uses. However, given the extremely low vapor pressure of lambda-cyhalothrin (1.5×10^{-9} millimeters of Hg) and the low use rates, it is anticipated that inhalation and dermal exposure from these uses will be insignificant.

D. Cumulative Effects

At this time, Zeneca cannot make a determination based on available and reliable information that lambda-cyhalothrin and other substances that may have a common mechanism of toxicity would have cumulative effects. Therefore for purposes of these tolerances it is appropriate only to consider the potential risks of lambda-cyhalothrin in an aggregate exposure assessment.

E. Safety Determination

The acceptable Reference Dose (RfD) based on a NOEL of 0.1 mg/kg/body weight/day from the chronic dog study and a safety factor of 100 is 0.001 mg/kg/body weight/day. A chronic dietary exposure/risk assessment has been performed for lambda-cyhalothrin using the above RfD. Available information on anticipated residues and percent crop treated was incorporated into the analysis to estimate the Anticipated Residue Contribution (ARC) for all existing and the proposed tolerances. The ARC is generally considered a more realistic estimate than an estimate based on tolerance level residues.

1. *US population.* The ARC from established tolerances and the current and pending actions are estimated to be 0.000310 mg/kg/bwt/day and utilize 31.04 per cent of the RfD for the U.S. population.

2. *Infants and children.* The ARC for children, aged 1 to 6 years old, and nonnursing infants (subgroups most highly exposed) utilizes 60 and 67% of the RfD, respectively. Generally speaking, the Agency has no cause for concern if anticipated residues contribution for all published and proposed tolerances is less than the RfD.

F. International Tolerances

There are no Codex maximum residue levels [MRL] established for residues of lambda-cyhalothrin in or on alfalfa hay, forage, leaf lettuce, or Brassica crop subgroup. (George LaRocca)

[FR Doc. 97–18256 Filed 7–10–97; 8:45 am]
BILLING CODE 6560–50–F

ENVIRONMENTAL PROTECTION AGENCY

[PF–741; FRL–5723–1]

Notice of Filing of Pesticide Petitions

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

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

DATES: Comments, identified by the docket control number PF–741, must be received on or before August 11, 1997.

ADDRESSES: By mail submit written comments to: Public Response and Program Resources Branch, Field Operations Division (7505C), Office of Pesticides Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. In person bring comments to: Rm. 1132, CM #2, 1921 Jefferson Davis Highway, Arlington, VA.

Comments and data may also be submitted electronically by following the instructions under ''SUPPLEMENTARY INFORMATION.'' No confidential business information should be submitted through e-mail.

Information submitted as a comment concerning this document may be claimed confidential by marking any part or all of that information as ''Confidential Business Information'' (CBI). CBI should not be submitted through e-mail. Information marked as CBI will not be disclosed except in accordance with procedures set forth in 40 CFR part 2. A copy of the comment that does not contain CBI must be submitted for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice. All written comments will be available for public inspection in Rm. 1132 at the address given above, from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays.

FOR FURTHER INFORMATION CONTACT: The product manager listed in the table below:

Product Manager	Office location/telephone number	Address
George LaRocca (PM 13).	Rm. 204, CM #2, 703–305–6100, e-mail:.@epamail.epa.gov.	1921 Jefferson Davis Hwy, Arlington, VA
Mary Waller (PM 21)	Rm. 265, CM #2, 703–308–9354, e-mail:waller.mary@epamail.epa.gov.	Do.
Cynthia Giles-Parker (PM 22).	Rm. 229, CM #2, 703–305–5540, e-mail: giles-parker.cynthia@epamail.epa.gov.	Do.

SUPPLEMENTARY INFORMATION: EPA has received pesticide petitions as follows proposing the establishment and/or amendment of regulations for residues of certain pesticide chemicals in or on various raw food commodities under section 408 of the Federal Food, Drug, and Comestic Act (FFDCA), 21 U.S.C. 346a. EPA has determined that these petitions contain data or information regarding the elements set forth in section 408(d)(2); however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

The official record for this notice, as well as the public version, has been established for this notice of filing under docket control number PF–741 (including comments and data submitted electronically as described below). A public version of this record, including printed, paper versions of electronic comments, which does not include any information claimed as CBI, is available for inspection from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The official record is located at the address in ''ADDRESSES''.

Electronic comments can be sent directly to EPA at:
opp-docket@epamail.epa.gov

Electronic comments must be submitted as an ASCII file avoiding the use of special characters and any form of encryption. Comment and data will also be accepted on disks in Wordperfect 5.1 file format or ASCII file format. All comments and data in electronic form must be identified by the docket control number PF–741 and appropriate petition number. Electronic comments on this notice may be filed online at many Federal Depository Libraries.

Authority: 21 U.S.C. 346a.

List of Subjects

Environmental protection, Agricultural commodities, Food

additives, Feed additives, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: July 2, 1997.

Peter Caulkins,

Acting Director, Registration Division, Office of Pesticide Programs.

Summaries of Petitions

Below petitioner summaries of the pesticide petitions are printed as required by section 408(d)(3) of the FFDCA. The summaries of the petitions were prepared by the petitioners and represent the views of the petitioners. EPA is publishing the petition summaries verbatim without editing them in any way. The petition summary announces the availability of a description of the analytical methods available to EPA for the detection and measurement of the pesticide chemical residues or an explanation of why no such method is needed.

1. ISK Biosciences Corporation

PP 6F4611

EPA has received a pesticide petition (PP 6F4611, (dated 6/25/95) from ISK Biosciences Corporation (''ISK''), 5966 Heisley Road, P.O. Box 8000, Mentor, Ohio 44061–8000 proposing pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. section 346a(d), to amend 40 CFR part 180.275 by establishing tolerances for residues of 4-hydroxy-2,5,6-trichloroisophthalonitrile (SDS–3701), a metabolite of the fungicide chlorothalonil, in/on raw agricultural meat and milk commodities as follows:

Commodity	Parts per million
Cattle, fat	0.1
Cattle, kidney	0.5
Cattle, meat	0.03
Cattle, mbyp (except kidney)	0.05
Goats, fat	0.1
Goats, kidney	0.5
Goats, meat	0.03
Goats, mbyp (except kidney)	0.05
Hogs, fat	0.1
Hogs, kidney	0.5
Hogs, meat	0.03
Hogs, mbyp (except kidney)	0.05
Horses, fat	0.1
Horses, kidney	0.5
Horses, meat	0.03
Horses, mbyp (except kidney)	0.05
Milk	0.1
Sheep, fat	0.1
Sheep, kidney	0.5
Sheep, meat	0.03
Sheep, mbyp (except kidney)	0.05

A. Residue Chemistry

1. *Plant/Animal metabolism.* The nature of the residue of chlorothalonil in plants and animals, including ruminants, is adequately understood. Chlorothalonil is not systemic in plants. Chlorothalonil is rapidly metabolized in the ruminant and is not transferred in animals to meat and milk through dietary consumption of feedstuffs from crops treated with chlorothalonil products. Analytical method development studies and storage stability studies with chlorothalonil demonstrated that it is not stable in meat or milk. Studies have determined that the chlorothalonil metabolite, 4-hydroxy-2,5,6-trichloroisophthalonitrile, may be present in meat and milk from dietary intake of animal feed items from chlorothalonil treated crops. The metabolite, 4-hydroxy-2,5,6-trichloroisophthalonitrile, is stable in meat and milk.

2. *Analytical method.* The analytical method (electron capture gas chromatography) is adequate for analysis of 4-hydroxy-2,5,6-trichloroisophthalo-nitrile in meat and milk and has been submitted to the Agency for inclusion in PAM Vol. II. The method has undergone a successful method validation by an independent laboratory.

3. *Magnitude of the residues.* Residue studies and metabolism studies have shown that residues of chlorothalonil per se are not expected to transfer from feed items to meat/milk but residues of 4-hydroxy-2,5,6-trichloroisophthalonitrile could occur in these commodities both from direct transfer of residues of the metabolite found on feedstuffs in the diet and from a low percentage conversion of chlorothalonil to the metabolite in the animal. Due to the instability of chlorothalonil per se in meat and milk tissues, residues would not be expected to occur even from misuse of chlorothalonil. The chlorothalonil related residue found in meat and milk is 4-hydroxy-2,5,6-trichloroisophthalonitrile. The submitted lactating dairy cow feeding study is adequate to determine appropriate tolerance levels in meat and milk. Analytical results are supported by frozen storage stability data. No significant losses of 4-hydroxy-2,5,6-trichloroisophthalonitrile occurred during frozen storage of spiked analytical samples. Studies have shown that 4-hydroxy-2,5,6-trichloroisophthalonitrile does not persist long in animals and that it does not bioaccumulate in animal tissues.

The proposed tolerances are adequate to cover residues of 4-hydroxy-2,5,6-trichloroisophthalonitrile that might occur in meat and milk as a result of chlorothalonil uses on presently-registered crops that may involve animal feed items.

B. Toxicological Profile

The following studies on file with the Agency support this petition.

1. *Acute toxicity.* Acute toxicity studies include an acute oral rat study on technical chlorothalonil with an LD_{50} >10,000 mg/kg, an acute dermal toxicity study in the rabbit with an LD_{50} >20,000 mg/kg, a four-hour inhalation study with finely ground technical chlorothalonil resulting in a 4-hour LC_{50} of 0.092 mg/L (actual airborne concentration), a primary eye irritation study with irreversible eye effects in the rabbit at 21 days, a primary dermal irritation study showing technical chlorothalonil is not a dermal irritant, and a dermal sensitization study showing technical chlorothalonil is not a skin sensitizer.

Acute oral toxicity studies with the 4-hydroxy metabolite, indicate the oral LD_{50}s in male and female rats were 332 and 242 mg/kg respectively.

2. *Genotoxicity.* The mutagenic potential of chlorothalonil has been evaluated in a large number of studies covering a variety of endpoints. The overall conclusion is that chlorothalonil is not mutagenic.

Mutagenicity studies with chlorothalonil include gene mutation assays in bacterial and mammalian cells; *in vitro* and *in vivo* chromosomal aberration assays; DNA repair assays in bacterial systems; and cell transformation assays. All were negative with the following two exceptions:

a. Chlorothalonil was positive in an *in vitro* chromosomal aberration assay in (Chinese Hamster Ovary (CHO) cells without metabolic activation but was negative with metabolic activation.

b. In vivo chromosomal aberration studies in rats and mice were negative and one study in the Chinese hamster was equivocal. The results of this study could not be confirmed in a subsequent study at higher doses. The conclusion was that chlorothalonil does not cause chromosome aberrations in bone marrow cells of the Chinese hamster. It can be concluded that chlorothalonil

does not have clastogenic potential in intact mammalian systems.

In bacterial DNA repair tests, chlorothalonil was negative in *Bascillus subtilis*, but was positive in *Salmonella typhimurium*. In an *in vivo* DNA binding study in rats with 14C-chlorothalonil, there was no covalent binding of the radiolabel to the DNA of the kidney, the target organ for chlorothalonil toxicity in rodents.

c. The mutagenic potential of the 4-hydroxy metabolite has also been evaluated for a variety of endpoints and it is concluded that it is not mutagenic. The 4-hydroxy metabolite has been tested in gene mutations assays in bacterial and mammalian cells; *in vivo* and *in vitro* chromosome aberration studies; a DNA repair assay in the *Salmonella typhimurium*; and a cell transformation assay.

The 4-hydroxy metabolite was positive in only one assay, an *in vitro* chromosome aberration assay in CHO cells. *In vivo*, the 4-hydroxy metabolite was negative in a bone marrow chromosome aberration study in Chinese hamsters. Dominant lethal studies in rats and mice were clearly negative in rats and equivocal in mice. Because it was negative *in vivo* in studies to test for chromosome damage, it can be concluded that the 4-hydroxy metabolite does not have clastogenic potential in intact mammalian systems

3. *Developmental and reproductive toxicity. a.* A developmental toxicity study with rats given gavage doses of 0, 25, 100, and 400 mg/kg body weight/day of chlorothalonil from days 6 through 15 of gestation resulted in a no observed effect level (NOEL) for maternal toxicity of 100 mg/kg/day based on increased mortality, reduced body weight, and a slight increase in early resorptions at the highest dose. There were no developmental effects observed at any dose in this study.

b. A developmental toxicity study in rabbits given gavage doses of 0, 5, 10, or 20 mg/kg/day of chlorothalonil on days 7 through 19 of gestation resulted in a maternal NOEL of 10 mg/kg/day. Effects observed in the dams in the high-dose group were decreased body weight gain and reduced food consumption. There were no developmental effects observed in this study.

c. A two-generation reproduction study in rats fed diets containing 0, 500, 1,500 and 3,000 ppm of chlorothalonil resulted in a reproductive NOEL of 1,500 ppm (equivalent to 115 mg/kg/day) based on lower neonatal body weights by day 21.

There were no effects seen on any reproductive parameter at any dose level in this study.

d. A developmental toxicity study in rabbits receiving gavage doses of 0, 1, 2.5 or 5 mg/kg/day of the 4-hydroxy metabolite on days 6 through 18 of gestation resulted in a maternal NOEL of 2.5 mg/kg/day. Effects observed in the dams in the high-dose group were an increase in the number of females with dead or resorbed fetuses and in the number of aborted fetuses. There were no developmental effects observed in this study.

e. A three-generation reproduction study in rats fed diets containing 0, 10, 60 and 125 ppm of the 4-hydroxy metabolite, resulted in a NOEL of 10 ppm (equivalent to 0.5 mg/kg/day) based on lower neonatal body weights on days 14 and 21 of lactation. The reduction of pup growth at the two highest dose levels during the later part of the gestation period can be attributed to the direct ingestion of the adult diet by the pups which resulted in inordinately high doses (per kg of body weight) of the test material for the pups as compared to the adults. There were no effects seen on any reproductive parameter at any dose level in this study. The reproductive NOEL was the highest dose tested.

f. A one generation reproduction study in rats was conducted to further define the NOEL for the reduction in pup growth observed during lactation in the three generation reproduction study with the 4-hydroxy metabolite. Dietary levels of 0, 10, 20, 30, 60 and 120 ppm of the 4-hydroxy metabolite were fed to rats. Two litters, F1a and F1b were evaluated. The NOEL in this study was determined to be 30 ppm (equivalent to 1.5 mg/kg/day).

4. *Subchronic toxicity. a.* A subchronic toxicity study (90-days) was conducted in rats with chlorothalonil at doses of 0, 1.5, 3.0, 10 and 40 mg/kg bwt. Treatment-related hyperplasia and hyperkeratosis of the forestomach were observed at the two highest dose levels. Although the initial histopathological evaluation did not demonstrate any nephrotoxicity, a subsequent evaluation observed a treatment-related increase in hyperplasia of the proximal tubule epithelium at 40 mg/kg bwt. in the male rats but not in the females. The no effect level for renal histopathology was 10 mg/kg bwt. in males and 40 mg/kg bwt. in females.

b. A 90-day oral toxicity study was conducted in dogs with dose levels of technical chlorothalonil of 15, 150 and 750 mg/kg bwt./day. The two highest dosages resulted in lower body weight gain in male dogs. The NOAEL was 15 mg/kg/day. There were no macroscopic or microscopic tissue alterations related to chlorothalonil and there were no signs of renal toxicity.

c. A subchronic toxicity study (60-days) was conducted in rats with the 4-hydroxy metabolite at doses of 0, 10, 20, 40, 75, 125, 250, 500, and 750 mg/kg bwt. The NOEL was determined to be 20 mg/kg/day. Treatment-related effects observed at higher doses included changes in hematopoietic and clinical chemistry parameters, mild hemosiderosis, toxic hepatitis, and microscopic degeneration in several organs.

d. Two 21-day dermal toxicity studies have been conducted with technical chlorothalonil. In the initial study doses of 50, 2.5 and 0.1 mg/kg bwt./day were administered to rabbits. The NOEL for systemic effects was greater than 50 mg/kg bwt./day and the NOEL for dermal irritation was 0.1 mg/kg bwt./day.

e. A subsequent 21-day dermal study was conducted in male rats, to specifically evaluate the potential for nephrotoxicity in this laboratory species following dermal dosing. In this study the doses were 60, 100, 250 and 600 mg/kg bwt./day. The NOEL for nephrotoxicity was greater than 600 mg/kg bwt./day.

5. *Estrogenic effects.* Based upon all of the chronic toxicity, teratogenicity, mutagenicity and reproductive studies conducted with chlorothalonil and its metabolites, including the 4-hydroxy metabolite, there were no results which indicate any potential to cause estrogenic effects, or endocrine disruption. These effects would have manifested themselves in these studies as reproductive or teratogenic effects, or by producing histopathological changes in estrogen sensitive tissues such as the uterus, mammary glands or the testes. Thus, it can be concluded based upon the *in vivo* studies, that chlorothalonil does not cause estrogenic effects.

6. *Chronic toxicity. a.* A 12-month chronic oral toxicity study in Beagle dogs was conducted with technical chlorothalonil at dose levels of 15, 150 and 500 mg/kg/day. The NOAEL was 150 mg/kg/day based on lower blood albumin levels at the highest dose. There was no nephrotoxicity observed at any dose in this study. This study replaced an old outdated study that was not conducted under current guidelines and did not use the current technical material.

b. A chronic feeding/carcinogenicity study with Fischer 344 rats at dose levels of 0, 40, 80 or 175 mg/kg/day of technical chlorothalonil for 116 weeks in males or 129 weeks in females, resulted in a statistically higher incidence of combined renal adenomas and carcinomas. At the high dose,

which was above the MTD, there was also a statistically significant higher incidence of tumors of the forestomach in female rats.

c. In a second chronic feeding/carcinogenicity study with technical chlorothalonil in Fischer 344 rats, designed to define the NOEL for tumors and the preneoplastic hyperplasia, animals were fed diets which resulted in dose levels of 0, 2, 4, 15 or 175 mg/kg/day. The NOEL in this study, based on renal tubular hyperplasia, was a nominal dose of 2 mg/kg bwt./day. Because of the potential for chlorothalonil to bind to diet, the 2 mg/kg bwt./day dose, expressed as unbound chlorothalonil is 1.8 mg/kg bwt./day. The NOEL for hyperplasia and hyperkeratosis of the forestomach was 4 mg/kg bwt./day or a dose of 3.8 mg/kg bwt./day based on unbound chlorothalonil.

d. A 2-year carcinogenicity study, conducted in CD-1 mice with technical chlorothalonil at dietary levels of 0, 750 and 1,500 or 3,000 ppm (equivalent to 0, 107, 214 or 428 mg/kg/day), resulted in a statistically higher incidence of squamous cell carcinoma of the forestomach in both sexes, and a statistically higher incidence of combined renal adenoma/carcinoma in only the male mice receiving the low dose. There were no renal tumors in any female mouse in this study.

e. A 2-year carcinogenicity study in male CD-1 mice for the purpose of establishing the no effect level for renal and forestomach effects associated with technical chlorothalonil, was conducted at dietary levels of 0, 10/15, 40, 175, or 750 ppm (equivalent to 0, 1.4/2.1, 5.7, 25 or 107 mg/kg/day). The NOEL level for renal effects was 40 ppm and the NOEL for forestomach effects was 15 ppm. This study did not duplicate the results from the previous study where a statistically higher incidence of renal tumors, when compared to controls, was observed at 750 ppm. No tumors were observed at this dose level in this study.

f. A chronic feeding/carcinogenicity study with CD rats at doses of 0, 0.5, 3.0, 15, or 30 mg/kg/day has been conducted with the 4-hydroxy metabolite. Because of the severity of the toxicity observed during the first six months of the study, the two highest dose levels were reduced to 10 and 20 mg/kg/day. The animals receiving the highest dose were terminated at 12 months. There were no neoplastic effects at any dose level and the NOEL for chronic toxicity was 3 mg/kg/day. At the higher dose levels, the treatment related effects included microcytic anemia with an increased number of reticulocytes and metarubricytes, hypocellular bone marrow, hemosiderin deposition in liver and bone marrow and serum biochemistry changes and degenerative tissue changes related to hypoxia.

g. A carcinogenicity study in CD-1 mice was conducted at dietary levels of 0, 375, 750 and 1500 ppm of the 4-hydroxy metabolite. The mean body weights of the high dose males and females were 4-15% and 5-18% lower, respectively, when compared to controls. Liver weights were also higher at the highest dietary level. There was no increase in the incidence of any malignant or benign tumor at any dose in this study.

In 1987, the Office of Pesticide Programs' Toxicology Branch Peer Review Committee classified chlorothalonil as a B2 (probable human carcinogen), based on evidence of carcinogenicity in the forestomach and kidneys of rats and mice. The Agency currently regulates chlorothalonil as a B2 carcinogen although ISK Biosciences Corporation has provided a significant amount of mechanistic data indicating that the tumors result from a threshold mechanism. A potency factor, Q_1*, of 0.00766 (mg/kg/day)-1 has been used by the Agency when conducting mathematical modeling to estimate carcinogenic risk to man. ISK Biosciences Corporation believes that because the nephrotoxicity seen in the rat is due to a threshold mechanism, any risk associated with chlorothalonil can be managed using the margin of safety (exposure) approach.

Numerous metabolism and toxicology studies indicate that chlorothalonil is non-genotoxic, and produces a species specific renal toxicity in the rat that eventually may lead to tumor formation through an epigenetic mechanism. Studies comparing metabolism and toxicological effects in dogs with those in rats demonstrate that the renal effects observed in the rat are due to the exposure of the kidney of the rat to significant levels of nephrotoxic thiol metabolites of chlorothalonil.

The 4-hydroxy metabolite was not tumorigenic in either the rat or mouse. Reference Dose (RfD): The no effect level for chlorothalonil in the rat is 1.8 mg/kg bwt. based on the nephrotoxicity observed in the chronic study. The no effect level in the dog was 15 mg/kg bwt. in the 90-day study and 150 mg/kg bwt. based on the one-year study. No effect levels for maternal toxicity from developmental studies are 10 mg/kg bwt. in rabbits and 100 mg/kg bwt. in the rat. The no effect level for pup growth in the reproduction study was 1,500 mg/kg bwt. which would be most conservatively estimated as equating to approximately 75 mg/kg bwt. The data indicate that the nephrotoxicity in the rat is produced through a mechanism for which there is a clear threshold. In a study which measured cell turnover in the rat kidney with BRDU, a NOEL was established at 1.5 mg/kg bwt. Other chronic studies have established the NOEL for hyperplasia in the kidney to be 1.8 mg/kg bwt. If all the available toxicity data in laboratory animals are considered without regard to applicability to humans, the lowest NOEL for any adverse effect would be 1.5 mg/kg bwt./day. Because the mechanism of toxicity which is related to the tumor formation in the kidney has been shown to have a threshold, the use of the normal 100-fold safety factor in conjunction with the 1.5 mg/kg no observable effect level would produce a reference dose which would provide more than adequate safety for all of the possible effects seen in any laboratory animal.

In the two reviews of chlorothalonil by the Joint Meeting of Pesticide Residue Experts, and the review by the World Heath Organization's International Program For Chemical Safety, these esteemed groups concluded that the rat was not the appropriate species to use in consideration of the risk assessment for man. They concluded that the dog was the more appropriate species for determination of subchronic and chronic effects. If the toxicological data for the dog were used, the NOEL would be at least 15 mg/kg bwt., based on the most recent 90-day study in the dog.

The NOEL for the 4-hydroxy metabolite based on the reduction of weight gain late in the lactation period in a reproduction study would be 30 ppm or 1.5 mg/kg/ day. This was not a reproductive effect. The NOEL based on chronic toxicity in the rat would be 3.0 mg/kg bwt/day.

Therefore, under the most conservative scenario, the reference dose for chlorothalonil including its 4-hydroxy metabolite would be 1.5 mg/kg bwt./day divided by a 100-fold safety factor or 0.015 mg/kg bwt./day with a threshold model being used for carcinogenic risk assessment. In the scenario that uses the toxicological data in the dog, the reference dose would be 15 mg/kg bwt./day. divided by a safety factor of 100 or 0.15 mg/kg bwt./day.

C. Aggregate Exposure

The following is a description of the likelihood of exposure to chlorothalonil from various routes:

1. *Dietary exposure (Food).* No residues of chlorothalonil per se will be added to the total exposure of chlorothalonil from consumption of

meat or milk from livestock which were fed chlorothalonil-treated commodities. Residues of 4-hydroxy-2,5,6-trichloroisophthalo-nitrile on crops treated with products containing chlorothalonil are a very low percentage of the total crop residue. Although 4-hydroxy-2,5,6-trichloroisophthalonitrile will transfer to meat and milk, the levels present on feedstuffs which are available for transfer are low. Presently, there are very few uses of chlorothalonil which involve livestock commodities. Meat and milk tolerances for 4-hydroxy-2,5,6-trichloroisophthalonitrile are needed to support the reregistration of chlorothalonil.

2. *Drinking water.* Chlorothalonil was included for monitoring in the National Survey of Pesticides in Drinking Water Wells conducted by EPA. No chlorothalonil residues were detected in any of the 1,300 community water systems and domestic wells (using methodology for chlorothalonil having a limit of detection [LOD] of 0.06 mg/l and limit of quantitation of 0.12 mg/l). The absence of chlorothalonil detections in the National Survey provides adequate information to conclude that chlorothalonil is not a contaminant in drinking water wells and that the population is not exposed to chlorothalonil in these water sources. These findings are consistent with the known physical/ chemical properties of chlorothalonil including low water solubility (0.9 ppm) and high affinity for organic matter including soil. It has also been demonstrated that chlorothalonil does not leach into groundwater from applications made to growing crops.

Aerobic aquatic metabolism studies with chlorothalonil establish a half-life in natural aquatic habitats of less than 10 hours, depending on environmental conditions. Considering the short half-life of chlorothalonil in natural water/ sediment systems and that surface water is filtered and treated prior to consumption, chlorothalonil is not likely to be present in drinking water obtained from natural surface water systems.

If the exposure estimate is based on the surface water concentration recently cited by EPA, it is concluded that the average concentration in surface water would be less than 0.002 ppb. Assuming that everyone in the US consumed untreated surface water, the exposure to chlorothalonil to the general population would be less than $5.8 \times 10_{-7}$ mg/kg bwt./day. This would be a worst case scenario.

The 4-hydroxy metabolite did not leach into ground water in a prospective groundwater study, therefore, no intake of this metabolite would be anticipated from drinking water.

3. *Non-dietary exposure.* Potential non-dietary exposures to chlorothalonil may result from the following uses of chlorothalonil. In each case, the exposure would be from the dermal route and only for an intermittent duration. The two 21-day dermal studies that have been conducted in the rabbit and rat indicate that there is no nephrotoxicity associated with the dermal exposure to chlorothalonil at dose levels up to 600 mg/kg/day. Therefore, the exposures from the uses of chlorothalonil listed below, would not be expected to add to the carcinogenic risk associated with chlorothalonil.

Because the 4-hydroxy metabolite is a soil metabolite, no significant exposure would be anticipated through non-dietary routes. Although some hydrolysis of chlorothalonil to the 4-hydroxy metabolite may occur at a basic pH in some paint or wood treatment products, the anticipated exposure when the products dry would be negligible.

a. Golf course uses. Chlorothalonil products are commonly applied to golf course tees and greens to control a broad complex of turf diseases. Application to golf course fairways is much less common. Golf is not a game played by infants or small children, therefore no exposure to infants and children would be anticipated.

b. Residential owner uses. Applications of chlorothalonil products to home lawns are rare. Thus, there is very little exposure to chlorothalonil related to use on residential turf. Applications to roses and other ornamentals in home gardens is also a minor use of chlorothalonil.

c. Paint. Chlorothalonil is used in paints and stains for control of mildew and molds on exterior surfaces of buildings. Chlorothalonil is also occasionally used for interior paints, but this use represents only a small proportion of the chlorothalonil used in paints. About 2% of the chlorothalonil used in paint is used in interior paint; however, only 0.2% or less of the interior paints in the United States contain chlorothalonil. In paints, chlorothalonil is tightly bound within the matrices of the paint; thus, effective control of mildew may last for several years.

d. Grouts. Chlorothalonil is used in cement tile grouts for control of mildew and molds. Chlorothalonil is bound within the grout matrices and very little is available for exposure. This is a minor use of chlorothalonil and non-occupational dermal exposure of humans to chlorothalonil from this source is extremely low.

e. Wood treatment. Chlorothalonil is not used for pressure-treating wood. It is used for control of sapstain as a surface treatment on rough-cut, newly-sawn lumber to protect it from molds and mildews while drying. Being a surface residue, it is removed during the finishing operations prior to sale of the wood. Chlorothalonil does not occur in structural wood used for residential or occupational scenarios.

D. Cumulative Effects

ISK Biosciences has considered the potential for cumulative effects of chlorothalonil and other substances that have a common mechanism of toxicity. Chlorothalonil is a halogenated benzonitrile fungicide which readily undergoes displacement of the chlorines in the 2, 4 and 6 positions by glutathione and other thiol containing amino acids and proteins. In the rat, the glutathione binding, absorption and subsequent metabolism to form the di- and tri-thiol metabolites occur at sufficient levels to produce a nephrotoxic effect. In dogs where this mechanism does not occur to produce thiol metabolites, nephrotoxicity does not occur. ISK Biosciences does not have any information to indicate that toxic effects observed in rats occur through a mechanism which is common to any other agricultural chemical. Thus, consideration of common mechanisms of toxicity is not appropriate at this time.

Chlorothalonil should not be confused with chemicals classified as chlorinated hydrocarbon pesticides which have significantly different chemical and biological properties.

There would be no cumulative effects expected between chlorothalonil and its 4-hydroxy metabolite because each affects a different toxicological endpoint.

E. Safety Determination

1. *U.S. population.* The majority of exposure to chlorothalonil and its 4-hydroxy metabolite would be expected to occur from the diet. In EPA's Dietary Exposure Analysis for the Use of Chlorothalonil in/on Meat and Milk Products, dated April 23, 1996, the Agency determined that ''Chlorothalonil does not pose a significant chronic or acute dietary risk for uses that are currently published or for uses recommended by CBRS for registration''. The Agency concluded that because of the instability of chlorothalonil in meat and milk, that even in misuse, residues of chlorothalonil would not transfer from

animal feed items to meat and milk. The EPA determined that the 4-hydroxy metabolite would be a residue in meat and milk and that the chronic RfD for chlorothalonil would be sufficient for the metabolite.

The Agency calculated that the Anticipated Residue Contribution when the tolerances for meat and milk are approved, would be 6.8% for the general population and 37% for non-nursing infants (<1 yr. old). In estimating the carcinogenic risk, the Agency indicated that since the 4-hydroxy metabolite was not carcinogenic, and that no residues of chlorothalonil would transfer to meat and milk, the carcinogenic risk calculated for chlorothalonil would not be affected by this tolerance.

The Agency has used a linearized model to estimate the carcinogenic risk associated with chlorothalonil, whereas ISK Biosciences believes that a threshold based model is appropriate.

Because the worst case assumptions for human exposure from drinking water indicate that exposure would be only 1% of the dietary exposure, the risk assessment is not significantly altered by considering the exposure from drinking water.

2. *Infants and children.* There is a complete database for chlorothalonil which includes pre- and post-natal developmental toxicity data as well as mechanistic data related to the rodent specific nephrotoxicity observed in subchronic and chronic studies. The toxicological effects of chlorothalonil in rodents are well understood. Chlorothalonil has a low level of toxicity in dogs.

In a two-generation reproduction study in rats, all reproductive parameters investigated showed no treatment-related effects except pup weight gain. Specifically, the weights of pups exposed to chlorothalonil were comparable to controls at parturition through day four of lactation. It was only after day four of lactation, when the pups begin to consume the test diet, that body weight gain lags behind controls. This only occurred at the highest dose tested, 3,000 ppm. The dose of chlorothalonil the pups would receive would be far in excess of the estimated adult dose of 150 mg/kg (3,000 ppm/20). The doses for the pups could have easily exceeded 500 mg/kg bwt./day. Dose levels of 375 mg/kg bwt. and above have been shown to significantly affect body weight in the rat. Therefore, the reduction of body weight gain observed in the reproduction study is considered to be comparable to the effects that have been observed in older rats. The NOEL for this effect was 1,500 ppm.

In a three generation reproduction study and a subsequent one generation study with the 4-hydroxy metabolite, there were no reproductive effects even at a dose that produced parental toxicity. Although a reduction in pup growth was noted at dietary concentrations of 60 ppm and higher, it could be attributed to an inordinately high dose of the test material received by the pups when compared to adults.

In developmental toxicity studies conducted in the rat and the rabbit, chlorothalonil did not cause any developmental effects even at dose levels that produced significant maternal toxicity. In the rabbit a dose level of 20 mg/kg caused maternal toxicity, but there were no developmental effects, and in the rat a dose level of 400 mg/kg caused maternal toxicity without developmental toxicity.

In a developmental toxicity study conducted with the 4-hydroxy metabolite there were no developmental effects even at doses that produced significant maternal toxicity. A dose of 5 mg/kg produced maternal toxicity but there were no developmental effects.

The extensive database that is available for chlorothalonil and its 4-hydroxy metabolite is devoid of any indication that either material would represent any unusual or disproportionate hazard to infants or children. Therefore, there is no need to impose an additional 10X safety factor for infants or children. The standard uncertainty factor of 100X should be used for all segments of the human population when calculating risks associated with chlorothalonil or its 4-hydroxy metabolite.

F. International Tolerances

A maximum residue level has not been set for the 4-hydroxy metabolite of chlorothalonil in milk and meat by the Codex Alimentarius Commission. The data indicate that no tolerance would be necessary for chlorothalonil on milk and meat since it would not be expected to transfer from animal feed items to these commodities. (PM 22)

2. Novartis

PP 9F3740, PP 5F4424, PP 5F4591, PP 5F4498

EPA has received pesticide petitions (PP) 9F3740, 5F4424, 5F4591, 5F4498 from Novartis Crop Protection Inc., PO Box 18300, Greensboro, NC 27419. The petition proposes, to amend 40 CFR part 180, by establishing a tolerance for the residues of the fungicide Propiconazole, which is a triazole fungicide registered for use on many crops, including bananas, celery, corn, grasses grown for seed, mint (West of the Cascade Mountains), pecans, peanuts, rice, small grains (barley, oats, rye, wheat), stone fruit, and wild rice. Use rates range from 0.07 to 0.22 pound (lb.) active ingredient per acre. Petitions currently pending for propiconazole include: the tree nuts (PP 9F3740); drybean and soybeans (PP 5F4424); berry crop grouping, carrots, and onions (PP 5F4591); and alfalfa and sorghum (PP 5F4498).

A. Residue Chemistry

1. *Metabolism.* Novartis believes the studies supporting propiconazole adequately characterize metabolism in plants and animals. The metabolism profile supports the use of an analytical enforcement method that accounts for combined residues of propiconazole and its metabolites which contain the 2,4-dichlorobenzoic acid (DCBA) moiety.

2. *Analytical methodology.* Novartis has submitted a practical analytical method involving extraction, filtration, conversion, partition, derivitization, and solid phase cleanup with analysis by confirmatory gas chromatography using electron capture detection (ECD). The total residue method is used for determination of propiconazole and its metabolites. The limit of quantitation (LOQ) for the method is 0.05 part per million (ppm).

3. *Magnitude of residue.* Field residue trials have been conducted at various rates, timing intervals, and applications methods to represent the use patterns which would most likely result in the highest residues. For all samples, the total residue method was used for determination of the combined residues of parent and its metabolites which contain the DCBA moiety.

B. Toxicological Profile

The following mammalian toxicity studies have been conducted to support the tolerances of propiconazole:

A rat acute oral study with a LD_{50} of 1,517 mg/kg.

A rabbit acute dermal study with a LD_{50} > 6,000 mg/kg.

A rat inhalation study with a LC_{50} > 5.8 mg/liter air.

A primary eye irritation study in rabbits which showed mild irritation.

A primary dermal irritation study in rabbits which showed slight irritation.

A skin sensitization study in guinea pigs which showed no sensitization.

A 21–day dermal study in the rabbit with a No Observed Effect Level (NOEL) of 200 mg/kg based on clinical signs of systemic toxicity.

A 28–day oral toxicity study in the rat with a No Observed Adverse Effect Level (NOAEL) of 50 mg/kg based on increased liver weight.

A subchronic feeding study in the mouse with a NOEL of 20 ppm (3 mg/kg) based on liver pathologic changes.

A 13–week feeding study in the male mouse with a NOEL of 20 ppm (3 mg/kg) based on liver pathologic changes.

A 90–day feeding study in the rat with a NOEL of 240 ppm (24 mg/kg) based on reduction in body weight gain.

A 90–day feeding study in the dog with a NOEL of 250 ppm (6.25 mg/kg) based on reduced food intake and stomach histologic changes.

A 12–month feeding study in the dog with a NOEL of 50 ppm (1.25 mg/kg) based on stomach histologic changes.

A 24–month oncogenicity feeding study in the mouse with a NOEL of 100 ppm (15 mg/kg). The MTD was exceeded at 2,500 ppm in males based on decreased survival and body weight. Increased incidence of liver tumor was seen in these males but no evidence of carcinogenicity was seen at the next lower dose of 500 ppm in either sex.

A 24–month chronic feeding/oncogenicity study in the rat with a NOEL of 100 ppm (5 mg/kg) based on body weight and blood chemistry. The MTD was 2,500 ppm based on reduction in body weight gain and no evidence of oncogenicity was seen.

An oral teratology study in the rabbit with a maternal NOEL of 30 mg/kg based on reduced food intake but without any fetotoxicity even at the top dose of 180 mg/kg.

An oral teratology study in the rabbit with a maternal NOEL of 100 mg/kg based on reductions in body weight gain and food consumption and a fetal NOEL of 250 mg/kg based on increased skeletal variations at 400 mg/kg.

An oral teratology study in the rat with a maternal and fetal NOEL of 100 mg/kg based on decreased survival, body weight gain, and food consumption in the dams and delayed ossification in the fetuses at 300 mg/kg.

A second teratology study in the rat with a maternal and fetal NOEL of 30 mg/kg based on reductions in body weight gain and food consumption in the dams and delayed development in the fetuses at 90 and 360/300 mg/kg.

A supplemental teratology study in the rat involving eight times as many animals pergroup as usually required and showing no teratogenic potential for the compound.

A 2-generation reproduction study in the rat showing excessive toxicity at 5,000 ppm without any teratogenic effects.

A 2-generation reproduction study in the rat with no effects on reproductive or fetal parameters at any dose level. Postnatal growth and survival were affected at the top dose of 2,500 ppm, where parental toxicity was also evident. The NOEL for development toxicity is 500 ppm.

In vitro gene mutation test: Ames assay - negative; rat hepatocyte DNA repair test - negative; human fibroblast DNA repair test - negative.

In vitro chromosome test: human lymphocyte cytogenetic test - negative.

In vivo mutagenicity test: Chinese hamster bone marrow cell nucleus aunomaly test -negative; Chinese hamster bone marrow cell micronucleus test - negative; mouse dominant lethal test - negative.

Other mutagenicity test: BALB/3T3 cell transformation assay - negative.

C. Threshold Effects

1. *Chronic effects.* Based on the available chronic toxicity data, Novartis believes the Reference dose (RfD) for propiconazole is 0.0125 mg/kg/day. This RfD is based on a 1-year feeding study in dogs with a No-Observed Effect Level of 1.25 mg/kg/day (50 ppm) and an uncertainly factor of 100. No additional modifying factor for the nature of effects was judged to be necessary as stomach mucosa hyperemia was the most sensitive indicator of toxicity in that study.

2. *Acute toxicity.* The risk from acute dietary exposure to propiconazole is considered to be very low. The lowest NOEL in a short term exposure scenario, identified as 30 mg/kg in the rat teratology study, is 24-fold higher than the chronic NOEL (see above). Based on worst-case assumptions the chronic exposure assessment (see below) did not result in any margin of exposure less than 150 for even the most impacted population subgroup. Novartis believes that the margin of exposure for acute exposure would be more than one hundred for any population groups; margins of exposure of 100 or more are considered satisfactory.

3. *Non-threshold effects.* Using the Guidelines for Carcinogenic Risk Assessment published on September 24, 1986 (51 FR 33992), the USEPA has classified propiconazole in group C for carcinogenicity (evidence of possible carcinogenicity for humans). The compound was tested in 24-month studies with both rats and mice. The only evidence of carcinogenicity was an increase in liver tumor incidence in male mice at a dose level that exceeded the maximum tolerated dose (MTD). Dosage levels in the rat study were appropriate for identifying a cancer risk. The Cancer Peer Review Committee recommended the RfD approach for quantitation of human risk. Therefore, the RfD is deemed protective of all chronic human health effects, including cancer.

D. Aggregate Exposure

1. *Dietary exposure.* For the purposes of assessing the potential dietary exposure under the existing, pending, and proposed tolerances for the residue of propiconazole and its metabolites determined as 2,4-dichlorobenzoic acid, Novartis has estimated aggregate exposure based upon the Theoretical Maximum Residue Concentration (TMRC). The TMRC is a ''worst case'' estimate of dietary exposure since it assumes 100 percent of all crops for which tolerances are established are treated and that pesticide residues are at the tolerance levels, resulting in an overestimate of human exposure.

Currently established tolerances range from 0.05 ppm in milk to 60 ppm in grass seed screenings and include: apricots (1.0 ppm); bananas (0.2 ppm); barley grain (0.1 ppm); barley straw (1.5 ppm); cattle kidney and liver (2.0 ppm); cattle meat, fat, and meat by products except kidney and liver (0.1 ppm); celery (5.0 ppm); corn forage and fodder (12.0 ppm); corn grain and sweet (0.1); eggs (0.1 ppm); goat kidney and liver (2.0 ppm); goat meat, fat, and meat by products except kidney and liver (0.1 ppm); grass forage (0.5 ppm); grass hay/straw (40.0 ppm); grass seed screenings (60.0 ppm); hogs kidney and liver (2.0 ppm); hog meat, fat, and meat by products except kidney and liver (0.1 ppm); horses kidney and liver (2.0 ppm); horse meat, fat, and meat by products except kidney and liver (0.1 ppm); milk (0.05 ppm); mint tops (0.3 ppm - regional tolerance west of Cascade Mountains); mushrooms (0.1 ppm); nectarines (1.0 ppm); oat forage (10.0 ppm); oat grain (0.1 ppm); oat hay (30.0 ppm); oat straw (1.0 ppm); peaches (1.0 ppm); peanut hay (20.0 ppm); peanut hulls (1.0 ppm); peanuts (0.2 ppm);, pecans (0.1 ppm); pineapple (0.1 ppm); pineapple fodder (0.1 ppm); plums (1.0 ppm); poultry liver and kidney (0.2 ppm); poultry meat, fat, and meat by products except kidney and liver (0.1 ppm); prunes, fresh (1.0 ppm); rice grain (0.1 ppm); rice straw (3.0 ppm); wild rice (0.5 ppm regional tolerance Minnesota); rye grain (0.1 ppm); rye straw (1.5 ppm); sheep kidney and liver (2.0 ppm); sheep meat, fat, and meat by products except kidney and liver (0.1 ppm); stone fruit crop group 12 (1.0 ppm); wheat grain (0.1 ppm); and wheat straw (1.5 ppm). In addition, time-limited regional tolerances for

sorghum grain and stover at 0.1 ppm and 1.5 ppm, respectively were established to support a section 18 Crisis exemption in Texas (expiration date 10/31/98).

Additional uses of propiconazole have been requested in several pending petitions.

Proposed tolerances include: PP 5F4424 for use of propiconazole on drybean and soybean -- dry bean forage (8.0 ppm); dry bean hay (8.0 ppm); dry bean vines (0.5 ppm); dry bean (0.5 ppm), soybeans (0.5 ppm); soybean fodder (8.0 ppm); soybean forage (8.0 ppm); soybean hay (25.0 ppm); and soybean straw (0.1 ppm).

PP 5F4591 for use of propiconazole on berries, carrots and onions -- berry crop grouping (1.0 ppm); dry bulb onion (0.3 ppm); green onion (8.0).

PP 9F3740 -- tree nut crop grouping (0.1 ppm);

PP 5F4498 -- inadvertent/rotational crop tolerances for alfalfa forage (0.1 ppm), alfalfa hay (0.1 ppm), grain sorghum fodder (0.3 ppm), grain sorghum forage (0.3 ppm) and grain sorghum grain (0.2 ppm). Other potential sources of exposure of the general population to residues of propiconazole are residues in drinking water and exposure from non-occupational sources. Review of environmental fate data by the Environmental Fate and Effects Division of USEPA indicates that propiconazole is persistent and moderately mobile to relatively immobile in most soil and aqueous environments. No Maximum Concentration Level (MCL) currently exists for residues of propiconazole in drinking water and no drinking water health advisory levels have been established for propiconazole.

2. *Drinking water exposure.* The degradation of propiconazole is microbially mediated with an aerobic soil metabolism half-life of 70 days. While propiconazole is hydrolytically and photochemically stable (T1/2 >100 days), it binds very rapidly and tightly to soil particles following application. Adsorption/desorption and aged leaching data indicate that propiconazole and its degradates will primarily remain in the top 0–6 inches of the soil. It has been determined that under field conditions propiconazole will degrade with a half-life of approximately 100 days.

3. *Non-dietary exposure.* Propiconazole is registered for residential use as a preservative treatment for wood and for lawn and ornamental uses. At this time, no reliable data exist which would allow quantitative incorporation of risk from these uses into a human health risk assessment. The exposure to propiconazole from contacting treated wood products is anticipated to be very low since the surface of wood is usually coated with paint or sealant when used in or around the house. The non-occupational exposure from lawn and ornamental applications is also considered to be minor. It is estimated that less than 0.01 percent of all households nationally use propiconazole in a residential setting.

Consideration of a common mechanism of toxicity is not appropriate at this time since there is no reliable information to indicate that toxic effects produced by propiconazole would be cumulative with those of any other types of chemicals. While other triazoles are available on the commercial or consumer market, sufficient structural differences exist among these compounds to preclude any categorical grouping for cumulative toxicity. Consequently, Novartis is considering only the potential risks of propiconazole in its aggregate exposure assessment.

E. Safety Determiniation

1. *U.S. population.* Reference dose. Using the conservative exposure assumptions described above (100 percent stone fruit acres treated and tolerance level residues) and based on the completeness and reliability of the toxicity data base for propiconazole, Novartis has calculated aggregate exposure levels for this chemical. The calculation shows that only 16 percent of the RfD will be utilized for the U.S. population based on chronic toxicity endpoints. EPA generally has no concern for exposures below 100 percent 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 propiconazole residues.

2. *Infants and children.* Developmental toxicity (e.g., reduced pup weight and ossification) was observed in the rat teratology studies and 2-generation rat reproduction studies at maternally toxic doses. Some of these findings are judged to be nonspecific, secondary effects of maternal toxicity. The lowest NOEL for developmental toxicity was established in the rat teratology study at 30 mg/kg, a level 24–fold higher than the NOEL of 1.25 mg/kg on which the RfD is based.

Reference dose. Using the same conservative exposure assumptions as employed for the determination in the general population, Novartis has calculated that the percent of the RfD that will be utilized by aggregate exposure to residues of propiconazole is 26 percent for nursing infants less than 1 year old, 65 percent for non-nursing infants less than 1 year old, 35 percent for children 1–6 years old, and 23 percent for children 7–12 years old. Therefore, based on the completeness and reliability of the toxicity data base and the conservative exposure assessment, Novartis concludes that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to propiconazole residues.

F. Estrogenic Effects

Propiconazole does not belong to a class of chemicals known or suspected of having adverse effects on the endocrine system.

Developmental toxicity studies in rats and rabbits and reproduction studies in rats gave no indication that propiconazole might have any effects on endocrine function related to development and reproduction. The subchronic and chronic studies also showed no evidence of a long-term effect related to the endocrine system.

G. International Tolerances

International CODEX values are established for almond, animal products, bananas, barley, coffee, eggs, grapes, mango, meat, milk, oat, peanut-whole, peanut grains, pecans, rape, rye, stone fruit, sugar cane, sugar beets, sugar beet tops, and wheat. The U.S. residue definition includes both propiconazole and metabolites determined as 2,4-dichlorobenzoic acid (DCBA), while the CODEX definition is for propiconazole, per se, i.e. parent only. This difference results in unique tolerance expressions with the U.S. definition resulting in the higher tolerance levels. (PM 21)

3. Novartis Crop Protection, Inc.

PP 5E4450, 6F3332, 5F4546, 5F4576, and 6F4613

EPA has received pesticide petitions (PP) 5E4450, 6F3332, 5F4546, 5F4576, and 6F4613) from Novartis Crop Protection, Inc., 410 Swing Road, Greensboro, NC 27419, proposing to amend 40 CFR part 180 by establishing a tolerance for residues of the insecticide, cyromazine, and its metabolite, melamine, in or on the raw agricultural commodities of potatoes (potato tubers) at 1.5 ppm, green onions at 3 ppm, dry bulb onions at 0.3 ppm, cottonseed at 0.2 ppm, sweet corn (kernels plus cobs with husks removed, forage, and fodder) at 0.5 ppm, radishes (roots and tops) at 0.5 ppm, and

mangoes at 0.3 ppm. A tolerance of 0.04 ppm is requested for residues of cyromazine in milk; a tolerance of 0.02 ppm is requested for residues of melamine in milk.

Residues of cyromazine and its metabolite, melamine, were determined by Analytical Methods AG-408 and AG-417A which, combined, are the EPA tolerance enforcement method published in the Pesticide Analytical Manual, Volume II. Cyromazine is determined by High Performance Liquid Chromatography (HPLC) on a LiChrosorb-NH2 column at 214 nm. The limit of determination in potatoes is 0.05 ppm.

Method AG-417A has been validated as reported in report ABR-84069 and by the EPA method trial reported in the Pesticide Analytical Manual (PAM). EPA has accepted AG-408, 417A as the regulatory enforcement method for crops.

Storage stability data for cyromazine have been reported in ABR-92019 and Special Study 134/93: Interim Report. Stability of field-incurred residues of cyromazine was demonstrated for 23 months in head and leaf lettuce, 24 months in celery, 9½ months in tomatoes, and 11 months in mushrooms. In Special Study 134/93: Interim report, no degradation of laboratory-spiked cyromazine was observed for 6 months in mangoes (the time period required to validate the mango analyses). No deterioration of cyromazine residues has been observed in any substrate under freezer storage conditions. In this study, the storage period for potatoes ranged from 3.5 to 24 months, which is within the demonstrated freezer stability period.

A. Chemical Uses

Cyromazine, the active ingredient in Trigard Insecticide, is a synthetic insect growth regulator. Cyromazine is highly efficacious against dipterous leafminer larvae developing in the foliage of certain agronomic, vegetable, and ornamental crops, and it can be used to control flies in mushroom houses. Cyromazine is compatible with integrated pest management (IPM) programs.

B. Residue Chemistry

Six field trials were conducted in three mango production areas of Mexico. Residues of cyromazine ranged from less than the detection limit (0.03 ppm) to 0.25 ppm. These data support the proposed tolerance of 0.3 ppm in mangoes.

The maximum combined residue of cyromazine and melamine in cottonseed from cotton grown as a rotational crop following lettuce treated six times at the 1X use rate was 0.18 ppm. These data support the proposed tolerance of 0.2 ppm in cottonseed.

Application of Trigard OMC to onion seed (pelletization) resulted in maximum residues in immature whole onion plants of 2.71 ppm. These data support the proposed tolerances for combined residues of cyromazine and melamine at 3.0 ppm in green onions and 0.3 ppm in dry bulb onions.

Residue data in rotational sweet corn and radishes and potatoes have been previously submitted to EPA for review and have been found by EPA to support tolerances of 0.5 ppm in sweet corn (kernels & cobs with husks removed), sweet corn forage, sweet corn fodder, radish roots and radish tops and to support tolerances of 1.5 ppm in/on potatoes. The proposed 1.5 ppm for the RAC potatoes will cover any expected residues including residues in processed potato wastes.

C. Toxicological Profile

Novartis has submitted toxicology studies in support of tolerances for cyromazine. Cyromazine has low acute toxicity, no indication of irritation potential and no sensitization potential. Cyromazine is not genotoxic, fetotoxic, embryolethal, or teratogenic. It is not a reproductive toxin. High-dose chronic toxicity included bronchiectasis in male and female rats, testicular degeneration in dogs, and decreased body weights in rats, dogs, and mice. No tumorigenic effects were noted in any species tested and EPA has classified cyromazine as Group E, no evidence of carcinogenicity in humans. Therefore, Novartis proposes that a Margin of Exposure (MOE) or percentage of reference dose (RfD) approach be used for characterizing human risk. For cyromazine, Novartis concludes that aggregate MOE's are acceptable for the U.S. population and all population subgroups for both acute toxicity and chronic effects.

The following mammalian toxicity studies were conducted to support proposed tolerances for cyromazine:

A rat acute oral toxicity study with an LD_{50} of approximately 3,387 mg/kg.

A rat acute dermal toxicity study with an LD_{50} >3,100 mg/kg.

A rat acute inhalation study with an LC_{50} >3,600 mg/m^3.

A primary eye irritation study in the rabbit that showed no eye irritation.

A primary dermal irritation study in the rabbit that showed no dermal irritation.

A dermal sensitization study in the guinea pig that showed no sensitization.

A 21-day dermal study in rabbits demonstrated no target organ toxicity at doses up to 2,000 mg/kg/day.

A 13-week rat feeding study demonstrated no specific target organ toxicity and a no observed effect level (NOEL) of 300 ppm (25 mg/kg/day).

A 13-week feeding study in dogs demonstrated no specific target organ toxicity, although some red blood cell parameters were affected in high-dose males. The NOEL was 1,000 ppm (34 mg/kg/day).

A six-month feeding study in dogs showed reversible red blood cell effects and transient changes in clinical parameters in high dose males. No specific target organs were identified histologically, although changes in some organ to body weight ratios were observed. The NOEL was 30 ppm (0.75 mg/kg).

A 24-month feeding study in rats identified no specific target organs. There was no oncogenic effect and the NOEL for the study was 30 ppm (1.5 mg/kg/day).

A 24-month mouse feeding study identified no specific target organs. There was no oncogenic effect and the NOEL was 50 ppm (7.0 mg/kg/day).

A rat teratology study demonstrated no developmental toxicity. The maternal NOEL is 100 mg/kg/day and the developmental NOEL was 300 mg/kg/day.

Several rabbit teratology studies were conducted. Based on a weight of the evidence, no teratogenic effect was demonstrated. The maternal NOEL was 10 mg/kg/day, whereas the developmental NOEL was 60 mg/kg/day.

A multigeneration study in rats demonstrated no impairment of reproductive performance or fetal and/or pup effects, although pup body weights were slightly decreased at the highest dose. The parental NOEL and developmental NOEL's were 1,000 ppm (50 mg/kg/day).

There was no evidence of induction of point mutations in an Ames test.

There was no indication of a mutagenic effect in a dominant lethal test.

There was no evidence of a mutagenic effect in a nucleus anomaly test in Chinese hamsters.

D. Threshold Effects

1. *Chronic effects*. EPA has established a reference dose for cyromazine at 0.0075 mg/kg/day based on the 6 month dog study using the NOEL of 0.75 mg/kg/day (30 ppm) and an uncertainty factor of 100.

2. *Acute toxicity*. Based on the low degree of acute toxicity, it can be

concluded that cyromazine does not pose any acute dietary risks.

Non-threshold effects (Carcinogenicity). Based on the Guidelines for Carcinogenic Risk Assessment published by EPA September 24, 1986 (51 FR 33992), EPA has classified cyromazine as not carcinogenic (Group E). This classification was issued by the Health Effects Division Carcinogenicity Peer Review Committee on September 14, 1994.

E. Aggregate Exposure

1. *Dietary exposure.* For purposes of assessing the potential dietary exposure to cyromazine, Novartis has estimated aggregate exposure based on the TMRC from the use of cyromazine in or on raw agricultural commodities for which tolerances have been established (40 CFR 180.368) or are pending.

The TMRC is obtained by multiplying the tolerance level residue for all these raw agricultural commodities by the consumption data that estimate the amount of these products consumed by various population subgroups. Since these raw agricultural commodities (e.g. soybean forage and fodder) are fed to animals, the transfer of residues in these fed commodities to meat, milk, poultry, or eggs has been calculated and tolerances have either been proposed or established.

In conducting this exposure assessment, Novartis has used either EPA's estimate of market share or used best estimates provided by Novartis Product Management which assume plateau market share values. In addition, the dietary exposure assessment includes residue assumptions for meat and milk that provide very conservative estimates.

2. *Drinking Water.* The environmental fate database for cyromazine indicates that, when used according to label directions, the compound is not likely to be found in ground or surface water at biologically significant concentrations. To date, cyromazine has never been detected in ground or surface water. The primary environmental degradate of cyromazine, melamine, has rarely been detected, and melamine detections have always been less than 0.3 ppb in water. To evaluate the potential impact of exposure to cyromazine in drinking water, Novartis calculated a theoretical lifetime Maximum Contaminant Level (MCL). The theoretical MCL, 50 ppb, is orders of magnitude greater than levels that are likely to be found in the environment under current conditions of use.

3. *Non-dietary exposure.* Non-occupational exposure to the general population is unlikely since cyromazine is not used in or around the home, including home lawns.

F. Cumulative Effects

Novartis considered the potential for cumulative effects of cyromazine and other chemicals in this class that may have a common mechanism of toxicity. Consideration of a common mechanism of toxicity is not appropriate for cyromazine since the existing data do not suggest a common mechanism.

G. Safety Determination

1. *U.S. population.* Using the conservative exposure assumptions described above, and based on the completeness and reliability of the toxicity data, Novartis has concluded that aggregate exposure to cyromazine will utilize approximately 35% percent of the RfD for the U.S. population based on chronic toxicity endpoints. EPA generally has no concern for exposures below 100% of the RfD, because the RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. Therefore, Novartis concludes that there is reasonable certainty that no harm will result from aggregate exposure to cyromazine or residues of cyromazine that may appear in raw agricultural commodities.

2. *Infants and* children. In assessing the potential for additional sensitivity of infants and children to residues of cyromazine, Novartis has considered data from developmental toxicity studies in the rat and rabbit, and a 2-generation reproduction study in the rat. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from chemical exposure during prenatal development. Reproduction studies provide information relating to effects from exposure to a chemical on the reproductive capability of mating animals, on postnatal development, and systemic toxicity, particularly to the reproductive system.

Developmental toxicity (reduced mean fetal body weight and an increased incidence of skeletal variations due to delayed ossification) was observed in the rat only at the maternally toxic dose of 600 mg/kg/day. The no observed effect level for developmental toxicity in the rat was 300 mg/kg/day, a dose that was still maternally toxic. Similarly, the developmental no observed effect level in the rabbit (60 mg/kg/day) was higher than the maternal no observed effect level (10 mg/kg/day), which suggests that the developmental toxicity associated with high doses of cyromazine occurs secondarily to maternal toxicity.

A 2-generation reproduction study was conducted with cyromazine at feeding levels of 0, 30, 1,000, and 3,000 ppm. Reproductive performance was unaffected by treatment with cyromazine at feeding levels up to 3,000 ppm. Evidence of parental toxicity, as indicated by decreased body weight gain, was observed in males and females at feeding levels >1,000 ppm. Similar effects were noted in the offspring at 3,000 ppm. The maternal and developmental no observed effect levels were established at 1,000 ppm (50 mg/kg/day).

FFDCA section 408 provides that EPA may apply an additional safety factor for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the database. Based on the current toxicological data requirements, the database relative to pre- and post-natal effects for children is complete. Furthermore, the NOEL of 0.75 mg/kg/day from the chronic dog study used to calculate the RfD, is approximately 100 fold lower than the lowest developmental NOEL in the teratology studies (Rabbit Developmental NOEL = 60 mg/kg/day) and the developmental NOEL (50 mg/kg/day) established in the multigeneration reproduction study. Based on these data, Novartis concludes that there is no evidence to suggest that developing organisms are more sensitive to the effects of cyromazine than are adults.

The percentage of the RfD utilized by the U.S. population for 48 states using aggregate exposure estimates is approximately 70%, if drinking water intake is assumed to be 100% of the MCL for the respective subgroup. It is highly unlikely that concentrations in drinking water will approach the MCL for even short periods of time. Consequently, this calculation of the percentage of the RfD that would be utilized is extremely conservative.

The percentage of the RfD that is utilized is somewhat higher for non-nursing infants if the chronic NOEL is used to estimate exposure using the conservative exposure assumptions described above. Novartis has determined that the percentage of the lowest developmental NOEL (50 mg/kg/day from the rat multigeneration study) utilized by aggregate exposure to residues of cyromazine is approximately 20% for nursing infants less than 1 year old, approximately 21% for non-nursing infants and for children 1 to six years old, and 62% for children 7 to 12 years old.

Therefore, based on the completeness and reliability of the toxicity data and the conservative exposure assessment, Novartis concludes that there is reasonable certainty that no harm will result to infants and children from aggregate exposure to cyromazine residues.

H. Estrogenic Effects

Cyromazine does not belong to a class of chemicals known to have or suspected of having adverse effects on the endocrine system. No adverse effects on fertility or reproduction were observed in high dose females (3000 ppm) in the rat reproduction study. Although residues of cyromazine have been found in raw agricultural commodities, there is no evidence that cyromazine bioaccumulates in the environment.

I. Environmental Fate

Soil metabolism and soil dissipation studies on various soil types have shown that cyromazine dissipates moderately over time, while melamine is slightly more stable.

J. International Tolerances

Compatibility problems exist between Codex limits, Mexican limits, and the proposed US tolerances. In Codex and Mexican limits, cyromazine is the only residue of concern; the metabolite melamine is not included in the residue expression. There are no established cyromazine limits for the RAC potato, or the processed commodities, potato granules/flakes, or chips, or the feedstuff, processed potato waste. There is a 0.01 ppm (at or about the limit of determination) Codex limit in milk. (PM 13)

[FR Doc. 97–18085 Filed 7–10–97; 8:45 am]
BILLING CODE 6560–50–F

ENVIRONMENTAL PROTECTION AGENCY

[FRL–5857–2]

Water Pollution Control; Program Application by South Carolina to Administer the Sludge Management (Biosolids) Program

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of application and public comment period.

SUMMARY: Pursuant to 40 CFR 123.61, the State of South Carolina has submitted an application for EPA to approve the existing South Carolina Domestic Sewage Sludge Permitting Program for authorization to administer and enforce the federal sewage sludge management (biosolids) program. According to the State's proposal, this program would be administered by the South Carolina Department of Health and Environmental Control (SCDHEC).

The application from South Carolina is complete and is available for inspection and copying. Persons wishing to comment upon or object to any aspects of the application from South Carolina or wishing to request a public hearing, are invited to submit the same in writing by August 28, 1997 to the Office of Environmental Assessment, Environmental Protection Agency Region 4, 61 Forsyth Street, S.W., Atlanta, Georgia 30303–3104, Attention: Ms. Lena Scott. The public notice number and reference to the program application by South Carolina to administer the sludge management (biosolids) program should be included in the first page of comments.

FOR FURTHER INFORMATION CONTACT: Mr. Roosevelt Childress, Chief, Surface Water Permits Section, telephone (404) 562–9279, or Mr. Vince Miller, EPA Region 4 Sludge Management Coordinator, telephone (404) 562–9312, or write to the following address: Water Management Division, Surface Water Permits Section, U.S. EPA, Region 4, Atlanta Federal Center, 61 Forsyth Street, S.W., Atlanta, Georgia 30303–3104.

SUPPLEMENTARY INFORMATION: Section 405 of the Clean Water Act (CWA), 33 U.S.C. 1345, created the sludge management program, allowing EPA to issue permits for the disposal of sewage sludge under conditions required by the CWA. Section 405(c) of the CWA provides that a state may submit an application to EPA for administering its own program for issuing sewage sludge permits within its jurisdiction. EPA is required to approve each such submitted state program unless EPA determines that the program does not meet the requirements of the EPA regulations implementing those sections.

South Carolina's application for sludge management program approval contains a letter from the Governor requesting program approval, an Attorney General's Statement, copies of pertinent State statutes and regulations, the SCDHEC Program Description, and a draft SCDHEC/EPA Memorandum of Agreement(MOA).

Indian Tribes. The term ''Indian Tribe'' is defined under the Act as ''any Indian Tribe, band, nation, or other organized group of community, including any Alaskan Native village, which is federally recognized as eligible for the special programs, and services provided by the United States to Indians because of their status as Indians.'' EPA notes that South Carolina's application does not, nor does it intend to, include management of sewage sludge on lands within Indian Country. EPA will retain authority for administering the federal sewage sludge management program within Indian Country.

Availability of State Submittal

South Carolina's submittal may be reviewed by the public from 8:00 a.m. to 4:00 p.m., Monday through Friday, excluding holidays, at the South Carolina Department of Health and Environmental Control, Water Facilities Permitting Division; 2600 Bull Street, South Carolina 29201–1708 or at the EPA Regional Office in Atlanta, Georgia, at the address appearing earlier in this notice.

Copies of the submittal may be obtained at a cost of $0.25 per page by check made payable to the South Carolina Department of Health and Environmental Control. Requests for copies should be addressed to Mr. Michael J. Montebello, South Carolina Department of Health and Environmental Control at the address provided above or at telephone number (803) 734–5226.

EPA's Decision

After the close of the public comment period, EPA will decide whether to approve or disapprove South Carolina's sludge management program. The decision will be based on the requirements of Section 405 of the CWA and EPA regulations promulgated thereunder.

If the South Carolina program is approved, EPA will so notify the State. Notice will be published in the **Federal Register** and, as of the date of program approval, EPA will suspend issuance of sewage sludge permits in South Carolina (except, as discussed above, for those sewage sludge use or disposal management practices in ''Indian Country''). The State's program will operate in lieu of the EPA-administered program. However, EPA will retain the right, among other things, to object to sewage sludge permits proposed to be issued by South Carolina and to take enforcement actions for violations. If EPA disapproves South Carolina's sludge management program, EPA will notify the State of the reasons for disapproval and of any revisions or modifications to the State program that are necessary to obtain approval.