clay loam and loam soils characteristics respectively. Soil samples were taken over a period of 12 months following the herbicide application. Detectable residues of clomazone were found only in the 0-6'' horizon. Should movement into surface water occur, potential for clomazone residues to be detected in drinking water supplies at significant levels is minimal. Results from an aquatic field dissipation study (static water situation) demonstrated half-lives of 12-13 days, indicating even shorter durations are likely under flowing water situations. Accordingly, there is no reasonable expectation that there would be an additional incremental aggregate dietary contribution of clomazone through groundwater or surface water.

3. *Non-dietary exposure*. Clomazone is only registered for use on food crops. Since the proposed use on rice is consistent with existing registrations, there will be no non-dietary, non-occupational exposure.

D. Cumulative Effects

Clomazone is an isoxazolidinone herbicide. No other registered chemical exists in this class of chemistry. Therefore, given clomazone's unique chemistry low acute toxicity, the absence of genotoxic, oncogenic, developmental or reproductive effects, and low exposure potential (see sections A and C), the expression of cumulative human health effects with clomazone and other natural or synthetic pesticides is not anticipated.

E. Safety Determination

1. *U.S. population*. Using the conservative exposure assumptions described above, based on the completeness and reliability of the toxicology data, it is concluded that aggregate exposure due to existing registered uses of clomazone will utilize less than one of the RfD for the U.S. population. Additionally, an analysis concluded that aggregate exposure to clomazone adding rice at a 0.05 ppm tolerance level will utilize 0.17% of the RfD for the U.S. population. 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. It is concluded that there is a reasonable certainty that no harm will result from aggregate exposure to residues of clomazone, including all anticipated dietary exposure.

2. *Infants and children*. Based on the current toxicological data requirements, the database relative to pre- and post-natal effects for children is complete (See section B.3). Further, for clomazone, the NOAEL in the 2 year feeding study which was used to calculate the RfD (0.043 mg/kg/day) is already lower than the NOAELs from the reproductive and developmental studies by a factor of more than 10-fold. Therefore, it can be concluded that no additional uncertainty factors are warranted and that the RfD at 0.043 mg/kg/day is appropriate for assessing aggregate risk to infants, children as well as adults.

Using the conservative exposure assumptions described above, FMC has concluded that the percent of the RfD that will be utilized by aggregate exposure to residues of clomazone in/on rice for non-nursing infants (< 1 year old), the population subgroup most sensitive, is 0.15 and the percent of the RfD that will be utilized by the children (1-6 years old) population subgroup is 0.037. The percent of the RfD utilized for infants and children for rice plus all other current clomazone tolerances is 0.640 and 0.286 respectively.

Based on the above information, FMC has concluded that there is a reasonable certainty that no harm will result to infants, children or adults from dietary food consumption exposure to clomazone residues from either rice foods alone or rice foods plus all other clomazone treated human dietary food sources.

F. International Tolerances

There are Codex residue limits for residues of clomazone in or on cottonseed, oilseed, peas, potatoes, rape, rice, soybeans, sugarcane, and tobacco.

[FR Doc. 99–4025 Filed 2–17–99; 8:45 am]

BILLING CODE 6560–50–F

ENVIRONMENTAL PROTECTION AGENCY

[PF–859; FRL–6059–9]

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–859, must be received on or before March 22, 1999.

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. 1132, 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
Melody A. Banks (PM 03).	Rm. 205, CM #2, 703–305–5413, e-mail:banks.melody@epamail.epa.gov.	1921 Jefferson Davis Hwy, Arlington, VA
Joseph M. Tavano	Rm. 214, CM #2, 703–305–6411, e-mail: tavano.joseph@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 supports 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–859] (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 (insert docket number) and appropriate petition number. Electronic comments on this 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: February 10, 1999.

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. Nihon Nohyaku Co., Ltd.

PP 5E4435

EPA has received a pesticide petition (PP 5E4435) from Nihon Nohyaku Co., Ltd., 2-5, Nihonbashi 1-Chome, Chuo-ku, Tokyo 103, Japan, 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 an import tolerance for residues of fenpyroximate tert-butyl (E)-α-(1,3-dimethyl-5-phenoxypyrazol-4-ylmethyleneamino oxy)-p-toluate, CASRN 134098-61-6 in or on grapes and hops (green and dried). The proposed analytical method involves gas chromatography using nitrogen-sensitive detection against authentic standards for the parent and its two main metabolites. 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 completed a partial review of the sufficiency of the submitted data at this time. Nihon Nohyaku Co., Ltd. has submitted supplemental information to EPA which EPA believes it needs to review and evaluate before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism*. Radiolabel metabolism studies, using ^{14}C labeled fenpyroximate, were conducted with grapes, apples, and citrus. Radiolabeling was at two positions (in separate study series), in the pyrazole ring of the molecule and in the benzyl ring of the molecule. The studies established that: Fenpyroximate applied to growing grape vines leads to parent and metabolites being found mostly on leaves with less than 10% of the total residue being found in the grapes and generally less than 1% of the total residues being found in grape juice. In grapes, the predominant metabolites were the *Z-isomer* of the parent, terephthalic acid, terephthaldehydic acid, and species resulting from cleavage of the tert-butyl group and of the imino linkage. Fenpyroximate applied to apple trees leads to parent and metabolites being found mostly on leaves with less than 10% of the total residue being found in the grapes and generally less than 1% of the total residues being found in apple juice. In grapes, the predominant metabolites were the *Z-isomer* of the parent, terephthalic acid, terephthaldehydic acid, and species resulting from cleavage of the tert-butyl group and of the imino linkage. Application of fenpyroximate to citrus gave similar results. Comparison of the plant metabolites to metabolites in mammalian metabolism studies did not reveal novel metabolites in plants which were not seen in mammals. Nihon Nohyaku believes the results of these plant metabolism studies establish that: (i) fenpyroximate metabolism is similar among the different plant species studies; (ii) metabolism in hops will be similar to that in grapes, apples, and citrus; (iii) the dietary safety of the various plant metabolites of fenpyroximate is well addressed by the animal toxicology data on fenpyroximate since there do not appear to be novel plant metabolites not seen in mammalian metabolism; and, (iv) the tolerance expression for fenpyroximate TTR can be given as:

TTR = (parent + *Z-isomer*) x 3

where the factor of 3 accounts for the highest levels of TTR (including non-extractable residues) seen in the plant metabolism studies in relation to the combined parent + *Z-isomer* residues.

2. *Analytical method*. An adequate analytical method for detecting fenpyroximate parent and *Z-isomer* residues in plants is available. The method has been validated by several laboratories, is a standard European multi-residue method (DFG-S19: Manual of Pesticide Residue Analysis DFG, Deutsche Forschungsgemeinschaft Pesticides Committee), and EPA will independently validate this method as part of EPA's continued review of this petition. Analytical method for detecting fenpyroximate parent and *Z-isomer* residues in plants is available. In brief, plant material is extracted with acetone/water, maintaining an acetone/water ratio of 2:1 v/v (taking into account, also, the natural water content of the plant material). The extract is saturated with sodium chloride and then diluted with dichloromethane, resulting in the separation of excess water. The evaporative residue of the organic phase is cleaned up by gel permeation chromatography on Bio Beads S-x3 polystyrene gel (or equivalent) using a mixture of cyclohexane and ethyl acetate (1+1) as eluant and an automated gel permeation chromatograph. The residue containing fraction is concentrated and after supplemental clean-up on a small silica

gel column is analyzed by gas chromatography using a widebore capillary column and a nitrogen sensitive detector. Limits of detection are: (LOD) (i) 0.02 milligram/kilogram (mg/kg) for grapes, cider, and wine; and, (ii) 0.05 mg/kg for green hops; and, (iii) 1 mg/kg in dried hops. Limits of quantitation (LOQ) are: (i) 0.05 mg/kg for grapes, cider, and wine; and, (ii) 0.1 mg/kg for green hops; and, (iii) 2 mg/kg in dried hops.

3. *Magnitude of residues*. Four field trials were conducted for hops, in each of which residues in dried and green hops were determined. These trials were all conducted in Germany since it is the predominant growing area for hops and registration in that country is imminent. Czechoslovakia is the only other significant exporter of hops to the United States but fenpyroximate registration in Czechoslovakia is not imminent nor has Nihon Nohyaku filed for same at this time. Hops growing areas are, in any case, quite restricted in regard to their micro-climates. Therefore, essentially identical environmental conditions of degree-days, rainfall, and hours of daylight are to be found from one hops growing region to another. As such, Nihon Nohyaku believes that magnitude of the residue data from Germany would adequately represent residues on Czech hops should registration in Czechoslovakia someday be sought.

Twenty-six field trials were conducted in wine grapes, with eleven different grape varietals. These trials were conducted in Germany, Italy, and France since these are major wine producing countries and are major exporters of wines to the United States. No trials data from Spain, another major wine exporter to the United States, or Portugal, a minor exporter, were submitted. Nihon Nohyaku believes that micro-climate conditions in the south of France, and in Italy, which have mediterranean climates, are adequately representative of growing condition in Spanish, and Portuguese vineyards. As below noted: (i) quantifiable residues of fenpyroximate were found in only one juice sample from treated grapes and this was just at the LOQ = 0.02 ppm; (ii) residues in all other juice and in all wine samples were less than the LOQ;, and (iii) there is, therefore, no reasonable basis to expect that quantifiable residues would occur in wines from any country.

In the hops trials, residues in green hops ranged from 1.1 ppm at 7 days post-application and ranged from 0.8 ppm to 3.2 ppm at 21 days post-application (i.e., at harvest). In dried hops residue levels ranged from 2.1 ppm to 6.4 ppm at 21 days post-application (i.e., at harvest with immediate on site drying).

In the grapes trials, residues in grapes ranged from > 0.02 ppm (i.e., non-detect) to 0.41 ppm at 7 days post-application and ranged from > 0.02 ppm (i.e., non-detect) to 0.23 ppm at 36 days post-application (i.e., at harvest). The highest residue level found in grapes was 0.57 ppm in a 14 day post-application sample in one trial. In these trials, a 5-fold range of application rates was used. The label rate recommendation on grapes is 60 - 120 g AI/hectare. The application rates used in these grape trials was from a low of 60 g AI/hectare to a high of 360 g AI/hectare. At from 28 to 36 days post-application mean residues in grapes were > 0.02 ppm at the lowest application rate and were 0.15 - 0.23 ppm at the highest application rates. Residue levels were determined in juice and wines from grapes treated at from 120 to 360 g AI/hectare. In one juice sample residues were just at the (LOQ = 0.02ppm). Resudues in all other juice and in all wine samples were less than the LOQ.

B. Toxicological Profile

1. *Acute toxicity*. Technical fenpyroximate (99+% active ingredient) is moderately toxic by the oral route, with a rat acute oral LD50 of 480 mg/kg (95% CI: 298 <> 662) in males, 245 mg/kg (95% CI: 167 <> 323) in females, and 350 mg/kg (95% CI: 272 <> 428) for males and females combined (MRID 43560501). These LD50 values place fenpyroximate into EPA's acute oral toxicity Category II (signal word: WARNING). Data on acute dermal toxicity, acute inhalation toxicity, eye irritation, skin irritation, and dermal sensitization were not submitted since these are not relevant to the dietary safety ecaluation required in support of an import tolerance.

2. *Chronic and subchronic toxicity*. The following studies were submitted by Nihon Nohyaku: subchronic toxicity in rats (MRID 43429501), chronic toxicity rats (MRID 43560502), subchronic toxicity in dogs (MRID 43429502), and chronic toxicity in dogs (MRID 434329503).

i. *Rat subchronic toxicity*. Fenpyroximate (technical grade) was administered to ten rats/sex/dose in the diet at dose levels of 0, 20, 100 or 500 ppm (average 1.47, 7.43, or 36.9 mg/kg/day; 0 ppm =control) for 13 weeks. No treatment related effects were observed in the 20 ppm groups. Both sexes in the 100 ppm and 500 ppm groups had impaired growth performance, reduced food intake, and decreased body weights and body weight gains. The decrease in body weight gain was dose related. Males in the 100 ppm group had lower white cell counts. In males from the 500 ppm group, hematocrit, hemoglobin, and red cell counts were higher and white cell counts were lower than in controls. In females from the 500 ppm group, hematocrit, hemoglobin, red cell counts, and platelet counts were higher than in controls. Total plasma proteins were reduced in the 500 ppm males and in the 100 and 500 ppm females. Females in the 500 ppm group had lower plasma acetyl- and butyryl-cholinesterase activity and elevated alkaline phosphatase. Males in the 500 ppm group had lower urine volume and pH values. Various treatment related gross pathology changes were noted in the 500 ppm group for both sexes. Micropathology changes noted in the 100 ppm and 500 ppm groups were limited to minimal hepatocytic hypertrophy seen in both sexes. EPA has already reviewed this study and concluded that: (i) the study is acceptable; and, (ii) the no-observed adverse effect level (NOAEL), and lowest-observed adverse effect levels (LOAEL) in this study were 20 ppm (1.3 mg/kg/day) and 100 ppm (6.57 mg/kg/day) respectively based on reduced body weight gain in both sexes.

ii. *Rat chronic toxicity*. A combined oncogenicity/chronic toxicity study (Guideline 83-5) was conducted. For the chronic toxicity phase of this study, fenpyroximate (technical grade) was administered to 30 rats/sex/dose in the diet at dose levels of 0, 10, 25, 75, or 150 ppm (male average: 0.40, 0.97, 3.1, or 6.2 mg/kg/day; Female average: 0.48, 1.2, 3.8, or 7.6 mg/kg/day; 0 ppm = control) for 104 weeks. Chronic toxicity was observed in males and females receiving 75 or 150 ppm. This consisted of depressed growth rate and food efficiency. No treatment related effect on general condition, hematology, clinical chemistries, urinalysis, ophthalmology examinations, gross pathology, or micro pathology were observed. EPA has already reviewed this study and concluded that: (i) the study is acceptable; and, (ii) the NOAEL, and LOAEL in this were 25 ppm (0.97 mg/kg/day in males, and 1.2 mg/kg/day in females), and 75 ppm (3.1 mg/kg/day in males and 3.8 mg/kg/day in females) respectively based on reduced body weight gain in both sexes.

iii. *Dog subchronic toxicity*. Fenpyroximate (technical grade) was administered to four beagle dogs/sex/dose by capsule at dose levels of 2, 10, or 50 mg/kg/day plus a vehicle control group for 13 weeks. Two 50 mg/kg/day females were sacrificed in extremis

during weeks 4 or 5 after a period of appetite loss and body weight loss. Both sexes at all treatment levels exhibited slight bradycardia and a dose-dependent increase in diarrhea. Emaciation and torpor were observed in the 2 mg/kg/day females and in both sexes at 50 mg/kg/day. Emesis was observed in both sexes at 10 and 50 mg/kg/day. Reduced body weight gain and body weight was observed in all female treatment groups and in the 50 mg/kg/day. These effects on weight and weight gain were significant only at the mid and high doses for females. Decreased blood glucose and white cell counts were observed in the 10 and 50 mg/kg/day males. Prothrombin times and blood urea levels were increased in the 50 mg/kg/day females. Increased relative adrenal gland and liver weights were observed in the 50 mg/kg/day males, and females. The 50 mg/kg/day females exhibited depleted glycogen in their hepatocytes and a fine vacuolation of the cellular cytoplasm in the renal medullary rays. EPA has already reviewed this study and concluded that: (i) the study is acceptable; and,(ii) a NOAEL was not established and the LOAEL in this study was 2 mg/kg/day based on slight bradycardia and an increased incidence of diarrhea in both sexes and, in females only, reduced body weight gain, reduced body weight, reduced food consumption, emaciation, and torpor.

iv. *Dog chronic toxicity*. Fenpyroximate (technical grade) was administered to four beagle dogs/sex/dose by capsule at dose levels of 0.5, 1.5, 5.0, or 15 mg/kg/day plus a vehicle control group for 52 weeks. Dogs of both sexes in all treatment groups had 26% - 45% lower blood cholesterol concentrations compared to controls. No accompanying changes in liver function or pathology were noted. There was a more frequent occurrence of diarrhea in males of the 5 and 15 mg/kg/day groups. Males in the 15 mg/kg/day dose group had reduced body weight, consumed less food, and exhibited bradycardia during the first 24 hours after dosing. Aside from lowered cholesterol levels, the only effect noted in females was an increased incidence of diarrhea in the 5 and 15 mg/kg/day groups. No treatment related changes in ophthalmology, hematology, urinalysis, organ weights, electrocardiogram, clinic chemistry (aside from lower cholesterol), and in gross or micro pathology were observed. Relative prostate weights were elevated in all male treatment groups relative to contols. EPA has already reviewed this study and concluded that: (i) the study is acceptable; and, (ii) the NOAEL, and LOAEL in this study were 5 mg/kg/day, and 15 mg/kg/day, respectively, for both males, and females based on diarrehea, bradycardia decreased cholesterol, body weight and food consumption in males and on vomiting, diarrhea, excessive salivation, and decreased cholesterol in females. EPA has inquired as to the mechanism of the prostate weight effect and Nihon Nohyaku has recently sumitted historical control data and other information which demonstrate that in this study the control group has an unusually low mean relative prostate weight and that no fenpyroximate related effect on relative prostate weight in fact occurred in this study.

3. *Oncogenicity*. The following studies were submitted by Nihon Nohyaku: oncogenicity in rats (MRID 43560502), and oncogenicity in mice (MRID 43560503).

i. *Rat oncogenicity*. A combined oncogenicity/chronic toxicity study (Guideline 83-5) was conducted. For the oncogenicity phase of this study, fenpyroximate (technical grade) was administered to 50 rats/sex/dose in the diet at dose levels of 0, 10, 25, 75, or 150 ppm (Male average: 0.40, 0.97, 3.0, or 6.2 mg/kg/day; Female average: 0.49, 1.2, 3.8, or 8.0 mg/kg/day; 0 ppm = control) for 104 weeks. Chronic toxicity was observed in males, and females receiving 75 or 150 ppm. This consisted of depressed growth rate and food efficiency. No treatment related effect on general condition, hematology, clinical chemistries, urinalysis, ophthalmology examinations, gross pathology, or micro pathology were observed. There were no treatment related increases in tumor incidence when compared to controls. EPA has already reviewed this study and concluded that: (i) the study is acceptable; and, (ii) fenpyroximate was not oncogenic in the rat in this study.

ii. *Mouse oncogenicity*. Fenpyroximate (technical grade) was administered to 50 mice/sex/dose in the diet at dose levels of 0, 25, 100, 400, or 800 ppm (Male average: 2.4, 9.5, 38, or 70 mg/kg/day; Female average: 2.5, 10, 42, or 73 mg/kg/day; 0 = control) for 104 weeks. mption were dose related in magnitude and were significant throughout the study at 400 or 800 ppm and were significant during weeks 8 - 12 at 100 ppm. No other treatment related effects of biological significance were observed. There were no treatment related increases in tumor incidence when compared to controls. EPA has already reviewed this study and concluded that: (i) the study is acceptable; (ii) fenpyroximate was not oncogenic in mice in this study; and, (iii) the NOAEL, and the LOAEL in this study were 25 ppm (2.4 mg/kg/day in males, and 2.5 mg/kg/day in females) and 100 ppm (9.5 mg/kg/day in males, and 10 mg/kg in females) respectively based on decreased body weight and food comsumption.

4. *Developmental effects*. The following studies were submitted by Nihon Nohyaku: developmental toxicity in rats (MRID 43429505), and developmental toxicity in rabbits (MRID 43429504).

i. *Rat developmental toxicity*. Fenpyroximate was administered to 22 CD Sprague Dawley female rats per dose group, via gavage dosing, at levels of 0, 1.0, 5.0, or 25 mg/kg/day from days 6 - 15 of gestation. Maternal body weight and food consumption were significantly depressed at 25 mg/kg/day on days 6 - 11 of gestation. There were no treatment related effects on mortality, clinical signs, cesarean parameters, or fetal observations at necropsy at any dose level. Potential developmental effects were characterized as an increase in the litter incidence of additional thoracic ribs which was most marked in the 25 mg/kg/day group. EPA has already reviewed this study and concluded that: (i) the study is acceptable; (ii) the maternal NOAEL, and LOAEL are 5.0 mg/kg/day and, 25 mg/kg/day respectively based on the maternal toxicity data; and, (iii) the NOAEL, and LOAEL for developmental toxicity in this study were 5.0 mg/kg/day, and 25 mg/kg/day respectively based on the increased fetal incidence of thoracic ribs. EPA has requested more detailed historical control data to assess whether the increased incidence of thoracic ribs is indeed treatment related and Nihon Nohyaku has recently submitted these data for review.

ii. *Rabbit developmental toxicity*. Fenpyroximate was administered to 15 New Zealand white female rabbits per dose group, via gavage dosing, at levels of 0, 1.0, 2.5, or 5.0 mg/kg/day from days 6 - 19 of gestation. In its initial review of this study, EPA concluded that there were no treatment related effects on maternal body weight, mortality, clinical signs, cesarean parameters, or fetal observations at necropsy at any dose level. Potential developmental effects were characterized as an increase in retinal folding in the 5 mg/kg/day group. EPA has already reviewed this study and concluded in its initial review that: (i) the study is supplemental because overt maternal toxicity had not been demonstrated; (ii) the maternal NOAEL, and LOAEL are both > 5.0 mg/kg/day the highest dose tested (HDT); and, (iii) the NOAEL, and LOAEL for

developmental toxicity in this study were both > 5.0 mg/kg/day the HDT. EPA has requested more detailed historical control data on retinal folding in the performing laboratory, a combined analysis of unilateral and bilateral retinal folding in this study, and a justification for dose selection in this study (in the form of the range finding data and other re-analysis which may be developed). Nihon Nohyaku has recently submitted the requested historical control and range finding data, a combined analysis of unilateral and bilateral retinal folding, and a correlation analysis of weight losses and decreases in fecal output intreated dams for review. Nihon Nohyaku's evaluation of these additional data indicates that bilateral folding was not a treatment effect, falling into the range of historical controls, and that significant body weight decreases occurred in the 5 mg/kg/day group dams during a period critical to fetal organ development, this decrease exhibited a dose trend in magnitude of the effect, with no effect at 1 mg/kg/day, and that this effect on body weight correlated with a drop in fecal output but not in feed consumption. Nihon Nohyaku believes that the NOAEL for maternal toxicity should be 2.5 mg/kg/day; the LOAEL for maternal toxicity should be 5 mg/kg/day; the NOAEL for developmental effects should be 5 mg/kg/day HDT; and that maternal toxicity has been demonstrated and the dose selection in this study was reasonable.

5. *Reproductive effects.* A 2-generation reproductive effects study with fenpyroximate was performed in the rat (MRID 43429506). In this study the technical form of fenpyroximate was used. There were three dose groups (10, 30, and 100 ppm) and a control group. There were 24 males, and 24 females per group in the F0 generation and 24 per sex per group were selected to form the F_1 breeding generation. The age of the parent animals at the commencement of the study was approximately 6 weeks and the weight range was 168-217 g for males and 128-167 g for females. The F_0 generation was treated continuously by the dietary route throughout the study and until termination after the breeding phase. After 14 weeks of treatment, F0 animals were paired to produce F1 litters. The F_1 generation was treated from weaning until termination after the breeding phase. Both sexes received 14 weeks treatment before pairing to produce the F_2 litters. For each breedingcycle, a 7 day mating period was used. Females not mated within the mating period were then mated for an additional 7 day period with a different male, of a proven mating ability, from the same treatment group. The study was continued through weaning of the F_2 generation. During general, daily observations the condition of F_0 and F_1 males, and females was similar to that of the controls throughout the study. The general condition of the F_2 males and females up through weaning was similar among all group. The litter size, sex ratio, the offspring viability indices before and after culling and the rate of development (pinna unfolding, hair growth, tooth eruption and eye opening) were not adversely affected by treatment in the F_1 and F_2 generations. Macro- and micro-pathology examinations at sacrifice revealed no treatment related changes were in the F_0 animals, the F_1 animals, the F_2 offspring that were culled on day 4 post-partum, nor in the F_2 offspring at termination after weaning. Signs of toxicity which were observed in the high dose group included:

i. *Males (Fo).* Body weight was statistically, slightly lower, in the high dose group (100 ppm) compared to controls. Food consumption was reduced for the majority of the period before pairing.

ii. *Females (Fo).* Prior to pairing, at commencement of gestation, during gestation, and on day 1 post-partum the weight gain of females at the high dose was significantly lower than that of controls (P= < .05).

iii. *Offspring.* Body weight of male offspring at the high dose was significantly reduced at commencement of the F1 generation and subsequent weight gain to termination was reduced compared with the concurrent control group (P= <.001). Food consumption in the period before pairing was marginally reduced. The testes weight relative to body weight of F_1 males showed a significant increase at the high dose. In females, weight gain was slightly reduced with the result that absolute body weight was significantly reduced at the commencement of gestation (p =< 0.05), was further reduced during gestation, but recovered during lactation. EPA has already reviewed this study and concluded that: (a) the study is acceptable; (b) there were no adverse effects on reproductive performance; and, (c) the NOAEL, and LOAEL for reproductive and systemic toxicity in this study were 30 ppm (2.44 mg/kg/day) and, 100 ppm (8.60 mg/kg/day) respectively based on reduced pup weights after birth.

6. *Genotoxicity*. Fenpyroximate was tested for genotoxic effects in several standard test systems with the following results:

Test	Endpoint	Result
Ames test (S. typhimurium)	mutagenicity	negative
Chinese Hamster V79 Forward Mutation	mutagenicity	negative
Cultured Human Lymphocytes	chromosome damage	negative
Mouse Micronucleus Test	chromosome damage	negative
DNA Repair Test (RecA-Assay)	non-specific gene damage	negative
Unscheduled DNA Synthesis	non-specific gene damage	negative

On the basis of the above genotoxicity test battery results, Nihon Nohyaku Co., Ltd. concludes that fenpyroximate is not mutagenic, clastogenic, or otherwise genotoxic.

7. *General metabolism*. In support of the import tolerance for fenpyroximate, severalmammalian metabolism studies were submitted by Nihon Nohyaku Co., Ltd.. These studies are:

1. *MRID 43560504*. Metabolism and Disposition of Benzyl-^{14}C NNI-850 in Rats HLA 6283-101

2. *MRID 43560505*. Metabolism and Disposition of Pyrazole-^{14}C NNI-850 in Rats HLA 6283-102

3. *MRID 43429513*. Pharmacokinetics of a Benzyl-^{14}C NNI-850 in Rats (High and Low Doses) HLA 6283-103 and Pharmacokinetics of a Pyrazole-^{14}C NNI-850 in Rats (High and Low Doses) HLA 6283-103 (note: reports for two studies submitted as one combined volume under a single MRID)

These studies are summarized, here, in aggregate so as to provide a more comprehensive picture of the mammalian metabolism of fenpyroximate.

The test article was purified fenpyroximate (99+% purity) with ^{14}C radio-labeled fenpyroximate. Labeling was in either the pyrazole or the benzyl rings of the compound so as to assure

detection of metabolites resulting from cleavage of the imine linkage between these two ring systems. Young, healthy Sprague Dawley rats were used. Five animals were assigned per sex/time point group for pharmacokinetic studies and for time course determinations of urinary and fecal metabolites. Three animals per sex/time point were assigned for tissue distribution as a function of time studies. Both low and a high doses were tested (2 mg/kg, and 400 mg/kg). Test article administration was by the oral route for all dose groups. The sample collection schedules (blood, urine, and feces) for pharmacokinetics (absorption and elimination) were at 1, 3, 6, 9, 12, 18, 24, 48, 72, 96, 120, 144, and 168 hours post-dose. For metabolism and distribution, sample collection was as follows: urine and feces at the same time points as for pharmacokinetics; and, tissues taken at 24, 96, and 120 hours. Expired air was not collected since preliminary study showed negligible excretion of the label by this route. The results of these studies were as follows:

i. *Pharmacokinetics*—a. *Pyrazole labeled*. The half-life of elimination from blood for the low dose group was 8.9 hours (M & F) and the time to peak blood levels was 11.0 (M) - 11.4 hours (F). Mean maximum concentrations were 0.152 µg equivalents/g (M) and 0.176 µg eq./g (F). AUCs for males and females were 3.49 and 3.82 µg-hr/ml respectively. By 72 hours the level of label in blood declines to below detectable levels.

The half-life of elimination from blood for the high dose group was 48.7 hours (M), and 45.3 hours (F). The time to peak blood levels was 90 (F) -101 hours (M). Mean maximum concentrations were 4.67 µg eq./g (M), and 4.69 µg eq./g (F). AUCs for males and females were 377, and 411 µg-hr/ml respectively. By 216 hours the level of label in blood declines to below detectable levels.

b. *Benzyl labeled*. The half-life of elimination from blood for the low dose group was 6.1 hours (M), and 7.9 hours (F). Time to peak blood levels was 7.2 (F) - 7.8 hours (M). Mean maximum concentrations were 0.097 µg eq./g (M), and 0.181 µg eq./g (F). AUCs for males and females were 1.80, and 3.01 µg-hr/ml respectively. By 48 hours the level of label in blood declines to below detectable levels.

The half-life of elimination from blood for the high dose group was 47.0 hours (M), and 35.4 hours (F). The time to peak blood levels was 28.2 (M) -86.4 hours (F). Mean maximum concentrations were 5.10 µg eq./g (M), and 8.88 µg eq./g (F). AUCs for males and females were 425, and 728 µg-hr/ml respectively. After 168 hours the level of label in blood declines to below detectable levels.

ii. *Metabolism*—a. *Pyrazole labeled*. Fenpyroximate was not metabolized to volatiles to any significant degree. The majority of label is excreted in the feces (69.7% - 84.8% for males, and females). Urinary excretion accounts for from 10.8% - 17.8% of the label. Thus, feces and urine are the major routes of excretion for fenpyroximate. Tissue did not accumulate fenpyroximate or its metabolites to any great extent. The greatest levels of label were in liver, kidneys, heart, and urinary bladder. These tissues had much higher levels of label than did fat. In blood, nearly all of the label is in the plasma.

b. *Benzyl labeled*. Fenpyroximate was not metabolized to volatiles to any significant degree. The majority of label is excreted in the feces (77.9% - 91.6% for males, and females). Urinary excretion accounts for from 9.47% - 13.8% of the label. Thus, feces and urine are the major routes of excretion for fenpyroximate. Tissue did not accumulate fenpyroximate or its metabolites to any great extent. The greatest levels of label were in liver, kidneys, adrenals, and fat (to a lesser degree). In blood, nearly all of the label is in the plasma.

c. *Overall*. The major urinary metabolites of fenpyroximate were 1,3-dimetyl-5-phenoxypyrazole-4-carboxylic acid, 4-cyano-1-methyl-5-phenoxypyrazole-3-carboxylic acid, and terephthalic acid. In feces, there was a large amount of fenpyroximate itself with major fecal metabolites being (E)-α-(1,3-dimethyl-5-phenoxypyrazol-4-ylmethyleneamino-oxy)-p-toluic acid, (Z)-α-(1,3-dimethyl-5-phenoxypyrazol-4-ylmethyleneamino-oxy)-p-toluic acid, and (E)-2-4-(1,3-dimethyl-5-phenoxypyrazol-4-ylmethyleneamino-oxymethyl)benzoyloxy-2-methypropionic acid. The mammalian metabolism of fenpyroximate appears to proceed by oxidation of the tert-butyl and pyrazole-3-methyl groups, by p-hydroxylation of the phenoxy moiety, by N-demethylation, by hydrolysis of the ester and methyleneamino bonds, by conjugation, and by E/Z isomerization.

8. *Oral reference dose (RfD)*. In 1997, an oral RfD of 0.01 mg/kg/day for fenpyroximate was recommended by EPA. This is based on the 2 year rat feeding study in which the NOAEL for males, and females was 0.97 mg/kg/day, and 1.21 mg/kg/day (respectively), and application of a 100-fold uncertainty factor (UF).

C. Aggregate Exposure

1. *Dietary exposure—Food*. Nihon Nohyaku Co., Ltd. has submitted residue data and information on consumption of end-use processed foods from grapes, and hops (wine, and beer) which allow for estimation of the percent RfD utilization at the upper 99th percentile of consumption for beer or wine. These estimates are as follows:

i. *Wine*. According to data publicly available from the Department of Commerce and USDA, imports of wine to the United States, are in the range of 52.8 - 58.1 million gallons (from Italy, France, Spain, Germany, and Portugal combined) in comparison to an annual wine consumption in the United States of 721 million gallons per year. Thus, imported wines account for only 8% of wine consumption. USDA food and beverage consumption data establish that at the upper 99th percentile, male wine drinkers consume 0.89 L wine per day and females wine drinkers consume 0.45 L wine per day. Data submitted by Nihon Nohyaku establish that fenpyroximate residues in wines made from treated grapes are less than 20 parts per billion (ppb), and that TTR in grapes is at most 3-fold the measured fenpyroximate level (i.e., TTR will be less than 60 ppb in wines). Therefore, assuming that 100% of the grapes going into such imported wines are fenpyroximate treated (a deliberate over-estimate), the RfD percent utilization at the upper 99th percentile for wine consumption is 0.61% for males, and 0.36% for females. Nihon Nohyaku Co.,Ltd. has noted that wine drinkers at the upper 99th percentile will be less likely to consume imported wine than will wine drinkers at the median consumption levels. At median consumption levels (approximately 5-fold lower than the upper 99th percentile consumption) the percent RfD utilization is 0.12% for male wine drinkers, and 0.072% for female wine drinkers.

ii. *Beer*. Data available from the Hop Growers of America, Inc. indicate: (a) that United States hops production ranges, annually, from 75 million to 79 million pounds, of which between 43-million and 51 million pounds are exported annually; and, (b) that United States imports of hops from Germany are a maximum of 7.9-milion lbs/year, and from Czechoslovakia are a maximum of 2.0 million lbs/year (the combined maxima equal 9.9 million lbs/year). Therefore, domestic hops utilized in the United States are a minimum of 24 million lbs/year against a maximum of 9.9 million lbs/year of imported hops and an annual hop use of 34 million lbs/

year. This means that at most 29% of beer which is domestically brewed will contain imported hops. The exposure contribution of imported beer can be similarly estimated from BATF and USDA data which are publicly available. Annual production of domestic beer is 190-198 million barrels (31 gallons each = 6.13 billion gallons) with a total value of 13.6 - 14.3 billion. Of this, exports account for approximately 0.08 billion, meaning that nearly all domestic beer is consumed in the United States. Annual consumption of beer in the United States is 8.56 billion gallons, of which as above-noted, 6.13 billion gallons are produced domestically. Thus, comparing the domestic production to the annual consumption gives an estimate for imported beer as 28% of annual beer consumption. Imported beer in the United States derives primarily from the Netherlands, Canada, and Mexico with lesser contributions from other countries (USDA data). For purposes of exposure assessment, a prudent ''worst case'' assumption is that European derived beer is 33% of total imported beer, the balance being from Canada, Mexico, and other sources. Thus, European derived imported beer can be estimated to account for not more than 9.2% of beer consumed in the United States. Combining consumption of domestic beer utilizing imported hops (maximum of 29% of beer consumed), and the consumption of European derived imported beer (maximum of 9.2% of beer consumed) provides that not more than 38% of beer consumed has any potential to contain fenpyroximate residues as a result of approval of this petition. Hopping rates in beer production are less than 0.001 parts by weight in brew water (Hop Growers of America data) which means that fenpyroximate residues in hops will be diluted by at least 0.001 fold in finished beer. At the tolerance of 10 ppm in dried hops (which are what is used in brewing) and using the TTR fenpyroximate ratio of 3x, TTR in dried hops would be 30 ppm and would be not more than 30 ppb in finished beer. USDA food and beverage consumption data establish that at the upper 99th percentile, male beer and ale drinkers consume 2.76 L beer or ale per day, and females beer and ale drinkers consume 1.44 L beer or ale per day. Therefore, applying the factor of 38% for the maximum percent of beer which could contain fenpyroximate residues, the RfD percent utilization at the upper 99th percentile for beer consumption is 4.5% for males, and 2.7% for females. Nihon Nohyaku Co., Ltd. has noted: (a) that beer and ale drinkers at the upper 99th percentile will be less likely to consume imported beer and ale than will beer and ale drinkers at the median consumption levels; and, (b) that ales are not hopped. At median consumption levels (approximately 5 fold lower than the upper 99th percentile consumption) the percent RfD utilization is 0.90% for male beer and ale drinkers, and 0.54% for female beer and ale drinkers

iii. *Drinking water*. This is an import tolerance petition and there are no uses of fenpyroximate in the United States. Accordingly, there is no potential for drinking water exposure associated with the approval of this petition.

2. *Non-dietary exposure*. Fenpyroximate is not registered in the United States and is only an agricultural use miticide. Therefore, there are non-dietary exposure which could result from approval of this petition. Were fenpyroximate to be registered in the United States there would still be no potential for non-dietary, non-occupational exposures.

D. Cumulative Effects

There is no reliable information to indicate that fenpyroximate has a common mechanism of toxicity with any other chemical compound.

E. Endocrine Effects

There is no reliable information to indicate that fenpyroximate has a potential to produce endocrine effects.

F. Safety Determination

1. *U.S. population*. Since the proposed import tolerances for fenpyroximate in or on grapes and hops are, under worst case conditions, anticipated to lead to only negligible adult dietary exposures to fenpyroximate TTR (i.e., not greater than 0.61% of the RfD for adult wine drinkers at the upper 99th percentile of consumption, and not greater than 4.5% of the RfD for adult beer and ale drinkers at the upper 99th percentile of consumption, with ''negligible'' defined at 40 CFR 180.1(l) as ''ordinarily'' not greater than 5% of the RfD) Nihon Nohyaku Co., Ltd. concludes that there is a reasonable certainty that no harm to the general adult population will result from dietary exposure to residues which could occur as a result of approval of this petition.

2. *Infants and children*. The proposed import tolerance does not affect foods or beverages legally consumed by children and infants. Therefore, Nihon Nohyaku Co., Ltd. concludes that there is a reasonable certainty that no harm to infants and children will result from dietary exposure to residues which could occur as a result of approval of this petition.

3. *Sensitive individuals*. The toxicology data base for fenpyroximate demonstrates a consistency in effects, NOAELs, and LOAELs among rats, mice, and dogs. This suggests that inter-species differences in metabolism and sensitivity to fenpyroximate are not large which, in turn, suggests that metabolic and sensitivity differences among human subpopulations exposed to fenpyroximate will be small. Also, worst case exposure to residues is at negligible levels and the margins of exposure for wine drinkers are at least 16,000 for wine drinkers, and at least 2,200 for beer and ale drinkers, which suggests that differences in sensitivity to fenpyroximate among human subpopulations, including persons who were ill, would have to be quite large in order to lead to exposures of concern in sensitive individuals. Therefore, Nihon Nohyaku Co., Ltd. concludes that there is a reasonable certainty that no harm to sensitive persons will result from dietary exposure to residues which could occur as a result of approval of this petition.

G. International Tolerances

There are no Codex maximum residue levels (MRLs) established for residues of fenpyroximate resulting from the application of fenpyroximate to grapes or hops. Proposals for a German MRL of 10 ppm on green hops and, 0.5 ppm on grapes and for Italian and Spanish MRLs of 0.3 ppm on grapes are being reviewed by the respective countries. Since these are lower than the proposed import tolerances, there is very little likelihood that residues in violation of the import tolerances could occur.

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2. Rohm and Haas Company

PP 7F4824

EPA has received a revised pesticide petition (7F4824) from Rohm and Haas Company, 100 Independence Mall West, Philadelphia, PA 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 by establishing a tolerance for residues of tebufenozide benzoic acid, 3,5-dimethyl-,1-(1,1-dimethylethyl)-2-(4-ethylbenzoyl) hydrazide in or on the raw agricultural commodity crop subgroup leafy greens, crop subgroup leaf petioles, crop subgroup head and stem Brassica and crop subgroup leafy Brassica greens at 10.0, 2.0, 5.0, and 10.0 parts per million (ppm) respectively. 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 tebufenozide in plants (grapes, apples, rice, and sugar beets) is adequately understood for the purpose of this tolerance. The metabolism of tebufenozide in all crops was similar and involves oxidation of the alkyl substituents of the aromatic rings primarily at the benzylic positions. The extent of metabolism and degree of oxidation are a function of time from application to harvest. In all crops, parent compound comprised the majority of the total dosage. None of the metabolites were in excess of 10% of the total dosage.

2. *Analytical method*. A high performance liquid chromatographic (HPLC) analytical method using ultraviolet (UV) or mass spectrometry (MS) detection has been validated for leafy and cole crop vegetables. For all matrices, the methods involve extraction by blending with solvents, purification of the extracts by liquid-liquid partitions and final purification of the residues using solid phase extraction column chromatography. The limit of quantitation (LOQ) of the method is 0.01 part per million (ppm) for all representative crops of these crop subgroups except for celery which is 0.05 ppm.

3. *Magnitude of residues*. Magnitude of the residue studies were conducted in celery, and mustard greens using the maximum proposed label rate. Samples were collected 7 days after the last application and were analyzed for residues of tebufenozide. The residue data support a tolerance of 5.0 ppm for the crop subgroup leaf petioles (4A), and 10.0 ppm for the crop subgroup Leafy Brassica Green Vegetables (5B).

B. Toxicological Profile

1. *Acute toxicity*. Acute toxicity studies with technical grade: Oral LD_{50} in the rat is > 5 grams for males and females - Toxicity Category IV; dermal LD_{50} in the rat is = 5,000 milligram/kilogram (mg/kg) for males and females - Toxicity Category III; inhalation LD_{50} rat is > 4.5 mg/l - Toxicity Category III; primary eye irritation study in the rabbit is a non-irritant; primary skin irritation in the rabbit > 5 mg - Toxicity Category IV. Tebufenozide is not a sensitizer.

2. *Genotoxicty*. Several mutagenicity tests which were all negative. These include an Ames assay with and without metabolic activation, an *in vivo* cytogenetic assay in rat bone marrow cells, and *in vitro* chromosome aberration assay in CHO cells, a CHO/HGPRT assay, a reverse mutation assay with *E. Coli*, and an unscheduled DNA synthesis assay (UDS) in rat hepatocytes.

3. *Reproductive and developmental toxicity*. In a prenatal developmental toxicity study in Sprague-Dawley rats 25/group, tebufenozide was administered on gestation days 6-15 by gavage in aqueous methyl cellulose at dose levels of 50, 250, or 1,000 mg/kg/day, and a dose volume of 10 ml/kg. There was no evidence of maternal or developmental toxicity; the maternal and developmental toxicity no-observed adverse effect level (NOAEL) was 1,000 mg/kg/day.

In a prenatal developmental toxicity study conducted in New Zealand white rabbits 20/group, tebufenozide was administered in 5 ml/kg of aqueous methyl cellulose at gavage doses of 50, 250, or 1,000 mg/kg/day on gestation days 7-19. No evidence of maternal or developmental toxicity was observed; the maternal and developmental toxicity NOAEL was 1,000 mg/kg/day.

In a 1993 2-generation reproduction study in Sprague-Dawley rats tebufenozide was administered at dietary concentrations of 0, 10, 150, or 1,000 ppm (0, 0.8, 11.5, or 154.8 mg/kg/day for males, and 0, 0.9, 12.8, or 171.1 mg/kg/day for females). The parental systemic NOAEL was 10 ppm (0.8/0.9 mg/kg/day for males and females, respectively), and the lowest-observed adverse effect level (LOAEL) was 150 ppm (11.5/12.8 mg/kg/day for males and females, respectively) based on decreased body weight, body weight gain, and food consumption in males, and increased incidence and/or severity of splenic pigmentation. In addition, there was an increased incidence and severity of extramedullary hematopoiesis at 2,000 ppm. The reproductive NOAEL was 150 ppm. (11.5/12.8 mg/kg/day for males and females, respectively), and the LOAEL was 2,000 ppm (154.8/171.1 mg/kg/day for males and females, respectively) based on an increase in the number of pregnant females with increased gestation duration and dystocia. Effects in the offspring consisted of decreased number of pups per litter on postnatal days 0 and/or 4 at 2,000 ppm (154.8/171.1 mg/kg/day for males and females, respectively) with a NOAEL of 150 ppm (11.5/12.8 mg/kg/day for males and females, respectively).

In a 1995 2-generation reproduction study in rats, tebufenozide was administered at dietary concentrations of 0, 25, 200, or 2,000 ppm (0, 1.6, 12.6, or 126.0 mg/kg/day for males, and 0, 1.8, 14.6, or 143.2 mg/kg/day for females). For parental systemic toxicity, the NOAEL was 25 ppm (1.6/1.8 mg/kg/day in males and females, respectively), and the LOAEL was 200 ppm (12.6/14.6 mg/kg/day in males, and females), based on histopathological findings (congestion and extramedullary hematopoiesis) in the spleen. Additionally, at 2,000 ppm (126.0/143.2 mg/kg/day in M/F), treatment-related findings included reduced parental body weight gain and increased incidence of hemosiderin-laden cells in the spleen. Columnar changes in the vaginal squamous epithelium and reduced uterine and ovarian weights were also observed at 2,000 ppm, but the toxicological significance was unknown. For offspring, the systemic NOAEL was 200 ppm. (12.6/14.6 mg/kg/day in males, and females), and the LOAEL was 2,000 ppm (126.0/143.2 mg/kg/day in M/F) based on decreased body weight on postnatal days 14 and 21.

4. *Subchronic toxicity*. In a prenatal developmental toxicity study in Sprague-Dawley rats 25/group, tebufenozide was administered on gestation days 6-15 by gavage in aqueous methyl cellulose at dose levels of 50, 250, or 1,000 mg/kg/day and a dose volume of 10 ml/kg. There was no evidence of maternal or developmental toxicity; the maternal and developmental toxicity NOAEL was 1,000 mg/kg/day.

5. *Chronic toxicity*. A 1 year dog feeding study with a LOAEL of 250 ppm, 9 mg/kg/day for male and female dogs based on decreases in RBC, HCT, and HGB, increases in Heinz bodies, methemoglobin, MCV, MCH, reticulocytes, platelets, plasma total bilirubin, spleen weight, and spleen/body weight ratio, and liver/body weight ratio. Hematopoiesis and sinusoidal engorgement occurred in the spleen, and hyperplasia occurred in the marrow of the femur and sternum. The

liver showed an increased pigment in the Kupffer cells. The NOAEL for systemic toxicity in both sexes is 50 ppm (1.9 mg/kg/day).

An 18 month mouse carcinogenicity study with no carcinogenicity observed at dosage levels up to and including 1,000 ppm.

A 2 year rat carcinogenicity with no carcinogenicity observed at dosage levels up to and including 2,000 ppm (97 mg/kg/day and 125 mg/kg/day for males and females, respectively).

6. *Animal metabolism*. The adsorption, distribution, excretion and metabolism of tebufenozide in rats was investigated. Tebufenozide is partially absorbed, is rapidly excreted and does not accumulate in tissues. Although tebufenozide is mainly excreted unchanged, a number of polar metabolites were identified. These metabolites are products of oxidation of the benzylic ethyl or methyl side chains of the molecule. These metabolites were detected in plant and other animal (rat, goat, hen) metabolism studies.

7. *Metabolite toxicology*. Common metabolic pathways for tebufenozide have been identified in both plants (grape, apple, rice, and sugar beet), and animals (rat, goat, hen). The metabolic pathway common to both plants and animals involves oxidation of the alkyl substituents (ethyl and methyl groups) of the aromatic rings primarily at the benzylic positions. Extensive degradation and elimination of polar metabolites occurs in animals such that residue are unlikely to accumulate in humans or animals exposed to these residues through the diet.

8. *Endocrine disruption*. The toxicology profile of tebufenozide shows no evidence of physiological effects characteristic of the disruption of the hormone estrogen. Based on structure-activity information, tebufenozide is unlikely to exhibit estrogenic activity. Tebufenozide was not active in a direct *in vitro* estrogen binding assay. No indicators of estrogenic or other endocrine effects were observed in mammalian chronic studies or in mammalian and avian reproduction studies. Ecdysone has no known effects in vertebrates. Overall, the weight of evidence provides no indication that tebufenozide has endocrine activity in vertebrates.

C. Aggregate Exposure

1. *Dietary exposure*—i. *Food*. Tolerances have been established (40 CFR 180.482) for the residues of tebufenozide, in or on walnuts at 0.1 ppm, apples at 1.0 ppm, pecans at 0.01 ppm and wine grapes at 0.5 ppm. Numerous section 18 tolerances have been established at levels ranging from 0.3 ppm in sugar beet roots to 5.0 ppm in turnip tops. Other tolerance petitions are pending at EPA with proposed tolerances ranging from 0.3 ppm in or on sugarcane to 10 ppm in cole crop vegetables. Risk assessments were conducted by Rohm and Haas to assess dietary exposures and risks from tebufenozide, benzoic acid, 3,5-dimethyl-1-(1,1-dimethylethyl)-2-(4-ethylbenzoyl) hydrazide as follows:

ii. *Acute exposure and risk*. Acute dietary risk assessments are performed for a food-use pesticide if a toxicological study has indicated the possibility of an effect of concern occurring as a result of a 1 day or single exposure. Toxicity observed in oral toxicity studies were not attributable to a single dose (exposure). No neuro or systemic toxicity was observed in rats given a single oral administration of tebufenozide at 0, 500, 1,000 or 2,000 mg/kg. No maternal or developmental toxicity was observed following oral administration of tebufenozide at 1,000 mg/kg/day (Limit-Dose) during gestation to pregnant rats or rabbits. This risk is considered to be negligible.

iii. *Chronic exposure and risk*. The RfD used for the chronic dietary analysis is 0.018 mg/kg/day. In conducting this exposure assessment, Rohm and Haas has made very conservative assumptions 100% of pecans, walnuts, wine and sherry, pome fruit, and all other commodities having tebufenozide tolerances or pending tolerances will contain tebufenozide residues, and those residues would be at the level of the tolerance which result in an over estimate of human dietary exposure. Thus, in making a safety determination for this tolerance, Rohm and Haas is taking into account this conservative exposure assessment. Using the Dietary Exposure Evaluation Model (Version 5.03b, licensed by Novigen Sciences Inc.) which uses USDA food consumption data from the 1989-1992 survey and the appropriate concentration or reduction factors, the existing tebufenozide tolerances published, pending, and including the necessary section 18 tolerance(s) resulted in a Theoretical Maximum Residue Contribution (TMRC) that is equivalent to the following percentages of the RfD:

U.S. Population (35.8% of RfD);

Northeast Region (37.5% of RfD);

Western Region (39.8%);

Pacific Region (40.9%)All Infants (<1 year) (36.3%);

Nursing Infants (<1 year old) (16.8% of RfD);

Non-Nursing Infants (<1 year old) (44.5% of RfD);

Children (1-6 years old) (61.9% of RfD);

Children (7-12 years old) (45.6% of RfD);

Females (13 + years old, nursing) (30.6% of RfD);

Non-Hispanic Whites (36.0%);

Non-Hispanic Other than Black or White (43.1% of RfD).

The subgroups listed above are subgroups for which the percentage of the RfD occupied is greater than that occupied by the subgroup U.S. population (48 States).

iv. *Drinking water— Acute exposure and risk*. Because no acute dietary endpoint was determined, Rohm and Haas concludes that there is a reasonable certainty of no harm from acute exposure from drinking water.

v. *Chronic exposure and risk*. Submitted environmental fate studies suggest that tebufenozide is moderately persistent to persistent and mobile. Under certain conditions tebufenozide appears to have the potential to contaminate ground and surface water through runoff and leaching; subsequently potentially contaminating drinking water. There are no established Maximum Contaminant Levels (MCL) for residues of tebufenozide in drinking water and no Health Advisories (HA) have been issued for tebufenozide therefore, these could not be used as comparative values for risk assessment. Therefore, potential residue levels for drinking water exposure were calculated using GENEEC (surface water) and SCIGROW (ground water) for human health risk assessment. Because of the wide range of half-life values (66-729 days) reported for the aerobic soil metabolism input parameter a range of potential exposure values were calculated. In each case the worst case upper bound exposure limits were then compared to appropriate chronic drinking water level of concern (DWLOC). In each case the calculated exposures based on model data were below the DWLOC.

2. *Non-dietary exposure*. Tebufenozide is not currently registered for use on any residential non-food sites. Therefore, there is no chronic, short- or intermediate-term exposure scenario.

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.'' The Agency believes that ''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).

EPA does not have, at this time, available data to determine whether tebufenozide, benzoic acid, 3,5-dimethyl-1-(1,1-dimethylethyl)-2-(4-ethylbenzoyl) hydrazide has a common mechanism 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, tebufenozide, benzoic acid, 3,5-dimethyl-1-(1,1-dimethylethyl)-2-(4-ethylbenzoyl) hydrazide does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, Rohm and Haas has not assumed that tebufenozide, benzoic acid, 3,5-dimethyl-1-(1,1-dimethylethyl)-2-(4-ethylbenzoyl) hydrazide has a common mechanism of toxicity with other substances.

E. Safety Determination

1. *U.S. population*. Using the conservative exposure assumptions described above, and taking into account the completeness and reliability of the toxicity data, Rohm and Haas has concluded that dietary (food only) exposure to tebufenozide will utilize 35.8% of the RfD for the U.S. population. Submitted environmental fate studies suggest that tebufenozide is moderately persistent to persistent and mobile; thus, tebufenozide could potentially leach to ground water and runoff to surface water under certain environmental conditions. The modeling data for tebufenozide indicate levels less than OPP's DWLOC. 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. There are no registered residential uses of tebufenozide. Since there is no potential for exposure to tebufenozide from residential uses, Rohm and Haas does not expect the aggregate exposure to exceed 100% of the RfD.

Short- and intermediate-term risk. 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. Since there are currently no registered indoor or outdoor residential non-dietary uses of tebufenozide and no short- or intermediate-term toxic endpoints, short- or intermediate-term aggregate risk does not exist.

Since, tebufenozide has been classified as a Group E, ''no evidence of carcinogenicity for humans,'' this risk does not exist.

2. *Infants and children*. In assessing the potential for additional sensitivity of infants and children to residues of tebufenozide, data from developmental toxicity studies in the rat and rabbit, and two 2-generation reproduction studies in the rat are considered. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during prenatal development to one or both parents. Reproduction studies provide information relating to effects from exposure to the pesticide on the reproductive capability of mating animals and data on systemic toxicity. Developmental toxicity was not observed in developmental studies using rats and rabbits. The NOAEL for developmental effects in both rats and rabbits was 1,000 mg/kg/day, which is the limit dose for testing in developmental studies.

In the 2-generation reproductive toxicity study in the rat, the reproductive/developmental toxicity NOAEL of 12.1 mg/kg/day was 14-fold higher than the parental (systemic) toxicity NOAEL (0.85 mg/kg/day). The reproductive (pup) LOAEL of 171.1 mg/kg/day was based on a slight increase in both generations in the number of pregnant females that either did not deliver or had difficulty and had to be sacrificed. In addition, the length of gestation increased and implantation sites decreased significantly in F1 dams. These effects were not replicated at the same dose in a second 2-generation rat reproduction study. In this second study, reproductive effects were not observed at 2,000 ppm (the NOAEL equal to 149-195 mg/kg/day), and the NOAEL for systemic toxicity was determined to be 25 ppm (1.9-2.3 mg/kg/day).

Because these reproductive effects occurred in the presence of parental (systemic) toxicity and were not replicated at the same doses in a second study, these data do not indicate an increased pre-natal or post-natal sensitivity to children and infants (that infants and children might be more sensitive than adults) to tebufenozide exposure. FFDCA section 408 provides that EPA shall 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 data base unless EPA concludes that a different margin of safety is appropriate. Based on current toxicological data discussed above, an additional uncertainty factor is not warranted and the RfD at 0.018 mg/kg/day is appropriate for assessing aggregate risk to infants and children. Rohm and Haas concludes that there is a reasonable certainty that no harm will occur to infants and children from aggregate exposure to residues of tebufenozide.

F. International Tolerances

There are no approved CODEX maximum residue levels (MRLs) established for residues of tebufenozide. (Melody Banks)

3. Rohm and Haas Company

PP 7F4869

EPA has received a revised pesticide petition (7F4869) from Rohm and Haas Company, 100 Independence Mall West, Philadelphia, PA 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 by establishing a tolerance for residues of tebufenozide benzoic acid, 3,5-dimethyl-, 1-(1,1-dimethylethyl)-2-(4-ethylbenzoyl) hydrazide] in or on the raw agricultural commodity crop grouping, fruiting vegetables except cucurbits at 1.0 parts per million (ppm). 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 tebufenozide in plants (grapes, apples, rice, and sugar beets) is adequately understood for the purpose of this tolerance. The metabolism of tebufenozide in all crops was similar and involves oxidation of the alkyl substituents of the aromatic rings primarily at the benzylic positions. The extent of metabolism and degree of oxidation are a function of time from application to harvest. In all crops, parent compound comprised the majority of the total dosage. None of the metabolites were in excess of 10% of the total dosage.

2. *Analytical method*. A validated high performance liquid chromatographic (HPLC) analytical method using ultraviolet (UV) detection is employed for measuring residues of tebufenozide in peppers, tomatoes, and tomato process fractions. The method involves extraction by blending with solvents, purification of the extracts by liquid-liquid partitions and final purification of the residues using solid phase extraction column chromatography. The limit of quantitation (LOQ) of the method for all matrices is 0.02 ppm.

3. *Magnitude of residues*. Field residue trials in tomatoes, and peppers were conducted in geographically representative regions of the U.S. The highest field residue value for a single replicate sample was 0.76 parts per million (ppm). Results of analysis of tomato paste and puree samples from a processing study with treated tomatoes showed no concentration of residues.

B. Toxicological Profile

1. *Acute toxicity*. Acute toxicity studies with technical grade: Oral LD_{50} in the rat is > 5 grams for males and females - Toxicity Category IV; dermal LD_{50} in the rat is = 5,000 milligram/kilogram (mg/kg) for males, and females - Toxicity Category III; inhalation LD_{50} in the rat is > 4.5 mg/l - Toxicity Category III; primary eye irritation study in the rabbit is a non-irritant; primary skin irritation in the rabbit > 5 mg - Toxicity Category IV. tebufenozide is not a sensitizer.

2. *Genotoxicty*. Several mutagenicity tests which were all negative. These include an Ames assay with and without metabolic activation, an *in vivo* cytogenetic assay in rat bone marrow cells, and *in vitro* chromosome aberration assay in CHO cells, a CHO/HGPRT assay, a reverse mutation assay with *E. Coli*, and an unscheduled DNA synthesis assay (UDS) in rat hepatocytes.

3. *Reproductive and developmental toxicity*. In a prenatal developmental toxicity study in Sprague-Dawley rats 25/group tebufenozide was administered on gestation days 6-15 by gavage in aqueous methyl cellulose at dose levels of 50, 250, or 1,000 mg/kg/day and a dose volume of 10 ml/kg. There was no evidence of maternal or developmental toxicity; the maternal and developmental toxicity no-observed adverse effect level (NOAEL was 1,000 mg/kg/day.

In a prenatal developmental toxicity study conducted in New Zealand white rabbits 20/group tebufenozide was administered in 5 ml/kg of aqueous methyl cellulose at gavage doses of 50, 250, or 1,000 mg/kg/day on gestation days 7-19. No evidence of maternal or developmental toxicity was observed; the maternal and developmental toxicity NOAEL was 1,000 mg/kg/day.

In a 1993 2-generation reproduction study in Sprague-Dawley rats tebufenozide was administered at dietary concentrations of 0, 10, 150, or 1,000 ppm (0, 0.8, 11.5, or 154.8 mg/kg/day for males, and 0, 0.9, 12.8, or 171.1 mg/kg/day for females). The parental systemic NOAEL was 10 ppm (0.8/0.9 mg/kg/day for males and females, respectively) and the lowest-observed adverse level (LOAEL) was 150 ppm (11.5/12.8 mg/kg/day for males, and females respectively), based on decreased body weight, body weight gain, and food consumption in males, and increased incidence and/or severity of splenic pigmentation. In addition, there was an increased incidence and severity of extramedullary hematopoiesis at 2,000 ppm. The reproductive NOAEL was 150 ppm. (11.5/12.8 mg/kg/day for males, and females respectively), and the LOAEL was 2,000 ppm (154.8/171.1 mg/kg/day for males, and females respectively), based on an increase in the number of pregnant females with increased gestation duration and dystocia. Effects in the offspring consisted of decreased number of pups per litter on postnatal days 0 and/or 4 at 2,000 ppm (154.8/171.1 mg/kg/day for males, and females respectively), with a NOAEL of 150 ppm (11.5/12.8 mg/kg/day for males, and females respectively).

In a 1995 2-generation reproduction study in rats, tebufenozide was administered at dietary concentrations of 0, 25, 200, or 2,000 ppm (0, 1.6, 12.6, or 126.0 mg/kg/day for males, and 0, 1.8, 14.6, or 143.2 mg/kg/day for females). For parental systemic toxicity, the NOAEL was 25 ppm (1.6/1.8 mg/kg/day in males, and females respectively), and the LOAEL was 200 ppm (12.6/14.6 mg/kg/day in males, and females), based on histopathological findings (congestion and extramedullary hematopoiesis) in the spleen. Additionally, at 2,000 ppm (126.0/143.2 mg/kg/day in M/F), treatment-related findings included reduced parental body weight gain and increased incidence of hemosiderin-laden cells in the spleen. Columnar changes in the vaginal squamous epithelium and reduced uterine and ovarian weights were also observed at 2,000 ppm, but the toxicological significance was unknown. For offspring, the systemic NOAEL was 200 ppm. (12.6/14.6 mg/kg/day in males, and females), and the LOAEL was 2,000 ppm (126.0/143.2 mg/kg/day in M/F) based on decreased body weight on postnatal days 14 and 21.

4. *Subchronic toxicity*. In a prenatal developmental toxicity study in Sprague-Dawley rats 25/group tebufenozide was administered on gestation days 6-15 by gavage in aqueous methyl cellulose at dose levels of 50, 250, or 1,000 mg/kg/day and a dose volume of 10 ml/kg. There was no evidence of maternal or developmental toxicity; the maternal and developmental toxicity NOAEL was 1,000 mg/kg/day.

5. *Chronic toxicity*. A 1 year dog feeding study with a LOAEL of 250 ppm, 9 mg/kg/day for male, and female dogs based on decreases in RBC, HCT, and HGB increases in Heinz bodies, methemoglobin, MCV, MCH, reticulocytes, platelets, plasma total bilirubin, spleen weight, and spleen/body weight ratio, and liver/body weight ratio. Hematopoiesis and sinusoidal engorgement occurred in the spleen, and hyperplasia occurred in the

marrow of the femur and sternum. The liver showed an increased pigment in the Kupffer cells. The NOAEL for systemic toxicity in both sexes is 50 ppm (1.9 mg/kg/day).

An 18 month mouse carcinogenicity study with no carcinogenicity observed at dosage levels up to and including 1,000 ppm.

A 2 year rat carcinogenicity with no carcinogenicity observed at dosage levels up to and including 2,000 ppm (97 mg/kg/day and 125 mg/kg/day for males, and females respectively).

6. *Animal metabolism*. The adsorption, distribution, excretion and metabolism of tebufenozide in rats was investigated. Tebufenozide is partially absorbed, is rapidly excreted and does not accumulate in tissues. Although tebufenozide is mainly excreted unchanged, a number of polar metabolites were identified. These metabolites are products of oxidation of the benzylic ethyl or methyl side chains of the molecule. These metabolites were detected in plant and other animal (rat, goat, and hen) metabolism studies.

7. *Metabolite toxicology*. Common metabolic pathways for tebufenozide have been identified in both plants (grape, apple, rice, and sugar beet), and animals (rat, goat, and hen). The metabolic pathway common to both plants and animals involves oxidation of the alkyl substituents (ethyl and methyl groups) of the aromatic rings primarily at the benzylic positions. Extensive degradation and elimination of polar metabolites occurs in animals such that residue are unlikely to accumulate in humans or animals exposed to these residues through the diet.

8. *Endocrine disruption*. The toxicology profile of tebufenozide shows no evidence of physiological effects characteristic of the disruption of the hormone estrogen. Based on structure-activity information, tebufenozide is unlikely to exhibit estrogenic activity. Tebufenozide was not active in a direct *in vitro* estrogen binding assay. No indicators of estrogenic or other endocrine effects were observed in mammalian chronic studies or in mammalian and avian reproduction studies. Ecdysone has no known effects in vertebrates. Overall, the weight of evidence provides noindication that tebufenozide has endocrine activity in vertebrates.

C. Aggregate Exposure

1. *Dietary exposure*. The dietary exposure is discussed below.

i. *Food*. Tolerances have been established (40 CFR 180.482) for the residues of tebufenozide, in or on walnuts at 0.1 ppm, apples at 1.0 ppm, pecans at 0.01 ppm, and wine grapes at 0.5 ppm. Numerous section 18 tolerances have been established at levels ranging from 0.3 ppm in sugar beet roots to 5.0 ppm in turnip tops. Other tolerance petitions are pending at EPA with proposed tolerances ranging from 0.3 ppm in or on sugarcane to 10 ppm in cole crop vegetables. Risk assessments were conducted by Rohm and Haas to assess dietary exposures and risks fromtebufenozide, benzoic acid, 3,5-dimethyl-1-(1,1-dimethylethyl)-2-(4-ethylbenzoyl) hydrazide as follows:

ii. *Acute exposure and risk*. Acute dietary risk assessments are performed for a food-use pesticide if a toxicological study has indicated the possibility of an effect of concern occurring as a result of a 1 day or single exposure. Toxicity observed in oral toxicity studies were not attributable to a single dose (exposure). No neuro- or systemic toxicity was observed in rats given a single oral administration of tebufenozide at 0, 500, 1,000 or 2,000 mg/kg. No maternal or developmental toxicity was observed following oral administration of tebufenozide at 1,000 mg/kg/day limit-dose (LTD) during gestation to pregnant rats or rabbits. This risk is considered to be negligible.

iii. *Chronic exposure and risk*. The refrence dose (RfD) used for the chronic dietary analysis is 0.018 mg/kg/day. In conducting this exposure assessment, Rohm and Haas has made very conservative assumptions that 100% of pecans, walnuts, wine and sherry, imported apples and all other commodities having tebufenozide tolerances or pending tolerances will contain tebufenozide residues, and those residues would be at the level of the tolerance which result in an over estimate of human dietary exposure. The existing tebufenozide tolerances published, pending, and including the necessary section 18 tolerance(s) resulted in a Theoretical Maximum Residue Contribution (TMRC) that is equivalent to the following percentages of the RfD:

U.S. population (34.5% of RfD);

All Infants (> 1 year) (61.4%);

Nursing Infants (> 1 year old) (39.9% of RfD);

Non-Nursing Infants (> 1 year old) (70.4% of RfD);

Children (1-6 years old) (79.8% of RfD);

Children (7-12 years old) (48.5% of RfD);

Females (13 + years old, nursing) (39.5% of RfD);

Non-Hispanic Whites (34.8%);

Non-Hispanic Other than Black or White (40.2% of RfD);

Northeast Region (37.4% of RfD);

Western Region (36.8%);

Pacific Region (36.8%).

The subgroups listed above are subgroups for which the percentage of the RfD occupied is greater than that occupied by the subgroup U.S. population (48 States).

iv. *Drinking water—Acute exposure and risk*. Because no acute dietary endpoint was determined, Rohm and Haas concludes that there is a reasonable certainty of no harm from acute exposure from drinking water.

v. *Chronic exposure and risk*. Submitted environmental fate studies suggest that tebufenozide is moderately persistent to persistent and mobile. Under certain conditions tebufenozide appears to have the potential to contaminate ground and surface water through runoff and leaching; subsequently potentially contaminating drinking water. There are no established Maximum Contaminant Levels (MCL) for residues of tebufenozide in drinking water and no Health Advisories (HA) have been issued for tebufenozide therefore these could not be used as comparative values for risk assessment. Therefore, potential residue levels for drinking water exposure were calculated previously by EPA using GENEEC (surface water), and SCIGROW (ground water) for human health risk assessment. Because of the wide range of half-life values (66-729 days) reported for the aerobic soil metabolism input parameter a range of potential exposure values were calculated. In each case the worst case upper bound exposure limits were then compared to appropriate chronic drinking water level of concern (DWLOC). In each case the calculated exposures based on model data were below the DWLOC.

2. *Non-dietary exposure*. Tebufenozide is not currently registered for use on any residential non-food sites. Therefore, there is no chronic, short- or intermediate-term exposure scenario.

D. Cumulative Effects

Cumulative exposure to substances with common mechanism of toxicity. 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.'' The Agency believes that ''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).

EPA does not have, at this time, available data to determine whether tebufenozide, benzoic acid, 3,5-dimethyl-1-(1,1-dimethylethyl)-2-(4-ethylbenzoyl) hydrazide has a common mechanism 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, tebufenozide, benzoic acid, 3,5-dimethyl-1-(1,1-dimethylethyl)-2-(4-ethylbenzoyl) hydrazide does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, Rohm and Haas has not assumed that tebufenozide, benzoic acid, 3,5-dimethyl-1-(1,1-dimethylethyl)-2-(4-ethylbenzoyl) hydrazide has a common mechanism of toxicity with other substances.

E. Safety Determination

1. *U.S. population*. Using the conservative exposure assumptions described above, and taking into account the completeness and reliability of the toxicity data, Rohm and Haas has concluded that dietary (food only) exposure to tebufenozide will utilize 34.5% of the RfD for the U.S. population. Submitted environmental fate studies suggest that tebufenozide is moderately persistent to persistent and mobile; thus, tebufenozide could potentially leach to ground water and runoff to surface water under certain environmental conditions. The modeling data for tebufenozide indicate levels less than OPP's DWLOC. 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. There are no registered residential uses of tebufenozide. Since there is no potential for exposure to tebufenozide from residential uses, Rohm and Haas does not expect the aggregate exposure to exceed 100% of the RfD.

2. *Infants and children*. In assessing the potential for additional sensitivity of infants and children to residues of tebufenozide, data from developmental toxicity studies in the rat and rabbit and two 2-generation reproduction studies in the rat are considered. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during prenatal development to one or both parents. Reproduction studies provide information relating to effects from exposure to the pesticide on the reproductive capability of mating animals and data on systemic toxicity. Developmental toxicity was not observed in developmental studies using rats and rabbits. The NOAEL for developmental effects in both rats and rabbits was 1,000 mg/kg/day, which is the LTD for testing in developmental studies.

In the 2-generation reproductive toxicity study in the rat, the reproductive/developmental toxicity NOAEL of 12.1 mg/kg/day was 14-fold higher than the parental (systemic) toxicity NOAEL (0.85 mg/kg/day). The reproductive (pup) LOAEL of 171.1 mg/kg/day was based on a slight increase in both generations in the number of pregnant females that either did not deliver or had difficulty and had to be sacrificed. In addition, the length of gestation increased and implantation sites decreased significantly in F1 dams. These effects were not replicated at the same dose in a second 2-generation rat reproduction study. In this second study, reproductive effects were not observed at 2,000 ppm (the NOAEL equal to 149-195 mg/kg/day), and the NOAEL for systemic toxicity was determined to be 25 ppm (1.9-2.3 mg/kg/day).

Because these reproductive effects occurred in the presence of parental (systemic) toxicity and were not replicated at the same doses in a second study, these data do not indicate an increased pre-natal or post-natal sensitivity to children, and infants (that infants and children might be more sensitive than adults) to tebufenozide exposure. FFDCA section 408 provides that EPA shall 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 data base unless EPA concludes that a different margin of safety is appropriate. Based on current toxicological data discussed above, an additional uncertainty factor is not warranted and the RfD at 0.018 mg/kg/day is appropriate for assessing aggregate risk to infants, and children. Rohm and Haas concludes that there is a reasonable certainty that no harm will occur to infants, and children from aggregate exposure to residues of tebufenozide.

F. International Tolerances

There are currently no CODEX, Canadian or Mexican maximum residue levels (MRLs) established for tebufenozide in fruiting vegetables so no harmonization issues are required for this action.

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ENVIRONMENTAL PROTECTION AGENCY

[PF–861; FRL–6061–4]

Novartis Crop Protection; Pesticide Tolerance Petition Filing

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

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