EPA Registration Division Contact : Mr. J. A. Tompkins, 703-305-5697

1. E.I. du Pont de Nemours and Company

PP No. 7F7220

EPA has received a pesticide petition from E.I. du Pont de Nemours and Company, Crop Protection Products, Laurel Run Plaza, P.O. Box 80038, Wilmington, DE 19880-0038 (PP No. 7F7220) 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 180.451 by establishing a tolerance for residues of the herbicide, tribenuron methyl (methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)methylamino]carbonyl]amino]sulfonyl] benzoate) in or on the following raw agricultural commodities: Wheat Forage at 0.3 ppm, Wheat Hay at 0.3 ppm, Barley Hay at 0.3 ppm, Oat Forage at 0.3 ppm, and Oat Hay at 0.8 ppm. EPA has determined that the petition contains data or information regarding the elements set forth in section 408 (d) (2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. Plant Metabolism

The qualitative nature of the residues of tribenuron methyl is adequately understood.

Tribenuron methyl is rapidly metabolized in wheat plants with a half-life of less than 4 days. A major metabolic reaction was N-demethylation of tribenuron methyl to form metsulfuron methyl. Metsulfuron methyl was further metabolized, primarily through rapid hydroxylation of the phenyl ring, followed by conjugation with glucose. Hydrolysis of the sulfonylurea bridge of tribenuron methyl to release sulfonamide and triazine amine was also observed. The sulfonamide may be further metabolized to hydroxylated sulfonamide or cyclized to saccharin. The presence of alpha-hydroxy triazine amine, N-demethyl triazine amine, and O-demethyl N-demethyl triazine amine demonstrated that the released triazine moiety of tribenuron methyl was also extensively degraded in wheat. Metabolism studies were conducted with radioactive [^{14}C]-tribenuron methyl on wheat under field conditions. Wheat plants at the tillering stage were treated with 72-75 g active ingredient (ai)/ha of [^{14}C]-phenyl and [^{14}C]-triazine labeled tribenuron methyl. Samples were harvested 0, 4, 8, 14, 21, 28, and 63 days after treatment. Total [^{14}C] residue levels in the foliage declined rapidly from 5.5 ppm at time of application to 0.55 ppm in the mature straw and 0.05 ppm in the grain ([^{14}C]-phenyl), and from 4.2 ppm to 0.37 ppm in the mature straw and 0.01 ppm in the grain ([^{14}C]-triazine). Analysis of the wheat foliage and straw extracts by HPLC and TLC revealed that tribenuron methyl was rapidly and extensively

metabolized. Metabolites were identified based on chromatography with authentic standards. The major metabolites were the glucose conjugate of hydroxylated metsulfuron methyl, hydroxylated saccharin, the glucose conjugate of hydroxylated saccharin, saccharin, triazine amine, O-demethyl triazine amine, and O-hydroxy triazine amine.

A metabolism study was conducted with [^{14}C] Tribenuron methyl on ALS-Tolerant Canola. [^{14}C] Tribenuron methyl was applied at 25 g ai/ha as a topical spray treatment at the 2 true leaf stage to bolting. Whole canola plants were harvested at 0, 2, and 35 days after treatment, and at maturity (78 days after treatment). Total reactive residue (TRR) in canola foliage, when expressed as tribenuron methyl equivalents, declined from, on average, 0.26 ppm at day 0 to 0.04 ppm at day 35. TRR in immature 35-day canola seed pods was not higher than 0.04 ppm, and was 0.02 ppm in 78-day seed samples. [^{14}C] Tribenuron methyl accounted for greater than 81% of the radioactive residue in the 0 and 2 day foliage samples. Other minor components were polar metabolites or conjugates, each less than 10% of the TRR. No single component in the polar metabolites exceeded 0.01 ppm. In the 35-day foliage samples, [^{14}C] tribenuron methyl accounted for only about 11-25.5% of the TRR, which is less than 0.01 ppm. The average half life for [^{14}C] tribenuron methyl was 15 days. Several metabolic processes in the foliage are involved. They include a hydrolytic cleavage of tribenuron methyl as well as N-demethylation of tribenuron methyl. Other demethylation and hydroxylation processes continued up to final harvest. The results of the study suggest that the tribenuron methyl metabolic process in canola follows a typical plant metabolism pattern, and no accumulation of tribenuron methyl is anticipated in canola when it is used in accordance with the proposed labels.

A metabolism study was conducted to determine the nature and magnitude of the residues of tribenuron methyl in cotton plants after exposure to [2-^{14}C] tribenuron methyl. Soil treatments were applied at 0.3 oz ai/acre as a direct spray in an aqueous suspension containing inert dry-flowable formulation ingredients. The application was made immediately after planting cotton to provide the data for the shortest anticipated time between application and planting. No terminal residues at or above 0.01 ppm were observed in any triazine-label treated fractions of mature cotton after treatment with tribenuron methyl. No detectable residues were found in the undelinted seed, and very low residues (0.028 ppm) were observed in the gin trash after treatment. Tribenuron methyl and its known metabolites are not expected to be present in the terminal residues in gin trash or undelinted seed, when applied according to the proposed label.

A confined crop rotation study with [^{14}C]-phenyl tribenuron methyl was conducted using red beets, cabbage, sorghum, soybeans and wheat planted in pots of sandy loam soil 30 and 120 days after a single application of [^{14}C]-phenyl-labeled tribenuron methyl. For the 30-day aging period, samples from both treated and control crops were taken at 28, 49, and 67 days after planting with additional samples taken from the sorghum and soybeans plantings at 90 and 115 days. At maturity, all remaining plants were harvested and subdivided into edible and nonedible portions. Harvest dates, expressed as days after planting, were: 90 days (cabbage), 115 days (beets and wheat), and 168 days (sorghum and soybeans). Samples from all crops from the 120-day aging

study were taken at 28, 48, 69, and 90 days (maturity for wheat, beets and cabbage) and 120 days and 169 days (maturity for sorghum and soybeans). Tribenuron methyl dissipated rapidly in the soil with none of the intact material detected after the 30-day aging period. The major radiolabeled residue extracted from the soil was saccharin, which remained in the soil at very low levels throughout the study. Some accumulation of total radioactive residues was apparent in the mature wheat, soybean, and sorghum foliage due to the dehydrated nature of samples harvested. The major residue in the plants was identified as saccharin.

A confined crop rotation study with [^{14}C]-triazine tribenuron methyl was conducted using sorghum, red beets, and cabbage. Sandy loam soil was treated at 32 g ai/ha with [^{14}C]-phenyl tribenuron methyl in the greenhouse. Rotational crops were sown 30 and 120 days post-treatment. Tribenuron methyl degraded rapidly in the soil with no detectable intact material present 30 days post-treatment. The major radiolabeled metabolite was the triazine amine. No significant accumulation (i.e., less than 0.01 ppm) of radiolabeled materials from the soil were observed in the mature crops of cabbage foliage. Some accumulation of the radioactivity was observed in the mature beet foliage in the 30-day study (0.029 ppm) and the 120-day study (0.011 ppm). Major metabolites were N-demethyl triazine amine and O-hydroxy triazine amine. Accumulation of radioactivity was observed in the mature sorghum straw due to the dehydrated nature of this plant tissue at harvest. Levels of radiolabeled materials detected were 0.108 and 0.057 ppm in the 30-day and 120-day studies, respectively. The major metabolites were highly polar materials. Tribenuron methyl rapidly decomposes in soil to the triazine amine, which is then degraded, not accumulated, in plants.

Based on the absence of quantifiable residues in food commodities (barley and oat grain), on the expected low residue levels of individual substances in feed items (straw) under normal conditions, and the Residue Chemistry Guidelines (OPPTS 860-1300, D, ii) which state that one metabolism study will be required for each of the crop groups defined in CFR 40 180.34 (f) except for herbs and spices, a plant metabolism study in barley and oat was not required.

2. Analytical Methods

Various analytical methods are available for the determination of residues of tribenuron methyl in barley grain, wheat grain, wheat straw, and wheat forage samples. One method uses normal phase liquid chromatography and a photoconductivity detector; and is based on extraction of tribenuron methyl from crops with acetonitrile, and cleanup on a silica cartridge. Recoveries for grain, straw and green forage samples fortified between 0.01 and 0.10 ppm averaged 88% with a standard deviation of 14%. The lower level of quantitation for grain and green forage is 0.01 ppm and for straw 0.02 ppm. This method was updated to a HPLC method with UV detection. The method provides a means to quantitate tribenuron methyl in these matrices at levels as low as 0.05 ppm, based on a 5-gram sample, using column and eluent switching. More recently, this method was further updated and provides for analysis of wheat grain, straw, and forage by HPLC

column switching and UV detection. The limit of quantitation (LOQ) for this updated method is 0.01 ppm for wheat grain and wheat forage, and 0.05 ppm for wheat hay.

The analyses of sunflower samples were conducted with this further updated method. The LOQ for the analysis of sunflower seed was 0.05 ppm based on a 5-gram sample. This method was validated at 0.05 and 0.5 ppm, with an average recovery of 70 % (+/- 6%) and 70% (+/- 3%), respectively.

Methods have been developed for the analysis of Tribenuron methyl in other crops. Residues of tribenuron methyl at levels of 0.02 ppm or above in grass seed, straw, and seed screenings are quantified using gel permeation chromatography and solid-phase extraction. Purified column eluent is taken to dryness, dissolved in ethyl acetate, and analyzed by capillary gas chromatography using a mass spectral detector. In fortification recovery trials, an average recovery of 87.6 % with a standard deviation of 21 % was obtained for eighteen grass seed samples over a fortification range of 0.02 to 0.06 ppm. Tribenuron methyl residues in canola and flax samples were determined by an analytical method, based on the use of liquid chromatography with eluent and column switching with UV detection at 258 nm, at levels as low as 0.02 ppm (limit of quantitation) using a 5 gram sample. Residues in cotton seed and cotton gin trash were determined based on the use of column-switching liquid chromatography with detection via positive ion electrospray mass spectroscopy. The limit of quantitation was determined to be 0.02 ppm and the limit of detection was estimated to be 0.006 ppm, based on a 5 gram sample.

Residues in rice grain and straw, corn forage and stover, and grain sorghum forage and stover were determined with an analytical method utilizing sample extraction by homogenization in a potassium phosphate buffer solution. The extracts were cleaned-up and concentrated by solid-phase extraction. Analysis was performed by reversed-phase HPLC and quantitatively analyzed by tandem mass spectrometric detection. The target limit of quantitation (LOQ) was 0.05 ppm in these commodities.

Tribenuron methyl residues in field corn grain, grain sorghum grain, and soybean seed were determined by an analytical method utilizing LC/MS/MS analysis. The analytes were resolved by HPLC chromatography and quantitatively analyzed by tandem mass spectrometric detection. The LOQ was 0.05 ppm in these commodities.

Tribenuron methyl residues in wheat forage and hay, barley hay, and oat forage and hay also were determined by an analytical method utilizing LC/MS/MS analysis. The analytes were resolved by HPLC chromatography and quantitatively analyzed by using the Total Ion

Chromatogram (TIC) from two molecular ion transitions for each analyte. The LOQ was 0.01 ppm in these commodities.

3. Magnitude of Residue

a. Wheat and Barley, Grain and Straw

A study was conducted to determine the extent of residues of tribenuron methyl in wheat when applied at the maximum use rate (0.25 oz ai/A) 40 days before maturity. Samples of mature wheat grain and straw were taken from treated and control plots at preharvest intervals ranging from 25 to 40 days after the test substance was applied. A two-step HPLC method was used to determine tribenuron methyl at levels as low as 0.0075 ppm in wheat grain based on a 20 gram sample, and 0.014 ppm in wheat straw based on a 10 gram sample. No grain or straw samples showed quantifiable residues of tribenuron methyl.

A study was conducted to determine the extent of residues of tribenuron methyl in barley when applied at the maximum use rate (0.25 oz ai/A) 40 days before maturity. Samples of mature barley grain and straw were taken from each plot at preharvest intervals ranging from 24 to 43 days after the test substance was applied. A two-step HPLC method was used to determine tribenuron methyl at levels as low as 0.0066 ppm in barley grain based on a 20 gram sample, and 0.013 ppm in barley straw based on a 10 gram sample. One of the grain samples showed a detectable residue (0.0064 ppm) of tribenuron methyl, which is below the established grain tolerance of 0.05 ppm. A straw sample from one of the sites contained tribenuron methyl at 0.034 ppm, which is below the established straw tolerance of 0.10 ppm. The remaining grain and straw samples showed no detectable or quantifiable residues of tribenuron methyl.

The results of the analyses of grain and straw from wheat and barley show that no residues were found in either grain or straw from plants treated at or below the maximum recommended application rate of 0.25 oz. ai/acre, with a 0.02 - 0.05 ppm LOQ. The preharvest intervals ranged from 42-140 days. A small percentage of plants treated at higher rates showed some residues in straw.

b. Grass, Forage and Hay

Established plots of bluegrass, tall fescue, and perennial ryegrass grown for production of grass seed were each treated with 0.25 oz ai/A and 0.50 oz ai/A of tribenuron methyl. Sampling preharvest intervals ranged from 56 to 85 days. Reliable detected residues of tribenuron methyl (0.016 ppm or above) were not found in any crop fraction from any test site, with one exception for a screenings waste sample with a residue level of 0.004 ppm for the 0.25 oz ai/A treatment, and 0.006 ppm for the 0.50 oz ai/A treatment. An attempt to reconfirm this result by reextracting a second screening waste sample failed to confirm the presence of these tribenuron methyl residues.

c. Oat, Grain and Straw

A study was conducted to determine the extent of residues of tribenuron methyl in oats when applied at one and two times the maximum use rate, approximately 40 days before harvest. Samples of mature oat grain and straw were taken from both treated and control plots at preharvest intervals ranging from 39 to 57 days after the application of the test substance. A two-step HPLC method was used to detect tribenuron methyl residues in oat grain at levels as low as 0.0055 ppm based on a 20 gram sample, and in oat straw at levels as low as 0.018 ppm based on a 10 gram sample. Residues of tribenuron methyl in oat grain from oats treated at 1x and 2x rates were below the LOQ of 0.013 ppm and 0.01 ppm, respectively. The residues of tribenuron methyl in oat straw were below the LOQ of 0.018 ppm and 0.04 ppm, respectively - and also below reported detection level of 0.009 ppm and 0.018 ppm, respectively, in oat straw from oats treated at 1x and 2x rates.

d. Canola and Flax

Magnitude of residue studies were conducted on seed fractions of canola varieties containing the Smart™ trait. CDC Triffid flax was also treated. The post-emergent broadcast application of tribenuron methyl at 0.07 and 0.14 oz. ai/acre represents one to two times the proposed use rate on these canola and flax varieties. No tribenuron methyl residues were found above the LOQ of 0.02 ppm in any seed samples treated with the test substance at a use rate of 0.7 to 0.14 oz of tribenuron methyl/acre.

e. Cotton Seed and Gin Trash

Magnitude of residue studies were also conducted to determine residues of tribenuron methyl in cotton seed and cotton gin trash. The study consisted of three treatments. Treatment 1: One broadcast application at 0.15 oz ai/A, applied approximately 14 days prior to planting. Treatment 2: One broadcast application at 0.15 oz ai/A, applied pre-plant, on the day of planting. Treatment 3: One broadcast application at 0.75 oz ai/A, applied pre-plant, the day of planting. The anticipated target PHI was approximately 120 days after the last application of the test substance; actual PHIs ranged from 123 to 196 days. The experimentally determined limit of quantitation was 20 ppb for both analytes. The limit of detection was estimated to be 6 ppb. No tribenuron methyl residues were found above the limit of quantitation of 0.02 ppm in any cotton seed and cotton gin trash samples treated with the test substance.

f. Sunflowers

Magnitude of the residue studies were conducted by IR-4 to determine residues of tribenuron methyl in sunflowers. Test plots were treated with three broadcast applications of tribenuron methyl, applied at rates of 0.25 – 1.3 oz ai/acre per application, for a total application rate of 0.75

to 3.9 oz ai/acre per crop season. Commercially mature sunflower seed samples were collected 67-84 days following the last application. The results from these trials show that maximum residues of tribenuron methyl are less than 0.05 ppm, which is the limit of quantitation. Sunflowers treated with the 5X exaggerated rate of tribenuron methyl, i.e., three applications at 1.3 oz ai/acre/application, also showed no residues of tribenuron methyl at or above the LOQ. A sunflower processing study was, therefore, not conducted.

g. Corn Grain, Forage and Stover

Studies were conducted to determine residues of tribenuron methyl in field corn grain, forage, and stover. Two test plots were established at each site. One plot was untreated and provided control samples for analysis. The other plot received one pre-planting or at-planting application of tribenuron methyl at a rate of 1.25 oz ai/acre, which was five times the maximum expected label rate. Field corn commodity samples – grain, forage, and stover - were collected at normal harvest (112-150 days after application, 75-106 days after application, and 112-150 days after application, respectively) and analyzed for residues of tribenuron methyl. In these exaggerated rate studies, at normal harvest, no residues were detected (limit of detection 0.02 ppm) in any untreated control or treated samples analyzed.

h. Soybeans

Studies were conducted to determine residues of tribenuron methyl in soybean seed. Two test plots were established at each site. One plot was untreated and provided control samples for analysis. The other plot received one pre-planting or at-planting application of tribenuron methyl at a rate of 1.25 oz ai/acre, which was five times the maximum expected label rate. Soybean seed samples were collected at normal harvest (135-148 days after application) and analyzed for residues of tribenuron methyl. In these studies, at normal harvest, no residues were detected (limit of detection 0.02 ppm) in any untreated control or treated samples analyzed.

i. Rice Grain and Straw

Studies were conducted to determine residues of tribenuron methyl in rice grain and straw. Two test plots were established at each site. One plot was untreated and provided control samples for analysis. The other plot received one pre-planting or at-planting application of tribenuron methyl at a rate of 1.25 oz ai/acre, which was five times the maximum expected label rate. Rice grain and straw samples were collected at normal harvest (106-129 days after application) and analyzed for residues of tribenuron methyl. In these exaggerated rate studies, at normal harvest, no residues were detected (limit of detection 0.02 ppm) in any untreated control or treated samples analyzed.

j. Grain Sorghum Forage, Stover and Grain

Studies were conducted to determine residues of tribenuron methyl in sorghum forage, stover, and grain. Two test plots were established at each site. One plot was untreated and provided control samples for analysis. The other plot received one pre-planting or at-planting application of tribenuron methyl at a rate of 1.25 oz ai/acre, which was five times the maximum expected label rate. Grain sorghum forage, stover, and grain samples were collected at normal harvest (87-103 days after application for forage, and 133-144 days after application for stover and grain) and analyzed for residues of tribenuron methyl. In these exaggerated rate studies, at normal harvest, no residues were detected (limit of detection 0.02 ppm) in any untreated control or treated samples analyzed.

k. Barley (Hay), Oat (Forage and Hay), and Wheat (Forage and Hay)

Magnitude of the residue studies in barley were conducted to determine the residues of tribenuron methyl in/on raw the agricultural commodity (RAC) barley hay after one post-emergence application of tribenuron methyl at a rate of 0.25 ounce ai/acre. This rate is 1X the label rate. The only RAC sample collected was barley hay. At 3 to 7 days after application, residues in barley hay ranged from 0.004 – 0.044 ppm, with an average residue of 0.023 ppm. At 13-31 days after application, residues in barley hay ranged from <0.003 – 0.27 ppm, with an average residue of 0.026 ppm.

Magnitude of the residue studies in oats were conducted to determine the residues of tribenuron methyl in/on raw the agricultural commodities (RACs) oat forage and hay after one post-emergence application of tribenuron methyl at a rate of 0.25 ounce ai/acre. This rate is 1X the label rate. At less than one day after application, residues in oat forage ranged from <0.003 – 1.4 ppm, with an average residue of 0.7 ppm. At 5 - 8 days after application, residues in oat forage ranged from <0.003 – 0.041 ppm, with an average residue of 0.009 ppm. At 5 - 8 days after application, residues in oat hay ranged from 0.003 – 0.021 ppm, with an average residue of 0.008 ppm. At 25 - 33 days after application, residues in oat hay ranged from <0.003 – 0.73 ppm, with an average residue of 0.06 ppm.

Magnitude of the residue studies in wheat were conducted to determine the residues of tribenuron methyl in/on raw the agricultural commodities (RACs) wheat forage and hay after one post-emergence application of tribenuron methyl at 0.25 ounce ai/acre. This rate is 1X the label rate. At less than one day after application, residues in wheat forage ranged from <0.003 – 2.7 ppm, with an average residue of 0.86 ppm. At 6 - 8 days after application, residues in wheat forage ranged from <0.003 – 0.24 ppm, with an average residue of 0.05 ppm. At 25 - 30 days after application, residues in wheat hay ranged from <0.003 – 0.29 ppm, with an average residue of 0.024 ppm.

B. Toxicological Profile

1. Acute Toxicity

Based on EPA criteria, technical tribenuron methyl is in acute toxicity Category IV for oral and inhalation routes of exposure, and for skin irritation. Tribenuron methyl is in acute toxicity Category III for the dermal route of exposure, and for eye irritation. It is not a skin sensitizer.

Acute oral toxicity in rats	LD_{50} > 5000 mg/kg
Acute dermal toxicity in rabbits	LD_{50} > 2000 mg/kg
Acute inhalation toxicity in rats	LC_{50} > 6.7 mg/L
Primary eye irritation in rabbits	Moderate effects reversed within 3 days
Primary dermal irritation in rabbits	Non-irritating
Dermal sensitization	Sensitizer

2. Genotoxicity

Technical tribenuron methyl has shown no genotoxic or mutagenic activity in the following *in vitro* and *in vivo* tests :

In vitro Mutagenicity Ames Assay	Negative
In vitro Mutagenicity CHO/HPRT Assay	Negative
In vitro Unscheduled DNA Synthesis	Negative
In vivo Cytogenetic	Negative
In vivo Bone Marrow Metaphase Analysis (Rat)	Negative
In vivo Micronuclei Induction (Mouse)	Negative

Tribenuron methyl was negative for mutagenicity in an *in vitro* bacterial gene mutation assay using *Salmonella typhimurium* and in an *in vitro* mammalian cell gene mutation assay using Chinese hamster ovary cells. In cultured primary rat hepatocytes *in vitro*, tribenuron methyl was negative for the induction of unscheduled DNA synthesis.

In a test measuring clastogenic damage *in vivo*, tribenuron methyl was negative for the induction of chromosome aberrations in male and female rat bone marrow cells at 5000 mg/kg. A study measuring chromosome damage *in vivo* was conducted. The study included the evaluation of micronuclei in bone marrow polychromatic erythrocytes of male and female mice. The result was negative when exposures were conducted at 5000 mg/kg body weight.

3. Reproductive and Developmental Toxicity

On long-term dietary administration, tribenuron methyl did not affect the reproduction or lactation performance of rats. Developmental studies in the rat and rabbit by gavage administration indicated that tribenuron methyl did not present a unique toxic risk to the fetus.

There were no effects in reproduction or lactation in a one-generation reproduction study with rats fed for 90 days with diets that contained 0, 100, 1750, or 5000 ppm active ingredient. The NOEL was 100 ppm (7 mg/kg/day for males and 8 mg/kg/day for females) based on lower mean dam and pup body weights for the intermediate and high dose groups.

There were no effects on fertility observed in a 2-generation reproduction study. In this study, rats were fed for at least 90 days with diets that contained 0, 25, 250, or 1000 ppm active ingredient. The NOEL was 25 ppm based on lower body weights for the dams and offspring at 250 and 1000 ppm. There were no differences attributed to administration of tribenuron methyl in the number of litters produced or other indices of reproductive performance. No compound-related effects on male fertility were noted. No effect on the number of pups born or pup survival were observed in any tribenuron methyl treated group.

In a study to evaluate developmental toxicity potential in rats, tribenuron methyl did not produce birth defects after administration via oral intubation to pregnant rats at dose levels of 0, 20, 125, and 500 mg/kg/day. The NOEL for this study was 20 mg/kg/day for both maternal and developmental toxicity. This was based on maternal effects at the 125 and 500 mg/kg/day. The effects included decreased body weight gain and food consumption, and an increased incidence of excess salivation. Fetal effects included decreased body weights (at 125 and 500 mg/kg/day) and increased number of resorptions (only at 500 mg/kg/day). In the rabbit developmental toxicity study, rabbits were fed dosage levels of 0, 5, 20, and 80 mg/kg/day. The NOEL for maternal and developmental toxicity was 20 mg/kg/day. This was based on maternal effects, including decreased feed consumption and an increased incidence of abortions at 80 mg/kg/day. Fetal effects included slightly reduced body weights at 80 mg/kg/day. No teratogenicity was observed.

4. Subchronic Toxicity

The most sensitive species to subchronic exposure of tribenuron methyl was the rat. In the rat study, rats were fed dosage levels of 0, 100, 1750 or 5000 ppm tribenuron methyl for 90 days. The findings show that the NOEL for tribenuron methyl was 100 ppm for both male and female rats (90-day dietary). This concentration is equivalent to 7 and 8 mg/kg/day in male and female rats, respectively. The NOEL was based on the decreased body weight and decreased feed consumption noted in the 1750 and 5000 ppm groups. The NOEL for the 90-day mouse feeding study was 500 ppm (70 mg/kg/day for males and 90 mg/kg/day for females) based on liver and spleen effects at 1250, 2500, and 5000 ppm at 4 weeks. An increase in liver weights at 2500 ppm was noted, with no histologic effects at any level. The NOEL for subchronic (90-day dietary) exposure in dogs was 73 mg/kg/day for male and 78 mg/kg/day for female dogs. This was highest dose tested, and no clear treatment related effects were observed. A specific target organ was not identified in any of the species studied.

5. Chronic Toxicity/Oncogenicity

The NOEL for chronic (18-month dietary) exposure in mice (males) was 20 ppm (equivalent to 3 mg/kg/day). This was based on an increased incidence of bilateral seminiferous degeneration and oligospermia in the mid- and high-dose groups. Within females, there was no LOAEL established, but the minimal body weight reductions in the highest dosed females suggested that the NOEL was 30 mg/kg/day. There were no neoplastic or other histopathological effects associated with this compound and no target organ was identified. Additionally, no evidence of tribenuron methyl induced oncogenicity was observed in the mouse study.

The NOEL for chronic (2-year dietary) exposure in rats was 25 ppm (0.95 and 1.2 mg/kg/day for male and female rats, respectively). Lower body weight gains, which paralleled lower food consumption and organ weight effects, were observed in the 250 and 1250 ppm groups. There were no clinical or histopathological effects associated with these organ weight effects. The incidence of mammary adenocarcinomas was greater than controls for female rats in the 1250 ppm group. This effect was only observed in this high-dose group and under conditions of significant physiological stress (mean body weights for female rats were 43% lower than the controls), which was determined to be above the maximum tolerated dose (MTD).

In a 1-year feeding study in dogs, the NOEL was determined by DuPont to be 250 ppm (8.16 and 8.18 mg/kg/day for male and female dogs, respectively). This was based on slightly lower body weights and increased serum creatinine concentrations for dogs in the high-dose group (1500 ppm). Upon review by the EPA, the NOEL was set at 25 ppm (0.8 mg/kg/day) based on observations such as elevated bilirubin blood levels and reduction in body weight gain in male dogs. There were no neoplastic or other histopathological effects associated with compound administration.

6. Animal Metabolism

The metabolism of tribenuron methyl was evaluated in rats using both phenyl and triazine labeling. Tribenuron methyl was extensively and rapidly converted to polar metabolites, and primarily excreted in the urine and feces. Urinary excretion accounted for two to four times the amount of radiolabel excreted via feces. Essentially all of the tribenuron methyl and its metabolites were excreted in the urine and feces of the rat within 96 hours after dosing. Levels of radiolabeled residues in tissues were correspondingly higher in those groups with slower elimination kinetics, but no evidence of bioconcentration was seen. None of the dosed label was expired as carbon dioxide or volatile metabolites.

The average excretion half-life values for male and female rats in the low-dose group (20 mg/kg) were approximately the same (26-33 hours), and independent of dietary preconditioning. The average excretion half-lives for male and female rats in the high-dose groups (1700, 1800, and 2000 mg/kg) were approximately 51-54 hours (males) and 68-96 hours (females). These results

indicate that the metabolism of tribenuron methyl in male and female rats is qualitatively similar, however, female rats metabolize and excrete this product much slower than male rats at the high doses. The low residual radioactivity in the rat indicated that tribenuron methyl does not covalently bind to tissue macromolecules. Based on these data, the body burden of this compound is not expected to increase significantly upon repeated, long-term administration.

The major metabolites of tribenuron methyl are those expected from the enzymatic hydroxylation and dealkylation activities of the hepatic microsomal mixed function oxidase system. The major urinary metabolites were identified as metsulfuron methyl and saccharin (phenyl labeled groups) and metsulfuron methyl and O-demethyl triazine amine (triazine labeled groups); no evidence of glucuronide or sulfate conjugation was seen.

Results from a metabolism study with two radioactive forms of tribenuron methyl ([^{14}C]-triazine and [^{14}C]-phenyl) in lactating goats show that most of the dosed radioactivity was recovered in the urine (61-71%) and feces (15-20%). In the urine, intact tribenuron methyl and metsulfuron methyl accounted for 17-23% and 20-22% of the administered dose, respectively. The third major component in phenyl-dosed goat urine was saccharin (23.5% of the dose); the third major metabolite in the triazine-dosed goat urine was O-demethyl N-demethyl triazine amine (10.9%). The highest levels of residues observed in the milk were 0.09 ppm (tribenuron methyl equivalents) from the triazine-dosed goat, and 0.006 ppm from the phenyl-dosed goat. Recoveries of the administered dose were 82.2% for the goat given the triazine label, and 86.8% for the goat dosed with the phenyl label. Throughout the dosing phase, the goats did not display any signs of toxicity, and there was no effect on milk production.

There were no significant levels of unique plant metabolites of tribenuron methyl found in food or feed products at crop maturity. Hence, toxicity testing of other degradation products of tribenuron methyl is not necessary.

7. Metabolite Toxicology

There is no evidence that the metabolites of tribenuron methyl, as identified in either the plant or animal metabolism studies, are of any toxicological significance.

8. Endocrine Effects

In the two-year study, female rats fed tribenuron methyl had a significant increase in mammary adenocarcinoma incidence, but only at a dose that greatly exceeded the maximum tolerated dose (43% decrease in body weight). In contrast, an 18-month feeding study demonstrated that

tribenuron methyl was not oncogenic in mice, nor was there oncogenicity in the rat study at doses which produced marked toxicity, but did not exceed the maximum tolerated dose.

A subsequent mechanistic study was conducted at a dose level that produced similar body weight gain decrements observed in the rat oncogenicity study. This mechanistic study demonstrated an increased incidence of rats with prolonged estrus and suggested that this may have been associated with the high-dose mammary adenomas observed in the rat oncogenicity study. However, the role of the body weight effect must be considered in interpreting this data. Numerous studies have demonstrated that nutritional deficits can also significantly impact the estrus cycle. Such hormone-mediated effects are considered to have a threshold below which growth of mammary tissue will not be affected. Thus potential endocrine effects of tribenuron methyl are unlikely to be a concern at biologically relevant doses. Adequate margins of safety protect humans from these threshold effects.

C. Aggregate Exposure

Tribenuron methyl is the active ingredient in various DuPont herbicides, with new proposed tolerances for barley hay, oat forage and hay, and wheat forage and hay uses on the following commercial crops: sunflowers, rice, field corn, soybeans, and grain sorghum. There are no residential uses for any tribenuron methyl containing herbicides.

1. Dietary Exposure

The chronic reference dose (cRfD) of 0.008 mg/kg/day is based on the NOEL determined by EPA of 0.8 mg/kg/day from the one-year dog feeding study and a 100X safety factor. Based on the acute toxicity profile of tribenuron methyl, there are no acute effects. Non-specific clinical signs and weight effects have been observed in developmental studies after high, multiple doses. However, in the acute LD_{50} study conducted at the limit dose of 5000 mg/kg, the only clinical sign observed was stained perineum in some animals. Therefore no relevant acute dietary endpoint attributable to a single dose was identified.
2. Food

a. Chronic Dietary Exposure Assessment

Chronic dietary exposure, resulting from the registered and proposed uses of tribenuron methyl on barley, canola, cotton, flax, grass, oats, wheat, rice, soybeans, grain sorghum, field corn, and sunflowers is well within the acceptable limits for all sectors of the population, as predicted by the Chronic Module of the Dietary Exposure Evaluation Model (DEEM, Exponent, Inc., 2003 Version 7.87). The percentage or proportion of a crop that is treated can have a significant effect on the exposure profile. In this case, it was assumed for the crop that 100% was treated with

tribenuron methyl. Based on a comparison with the use profile for most other herbicides, this is an extremely conservative estimate.

The predicted chronic exposure for the U.S. population subgroup was 0.00021 mg/kg bw/d. The population subgroup with the highest predicted level of chronic exposure was children 1- 6 years, with an exposure of 0.000477 mg/kg bw/day. Based on a chronic NOEL of 0.8 mg/kg bw/d and a 100-fold safety factor, the cRfD would be 0.008 mg/kg bw/d. For the U.S. population, the predicted exposure is equivalent to 2.7% of the cRfD. For the population subgroup with the highest level of exposure (children 1-6 years), the exposure would be equivalent to 6.0% of the cRfD. Because the predicted exposures, expressed as percentages of the cRfD, are well below 100%, there is reasonable certainty that no chronic effects would result from dietary exposure to tribenuron methyl.

b. Acute Dietary Exposure

Acute dietary risk assessments are performed for a food-use pesticide if a toxicological study indicates the possibility of an effect of concern as a result of a one day or a single exposure. No acute dietary endpoint attributable to a single dose was identified for tribenuron methyl. Therefore the quantification of acute dietary risk is not considered necessary. There is reasonable certainty that no acute effects would result from dietary exposure to tribenuron methyl.

3. Drinking Water

Surface water exposure was estimated using the Generic Expected Environmental Concentration (GENEEC) model. Groundwater exposures were estimated using SCI-GROW.

The EPA uses drinking water levels of comparison (DWLOCs) as a surrogate measure to capture risk associated with exposure to pesticides in drinking water. A DWLOC is the concentration of a pesticide in drinking water that would be acceptable as an upper limit in light of total aggregate exposure to that pesticide from food, water, and residential uses. Since there are no residential uses for tribenuron methyl, the aggregate exposure is due to food and water only. A DWLOC will vary depending on the residue level in foods, the toxicity endpoint, and with drinking water consumption patterns and body weights for specific subpopulations. Default body weights and consumption values, as used by the USEPA Office of Water, used to calculate the DWLOC values for tribenuron methyl are: 70kg and 2L (adult male), 60 kg and 2L (adult female), and 10 kg and 1L (child).

No acute dietary endpoint was identified. Therefore, an acute drinking water risk assessment is not considered necessary. One can conclude with reasonable certainty that residues of tribenuron methyl in drinking water do not contribute significantly to the aggregate acute human health risk.

The chronic DWLOCs are 0.28 ppm for adult men, 0.24 ppm for adult women, and 0.08 ppm for children 1-2 years old. These DWLOC values are substantially higher than the GENEEC 56-day estimated environmental concentration of 0.3 ppb for tribenuron methyl in surface water, estimated concentrations in ground water are even lower. Therefore, one can conclude with reasonable certainty that residues of tribenuron methyl in drinking water do not contribute significantly to the aggregate chronic human health risk.

4. Non-Dietary Exposure

Tribenuron methyl is not registered for any use which could result in non-occupational or non-dietary exposure to the general population.

D. Cumulative Effects

Tribenuron methyl belongs to the sulfonylurea class of crop protection chemicals. Other structurally similar compounds in this class are registered as herbicides. However, the herbicidal activity of sulfonylureas is due to the inhibition of acetolactate synthase (ALS), an enzyme found only in plants. This enzyme is part of the biosynthesis pathway leading to the formation of branched chain amino acids. Animals lack ALS and this biosynthetic pathway. This lack of ALS contributes to the relatively low toxicity of sulfonylurea herbicides in animals. There is no reliable information that would indicate or suggest that tribenuron methyl has any toxic effects on mammals that would be cumulative with those of any other chemical.

E. Safety Determination

Based on data and information submitted by DuPont, EPA previously determined that the establishment of tolerances of tribenuron methyl on wheat, barley, oats, cotton, canola, flax, and grass raw agricultural commodities would protect the public health, including the health of infants and children. Establishment of new tolerances for tribenuron methyl on sunflowers at 0.05 ppm, field corn commodities at 0.05 ppm, grain sorghum commodities at 0.05 ppm, rice commodities at 0.05 ppm, and soybean seed at 0.05 ppm will not adversely impact public health.

1. U.S. Population

Using the conservative exposure assumptions described above, and based on the most sensitive chronic NOEL of 0.79 mg/kg/day and a cRfD of 0.008 mg/kg/day, the chronic dietary exposure will utilize 2.7 % of the cRfD for the U.S. population. Generally, exposures below 100 % of the RfD are of no concern because the RfD represents the level at or below which daily dietary exposure over a lifetime will not pose risk to human health. Therefore, it is concluded that there is reasonable certainty that no harm will result from exposure to tribenuron methyl residues.

2. Infants and Children

Chronic dietary exposure of the most highly exposed subgroup in the population, children 1-6 years old, is 0.000477 mg/kg/day, or 6.0 % of the cRfD. There are no residential uses of tribenuron methyl and contamination of drinking water is extremely unlikely. Based on the completeness and reliability of the toxicity data, the lack of toxicological endpoints of special concern, the lack of any indication of greater sensitivity of children, and the conservative exposure assessment, there is a reasonable certainty that no harm will result to infants and children from the aggregate exposure to residues of tribenuron methyl from all anticipated sources of dietary and non-occupational exposure. Accordingly, there is no need to apply an additional safety factor for infants and children.

F. International Tolerances

The MRL in Canada for tribenuron methyl on canola is 0.1 ppm. Tolerances for tribenuron methyl on cereals, barley, and/or wheat commodities have been established or proposed in other countries – for example in Greece, France, Italy, Portugal, Spain and the United Kingdom at levels ranging from 0.01 to 0.2 ppm.