ENVIRONMENTAL PROTECTION AGENCY

[FRL–5955–6]

Public Stakeholders Meeting on the Process for Implementing the Guidelines for Carcinogen Risk Assessment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of meeting.

SUMMARY: This document announces a stakeholders meeting sponsored by the Environmental Protection Agency's (EPA's) Science Policy Council. EPA is presenting a process for reassessing cancer assessments as part of EPA's initiative for implementing the Guidelines for Carcinogen Risk Assessment. The Guidelines were proposed in 1996. EPA also proposed an implementation process for reassessing cancer assessments in 1996 and is revising the process based on public comments. EPA is now seeking additional public comment and input on its current implementation process. The implementation process will be finalized at the same time as the Guidelines for Carcinogen Risk Assessment. The agenda will include opportunities for short stakeholder presentations, as well as structured, informal discussion based on the issues.

DATES: The meeting will begin on Tuesday, February 24, 1998, at 8:30 a.m. and end on Wednesday, February 25, 1998, at approximately 12 noon. Members of the public are invited to attend.

ADDRESSES: The meeting will be held at the Sheraton Crystal City Hotel at 18th and Eads Streets in Arlington, VA.

Resolve, Inc., an EPA contractor, has sub-contracted to The Mediation Institute, the logistical support and facilitation for the meeting. EPA urges participants to pre-register with Alana Knaster or Janet Pittman, The Mediation Institute, 4508 Park Cordero, Calabasas, CA 91302, Tel: 818/591–9526, FAX: 818/591–0980 as soon as possible. Space is limited. Registrants will receive an information packet containing the draft meeting agenda, and a discussion document outlining EPA's position on several major issues, along with other meeting information.

PRESENTATIONS: Members of the public who are interested in making a short presentation on a particular issue at the stakeholder meeting are requested to sign up for one of the topic areas at the time of their registration. EPA would appreciate receiving a short summary of the presentation, which should be no more than one page. Presentations are limited to 5 minutes. Because EPA is seeking a variety of opinions, the facilitator will ensure that there is a balance of viewpoints.

SUBMITTING COMMENTS: To ensure that stakeholders who are unable to attend the meeting may present their views, EPA will also accept short written comments on the implementation process until March 27, 1998. Comments should be submitted to: Alana Knaster, same address and phone numbers as above.

Please note that all comments responding to this notice will be placed in a public administrative record. For that reason, commentors should not submit personal information such as medical data or home addresses, confidential business information or information protected by copyright. Due to limited time and resources, acknowledgments will not be sent.

FOR FURTHER INFORMATION CONTACT: For technical inquiries, as well as questions about the meeting, please contact Alana Knaster, same address and phone numbers as above. The main discussion document containing the implementation process can be obtained from the EPA World Wide Web site at http://www.epa.gov/ncea/riskassf.htm.

SUPPLEMENTARY INFORMATION: EPA is presenting a process for implementing the Guidelines for Carcinogen Risk Assessment for reassessing cancer assessments. The Guidelines were developed under the auspices of the EPA's Risk Assessment Forum (RAF) and proposed in 1996 (61 FR 17960). EPA also proposed an implementation process for reassessing cancer assessments in 1996 (61 FR 32799) and is revising the process based on public comments. The implementation process will be finalized at the same time as the Guidelines for Carcinogen Risk Assessment.

It is expected that once the Guidelines become final, existing cancer assessments will need reassessment based upon the revised Guidelines. The implementation process will help the EPA and the public select and prioritize the chemicals that would need a reassessment. It will also allow a selection of new assessments to be incorporated in the schedule for the reassessments.

The four main issues for which EPA specifically seeks public opinion include: (1) The implementation process, including opportunities for public input, (2) the criteria for selection of chemicals for reassessment, (3) whether small changes can be made in toxicity assessments without completely reassessing all toxicity information, and (4) the form of external review for identification and prioritization of chemicals.

Following this meeting, EPA will use the comments to finalize the implementation process for cancer reassessments once the Guidelines for Carcinogen Risk Assessment are final.

Dated: January 22, 1998.

Dorothy E. Patton,

Director, Office of Science Policy.

[FR Doc. 98–2083 Filed 1–27–98; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

[PF–787; FRL–5763–6]

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–787, must be received on or before February 27, 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. 1132, CM #2, 1921 Jefferson Davis Highway, Arlington, VA.

Comments and data may also be submitted electronically to: opp-docket@epamail.epa.gov. Follow 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
Amelia M. Acierto	Rm. 4W60, 4th. floor, CSI #2, 703–308–8377, e-mail:acierto.amelia@epamail.epa.gov.	2800 Crystal Drive, Arlington, VA
Adam Heyward	Rm. 206, CM #2, 703–305–5518, e-mail: heyward. adam@epamail.epa.gov.	1921 Jefferson Davis Hwy., Arlington, VA
Joseph 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–787] (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 [PF–787] and appropriate petition number. Electronic comments on notice may be filed online at many Federal Depository Libraries.

List of Subjects

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

Dated:January 20, 1998

James Jones,

Acting 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. Gowan Company

PP 6F4738

In May, 1996, EPA received a pesticide petition (PP 6F4738) from Gowan Company, P. O. Box 5569, Yuma, AZ 85366-5569. The petition proposed, pursuant to section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180 to establish tolerances for the acaricide hexythiazox and its metabolites in or on the raw agricultural commodities stone fruits (except plums) at 1 part per million (ppm), almonds at 0.2 ppm and almond hulls at 10 ppm, and also in milk, cattle meat and cattle fat at 0.05 ppm, and cattle meat byproducts at 0.1 ppm (April 30, 1997, 62 FR 23455-23457) (FRL-5600-8). In April 1997, the registrant amended the tolerance petition by proposing to establish a tolerance for stone fruits including plums at 1 ppm, a tolerance for prunes at 5 ppm, and a tolerance for all tree nuts at 0.2 ppm. The proposed tolerances for animal products were unchanged. EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data support granting of the petition. Additional data may be needed before EPA rules on the petition. The proposed analytical method is high performance liquid chromatography with an ultraviolet detector. As required by section 408(d) of the FFDCA, as recently amended by the Food Quality Protection Act (FQPA) Pub. L. 104-170, Gowan Company included in the petition a summary of the petition and authorization for the summary to be published in the Federal Register in a notice of receipt of the petition.

A. Residue Chemistry

1. *Plant metabolism*. The metabolism of hexythiazox in apples, citrus, grapes and pears has been studied. The major portion of the residue is parent compound. The metabolites are hydroxycyclohexyl and ketocyclohexyl analogs of hexythiazox and the amide formed by loss of the cyclohexyl ring.

2. *Analytical method*. An adequate analytical method (HPLC with UV detection) is available for enforcement purposes. Parent compound and all of its metabolites are converted to a common moiety before analysis.

3. *Magnitude of residues*. Twenty-four stone fruit residue trials were conducted over 3–years. The geographic distribution of the trials agrees with the recommendation given in the ''EPA Residue Chemistry Guidance''(1994). In these trials, the maximum combined residues of hexythiazox and its metabolites were 0.52 ppm. Twelve tree nut residue trials were conducted over 4 years. In these trials, the maximum combined residues of hexythiazox and its metabolites were 0.17 ppm in almond nutmeat and 7.5 ppm in the raw agricultural commodity almond hulls.

B. Toxicological Profile

1. *Acute toxicity*. The acute oral and dermal LD_{50} of technical hexythiazox is greater than 5,000 milligram/kilograms (mg/kg), and the 4-hour acute inhalation LC_{50} is greater than 2 mg/L. It is not a dermal irritant or sensitizer and is a mild eye irritant.

2. *Genotoxicity*. The following genotoxicity tests were all negative:

Ames gene mutation, CHO gene mutation, CHO chromosome aberration, mouse micronucleus and rat hepatocyte unscheduled DNA synthesis.

3. *Reproductive and developmental toxicity*. Hexythiazox has not been observed to induce developmental or reproductive effects. The lowest reproductive or developmental no-observed-effect-level (NOEL) observed was 200 milligram/kilograms/day (mg/kg/day), the highest dose tested, in a 2-generation rat reproduction study.

4. *Subchronic toxicity*. The Office of Pesticide Programs has established the RfD for hexythiazox at 0.025 mg/kg/day. The RfD for hexythiazox is based on a 1–year dog feeding study with a NOEL of 2.5 mg/kg/day and an uncertainty factor of 100. The endpoint effect of concern was hypertrophy of the adrenal cortex in both sexes, decreased red blood cell counts, hemoglobin content and hematocrit in males.

5. *Chronic toxicity*. The Agency has classified hexythiazox as a category C (possible human) carcinogen based on an increased incidence of hepatocellular carcinomas ($p = 0.028$) and combined adenomas/carcinomas ($p = 0.024$) in female mice at the highest dose tested (1,500 ppm) when compared to the controls as well as a significantly increased ($p > 0.001$) incidence of pre-neoplastic hepatic nodules in both males and females at the highest dose tested. The decision supporting a category C classification was based primarily on the fact that only one species was affected and mutagenicity studies were negative. In classifying hexythiazox as a category C carcinogen, the Agency concluded that a quantitative estimate of the carcinogenic potential for humans should be calculated because of the increased incidence of liver tumors in the female mouse. A Q^{1*} of 0.039 $(mg/kg/day)^{-1}$ in human equivalents was calculated.

C. Aggregate Exposure

Tolerances have been established (40 CFR 180.448) for the combined residues of hexythiazox [trans-5-(4-chlorophenyl)-N-cyclohexyl-4-methyl-2-oxothiazolidine-3-carboxamide] and its metabolites containing the (4-chlorophenyl)-4-methyl-2-oxo-3-thiazolidine moiety in or on apples at 0.02 ppm and pears at 0.3 ppm. The nature and metabolism of hexythiazox in plants and animals is adequately understood.

Hexythiazox is also registered for use on outdoor ornamental plants by commercial applicators only. It is believed that non-occupational exposure from this use is very low. Hexythiazox is not registered for greenhouse, lawn, garden, or residential use. The environmental fate of hexythiazox has been evaluated, and the compound is not expected to contaminate groundwater or surface water to any measurable extent.

1. *Dietary exposure*. The Agency has calculated in the **Federal Register** of February 21, 1996 (61 FR 6152-6154) (FRL-5350-6), that current uses on apples and pears would result in an exposure of 0.000051 mg/kg/day for the U.S. population, assuming that all residues are at tolerance levels and 100% of the crops are treated. Non-nursing infants, the subgroup having the highest exposure, would have an exposure of 0.000600 mg/kg/day. Using the same conservative assumptions, it is calculated that the current and proposed uses together would result in an exposure of 0.001133 mg/kg for the U.S. population and 0.007256 mg/kg/day for non-nursing infants, which remains the most highly exposed subgroup.

Actual exposure will be much lower, however. Only a small fraction of these crops will be treated with hexythiazox, and average residues are far below the tolerance levels. For example, residues in apples treated at 10 times the currently approved application rate remained below the limit of quantitation, 0.01 ppm. Also, residues in apple juice are expected to be less than 50% of the residue level in the whole fruit. Average residues in stone fruits except cherries are expected to be 7% of the proposed tolerance level, average residues in cherries are expected to be 11% of the tolerance level and average residues in almond nutmeat are expected to be below 20% of the proposed tolerance level. Furthermore, only a very small percentage of crops (less than 1% up to 5%, depending on the crop) are expected to be treated with hexythiazox. When actual residues rather than tolerance levels and the percentage of treated crop are taken into account, then the actual exposure is estimated to be 0.0000069 mg/kg/day for the U.S. population.

2. *Drinking water*. The Agency has not conducted a detailed analysis of potential exposure to hexythiazox via drinking water or outdoor ornamental plants. However, it is believed that chronic exposure from these sources is very small.

3. *Non-dietary exposure*. No developmental, reproductive or mutagenic effects have been observed with hexythiazox. Therefore, an analysis of acute exposure has not been conducted.

D. Cumulative Effects

At this time the Agency has not reviewed available information concerning the potentially cumulative effects of hexythiazox and other substances that may have a common mechanism of toxicity. For purposes of this petition only, the Agency is considering only the potential risks of hexythiazox in its aggregate exposure.

E. Determination of Safety for U.S. Population

1. *Chronic risk*. The Agency has calculated (FR 61 6152-6154), assuming that residues are at tolerance levels and 100% of crops are treated, that the current use on apples and pears utilizes 0.2% of the reference dose (RfD) for the U.S. population and 2.4% of the RfD for non-nursing infants. Using these same assumptions, it is calculated that all current and proposed uses would result in TMRCs equivalent to 4.5% of the RfD for the U.S. population and 29.0% of the RfD for non-nursing infants. However, when actual residues rather than tolerance levels and the percent of crop treated are taken into account, actual chronic risk for the U.S. population is expected to be only 0.43% of the RfD.

The actual dietary carcinogenic risk to the U.S. population is calculated to be 2.7×10^{-7}, which is below the Agency's criterion of 1×10^{-6}.

2. *Acute risk*. An estimate of acute risk with this compound has not been conducted since no acute reproductive or developmental effects have been observed.

F. Determination of Safety for Infants and Children

In assessing the potential for additional sensitivity of infants and children to residues of hexythiazox, EPA considered data from developmental toxicity studies in the rat and rabbit and a 2-generation study in the rat. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during pre-natal 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.

No developmental or reproductive effects have been observed in any study with hexythiazox. The lowest acute NOEL was 2,400 ppm in the diet (200 mg/kg/day), the highest dose tested, in the 2-generation rat reproduction study. In the rat developmental study, the maternal and fetotoxic NOEL was 240 mg/kg/day and the developmental

NOEL was 2,160 mg/kg/day, the highest dose tested. In the rabbit developmental study, the maternal and developmental NOEL was 1,080 mg/kg/day, the highest dose tested.

Taking into account current toxicological data requirements, the database for hexythiazox relative to pre-natal and post-natal effects is complete. In the rat developmental study, the NOELs for maternal toxicity and fetotoxicity were the same, which suggests that there is no special pre-natal sensitivity in the absence of maternal toxicity. Furthermore, the lowest developmental or reproductive NOEL is two orders of magnitude higher than the chronic NOEL on which the RfD is based. It is concluded that there is a reasonable certainty of no harm to infants and children from aggregate exposure to hexythiazox residues.

G. International Tolerances

Codex maximum residue levels (MRLs) of 1 mg/kg (1 ppm) have been established for residues of hexythiazox in cherries and peaches. The U.S. tolerance proposal for stone fruits is in harmony with these MRLs. There are no Codex MRLs for the other commodities in this petition. There are no Canadian or Mexican MRLs for hexythiazox. (Adam Heyward)

2. Monsanto Company

PP 5E4503

EPA has received a pesticide petition (PP 5E4503) from Monsanto Company, 700 14th St., NW., Washington, DC 20005, proposing pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 346a(d), to amend 40 CFR part 180 by establishing a tolerance for residues of the inert ingredient 4-(dichloroacetyl)-1-oxa-4-azospiro [4.5] decane (MON 4660) in or on the raw agricultural commodity, corn, resulting from early post-emergence applications. The analytical method, which determines the residue by gas-liquid chromatography using an electron-capture detector has been reviewed by the Agency and accepted for enforcement purposes. 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.

A. Residue Chemistry

1. *Plant metabolism*. The metabolism of MON 4660 in corn was studied with radiolabeled MON 4660 in the greenhouse and the field. Parent MON 4660 was not found in any of the corn samples. MON 4660 is rapidly and extensively metabolized to a large number of highly polar metabolites characterized as weak organic acids or residues conjugated to natural sugars.

2. *Analytical method*. Monsanto has developed an analytical method using gas liquid chromatography with electron capture detection that has a verified limit of quantitation of 0.005 ppm for parent MON 4660 in all corn matrices. This method has been validated by the Agency.

3. *Magnitude of residues*. Monsanto has conducted 14 residue field studies with MON 4660 applied pre-emergence to corn. Analysis of corn forage, silage, fodder and grain showed no residues above the limit of quantitiation of 0.005 ppm. Two residue field studies with MON 4660 applied pre-emergence to corn at rates 20 and 28 times the proposed maximum use rate showed no measurable residues (<0.005 ppm) in corn grain. Based on these results it was concluded that the potential for measurable concentration of MON 4660 in processed commodities of corn was very low. Eight residue field trials (2 samples per trial) were conducted with MON 4660 applied early post-emergence with corn plants 6 to 11 inches tall. Analysis of corn forage, fodder and grain again showed no measurable residues (<0.005 ppm). These residues, derived from postemergence applications are below the established Sensitivity of Method Tolerance for corn (0.005 ppm).

B. Toxicological Profile

The toxicology data considered in support of the revised tolerance include the following:

1. *Acute toxicity*— i. An acute oral toxicity study in the rat with an LD_{50} of 2,600 mg/kg. Toxicity Category III.

ii. An acute dermal toxicity study in the rabbit with an LD_{50} of > 5,000 mg/kg. Toxicity Category IV.

iii. An acute inhalation study in the rat with a 4-hour inhalation LC_{50} of 0.27 mg/L. Toxicity Category III.

iv. A rabbit eye irritation study in which 4-(dichloroacetyl)-1-oxa-4-azospiro [4.5] decane is determined not to be an eye irritant. Toxicity Category III.

v. A dermal irritation study which exhibited slight skin irritation. Toxicity Category IV.

vi. A guinea pig dermal sensitization study in which 4-(dichloroacetyl)-1-oxa-4-azospiro [4.5] decane is determined to be a skin sensitizer.

2. *Genotoxicity*. Mutagenicity studies including *Salmonella typhimurium*/mammalian plate incorporation (Ames) assay, CHO/HGPRT gene mutation assay, DNA repair studies (rat hepatocytes), and *Salmonella*/mammalian activation gene mutation (Ames) assay were negative with and without activation.

3. *Reproductive and developmental toxicity*— i. A rat developmental effects study with a NOEL for maternal toxicity of 10 mg/kg/day and developmental toxicity of 75 mg/kg/day.

ii. A rabbit developmental effects study with a NOEL for maternal toxicity of 10 mg/kg/day and developmental toxicity of 30 mg/kg/day.

iii. A 2-generation reproduction study in the rat fed diet levels of 0, 10, 100, and 1,000 ppm. There were no treatment-related effects on mating, fertility or offspring survival in this study. The NOEL for toxicity in parental animals and offspring was 100 ppm (6 to 7 mg/kg/day). As there were no adverse effects on reproductive performance, the NOEL for reproductive toxicity was 1,000 ppm (57 to 72 mg/kg/day).

4. *Subchronic toxicity*— i. A 90–day oral toxicity study in the rat with a NOEL of 120 parts per million (ppm) or 12 mg/kg/day.

ii. A 90-day oral (gavage) study in the dog with a NOEL of 30 mg/kg/day, the highest dose tested.

5. *Chronic toxicity*— i. A mouse oncogenicity study in which 5 groups of 60 male and 60 female CD-1 mice were administered diets containing 4-(dichloroacetyl)-1-oxa-4-azospiro [4.5] decane at concentrations 0, 5, 80, 800 or 2,500 ppm for approximately 18 months. These concentrations corresponded to 0, 0.7, 10.7, 108 and 350 mg/kg/day in males and 0, 1, 16.8, 167 and 556 mg/kg/day in females. The primary target organs were liver, lung and stomach. The NOEL for both oncogenic and non-oncogenic effects was considered to be 10.7 mg/kg/day in males and 116.8 mg/kg/day in females.

ii. A chronic toxicity/oncogenicity study in rats in which 5 groups of 60 male and 60 female rats were administered diets containing 4-(dichloroacetyl)-1-oxa-4-azospiro [4.5] decane for approximately 23 months. Target concentrations were 0, 5, 50, 500, or 1,600 ppm for males and, 0, 5, 50, or 1,200 ppm for females. These concentrations correspond to 0, 0.2, 2.2, 22 and 71 mg/kg/day in males and 0, 0.3, 2.8, 29 and 69 mg/kg/day in females. The primary effects in this study occurred in the liver and stomach. The NOEL for oncogenic effects is 22 mg/kg/day in males and 29 mg/kg/day in females. The NOEL for non-

oncogenic effects is 2.2 mg/kg/day in males and 2.8 mg/kg/day in females.

6. *Animal metabolism*. Because field trial residue data showed non-detectable residues of MON 4660 in corn, neither animal metabolism nor residue transfer studies with livestock were required. It is considered likely that metabolism will be similar to that of other dichloroacetamide safeners in mammals which are characterized by extensive metabolism and elimination of most of the residue from the body with very low levels of parent safener, if any, retained in the tissues. The major route of metabolism is typically glutathione conjugation followed by formation of an aldehyde intermediate which is then either oxidized to an oxamic acid or reduced to the corresponding alcohol.

7. *Metabolite toxicology*. The metabolism of MON 4660 is extensive and results in a large number of polar metabolites each of which is present in soil or corn plants in very low concentrations. These metabolites have not been identified as being of toxic concern.

Based on the available toxicity data, Monsanto believes the RfD for MON 4660 will be 0.02 mg/kg/day based on a 2–year feeding study in rats with a NOEL of 2.2 mg/kg/day and application of an uncertainty factor of 100. For cancer risk assessment for MON 4660, Monsanto believes that margin of exposure assessment should be calculated using the carcinogenic NOEL of 10.7 mg/kg/day observed in the mouse, which was the most sensitive species.

C. Aggregate Exposure

1. *Dietary exposure*— i. *Food*. Monsanto has used the Theoretical Maximum Residue Contribution as a conservative estimate of the potential dietary exposure for MON 4660. This approach assumes that 100% of all raw agricultural commodities for which tolerances have been established for acetochlor, bear tolerance-level (0.005 ppm) residues of MON 4660. This over-estimate of actual dietary exposure provides a quite conservative basis for risk assessment.

ii. *Drinking water*. Although MON 4660 is stable to hydrolyis and shows only a small amount of photodegradation in soil and in water, it is rapidly degraded in the soil. The aerobic soil half-life is approximately 18 days. This low persistence in the environment combined with the low application rate (maximum of 0.4 pound per acre) indicates that MON 4660 is not likely to be present in groundwater. Based on these considerations, Monsanto does not anticipate exposure to residues of MON 4660 in drinking water. The EPA has not established a Maximum Concentration Level or a health advisory level for residues of MON 4660 in drinking water.

2. *Non-dietary exposure*. MON 4660 is used only as a safener or antidote to the effects of acetochlor herbicide on corn seed or seedlings. It is sold only as part of acetochlor herbicide end-use products which are classified as Restricted Use by EPA which means they are used only by certified applicators and are not available to the general public. Herbicide products containing MON 4660 are not registered for residential, home owner, or other non-crop uses. They are thus not used in parks, school grounds, public buildings, roadsides or rights-of-way or other public areas. Commercial cornfields are generally located well away from public areas where incidental contact could occur. Therefore, the general public is very unlikely to have any non-dietary exposure to MON 4660.

D. Cumulative Effects

Monsanto has no reliable data or information to suggest that MON 4660 has toxic effects that arise from toxic mechanisms that are common to other substances. Therefore, a consideration of common toxic mechanism and cumulative effects with other substances is not appropriate for MON 4660, and Monsanto is considering only the potential effects of MON 4660 in this exposure assessment.

E. Safety Determination

1. *U.S. population*— i. *Chronic risk*. The conservative estimate of aggregate chronic exposure is 2.0×10^{-6} mg/kg/day. This potential exposure represents only 0.01% of the RfD of 0.02 mg/kg/day and provides a Margin of Exposure of 5,350,000 when compared to the 10.7 mg/kg/day carcinogenic reference point. EPA generally has no concern for exposures below 100% of the RfD and there are adequate margins of safety for cancer. Monsanto concludes there is a reasonable certainty of no harm resulting from exposure to MON 4660.

ii. *Acute risk*. The acute toxicity of MON 4660 is low, and there are no concerns for acute dietary, occupational or non-occupational exposures to MON 4660.

2. *Infants and children*. Employing the same conservative TMRC estimates of exposure used in the risk assessment for the general population, Monsanto has calculated that the aggregate exposures for nursing infants, non-nursing infants, children age 1–6 and children age 7–12 are less than one-tenth of 1% of the RfD for each group.

Monsanto notes the developmental toxicity NOELs for rats (75 mg/kg/day) and rabbits (30 mg/kg/day) are 34-fold and 14-fold higher than the NOEL of 2.2 mg/kg/day in the chronic rat study on which the RfD is based. This indicates that the RfD is adequate for assessing risk to children. Also, the developmental toxicity NOELs for rats and rabbits are higher than the NOELs for maternal toxicity (10 mg/kg/day in each specie) indicating that the offspring were no more sensitive to MON 4660 than were the parents.

In the 2-generation reproduction study in rats, the NOEL for pup toxicity (57-72 mg/kg/day) was higher than the NOEL for parental or systemic effects (6-7 mg/kg/day) indicating that offspring were no more sensitive to MON 4660 than were the parents. Also, the NOEL for pup toxicity (57-72 mg/kg/day) was 25 to 33-fold higher than the NOEL for chronic toxicity upon which the RfD is based.

Monsanto believes that these data do not indicate an increased pre-natal or post-natal sensitivity of children and infants to MON 4660 exposure and concludes that the 100-fold uncertainty factor used in the RfD is adequate to protect infants and children.

F. International Tolerances

The Codex Alimentarius Commission has not established a maximum residue level for MON 4660. (Amelia Acierto)

3. Rohm and Haas Company

PP 5F4587

EPA has received a pesticide petition (PP 5F4587) from Rohm and Haas Company, 100 Independence Mall West, Philadelphia, PA 19106-2399, 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 Tebufenozide, benzoic acid,3,5-dimethyl-,1-(1,1-dimethylethyl)-2-(4-ethylbenzoyl) hydrazide in or on the raw agricultural commodity pecans at .05 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 (apples, beets,

grapes, rice and sugar) is adequately understood for the purposes of these tolerances. 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. The metabolism of tebufenozide in goats and hens proceeds along the same metabolic pathway as observed in plants. No accumulation of residues in tissues, milk or eggs occurred.

2. *Analytical method*. High performance liquid chromatographic (HPLC) analytical method using ultraviolet (UV) or mass selective detection has been developed for pecans. The method involves Soxhlet extraction 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 of the method is 0.01 ppm (HPLC) analytical method using (UV) or mass selective detection has been developed for pecans. The method involves Soxhlet extraction 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 of the method is 0.01 ppm.

B. Toxicological Profile

1. *Acute toxicity*. Tebufenozide has low acute toxicity. Tebufenozide Technical was practically non-toxic by ingestion of a single oral dose in rats and mice (LD_{50} > 5,000 mg/kg) and was practically non-toxic by dermal application (LD_{50} > 5,000 mg/kg). Tebufenozide Technical was not significantly toxic to rats after a 4-hr inhalation exposure with an LC_{50} value of 4.5 mg/L (highest attainable concentration), is not considered to be a primary eye irritant or a skin irritant and is not a dermal sensitizer. An acute neurotoxicity study in rats did not produce any neurotoxic or neuropathologic effects.

2. *Genotoxicity*. Tebufenozide technical was negative (non-mutagenic) in an Ames assay with and without hepatic enzyme activation and in a reverse mutation assay with E. *coli*. Tebufenozide technical was negative in a hypoxanthine guanine phophoribosyl transferase (HGPRT) gene mutation assay using Chinese hamster ovary (CHO) cells in culture when tested with and without hepatic enzyme activation. In isolated rat hepatocytes, tebufenozide technical did not induce unscheduled DNA synthesis (UDS) or repair when tested up to the maximum soluble concentration in culture medium. Tebufenozide did not produce chromosome effects *in vivo* using rat bone marrow cells or *in vitro* using Chinese hamster ovary cells (CHO). On the basis of the results from this battery of tests, it is concluded that tebufenozide is not mutagenic or genotoxic.

3. *Reproductive and developmental toxicity*— i. No Observable Effect Levels (NOELs) for developmental and maternal toxicity to tebufenozide were established at 1,000 mg/kg/day (Highest Dose Tested) in both the rat and rabbit. No signs of developmental toxicity were exhibited.

ii. In a 2–generation reproduction study in the rat, the reproductive/developmental toxicity NOEL of 12.1 mg/kg/day was 14-fold higher than the parental (systemic) toxicity NOEL 10 ppm 0.85 mg/kg/day. Equivocal reproductive effects were observed only at the 2,000 ppm dose.

iii. In a second rat reproduction study, the equivocal reproductive effects were not observed at 2,000 ppm (the NOEL equal to 149-195 mg/kg/day) and the NOEL for systemic toxicity was determined to be 25 ppm (1.9-2.3 mg/kg/day).

4. *Subchronic toxicity*— i. The NOEL in a 90–day rat feeding study was 200 ppm (13 mg/kg/day for males, 16 mg/kg/day for females). The Lowest Observed Effect Level (LOEL) was 2,000 ppm (133 mg/kg/day for males, 155 mg/kg/day for females). Decreased body weights in males and females was observed at the LOEL of 2,000 ppm. As part of this study, the potential for tebufenozide to produce subchronic neurotoxicity was investigated. Tebufenozide did not produce neurotoxic or neuropathologic effects when administered in the diets of rats for 3 months at concentrations up to and including the limit dose of 20,000 ppm (NOEL = 1,330 mg/kg/day for males, 1,650 mg/kg/day for females).

ii. In a 90–day feeding study with mice, the NOEL was 20 ppm (3.4 and 4.0 mg/kg/day for males and females, respectively). The LOEL was 200 ppm (35.3 and 44.7 mg/kg/day for males and females, respectively). Decreases in body weight gain were noted in male mice at the LOEL of 200 ppm.

iii. A 90–day dog feeding study gave a NOEL of 50 ppm (2.1 mg/kg/day for males and females). The LOEL was 500 ppm (20.1 and 21.4 mg/kg/day for males and females, respectively). At the LOEL, females exhibited a decrease in rate of weight gain and males presented an increased reticulocyte.

iv. A 10-week study was conducted in the dog to examine the reversibility of the effects on hematological parameters that were observed in other dietary studies with the dog. Tebufenozide was administered for 6 weeks in the diet to 4 male dogs at concentrations of either 0 or 1,500 ppm. After the 6th week, the dogs receiving treated feed were switched to the control diet for 4 weeks. Hematological parameters were measured in both groups prior to treatment, at the end of the 6–week treatment, after 2–weeks of recovery on the control diet and after 4–weeks of recovery on the control diet. All hematological parameters in the treated/recovery group were returned to control levels indicating that the effects of tebufenozide on the hemopoietic system are reversible in the dog.

v. In a 28-day dermal toxicity study in the rat, the NOEL was 1,000 mg/kg/day, the highest dose tested. Tebufenozide did not produce toxicity in the rat when administered dermally for 4–weeks at doses up to and including the limit dose of 1,000 mg/kg/day.

5. *Chronic toxicity*— i. A 1–year feeding study in dogs resulted in decreased red blood cells, hematocrit, and hemoglobin and increased Heinz bodies, reticulocytes, and platelets at the LOEL of 8.7 mg/kg/day. The NOEL in this study was 1.8 mg/kg/day.

ii. An 18-month mouse carcinogenicity study showed no signs of carcinogenicity at dosage levels up to and including 1,000 ppm, the highest dose tested.

iii. In a combined rat chronic/oncogenicity study, the NOEL for chronic toxicity was 100 ppm (4.8 and 6.1 mg/kg/day for males and females, respectively) and the LOEL was 1,000 ppm (48 and 61 mg/kg/day for males and females, respectively). No carcinogenicity was observed at the dosage levels up to 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 (goat, hen, rat) metabolism studies.

7. *Metabolite toxicology*. Common metabolic pathways for tebufenozide have been identified in both plants (apple, beet, grape, and sugar) and animals (goat, hen, rat). 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 for residues of tebufenozide are currently expressed as benzoic acid, 3,5-dimethyl-1-(1,1-dimethylethyl)-2(4-ethylbenzoyl) hydrazide. Tolerances currently exist for residues on apples at 1.0 ppm (import tolerance) and on walnuts at 0.1 ppm (see 40 CFR 180.482). In addition to this action, a request to establish a tolerance for pecans, other petitions are pending for the following tolerances: pome fruit, livestock commodities, wine grapes (import tolerance), cotton, the crop subgroups leafy greens, leaf petioles, head and stem Brassica and leafy Brassica greens, and kiwifruit (import tolerance).

ii. *Acute risk*. No appropriate acute dietary endpoint was identified by the Agency. This risk assessment is not required.

iii. *Chronic risk*. For chronic dietary risk assessment, the tolerance values are used and the assumption that all of these crops which are consumed in the U.S. will contain residues at the tolerance level. The theoretical maximum residue contribution (TMRC) using existing and future potential tolerances for tebufenozide on food crops is obtained by multiplying the tolerance level residues (existing and proposed) by the consumption data which estimates the amount of those food products consumed by various population subgroups and assuming that 100% of the food crops grown in the U.S. are treated with tebufenozide. The Theoretical Maximum Residue Contribution (TMRC) from current and future tolerances is calculated 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. With the current and proposed uses of tebufenozide, the TMRC estimate represents 20.1% of the RfD for the U.S. population as a whole. The subgroup with the greatest chronic exposure is non-nursing infants (less than 1 year old), for which the TMRC estimate represents 52.0% of the RfD. Using anticipate residue levels for these crops utilizes 3.38% of the RfD for the U.S. population and 12.0% for non-nursing infants. The chronic dietary risks from these uses do not exceed EPA's level of concern.

3. *Drinking water*. An additional potential source of dietary exposure to residues of pesticides are residues in drinking water. Review of environmental fate data by the Environmental Fate and Effects Division concludes taht tebufenozide is moderately persistent to persistent and mobile, and could potentially leach to groundwater and runoff to surface water under certain environmental conditions. However, in terrestrial field dissipation studies, residues of tebufenozide and its soil metabolites showed no downward mobility and remained associated with the upper layers of soil. Foliar interception (up to 60% of the total dosage applied) by target crops reduces the ground level residues of tebufenozide. There is no established Maximum Concentration Level (MCL) for residues of tebufenozide in drinking water. No drinking water health advisory levels have been established for tebufenozide.

There are no available data to perform a quantitative drinking water risk assessment for tebufenozide at this time. However, in order to mitigate the potential for tebufenozide to leach into groundwater or runoff to surface water, precautionary language has been incorporated into the product label. Also, to the best of our knowledge, previous experience with more persistent and mobile pesticides for which there have been available data to perform quantitative risk assessments have demonstrated that drinking water exposure is typically a small percentage of the total exposure when compared to the total dietary exposure. This observation holds even for pesticides detected in wells and drinking water at levels nearing or exceeding established MCLs. Considering the precautionary language on the label and based on our knowledge of previous experience with persistent chemicals, significant exposure from residues of tebufenozide in drinking water is not anticipated.

4. *Non-dietary exposure*. Tebufenozide is not registered for either indoor or outdoor residential use. Non-occupational exposure to the general population is therefore not expected and not considered in aggregate exposure estimates.

D. Cumulative Effects

The potential for cumulative effects of tebufenozide with other substances that have a common mechanism of toxicity was considered. Tebufenozide belongs to the class of insecticide chemicals known as diacylhydrazines. The only other diacylhydrazine currently registered for non-food crop uses is halofenozide. Tebufenozide and halofenozide both produce a mild, reversible anemia following subchronic/chronic exposure at high doses; however, halofenozide also exhibits other patterns of toxicity (liver toxicity following subchronic exposure and developmental/systemic toxicity following acute exposure) which tebufenozide does not. Given the different spectrum of toxicity produced by tebufenozide, there is no reliable data at the molecular/mechanistic level which would indicate that toxic effects produced by tebufenozide would be cumulative with those of halofenozide (or any other chemical compound).

In addition to the observed differences in mammalian toxicity, tebufenozide also exhibits unique toxicity against target insect pests. Tebufenozide is an agonist of 20-hydroxyecdysone, the insect molting hormone, and interferes with the normal molting process in target lepidopteran species by interacting with ecdysone receptors from those species. Unlike other ecdysone agonists such as halofenozide, tebufenozide does not produces symptoms which may be indicative of systemic toxicity in beetle larvae (Coleopteran species). Tebufenozide has a different spectrum of activity than other ecdysone agonists. In contrast to the other agonists such as halofenozide which act mainly on coleopteran insects, tebufenozide is highly specific for lepidopteran insects.

Based on the overall pattern of toxicity produced by tebufenozide in mammalian and insect systems, the compound's toxicity appears to be distinct from that of other chemicals, including organochlorines,

organophosphates, carbamates, pyrethroids, benzoylureas, and other diacylhydrazines. Thus, there is no evidence to date to suggest that cumulative effects of tebufenozide and other chemicals should be considered.

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, the dietary exposure to tebufenozide from the current and future tolerances will utilize 20.1% of the RfD for the U.S. population and 52.0% for non-nursing infants under 1–year old. Using anticipate residue levels for these crops utilizes 3.38% of the RfD for the U.S. population and 12.0% for non-nursing infants. 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. Rohm and Haas concludes that there is a reasonable certainty that no harm will result from aggregate exposure to tebufenozide residues to the U.S. population and non-nursing infants.

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 pre-natal 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 NOEL 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 NOEL of 12.1 mg/kg/day was 14-fold higher than the parental (systemic) toxicity NOEL (0.85 mg/kg/day). The reproductive (pup) LOEL 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 NOEL equal to 149-195 mg/kg/day) and the NOEL 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. (Joseph Tavano)

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ENVIRONMENTAL PROTECTION AGENCY

[OPP–00518; FRL–5761–7]

Test Guidelines; Notice of Availability

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of availability.

SUMMARY: EPA has established a unified library for Test Guidelines issued by the Office of Prevention, Pesticides and Toxic Substances (OPPTS), and is announcing the availability of final test guidelines for Series 835—Fate, Transport and Transformation. These final guidelines are for the Office of Pollution Prevention and Toxics (OPPT) and have been harmonized with test guidelines of the Organization for Economic Cooperation and Development (OECD). The draft guidelines were made available by notice in the **Federal Register** (61 FR 16486, April 15, 1996)(FRL–5363–1) and were peer reviewed at a Scientific Advisory Panel (SAP) meeting on May 30, 1996. These final guidelines incorporate changes recommended by the SAP and other changes resulting from public comment. This notice also describes the unified library of OPPTS Test Guidelines. The Agency issues Federal Register notices periodically as new test guidelines are added to the OPPTS unified library.

ADDRESSES: The guidelines are available from the U.S. Government Printing Office, Washington, DC 20402 on *The Federal Bulletin Board*. By modem dial (202) 512–1387, telnet and ftp: fedbbs.access.gpo.gov (IP 162.140.64.19), or call (202) 512–0132 for disks or paper copies. The guidelines are also available electronically in ASCII and PDF (portable document format) from the EPA's World Wide Web site (http://www.epa.gov/epahome/research.htm) under the heading ''Researchers and Scientists/Test Methods and Guidelines/Harmonized Test Guidelines.''

FOR FURTHER INFORMATION CONTACT: For general information: By mail:

Toxic Substances Control Act (TSCA) information: Contact the TSCA Hotline at: TATS/7408, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. Telephone number: (202) 554–1404; fax: (202) 554–5603, e-mail: TSCA-hotline@epamail.epa.gov.

Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) information: Contact the Communications Services Branch (7506C), Field and External Affairs Division, Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. Telephone number: (703) 305–5017; fax: (703) 305–5558.

For technical questions only on Series 835 OPPT test guidelines: Robert Boethling, (202) 260–3912, or e-mail: boethling.bob@epamail.epa.gov.

SUPPLEMENTARY INFORMATION:

I. EPA's Process for Developing a Unified Library of Test Guidelines

EPA's Office of Prevention, Pesticides and Toxic Substances (OPPTS) has been engaged in a multi-year project to harmonize and/or update test guidelines among the Office of Pesticide Programs (OPP), the Office of Pollution Prevention and Toxics (OPPT), and the Organization for Economic Cooperation and Development (OECD). The goals of the project include the formulation of