care) and receptor subpopulation (i.e., adults, children 1-6 years and infants <1–year) are compared to the systemic absorbed dose NOAEL for bifenthrin to provide estimates of the MOEs. Based on the toxicity endpoints selected by EPA for bifenthrin, inhalation and incidental oral ingestion absorbed doses were combined and compared to the relevant systemic NOAEL for estimating MOEs.

In the case of potential aggregate health risks, the above mentioned conservative point estimates of inhalation and incidental ingestion non-dietary exposure (expressed as systemic absorbed dose) are combined with estimates (arithmetic mean values) of chronic average dietary (oral) absorbed doses. These aggregate absorbed dose estimates are also provided for adults, children 1-6 years and infants <1–year. The combined or aggregated absorbed dose estimates (summed across non-dietary and chronic dietary) are then compared with the systemic absorbed dose NOAEL to provide estimates of aggregate MOEs.

The non-dietary and aggregate (non-dietary + chronic dietary) MOEs for bifenthrin indicate a substantial degree of safety. The total non-dietary (inhalation + incidental ingestion) MOEs for post-application exposure for the lawn care product evaluated was estimated to be 194,000 for adults, 52,400 for children 1-6 years old and 56,700 for infants <1–year. The aggregate MOE (inhalation + incidental oral + chronic dietary, summed across all product use categories) was estimated to be 4,878 for adults, 1,117 for children 1-6 years old and 1,361 for infants (<1–year). It can be concluded that the potential non-dietary and aggregate (non-dietary + chronic dietary) exposures for bifenthrin are associated with substantial margins of safety.

D. Cumulative Effects

In consideration of potential cumulative effects of bifenthrin and other substances that may have a common mechanism of toxicity, to our knowledge there are currently no available data or other reliable information indicating that any toxic effects produced by bifenthrin would be cumulative with those of other chemical compounds; thus only the potential risks of bifenthrin have been considered in this assessment of its aggregate exposure. FMC Corporation intends to submit information for the EPA to consider concerning potential cumulative effects of bifenthrin consistent with the schedule established by EPA in the Federal Register at 62 FR 42020 (August 4, 1997), FRL–5734–6 and other EPA publications pursuant to the Food Quality Protection Act.

E. Safety Determination

1. *U.S. population*. For the overall U.S. population, the calculated MOE at the 95th percentile was estimated to be 650, 359 at the 99th percentile; and 181 at the 99.9th percentile. For all infants <1–year old, the calculated MOE at the 95th percentile was estimated to be 540; 241 at the 99th percentile; and 171 at the 99.9th percentile. For nursing infants <1–year old, the calculated MOE at the 95th percentile was estimated to be 1,311; 451 at the 99th percentile; and 246 at the 99.9th percentile. For non-nursing infants <1–year old, the calculated margins of exposure MOE at the 95th percentile was estimated to be 476, 197 at the 99th percentile; and 169 at the 99.9th percentile. For the most highly exposed population subgroup, children 1-6 years old, the calculated MOE at the 95th percentile was estimated to be 330, 214 at the 99th percentile; and 102 at the 99.9th percentile. Therefore, FMC Corporation concludes that there is reasonable certainty that no harm will result from acute exposure to bifenthrin.

2. *Infants and children*—a. *General*. In assessing the potential for additional sensitivity of infants and children to residues of bifenthrin, FMC Corporation considered data from developmental toxicity studies in the rat and rabbit, and a 2–generation reproductive study in the rat. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during prenatal development to one or both parents. Reproduction studies provide information relating to effects from exposure to the pesticide on the reproductive capability of mating animals and data on systemic toxicity. FFDCA section 408 provides that EPA may apply an additional margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the data base.

b. *Developmental toxicity studies*. In the rabbit developmental study, there were no developmental effects observed in the fetuses exposed to bifenthrin. The maternal NOAEL was 2.67 mg/kg/day based on head and forelimb twitching at the LOAEL of 4 mg/kg/day. In the rat developmental study, the maternal NOAEL was 1 mg/kg/day, based on tremors at the LOAEL of 2 mg/kg/day. The developmental (pup) NOAEL was also 1 mg/kg/day, based upon increased incidence of hydroureter at the LOAEL 2 mg/kg/day. There was 5/23 (22%) litters affected (5/141 fetuses since each litter only had one affected fetus) in the 2 mg/kg/day group, compared with zero in the control, 1, and 0.5 mg/kg/day groups. According to recent historical data (1992–1994) for this strain of rat, incidence of distended ureter averaged 11% with a maximum incidence of 90%.

c. *Reproductive toxicity study*. In the rat reproduction study, parental toxicity occurred as decreased bwt at 5.0 mg/kg/day with a NOAEL of 3.0 mg/kg/day. There were no developmental (pup) or reproductive effects up to 5.0 mg/kg/day HDT.

d. *Prenatal and postnatal sensitivity*—i. *Prenatal*. Since there was not a dose-related finding of hydroureter in the rat developmental study and in the presence of similar incidences in the recent historical control data, the marginal finding of hydroureter in rat fetuses at 2 mg/kg/day (in the presence of maternal toxicity) is not considered a significant developmental finding. Nor does it provide sufficient evidence of a special dietary risk (either acute or chronic) for infants and children which would require an additional safety factor. Based on the absence of pup toxicity up to dose levels, which produced toxicity in the parental animals, there is no evidence of special postnatal sensitivity to infants and children in the rat reproduction study.

e. *Conclusion*. Based on the above, FMC Corporation concludes that reliable data support use of the standard 100–fold UF, and that an additional UF is not needed to protect the safety of infants and children. As stated above, aggregate exposure assessments utilized less than 10% of the RfD for either the entire U. S. population or any of the 26 population subgroups including infants and children. Therefore, it may be concluded that there is reasonable certainty that no harm will result to infants and children from aggregate exposure to bifenthrin residues.

F. International Tolerances

There are no Codex, Canadian, or Mexican residue limits for residues of bifenthrin in or on bananas.

[FR Doc. 01–3621 Filed 2–13–01; 8:45 am]

BILLING CODE 6560–50–S

ENVIRONMENTAL PROTECTION AGENCY

[PF–996; FRL–6765–8]

Notice of Filing a Pesticide Petition to Establish a Tolerance for a Certain Pesticide Chemical 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–996, must be received on or before March 16, 2001.

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–996 in the subject line on the first page of your response.

FOR FURTHER INFORMATION CONTACT: By mail: Joanne Miller, Registration Division (7505C), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (703) 305–6224; e-mail address: miller.joanne@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 codes	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–996. 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–996 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, 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–996. 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 Cosmetic 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 support 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: February 1, 2001.

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 represents the view of the petitioner. EPA is publishing the petition summary verbatim without editing them in any way. The petitioner 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.

Valent U.S.A. Corporation

7F4841 and 0F6171

EPA has received pesticide petitions (7F4841 and 0F6171) from Valent U.S.A. Corporation, 1333 North California Boulevard, Suite 600, Walnut Creek, CA 94596–8025, proposing, pursuant to section 408(d) of the FFDCA, 21 U.S.C. 346a(d), to amend 40 CFR part 180 by establishing tolerances for residues of flumioxazin, 2-[7-fluoro-3,4-dihydro-3-oxo-4-(2-propynyl)-2H-1,4-benzoxazin-6-yl]-4,5,6,7-tetrahydro-1H-isoindole-1,3(2H)-dione, in or on the raw agricultural commodities (RACs) soybean seed and peanut nutmeat at 0.01 parts per million (ppm), and on sugar cane at 0.2 ppm. EPA has determined that the petitions 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 petitions. Additional data may be needed before EPA rules on the petitions.

A. Residue Chemistry

Summary. Radiocarbon plant and animal metabolism studies have demonstrated that the residue of concern is adequately understood for the purposes of these tolerances and is best defined as parent, flumioxazin. Practical, validated residue methodology is available to analyze all appropriate matrices for flumioxazin residue with a limit of quantification (LOQ) of 0.01 ppm, adequate to enforce all proposed tolerances. The potential magnitude of residues of flumioxazin has been evaluated in peanuts, soybeans, and sugarcane and in appropriate processed products and animals. These studies are adequate to support appropriate tolerances and dietary risk analyses.

1. *Plant metabolism*. Metabolism of ^{14}C-flumioxazin labelled in the phenyl- or tetrahydrophthalimido-rings has been studied in soybeans and peanuts. Flumioxazin was rapidly and extensively metabolized to many metabolites in both plants. Even with exaggerated treatment, individual metabolites and parent were only found at very low concentrations. Comparisons of metabolites detected and quantified from plants and animals show that there are no significant aglycones in plants which are not also present in the excreta or tissues of animals. The residue of concern is best defined as the parent.

2. *Analytical method*. Practical analytical methods for detecting and measuring levels of flumioxazin have been developed and validated in/on all appropriate agricultural commodities and respective processing fractions. The extraction methodology has been validated using aged radiochemical residue samples from ^{14}C-metabolism studies. The enforcement method has been validated in soybean at an independent laboratory and by EPA. The LOQ of flumioxazin in the methods is 0.01 ppm which will allow monitoring of food with residues at the levels proposed for the tolerances.

3. *Magnitude of residues*—i. *Soybean*. Forty-two (42) field trials in soybeans were conducted in 1989 through 1993 in EPA regions II (2 trials), IV (9 trials, and V (31 trials), representing approximately 99% of the U.S. soybean growing region. Treatments ranged from 0.09 to 0.47 pounds active per acre, 1–to 5–times the proposed application rate. No residues of flumioxazin were detected in soybean seed from any of the trials, even when application rates were 5 times the proposed label rate. Analysis for the major plant metabolite, 1–OH-HPA, was conducted on seed samples from 13 residue trials. In all cases no residues of the degradate were found, including 2 trials which at a 5X treatment rate.

No residues of flumioxazin were found in any of the processed commodities in 2 processing studies of soybeans treated at 5 times the proposed label rate. In 1 of the processing studies, no residue of 1–OH-HPA was found in any processed fraction. All the data support a proposed tolerance for flumioxazin in/on soybean seed at 0.01 ppm, the LOQ of the enforcement method. No separate tolerances are needed for soybean processed commodities.

ii. *Peanut*. Sixteen (16) field trials in peanuts were conducted in 1992, 1993, and 1996 in EPA regions II (8 trials), III (3 trials), IV (3 trials), and VIII (2 trials), representing virtually all of the U.S. peanut growing regions. Treatments ranged from 0.09 to 0.47 pounds active per acre, 1–to 5–times the proposed application rate. No residues of flumioxazin were detected in any peanut seed sample from any of the trials, even when application rates were 5 times the proposed label rate. Analysis for the major plant metabolite, 1–OH-HPA, was conducted on seed samples from 1 5X processing trial. No residues of the degradate were found.

No residues of flumioxazin were found in any of the processed commodities in 2 processing studies of peanuts treated at 5 times the proposed label rate. One of the processing studies was analyzed for degradate, no residue of 1–OH-HPA was found in any processed fraction.

All the data support a proposed tolerance for flumioxazin in/on peanut seed at 0.01 ppm, the LOQ of the enforcement method. No separate tolerances are needed for peanut processed commodities.

iii. *Sugarcane*. Nine (9) field trials in sugarcane were conducted in 1998 in EPA regions III (4 trials), IV (3 trials), VI (1 trial), and XIII (1 trial), representative of all of the U.S. sugarcane growing

regions. Treatments ranged from 0.37 to 1.12 pounds active per acre, 1–to 3–times the proposed application rate for high organic soils. Finite residues of flumioxazin were detected in fourteen (14) of eighteen (18) duplicate samples. Residues of flumioxazin averaged 0.039 ppm (standard deviation = 0.033 ppm) from the trials conducted at the proposed maximum application rate. Analysis for the major plant metabolite, 1–OH-HPA, was conducted on all cane samples including those from the 2 3X processing trials. No residues of the degradate were found in any cane sample.

No residues of flumioxazin or its degradate were found in the processed commodity refined sugar. In molasses, produced from cane treated at 3 times the proposed label rate, flumioxazin was detected (0.055 ppm) at approximately half of the concentration in the starting sugarcane. The degradate, 1–OH-HPA, was also detected in molasses (0.036 ppm). Because these detections were in a processed sample from cane treated at 3X, and are still less than the proposed RAC tolerance, no separate processed product tolerances are necessary.

All the data support a proposed tolerance for flumioxazin in/on sugarcane at 0.2 ppm. No separate tolerances for parent or degradate are needed for processed commodities.

iv. *Secondary residues*. Using proposed tolerances to calculate the maximum feed exposure to fed animals, and using the very low potential for residue transfer demonstrated in the goat and hen metabolism studies, detectable secondary residues in animal tissues, milk, and eggs are not expected. Therefore, no cow or hen residue feeding studies were performed,and tolerances are not proposed for these commodities.

v. *Rotational crops*. The results of a confined rotational crop accumulation study indicate that no rotational crop planting restrictions or rotational crop tolerances are required.

B. Toxicological Profile

Summary. A full battery of toxicology testing has been performed on flumioxazin including acute, chronic, oncogenicity, developmental, mutagenicity, and reproductive effects. Flumioxazin has low toxicity via oral and dermal routes and is not carcinogenic. Overall, it does not present a genetic hazard. Although developmental and reproductive effects were observed in rats, acute and chronic dietary assessments and worker exposure assessments demonstrate large margins of safety when worst case exposures are compared to the proposed toxic endpoints, along with appropriate uncertainty factors (UF). Valent proposes a chronic population adjusted dose (c-PAD) of 0.018 milligram/kilogram (mg/kg)/day for adults and 0.0018 mg/kg/day for women of child bearing age and infants and children based on the no observed adverse effect level (NOAEL) of 1.8 mg/kg/day for males in the rat 2 year chronic toxicity oncogenicity study. Valent also proposes 3.0 mg/kg/day as the acute oral endpoint based on the developmental toxicity NOAEL from the rat oral developmental toxicity study.

1. *Acute toxicity*. The acute toxicity of technical grade flumioxazin is low by all routes. The battery of acute toxicity studies place flumioxazin in toxicity category III.

i. No abnormal clinical signs, body weight (bwt) changes, or gross pathological findings were observed and no rats died following administration of an oral dose of 5 gram/kilogram (g/kg) of flumioxazin technical. The LD_{50} was greater than 5 g/kg.

ii. No deaths, abnormal clinical signs, bwt changes, or gross pathological findings were observed in rats exposed to a 2.0 g/kg dermal dose of flumioxazin technical. The LD_{50} was greater than 2.0 g/kg.

iii. Rats were exposed to a dust aerosol of flumioxazin technical for 4 hours at measured concentrations of 1.55 or 3.93 milligrams/Liter (mg/L), the maximum attainable concentration. Irregular respiration, bradypnea and a decrease in spontaneous activity were observed in many of the rats, but these effects disappeared within 2 hours after termination of the exposure. No deaths, bwt changes, gross pathological findings or histopathological changes in the respiratory organs were observed. The LC_{50} for flumioxazin technical was determined to be greater than 3.93 mg/L.

iv. Flumioxazin technical produced minimal eye irritation in rabbits which cleared within 48 hours.

v. Flumioxazin technical did not produce any signs of skin irritation in abraded or intact skin of rabbits.

vi. Flumioxazin technical was not a skin sensitizer when tested in guinea pigs using the Magnussen and Kligman maximization test methodology.

2. *Genotoxicity*. Flumioxazin does not present a genetic hazard. Flumioxazin was evaluated in the following tests for mutagenicity:

i. A reverse gene mutation assay in *Salmonella typhimurium* and *Escherichia coli* was negative with or without metabolic activation.

ii. An *in vitro* chromosome aberration assay using chinese hamster ovary (CHO) cells was negative in the absence of metabolic activation. However, an increase in cells with aberrations was observed at doses of $1X10^{-4}$ M and higher in the presence of S9.

iii. An *in vivo* chromosomal aberration study in the rat was negative. No significant increase in the incidence of chromosomal aberrations in bone marrow cells was observed following treatments as high as 5,000 mg/kg.

iv. An *in vitro* unscheduled DNA synthesis (UDS) assay with rat hepatocytes was negative.

v. A mouse micronucleus assay was negative following intraperitoneal injection of 5,000 mg/kg.

3. *Reproductive and developmental toxicity*. Flumioxazin shows developmental toxicity in the absence of maternal toxicity in rats. Mechanistic studies demonstrate that the effect is specifically related to the inhibition of heme synthesis, that the effect shows considerable species specificity, and that the rat is a conservative surrogate species for the potential for developmental toxicity in man. No developmental toxicity was observed in rabbits. Developmental toxicity to the pups was seen in the rat reproduction study at doses that were not toxic to the parental animals.

i. *Rat—Developmental toxicity*. A pilot dose range-finding study was conducted to determine appropriate doses for the definitive oral developmental toxicity study. Flumioxazin technical was administered by oral gavage at dosages of 0, 30, 100, 200, and 500 mg/kg/day to pregnant rats on days 6 through 15 of gestation. No animals died during the course of this study and maternal toxicity was limited to decreased weight gain associated with high embryolethality observed in all dose groups. Fetuses obtained from the 30 mg/kg/day dams had significantly reduced bwts and were found to have both skeletal and visceral abnormalities primarily wavy ribs and ventricular septal defects (VSD). Because of the high degree of embryolethality at doses of 100 mg/kg/day and greater, the highest dose selected for the definitive study was 30 mg/kg/day.

In the definitive study, pregnant rats were administered oral doses of 0, 1, 3, 10, or 30 mg/kg/day of flumioxazin technical on days 6 through 15 of gestation. No maternal deaths were observed at any dosage and no treatment-related effects on clinical signs or food consumption were noted. A decrease in maternal bwt gain was found at 30 mg/kg/day. The number of live fetuses and fetal bwts were decreased in the 30 mg/kg/day group

and the incidence of embryo mortality tended to be higher but was not statistically significant. No effects on the number of implantations, sex ratios, or external abnormalities were found. The incidence of fetuses with cardiovascular abnormalities, primarily VSD, was increased in the 30 mg/kg/day group. Other developmental effects observed at 30 mg/kg/day included an increase in the incidence of wavy ribs and curvature of the scapula, and a decrease in the number of ossified sacrococcygeal vertebral bodies. Based on these findings, a maternal NOAEL of 30 mg/kg/day and a developmental NOAEL of 3 mg/kg/day are proposed.

In a range-finding dermal developmental toxicity study flumioxazin technical was administered dermally at levels of 100, 200, 400, and 800 mg/kg/day in corn oil. No adverse effects on the dams were observed at doses up to 800 mg/kg/day. Because of the high degree of embryolethality at doses of 400 mg/kg/day and greater, the highest dose selected for the definitive study was 300 mg/kg/day.

On days 6–15 of gestation, pregnant rats were exposed dermally to dose levels of 30, 100, or 300 mg/kg/day of flumioxazin technical in corn oil. No adverse effects were observed in the dams throughout the study. Increased fetal mortality was accompanied by decreases in the number of live fetuses and fetal bwts at doses of 300 mg/kg/day. No external abnormalities were observed at any dose level. An increase in cardiovascular abnormalities, primarily VSD, an increase in wavy ribs and a decrease in the number of ossified sacrococcygeal vertebral bodies was observed at 300 mg/kg/day. Based on these results, a maternal NOAEL of 300 mg/kg/day and a developmental NOAEL of 30 mg/kg/day are proposed.

To measure the dermal penetration of flumioxazin under the conditions of the dermal teratology study, 13–day pregnant rats were dermally exposed to (phenyl-^{14}C) flumioxazin. The systemic absorption ranged from 3.8% at 2 hours to 6.9% of the recovered ^{14}C at 48 hours.

ii. *Mechanistic studies.* A series of scientific studies were conducted to examine the mechanism and species differences in the production of developmental toxicity by flumioxazin. This research demonstrates clear species differences between rats, rabbits, mice, and (*in vitro*) humans and indicates a high degree of correlation between the interruption of heme synthesis and the production of developmental toxicity in rats. The data support that the rat is a conservative model for use in the risk assessment for humans. Specifically the studies demonstrate that:

- Flumioxazin interferes with normal heme biosynthesis resulting in sidroblastic anemia and porphyria in adult rats.
- ^{14}C-Flumioxazin administered to pregnant rats on day 12 of gestation crosses the placenta and reaches the rat fetus at maximum levels of radiocarbon (and flumioxazin), 4 hours later.
- No clear pattern of adsorption, distribution, metabolism, or excretion was evident which could account for the species-specific development toxicity in rats.
- The critical period of sensitivity to the developmental effects of flumioxazin in rats is day 12 of gestation. This correlates with the peak period of protoporphyrin IX (PPIX) accumulation in maternal rat liver and the rat fetus.
- A histological examination of rat fetus indicated signs of fetal anemia within 6 hours after dosing, but no histological changes in the fetal rat heart were observed until 36 or 48 hour after treatment. No effects were observed in rabbit fetus treated in the same manner as the rats.
- Other observations in the pathogenesis of the developmental effects of flumioxazin in rat fetuses included; enlarged heart, edema, anemia, (decreased red blood cell count, and hemoglobin), delayed closure of the interventricular foramen, reduced serum protein, and incomplete/delayed ossification of the ribs.
- The observation of enlarged heart, edema, and anemia preceding the occurrence of fetal mortality suggest these effects may be instrumental in the cause of fetal deaths.
- The occurrence of an enlarged heart preceding the failure of interventricular foramen closure could be related to the pathogenesis rather than a direct toxic effect of flumioxazin on cardiac tissue.
- A strong correlation exists between PPIX accumulation, an indicator of disrupted heme synthesis, and developmental toxicity. Evidence of this correlation exists on the basis of species differences between rats and rabbits; the critical period of sensitivity in the rat; and compound-specific differences with two chemicals structurally related to flumioxazin, one which produces developmental effects in rats and one which does not.

iii. *Rabbits.* In a pilot dose range-finding study in rabbits, flumioxazin technical was administered to rabbits on days 7 through 19 of gestation via oral intubation at dosages of 0, 300, 500, 1,000, and 1,500 mg/kg/day. Clinical observations were recorded and on day 29 of gestation, all does were sacrificed, caesarean sectioned, and examined for gross lesions, number of corpora lutea, and number and placement of implantation sites, early and late resorptions and live and dead fetuses. No deaths, abortions, or premature deliveries occurred during this study. Dosages of flumioxazin technical as high as 1,500 mg/kg/day did not result in significant clinical or necropsy observations nor affect maternal bwt gains or feed consumption values. Similarly, there were no adverse effects of dosages of flumioxazin technical up to 1,500 mg/kg/day on embryo-fetal viability, sex ratios, body weights or external morphology.

Based on these results, pregnant rabbits were administered 0, 300, 1,000, or 3,000 mg/kg/day of flumioxazin technical on days 7–19 of gestation by oral gavage. The highest dose was well in excess of the 1,000 mg/kg/day limit dose for developmental toxicity studies. The 3,000 mg/kg/day dosage tended to reduce maternal bwt gains and relative and absolute feed consumption values. No gross lesions were produced at any dose level. The 3,000 mg/kg/day dosage group litters tended to have reduced fetal bwts but these differences were not statistically different. No fetal external, soft tissue, or skeletal malformations or variants were attributable to the test substance. Based on the data, the maternal NOAEL was 1,000 mg/kg/day and the developmental NOAEL was 3,000 mg/kg/day.

iv. *Reproduction.* Two pilot range-finding rat reproduction studies were conducted with flumioxazin technical at dosages from 100 to 5,000 ppm in the diet. In the definitive 2–generation reproduction study in the rat dietary levels of 0, 50, 100, 200, and 300 ppm established a systemic NOAEL of 200 ppm based on increased clinical signs (both sexes and generations); mortality, gross, and histopathology findings in the liver (F_1 females); decreased body weight/weight w/w gain (F_0 and F_1 females during gestation, F_1 males during premating) and decreased food consumption (F_0 and F_1 females during lactation). The reproductive NOAEL of 100 ppm was mainly based on developmental toxicity at 200 ppm. Observed at 200 ppm were a decreased number of liveborn pups and reduced pup bwts. At 300 ppm the following effects were observed: decreased pup bwt (both generations); decreased number of live pups/litter and viability index (both generations); increased incidence of abnormalities of the reproductive organs (predominately atrophied or hypoplastic testes and/or epididymides in F_1 males); decreased gestation index (F_0 females); decreased

mating and fertility indices (F_1 males) and increased clinical signs (F_1 pups).

4. *Subchronic toxicity*. Subchronic toxicity studies conducted with flumioxazin technical in the rat (oral and dermal), mouse and dog indicate a low level of toxicity. Effects observed at high dose levels consisted primarily of anemia and histological changes in the spleen, liver and bone marrow related to the anemia.

i. *Rats*. A 90–day subchronic toxicity study was conducted in rats, with dietary intake levels of 0, 30, 300, 1,000 and 3,000 ppm flumioxazin technical (98.4% purity). The NOAEL of 300 ppm was based on decreased bwts; anemia; increases in absolute and/or relative liver, kidney, brain, heart, and thyroid weights, and histological changes in the spleen, liver, and bone marrow related to the anemia.

A second 90–day subchronic toxicity study was conducted with a sample of flumioxazin technical of typical purity (94.8%) at dietary concentrations of 0, 30, 300, 1,000, and 3,000 ppm. The NOAEL was 30 ppm based on anemia and related hematological changes; increases in liver, heart, kidney, and thyroid weights; and histological changes in the spleen, liver, and bone marrow related to the anemia.

ii. *Mice*. Dose levels for the mouse oncogenicity study were selected on the basis of results from a 4–week study of flumioxazin in the diets of mice at levels of 0, 1,000, 3,000, and 10,000 ppm. In this range-finding study, increases in absolute and/or relative liver weights were noted for males at 10,000 ppm, and at 3,000, and 10,000 ppm for females.

iii. *Dogs*. A 90–day study was conducted in dogs given gelatin capsules containing 0, 10, 100, or 1,000 mg/kg/day. The NOAEL of 10 mg/kg/day for this study was based on a slight prolongation of activated partial thromboplastin time; increased total cholesterol and phospholipid and elevated alkaline phosphatase activity; increased absolute and relative liver weights; and histological changes in the liver.

iv. A 21–day dermal toxicity study was conducted in rats at dose levels of 0, 100, 200, or 1,000 mg/kg/day. The NOAEL was determined to be 300 mg/kg/day based on significantly decreased hemoglobin and hematocrit values for females.

5. *Chronic toxicity*. Flumioxazin technical has been tested in chronic studies with dogs, rats and mice. Valent proposes a chronic oral endpoint of 1.8 mg/kg bw/day, based on the NOAEL for male rats in the 2–year chronic toxicity oncogenicity feeding study.

i. *Rats*. In a 2–year study in rats, flumioxazin technical administered in the diet at levels of 0, 50, 500, and 1,000 ppm produced anemia and chronic nephropathy in rats of the 500 and 1,000 ppm groups. The anemia lasted throughout the treatment period, however, it was not progressive nor aplastic in nature. No evidence of an oncogenic effect was observed in rats and the NOAEL for this study was 50 ppm (1.8 mg/kg/day for males and 2.2 mg/kg/day for females).

ii. *Mice*. Flumioxazin technical was administered to mice at doses of 0, 300, 3,000, and 7,000 ppm in diet for 78 weeks. An increased incidence of hypertrophy of centrilobular hepatocytes was observed in males of the 3,000 and 7,000 ppm groups. Increases in the incidence of diffuse hypertrophy and single cell necrosis of hepatocytes were observed in females of the 3,000 and 7,000 ppm groups. There was no evidence of any treatment-related effect on the incidence of tumors. Flumioxazin technical was not carcinogenic to mice, and the NOAEL for this study was 300 ppm (31.1 mg/kg/day for males and 36.6 mg/kg/day for females).

iii. *Dogs*. Flumioxazin technical was administered to dogs in capsules at daily doses of 0, 10, 100, and 1,000 mg/kg bwt/day for one year. Treatment-related changes in blood biochemistry included increased total cholesterol and phospholipid values, elevated *alpha*-2-globulin ratio at 1,000 mg/kg/day and increased alkaline phosphatase activity in the 100 and 1,000 mg/kg/day groups. The absolute and/or relative liver weights were elevated in one animal in the 100 mg/kg/day group and four animals of the 1,000 mg/kg/day group. Minimal treatment-related histological changes were noted in the livers of animals at the 1,000 mg/kg/day group. Based on these data the NOAEL was determined to be 10 mg/kg/day.

iv. *Carcinogenicity*. Flumioxazin is not a carcinogen. Adequately designed studies with both rats and mice have shown that repeated high dose exposures produced anemia, liver effects, and nephropathy, but did not produce cancer in test animals. No oncogenic response was observed in a rat 2–year chronic feeding/oncogenicity study or in a 78 week study on mice. Valent anticipates that the oncogenicity classification of flumioxazin will be ''E'' (no evidence of carcinogenicity for humans).

6. *Animal metabolism*. The absorption, tissue distribution, metabolism and excretion of phenyl–^{14}C-labeled flumioxazin were studied in rats after single oral doses of 1 or 100 mg/kg, and after a single oral dose of 1 mg/kg following 14 daily oral doses at 1 mg/kg of unlabelled material. For all dose groups, most (97.9–102.3%) of the administered radiolabel was excreted in the urine and feces within seven days after radiolabeled test material dosing. Radiocarbon tissue residue levels were generally low on the seventh day post-dosing. Radiocarbon residues were higher in blood cells than tissues. Tissue ^{14}C-residue levels, including those for fat, were lower than blood levels which suggests little potential for bioaccumulation. Urinary radiocarbon excretion was greater in females than males in all dose groups.

Flumioxazin was extensively metabolized by rats and 35 metabolites were detected and quantitated. The main metabolic reactions in rats were:

- Hydroxylation of the tetrahydrophthalimide moiety.
- Incorporation of the sulfonic acid group into the tetrahydrophthalimide moiety.
- Cleavage of the imide linkage.
- Cleavage of the benzoxazinoneamide.
- Acetylation of the aniline nitrogen group.

7. *Metabolite toxicology*. Metabolism studies of flumioxazin in rats, goats, hens, soybeans, and peanuts, as well as the fish bioaccumulation study demonstrate that the parent is very rapidly metabolized and, in animals, eliminated. The metabolites detected and quantified from plants and animals show that there are no significant aglycones in plants which are not also present in the excreta or tissues of animals. Because parent and metabolites are not retained in the body, the potential for acute toxicity from *in situ* formed metabolites is low. The potential for chronic toxicity is adequately tested by chronic exposure to the parent at the MTD and consequent chronic exposure to the internally formed metabolites.

8. *Endocrine disruption*. No special studies to investigate the potential for estrogenic or other endocrine effects of flumioxazin have been performed. However, as summarized above, a large and detailed toxicology data base exists for the compound including studies in all required categories. These studies include acute, sub-chronic, chronic, developmental, and reproductive toxicology studies including detailed histology and histopathology of numerous tissues, including endocrine organs, following repeated or long term exposures. These studies are considered capable of revealing endocrine effects. The results of all of these studies show no evidence of any endocrine-mediated effects and no pathology of the

endocrine organs. Consequently, it is concluded that flumioxazin does not possess estrogenic or endocrine disrupting properties.

C. Aggregate Exposure

1. *Dietary exposure*. A full battery of toxicology testing including studies of acute, chronic, oncogenicity, developmental, mutagenicity, and reproductive effects is available for flumioxazin. EPA has not had the opportunity to review all of the toxicity studies on flumioxazin and has not established toxic endpoints. Thus, in these risk assessments Valent proposes as chronic oral toxic endpoint the NOAEL for males from the rat chronic/oncogenicity feeding study, 1.8 mg/kg/day; and as the acute oral toxic endpoint the NOAEL (proposed by EPA) from the rat oral developmental toxicity study of 3.0 mg/kg/day. Because the acute oral endpoint is for fetal toxicity to rats, Valent has chosen to use the full, extra 10X uncertainty factor for appropriate sub-groups of the population as mandated by FQPA.

i. *Food*. a. Acute dietary exposure to flumioxazin residues was calculated for the U.S. population, women 13 years and older, and 5 children subgroups. The calculated exposure values are very conservative because tolerance-level residues and 100% of the crop treated are assumed. The calculated exposures and margins of exposure (MOE) for the higher exposed proportions of the subgroups are listed below. In all cases, margins of exposure relative to the acute endpoint from the rat oral developmental toxicity study exceed 1–thousand.

Tier I Calculated Acute Dietary Exposures to the Total U.S. Population and Selected Sub-Populations to Flumioxazin Residues in Food.

		Population subgroup	95th Percentile	99.9th Percentile
	Exposure (mg/kg/day)	MOE	Exposure (mg/kg/day)	MOE
Total U.S. population	0.000226	13,260	0.000791	3,791
Women 13 years and older	0.000146	20,592	0.000379	7,916
Children 7 to 12 years	0.000295	10,165	0.000758	3,956
Children 1 to 6 years	0.000397	7,559	0.000937	3,202
All infants	0.000801	3,744	0.001414	2,121
Non-nursing infants (<1–year old)	0.000861	3,483	0.001417	2,117
Nursing infants (<1–year old)	0.000338	8,877	0.001244	2,411

b. Chronic dietary exposures to flumioxazin residues was calculated for the U.S. population and 25 population subgroups. This Tier I analysis assumes tolerance-level residues and 100% of the crops treated. The results from several representative subgroups are listed below. All calculated chronic dietary exposures were below 13% of the c-PAD. The c-PAD was defined as the NOAEL from the rat oral 2–year combined chronic toxicity oncogenicity study (1.8 mg/kg/day for males) divided by the 100X UF for the adult exposures (0.018 mg/kg/day), or divided by 1,000 to include the extra 10X uncertainty factor for adult females of child-bearing age and infant and children population subgroups (0.0018 mg/kg/day). Generally speaking, the Agency has no cause for concern if total residue contribution for published and proposed tolerances is less than 100% of the c-PAD.

Tier I Calculated Chronic Dietary Exposures to the Total U.S. Population and Selected Sub-Populations to Flumioxazin Residues in Food.

RESULTS OF CHRONIC DIETARY EXPOSURE ESTIMATE

Population Subgroup	Exposure (mg/kg/day)	Percent of c-PAD
Total U.S. population (total) (0.018)*	0.000075	0.42
Females 13 + (nursing) (0.0018)*	0.000053	2.94
Females 13 + (preg/not nursing) (0.0018)*	0.000070	3.89
Children 7–12 yrs (0.018)*	0.000132	0.73
Children 1–6 yrs (0.0018)*	0.000163	9.06
All infants (<1 year) (0.0018)*	0.000190	10.56
Non-nursing infants (0.0018)*	0.000229	12.72
Nursing infants (0.0018)*	0.000058	3.22

* C-PAD value used to calculate percent of occupancy.

ii. *Drinking water*. Since flumioxazin is applied outdoors to growing agricultural crops, the potential exists for the parent or its metabolites to reach ground or surface water that may be used for drinking water. Because of the physical properties of flumioxazin, it is unlikely that flumioxazin or its metabolites can leach to potable groundwater. To quantify potential exposure from drinking water, surface water concentrations for flumioxazin were estimated using generic expected environmental concentration (GENEEC) 1.2. Because K_{OC} could not be measured directly in adsorption-desorption studies because of chemical stability, GENEEC values representative of a range of K_{OC} values were modeled. The simulation that was selected for these exposure estimates used a K_{OC} of 150, indicating high mobility. The peak GENEEC concentration predicted in the simulated pond water was 12.59 parts per billion (ppb). Using standard assumptions about body weight and water consumption, the acute exposure from this drinking water would be 0.00036 and 0.0013 mg/kg/day for adults and children, respectively. The 56–day GENEEC concentration predicted in the simulated pond water was 0.45 ppb. Chronic exposure from this drinking water would be 0.0000129 and 0.000045 mg/kg/day for adults and children, respectively; 2.5% of the c-PAD of 0.0018 mg/kg/day for children.

Based on this worse case analysis, the contribution of drinking water to the dietary exposure is comparable to that from food, but the risk is still negligible.

2. *Non-dietary exposure*. Flumioxazin is proposed only for agricultural uses and no homeowner, turf, or industrial uses. Thus, no non-dietary risk assessment is needed.

D. Cumulative Effects

Section 408(b)(2)(D)(v) requires that the Agency must consider ''available information'' concerning the cumulative effects of a particular pesticide's residues and ''other substances that have a common mechanism of toxicity.'' Available information in this context include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodologies to resolve the complex scientific issues concerning common mechanism of toxicity in a meaningful way.

There are other pesticidal compounds that are structurally related to flumioxazin and have similar effects on animals. In consideration of potential cumulative effects of flumioxazin and other substances that may have a common mechanism of toxicity, there are currently no available data or other reliable information indicating that any toxic effects produced by flumioxazin would be cumulative with those of other chemical compounds. Thus, only the potential risks of flumioxazin have been considered in this assessment of aggregate exposure and effects.

Valent will submit information for EPA to consider concerning potential cumulative effects of flumioxazin consistent with the schedule established by EPA in the **Federal Register** at 62 FR 42020 (August 4, 1997), FRL–5734–6 and other subsequent EPA publications pursuant to the Food Quality Protection Act (FQPA).

E. Safety Determination

The FQPA of 1996 introduced a new standard of safety, a reasonable certainty of no harm. To make this determination, at this time the Agency should consider only the incremental risk of flumioxazin in its exposure assessment. Since the potential chronic and acute exposures to flumioxazin are small (<<100% of c-PAD, MOE >>1,000) the provisions of the FQPA of 1996 will not be violated.

1. *U.S. population*—i. *Acute risk*: The potential acute exposure from food to the U.S. population and various non-child/infant population subgroups (shown above) provide MOE values exceeding 1,000. Addition of the worse case, but small ''background'' dietary exposure from water reduces the MOE value at the 99.9th percentile from 3,791 to 2,606. In a conservative policy, the Agency has no cause for concern if total acute exposure to adults calculated for the 99.9th percentile yields a MOE of 100 or larger. For Women of child bearing age where a MOE of 1,000 or larger is appropriate, the addition of water to the diet of women, 13 years and older, reduces the MOE (99.9th percentile) from 20,592 to 7,916. It can be concluded that there is a reasonable certainty that no harm will result to the overall U.S. population and many non-child/infant subgroups from aggregate, acute exposure to flumioxazin residues.

ii. *Chronic risk*. Using the dietary exposure assessment procedures described above for flumioxazin, calculated chronic dietary exposure resulting from residue exposure from proposed uses of flumioxazin is minimal. The estimated chronic dietary exposure from food for the overall U.S. Population and many non-child/infant subgroups is 0.42 to 3.89% of the appropriate c-PAD. Addition of the small but worse case potential exposure from drinking water (calculated above) increases exposure by 0.000013 mg/kg /day and the maximum occupancy of the c-PAD from 3.89% to 5.22% (women 13 +). Generally, the Agency has no cause for concern if total residue contribution is less than 100% of the appropriate c-PAD. It can be concluded that there is a reasonable certainty that no harm will result to the overall U.S. Population and many non-child/infant subgroups from aggregate, chronic exposure to flumioxazin residues.

2. *Infants and children—Safety factor for infants and children*. In assessing the potential for additional sensitivity of infants and children to residues of flumioxazin, FFDCA section 408 provides that EPA shall apply an additional margin of safety, up to ten-fold, for added protection for infants and children in the case of threshold effects unless EPA determines that a different margin of safety will be safe for infants and children.

i. *Children*. The toxicological data base for evaluating prenatal and postnatal toxicity for flumioxazin is complete with respect to current data requirements. Developmental toxicity was observed by both oral and dermal routes in rats. Therefore, reliable data support use of the standard 100–fold UF and an additional UF of 10X for flumioxazin to be further protective of infants and children.

ii. *Developmental toxicity studies*. Flumioxazin shows developmental toxicity in the absence of maternal toxicity in rats. Mechanistic studies demonstrate that the effect is specifically related to the inhibition of heme synthesis, that the effect shows considerable species specificity, and that the rat is a conservative surrogate species for the potential for developmental toxicity in man. No developmental toxicity was observed in rabbits. Developmental toxicity to the pups was seen in the rat reproduction study at doses that were not toxic to the parental animals.

a. *Rats*. In the definitive rat oral developmental toxicity study, pregnant rats were administered oral doses of 0, 1, 3, 10, or 30 mg/kg/day of flumioxazin technical on days 6 through 15 of gestation. No maternal deaths were observed at any dosage and no treatment-related effects on clinical signs or food consumption were noted. A decrease in maternal body weight gain was found at 30 mg/kg/day. The number of live fetuses and fetal body weights were decreased in the 30 mg/kg/day group and the incidence of embryo mortality tended to be higher but was not statistically significant. No effects on the number of implantations, sex ratios, or external abnormalities were found. The incidence of fetuses with cardiovascular abnormalities, primarily VSD, was increased in the 30 mg/kg/day group. Other developmental effects observed at 30 mg/kg/day included an increase in the incidence of wavy ribs and curvature of the scapula, and a decrease in the number of ossified sacrococcygeal vertebral bodies. Based on these findings, a maternal NOAEL of 30 mg/kg/day and a developmental NOAEL of 3 mg/kg/day are proposed.

On days 6–15 of gestation, pregnant rats were exposed dermally to dose levels of 30, 100, or 300 mg/kg/day of flumioxazin technical in corn oil. No adverse effects were observed in the dams throughout the study. Increased fetal mortality was accompanied by decreases in the number of live fetuses and fetal body weights at doses of 300 mg/kg/day. No external abnormalities were observed at any dose level. An increase in cardiovascular abnormalities, primarily VSD, an increase in wavy ribs and a decrease in the number of ossified vertebral bodies was observed at 300 mg/kg/day. Based on these results, a maternal NOAEL of

300 mg/kg/day and a developmental NOAEL of 30 mg/kg/day are proposed.

To measure the dermal penetration of flumioxazin under the conditions of the dermal teratology study, 13–day pregnant rats were dermally exposed to (phenyl-^{14}C) flumioxazin. The systemic absorption ranged from 3.8% at 2 hours to 6.9% of the recovered ^{14}C at 48 hours.

b. *Mechanistic studies.* A series of scientific studies were conducted to examine the mechanism and species differences in the production of developmental toxicity by flumioxazin. This research demonstrates clear species differences between rats, rabbits, mice, and (*in vitro*) humans and indicates a high degree of correlation between the interruption of heme synthesis and the production of developmental toxicity in rats. The data support that the rat is a conservative model for use in the risk assessment for humans. Specifically the studies demonstrate that:

• Flumioxazin interferes with normal heme biosynthesis resulting in sidroblastic anemia and porphyria in adult rats.

• ^{14}C-Flumioxazin administered to pregnant rats on day 12 of gestation crosses the placenta and reaches the rat fetus at maximum levels of radiocarbon (and flumioxazin), 4 hours later.

• No clear pattern of adsorption, distribution, metabolism, or excretion was evident which could account for the species-specific development toxicity in rats.

• The critical period of sensitivity to the developmental effects of flumioxazin in rats is day 12 of gestation. This correlates with the peak period of protoporphyrin IX (PPIX) accumulation in maternal rat liver and the rat fetus.

• A histological examination of rat fetus indicated signs of fetal anemia within 6 hours after dosing, but no histological changes in the fetal rat heart were observed until 36 or 48 hour after treatment. No effects were observed in rabbit fetus treated in the same manner as the rats.

• Other observations in the pathogenesis of the developmental effects of flumioxazin in rat fetuses included; enlarged heart, edema, anemia, (decreased red blood cell count and hemoglobin), delayed closure of the interventricular foramen, reduced serum protein and incomplete/delayed ossification of the ribs.

• The observation of enlarged heart, edema, and anemia preceding the occurrence of fetal mortality suggest these effects may be instrumental in the cause of fetal deaths.

• The occurrence of an enlarged heart preceding the failure of interventricular foramen closure could be related to the pathogenesis rather than a direct toxic effect of flumioxazin on cardiac tissue.

• A strong correlation exists between PPIX accumulation, an indicator of disrupted heme synthesis, and developmental toxicity. Evidence of this correlation exists on the basis species differences between rats and rabbits; the critical period of sensitivity in the rat; and compound-specific differences with two chemicals structurally related to flumioxazin, one which produces developmental effects in rats and one which does not.

c. *Rabbits.* Pregnant rabbits were administered 0, 300, 1,000, or 3,000 mg/kg/day of flumioxazin technical on days 7–19 of gestation by oral gavage. The highest dose was well in excess of the 1,000 mg/kg/day limit dose for developmental toxicity studies. The 3,000 mg/kg/day dosage tended to reduce maternal body weight gains and relative and absolute feed consumption values. No gross lesions were produced at any dose level. The 3,000 mg/kg/day dosage group litters tended to have reduced fetal body weights but these differences were not statistically different. No fetal external, soft tissue, or skeletal malformations or variants were attributable to the test substance. Based on these data, the maternal NOAEL was 1,000 mg/kg/day and the developmental NOAEL was 3,000 mg/kg/day.

iii. *Reproductive toxicity study.* In the 2–generation reproduction study in the rat dietary levels of 0, 50, 100, 200, and 300 ppm established a systemic NOAEL of 200 ppm based on increased clinical signs (both sexes and generations); mortality, gross and histopathology findings in the liver (F_1 females); decreased body weight/weight gain (F_0 and F_1 females during gestation, F_1 males during premating) and decreased food consumption (F_0 and F_1 females during lactation). The reproductive NOAEL of 100 ppm was mainly based on developmental toxicity at 200 ppm. Observed at 200 ppm were a decreased number of liveborn pups and reduced pup body weights. At 300 ppm the following effects were observed:

• Decreased pup body weight (both generations).

• Decreased number of live pups/litter and viability index (both generations).

• Increased incidence of abnormalities of the reproductive organs (predominately atrophied or hypoplastic testes and/or epididymides in F_1 males).

• Decreased gestation index (F_0 females).

• Decreased mating and fertility indices (F_1 males) and increased clinical signs (F_1 pups).

iv. *Prenatal and postnatal sensitivity.* Flumioxazin interferes with normal heme biosynthesis resulting in sidroblastic anemia and porphyria in adult rats. Clear species differences between rats, rabbits, mice, and (*in vitro*) humans were demonstrated. There is a high degree of correlation between the interruption of heme synthesis, consequent PPIX accumulation, and the production of developmental toxicity in rats. The data support that the rat is a conservative model for use in the risk assessment for humans.

v. *Acute exposure and risk.* The potential acute exposure from food to the various child and infant population subgroups (shown above) all provide MOE values exceeding 1,000. Addition of the worse case, but small ''background'' dietary exposure from water (0.00126 mg/kg/day) to the 99.9th percentile food exposure for infants reduces the MOE value from 2,117 to 1,121. In a conservative policy with the addition of the FQPA extra 10X UF, the Agency has no cause for concern if total acute exposure to infants and children calculated for the 99.9th percentile yields a MOE of 1,000 or larger. It can be concluded that there is a reasonable certainty that no harm will result to infants and children from aggregate, acute exposure to flumioxazin residues.

vi. *Chronic exposure and risk.* Using the conservative exposure assumptions described above, the percentage of the c-PAD that will be utilized by dietary (food only) exposure to residues of flumioxazin ranges from 0.73% for children 7–12 years, to 12.72% for non-nursing infants. Adding the worse case potential incremental exposure to infants and children from flumioxazin in drinking water (0.000045 mg/kg/day) increases the aggregate, chronic dietary exposure by 2.5%. The addition of the exposure attributable to drinking water increases the occupancy of the c-PAD for non-nursing infants to 15.22%. EPA generally has no concern for exposures below 100% of the c-PAD because the c-PAD, in this case including the extra 10X FQPA UF, represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. It can be concluded that there is a reasonable certainty that no harm will result to infants and children from aggregate, chronic exposure to flumioxazin residues.

vii. *Determination of safety—Safety determination summary.* Aggregate acute or chronic dietary exposure to various sub-populations of children and adults demonstrate acceptable risk. Chronic dietary exposures to flumioxazin occupy considerably less

than 100% of the appropriate c-PAD, and all acute dietary MOE values exceed 1,000. Chronic and acute dietary risk to children from flumioxazin should not be of concern. Further, flumioxazin has only agricultural uses and no other uses, such as indoor pest control, homeowner or turf, that could lead to unique, enhanced exposures to vulnerable sub-groups of the population. It can be concluded that there is a reasonable certainty that no harm will result to the U.S. population or to any sub-group of the U.S. population, including infants and children, from aggregate chronic or aggregate acute exposures to flumioxazin residues resulting from proposed uses.

F. International Tolerances

Flumioxazin has not been evaluated by the JMPR and there are no Codex maximum residue limits (MRL) for flumioxazin. MRL values have been established to allow the following uses of flumioxazin in the following countries.

Country	Crop	MRL (ppm)
Brazil	Soybean	0.05
Argentina	Soybean	0.015
	Sunflower	0.02
Paraguay	Soybean	0.015
South Africa	Soybean	0.02
	Groundnut	0.02

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ENVIRONMENTAL PROTECTION AGENCY

[OPP–50879; FRL–6765–2]

Experimental Use Permit; Cry1Ac Soybean Receipt of Application for Extension

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This notice announces receipt of an application 524–EUP–91 from Monsanto Company requesting an extension for an experimental use permit (EUP) for the *Bacillus thuringiensis* Cry1Ac protein and the genetic material necessary for its production (vectors PV-GMBT01 and PV-GMBT02) in soybean. The Agency has determined that the application may be of regional and national significance. Therefore, in accordance with 40 CFR 172.11(a), the Agency is soliciting comments on this application.

DATES: Comments, identified by docket control number OPP–50879, must be received on or before April 2, 2001.

ADDRESSES: Comments and data may be submitted by mail, electronically, or in person. Please follow the detailed instructions for each method as provided in Unit I. of the **SUPPLEMENTARY INFORMATION**. To ensure proper receipt by EPA, it is imperative that you identify docket control number OPP–50879 in the subject line on the first page of your response.

FOR FURTHER INFORMATION CONTACT: By mail: Alan Reynolds, Biopesticides and Pollution Prevention Division (7511C), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (703) 605–0515; e-mail address: *reynolds.alan@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

This action is directed to the public in general. This action may, however, be of interest to those persons interested in plant-pesticides or who are or may be required to conduct testing of chemical substances under the Federal Food, Drug and Cosmetic Act (FFDCA), or the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Since other entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any 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,'' ''Regulations and Proposed Rules,'' 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 OPP–50879. The official record consists of the documents specifically referenced in this action, 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 Hwy., 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 OPP–50879 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, 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 Hwy., 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 OPP–50879. Electronic comments may also be filed online at many Federal Depository Libraries.