UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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Memorandum

Subject: Flumetsulam: HED Risk Assessment for the Tolerance Reassessment Eligibility Document (TRED). [PC Code 129016, DP Barcode 306277].

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Background:

Attached is Health Effects Division's (HED's) risk assessment of flumetsulam for purposes of issuing a Tolerance Reassessment Eligibility Decision (TRED) document for this active ingredient. A new use has been requested by Dow AgroSciences LLC for use on dry beans (i.e., kidney bean, navy bean, pinto bean) and the data review and occupational and residential exposure assessment for this new use will be addressed in a separate document. However, the dietary assessment for this new use will be addressed in this TRED. This document was reviewed by the Risk Assessment Review Committee (RARC), an expedited process used for lower risk chemicals. Toxicity endpoints were concurred upon and the document has been revised in response to Review Committee comments. HED is confident that this analysis does not underestimate the risk associated with exposures to flumetsulam. Residue chemistry and dietary analysis was performed by Samuel Ary, drinking water analysis by James Lin and Stephanie Syslo, and hazard assessment and toxicological profile by Elissa Reaves.

I. Executive Summary:

This assessment provides information to support the issuance of a Tolerance Reassessment Eligibility Document for flumetsulam. EPA's pesticide reregistration process provides for the review of older pesticides (those initially registered prior to November 1984) under the Federal Insecticide, Fungicide, and Rodenticide Act to ensure that they meet current scientific and regulatory standards. The process considers the human health and ecological effects of pesticides and incorporates a reassessment of tolerances (pesticide residue limits in food) to ensure that they meet the safety standard established by the Food Quality Protection Act (FQPA) of 1996.

Flumetsulam is in the triazolopyrimidine chemical class and has a mode of action similar to the sulfonylurea herbicides that are acetolactate synthase inhibitors (regulate plant growth). Flumetsulam is currently registered by Dow AgroSciences LLC for use as a herbicide at the pre-plant, pre-emergence, or post-emergence stage to control broadleaf weeds in field corn and soybeans. Flumetsulam as an active ingredient ranges in formulations from 2.1 to 80% and may be applied alone or in formulation with other active ingredients. The maximum application rate for flumetsulam is 0.07 lb a.i./acre with a minimum pre-harvest interval range of 70 to 85 days.

Flumetsulam is in Toxicity Category III or IV for acute oral, dermal, and inhalation exposure and for dermal and ocular irritation, and is not a dermal sensitizer. The kidney appears to be the primary target organ of rats and dogs following subchronic to chronic exposures. There was no indication of reproductive or neurotoxicant effects from flumetsulam in the reviewed studies. Flumetsulam is classified as Group E (evidence of non-carcinogenicity for humans) and is not mutagenic. Flumetsulam is rapidly excreted mainly in the urine unchanged. Therefore, there are no metabolites of toxicological concern for flumetsulam. The chronic reference dose is based on a chronic dog study with a NOAEL of 100 mg/kg/day and an uncertainty factor (UF) of 100 for inter-species extrapolation and intra-species variability. There are no studies that identify an acute hazard based on toxic effects observed following a single oral exposure (dose) of flumetsulam. No effects in the developmental toxicity studies in the rabbit or rat were attributed from a single oral exposure during gestation. Therefore, a dose and endpoint are not proposed for the general population including infants and children or females 13-49 years of age.

Flumetsulam is soluble in water and is stable under photolysis. Degradation studies indicate the soil half-life ranges from approximately two weeks to four months with the majority degrading in less than two months (mean of 69.5 days).

Analyses of dietary and drinking water exposure pathways were included in the flumetsulam risk assessment. Drinking water exposure may occur due to run-off from agricultural uses of flumetsulam to regulate plant growth. The estimated drinking water concentrations of flumetsulam in surface water indicate the highest 1-in-10 year annual mean was 0.59 μg/L. The estimated chronic drinking water concentration from ground water sources is 0.823 ppb.

Sources of dietary exposure include food crops to which flumetsulam is applied as an acetolactate synthase inhibitor. A conservative dietary (food and water) risk assessment concludes that for all supported commodities (including proposed dry bean), the chronic dietary exposure estimates are below the HED's level of concern for all population subgroups at less than 1% of the cPAD.

EPA has determined that flumetsulam does not have a common mechanism of toxicity with the other sulfonylurea pesticides. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to flumetsulam and any other substances, and flumetsulam does not appear to produce a toxic metabolite produced by other substances.

II. Use Information:

A screening level estimate of flumetsulam usage performed by HED's Biological and Economic Analysis Division (BEAD) indicate that the highest usage of flumetsulam is on corn.

Older reports on use of flumetsulam indicate that the use of flumetsulam has increased over time. A Special Chemical Use Report by the Mississippi Ag Report released June 13, 2000 indicated flumetsulam was estimated to be applied at 17% of the total area in one application at a rate of 0.03 lbs per acre and 0.04 lbs per crop per year with a total amount applied at 12,000 lbs (Mississippi Ag Report available at www.nass.usda.gov/ms/vol100-09.txt). Estimates for flumetsulam use in the United States were also provided by the Pesticide National Synthesis Project of the U.S. Geological Survey's National Water Quality Assessment Program. A map of use indicated that flumetsulam was applied to corn at a total of 41,443 lbs and 36,916 lbs to soybeans. The map was based on state-level estimates of pesticide use rates for individual crops, which were compiled by the National Center for Food and Agricultural Policy (NCFAP) for 1991-1993 and 1995, and on county-based crop acreage data obtained from the 1992 Census of Agriculture (as cited on FAN).

III. Physical/Chemical Properties

Table 1. Test Compound Nomenclature.

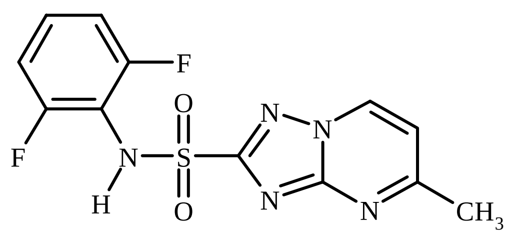
Chemical Structure	
Common name	Flumetsulam
Company experimental name	DE-498 and TSN-100986
Molecular formula	$C_{12}H_9F_2N_5O_2S$
Molecular weight	325.30
IUPAC name	2-(2,6-difluorophenylsulphamoyl)-5-methyl(1,2,4)-Triazolo(1,5-a)pyrimidine
CAS name	N-(2,6-difluorophenyl)-5-methyl-(1,2,4)triazolo(1,5-a)pyrimidine-2-sulfonamide
CAS number	98967-40-9
Current food/feed site registrations	Corn and soybean (a petition for dry beans has been submitted)

Table 2. Physicochemical Properties of the Technical Grade Test Compound.		
Parameter	**Value**	**Reference**
Melting point	252.9°C	N. Dodd, PP# 1G4006, 3/27/92
pH	3.44 at 24.4°C for a 10% suspension in water	
Density	1.77 g/cm^3 at 21°C	
Water solubility	49.1 ± 0.5 mg/L at 25 °C, pH 2.5 5.65 ± 0.01 g/L at 25 °C, pH 7.0	
Solvent solubility	17.0 g/L in acetone 5.2 g/L in acetonitrile 0.0016 g/L in aromatic 100 9.0 g/L in cyclohexanone 261.0 g/L in dimethylformamide Less than 0.001 g/L in hexane 3.3 g/L in methanol Less than 0.001 g/L in o-xylene 0.06 g/L in octanol 11.0 g/L in tetrahydrofuran	N. Dodd, PP# 2F4036, 4/14/93
Vapor pressure	1.0 x 10^{-15} mm Hg at 25 °C	N. Dodd, PP# 1G4006, 3/27/92
Dissociation constant	pK_a = 4.6	
Octanol-water partition coefficient Log(K_{OW})	log P = 0.21	

IV. Hazard Assessment:

A. Hazard Profile

The Agency based its hazard assessment upon required acute toxicity data, subchronic feeding studies, developmental toxicity, chronic toxicity, carcinogenic toxicity, reproduction toxicity, and mutagenicity studies. Please refer to Appendix A for the hazard profile table.

Flumetsulam is in Toxicity Category III or IV for acute oral, dermal, and inhalation exposure and for dermal and ocular irritation, but it is not a dermal sensitizer. The kidney appears to be the primary target organ of flumetsulam following exposure of rats and dogs to high doses of the test material in subchronic to chronic toxicity studies. Following subchronic oral exposure, rats developed bilateral tubular nephritis at concentrations equal to the limit dose; however, no renal effects were found in mice at doses five times the limit dose. Decreased kidney weights were found in rat dams, and anorexia, moribundity, and decreased body weight gain in rabbit does, but no developmental effects were found. Also, no reproductive effects attributable to flumetsulam were found in male and female rats treated at the limit dose. In chronic dog and rat studies, renal calculi, inflammation, and atrophic changes were found in the kidney of male animals. These effects were not observed in female rats or dogs, nor in treated male and female mice. In addition, no systemic toxicity was observed in rats treated with dermal doses that exceeded the limit dose, although diffuse epidermal hyperplasia was present.

Available metabolism and pharmacokinetics studies in mice and rats indicate that flumetsulam is primarily eliminated within 48 hours from all test animals following oral administration. The primary route was urinary excretion of unchanged flumetsulam. The rapid clearance of flumetsulam demonstrated little potential for bioaccumulation. Metabolic studies show that approximately 52-63% of the administered test material was absorbed by male and female rats. Plasma pharmacokinetic studies suggest that increased doses were associated with increased clearance, possibly due to saturation of plasma binding sites. In addition, there was a dose-dependant decrease in the rate of plasma absorption and elimination for both rats and mice. Two very minor metabolites were detected in the urine of mice (not identified). At the limit dose, mice showed a greater capacity for absorption and elimination than rats.

Genotoxicity studies with flumetsulam were negative and no evidence of carcinogenicity was found in life-time rat and mouse studies.

A neurotoxicity study was not conducted, however, flumetsulam showed no indication of being a neurotoxicant in the reviewed studies. A 90-day inhalation study and a subchronic dog study were not conducted, but it is doubtful these would provide any additional useful information.

B. Special Considerations for Infants and Children (FQPA Safety Determination)

The toxicology database for flumetsulam is adequate for FQPA considerations. The data available for evaluation suggest that there is no evidence of increased quantitative or qualitative susceptibility of the offspring after *in utero* or post-natal exposure to flumetsulam. Neither acceptable Developmental Toxicity Studies in rats or rabbits revealed increased susceptibility of the fetus after *in utero* exposure. Similarly, the results of the Two Generation Reproduction Study did not indicate an increased susceptibility to the test article *in utero* or during post-natal exposure. Therefore, no special FQPA safety factor (i.e. 1X) is required for risk assessments for this chemical. A developmental neurotoxicity study is not required since there was no evidence of neurotoxicity or neuropathy from the available studies.

Based on the hazard data, HED recommended the special FQPA Safety Factor be reduced to 1X because there are low concerns, and no residential uncertainties with regard to pre- and/or post-natal toxicity. Also, based on the quality of the exposure data, the flumetsulam risk assessment team recommended that the special FQPA Safety Factor be reduced to 1X. The recommendation is based on the following: 1) the dietary food exposure assessment utilizes proposed tolerance level residues and 100% crop treatment information for all commodities, 2) by using these screening-level assessments chronic exposure will not be underestimated, and 3) the dietary drinking water assessment utilizes values generated by model and associated modeling parameters which are designed to provide health protective, high-end estimates of water concentrations.

C. Endocrine Disruption

EPA is required under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). In the available toxicity studies on flumetsulam, there was no estrogen, androgen, and/or thyroid mediated toxicity. When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, flumetsulam may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

D. Classification of Carcinogenic Potential

The Health Effects Division RfD/Peer Review Committee determined the high dose tested in the carcinogenicity studies in rats and mice were considered a "limit dose". Flumetsulam did not alter the spontaneous tumor profile in these strains of rats and mice under the test conditions. Therefore, on the basis of the two studies, the Committee classified flumetsulam as a "Group E", evidence of non-carcinogenicity for humans (G. Ghali Memorandum, 3/24/93, TXR 011039).

E. Toxicological Endpoint for Dietary Exposure

The doses and toxicological endpoints selected for various exposure scenarios are summarized below. There are no residential uses listed for this chemical, therefore, no endpoints were identified for these exposure scenarios.

1. <u>Acute Reference Dose (aRfD)</u>

There are no studies that identify an acute hazard based on toxic effects observed following a single oral exposure (dose) of flumetsulam. No effects in the developmental toxicity studies in the rabbit or rat were attributed from a single oral exposure during gestation. Therefore, a dose and endpoint are not proposed for the general population including infants and children or females 13-49 years of age (G. Ghali Memorandum, 3/24/93, TXR 011039).

2. <u>Chronic Reference Dose (cRfD)</u>

The chronic feeding study in the dog (MRID 41952103) supports the toxicity endpoint for chronic dietary exposure because the study encompasses the appropriate duration of exposure and has the most conservative NOAEL. The NOAEL was 100/500 mg/kg/day [M/F] and LOAEL 500/not identified mg/kg/day [M/F], based on renal inflammatory and atrophic changes secondary to renal calculi and hepatic effects consisting of inflammation, focal necrosis, and biliary stasis. Similar renal effects were found in male rats given 1000 mg/kg/day for 2 years. The male rats had increased incidences of dilated renal pelvises that contained renal calculi, and atrophic renal papillae along with renal pelvic epithelial hyperplasia and mineralization (G. Ghali Memorandum, 3/24/93, TXR 011039). An uncertainty factor (UF) of 100 (10X for interspecies extrapolation and 10X for intraspecies variability) was applied to the chronic toxicity endpoint.

$$\text{Chronic RfD} = \frac{\text{100 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \text{1.0 mg/kg/day}$$

3. Toxicological Endpoint for Dermal Exposure

A 21-Day dermal toxicity study (MRID 41931706) in New Zealand white rabbits exposed dermally at 0, 100, 500, or 1000 mg/kg/day for 3 weeks caused no systemic compound-related changes in males or females at any dose level [NOAEL > 1000 mg/kg/day (HDT)]. The only treatment-related effect was epidermal hyperplasia at the application site.

Since the limit dose was achieved in the 21-day dermal toxicity study, there is no hazard identified for dermal exposure. Quantification of dermal risk assessment is not required for this exposure due to lack of dermal, systemic, neuro, or developmental toxicity concerns.

4. Toxicological Endpoint for Inhalation Exposure (All Durations)

Due to the lack of repeated dose inhalation toxicity study, oral studies were selected for the appropriate duration of exposure. Absorption via inhalation is assumed to be equivalent to oral absorption.

a. Short-term (1-30 days)

The chronic feeding dog study (MRID 41952103) encompasses the appropriate exposure duration and provides a screening level hazard with a NOAEL of 100/500 mg/kg/day [M/F] and LOAEL of 500/not identified mg/kg/day [M/F], based on renal inflammatory and atrophic changes secondary to renal calculi and hepatic effects consisting of inflammation, focal necrosis, and biliary stasis.

b. Intermediate- and Long -term (1-6 months and > 6 months)

The chronic feeding study in the dog (MRID 41952103) supports the toxicity endpoint for intermediate and long-term dietary exposure because the study encompasses the appropriate duration of exposure and has the most conservative NOAEL. The NOAEL was 100/500 mg/kg/day [M/F] and LOAEL 500/not identified mg/kg/day [M/F], based on renal inflammatory and atrophic changes secondary to renal calculi and hepatic effects consisting of inflammation, focal necrosis, and biliary stasis.

5. Incidental Oral Exposure

Flumetsulam has not been approved for residential uses; therefore, toxicity endpoint selection is not necessary for this scenario.

6. Margins of Exposure

Summary of target Margins of Exposure (MOEs) for risk assessment.

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Inhalation	100	100	100

For **occupational exposure short-, intermediate-, and long-term inhalation** exposure risk assessment, a MOE of 100 is adequate. This is based on the conventional uncertainty factor of 100X, which includes the 10X for intraspecies extrapolation and 10X for interspecies variation.

Table 3. Summary of Toxicological Dose and Endpoints for Flumetsulam

Exposure Scenario	Dose (mg/kg/day)	Special FQPA SF* and Level of Concern for Risk Assessment	Endpoint for Risk Assessment
Acute Dietary (Females 13-50 years of age)	Not applicable. No hazard identified.		
Acute Dietary (General population including infants and children)	Not applicable. No hazard identified.		
Chronic Dietary (All populations)	NOAEL= 100 mg/kg/day UF =100 **Chronic RfD** = 1.0 mg/kg/day	FQPA SF =1 **cPAD** = chronic RfD / FQPA SF =1.0 mg/kg/day	**Chronic** feeding, dog LOAEL = 500 mg/kg/day based on renal inflammatory and atrophic changes secondary to renal calculi and hepatic effects (inflammation, focal necrosis, biliary stasis)

Table 3. Summary of Toxicological Dose and Endpoints for Flumetsulam			
Exposure Scenario	**Dose (mg/kg/day)**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Endpoint for Risk Assessment**
Incidental Oral	No Residential uses are proposed for flumetsulam.		
Dermal Exposure- all time periods	Not applicable. No hazard identified.		
Short-Term Inhalation (1 to 30 days)	Oral NOAEL= 100 mg/kg/day (inhalation absorption rate = 100%)	**Occupational** LOC for MOE = 100	Chronic feeding, dog LOAEL = 500 mg/kg/day based on renal inflammatory and atrophic changes secondary to renal calculi and hepatic effects (inflammation, focal necrosis, biliary stasis)
Intermediate-Term Inhalation (1 to 6 months)	Oral NOAEL = 100 mg/kg/day (inhalation absorption rate = 100%)	**Occupational** LOC for MOE = 100	Chronic feeding, dog LOAEL = 500 mg/kg/day based on renal inflammatory and atrophic changes secondary to renal calculi and hepatic effects (inflammation, focal necrosis, biliary stasis)
Long-Term Inhalation (>6 months)	Oral NOAEL= 100 mg/kg/day (inhalation absorption rate = 100%)	**Occupational** LOC for MOE = 100	Chronic feeding, dog LOAEL = 500 mg/kg/day based on renal inflammatory and atrophic changes secondary to renal calculi and hepatic effects (inflammation, focal necrosis, biliary stasis)
Cancer (oral, dermal, inhalation)	Flumetsulam is classified as Group E (Evidence of non-carcinogenicity for humans) (6/23/93). Not mutagenic.		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose © = chronic RfD = reference dose, MOE = margin of exposure, LOC = level of concern,
*No systemic toxicity was found in 21-day dermal study at the limit dose.

V. Exposure Assessment:

The residue chemistry data submitted in support of the proposed petitions were reviewed in the HED memorandum dated 8/31/04 (S. Ary, D306242). The chronic dietary exposure assessment was completed in the HED memorandum dated 8/30/04 (S. Ary, D306279). The drinking water assessment was completed in the EFED memorandum dated 5/19/04 (J. Lin and S. Syslo, D301361).

A. Summary of Registered Food Uses

Tolerances have been established under 40 CFR §180.468 for residues of flumetsulam in/on field corn (forage, grain, and stover) and soybean at 0.05 ppm. Available residue data indicate that the established tolerances for these commodities are adequate. Dow has petitioned for the establishment of a tolerance for residues of flumetsulam in/on dry beans at 0.05 ppm. HED recommends that the tolerance level in/on dry beans be established at the proposed rate. Table 7 presents the established/proposed and recommended tolerance levels for all commodities.

There are no Codex, Canadian, or Mexican maximum residue limits (MRLs) for flumetsulam; therefore, no questions of compatibility with U.S. tolerances exist.

Table 4. Tolerance Summary for Flumetsulam.

Commodity	Established/Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Corn, field, forage	0.05 (established)	0.05	None
Corn, field, grain	0.05 (established)	0.05	None
Corn, field, stover	0.05 (established)	0.05	None
Soybean	0.05 (established)	0.05	None
Bean, dry	0.05 (proposed)	0.05	None

B. Residue Profile

1. Nature of the Residue-Plants and Livestock

The nature of residues in corn and soybeans is adequately delineated based on acceptable plant metabolism studies. The Health Effects Division (HED) Metabolism Committee concluded that the residue of concern resulting from the uses on field corn and soybeans is flumetsulam *per se (*N. Dodd, HED Metabolism Committee Memo, 4/26/93). Plant metabolism studies for dry beans have not been submitted; however, metabolism data from soybeans may be translated to dry beans because of the similarities between the two crops.

The HED Metabolism Committee has not determined the residue of concern in livestock; however, based on the submitted data, the nature of the residue in livestock (goats and hens) is adequately defined because no detectable residues of flumetsulam *per se* were found in feed items.

2. Residue Analytical Method

The available analytical methodology (GC/MS method) is considered adequate for tolerance enforcement of flumetsulam in/on plant commodities. The method is available and has been submitted for inclusion in the Pesticide Analytical Manual (PAM) Volume II; however, the method has not yet been included. The limit of quantitation (LOQ) for the method is 0.010 ppm and the estimated limit of detection (LOD) is 0.005 ppm. Using the analytical method, flumetsulam is extracted from the crop material with a 90%

acetone/10% 0.1 N HCl solution. The acetone is evaporated from an aliquot of the extract and the residue is diluted with 0.005 N HCl and washed with hexane. The sample is cleaned up on C_{18} and alumina SPE cartridges and derivatized with methyl iodide. The resulting N-methyl derivative is dissolved in N-d_3-methyl flumetsulam internal standard solution and quantitated by gas chromatography.

3. Meat, Milk, Poultry, and Eggs

The dietary burdens of beef cattle, dairy cattle, and poultry are presented in Table 5. Using a diet containing field corn forage, field corn grain, and field corn milled byproducts, the maximum theoretical dietary burden for beef cattle is 0.07 ppm, 0.09 ppm for dairy cattle, and 0.05 ppm for poultry.

Table 5. Calculation of Theoretical Dietary Burdens of Flumetsulam to Livestock.

Feedstuff	% Dry Matter[1]	Residue (ppm)[2]	Beef Cattle		Dairy Cattle		Poultry	
			% in Diet	Dietary Burden (ppm)[3]	% in Diet	Dietary Burden (ppm)[2]	% in Diet	Dietary Burden (ppm)[2]
Corn, field, forage	40	0.05	30	0.04	50	0.06	0	0
Corn, field, grain	88	0.05	60	0.03	40	0.02	80	0.04
Corn, field, milled byproducts	85	0.05	10	0.01	10	0.01	20	0.01
		Total	100	0.07	100	0.09	100	0.05

1. OPPTS Guideline 860.1000, Table 1.
2. Established tolerance levels of 0.05 ppm on field corn were used.
3. Dietary Burden = % in diet x (residue / percent dry matter).

Flumetsulam is not presently registered for use as a direct livestock treatment and residues of flumetsulam were not detected in the feed items. The nature of the residue in animals is adequately defined for the current and proposed uses. HED concludes that the registered uses on corn and soybeans and the proposed use on dry beans results in a 40 CFR §180.6(a)(3) situation for ruminant and poultry commodities; i.e., there is no reasonable expectation of finite residues in ruminant and poultry commodities. Therefore, additional data on the transfer of residues to meat, milk, and poultry are not required. However, for uses which may result in detectable residues in feed items, additional animal metabolism data on ruminants and poultry may be required. Such data may, in turn, trigger the need for magnitude of the residue (feeding) studies in livestock.

4. Confined and Field Accumulation in Rotational Crops

The current use labels for flumetsulam restricts crop rotation after treatment to four months or greater for all crops except soybean. Feeding of soybean forage, hay, or straw to livestock is restricted. Under these restrictions, the total quantifiable ^{14}C residues accumulated in crop fractions is less than 0.006 ppm with the exception of wheat straw/chaff. The highest wheat straw/chaff residue occurred for the 30-day planting at 0.060 ppm. The total ^{14}C residue levels in wheat straw/chaff samples were 0.029 ppm in the 120-day study and 0.010 ppm in the 365-day study.

The results of the 30-day, 120-day, and 365-day rotational crop studies indicate that the total ^{14}C residue accumulation in lettuce, carrot roots and tops, turnip roots and tops, wheat grain, and soybeans was less than or equal to 0.01 ppm. However, total ^{14}C residues reported in wheat straw/chaff ranged from 0.010 to 0.047 ppm (MRID Nos.: 41263232 and 41931738). In a separate study (MRID No.: 41931739), wheat forage, soybean forage, soybean trash, and wheat straw/chaff had reported total ^{14}C residues of 0.039, 0.056, 0.082, 0.060 ppm, respectively. Therefore, for leafy and root crops, a 30-day rotational crop interval is satisfactory. For cereal grains, a 120-day rotational crop interval is satisfactory.

C. Dietary Exposure and Risk Assessment

A chronic dietary (food and water) risk assessment was conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analysis was performed to support the tolerance reassessment eligibility decision for current uses and to support the proposed tolerance in/on dry beans (Petition Number: 7F4851). No acute dietary exposure was identified, so no acute dietary assessment was performed. The chronic dietary exposure/risk analysis was conducted using current and proposed tolerance values for corn (forage, grain, and stover), soybean, and dry beans. Also, default processing factors, 100% crop treated for all commodities, and the highest estimated chronic drinking water concentration were used to conduct this Tier 1 (unrefined) assessment.

Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population-adjusted dose (PAD). The PAD is equivalent to the reference dose (RfD) divided by the special Food Quality Protection Act (FQPA) Safety Factor.

Dietary risk estimates are provided for the general U.S. population and various population subgroups. This assessment concludes that for all supported commodities, the chronic dietary exposure estimates are below the Health Effects Division's (HED) level of concern for all population subgroups at less than 1% of the cPAD.

Table 6. Summary of Chronic Dietary (food and water) Exposure and Risk for Flumetsulam.			
Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
General U.S. Population	1	0.000113	less than 1
All Infants (less than 1 year old)		0.000219	less than 1
Children 1-2 years old		0.000223	less than 1
Children 3-5 years old		0.000244	less than 1
Children 6-12 years old		0.000181	less than 1
Youth 13-19 years old		0.000135	less than 1
Adults 20-49 year old		0.000094	less than 1
Adults 50+ years old		0.000066	less than 1
Females 13-49 year old		0.000092	less than 1

(S. Ary Memorandum, 8/30/04 D306279)

D. Drinking Water Exposure and Risk Assessment

Estimated Drinking Water Environmental Concentrations

Flumetsulam is soluble in water and is stable under photolysis. Degradation studies indicate the soil half-life ranges from approximately two weeks to four months with majority degrading in less than two months (mean of 69.5 days)

The Environmental Fate and Effects Division (EFED) calculated estimated drinking water concentrations (EDWCs) by using a Tier I SCI-GROW model for ground water concentrations and Tier II PRZM and EXAMS models for surface water concentrations. The highest modeled (PRZM and EXAMS) 1-in-10 year annual mean for surface water was 0.59 μg/L (ppb), based on application on corn. The modeled EDWCs (SCI-GROW) for chronic ground water was 0.823 μg/L (J. Lin and S. Syslo Memorandum, D301361, 5/19/04).

The application rate for the proposed new use on dry beans is the same as for corn (0.07 lb a.i./acre). The 2004 NASS data indicate 81 million acres of corn compared with only 1.4 million acres of dry edible beans. This new use on dry bean accounts for only 1.4% of the acres currently estimated in the EDWCs based on corn. Therefore, the EDWCs are not expected to be significantly higher when dry bean is included than the presently estimated concentration based on corn.

E. Occupational Exposure and Risk Assessment

Occupational exposure scenarios for the new uses of flumetsulam will be addressed in a supplemental document. Therefore, the occupational exposure and risk assessment will not be discussed in this TRED.

G. Aggregate Exposure and Risk Assessment

The aggregate risk assessment integrates the assessments conducted for dietary, drinking water, and residential exposure if applicable. Since there is potential for concurrent exposure via the food and water, the combined exposures from both water and dietary risk are estimated and compared with modeling-based estimates of drinking water contamination determined by EFED.

Taking into account the present uses in this action, the Agency can conclude with reasonable certainty that residues of flumetsulam in food and drinking water would **not likely result in an aggregate chronic dietary risk** above the Agency's level of concern, particularly to infants and children. The estimates of flumetsulam in surface waters were derived from a refined Tier II model. Conservative ground water concentrations (chronic 0.82 μg/L) from modeled Tier 1 estimates were similar to refined chronic surface waters numbers (0.59 μg/L).

G. Cumulative Risk Assessment

Section 408(b)(2)(D)(v) of FIFRA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA has determined that flumetsulam does not have a common mechanism of toxicity with the other sulfonylurea pesticides. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to flumetsulam and any other substances, and flumetsulam does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that flumetsulam has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

References:

G. Ghali Memorandum, 3/24/93. RfD/Peer Review Report of XRD-498 (flumetsulam), TXR 011039.

J. Lin and S. Syslo Memorandum. 5/19/04. Drinking Water Assessment for Flumetsulam for Uses on Field Corn and Soybeans. D301361

N. Dodd, HED Metabolism Committee Memo. Flumetsulam Metabolism in Soybeans and Field Corn. 4/26/93.

S. Ary Memorandum, 8/30/04. Flumetsulam. Chronic Dietary Exposure Assessment for the Tolerance Reassessment Eligibility Decision (TRED) Document. D306279.

S. Ary Memorandum, 8/31/04. Flumetsulam. Summary of Analytical Chemistry and Residue Data for the Tolerance Reassessment Eligibility Decision (TRED) Document. D306242.

Appendix A: Toxicological Profile and Executive Summaries of Key studies for Flumetsulam

The requirements (CFR 158.340) for a food use for flumetsulam are in Table 1. Use of the new guideline numbers does not imply that new (1998) guideline protocols were used.

Table 1: Toxicology data requirements for a food use pesticide and whether or not they have been satisfied.

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes [1]
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	no
870.3465 90-Day Inhalation	no	no
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes[1]
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	no
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	no	no
870.6100a Acute Delayed Neurotox. (hen)	no[2]	-
870.6100b 90-Day Neurotoxicity (hen)	no[2]	-
870.6200a Acute Neurotox. Screening Battery (rat)	no	no
870.6200b 90 Day Neuro. Screening Battery (rat)	no	no
870.6300 Develop. Neuro	no	no
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	no
Special Studies for Ocular Effects		
Acute Oral (rat)	no	no
Subchronic Oral (rat)	no	no
Six-month Oral (dog)	no	no

[1]Either 870.4300 or 870.4100 can fulfil this requirement. [2]Required only for organophosphate pesticides.

Toxicological Profile of Flumetsulam

TOXICOLOGY PROFILE: FLUMETSULAM			
Type of Study/Guide line	**Study Title**	**MRID**	**Results**
81-1 870.1000	Acute oral LD_{50}, Rat (99.6%)	41263202	LD_{50} (M/F) >5000 mg/kg (99.6% a.i.) Tox Category IV
81-2 870.1200	Acute dermal LD_{50}, Rabbit (99.6%)	41263203	LD_{50} (M/F) >2000 mg/kg (99.6% a.i.) Tox Category III
81-3 870.1300	Acute inhalation toxicity, Rat (99.8%)	41556501 (41931703)	LC_{50} (M/F) >0.6 mg/L (99.8% a.i.) Tox Category III
81-4 870.2400	Primary eye irritation, Rabbit (99.6%)	41263204	Slight conjunctival reddening and chemosis and iridal redness at 1 hour Tox Category IV
81-5 870.2500	Primary dermal irritation, Rabbit (99.6%)	41263205	No irritation Tox Category IV
81-6 870.2600	Dermal sensitization, Guinea Pig (99.6%)	41263206	Not a sensitizer
82-1a 870.3100	90-Day oral toxicity, Rat	41263212	Levels tested: 0, 250, 1000, 2000/2500 [M/F] mg/kg/day NOAEL (M/F) 250 mg/kg/day LOAEL (M/F) 1000 mg/kg/day based on severe bilateral tubular-interstitial nephritis.
82-1a 870.3100	90-Day oral toxicity, Mice	41931704	Levels tested: 0, 100, 500, 1000, 5000 mg/kg/day NOAEL (M/F) 5000 mg/kg/day (98.6% a.i.) LOAEL (M/F) Not identified. Statistically increased full cecum weights and decreased kidney weights were found at 5000 mg/kg/day but were considered adaptive and/or toxicologically irrelevant.
82-1b 870.3150	90-Day oral toxicity, Dog		See guideline 870.4100b
82-2 870.3200	21-Day Dermal, Rabbit	41931706	Levels tested: 0, 100, 500, 1000 mg/kg/day Systemic & dermal NOAEL (M/F) >1000 mg/kg/day. LOAEL (M/F) Not identified Diffuse treatment-related epidermal hyperplasia observed at application site.

TOXICOLOGY PROFILE: FLUMETSULAM			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
83-3a 870.3700a	Developmental Toxicity, Rat (GD 7-19)	41263213	Levels tested: 0, 100, 500, 1000, 5000 mg/kg/day Maternal NOAEL 5000 mg/kg/day Maternal LOAEL Not identified Developmental NOAEL >1000 mg/kg/day Developmental LOAEL Not identified Statistically increased full cecum weights and decreased kidney weights were found at 5000 mg/kg/day but considered adaptive and/or toxicologically irrelevant.
83-3b 870.3700b	Developmental Toxicity, Rabbit (GD 7-19)	41931709	Levels tested: 0, 100, 500, 700 mg/kg/day Maternal NOAEL=100 mg/kg/day Maternal LOAEL= 500 mg/kg/day based on anorexia, moribundity, and decreased body weight gain (GD 10-13 at 500 and GD 7-10 at 700 mg/kg/day) Developmental NOAEL> 700 mg/kg/day Developmental LOAEL= Not identified
83-4 870.3800	Reproduction (2-Generation), Rat	41931710 (42474001)	Levels tested: 0, 100, 500, 1000 mg/kg/day Reproductive NOAEL >1000 mg/kg/day Reproductive LOAEL Not identified Offspring NOAEL > 1000 mg/kg/day Offspring LOAEL Not identified Parental NOAEL >1000 mg/kg/day Parental LOAEL Not identified
83-1a 870.4100a	Chronic Feeding, Rodent		See guideline 870.4300 (83-5)
83-1b 870.4100b	Chronic Feeding, Dog	41952103	Levels tested: 0, 20, 100, 500 mg/kg/day Systemic NOAEL (M) = 100 mg/kg/day Systemic NOAEL (F) >500 mg/kg/day Systemic LOAEL (M) = 500 mg/kg/day based on renal inflammatory and atrophic changes secondary to renal calculi and hepatic effects consisting of inflammation, focal necrosis, and biliary stasis LOAEL (F) Not identified
83-2b 870.4200b	Carcinogenicity, Mouse	41931708	Levels tested: 0, 100, 500, 1000 mg/kg/day Systemic NOAEL (M/F) > 1000 mg/kg/day LOAEL (M/F) Not identified Not evidence for carcinogenicity in M/F

TOXICOLOGY PROFILE: FLUMETSULAM			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
83-5 870.4300	Chronic/Oncogenicity, 2-Year-Rat	41931707	Levels tested: 0, 100, 500, 1000 mg/kg/day NOAEL (M) = 500 mg/kg/day NOAEL (F) > 1000 mg/kg/day LOAEL (M) = 1000 mg/kg/day based on dilated renal pelvises containing renal calculi, atrophy of renal papillae, renal pelvic epithelial hyperplasia, and mineralization of pelvic epithelium LOAEL (F) Not identified Not evidence for carcinogenicity in M/F
84-2 870.5100	Ames bacterial mutagenicity test	41263214	Salmonella - Negative in strains TA98, TA100, TA1535, TA1537, and TA1538 with and without metabolic activation at concentrations of 0.01-1.0 mg/plate
84-2 870.5300	In vitro mammalian cell gene mutation test (Chinese hamster ovary cells)	41263217	The study was negative at concentrations from 500 to 3000 μg/mL with and without metabolic activation with Arochlor 1254 induced rat liver S-9
84-2 870.5395	*In Vivo* Micronucleus Assay	41263216	Negative for micronucleus induction in bone marrow cells of male and female CD-1 mice at 24 hrs after oral gavage administration of 500 to 5000 mg/kg.
84-2 870.5550	Unscheduled DNA Synthesis	41263215	Negative at concentrations from 3.16 x 10^{-6} to 3.16 x 10^{-4} M
85-1 870.7485	General Metabolism, rats and mice	41931711 41993801	Absorbed test material (52-63%) excreted unchanged in urine. Unabsorbed test material eliminated unchanged in feces. Test material essentially eliminated within 48 hours by male and female rats. Plasma ^{14}C exhibited a dose-dependant increase in absorption and elimination. Increasing dose associated with increasing clearance possibly due to saturation of plasma binding sites. Male mice exhibited faster absorption and elimination at 1000 mg/kg than male rats. Urine primary elimination route in both male and female rats and mice. Two minor metabolites identified in urine in mice.
85-2 870.7600	Dermal Absorption		Study not available

Executive Summaries of Key Studies in the Flumetsulam Hazard Assessment

1. MRID 41952103- Chronic Feeding Study, Dog

<u>CITATION</u>: Yano BL., Cosse PF., and Corley RA. (1991). XRD-498: One-year dietary toxicity study in beagle dogs. The Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Company, Midland, MI 48674. Laboratory project study ID: DR-0238-5651-024 MRID 41952103. Unpublished

<u>EXECUTIVE SUMMARY</u>:

In a chronic toxicity study (MRID 41952103) flumetsulam [99.0% a.i. by HPLC and 99.2% a.i. by DSC, batch/lot # not provided] was administered to 4 Beagle dog/sex/dose in diet at dose levels of 0, 20, 100, or 500 mg/kg bw/day for up to one year (369 days).

In the high-dose group, 3 of 4 male dogs had pale looking mucous membranes and 2/4 appeared icteric and thin. Because of its deteriorating condition, one male high-dose dog was euthanized on Day 81. At termination (day 369), the surviving dogs showed no signs of icterus or pale mucous membranes. All four females in the high-dose group had pale mucous membranes, but by the end of the study, this was present in only one female. No clinical signs were observed in dogs from the other dose groups.

There was no compound-related effects on ophthalmological examination or urinalysis.

Body weights of male and females dogs were decreased in the high-dose group only. Food consumption was also decreased in the high-dose group, which indicates the decreased body weights were likely due to the unpalatability of the test diets at this dose.

The male high-dose dog that was euthanized on Day 81 of the study had significant decreases in glucose, albumin, total protein, cholesterol, creatinine, calcium, sodium, potassium and chloride and a significant increase in alanine aminotransferase activity, alkaline phosphatase (ALP) activity, aspartate aminotransferase activity, creatine phosphokinase activity, triglycerides and total bilirubin, when compared to control males at 3 months.

At 12 months, alkaline phosphatase (ALP) activities of both male and female dogs in the mid-dose group were within or close in proximity to concurrent and historical control values for each sex. ALP activities of both male and female dogs in the high-dose group were increased compared to concurrent and historical controls (M: 339 mu/ml vs. range 32-61; F: 482 mu/ml vs. 36-55). Albumin levels at 12 months in high-dose dogs were lower than concurrent and historical controls (M: 2.9 g/dl vs range 3.4-3.8; F: 2.3 g/dl vs. range 3.3-3.7). Cholesterol and triglycerides in the high-dose group were decreased throughout the study. Aspartate aminotransferase (at 3 and 6 months) and total bilirubin values (at 3 months) of both male and female dogs of the high-dose group were statistically significantly increased. However, at 12 months these previous elevated levels appeared more normal. The alterations in the chemistry parameters in the high-dose dogs was likely attributable to decreased body weight and food consumption seemingly due to palatability problems. Clinical chemistry parameters were normal for all of the other dose groups compared to controls.

After 12 months, 2/4 female dogs from the high-dose group had calculi in the renal pelvis of both kidneys and a rough cortical surface of the kidneys. Microscopically, kidneys of these females shoed signs of inflammation, atrophy of the renal papillae, and distension and atrophy of tubules. One of three surviving high-dose males had pale foci in the cortex of both kidneys. Microscopically, kidneys of the high-dose male had multifocal tubular atrophic lesions. Histopathology of all other animals were normal compared with controls.

Therefore, the LOAEL is 500 mg/kg/day, based on renal effects (inflammatory and atrophic changes secondary to renal calculi), and hepatic effects (significantly elevated alkaline phosphatase, inflammation and necrosis of individual hepatocytes, and bile duct stasis. The NOAEL is 100 mg/kg/day.

2. MRID 41931709- Prenatal Developmental Toxicity Study-Rabbit

<u>CITATION</u>: Hanley, TR (1989) XRD-498: Gavage teratology study in new zealand white rabbits. Toxicology Research Lab; Health and Environmental Sciences; Dow Chemical Co., Midland, MI 48674. Lab Project No.: DR-0238-5651-023. MRID 41931709. Unpublished.

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 41931709*)* flumetsulam (99.8% a.i., batch # /ARG 240043) was administered to 64 inseminated female New Zealand white rabbits by gavage at dose levels of 0, 100, 500, or 700 mg/kg nominal (dosage volume 2 ml/kg/day was adjusted daily for each rabbits body weight) from days 7 through 19 of gestation. Dams were sacrificed on day 28 of gestation and all fetuses were weighed, sexed, and examined externally.

Six of 16 rabbits of the mid-dose group showed signs of anorexia. Four of these 6 exhibited prolonged periods of anorexia from days 5-11 associated with abortion in 2 rabbits (GD 20 and 26) and moribundity in a third (GD 20). Eight of 16 high-dose dams also showed signs of anorexia and 4/16 died. Two of these deaths were determined to be treatment-related (GD 13 and 16) and the other two that died were due to technical errors. In the low-dose group, one animal aborted on Day 25 of gestation. The non-specific signs of toxicity included perineal soiling, fresh blood in the pan, stomach erosions or ulcers and were considered to be consistent with the deteriorated clinical condition of the rabbits.

High-dose animals had significantly decreased body weight on days 16 and 20 of gestation (↓11% vs. controls). In the mid-dose group, maternal body weight was lower, but not statistically significant compared to controls on days 7-20. Feed consumption was not reported.

There were no significant differences in absolute or relative organ weights after cesarean section. There were no dose-related trends in the number of corpora lutea or gravid uterine weights or significant differences in the incidence of fetal alteration, or the degree of skeletal ossification to suggest any fetotoxic effect at the low-, mid-, or high-dose groups.

The maternal LOAEL is 500 mg/kg bw/day, based on anorexia, moribundity, and decreased body weight gain. The maternal NOAEL is 100 mg/kg bw/day.

There were no fetal malformations or variations associated with administration of the test substance in pregnant rabbits.

The developmental LOAEL is not established. The developmental NOAEL is 700 mg/kg bw/day.

3. MRID 41263212- Subchronic Oral Toxicity (90 days)-Rat

CITATION: Zempel, JA, Grandjean M, and Szabo JR. (1988) XRD-498: Results of a 13-week dietary toxicity study in Fischer-344 Rats. Health and Environmental Sciences, Texas, Dow Chemical Company, Lake Jackson Research Center, Freeport, Texas 77541 Study No.: DR-0238-5651-007, July 29, 1989. MRID 41263212. Unpublished.

In a 90-day oral toxicity study (MRID 41263212*)* flumetsulam (97.8-98.1% a.i., batch/lot # AGR 229750) was administered to 10 Fischer-344 rats/sex/dose in diet at dose levels of 0, 250, 1000, or 2000 [M] and 2500 [F] mg/kg bw/day. Ten males and 10 females from each dose group were sacrificed at 91 days. The remaining animals in the control and high-dose group (10/sex/group) were continued on to day 199 as a recovery group.

Animals were subjected to the following (1) observed daily and handled once weekly, (2) body weights measured weekly, (3) food consumption measured weekly, (4) hematology, clinical chemistry, urinalysis at scheduled necropsy, (5) functional observational battery, and (6) at day of sacrifice, recorded organ weights and gross examination and microscopic examination of selected tissues and organs.

No treatment related clinical signs from flumetsulam. High-dose animals displayed clinical signs related to feed refusal. Two high-dose males were found dead on days 35 and 37 and one female on day 50. All other rats survived to scheduled sacrifice.

High-dose males and females had significantly decreased body weights from controls beginning on day 7 in males (8%) and day 35 in females (6%) and continuing to termination of the study (16% and 5%, respectively). Absolute body weights were similar to the control until day 35 at which time the difference from the control became statistically significant. Food wastage during this period may have contributed to this loss in body weights, especially in high-dose males. Body weight gain was similarly reduced beginning on day 7 and continuing until day 91 sacrifice. Body weights in the low- and mid-dose animals were not affected by treatment. Feed consumption was significantly (not statistically) lower in high-dose males during the period from day 1 to day 64. After day 64, feed consumption was similar for all groups.

High-dose males has significantly and statistically reduced RBC (12%), HGB (6.5%), and PCV (packed cell volume, 8%) relative to controls. Platelet counts were significantly increased in the mid- and high-dose males (8% and 16%, respectively). High-dose females had statistically increased platelet concentrations relative to control (11%). No other treatment related hematological effects were reported in female rats.

High-dose males had increased alkaline phosphatase (29%), BUN (186%), creatinine (140%), cholesterol (63%) and calcium (7%). Decreased values were reported for high-dose males in albumin (5%), SGOT (10%), SGPT (16%), total protein (7%), and globulin (10%). A dose-related decrease was reported for glucose in the mid- and high-dose groups, a dose related increase for potassium in all treated groups and for sodium in the mid- and high-dose groups, and reduced triglycerides in all treated groups relative to controls. The recovery animals in the high-dose group retained the differences in clinical chemistries reported at the 13 week sacrifice.

Female rats exhibited dose-related increases in SGOT and SGPT in all treated groups. BUN was increased in high-dose females only (63%). At recovery sacrifice, all values in females were comparable to the control. Increased BUN levels in the high-dose males and females and creatinine levels reported in high-dose males indicate reduced renal function.

Urinalysis profiles of low- dose males and low- and mid-dose females were similar to control. High-dose males had significantly reduced urinary specific gravity to control. Recovery males persisted in having reduced urinary specific gravity and decreased levels of ketones and blood. In females, only urinary specific gravity was affected by treatment. The data presented indicated more severe effects in males than females, and only limited recovery in high-dose males.

All measured organ weights of high-dose males except brain were affected by treatment. At the 119 days sacrifice, high-dose males demonstrated recovery with respect to organ weights except for kidney weights which remained significantly lower than control and at similar levels as on day 91. High-dose females were less severely affected than high-dose males.

High-dose males had kidneys that were notable smaller in size with rough and pitted surfaces upon examination. Microscopic pathology revealed severe bilateral tubule-interstitial nephritis in all high-dose males, 6/10 high-dose females, and 1/10 mid-dose males. This condition was described by marked interstitial and peritubular fibrosis, variable interstitial edema of the renal papillae, focal necrosis of the tubular epithelium, interstitial suppurative inflammatory microfocal and microfocal dystrophic, and interstitial mineralization.

Necropsy of the three rats that died during the study indicate the death were likely due to severe renal disease which appeared to become more extensive with increasing time on treatment.

The LOAEL is 1000 mg/kg/day for males and females, based on kidney pathology, clinical chemistries, and organ weights. The NOAEL is 250 mg/kg/day in males and females.