladder. The NOEL was 150 ppm (9.66 mg/kg in males and 10.2 mg/kg in females).

In a 90-day study in beagle dogs, a level of 40,000 ppm resulted in deterioration of general condition so that the feeding level was reduced in a stepwise fashion to 15,000 ppm. Anemia was noted at 15,000 ppm and the feeding level of 1,000 ppm. The NOEL of 100 ppm was equivalent to a mean daily intake of 2.9 mg/kg in males and females.

5. *Chronic toxicity*. In a 12-month feeding study in dogs, 15,000 ppm resulted in inappetence and body weight loss. As a result, this feeding level was adjusted to 10,000 ppm after 2-weeks. Animals fed this level exhibited anemia and an elevation in blood urea levels. The kidney was considered the target organ. The NOEL of 1,500 ppm was equivalent to a mean daily intake of 43.2 mg/kg in males and 44.8 mg/kg in females.

Lifetime dietary administration of cloquintocet-mexyl to mice resulted in reduced body weights in both sexes at 5,000 ppm. Overall body weight gain was reduced by 17% to 22% in males and females, respectively, indicating the MTD was achieved or exceeded. Histopathological examination revealed chronic inflammation of the urinary bladder. There was no indication of any tumorigenic response due to treatment. The NOEL of 1,000 ppm was equivalent to a mean daily dose of 111 mg/kg in males and 102 mg/kg in females.

A top feeding level of 2,000 ppm was selected, based on the 90-day study, for the lifetime feeding study in the rat. This feeding level was well-accepted, but produced hyperplasia of the thymus in males and hyperplasia of the thyroid in females. There was no increase in tumors of any type and the total number of tumor- bearing animals showed no dose-related trends. The NOEL of 100 ppm was equivalent to a mean daily dose of 3.77 mg/kg in males and 4.33 mg/kg in females.

6. *Animal metabolism*. In rats, approximately 50% of an oral dose of cloquintocet-mexyl was rapidly absorbed through the gastrointestinal tract and excreted *via* urine and bile. The administered dose was excreted independent of sex and was essentially complete within 48 hours. 95% of the excreted dose was associated with one metabolite, an acid residue of cloquintocet-mexyl, CGA–153433. Simultaneous administration of the cloquintocet-mexyl and clodinafop-propargyl did not alter the rate of excretion of cloquintocet-mexyl or its metabolite pattern.

7. *Metabolite toxicology*. At the present time there is no evidence which affords an association of the toxicities noted with the highest feeding levels of cloquintocet-mexyl with its primary metabolite, CGA–153433.

8. *Endocrine disruption*. A special study was conducted to investigate a histological finding of hyperplasia of thyroid gland epithelium noted in the female rat in the standard lifetime combined chronic toxicity and carcinogenicity study. This study was a 28-day oral gavage study with a 28-day recovery period at dose levels as high as 400 mg/kg/day or approximately 4,000 ppm. No effect was noted on the level of thyroid hormones at any of the treatment levels. Although thyroid hyperplasia and an accompanying increase in pituitary basophilic cells were noted at the end of 28-days, these effects were reversible in the recovery period.

C. Aggregate Exposure

1. *Dietary exposure*. Cloquintocet-mexyl is intended to be used as a safener for the post emergence herbicide, clodinafop-propargyl, used in wheat. The use rate is very low (formulated at a 1:4 ratio of safener to active ingredient). Results from plant metabolism and residue studies show that residues of the safener cloquintocet-mexyl or its metabolites are below the detection limit in wheat grains and other wheat byproducts including green wheat used for forage. Tolerances in wheat and wheat products are being proposed at the detection limit of 0.02 ppm (LOQ) for the parent active ingredient in wheat grain and 0.05 ppm (LOQ) in wheat straw. For cloquintocet, similar tolerances will be proposed in wheat grain (0.02 ppm) and wheat straw (0.05 ppm).

i. *Chronic*. The RfD of 0.0377 mg/kg/day was derived from the male NOEL of 3.77 mg/kg/day. Based on the assumption that 100% of all wheat used for human consumption would contain residues of cloquintocet-mexyl and anticipated residues would be at the level of ½ the LOQ, the potential dietary exposure was calculated using the TAS exposure program based on the food survey from the year of 1977–1978. Calculations were made for anticipated residues using ½ the LOQ or 0.01 ppm. Calculated on the basis of the assumptions above, the chronic dietary exposure of the U.S. population to cloquintocet-mexyl would correspond to 0.000014 mg/kg/day or 0.04% of its RfD. MOE against NOEL in the most sensitive species is 269,286-fold.

Using the same conservative exposure assumptions, the percent of the RfD that will be utilized is 0.01% for nursing infants less than 1–year old, 0.03% for non-nursing infants, 0.08% for children 1-6 years old and 0.06% for children 7-12 years old. It is concluded that there is a reasonable certainty that no harm will result to infants and children from exposure to residues of cloquintocet-mexyl.

ii. *Acute*. Using the same computer software package used for the calculation of chronic dietary exposure, the acute dietary exposure was calculated for the general population and several sub-populations including children and women of child bearing age. The USDA Food Consumption Survey of 1989–1992 was used, however, instead of the 1977–1978 survey used for the chronic assessment. MOEs were calculated against the NOEL of 2.9 mg/kg found in a 90–day dietary toxicity study in dogs, which is the lowest NOEL observed in a short term or reproductive toxicity study. NOELs from reproductive or developmental toxicity studies were significantly higher and there was no evidence that cloquintocet-mexyl has any potency to affect these endpoints.

The exposure model predicted that 99.9% of the general population will be exposed to less than 0.000104 mg/kg cloquintocet-mexyl per day, which corresponds to a MOE of almost 27,944 when compared to the NOEL of 2.9 mg/kg. Children 1–6 years constitute the sub-population with the highest predicted exposure. Predicted acute exposure for this subgroup is less than 0.000134 mg/kg/day, corresponding to a MOE of at least 21,721 for 99.9% of the individuals.

2. *Drinking water*. Other potential sources of exposure of the general population to residues of pesticides are residues in drinking water. Results of studies have shown that cloquintocet-mexyl or its degradation products do not have any leaching potential. Accordingly, there is no risk of groundwater contamination with cloquintocet-mexyl or its metabolites. Thus, aggregate risk of exposure to cloquintocet-mexyl does not include drinking water. Cloquintocet-mexyl is not intended for uses other than the agricultural use on wheat. Thus, there is no potential for non-occupational exposure.

The Maximum Contaminant Level Goal (MCLG) calculated for cloquintocet-mexyl according to EPA's procedure leads to an exposure value substantially above levels that are likely to be found in the environment under proposed conditions of use.

MCLG = RfD x 20% x 70 kg/2 L

MCLG = 0.0377 mg/kg x 0.2 x 70 kg/2 L

MCLG = 0.264 ppm = 264 ppb

3. *Non-dietary exposure*. Exposure to cloquintocet-mexyl for the mixer/loader/ground boom/aerial applicator was calculated using the Pesticide Handlers Exposure Database (PHED). It was assumed that the product would be applied 10–days per year by ground boom application to a maximum of 300 acres per day by the grower, 450 acres per day by the commercial groundboom applicator, and 741 acres per day for the aerial applicator at a maximum use rate of 28 grams active ingredient (7 grams of cloquintocet-mexyl) per acre. For purposes of this assessment, it was assumed that an applicator would be wearing a long-sleeved shirt and long pants and the mixer/loader would, in addition, wear gloves. Daily doses were calculated for a 70 kg person assuming 100% dermal penetration.

The results indicate that large margins of safety exist for the proposed experimental use of cloquintocet-mexyl. The use pattern of cloquintocet indicates that the NOEL(1,000 mg/kg/day) from the 28–day rat dermal study is appropriate for comparison to mixer/loader-applicator exposure. The chronic NOEL of 3.77 mg/kg/day from the 2–year feeding study in rats is used to examine longer term exposure.

For short-term exposure, MOEs for cloquintocet ranged from 2.4E+05 for commercial open mixer-loader to 2.5E+06 for commercial groundboom enclosed-cab applicator. For chronic exposure, MOEs ranged from 3.2E+04 for commercial open mixer-loader to 3.5E+05 for commercial groundboom enclosed-cab applicator. Aerial application of cloquintocet results in short-term MOEs of 1.4E+05 for the mixer-loader and 2.5E+05 for pilots. Chronic MOEs are 2.0E+04 for the mixer-loader and 3.4E+04 for the pilot. Based on this assessment, occupational exposure to cloquintocet-mexyl results in acceptable MOEs.

In reality, the proposed label for the end use product containing the active ingredient plus cloquintocet-mexyl will require more restrictive personal protective equipment for applicators and other handlers, resulting in additional margins of safety.

D. Cumulative Effects

Novartis has considered the potential for a cumulative exposure assessment for effects of cloquintocet-mexyl and other substances with the same mechanism of toxicity. It is concluded that such a determination would be inappropriate at this time because of the unique role of cloquintocet-mexyl as a product specific safener.

E. Safety Determination

1. *U.S. population*. Using the same conservative exposure assumptions as described for chronic and acute dietary exposure, aggregrate exposure of the

U.S. population to cloquintocet-mexyl would correspond to 0.000014 mg/kg/day or 0.04% of its RfD. The chronic MOE against the NOEL in the most sensitive species is 269,286-fold. EPA generally has no concern for exposures below 100% of the RfD because the RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. Therefore, it is concluded that there is a reasonable certainty that no harm will result from aggregate exposure to residues of cloquintocet-mexyl.

2. *Infants and children*. In assessing the potential for additional sensitivity of infants and children to residues of cloquintocet-mexyl, data from developmental toxicity studies in the rat and rabbit and a 2- generation reproduction study in the rat have been considered. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from chemical exposure during prenatal development to one or both parents. Reproduction studies provide information relating to effects from exposure to a chemical on the reproductive capability of mating animals and data on systemic toxicity.

The highest dose level of 400 mg/kg/day in a developmental toxicity study in rats resulted in reduced body weight gain of the dams and signs of retarded fetal development. No teratogenic activity due to the test article was detected. The NOEL for dams and fetuses was 100 mg/kg/day. Although mortality was observed in rabbit dams at the dose level of 300 mg/kg/day, no teratogenic effects were noted. The NOEL for both dams and fetuses was 60 mg/kg/day.

Dietary administration of cloquintocet-mexyl over 2-generations at levels as high as 10,000 ppm did not affect mating performance, fertility, or litter sizes in rats, but a slightly reduced body weight development of adults and pups was noted at this level. The target organ was kidney in adults and pups. The treatment had no effect on reproductive organs. The developmental and reproductive NOEL was 5,000 ppm, corresponding to a mean daily intake of 350 mg/kg cloquintocet-mexyl.

FFDCA section 408 provides that EPA may apply an additional safety factor for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the database. Based on the current toxicological data requirements, the database relative to pre- and post-natal effects for children is complete. Further, for cloquintocet-mexyl, the NOEL of 3.77 mg/kg/day from the combined chronic/oncogenicity study in rats, which was used to calculate the RfD, is already lower than the NOEL's of 100 and 60 mg/kg/day for the rat and rabbit developmental toxicity studies, respectively. Further, the developmental and reproductive NOEL of 350 mg/kg/day from the cloquintocet-mexyl reproduction study is nearly 100 times greater than the NOEL for the combined chronic/oncogenicity rat study. These data would indicate there is no additional sensitivity of infants and children to cloquintocet-mexyl. Therefore, it is concluded that an additional uncertainty factor is not warranted to protect the health of infants and children from the use of cloquintocet-mexyl.

Using the conservative exposure assumptions described above, it is concluded that the percentage of the RfD that will utilized by aggregate exposure to residues of cloquintocet-mexyl for its proposed use as a safener for clodinafop-propargyl on wheat is 0.01% for nursing infants less than 1–year old, 0.03% for non-nursing infants, 0.08% for children 1-6 years old and 0.06% for children 7-12 years old. Therefore, based on the completeness and reliability of the toxicity data and the conservative nature of the exposure assessment, it is concluded that there is a reasonable certainty that no harm will result to infants and children from exposure to residues of cloquintocet-mexyl.

F. International Tolerances

Cloquintocet-mexyl is used as a safener for the herbicide, clodinafop-propargyl. There are no Codex Alimentarius Commission (CODEX) maximum residue levels (MRLs) established for residues of cloquintocet-mexyl in or on raw

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ENVIRONMENTAL PROTECTION AGENCY

[OPP–181060; FRL 5782–4]

Carfentrazone ethyl; Receipt of Application for Emergency Exemption, Solicitation of Public Comment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: EPA has received a specific exemption request from the California Environmental Protection Agency, Department of Pesticide Regulation (hereafter referred to as the ''Applicant'') to use the pesticide carfentrazone ethyl (CAS 128639–02–1) to treat up to 70,000 acres of rice to control California arrowhead *Sagittaria montevidensis spp. Calcycina*) and Ricefield bulrush *Scirpus mucronatus*. The Applicant proposes the use of a new (unregistered) chemical. Therefore, in accordance with 40 CFR 166.24, EPA is soliciting public comment before making the decision whether or not to grant the exemption.

DATES: Comments must be received on or before April 30, 1998.

ADDRESSES: Three copies of written comments, bearing the identification notation ''OPP–181060,'' should be submitted by mail to: Public Information and Records Integrity Branch, Information Resources and Services Division (7502C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. In person, bring comments to: Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, VA.

Comments and data may also be submitted electronically by sending electronic mail (e-mail) to: opp-docket@epamail.epa.gov. Follow the instruction under ''SUPPLEMENTARY INFORMATION.'' No Confidential Business Information (CBI) should be submitted through e-mail.

Information submitted in any comment concerning this notice may be claimed confidential by marking any part or all of that information as CBI. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2. A copy of the comment that does not contain CBI must be submitted for inclusion in the public record. Information not marked confidential may be included in the public record by EPA without prior notice.

The public docket is available for public inspection in Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, VA, from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays.

FOR FURTHER INFORMATION CONTACT: By mail: Stephen Schaible, Registration Division (7505C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. Office location, telephone number, and e-mail: Floor 2, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, VA, (703–308–9362); e-mail: schaible.stephen@epamail.epa.gov.

SUPPLEMENTARY INFORMATION: Pursuant to section 18 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136p), the Administrator may, at her discretion, exempt a state agency