to a data call-in. In all cases, product-specific disposition dates will be given in the cancellation orders.

Existing stocks are those stocks of registered pesticide products which are currently in the United States and which have been packaged, labeled, and released for shipment prior to the effective date of the cancellation action. Unless the provisions of an earlier order apply, existing stocks already in the hands of dealers or users can be distributed, sold or used legally until they are exhausted, provided that such further sale and use comply with the EPA-approved label and labeling of the affected product(s). Exceptions to these general rules will be made in specific cases when more stringent restrictions on sale, distribution, or use of the products or their ingredients have already been imposed, as in Special Review actions, or where the Agency has identified significant potential risk concerns associated with a particular chemical.

List of Subjects

Environmental protection, Pesticides and pests, Product registrations.

Dated: July 21, 1998.

Linda A. Travers,

Director, Information Resources and Services Division, Office of Pesticide Programs.

[FR Doc. 98–20767 Filed 8–4–98; 8:45 am]

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ENVIRONMENTAL PROTECTION AGENCY

[PF–817; FRL–5799–6]

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–817, must be received on or before September 4, 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. 119, 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. 119 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
Hoyt Jamerson	Rm. 268, CM #2, 703–308–9368, e-mail:jamerson.hoyt@epamail.epa.gov.	1921 Jefferson Davis Hwy, Arlington, VA
Cynthia Giles-Parker	Rm. 247, CM #2, 703–305–7740, e-mail:giles-parker.cynthia@epamail.epa.gov.	
Jim Tomopkins	Rm. 239, CM #2, 703–305–5697,e-mail:tompkins.jim@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–817] (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 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: July 15, 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. BASF Corporation

PP 6F4695

EPA has received a pesticide petition (PP 6F4695) from BASF Corporation, Agricultural Products, PO Box 13528, Research Triangle Park, NC 27709, 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 tolerances for residues of sethoxydim (2-[1-ethoxyimino]butyl)-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one) and its metabolites containing the 2-cyclohexen-1-one moiety (calculated as the herbicide) in or on the raw agricultural commodities (RACs) grapes at 1.0 part per million (ppm), succulent beans at 15.0 ppm, bean forage at 15.0 ppm, soybeans at 16.0 ppm, and raisins at 2.0 ppm. BASF Corporation also requested that the established tolerances for raisin waste at 1.0 ppm and grape pomace (dry and wet) at 6.0 ppm be revoked, since they are considered insignificant animal feed commodities and are no longer of regulatory concern.

PP 4F4075

EPA has received a pesticide petition (PP 4F4075) from BASF Corporation, 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 tolerances for residues of sethoxydim (2-[1-ethoxyimino]butyl)-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one) and its metabolites containing the 2-cyclohexen-1-one moiety (calculated as the herbicide) in or on the raw agricultural commodities (RACs) rice grain at 0.1 ppm, rice straw at 0.5 ppm, rice hulls at 0.2 ppm, and rice bran at 0.2 ppm.

2. Interregional Research Project Number 4 (IR-4)

PP 6E4753, 6E4725, 6E4698, 6E4697

EPA has received pesticide petitions (PP 6E4753, 6E4725, 6E4698, and 6E4697) from IR-4, New Jersey Agricultural Experiment Station, Rutgers University, New Brunswick, New Jersey 08903 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 tolerances for residues of the herbicide sethoxydim (2-[1-(ethoxyimino)butyl]-5-[2-(ethylthio)propyl]-3-hydoxy-2-cyclohexen-1-one) and its metabolites containing the 2-cyclohexen-1-one moiety (calculated as the herbicide)) in or on the raw agricultural commodities as follows:

PP 6E4753

Petition submitted on behalf of Agricultural Experiment Stations of Oregon and Washington proposing tolerances for the leafy vegetable (except Brassica) crop group at 4.0 ppm and cilantro at 4.0 ppm. The petitioner also requested that established tolerances for combined residues of sethoxydim and its metabolites on celery at 1.0 ppm, head lettuce at 1.0 ppm, leaf lettuce at 2.0 ppm, spinach at 4.0 ppm, and endive (escarole) at 2.0 ppm be removed, since these commodities are members of the leafy vegetable (except Brassica) crop group.

PP 6E4725

Petition submitted on behalf of the Agricultural Experiment Stations of California, Florida, Georgia, Illinois, Michigan, New York, Oklahoma, Oregon, South Carolina, Virginia, Washington, and Wisconsin proposing tolerances for the tuberous and corm vegetable subgroup at 4.0 ppm and garden beet at 1.0 ppm. The petitioner also requested that established tolerances for combined residues of sethoxydim and its metabolites in or on potato and sweet potato at 4.0 ppm be removed, since these commodities are members to the tuberous and corm vegetable subgroup.

PP 6E4698

Petition submitted on behalf of the Agricultural Experiment Station of California proposing that the existing tolerance for combined residues of sethoxydim and its metabolites in or on artichoke be increased from 3.0 ppm to 5.0 ppm

PP 6E4697

Petition submitted on behalf of the Agricultural Experiment Station of Oregon proposing a tolerance for the caneberry crop subgoup at 5.0 ppm. The petitioner also requested that the established tolerance for combined residues of sethoxydim and its metabolites in or on raspberry at 5.0 ppm be removed, since the caneberry subgroup includes raspberry.

EPA has determined that the 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 the submitted data at this time or whether the data support granting of the petitions. Additional data may be needed before EPA rules on the petitions. This notice includes a summary of the petitions prepared by BASF Corporation, Agricultural Products, P.O. Box 13528, Research Triangle Park, NC 27709.

A. Residue Chemistry

1. *Plant metabolism*. The qualitative nature of the residues in plants and animals is adequately understood for the purposes of registration. Analytical method for detecting levels of sethoxydim and its metabolites in or on food with a limit of detection that allows monitoring of food with residues at or above the levels set in these tolerances were submitted to EPA.

2. *Analytical method*. The proposed analytical method involves extraction, partition, and clean-up. Samples are then analyzed by gas chromatography with sulfur-specific flame photometric detection. The limit of quantitation is 0.05 ppm.

B. Toxicological Profile

1. *Acute toxicity*. Based on the available acute toxicity data, BASF concludes that sethoxydim does not pose any acute dietary risks. A summary of the acute toxicity studies follows.

i. *Acute oral toxicity—Rat*. Toxicity Category III; lethal dose (LD_{50}=3125 milligram/kilogram (mg/kg) (male), 2676 mg/kg (female)

ii. *Acute dermal toxicity-Rat*. Toxicity Category III; $LD_{50} \leq 5{,}000$ mg/kg (male and female)

iii. *Acute inhalation toxicity—Rat*. Toxicity Category III; lethal concentration (LC_{50} (4-hour)=6.03 mg/liter (L) (male), 6.28 mg/L (female)

iv. *Primary eye irritation-rabbit*. Toxicity Category IV; no irritation

v. *Primary dermal irritation-rabbit*. Toxicity Category IV; no irritation

vi. *Dermal sensitization- guinea pig*. Waived because no sensitization was seen in guinea pigs dosed with the end-use product Poast (18% active ingedient).

2. *Genotoxicity*. Ames assays were negative for gene mutation in *Salmonella* typhimurium strains TA98, TA100, TA1535, and TA 1537, with and without metabolic activity.

A Chinese hamster bone marrow cytogenetic assay was negative for structural chromosomal aberrations at doses up to 5,000 mg/kg in Chinese hamster bone marrow cells *in vivo*.

Recombinant assays and forward mutations tests in Bacillus subtilis, Escherichia *coli*, and *S* typhimurium were all negative for genotoxic effects at concentrations of greater than or equal to 100%.

3. *Reproductive and developmental toxicity*. A developmental toxicity study

in rats fed dosages of 0, 50, 180, 650, and 1,000 mg/kg/day with a maternal no-observed adverse effect level (NOAEL) of 180 mg/kg/day and a maternal lowest effect level (LEL) of 650 mg/kg/day (irregular gait, decreased activity, excessive salivation, and anogenital staining); and a developmental NOAEL of 180 mg/kg/day, and a developmental LEL of 650 milligram/killograms/day (mg/kg/day) (21 to 22 percent decrease in fetal weights, filamentous tail, and lack of tail due to the absence of sacral and/or caudal vertebrae, and delayed ossification in the hyoids, vertebral centrum and/or transverse processes, sternebrae and/or metatarsals, and pubes).

A developmental toxicity study in rabbits fed doses of 0, 80, 160, 320, and 400 mg/kg/day with a maternal no-observed effect level (NOEL) of 320 mg/kg/day and a maternal LOEL of 400 mg/kg/day (37% reduction in body weight gain without significant differences in group mean body weights and decreased food consumption during dosing); and a developmental NOEL greater than 400 mg/kg/day (highest dose tested).

A 2-generation reproduction study with rats fed diets containing 0, 150, 600, and 3,000 ppm (approximately 0, 7.5, 30, and 150 mg/kg/day) with no reproductive effects observed under the conditions of the study.

4. *Subchronic toxicity*. A 21-day dermal study in rabbits with a NOAEL of ≤1,000 mg/kg/day limit dose (LD). The only dose-related finding was slight epidermal hyperplasia at the dosing site in nearly all males and females dosed at 1,000 mg/kg/day. This was probably an adaptive response.

5. *Chronic toxicity*. A summary of the chronic toxicity studies follows.

A 1-year feeding study with dogs fed diets containing 0, 8.86/9.41, 17.5/19.9, and 110/129 mg/kg/day (males/females) with a NOEL of 8.86/9.41 mg/kg/day (males/females) based on equivocal anemia in male dogs at the 17.5-mg/kg/day dose level.

A 2-year chronic feeding/carcinogenicity study with mice fed diets containing 0, 40, 120, 360, and 1,080 ppm (equivalent to 0, 6, 18, 54, and 162 mg/kg/day) with a systemic NOEL of 120 ppm (18 mg/kg/day) based on non-neoplastic liver lesions in male mice at the 360-ppm (54 mg/kg/day) dose level. There were no carcinogenic effects observed under the conditions of the study. The maximum tolerated dose (MTD) was not achieved in female mice.

A 2-year chronic feeding/carcinogenic study with rats fed diets containing 0, 2, 6, and 18 mg/kg/day with a systemic NOEL greater than or equal to 18 mg/kg/day HDT. There were no carcinogenic effects observed under the conditions of the study. This study was reviewed under current guidelines and was found to be unacceptable because the doses used were insufficient to induce a toxic response and a MTD was not achieved.

A second chronic feeding/carcinogenic study with rats fed diets containing 0, 360, and 1,080 ppm (equivalent to 18.2/23.0, and 55.9/71.8 mg/kg/day (males/females). The dose levels were too low to elicit a toxic response in the test animals and failed to achieve a MTD or define a LEL. Slight decreases in body weight in rats at the 1,080-ppm dose level, although not biologically significant, support a free-standing NOAEL of 1,080 ppm (55.9/71.8 mg/kg/day (males/females)). There were no carcinogenic effects observed under the conditions of the study.

In a rat metabolism study, excretion was extremely rapid and tissue accumulation was negligible.

6. *Metabolite toxicology*. As a condition to registration, BASF had been asked to submit additional toxicology studies for the hydroxymetabolites of sethoxydim. BASF's recommendation is to use the most abundant metabolite, 5-OH-MSO2, as surrogate for all metabolites. Based on these data, it was concluded that the toxicological potency of the plant hydroxymetabolites is likely to be equal to or less than that of the parent compound. The tolerance expression for sethoxydim measures sethoxydim and its metabolites containing the 2-cyclohexen-1-one moiety, measured as parent. Hence, the hydroxymetabolites are figured into all tolerance calculations.

7. *Endocrine disruption*. No specific tests have been performed with sethoxydim to determine whether the chemical may have an effect in humans that is similar to an effect produced by naturally-occurring estrogen or other endocrine effects.

C. Aggregate Exposure

1. *Dietary exposure*. For purposes of assessing the potential dietary exposure, BASF has estimated aggregate exposure based on the Theoretical Maximum Residue Contribution (TMRC) from existing and pending tolerances for sethoxydim. (The TMRC is a ''worst case'' estimate of dietary exposure since it is assumed that 100% of all crops for which tolerances are established are treated and that pesticide residues are at the tolerance levels.) The TMRC from existing tolerances for the overall US population is estimated at approximately 35% of the RfD. Dietary exposure to residues of sethoxydim in or on food from these proposed tolerances increases the TMRC by approximately 8% of the RfD for the overall US population. BASF estimates indicate that dietary exposure will not exceed the RfD for any population subgroup for which EPA has data. This exposure assessment relies on very conservative assumptions that 100% of crops will contain sethoxydim residues and those residues would be at the level of the tolerance which results in an overestimate of human exposure.

2. *Food-other- exposure*. Other potential sources of exposure of the general population to residues of pesticides are residues in drinking water and exposure from non-occupational sources. Based on the available studies submitted to EPA for assessment of environmental risk, BASF does not anticipate exposure to residues of sethoxydim in drinking water. There is no established Maximum Concentration Level (MCL) for residues of sethoxydim in drinking water under the Safe Drinking Water Act (SDWA).

BASF has not estimated non-occupational exposure for sethoxydim. Sethoxydim is labeled for use by homeowners on and around the following use sites: flowers, evergreens, shrubs, trees, fruits, vegetables, ornamental groundcovers, and bedding plants. Hence, the potential for non-occupational exposure to the general population exists. However, these use sites do not appreciably increase exposure. Protective clothing requirements, including the use of gloves, adequately protect homeowners when applying the product. The product may only be applied through hose-end sprayers or tank sprayers as a 0.14% solution. Sethoxydim is not a volatile compound so inhalation exposure during and after application would be negligible. Dermal exposure would be minimal in light of the protective clothing and the low application rate. Post-treatment (re-entry) exposure would be negligible for these use sites as contact with treated surfaces would be low. Dietary risks from treated food crops are already adequately regulated by the established tolerances. BASF concludes that the potential for non-occupational exposure to the general population is insignificant.

D. Cumulative Effects

BASF also considered the potential for cumulative effects of sethoxydim and other substances that have a common mechanism of toxicity. BASF is aware of one other active ingredient which is structurally similar, clethodim. However, BASF believes that

consideration of a common mechanism of toxicity is not appropriate at this time. BASF does not have any reliable information to indicate that toxic effects produced by sethoxydim would be cumulative with clethodim or any other chemical; thus BASF is considering only the potential risks of sethoxydim in its exposure assessment.

E. Safety Determination

1. *U.S. population*. Reference Dose (RfD) using the conservative exposure assumptions described above, BASF has estimated that aggregate exposure to sethoxydim will utilize 43% of the RfD for the U.S. population. EPA generally has no concern for exposures below 100% of the RfD. Therefore, based on the completeness and reliability of the toxicity data, and the conservative exposure assessment, BASF concludes that there is a reasonable certainty that no harm will result from aggregate exposure to residues of sethoxydim, including all anticipated dietary exposure and all other non-occupational exposures.

2. *Infants and children—i. developmental toxicity*. Developmental toxicity was observed in a developmental toxicity study using rats but was not seen in a developmental toxicity study using rabbits. In the developmental toxicity study in rats a maternal NOAEL of 180 mg/kg/day and a maternal LEL of 650 mg/kg/day (irregular gait, decreased activity, excessive salivation, and anogenital staining) was determined. A developmental NOAEL of 180 mg/kg/day and a developmental LEL of 650 mg/kg/day (21 to 22% decrease in fetal weights, filamentous tail and lack of tail due to the absence of sacral and/or caudal vertebrae, and delayed ossification in the hyoids, vertebral centrum and/or transverse processes, sternebrae and/or metatarsals, and pubes). Since developmental effects were observed only at doses where maternal toxicity was noted, BASF concludes that the developmental effects observed are believed to be secondary effects resulting from maternal stress.

ii. *Reproductive toxicity*. A 2-generation reproduction study with rats fed diets containing 0, 150, 600, and 3,000 ppm (approximately 0, 7.5, 30, and 150 mg/kg/day) produced no reproductive effects during the course of the study. Although the dose levels were insufficient to elicit a toxic response, the Agency has considered this study usable for regulatory purposes and has established a free-standing NOEL of 3,000 ppm (approximately 150 mg/kg/day) (ref. Proposed Rule 60 FR 13941).

iii. *Reference dose*. Based on the demonstrated lack of significant developmental or reproductive toxicity BASF believes that the RfD used to assess safety to children should be the same as that for the general population, 0.09 mg/kg/day. Using the conservative exposure assumptions described above, BASF has concluded that the most sensitive child population is that of children ages 1 to 6. BASF calculates the exposure to this group to be approximately 85% of the RfD for all uses (including those proposed in this document). Based on the completeness and reliability of the toxicity data and the conservative exposure assessment, BASF concludes that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the residues of sethoxydim, including all anticipated dietary exposure and all other non-occupational exposures.

F. International Tolerances

A maximum residue level has not been established for sethoxydim on artichoke, caneberry, leafy vegetables (except Brassica), root and tuber vegetables, cilantro, grapes, succulent beans, bean forage, soybeans or raisins by the Codex Alimentarius Commission. Individual countries have established tolerances on beans ranging from 0.1 to 5.0 ppm and soybeans ranging from 0.05 ppm to 5.0 ppm. No tolerances have been established for grapes in other countries. The proposed tolerances for leafy vegetables (except Brassica), cilantro, and root and tuber vegetables at 4.0 ppm are consistent with the international tolerances as they fall within the range of established tolerances and reflect the differences in application parameters and conditions (e.g., application rate, pre-harvest intervals, and environmental conditions). (Hoyt Jamerson).

3. K-I Chemical U.S.A., Inc.

PP 8F4941

EPA has received a pesticide petition (PP8F4941) from K-I Chemical U.S.A., Inc., Westchester Financial Center, 11 Martine Avenue, 9th Floor, White Plains, NY 10606 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 cyclohexanecarboxylic acid, 3, 5-dioxo-4-(1-oxopropyl)-, ion(1-), calcium, calcium salt in or on the raw agricultural commodity peanut nutmeat and hay at 0.8 and 0.4 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 in plants (peanuts) is adequately understood.

2. *Analytical method*. The proposed analytical method involves homogenization, extraction, filtration, partition and cleanup, methylation and analysis by a gas chromatography system with a mass selective detector. The limit of quantitation is 0.05 ppm.

3. *Magnitude of residues*. Peanut trials were conducted with prohexadione calcium in the principle peanut growing regions of the country (NC, SC, GA, AL, FL, OK, TX). Prohexadione calcium was applied to peanuts 3- times at the rate of 0.125 lbs ai/A. Peanut hay and nutmeat were analyzed for residues of prohexadione (free acid). Prohexadione residues in the nutmeat ranged from <0.05 to 0.30 ppm. Residues in hay ranged from <0.05 to 0.26 ppm. A study was conducted to determine the level of prohexadione calcium derived resides in or on processed commodites.

The proposed tolerance for prohexadione calcium in/on peanut nutmeat is 0.8 ppm and it is calculated by converting the highest peanut nutmeat RAC ppm for prohexadione (0.3 ppm) to prohexadione calcium equivalents (0.36 ppm), correcting for 50% storage stability loss (0.72), and rounding up to 0.8 ppm. The proposed tolerance for prohexadione calcium in/on peanut hay is 0.4 ppm and it is calculated by converting the highest peanut hay RAC ppm for prohexadione (0.26 ppm) to prohexadione calcium equivalents (0.31 ppm) and rounding up to 0.4 ppm.

Peanut samples treated at an exaggerated rate were processed into peanut meal and refined oil. Peanut nutmeat and processed commodities were analyzed for prohexadione. Residues in the meal were less than in the nuts, and no residues were detected in the refined oil. Therefore, there was no concentration of prohexadione residues in processed commodities.

B. Toxicological Profile

1. *Acute toxicity*. Based on available acute toxicity data prohexadione calcium does not pose any acute toxicity risks. The acute toxicity studies place technical prohexadione calcium in

acute toxicity category III for acute dermal; and in acute toxicity category IV for acute oral, acute inhalation, eye irritation, and skin irritation and the technical material is not a skin sensitizer.

2. *Genotoxicty*. Ames Test (1 Study; point mutation): Negative; *In Vitro* V79 Cells CH/HGPRT Locus Mammalian Cell Mutation Assay (1 Study; point mutation): Negative; *In Vitro* CHO Cytogenetic Assay (1 Study; Chromosome Damage): Negative; *In Vivo* Mouse Micronucleus (1 Study; Chromosome Damage): Negative; *In vivo* Rat Bone Marrow Cytogenetic Assay (1 Study; Chromosomal Damage): Negative; Rec Assay (1 Study; DNA damage and repair): Negative; *In Vitro* Rat Hepatocyte (1 Study; DNA damage and repair): Negative.

Prohexadione calcium has been tested in a total of 7 genetic toxicology assays consisting of *in vitro* and *in vivo* studies. Based on the results described above, it can be stated in summary that prohexadione calcium did not show any mutagenic activity when tested under the conditions of the studies mentioned above. Therefore, prohexadione calcium does not pose a mutagenic hazard to humans.

3. *Reproductive and developmental toxicity-developmental toxicity*— i. *Rat*. A developmental study was conducted via oral gavage in rats with dosages of 0, 100, 300, and 1,000 higest dose tested (HDT) mg/kg/day with a No-Adverse-Effect Level (NOAEL) of 1,000 mg/kg/day the HDT for developmental and maternal toxicity based on the fact that no effects were observed for any test parameter measured in this study. Therefore, these NOAEL values are significantly higher than the NOAEL from the 1-year feeding study in dogs used to establish the RfD.

ii. *Rabbit*. A developmental study was conducted via oral gavage in rabbits with dosages of 0, 40, 200, and 750 (HDT) mg/kg/day with a development toxicity NOAEL of 40 mg/kg/day and a maternal toxicity NOAEL of 40 mg/kg/day based on the following: (a) Excessive maternal mortality of 4/20 and 16/20 was observed in the 200 and 750 mg/kg/day dose levels tested, respectively; (b) significant weight loss was similarly observed in the 200 and 750 mg/kg/day dose group with accompanying clinical signs; (c) microscopic findings in the 750 mg/kg/day dose group revealed stomach erosion and lung congestion in many of the animals that died; (d) in the 40 mg/kg/day dose group a single rabbit lost its righting reflex and showed splayed limbs on day 25 due to a back injury it sustained; and (e) no teratogenic effects, as well as incidence of malformations and developmental effects were observed at any dose level tested (DLT), however due to the mortality seen in the 200 and 750 mg/kg/day dose groups and limited number of fetuses produced at these dose levels, an additional study was performed. (It should be noted that a oral gavage range-finding study of six rabbits per dose level was performed at dose levels of 0, 100, 250, 500, and 1,000 mg/kg/day, in which similar excessive mortality was observed in the 500 and 1,000 mg/kg/day dose groups test as shown above. Additionally, body weight was affected for all dose groups tested and the clinical signs and macroscopic findings observed in the study discussed above were also noted in the range-finding study. However, body weight gain (BWG) was not affected in the lowest dose group tested.)

The doses selected for the additional teratology study in the same strain of rabbits were 0, 30,75, and 150 mg/kg/day with a development toxicity NOAEL of 150 mg/kg/day and a maternal toxicity NOAEL that could not be determined in this study based on the following: (a) one low-, two mid-, and three high-dose animals died prior to cesarean section on day 29, however, at the high dose group one cause of death was determined to be due to gavage error during test substance administration, another dam in this dose level died as a result of pneumonia, and all other deaths could not be determined; (b) at cesarean section one to three animals/test group were found to be not pregnant, but this was not considered to be dose related; (c) as a result of the unusual sex ratio in the control group, a statistically significant change in sex distribution was found at the low dose group level, however, these finding in b and c were not dose dependent and were considered to be within the range of historical control data of this laboratory, they were not regarded as treatment related; and (d) no teratogenic effects, as well as incidence of malformations and developmental effects were observed at any dose level tested, however due to the inconsistent mortality (0 (control)-1-2-1) seen at all treated dose levels, an additional study with a range-finder was performed at a different independent laboratory.

An oral range-finding gavage teratology study in the same strain of rabbits (5 animals/dose level) was examined in another independent laboratory. The dose levels selected were 0, 20,100, 250, 500, and 1000 mg/kg/day. The finding in this study consist of the following: (a) one animal died in the 500 and 1,000 mg/kg/day dose groups, however, the animal which died in the 500 mg/kg/day dose group was due to administration error detected after necropsy; (b) no clinical signs were noted and body weights was unaffected throughout gestation, however, bwg and food consumption was effected temporarily from 250 mg/kg/day onwards during the early stages of test substance administration (day 6 to 9 of gestation); (c) the number of viable fetuses and fetal weights were unaffected; and (d) no teratogenic effects, as well as incidence of malformations and developmental effects were observed at any dose level tested.

Based on these results the dose levels selected for the main study at this independent laboratory were 0, 30, 100, and 350 mg/kg/day with a development toxicity NOAEL of 350 mg/kg/day and a maternal toxicity NOAEL of 100 mg/kg/day based on the following: (a) clinical signs were restricted to premature delivery in 2 dams at the 350 mg/kg/day dose level; (b) average body weights and food intake was not affected at any dose levels tested, however, body weight gain was temporarily affected at the beginning of test substance administration period at the high dose group level; and (c) no teratogenic effects, as well as incidence of malformations and developmental effects were observed at any dose level tested.

4. *Conclusions from the teratology studies*. Conflicting results have been reported from one laboratory (initial laboratory) at comparable dose levels using the same study protocol with respect to maternal toxicity in New Zealand White rabbits. The conclusion from the second study that maternal toxicity is obvious by effects on body weight during test substance administration and the death of one out of 20 does at the low dose level (30 mg/kg/day) does not appear to be plausible because:

i. Mortalities in this study showed no dose depended trend (O (control)-l-2-1). The cause of death of the other four animals including the one of the 30 mg/kg body weight group remained undetermined even after necropsy. Typical treatment related signs (gastric lesions) as described at high doses in range-finding or main studies were not reported. Furthermore no mortality was observed up to 350 mg/kg/day (approximately 12-fold the NOAEL of 30 mg/kg in question) in a collective of 54 dams (three test groups) of the same strain of rabbits under comparable experimental conditions in the independent different laboratory.

ii. The effect on body weight gain showed no statistical significance at 30 mg/kg body weight and the standard deviation was high. In addition, at the dose of 40 mg/kg/day there was no effect in the same strain of rabbits examined by the same laboratory in a previous study and no effect on body weight, body weight gain or food consumption were noted at doses of 30 or 100 mg/kg/day in a study performed in the same animal strain by the independent laboratory.

Thus the following overall NOAELs can be derived for the teratology studies:

a. *NOAEL maternal toxicity*. 100 mg/kg body weight (rabbit) and 1,000 mg/kg body weight (rat).

b. *NOAEL prenatal toxicity*. 100 mg/kg body weight (rabbit) and 1000 mg/kg body weight (rat).

The overall NOAEL on maternal toxicity in rabbits is based on the independent laboratory rabbit study due to reduction of bwg and food intake at dose levels of 250 mg/kg body weight onwards.

The NOAEL (100 mg/kg body weight) for prenatal toxicity in rabbits is based on abortions observed at doses equal or above 200 mg/kg body weight. The NOAEL for malformations and other developmental effects is even higher (350 mg/kg body weight). Due to excessive lethality of dams at doses above this value, no evaluation of fetuses was possible. No teratogenic effects have been observed up to the HDT of 350 mg/kg BW which could be evaluated for developmental effects.

The teratogenicity study in rabbits resulted in a developmental toxicity NOAEL of 100 mg/kg and a maternal toxicity NOAEL of 100 mg/kg. These NOAEL values are higher than the NOAEL from the 1-year feeding study in dogs used to establish the RfD.

B. Reproductive Toxicity

A 2-generation reproduction study with rats fed dosages of 0, 500, 5,000, and 50,000 ppm with a reproductive/developmental NOAEL of 50,000 ppm and a maternal/parental/offspring toxicity NOAEL of 500 ppm based on the following: (1) mortalities were noted for two mid-dose males (week 7 or 11), two males and one female of the high-dose (week 1), and one female died on gestation day 13 without visible abnormalities prior to death; (2) in the high-dose parental F0 and F1 statistically significant decreased body weights and increased water consumption was observed; (3) in the mid-dose level similar reduced body weights were observed in the F1 offspring and F1 parents and with increased water consumption being seen in the F0 and F1 animals; (4) for both high-dose generations, offspring growth was slightly reduced; (5) microscopic lesions in the glandular and non-glandular stomach consisting of papillary ancadthosis, diffuse ancanthosis, and hyperkeratosis were observed in male and female rats of the mid-dose and high-dose levels tested with slight progression of severity from the mid- to upper dose level; and (6) no effects on reproductive or fertility parameter was observed for any dose group tested.

Therefore, these NOAEL values are similar for maternal toxicity and significantly higher for reproductive effects (above the limit dose of 1,000 mg/kg/day) than the NOAEL from the 1-year feeding study in dogs used to establish the RfD.

1. *Subchronic toxicity*— teratology— *Rat*. A developmental study was conducted via oral gavage in rats with dosages of 0, 100, 300, and 1,000 HDT mg/kg/day with a NOAEL of 1,000 mg/kg/day the HDT for developmental and maternal toxicity based on the fact that no effects were observed for any test parameter measured in this study.

2. *Teratology— Rabbits*. A developmental study was conducted via oral gavage in rabbits with dosages of 0, 40, 200, and 750 (HDT) mg/kg/day with a development toxicity NOAEL of 40 mg/kg/day and a maternal toxicity NOAEL of 40 mg/kg/day based on the following: (a) excessive maternal mortality of 4/20 and 16/20 was observed in the 200 and 750 mg/kg/day dose levels tested, respectively; (b) significant weight loss was similarly observed in the 200 and 750 mg/kg/day dose group with accompanying clinical signs; (c) microscopic findings in the 750 mg/kg/day dose group revealed stomach erosion and lung congestion in many of that animals that died; (d) in the 40 mg/kg/day dose group a single rabbit lost its righting reflex and showed splayed limbs on day 25 due to a back injury it sustained; and (e) no teratogenic effects, as well as incidence of malformations and developmental effects were observed at any dose level tested, however due to the mortality seen in the 200 and 750 mg/kg/day day dose groups and limited number of fetuses produced at these dose levels, an additional study was performed. (It should be noted that an oral gavage range-finding study of six rabbits per dose level was performed at dose levels of 0, 100, 250, 500, and 1,000 mg/kg/day, in which similar excessive mortality was observed in the 500 and 1,000 mg/kg/day dose groups test as shown above. Additionally, body weight was affected for all dose groups tested and the clinical signs and macroscopic findings observed in the study discussed above were also noted in the range-finding study. However, body weight gain was not affected in the lowest dose group tested.)

The doses selected for the additional teratology study in the same strain of rabbits were 0, 30, 75, and 150 mg/kg/day with a development toxicity NOAEL of 150 mg/kg/day and a maternal toxicity NOAEL that could not be determined in this study based on the following: (a) one low-, two mid-, and three high-dose animals died prior to cesarean section on day 29, however, at the high dose group one cause of death was determined to be due to gavage error during test substance administration, another dam in this dose level died as a result of pneumonia, and all other deaths could not be determined; (b) at cesarean section one to three animals/test group were found to be not pregnant, but this was not considered to be dose related; (c) as a result of the unusual sex ratio in the control group, a statistically significant change in sex distribution was found at the low dose group level, however, these finding in (b) and (c) were not dose dependent and were considered to be within the range of historical control data of this laboratory, they were not regarded as treatment related; and (d) no teratogenic effects, as well as incidence of malformations and developmental effects were observed at any dose level tested, however due to the inconsistent mortality (0 (control)-1-2-1) seen at all treated dose levels, an additional study with a range-finder was performed at a different independent laboratory.

An oral range-finding gavage teratology study in the same strain of rabbits (5 animals/dose level) was examined in another independent laboratory. The dose levels selected were 0, 20, 100, 250, 500, and 1000 mg/kg/day. The finding in this study consist of the following: (a) one animal died in the 500 and 1,000 mg/kg/day dose groups, however, the animal which died in the 500 mg/kg/day dose group was due to administration error detected after necropsy; (b) no clinical signs were noted and body weights was unaffected throughout gestation, however, body weight gain and food consumption was effected temporarily from 250 mg/kg/day onwards during the early stages of test substance administration (day 6 to 9 of gestation); (c) the number of viable fetuses and fetal weights were unaffected; and (d) no teratogenic effects, as well as incidence of malformations and developmental

effects were observed at any dose level tested.

Based on these results the dose levels selected for the main study at this independent laboratory were 0, 30, 100, and 350 mg/kg/day with a development toxicity NOAEL of 350 mg/kg/day and a maternal toxicity NOAEL of 100 mg/kg/day based on the following: (1) clinical signs were restricted to premature delivery in 2 dams at the 350 mg/kg/day dose level; (2) average body weights and food intake was not affected at any dose levels tested, however, body weight gain was temporarily affected at the beginning of test substance administration period at the high dose group level; and (3) no teratogenic effects, as well as incidence of malformations and developmental effects were observed at any dose level tested.

3. *Conclusions from the teratology studies*. i. Conflicting results have been reported from one laboratory (initial laboratory) at comparable dose levels using the same study protocol with respect to maternal toxicity in New Zealand White rabbits. The conclusion from the second study that maternal toxicity is obvious by effects on body weight during test substance administration and the death of one out of 20 does at the low dose level (30 mg/kg/day) does not appear to be plausible because: i. Mortalities in this study showed no dose depended trend (O (control)-l-2-1). The cause of death of the other four animals including the one of the 30 mg/kg body weight group remained undetermined even after necropsy. Typical treatment related signs (gastric lesions) as described at high doses in range-finding or main studies were not reported. Furthermore no mortality was observed up to 350 mg/kg/day (approximately 12-fold the NOAEL of 30 mg/kg in question) in a collective of 54 dams (three test groups) of the same strain of rabbits under comparable experimental conditions in the independent different laboratory.

ii. The effect on BWG showed no statistical significance at 30 mg/kg body weight and the standard deviation was high. In addition, at the dose of 40 mg/kg/day there was no effect in the same strain of rabbits examined by the same laboratory in a previous study and no effect on body weight, BWG or food consumption were noted at doses of 30 or 100 mg/kg/day in a study performed in the same animal strain by the independent laboratory.

iii. Thus the following overall NOAELs can be derived for the teratology studies:

iv. NOAEL maternal toxicity. 100 mg/kg body weight (rabbit) and 1,000 mg/kg body weight (rat).

v. NOAEL prenatal toxicity. 100 mg/kg body weight (rabbit) and 1,000 mg/kg body weight (rat).

The overall NOAEL on maternal toxicity in rabbits is based on the independent laboratory rabbit study due to reduction of BWG and food intake at dose levels of 250 mg/kg body weight onwards.

The NOAEL (100 mg/kg body weight) for prenatal toxicity in rabbits is based on abortions observed at doses equal or above 200 mg/kg body weight. The NOAEL for malformations and other developmental effects is even higher (350 mg/kg body weight). Due to excessive lethality of dams at doses above this value, no evaluation of fetuses was possible. No teratogenic effects have been observed up to the highest dose level of 350 mg/kg body weight which could be evaluated for developmental effects.

4. *Chronic toxicity*. Based on review of the available data, the Reference Dose (RfD) for prohexadione calcium will be based on a 1-year feeding study in dogs with a threshold NOAEL of 20 mg/kg/day. Using an uncertainty factor of 100, the RfD is calculated to be 0.2 mg/kg/day. The following are summaries of studies submitted to EPA.

i. *Chronic feeding - Nonrodent*. A 1-year feeding study in dogs fed dosages of 0, 20, 200, or 1,000 mg/kg/day (HTD) with a NOAEL of 20 mg/kg/day for female and male dogs based on the following effects: (a) clinical signs consisting of pale colored feces were observed with the highest incidence being recorded at HDLT; (b) slightly reduced clinical chemical values were observed in high dose male and female dogs for serum albumin and potassium and increased phosphorus levels for both male and female dogs of the HDT; (c) red blood cell parameters (packed cell volume, hemoglobin, and red blood cell count) were slightly lower at the HDT for males and females dogs, only red blood cell counts were reduced in the male and female dogs at the 200 mg/kg/day dose level in week 52; and (d) histopathological examination revealed dilated/basophilic renal cortical tubules with and without fibrosis in both male and female dogs at the 200 and 1,000 mg/kg/day dose levels.

ii. *Chronic feeding/oncogenicity — Rats*. A combined chronic/oncogenicity in rats (Fischer 344) fed dosages of 0, 18, 94, 469, and 968 mg/kg/day for male rats and 0, 22, 114, 572, and 1,180 mg/kg/day for female rats with a NOAEL of 94 mg/kg/day for male rats and 114 mg/kg/day for female rats based on the following effects: (a) decreased in body weights were observed in both male and female rat at the 968 and 1,180 mg/kg/day DLT; (b) clinical chemical effects (i.e., lower potassium, bilirubin, and glucose levels) were observed in male and female rats at the 968 and 1,180 mg/kg/day DLT, in the 469 mg/kg/day dose level, reduced glucose levels were only seen in the males, and increased albumin/globulin ratios, sodium, chloride and calcium levels were observed only in the 1,180 mg/kg/day dose level in females; (c) increased urine volumes and lower specific gravity were observed in the mid-high and high-dose groups for both male and female rats; (d) minor changes in organ weights were noted for animals of the high dose group only, which consisted of increased relative liver, adrenal and kidney weights, the latter also absolute in females only, at week 26; at the end of the study decreased liver weights and increased relative brain and testis weights were noted and these changes were considered to be associated with the decreased body weights; (e) macroscopic finding revealed an increase of pituitary nodules in the high dose group tested for male and female rats which was not confirmed histopathologically and submucosal ectopic tissue in the glandular stomach was found in both male and female rats in the highest dose levels that was confirmed by histopathology which showed an increase of squamous cell hyperplasia in males and of basal cell hyperplasia in the forestomach at this dose level; (f) a higher incidence of cellular hyperplasia was observed in the thyroid in the mid-high and high dose levels for male and female rats; and (g) no increased incidence of neoplasms occurred at any dose levels tested in this study.

iii. *Oncogenicity - Mice*. A carcinogenicity study in B6C3F1 mice fed dosages of 0, 55, 279, 2,847, and 5,911 mg/kg/day for male mice and 0, 68, 351, 3,489, and 7334 mg/kg/day for female mice with a NOAEL of 279 mg/kg/day for male mice and 351 mg/kg/day for female mice based on the following effects: (a) statistically significant decreases in body weights were observed in male mice at the 2,847 and 5,911 mg/kg/day dose levels and in female mice at the 7,334 mg/kg/day dose levels tested; (b) a variety of changes in hematological parameter was noted in the respective investigations at weeks 52, 78, and 104, however, most of the changes were not dose related or consistent over time; (c) increased absolute and/or relative heart, brain, testes, liver, ovary, and kidney weights

were observed in the mid-high and highest dose group test with a slight progression of severity to the highest dose group tested; (d) a higher incidence of splenomegaly was observed only in the male mice of the highest dose group; (e) histopathological examinations revealed an ectopic proliferation of the mucosal and glandular epithelium in the submucosal layer of the glandular stomach in male and female mice in the highest dose group tested, these changes were assessed to represent heteroplastic, ectopic proliferative changes accompanied by lumen dilatation and cytological degeneration; (f) a higher incidence of hyperkeratosis of the forestomach was observed in both male and female mice and hyperplasia of the squamous epithelium of the forestomach of female male mice was observed in the highest dose group tested; (g) vacuolic changes in the exocrine pancreas of the high dose female was observed; (h) no increased incidence of neoplasms occurred at any dose levels tested in this study.

iv. *Carcinogenicity*. Prohexadione calcium was shown to be non-carcinogenic in mice, rats, and dogs. Therefore, based on the results of the carcinogenicity studies in mice, rats, and dogs and the results of genotoxicity testing, the threshold approach to regulating prohexadione calcium is appropriate

5. *Animal metabolism*. The metabolism in animals (goats and poultry) is adequately understood.

6. *Endocrine disruption*. No specific tests have been conducted with prohexadione calcium to determine whether the chemical may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen or other endocrine effects. However, there were no significant findings in other relevant toxicity studies, *i.e.*, teratology and multi-generation reproductive studies, which would suggest that prohexadione calcium produces endocrine related effects.

C. Aggregate Exposure

1. *Dietary exposure*. For purposes of assessing the potential dietary exposure, K-I has estimated aggregate exposure based on the Theoretical Maximum Residue Contribution (TMRC) from the proposed tolerance for prohexadione calcium in/on peanut nutmeat at 0.8 ppm. The TMRC is a ''worse case'' estimate of dietary exposure since it is assumed that 100% of all crops for which tolerances are established are treated and that pesticide residues are always found at the tolerance levels. Dietary exposure to residues of prohexadione calcium in or on food will be limited to residues on peanut nutmeat. Peanut hay and meal are fed to animals; thus exposure of humans to residues in peanut hay and meal might result if such residues carry through to meat, milk, poultry, or eggs. However, K-I has concluded that there is no reasonable expectation that measurable residues of prohexadione calcium will occur in meat, milk, poultry, or eggs from this use. There are no other established U.S. tolerances for prohexadione calcium, and there are no currently registered uses for prohexadione calcium on food or feed crops in the U.S.

Dietary exposure to residues of prohexadione calcium from the proposed tolerances on peanuts would account for less than 0.14% of the RfD (0.20 mg/kg/day) for the general population of the US and all subpopulation groups. The most highly exposed group in the subpopulation groups would be non-nursing infants (< 1 year old), which uses 0.39% of the RfD.

2. *Drinking water*. Other potential sources of exposure to prohexadione calcium for the general population are residues in drinking water and exposure from non-occupational sources. Exposure to residues of prohexadione calcium in drinking water is not anticipated. There is no established Maximum Concentration Level (MCL) or Health Advisory Level (HAL) for prohexadione calcium under the Safe Drinking Water Act (SDWA).

3. *Non-dietary exposure*. Prohexadione calcium is not currently registered for any nonagricultural use. The potential for non-occupational exposure to the general population is therefore not present.

D. Cumulative Effects

The potential for cumulative effects of prohexadione calcium and other substances that have a common mechanism of toxicity has been considered. No evidence or information exists to suggest that toxic effects produced by prohexadione calcium would be cumulative with those of any other chemical compound.

E. Safety Determination

1. *U.S. population— Reference dose (RfD)*. Using the conservative exposure assumptions described above and based on the completeness and the reliability of the toxicity data, it has estimated that aggregate exposure to prohexadione calcium will utilize 0.14% of the RfD for the U.S. population. K-I concludes that there is a reasonable certainty that no harm will result from the aggregate exposure to residues of prohexadione calcium, including anticipated dietary exposure and non-occupational exposures.

2. *Infants and children*. Since developmental and reproductive toxicity occurs at levels at or above the levels shown to exhibit parental toxicity and since these levels are significantly higher than those used to calculate the RfD, K-I believes the RfD of 0.20 mg/kg/day is an appropriate measure of safety for infants and children.

Using the conservative exposure assumptions described above, it is concluded that the portion of the RfD that will be utilized by aggregate exposure to residues of prohexadione calcium resulting from the proposed tolerances will be less than 0.14% for all populations of infants and children. The most highly exposed group in the subpopulation groups would be non-nursing infants (< 1 year old) which uses 0.39% of the RfD. Therefore, based on the completeness and reliability of the toxicity data and the conservative exposure assessment, it is concluded that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the residues of prohexadione calcium, including all anticipated dietary exposure and all other non-occupational exposures.

F. International Tolerances

A maximum residue level has not been established for prohexadione calcium by the Codex Alimentarius Commission.

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ENVIRONMENTAL PROTECTION AGENCY

[PF–818; FRL–6017–1]

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–818, must be received on or before September 4, 1998.

ADDRESSES: By mail submit written comments to: Public Information and Records Integrity Branch, Information Resources and Services Division