bodies of water. This expectation is based on the rapid degradation of cyprodinil and the recommended low use rates that will further restrict the amount of chemical available for leaching or run-off.

2. *Non-dietary exposure.* Novartis believes that the potential for non-occupational exposure to the general public is unlikely except for potential residues in food crops discussed above. The proposed uses for cyprodinil are for agricultural crops and the product is not used residentially in or around the home.

D. Cumulative Effects

Consideration of a common mechanism of toxicity is not appropriate at this time since there is no information to indicate that toxic effects produced by cyprodinil would be cumulative with those of any other chemicals. Consequently, only the potential exposure to cyprodinil is considered in this risk assessment.

E. Safety Determination

1. *U.S. population.* For the U.S. population (48 contiguous states) chronic exposure was 11% of the RfD. EPA usually 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. Novartis concludes that there is a reasonable certainty that no harm will result from aggregate exposure to cyprodinil.

2. *Infants and children.* Maximum expected chronic exposure to cyprodinil in the diets of the most sensitive sub-populations, for non-nursing infants (<1–year old) and 31.1% of the RfD for childern (1–6 years old) was calculated to be 28.6% of the RfD.

F. International Tolerances

Codex maximum residue levels (MRLs) have not been established for residues.

[FR Doc. 00–15161 Filed 6–20–00; 8:45 am]

BILLING CODE 6560–50–F

ENVIRONMENTAL PROTECTION AGENCY

[PF–942; FRL–6557–3]

Notice of Filing a Pesticide Petition to Establish a Tolerance for Certain Pesticide Chemicals in or on Food

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

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

DATES: Comments, identified by docket control number PF–942, must be received on or before July 21, 2000.

ADDRESSES: Comments may be submitted by mail, electronically, or in person. Please follow the detailed instructions for each method as provided in Unit I.C. of the ''SUPPLEMENTARY INFORMATION.'' To ensure proper receipt by EPA, it is imperative that you identify docket control number PF–942 in the subject line on the first page of your response.

FOR FURTHER INFORMATION CONTACT: By mail: Richard J. Gebken, Registration Support Branch, Registration Division (7505C), Office of Pesticide Programs, Environmental Protection Agency, Ariel Rios Bldg., 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (703) 305–6701; e-mail address: gebken.richard@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

You may be affected by this action if you are an agricultural producer, food manufacturer or pesticide manufacturer. Potentially affected categories and entities may include, but are not limited to:

Categories	NAICS	Examples of potentially affected entities
Industry	111 112 311 32532	Crop production Animal production Food manufacturing Pesticide manufacturing

This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in the table could also be affected. The North American Industrial Classification System (NAICS) codes have been provided to assist you and others in determining whether or not this action might apply to certain entities. If you have questions regarding the applicability of this action to a particular entity, consult the person listed under ''FOR FURTHER INFORMATION CONTACT.''

B. How Can I Get Additional Information, Including Copies of this Document and Other Related Documents?

1. *Electronically.* You may obtain electronic copies of this document, and certain other related documents that might be available electronically, from the EPA Internet Home Page at http://www.epa.gov/. To access this document, on the Home Page select ''Laws and Regulations'' and then look up the entry for this document under the ''**Federal Register**—Environmental Documents.'' You can also go directly to the **Federal Register** listings at http://www.epa.gov/fedrgstr/.

2. *In person.* The Agency has established an official record for this action under docket control number PF–942. The official record consists of the documents specifically referenced in this action, any public comments received during an applicable comment period, and other information related to this action, including any information claimed as confidential business information (CBI). This official record includes the documents that are physically located in the docket, as well as the documents that are referenced in those documents. The public version of the official record does not include any information claimed as CBI. The public version of the official record, which includes printed, paper versions of any electronic comments submitted during an applicable comment period, is available for inspection in the Public Information and Records Integrity Branch (PIRIB), Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, VA, from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The PIRIB telephone number is (703) 305–5805.

C. How and to Whom Do I Submit Comments?

You may submit comments through the mail, in person, or electronically. To ensure proper receipt by EPA, it is imperative that you identify docket control number PF–942 in the subject line on the first page of your response.

1. *By mail.* Submit your comments to: Public Information and Records Integrity Branch (PIRIB), Information Resources and Services Division (7502C), Office of Pesticide Programs (OPP), Environmental Protection Agency, Ariel Rios Bldg., 1200 Pennsylvania Ave., NW., Washington, DC 20460.

2. *In person or by courier.* Deliver your comments to: Public Information and Records Integrity Branch (PIRIB), Information Resources and Services

Division (7502C), Office of Pesticide Programs (OPP), Environmental Protection Agency, Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, VA. The PIRIB is open from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The PIRIB telephone number is (703) 305–5805.

3. *Electronically.* You may submit your comments electronically by e-mail to: ''*opp-docket@epa.gov*,'' or you can submit a computer disk as described above. Do not submit any information electronically that you consider to be CBI. Avoid the use of special characters and any form of encryption. Electronic submissions will be accepted in Wordperfect 6.1/8.0 or ASCII file format. All comments in electronic form must be identified by docket control number PF–942. Electronic comments may also be filed online at many Federal Depository Libraries.

D. How Should I Handle CBI That I Want to Submit to the Agency?

Do not submit any information electronically that you consider to be CBI. You may claim information that you submit to EPA in response to this document as CBI by marking any part or all of that information as CBI. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2. In addition to one complete version of the comment that includes any information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public version of the official record. Information not marked confidential will be included in the public version of the official record without prior notice. If you have any questions about CBI or the procedures for claiming CBI, please consult the person identified under ''FOR FURTHER INFORMATION CONTACT.''

E. What Should I Consider as I Prepare My Comments for EPA?

You may find the following suggestions helpful for preparing your comments:

1. Explain your views as clearly as possible

2. Describe any assumptions that you used.

3. Provide copies of any technical information and/or data you used that support your views.

4. If you estimate potential burden or costs, explain how you arrived at the estimate that you provide.

5. Provide specific examples to illustrate your concerns.

6. Make sure to submit your comments by the deadline in this notice.

7. To ensure proper receipt by EPA, be sure to identify the docket control number assigned to this action in the subject line on the first page of your response. You may also provide the name, date, and **Federal Register** citation.

II. What Action is the Agency Taking?

EPA has received a pesticide petition as follows proposing the establishment and/or amendment of regulations for residues of a certain pesticide chemical 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 this petition contains 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.

List of Subjects

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

Dated: June 7, 2000.

James Jones,

Director, Registration Division, Office of Pesticide Programs.

Summary of Petition

The petitioner summary of the pesticide petition is printed below as required by section 408(d)(3) of the FFDCA. The summary of the petition was prepared by the petitioner and represent the views of the petitioner. EPA is publishing the petition summary verbatim without editing it 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.

AgrEvo USA Company

0F6087

EPA has received a pesticide petition [0F6087] from Aventis CropScience (fomerly AgrEvo USA Company), Aventis CropScience USA LP, 2, T.W. Alexander Drive, Research Triangle Park, NC 27709 proposing, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180 by establishing a tolerance for residues of buprofezin in or on the following raw agricultural commodities: almonds, nutmeats at 0.05 part per million (ppm); almonds, hulls, at 0.7 ppm; bananas at 0.1 ppm; the citrus crop group, fruit, at 0.7 ppm; cotton seed at 1.0 ppm; grapes at 0.4 ppm; and tomatoes, fruit at 0.8 ppm; in or on the following processed commodities: citrus oil at 26 ppm; citrus pulp, dried, at 2.5 ppm; cotton gin by-products at 23 ppm; and raisins at 1.0 ppm; and in or on the following meat and milk commodities: the fat, meat and meat byproducts of cattle, goats, hogs, horses, and sheep at 0.05 ppm; and milk at 0.01 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 metabolic profile of buprofezin has been elucidated in a wide range of crops, including tomatoes, lettuce, cotton, and citrus. For convenience, buprofezin metabolites are identified in this document by an internal code, BF 1 through 13. Corresponding structures are available in the tolerance petition. In tomatoes, lettuce, and cotton unchanged buprofezin was the only significant residue. In citrus, although buprofezin was a major component of the residue, a chromatographically well-defined region of radioactivity, clearly associated with polar conjugates, was observed. Mass spectrometry identified the principal polar residue as a hexose conjugate of BF4 (buprofezin hydroxylated in the t-butyl group). Although the conjugate was resistant to enzyme hydrolysis, acid hydrolysis of the polar fraction released predominantly BF26 with minor amounts of BF9 and BF12. The same compounds were observed following acid hydrolysis of a standard of BF4 clearly indicating that BF4 is the conjugated metabolite existing in citrus. Although only limited metabolism was observed in lettuce and cotton, trace levels of BF4/BF26, BF9 and BF12 were observed indicating that the metabolic pathway does not differ with plant species. In the tomato study, which was run prior to the citrus, cotton, and metabolism studies, these trace level metabolites were not specifically looked for due to the high percentage of the residue accounted for by the parent;

they may however have existed in trace amounts.

2. *Analytical method*—i. *Background*. Metabolism studies on lettuce and tomatoes have shown that the only significant residue in these crops is buprofezin. Development of the analytical method took place in parallel with the metabolism studies and the method was designed to quantify two metabolites (BF9 and BF12) in addition to the parent compound. This method was used for analysis of samples from the field trials on all crops except citrus, but for tolerance enforcement only the parent compound is considered.

In the case of citrus, the conjugate of another metabolite (BF4) was significant, and intensive efforts were made to include it in the analytical method. The technical problems proved to be very severe however and the effort was abandoned. As in all other crops, the parent compound is by far the largest component of the residue and this together with the aforementioned metabolites (BF9 and BF12) were the only residues quantified. The only modification made to the method for citrus was to add an amino column cleanup to take out some of the co-extractives unique to citrus.

ii. *Data collection method*. Samples are extracted with acetone. The extracts are filtered and the acetone removed by rotary evaporation. The remaining aqueous extract is acidified with hydrochloric acid and partitioned with hexane. The hexane is applied to a Florisil column and the residues are then eluted from the column with ether/hexane (50/50). The acidic aqueous phase is adjusted to pH 7 and partitioned with ethyl acetate/hexane (50/50). This organic extract is combined with the eluate from the Florisil column, evaporated to dryness, taken up in toluene and analyzed by gas chromatography (GC) with NP detection. The limit of quantitation (LOQ) of this method is 0.01 ppm in the sample.

iii. *Tolerance enforcement method*. The metabolism work and field sample analyses indicated that the only significant residue in treated crops was buprofezin. Accordingly, the method proposed for tolerance enforcement quantifies only buprofezin. The method is identical to the data collection method except that the acid partition step was omitted. The method was validated by an independent laboratory using lettuce, tomato, and cucumber as the test matrices. Since the method used for citrus differs so little from that used for the other crops, no separate ILV was performed for that method.

iv. *Multiresidue methods*. Buprofezin was tested through protocols D and F using tomatoes (a representative non-fatty food) and cottonseed (a representative fatty food). Recoveries were satisfactory such that the multiresidue methods could be used for tolerance enforcement or as confirmatory methods.

v. *Animal methods*. Because of the complexity of the metabolism picture in ruminants, methods were developed to separately quantify buprofezin and three metabolites (BF02, BF12 and BF23) in milk and cattle tissues. The methods were validated to a LOQ of 0.01 ppm in milk and to an LOQ of 0.05 ppm in tissues. These methods were used to analyze the samples from a cattle feeding study. On completion of the study, only buprofezin could be detected in any of the samples and accordingly, the method for determination of buprofezin in milk and tissues is proposed for tolerance enforcement. This method was validated at an external laboratory.

3. *Magnitude of residues*. Field trials were conducted on almonds, bananas, citrus, cotton, grapes, and tomatoes. In all crops buprofezin was the principal residue and in all crops except citrus, it was the only residue. Decline trials conducted in every crop demonstrated that the residue declined with time. In most cases, the residues declined approximately 50% in 3 to 7 days. In addition, processing studies were performed on tomatoes, grapes, citrus, and cotton. Residues concentrated significantly in orange oil, dry orange pulp, wet and dry tomato pomace, and in raisins, Two different formulations were used in the field trials, a 40SC and a 70WP. Bridging trials demonstrated that there was no difference in the residues produced by these two formulations.

i. *Residues in tomatoes*. Field grown tomatoes were treated with sequential applications of APPLAUD 40 SC or APPLAUD 70 WP at the maximum and the minimum application and preharvest intervals. (This is twice the seasonal maximum on the proposed label.) A total of 20 sites were used, distributed throughout the United States.

In the samples collected 7 days after treatment, the residues of buprofezin ranged from 0.02 ppm to 0.64 ppm. There was no apparent difference between tomatoes treated with the 70WP formulation and those treated with the 40SC formulation.

ii. *Residues in processed tomato commodities*. Tomatoes at one trial site in California were treated four times with APPLAUD 40 SC at 2.4 times the proposed maximum rate and at the minimum application and preharvest intervals. After the final application, whole tomatoes were harvested and processed into wet pomace, dry pomace, juice, puree, and paste.

The results indicate that following typical commercial processing of APPLAUD 40 SC-treated tomatoes, buprofezin residues concentrated slightly in the processed commodity, tomato paste, relative to the whole unwashed tomatoes. Buprofezin was detected in paste at 0.68 ppm. This value represents a concentration factor of 1.26x for paste; however this factor does not trigger a separate tolerance for paste. No concentration was observed for buprofezin in the other processed commodity, puree.

iii. *Residues in almonds*. Almonds at 6 sites in California were given a single treatment of APPLAUD 70 WP at the maximum application rate and minimum application and preharvest intervals. No residues above the LOQ (0.05 ppm) were present in any of the nut meat samples. The residues in the hulls ranged from < 0.05 ppm to 0.55 ppm. Only buprofezin was detected.

iv. *Residues in grapes*. Trials were conducted at 15 different sites, which represent 5 major grape producing regions within the United States. APPLAUD was applied twice to grapevines at the maximum application rate and minimum application and preharvest intervals.

Results showed that the residues for parent buprofezin ranged between 0.01 ppm and 0.27 ppm.

v. *Residues in processed grape commodities*. A single trial was conducted in California representing a major grape-producing region within the United States. APPLAUD 70WP was applied twice to grape vines at an exaggerated (5x) rate at the minimum application and preharvest intervals. Samples of treated grapes were harvested after the final application of APPLAUD and were processed into grape juice and raisins.

Buprofezin residues were observed to concentrate (2.41x) in raisins relative to those found in whole grapes. No concentration was observed for any analyte in grape juice.

vi. *Residues in cotton*. Trials were conducted at 15 different sites that represent 5 major cotton producing regions within the United States. APPLAUD 70WP was applied four times to plots of cotton at the maximum application rate, and minimum application and preharvest intervals. (This is twice the seasonal maximum on the proposed label). Duplicate samples of treated cottonseed were harvested

after the final application of APPLAUD and ginned at six sites to produce gin trash.

Five of the six samples of gin trash harvested 14 days after the last application of APPLAUD had residues which ranged between 2.38 ppm and 6.12 ppm. The sixth sample had a residue of 22.52 ppm.

Residues in cottonseed at 14 days after the last application ranged between 0.06 ppm and 0.82 ppm. Residues were observed to decline significantly for the two sites randomly selected to be used to generate decline data.

vii. *Residues in processed cotton commodities*. A single trial was conducted in California representing a major cotton-producing region within the United States. APPLAUD 70WP was applied four times to cotton plants at an exaggerated (5x) rate, and minimum application and preharvest interval.

Samples of treated cotton were harvested after the final application of APPLAUD and were processed into cottonseed, cottonseed by-products (gin trash), meal, hulls, crude oil, refined oil, and soapstock.

Following typical commercial processing of cotton treated with APPLAUD 70WP, at an exaggerated rate, buprofezin residues were observed to be 37.99x higher in gin trash relative to those found in cottonseed. No concentration was observed for buprofezin in any other cottonseed fraction.

viii. *Residues in citrus*. A total of 30 citrus trials were conducted throughout the major citrus producing regions within the United States. The trials consisted of orange, grapefruit, and lemon sites. APPLAUD 70WP was applied twice to the citrus trees at the maximum rate and minimum application and preharvest intervals. Duplicate samples of treated oranges were harvested after the final application of APPLAUD, including samples taken to observe residue decline.

The highest of the citrus residues were found in grapefruit (2.20 ppm) harvested 60 days after the last application of APPLAUD. This result is inconsistent with the rest of the samples in the study and no explanation can be offered for it. The 2.20 ppm result appears to be an outlier and if it is excluded the range of the grapefruit results is < 0.01 to 0.11, which is consistent with the other results in the study. Residues in oranges ranged from below 0.01 ppm to 0.47 ppm. Residues in lemons ranged between 0.01 ppm and 0.51 ppm.

Residues in citrus declined with time after the last application.

ix. *Residues in processed citrus commodities*. A single trial was conducted in California representing a major citrus producing region within the United States. APPLAUD 70WP was applied twice to orange trees at an exaggerated (5x) rate and minimum application and preharvest intervals.

Samples of treated oranges were harvested after the final application of APPLAUD and were processed into orange oil, juice and dry pomace.

Following typical commercial processing of oranges treated with APPLAUD 70WP at 5x the highest recommended application rate, buprofezin residue was detected and observed to concentrate (43.34x) in citrus oil relative to that found in whole fruit. The maximum average detected residue consisting of buprofezin was observed in orange oil at 15.17 ppm. Concentration was also observed for buprofezin at 4.14x in dry pulp relative to that found in the whole fruit. No concentration was observed for any analyte in orange juice.

x. *Residues in bananas*. Trials were conducted at one site in Puerto Rico and four sites on the island of Hawaii. Bananas were treated with four foliar applications of APPLAUD 70WP at the maximum application rate and minimum application and preharvest intervals. One half of the bananas site was protected with plastic bags and the other half was not. Samples were collected from both bagged and unbagged bananas at normal harvest. At one site, samples were also collected to develop data for a decline curve. Residues were determined in both peeled and unpeeled bananas.

Residues of buprofezin ranged from < 0.01 ppm (the LOQ) to 0.077 ppm in the 1-day PHI bananas. Residues were detected only in the unbagged, unpeeled bananas, indicating that these are strictly surface residues. No residues were detected in/on any bagged bananas nor in/on any peeled bananas.

xi. *Residues in milk and meat*. Twelve Holstein dairy cows were randomly assigned to four groups consisting of three cows each. Following quarantine, each cow was orally dosed twice daily for 28 consecutive days with one gelatin capsule containing a known amount of buprofezin. The control (T-0) group received capsules containing no buprofezin. Cattle in the T-I group received 119 mg of buprofezin per cow per day. Cattle in the T-II group received 357 mg per cow per day, and cattle in the T-III group, 1,190 mg per cow per day. These doses are equivalent to consumption of diets containing 0, 5, 15, and 50 ppm buprofezin (0, 1x, 3x, and 10x the maximum theoretical intake).

Milk was sampled on the day prior to the first dosing (day 1), on the day of the first dosing (day 1), and on days 2, 4, 7, 10, 14, 17, 21, 24, and 28. Cream and skim milk samples were prepared from whole milk collected on day 28. All cows were sacrificed on day 29 within 24 hours of the last dose. Sub-samples of muscle (hind-quarter), fat (perinephric), liver, and kidney were taken for analysis.

Milk and tissues were analyzed by methods that separately quantify buprofezin and the metabolites BF02, BF12, and BF23. The methods were validated to an LOQ of 0.01 ppm in milk and 0.05 ppm in tissues.

No buprofezin-derived residues were found in meat or milk commodities in the ruminant feeding study at a feeding level equivalent to the maximum theoretical intake of buprofezin.

B. Toxicological Profile

An extensive battery of toxicology studies has been conducted with buprofezin. These studies have been reviewed and summarized by the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (JMPR, 1991 and 1995). They have also been reviewed by the USEPA as part of the submission for an Experimental Use Permit. Supplemental information on several studies (acute dermal, acute inhalation, chronic dog, rat reproduction, and rat chronic toxicity/oncogenicity study) is being submitted with this petition. These studies indicate that buprofezin has a relatively low degree of toxicity, is neither genotoxic nor oncogenic, and does not cause any significant reproductive or developmental effects. Thus, the use of buprofezin on lettuce and cucurbits (as well as on cotton (Arizona and California) and citrus (California) under the current section 18 emergency exemptions) will not pose a significant risk to human health.

1. *Acute toxicity*. The acute rat oral LD_{50} for buprofezin was 1,635 mg/kg in males and 2,015 mg/kg in females. The acute rat dermal LD_{50} was ≥ 5,000 mg/kg in both sexes. The 4-hour rat inhalation LC_{50} was > 4.57 milligram/liter (mg/L). Buprofezin was slightly irritating to rabbit eyes and skin and did not induce dermal sensitization in guinea pigs.

2. *Genotoxicty*. No evidence of genotoxicity was noted in a battery of *in vitro* and *in vivo* studies. Studies included *Ames Salmonella* and mouse lymphoma gene mutation assays, a

mouse micronucleus assay, an *in vitro* human lymphocyte cytogenetics assay and an *in vitro* rat hepatocyte unscheduled DNA synthesis (UDS) assay.

3. *Reproductive and developmental toxicity*. A developmental toxicity study was conducted in rats at dose levels of 0, 50, 200, or 800 mg/kg/day. The (systemic) maternal no observed adverse effect level (NOAEL) for this study was 200 mg/kg/day based on weight loss, decreased food consumption, clinical signs, increased resorption rate, increased loss of entire litters and one maternal death at 800 mg/kg/day. The developmental (fetal) NOAEL was also 200 mg/kg/day based on reduced fetal body weights and increased incidence of delayed ossification at 800 mg/kg/day. Slightly reduced ossification was also noted at 200 mg/kg/day but this was within historical control range and thus not considered to be significant.

A developmental toxicity study was conducted in rabbits at dose levels of 0, 10, 50, or 250 mg/kg/day. The maternal (systemic) NOAEL was 50 mg/kg/day based on decreased weight gain, decreased food consumption and the complete resorption of 2 litters at 250 mg/kg/day. No evidence of developmental toxicity was noted; therefore, the developmental (fetal) NOAEL was 250 mg/kg/day, the highest dose tested (HDT).

Two rat reproduction studies have been conducted at dietary concentrations of 0, 10, 100, or 1,000 ppm. One was a 2-generation study that included a teratological evaluation. The other was a 1-generation reproduction study conducted to further evaluate some possible changes noted in the first study. Based on the results from both studies, the parental NOAEL was 1,000 ppm HDT. There were no effects on any reproductive parameters but pup weights were decreased at 1,000 ppm. Thus, the reproductive NOAEL was 100 ppm.

4. *Subchronic toxicity*. A 90-day feeding study was conducted in rats at dietary concentrations of 0, 40, 200, 1,000, or 5,000 ppm. Effects noted at 1,000 and/or 5,000 ppm included decreased weight gain, clinical pathology changes, increased liver and thyroid weights, and gross and/or microscopic evidence of liver, thyroid and kidney lesions. Only marginal effects, consisting of slightly reduced feed intake and slightly decreased glucose levels, were noted at 200 ppm. Although the report conservatively concluded the NOAEL to be 40 ppm, the NOAEL was considered by the EPA to be 200 ppm (15 mg/kg/day).

A 90-day study was conducted in which beagle dogs were administered buprofezin via capsule at dose levels of 0, 2, 10, 50, or 300 mg/kg/day. Effects noted at 50, and/or 300 mg/kg/day included various clinical signs of toxicity, substantially decreased weight gain, clinical pathology changes, increased liver, kidney and thyroid weights, and microscopic liver lesions. The NOAEL was 10 mg/kg/day.

5. *Chronic toxicity*. A 2-year study was conducted in which beagle dogs were administered buprofezin via capsule at dose levels of 0, 2, 20, or 200 mg/kg/day. Effects noted at 20 and/or 200 mg/kg/day included decreased weight gain, clinical pathology changes, increased liver and thyroid weights, decreased liver function (measured by BSP clearance) and microscopic liver lesions. Although the report concluded that the NOAEL for this study was 2 mg/kg/day, marginal effects in females at 2 mg/kg/day were considered to be a possible effect by the EPA reviewer pending receipt of additional historical control data. These data are being submitted with this petition and will establish that the dose of 2 mg/kg/day is a NOAEL for this study.

A 2-year rat feeding study was conducted at dietary concentrations of 0, 5, 20, 200, or 2,000 ppm. No evidence of oncogenicity was noted at any dose level. Effects noted at 2,000 ppm included decreased weight gain, increased liver and thyroid weights, and an increased incidence of non-neoplastic liver and thyroid lesions. A possible increase in thyroid lesions was also noted at 200 ppm. According to the EPA reviewer, the NOAEL for this study was 200 ppm (10 mg/kg/day). However, the conclusions of the original report and a subsequent histopathological reevaluation, not yet reviewed by the Agency, indicate that the NOAEL should be considered to be 20 ppm (1 mg/kg/day).

A 2-year mouse feeding study was conducted at dietary concentrations of 0, 20, 200, 2,000, and 5,000 ppm. Effects observed at 2,000 and/or 5,000 ppm included decreased weight gain, minor clinical pathology changes, increased liver weights and an increased incidence of non-neoplastic liver lesions. Increased liver weights were also noted at 200 ppm. Thus, the NOAEL was considered to be 20 ppm (1.8 mg/kg/day). There were slightly increased incidences of liver tumors in females at 5,000 ppm and of lung tumors in males at 200 and 5,000 ppm. The increased incidences of these common tumors were not considered to be treatment-related by either the study director or EPA reviewer but the study was referred to EPA Carcinogenicity Peer Review Group for further valuation.

6. *Animal metabolism*. The metabolism of buprofezin has been extensively studied in various species of animals and fish. Buprofezin has several groups that can metabolize in a variety of ways thus potentially producing a very large number of metabolites. Indeed extensive metabolism to many minor metabolites was observed in all the animal species. Metabolism in fish was, however, much more limited and clearly defined. Although not all metabolic intermediates have been detected in all the species, the major routes of metabolism have been identified in animals and fish and a consistent pattern is observed throughout these species. The proposed metabolic pathway was provided in the tolerance petition. For convenience, degradates are referred to by an internal code: BF 1 through 13. Corresponding chemical structures were provided in the tolerance petition.

i. *Metabolism in rats*. The major metabolite found in rat excreta was parent buprofezin in addition to several compounds formed after extensive metabolism. Whereas plant metabolism appeared restricted mainly to oxidation of the tertiary butyl group, oxidation of the butyl group and hydroxylation of the phenyl ring were both observed in rats. Oxidation of the t-butyl group proceeded beyond an alcohol to an acid and was accompanied by ring opening. The most extensively metabolized compound identified in rats was BF23 (acetylated p-aminophenol)

ii. *Metabolism in ruminants and hens*. Residue levels were low (< 0.05 ppm) in all ruminant and poultry tissues and commodities, following treatment at exaggerated rates (approximately 20x and 7,500x the anticipated dietary burden, respectively). The only exceptions were cow liver (1.21 ppm), cow kidney (0.41 ppm), hen liver (0.15 ppm), and egg yolk (0.11 ppm). Extensive metabolism was observed in both species with a large number of minor metabolites being produced.

The principal metabolites identified in the cow were BF2 and BF23 indicating that the major pathway of degradation in ruminants is hydroxylation of the phenyl ring followed by opening and degradation of the heterocyclic ring. The identification of trace levels of BF13 confirms this pathway. As in rats, BF23 was the most extensively metabolized compound identified. Trace levels of BF12 were also detected. This indicates that the parallel pathway of heterocyclic ring opening without hydroxylation of the

phenyl ring is also in operation. Similarly in hens, the identified metabolites were derived from degradation of the heterocyclic ring either with (BF13) or without (BF9 and BF12) phenyl ring hydroxylation. No single unidentified compound accounted for more than 6% of the total residue in any animal tissue or commodity, with the exception of a component comprising 8.7% of egg white. The total residue in egg white was, however, only 0.02 ppm even at this highly exaggerated dose rate.

iii. *Metabolism in fish*. Analysis of fish tissues, following a bioaccumulation study, found a much simpler metabolic profile. Buprofezin was present in both edible and non-edible tissues, but the principle metabolites were polar conjugates of BF4. Trace levels of BF12 were also detected.

7. *Endocrine disruption*. No special studies have been conducted to investigate the potential of buprofezin to induce estrogenic or other endocrine effects. The standard battery of required toxicity studies has been completed. These studies include an evaluation of the potential effects on reproduction and development and an evaluation of the pathology of the endocrine organs following repeated or long-term exposure. These studies are generally considered to be sufficient to detect any endocrine effects. The only effect noted on endocrine organs was an increased incidence of follicular cell hypertrophy and C-cell hyperplasia of the thyroid gland in rats administered buprofezin at dietary concentrations of 2,000 ppm for 24 months. Buprofezin also caused mild to moderate hepatotoxic effects at this dietary concentration. AgrEvo believes that the effect on the thyroid most likely resulted from increased turnover of T3/T4 in the liver with a resultant rise in TSH secretion (due to the hepatotoxicity). The rat is known to be much more susceptible than humans to these effects due to the very rapid turnover of thyroxine in the blood in rats (12 hours vs. about 5-9 days in humans). Therefore, the thyroid pathological changes which have been noted following administration of high doses of buprofezin are considered to be of minimal relevance to human risk assessment, particularly considering the low levels of buprofezin to which humans are likely to be exposed.

C. Aggregate Exposure

Buprofezin is an insect growth regulator, which is approved for use under a section 18 emergency exemption for control of red scale on citrus in California. Section 18 applications are pending at EPA for the control of whitefly on cotton in Arizona and California, on cucurbits in Arizona, and on tomatoes in Florida. Non-crop uses of buprofezin are limited to an Experimental Use Permit for use on ornamentals in greenhouses, thus only dietary exposures are being considered.

1. *Dietary exposure*—i. *Food*. Potential dietary exposures from food commodities under the proposed food tolerances for buprofezin, including those in the previously submitted tolerance petition number 7F4923, were estimated using the exposure I software system (TAS, Inc.) and the 1977-78 Department of Agriculture (USDA) consumption data. A single, worst-case scenario was evaluated.

In this case, it was assumed that all uses contained residues at the proposed tolerance levels of: Leaf lettuce (13 ppm), head lettuce (5 ppm), the cucurbits crop group (0.5 ppm), almonds, nutmeats (0/05 ppm), bananas (0.8 ppm), citrus (0.6 ppm), grapes (0.3 ppm), raisins (0.8 ppm), tomatoes (0.7 ppm), animal fat, meat and meat by-products (0.05 ppm), and milk (0.01 ppm). This very worst-case scenario also assumed 100% of the crop treated.

ii. *Drinking water*. Exposure to buprofezin from drinking water is expected to be negligible. The potential for buprofezin to leach into ground water was assessed in various laboratory studies as well as terrestrial field dissipation studies conducted in two locations and in varying soil types. The degradation of buprofezin occurs rapidly with half-lives in soil ranging from 22 to 59 days. No evidence of leaching of parent or degradation products was observed in aged leaching or terrestrial field dissipation studies. The major routes of degradation result in mineralization to carbon dioxide and the formation of ''bound'' residues. Buprofezin tends to bind to the top layers of soil with low mobility. The Koc for most soils fell in the range 2,100-4,800. The solubility in water is low (0.382 mg/L).

A screening evaluation of worst-case shallow ground water concentrations was conducted using EPA model SCI/GROW. A number of uses were compared and the results are summarized in the following table:

Crop	Annual application rate (lbs./acre)	Aerobic half-life (days)	Koc	Relative Intrinsic Leaching Potential	Screening Concentration in Ground water (ppb)
Almonds	2	41 [a]	3008[b]	0.811[c]	0.036
Citrus	4				0.072
Grapes	1				0.018
Vegetables & cotton	076				0.014

[a] Average of laboratory aerobic soil metabolism studies
[b] Average of all tested soils excluding one abnormally highly value (Koc = 18836)
[c] Relative Intrinsic Leaching Potential = (log(t1/2 5))*(4-log(Koc + 5))

The potential exposure of buprofezin in drinking water abstracted from surface water was assessed using a Tier 2, modeling approach. PRZM was used to generate potential runoff loads from a standardized agricultural field (10-ha) to a standardized aquatic system (1-ha 2-m deep pond) following application of buprofezin to citrus (the maximum proposed use rate for all crops). EXAMS was used to estimate the exposure concentration (EEC) in surface water. The ''once-in-10-year'' exceedance probability corresponded to a concentration at 0.52 part per billion (ppb). This value refers to the 56-day average estimated concentration in a farm pond draining agricultural land and must be considered a gross over-estimate of concentrations of buprofezin at the point of drinking water abstraction.

The calculated worst-case maximum exposure of buprofezin in drinking water (assuming consumption of 2 liters per day) will be no more than 1.04 µg per day. Exposure from drinking water abstracted from ground water will be an order of magnitude lower (> 0.14 g per day). However, the contribution of any such residues to the total dietary intake of buprofezin will be negligible.

2. *Non-dietary exposure.* There is a current Experimental Use Permit (EUP) for the use of buprofezin on ornamentals in greenhouses. Exposure to the general population would be minimal in this use and thus was not considered.

D. Cumulative Effects

At the present time, there are insufficient data available to allow AgrEvo to properly evaluate the potential for cumulative effects with other pesticides to which an individual may be exposed. For the purposes of this assessment, therefore, AgrEvo has assumed that buprofezin does not have a common mechanism of toxicity with any other registered pesticides. Therefore, only exposure from buprofezin is being addressed at this time.

E. Safety Determination

The toxicity and residue data bases for buprofezin are considered to be valid, reliable and essentially complete. The standard margin of safety approach is considered appropriate to assess the risk of adverse effects from exposure to buprofezin for both acute and chronic effects. EPA has adopted a temporary reference dose (RfD) for buprofezin at 0.002 mg/kg/day. This RfD was based on the systemic lowest effect level (LEL) of 2.0 mg/kg/day limit dose tested (LDT) from a 2-year dog study and using a 1,000-fold uncertainty factor (UF). An extra factor of 10 was added to the standard 100 fold safety factor since the RfD was based on a LEL (rather than a NOAEL) and the data base lacked an acceptable reproductive study. Additional data have been submitted to upgrade the reproduction study and to support the lowest dose in the 2-year dog study as a NOAEL. With the upgrading of these studies, the critical study for the establishment of a permanent RfD would be the rat chronic/oncogenicity study. The NOAEL for this study is 1 mg/kg/day. Applying a standard safety factor of 100 for this study, to account for interspecies extrapolation and intraspecies variation, would result in a RfD of 0.01 mg/kg/day. It is this proposed RfD which was used to assess risk to the public.

1. *U.S. population*—i. *Acute risk.* EPA has previously selected, in their approval of the section 18 emergency exemption use, a developmental NOAEL of 200 mg/kg/day from a rat developmental study for the acute dietary endpoint. However, it appears that this is an inappropriate acute endpoint since the clinical effects noted at the higher dose (800 mg/kg/day) occurred only after at least 5 days of dosing and the fetal effects (reduced fetal body weight and delayed ossification) are not likely to be due to an acute (1-day) exposure.

Based on this assessment, AgrEvo has not evaluated the risk from acute exposure to any subgroup of the population. Previously, EPA has assessed the acute risk from use of buprofezin on citrus and cotton to the population subgroup of females 13+ years of age. Using the developmental NOAEL of 200 mg/kg/day, the margin of exposure (MOE), according to EPA calculations, was 5,000 for this subgroup.

ii. *Chronic risk.* Chronic dietary exposures for the U.S. population as a whole utilize 30% of the buprofezin RfD in the worst-case scenario of 100% of crop treated and all residues at the proposed tolerance levels. There is generally no concern for exposures below 100% of the RfD since it represents the level at or below which no appreciable risks to human health is posed. Therefore, there is reasonable certainty that no harm would result to the U.S. population from exposure to buprofezin.

2. *Infants and children.* Data from rat and rabbit developmental toxicity studies and rat multigeneration reproduction studies are generally used to assess the potential for increased sensitivity to infants and children. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during prenatal development. Reproduction studies provide information relating to reproductive and other effects on adults and offspring from prenatal and postnatal exposure to the pesticide.

No indication of increased sensitivity to infants and children was noted in either of the developmental studies. However, in the reproduction studies, the NOAEL for pups (100 ppm) was lower than for adults (1,000 ppm). Based on the intake of buprofezin in pups up to 8 weeks of age, the RfD for children, using a 1,000 fold safety factor, would be 0.01 mg/kg/day. This is the same RfD that is calculated for chronic exposure utilizing the rat chronic/oncogenicity study.

Evaluation of the dietary exposure to infants and children was conducted utilizing the same assumptions as for the U.S. population as a whole. In the worst-case scenario, assuming residues at the proposed tolerance levels and with no adjustment for the percent crop treated, the dietary exposure for children, 1–6 years, was 50% of the RfD. There is generally no concern for exposures below 100% of the RfD since it represents the level at or below which no appreciable risks to human health is posed. Thus, there is a reasonable certainty that no harm will result to the most highly exposed population subgroup, children between 1 and 6 years of age, from exposure to buprofezin.

F. International Tolerances

Buprofezin was reviewed by the Joint Meeting of the Food and Agriculture Organization Panel of Experts on Pesticide Residues in Food and the Environment and the World Health Organization Expert Group on Pesticide Residues (JMPR) to establish Codex maximum residue levels (MRLs) in 1991, 1995, and 1997. Permanent MRLs were granted for cucumbers and tomatoes and a temporary MRL was granted for oranges as described below. Additional residue trial data on oranges will be available for the 1999 JMPR meeting to determine if this MRL should also be made permanent.

Commodity	MRL
Cucumber	0.3 ppm
Tomato	0.5 ppm
Oranges, Sweet, Sour	0.3 ppm (temporary)

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