ENVIRONMENTAL PROTECTION AGENCY

[PF–842; FRL–6042–1]

Notice of Filing of Pesticide Tolerance 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–842, must be received on or before December 21, 1998.

ADDRESSES: By mail submit written comments to: Information and Records Integrity Branch, Public Information and Services Divison (7502C), Office of Pesticides Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. In person bring comments to: Rm. 119, CM #2, 1921 Jefferson Davis Highway, Arlington, VA.

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

Information submitted as a comment concerning this document may be claimed confidential by marking any part or all of that information as ''Confidential Business Information'' (CBI). CBI should not be submitted through e-mail. Information marked as CBI will not be disclosed except in accordance with procedures set forth in 40 CFR part 2. A copy of the comment that does not contain CBI must be submitted for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice. All written comments will be available for public inspection in Rm. 119 at the address given above, from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays.

FOR FURTHER INFORMATION CONTACT: Mary L. Waller, Registration Support Branch, Registration Division (7505W), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW, Washington, DC 20460. Office location, telephone number, and e-mail address: Rm. 247, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, VA 22202, (703) 308–9354; e-mail: waller.mary@epamail.epa.gov.

SUPPLEMENTARY INFORMATION: EPA has received pesticide petitions as follows proposing the establishment and/or amendment of regulations for residues of certain pesticide chemicals in or on various food commodities under section 408 of the Federal Food, Drug, and 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 supports granting of the petition. Additional data may be needed before EPA rules on the petition.

The official record for this notice of filing, as well as the public version, has been established for this notice of filing under docket control number [PF–842] (including comments and data submitted electronically as described below). A public version of this record, including printed, paper versions of electronic comments, which does not include any information claimed as CBI, is available for inspection from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The official record is located at the address in ''ADDRESSES'' at the beginning of this document.

Electronic comments can be sent directly to EPA at:

opp-docket@epamail.epa.gov

Electronic comments must be submitted as an ASCII file avoiding the use of special characters and any form of encryption. Comment and data will also be accepted on disks in Wordperfect 5.1/6.1 file format or ASCII file format. All comments and data in electronic form must be identified by the docket control number (PF–842) and appropriate petition number. Electronic comments on this notice may be filed online at many Federal Depository Libraries.

List of Subjects

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

Dated: November 10, 1998.

James Jones,

Director, Registration Division, Office of Pesticide Programs.

Summary of Petition

Petitioner summaries of the pesticide petitions are printed below as required by section 408(d)(3) of the FFDCA. The summaries of the petitions were prepared by the petitioners and represent the views of the petitioners. EPA is publishing the petition summaries verbatim without editing them in any way. The petition summaries announce 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. Novartis Crop Protection, Inc.

PP 8F3654 PP 8F3674

EPA has received two pesticide petitions (PP 8F3654 & PP 8F3674) from Novartis Crop Protection, Inc., P.O. Box 18300, Greensboro, NC 27419, proposing pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 346a(d), to amend 40 CFR part 180 by establishing tolerances for residues of propiconazole (1-[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl-1H-1,2,4-triazole) in or on the raw agricultural commodities corn, fodder (12.0 parts per million (ppm)); corn, forage (12.0 ppm); corn, grain (0.1 ppm); corn, sweet (0.1 ppm); pineapples (0.1 ppm); pineapples, fodder (0.1 ppm) (PP 8F3674); peanuts (0.2 ppm); peanuts, hay (20 ppm); and peanuts, hulls (1.0 ppm) (PP 8F3654). EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant/animal 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 method*. 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 ppm.

3. *Magnitude of residues*. 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

1. *Acute toxicity—Propiconazole exhibits low toxicity*. Data indicated the following: a rat acute oral LD_{50} of 1,517 milligrams/kilograms (mg/kg); a rabbit acute dermal LD_{50} > 6,000 mg/kg; a rat inhalation LC_{50} > 5.8 mg/liter air; minimal skin and slight eye irritation; and nonsensitization.

2. *Genotoxicty*. Propiconazole exhibits no mutagenic potential based on the following data: *In vitro* gene mutation test (Ames assay, rat hepatocyte DNA repair test, (human fibroblast DNA repair test), *In vitro* chromosome test, (human lymphocyte cytogenetic test), *In vivo* mutagenicity test, (Chinese hamster bone marrow cell nucleus anomaly test, Chinese hamster bone marrow cell micronucleus test, mouse dominant lethal test), and other mutagenicity test (BALB/3T3 cell transformation assay).

3. *Reproductive and developmental toxicity*. In an oral teratology study in the rabbit, a maternal no observed adverse effect level (NOAEL) of 30 mg/kg was based on reduced food intake but without any fetotoxicity even at the top dose of 180 mg/kg. In an oral teratology study in the rabbit, a maternal NOAEL of 100 mg/kg was based on reductions in body weight gain and food consumption and a fetal NOAEL of 250 mg/kg was based on increased skeletal variations at 400 mg/kg. In an oral teratology study in the rat, a maternal and fetal NOAEL of 100 mg/kg was based on decreased survival, body weight gain, and food consumption in the dams and delayed ossification in the fetuses at 300 mg/kg. In a second teratology study in the rat, a maternal and fetal NOAEL of 30 mg/kg was 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 per group as usually required showed no teratogenic potential for the compound. A 2-generation reproduction study in the rat showed excessive toxicity at 5,000 ppm without any teratogenic effects. A 2-generation reproduction study in the rat showed 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, and parental toxicity was also evident. The NOAEL for development toxicity is 500 ppm.

4. *Subchronic toxicity*. In a 21 day dermal study in the rabbit, a NOAEL of 200 mg/kg was based on clinical signs of systemic toxicity. In a 28 day oral toxicity study in the rat, a NOAEL of 50 mg/kg was based on increased liver weight. In a subchronic feeding study in the mouse, a NOAEL of 20 ppm (3 mg/kg) was based on liver pathologic changes. In a 13 week feeding study in the male mouse, a NOAEL of 20 ppm (3 mg/kg) was based on liver pathologic changes. In a 90 day feeding study in rats, the NOAEL was 240 ppm (24 mg/kg) based on a reduction in body weight gain. In a 90 day feeding study in dogs, the NOAEL was 250 ppm (6.25 mg/kg) based on reduced food intake and stomach histologic changes.

5. *Chronic toxicity*. In a 12 month feeding study in the dog, a NOAEL of 50 ppm (1.25 mg/kg) was based on stomach histologic changes. In a 24 month oncogenicity feeding study in the mouse, the NOAEL was 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. In a 24 month chronic feeding/oncogenicity study in the rat, a NOAEL of 100 ppm (5 mg/kg) was 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. 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 NOAEL 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.

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.

C. Aggregate Exposure

1. *Dietary exposure*. The RfD for propiconazole is 0.0125 mg/kg/day and is based on a 1 year feeding study in dogs with a NOAEL of 1.25 mg/kg/day (50 ppm) and an uncertainly factor of 100.

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

ii. *Chronic risk*. 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% 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 October 31, 1998).

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 5F3740 - 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).

3. *Drinking water*. 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.

The degradation of propiconazole is microbially mediated with an aerobic soil metabolism half-life of 70 days. While propiconazole is hydrolytically and photochemically stable ($T_{1/2}$ >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.

4. *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% of all households nationally use propiconazole in a residential setting.

D. Cumulative Effects

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 Determination

1. *U.S. population—Reference dose*. Using the conservative exposure assumptions described above (100% 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% 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% 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 NOAEL for developmental toxicity was established in the rat teratology study at 30 mg/kg, a level 24-fold higher than the NOAEL of 1.25 mg/kg on which the RfD is based.

3. *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% for nursing infants less than 1 year old, 65% for non-nursing infants less than 1 year old, 35% for children 1-6 years old, and 23% 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. 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.

2. Tomen Agro, Inc. and Bayer Corporation, Agriculture Division

PP 7F4890

EPA has received a pesticide petition (PP 7F4890) from the TM-402 Fungicide Task Force comprised of Tomen Agro, Inc., 100 First Street, Suite 1610, San Francisco, CA 94105 and Bayer Corporation, Agriculture Division, 8400 Hawthorn Road, P.O. Box 4913, Kansas City, MO 64120-0013, proposing pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 346a(d), to amend 40 CFR part 180 by establishing a tolerance for residues of N-(2,3-dichloro-4-hydroxyphenyl)-1-

methyl-cyclohexanecarboxamide (TM-402 or Fenhexamid) in or on the raw agricultural commodities grapes and strawberries at 3.0 parts per million (ppm) and in raisens at 6.0 ppm. EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Analytical method*. An adequate method for purposes of enforcement of the proposed TM-402 tolerances in plant commodities is available. Bayer AG Analytical Method No. 00362 was used by Bayer AG to determine magnitude of TM-402 residues in fresh and processed grapes. This method has been independently validated. The limits of quantitation (LOQ) were determined to be 0.02 ppm for grapes, wine, and juice, and 0.05 ppm for strawberries, and raisins.

2. *Magnitude of residues*. The maximum TM-402 residues in fresh grapes, grape juice, raisins or wine permitted by the proposed label is 2.9 ppm. The maximum TM-402 calculated residue for grape juice is 1.7 ppm. For raisins the calculated residue value is 5.2 ppm, and for wine the value is 1.2 ppm. The maximum TM-402 residue for fresh strawberries permitted by the proposed label is 2.3 ppm. The average TM-402 residues for fresh grapes, grape juice, raisins and wine resulting from the treatment of grapes permitted by the proposed label are 1.3 ppm. The average TM-402 calculated residue for grape juice is 0.8 ppm. For raisins the average calculated residue value was 2.3 ppm, and for wine the values are 0.52 ppm. The average TM-402 residue for fresh strawberries permitted by the proposed label is 1.2 ppm. Since strawberries, grapes and processed grape commodities are not significant livestock feeds, a nature-of-the-residue discussion in livestock is not required. Additionally, since no aquatic uses are proposed, magnitude of the residue data in fish and irrigated crops are not required.

B. Toxicological Profile

1. *Acute toxicity*. Data from a complete battery of acute toxicity studies for TM-402 technical are available. The acute oral toxicity study resulted in an LD_{50} of >5,000 milligrams/kilogram (mg/kg) for both sexes. The acute dermal toxicity in rats resulted in an LD_{50} of > 5,000 mg/kg for both sexes. The acute inhalation was investigated in two studies in rats. Inhalation by aerosol at the maximum technically possible concentration of 0.322 mg/l resulted in no deaths or symptoms (LC_{50} >0.322 mg/l). A dust inhalation study resulted in an LC_{50} >5.057 mg/l. TM-402 was not irritating to the skin or eyes after a 4 hour exposure period. The Buehler dermal sensitization study in guinea pigs indicated that TM-402 is not a sensitizer. Based on these results TM-402 technical is placed in toxicity Category IV and does not pose any acute dietary risks.

2. *Genotoxicty*. The potential for genetic toxicity of TM-402 was evaluated in six assays including two Ames tests, an HGPRT forward mutation assay, a UDS assay, an *in vitro* chromosomal aberration assay in CHO cells, and a micronucleus test in mice. The compound was found to be devoid of any mutagenic activity in each of these assays including those tests that investigated the absence or presence of metabolic activating systems. The weight of evidence indicates that TM-402 technical does not pose a risk of mutagenicity or genotoxicity.

3. *Reproductive and developmental toxicity*. TM-402 has been tested for reproductive toxicity in rats and developmental toxicity in both rats and rabbits.

i. In a 2-generation reproduction study (one mating per generation), 30 Sprague-Dawley rats per sex per dose were administered 0, 100, 500, 5,000, or 20,000 ppm of TM-402 in the diet. The reproductive toxicity no observed adverse effect level (NOAEL) was 20,000 ppm. The neonatal NOAEL was 500 ppm, and the lowest observed effect level (LOAEL) was 5,000 ppm based on decreased pup body weight. The parental toxicity NOAEL was 500 ppm based on lower adult pre-mating body weights at 5,000 and 20,000 ppm, lower gestation body weights at 20,000 ppm, lower lactation body weights at 5,000 and 20,000 ppm, and statistically significant changes in clinical chemistry parameters, terminal body weights, and organ weights at 5,000 and 20,000 ppm. Based on this study, it is clear that the only toxic effects in the neonates occurred at parentally toxic doses.

ii. *In rats*. TM-402 was administered by gavage at doses of 0 or 1,000 mg/kg for gestation days 6-15. No maternal toxicity, embryotoxicity, fetotoxicity, or teratogenic effects were observed at the limit dose of 1,000 mg/kg/day. Therefore, the NOAEL for maternal and developmental toxicity was 1,000 mg/kg/day.

iii. *In rabbits*. TM-402 was administered by gavage at doses of 0, 100, 300, and 1,000 mg/kg for gestation days 6-18. Body weight gain and feed consumption of the dams were reduced at the two top doses. One abortion occurred in each of the top two dose groups and two total resorptions occurred in the top dose group. The placental weights were slightly decreased at 300 mg/kg/day and above. In the 1,000 mg/kg/day group slightly decreased fetal weights and a slightly retarded skeletal ossification were observed. All other parameters investigated in the study were unaffected. Therefore, the NOAELs for maternal and developmental toxicity were 100 mg/kg/day in this study.

Based on the 2-generation reproduction study in rats, TM-402 is not considered a reproductive toxicant and shows no evidence of endocrine effects. The data from the developmental toxicity studies on TM-402 show no evidence of a potential for developmental effects (malformations or variations) at doses that are not maternally toxic. The NOAEL for both maternal and developmental toxicity in rats was 1,000 mg/kg/day and for rabbits the NOAEL for both maternal and developmental toxicity was 100 mg/kg/day.

4. *Subchronic toxicity*. The subchronic toxicity of TM-402 has been evaluated in rats, mice, and dogs.

i. TM-402 was administered in the diet to rats for 13 weeks at doses of 0, 2,500, 5,000, 10,000 and 20,000 ppm. The NOAEL was 5,000 ppm (415 mg/kg/day in males and 549 mg/kg/day in females). Reversible liver effects were observed at 10,000 ppm.

ii. TM-402 was administered in the diet to mice for approximately 14 weeks at doses of 0, 100, 1,000 and 10,000 ppm. The NOAEL was 1,000 ppm (266.6 mg/kg/day in males and 453.9 mg/kg/day in females). Increased feed and water consumption and kidney and liver effects were observed at 10,000 ppm.

iii. TM-402 was administered in the diet to beagle dogs for 13 weeks at doses of 0, 1,000, 7,000 and 50,000 ppm. The NOAEL was 1,000 ppm (33.9 mg/kg/day in males and 37.0 mg/kg/day in females. Increased Heinz bodies were observed at 7,000 ppm.

5. *Chronic toxicity*. The chronic toxicity of TM-402 has been evaluated in a 1 year dog study and a 2 year chronic toxicity/oncogenicity study in rats.

i. TM-402 was administered in the feed at doses of 0, 500, 3,500, or 25,000 ppm to 4 male and 4 female beagle dogs per group for 52 weeks. A systemic

NOAEL of 500 ppm (an average dose of 17.4 mg/kg/day over the course of the study) was observed based on decreased food consumption and decreased body weight gain at 25,000 ppm, decreased erythrocyte, hemoglobin and hematocrit values at 25,000 ppm, increased Heinz bodies at 3,500 ppm and above, and a dose-dependent increase of alkaline phosphatase at 3,500 ppm and above. There were no treatment related effects on either macroscopic or histologic pathology.

ii. A combined chronic/oncogenicity study was performed in Wistar rats. Fifty animals/sex/dose were administered doses of 0, 500, 5,000, or 20,000 ppm for 24 months in the feed. A further 10 animals/sex/group received the same doses and were sacrificed after 52 weeks. The doses administered relative to body weight were 0, 28, 292, or 1,280 mg/kg/day for males and 0, 40, 415, or 2067 mg/kg/day for females. The NOAEL in the study was 500 ppm (28 mg/kg/day for males and 40 mg/kg/day for females) based on body weight decreases in females at 5,000 ppm and above, changes in biochemical liver parameters in the absence of morphological changes in both sexes at 5,000 ppm and above, and caecal mucosal hyperplasia evident at 5,000 ppm and above.

The NOAEL in the chronic dog study was 17.4 mg/kg/day based on body weight, hematology and clinical chemistry effects. The lowest NOAEL in the 2 year rat study was determined to be 28 mg/kg/day based on body weight, clinical chemistry parameters in the liver, and caecal mucosal hyperplasia.

6. *Oncogenicity*. The oncogenic potential of TM-402 has been in a 2 year oncogenicity study in mice and a 2 year chronic toxicity/oncogenicity study in rats.

i. *Mouse*. TM-402 was administered to 50 B6C3F1 mice/sex/group in their feed at concentrations of 0, 800 ,2,400 , or 7,000 ppm for 24 months. These concentrations resulted in a compound intake of 247.4,807.4 or 2354.8 mg,kg,day in males and 364.5, 1054.5 and 3178.2 mg/kg/day in females. A further 10 mice/sex/group received the same concentrations and were sacrificed after 12 months. There was no treatment effect on mortality, feed consumption,the hematological system or on the liver. Water consumption was increased in both sexes, and body weights were 8% lower in males at the highest dose of 7,000 ppm. At 7,000 ppm, elevated plasma creatinine concentrations, decreased kidney weights, and an increased occurrence of morphological lesions indicated a nephrotoxic effect of the compound. There was no shift in the tumor spectrum with treatment, and therefore, TM-402 was not oncogenic in this study.

ii. *Rat*. In the 2 year rat chronic/oncogenicity study described above, there was no indication of an oncogenic response. There was no indication of an oncogenic response in the 2 year rat and mouse studies on TM-402.

7. *Neurotoxicity*. The possibility for acute neurotoxicity of TM-402 was investigated. TM-402 was administered by gavage ina single dose to 12 Wistar rats/sex/group at doses of 0, 200, 630, 2,000 mg/kg. There was no evidence of neurotoxicity at any level tested.

8. *Endocrine disruption*. TM-402 has no endocrine-modulation characteristics as demonstrated by the lack of endocrine effects in developmental, reproductive, subchronic, and chronic studies.

C. Aggregate Exposure

1. *Dietary exposure*. Sources of dietary exposure to TM-402 are limited to the crops in the current submission. The following are the proposed tolerances: grapes - 3.0 ppm and strawberries - 3.0 ppm. A food additive tolerance of 6.0 ppm in raisins is also being proposed.

2. *Drinking water*. Review of the environmental fate data indicates the TM-402 is relatively immobile and rapidly degrades in the soil and water. TM-402 dissipates in the environment via several processes. Therefore, a significant contribution to aggregate risk from drinking water is unlikely.

3. *Non-dietary exposure*. There is no significant potential for non-occupational exposure to the general public. The proposed uses are limited to agricultural and horticultural use.

D. Cumulative Effects

Consideration of a common mechanism of toxicity is not appropriate at this time since there is no significant toxicity observed for TM-402. Even at toxicology limit doses, only minimal toxicity is observed for TM-402. Therefore, only the potential risks of TM-402 are considered in the exposure assessment.

E. Safety Determination

1. *U.S. population*. Based on the most sensitive species, Tomen Agro has calculated an appropriate Reference Dose (RfD) for TM-402. Using the NOAEL of 17.4 mg/kg/day in the 1 year dog study and an uncertainty factor (UF) of 100 to account for inter- and intra-species variability, an RfD of 0.177 mg/kg/day is recommended.

A chronic dietary risk assessment which included all proposed tolerances was conducted on TM-402 using U.S. EPA's Dietary Risk Evaluation System (DRES). The theoretical maximum residue contribution (TMRC) for the U.S. population (48 States) is 0.00125 mg/kg/day and this represents 0.71% of the propoed RfD. The most highly exposed subgroup was children (1- 6 years old) where the TMRC was 0.00382 mg/kg/day, representing only 2.15% of the proposed RfD. For non-nursing infants (>1 year old) the TMRC was 0.00101 mg/kg/day (0.57% of the RfD) and for children 7-12 years old the TMRC is 0.00156 mg/kg/day (0.88% of the RfD). If these calculations consider the average of anticipated residue values instead of assuming ''tolerance level'' residues, the values are reduced to approximately one-third of those listed above. Even under the most conservative assumptions, the estimates of dietary exposure clearly demonstrate adequate safety margins of all segments of the population.

2. *Infants and children*. In assessing the potential for additional sensitivity of infants and children to residues of TM-402, the available developmental toxicity and reproductive toxicity studies and the potential for endocrine modulation by TM-402 were considered. Developmental toxicity studies in two species indicate that TM-402 does not impose additional risks to developing fetuses and is not a teratogen. The 2-generation reproduction study in rats demonstrated that there were no adverse effects on reproductive performance, fertility, fecundity, pup survival, or pup development at non-maternally toxic levels. Maternal and developmental NOAELs and LOAELs were comparable, indicating no increase in susceptibility of developing organisms. No evidence of endocrine effects were noted in any study. It is therefore concluded that TM-402 poses no additional risk for infants and children and no additional uncertainty factor is warranted.

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