COMPANY FEDERAL REGISTER DOCUMENT SUBMISSION TEMPLATE (7/1/2006)

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TEMPLATE:

[BASF Corporation]

[7F7260]

EPA has received a pesticide petition **([7F7260])** from **[BASF Corporation], [P.O. Box 13528, Research Triangle Park, NC 27709]** proposing, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180.

1. by establishing a tolerance for residues of

[metaflumizone] in or on the raw agricultural commodity [grape] at [0.01] parts per million (ppm), [crop group 10: citrus fruits group] at [0.01] ppm, and [crop group 14: tree nuts group] at [0.01] ppm. EPA has determined that the petition contains data or information regarding the elements set forth in section 408 (d)(2) of the FDDCA; 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.* [In three plant metabolism studies (cabbage, tomato and cotton), the major component of the residue was metaflumizone. The major degradate was the ketone, M320I04 and an oxidized and cyclized metabolite, M320I23, was present in lesser amounts. These four compounds were defined as the residues of concern and were incorporated into an analytical method. In the

confined rotational crop studies plant uptake was very limited and the residues were a mixture of minor and polar components.]

2. *Analytical method.* [BASF Analytical Method No. 531/0 was developed to determine residues of metaflumizone and its metabolites M320I04 and M320I23, the residues of concern in plants, and in crop matrices. In this method, residues of metaflumizone are extracted from plant matrices with methanol/water (70:30; v/v) and then partitioned into dichloromethane. For oily matrices, the residues are extracted with a mixture of isohexane/acetonitrile (1:1; v/v). The final determination of metaflumizone and its metabolites is performed by LC/MS/MS.]

3. *Magnitude of residues.* [Field trials were carried out in order to determine the magnitude of residue in grapes, citrus, and tree nuts. Field trials were conducted in the required regions. Field trials were carried out using the maximum label rate, the maximum number of applications and the minimum preharvest interval. In addition, processing studies were conducted on grapes and citrus to determine the concentration factor during normal processing of the raw agricultural commodities.]

B. Toxicological Profile

1. *Acute toxicity.* [Based on the available acute toxicity data, metaflumizone and its formulated product do not pose acute toxicity risks. For metaflumizone:

Oral LD50	**Rat**	**LD50 > 5000 mg/kg b.w.**	**category IV**
Oral LD50	**Mouse**	**LD50 > 5000 mg/kg b.w.**	**category IV**
Dermal LD50	**Rat**	**LD50 > 5000 mg/kg b.w.**	**category IV**
Inhalation LC50	**Rat**	**> 5.2 mg/L**	**category IV**
Eye Irritation	**Rabbit**	**Not irritating**	**category IV**
Skin Irritation	**Rabbit**	**Not irritating**	**category IV**
Skin Sensitization	**Guinea pig**	**Not sensitizing (Maximization Test)]**	

2. *Genotoxicty.* [In a battery of three in vitro and two in vivo mutagenicity assays consisting of all required end-points (point mutation, chromosomal damage, and DNA damage and repair), the weight-of-the-evidence for metaflumizone indicates a lack of potential genotoxicity.

Specifically, for the battery of three in vitro mutagenicity assays with metaflumizone, no positive responses were observed for increased revertant frequencies with and without metabolic activation [bacterial reverse mutation assay] or for increased mutant frequencies with and without metabolic activation [HGPRT locus assay]. Although there was a positive result for a statistically increased number of structurally aberrant metaphases in the chromosomes, which

indicates clastogenic potential under in vitro conditions, this result was only observed without metabolic activation [cytogenicity study with V79 cells.

Importantly, the potential biological significance of this apparent chromosome damage observed in vitro only without metabolic activation, was evaluated in vivo using the mouse micronucleus assay. Testing in the in vivo micronucleus study with NMRI mice was conducted at a high dose level (2000 mg/kg b.w.) that demonstrated clinical symptoms of toxicity, including piloerection and poor general state, in 5 of 5 animals. No significant or dose-related increases in chromosomal damage were observed in this in vivo test, indicating that metaflumizone does not cause chromosomal aberrations in intact animals.

Moreover, it has also been recognized by U.S. EPA that more weight should be placed on in vivo systems than in vitro systems as expressed in the Agency's weight-of-evidence for genotoxic evaluation of a chemical included in the "Guidelines for Mutagenicity Risk Assessment" (Federal Register, September 24, 1986, Vol. 51: 34006-34012). Thus, the negative in vivo results (non-clastogenicity for chromosomal aberrations) observed in the mouse micronucleus assay and the rat hepatocytes assay, should override the positive results obtained in the in vitro assay only without metabolic activation. Furthermore, it has been noted that in vitro systems may simulate abnormal physiological conditions from prolonged exposure to a chemical in the absence of S-9 metabolic activation [Brusick, D.J. (editor) 1987. Genotoxicity Produced in Cultured Mammalian Cell Assay by Treatment Conditions. Mutation Research, Vol. 189, No.1: 1-69] and [Sofuni, T. 1993. Japanese Guidelines for Mutagenicity Testing. Environmental and Molecular Mutagenesis, Vol. 21, No.1: 2-7]. Consequently, based on the weight-of-the-evidence presented above, metaflumizone does not pose a genotoxic concern.]

3. *Reproductive and developmental toxicity.* [Potential reproductive toxicity of metaflumizone was investigated in a two-generation reproduction toxicity study in Wistar rats by oral gavage administration. Originally, the highest dose tested by oral gavage was 75 mg/kg b.w../day, which induced both excessive maternal toxicity (very high incidences of poor general health in females during premating, gestation, and lactation; and statistically decreased food consumption, body weights, and body weight gain) as well as excessive developmental toxicity (statistically impaired pup body weights and body weight gain), which altogether resulted in high pup mortality. Consequently, a meaningful assessment of the potential reproductive toxicity of the test compound at this excessively toxic dose level was not possible. Thereafter, for the next two successive parental generations of rats, which were originally derived from the parents treated at 75 mg/kg b.w./day, the highest dose tested was 50 mg/kg b.w./day.

Subsequently, the NOAEL for parental toxicity was 20 mg/kg b.w./day, based on the following effects for females at 50 mg/kg b.w./day (highest dose tested for two consecutive generations) -- increased incidences of poor general health in females during premating, gestation, and lactation; 3 of 25 dams with complete litter losses;

and statistically significantly reduced body weights during premating, gestation, and lactation.

The NOAEL for offspring/pup toxicity was 20 mg/kg b.w./day, based on a slight increased incidence of pup mortality at 50 mg/kg b.w./day. Whereas the NOAEL for fertility in this study was 50 mg/kg b.w./day (highest dose tested for two generations), the NOAEL for reproductive performance was considered to be 20 mg/kg b.w./day, based on 3 of 25 dams with complete litter losses, of which 2 of these 3 dams had indications of poor nursing for their first generation of pups. It is noteworthy that because most of the pup mortality was due to poor nursing in only 2 of 25 dams, this finding may be considered to be incidental. Importantly, no comparable impairment of reproductive performance occurred for the succeeding parental generation treated by oral gavage administration at 50 mg/kg b.w./day.

In a developmental (teratology) toxicity study in the Wistar rat, the results indicated that the NOAEL for maternal toxicity was 40 mg/kg b.w./day, based on statistically decreased food consumption and body weight gains at 120 mg/kg b.w./day (highest dose tested). The NOAEL for fetal (prenatal)/developmental toxicity was 120 mg/kg b.w./day (highest dose tested). In addition, there were no indications of any teratogenic effects in the rat fetuses at 120 mg/kg b.w./day (highest dose tested). Therefore, metaflumizone is considered to be neither a developmental toxicant nor a teratogenic agent in the rat.

In a developmental (teratology) toxicity study in the Himalayan rabbit, the results indicated that the NOAEL for maternal toxicity was 100 mg/kg b.w./day, based on several clinical symptoms of toxicity (including ataxia and poor general state) occurring in 4 of 25 does at 300 mg/kg b.w./day, for which 2 of these 4 does had abortions prior to being sacrificed early, with a third doe at 300 mg/kg b.w./day being sacrificed moribund. Similarly, the NOAEL for fetal (prenatal) / developmental toxicity was 100 mg/kg b.w./day, based on slightly decreased mean fetal body weights as well as an increased rate for a certain skeletal variation, namely incomplete ossification of sternabrae. Because developmental toxicity was only observed at dose levels that were maternally toxic, metaflumizone is not selectively toxic to the fetal rabbit.

Lastly, in this rabbit developmental toxicity study, there were no indications of any teratogenic effects in the rabbit fetuses at 300 mg/kg b.w./day (highest dose tested). Therefore, metaflumizone is not teratogenic in the rabbit.]

4. *Subchronic toxicity.* [In the Sprague-Dawley rat, treatment by oral gavage with metaflumizone for a subchronic duration (90-day timepoint in the chronic toxicity/carcinogenicity study) resulted in reduced food consumption and/or decreased mean body weight and/or body weight gains in males and females at 300 mg/kg b.w./day and in increased incidences of hepatocellular centrilobular hypertrophy in the livers of males at 300 mg/kg b.w./day. Under the conditions of

the study, the NOAEL for oral administration of metaflumizone for 90 days was 60 mg/kg b.w./day.

In the beagle dog, treatment by oral gavage with metaflumizone for a subchronic duration (90-day timepoint in the chronic toxicity study) resulted in reduced body weight gain and/or decreased food consumption in several dogs at 30 mg/kg b.w./day and slightly decreased mean MCHC at 30 mg/kg b.w./day. Under the conditions of the study, the NOAEL for oral administration of metaflumizone for 90 days was 12 mg/kg b.w./day.

Lastly, in a subchronic (90-day) dermal toxicity study conducted with metaflumizone in Wistar rats, the results support a NOAEL of 100 mg/kg b.w./day, based on decreased food consumption (females) and decreased body weight change in males and females at 300 mg/kg b.w./day, the next highest dose tested.]

5. *Chronic toxicity.* [In the Sprague-Dawley rat, treatment by oral gavage with metaflumizone for a 2-year chronic duration resulted in dose-related increased incidences of hepatocellular centrilobular hypertrophy in the livers of males and females at 60 mg/kg b.w./day and at 300/200 mg/kg b.w./day and hepatocellular basophilic alteration in males at 60 and 300 mg/kg b.w./day. [NOTE: Beginning the first day of Week 3, the dose level of the high-dose females was lowered from 300 to 200 mg/kg b.w./day, due to an adverse effect of -71% decreased body weight gain as compared to controls.]

Therefore, the no-observable-adverse-effect-level (NOAEL) for systemic toxicity following oral administration of metaflumizone for 24 months to Sprague-Dawley rats was 30 mg/kg b.w./day for males and females. Importantly, treatment with metaflumizone to rats for 2 years resulted in no test substance-related neoplastic findings, and therefore, the NOAEL for oncogenicity was 300/200 mg/kg b.w./day (highest dose tested).

In the CD-1 mouse, treatment by oral gavage with metaflumizone for an 18-month chronic duration resulted in a treatment-related increased incidence of increased brown pigment in the spleens of male and female animals administered 1000 mg/kg b.w./day (highest dose tested), as compared to controls. Under the conditions of the study, the NOAEL for systemic toxicity following oral administration of metaflumizone for 18 months to CD-1 mice was 250 mg/kg b.w./day (the next highest dose tested) for males and females. Importantly, treatment with metaflumizone to mice for 18 months resulted in no test substance-related neoplastic findings, and therefore, the NOAEL for oncogenicity was 1000 mg/kg b.w./day (highest dose tested).

In the beagle dog, treatment via gelatin capsules with metaflumizone for a 12-month chronic duration resulted in reduced body weight gain and/or decreased food consumption in several dogs at 30 mg/kg b.w./day and slightly decreased mean

MCHC at 30 mg/kg b.w./day. Under the conditions of the study, the NOAEL for oral administration of metaflumizone for 12 months was 12 mg/kg b.w./day.

Threshold Effect. For estimated chronic exposure, the calculation of the chronic reference dose (chronic RfD) is based on the results of the chronic toxicity studies in the rat, mouse, and dog, and the two-generation reproduction study in the rat. For metaflumizone, the lowest NOAEL for chronic toxic effects is 12 mg/kg b.w./day from the 12-month dog study. A safety factor of 100 is applied to the NOAEL of 12 mg/kg b.w./day, which results in a chronic RfD of 0.12 mg/kg b.w./day.

Non-Threshold Effect. Since there were no test substance-related neoplastic findings following long-term treatment with metalfumizone to mice for 18 months or to rats for 24 months, the NOAEL for oncogenicity in both studies was established at the respective highest doses tested. Therefore, metaflumizone should be classified as "not likely to be a human carcinogen."]

6. *Animal metabolism.* [In the rat, goat and hen metabolism studies, the majority of the dose was rapidly excreted in the feces. The low levels that were absorbed were distributed throughout various tissues. Metaflumizone was the major component of the extractable residues in all tissues, milk, eggs and is the only residue of concern. Metabolism of metaflumizone occurs by hydroxylation and conjugation on either of the phenyl rings or at the ethylene bridge and are the major routes of detoxification. Cleavage of the semicarbazide bond to yield M320I04 also occurs, usually with accompanying conjugation. The only residue of concern is metaflumizone.]

7. *Metabolite toxicology.* [Toxicity of the metabolites of metaflumizone with potential exposure to humans was concurrently evaluated during toxicity testing of the parent except for the metabolite M320I23 that was not observed in the rat metabolism study. The Z-isomer (M320I02) of metaflumizone was evaluated in additional toxicity tests to confirm no differences between the minor Z-isomer component and metaflumizone with a 9 to 1 E-isomer to Z-isomer ratio, respectively. The results show no toxicological concerns:

Toxicity Studies with the metabolite M320I23 of metaflumizone
(a) Acute Toxicity Study with Metabolite M 320I023
The metabolite M 320I023 of metaflumizone demonstrates low acute toxicity via the oral route of exposure in the rat.
Oral LD50 > 2000 mg/kg b.w. (category III).

(b) Subchronic Toxicity Study with Metabolite M 320I023
In the Sprague-Dawley rat, treatment by oral gavage with metabolite M 320I023 of metaflumizone for a subchronic (90-day) duration resulted in systemic toxicity effects of increased relative liver weights (females) and increased incidences of liver hepatocellular centrilobular hypertrophy in males and females at 1000 mg/kg b.w./day (highest dose tested), as compared to controls. Under the conditions of the

study, the NOAEL for oral administration of the metabolite M 320I023 of metaflumizone for 90 days was 200 mg/kg b.w./day (next highest dose tested) in males and females.

(c) Mutagenicity/Genotoxicity Studies with Metabolite M 320I023
In a battery of three in vitro and one in vivo mutagenicity assays consisting of all required end-points (point mutation, chromosomal damage, and DNA damage and repair), the weight-of-the-evidence for the metabolite M 320I023 (parent ketone) of metaflumizone insecticide indicates a lack of potential genotoxicity.

Specifically, for the battery of three in vitro mutagenicity assays with metabolite M 320I023 of metaflumizone, no positive responses were observed for increased revertant frequencies with and without metabolic activation [bacterial reverse mutation assay] or for increased mutant frequencies with and without metabolic activation [HGPRT locus assay]. Although there was a positive result for a statistically increased number of structurally aberrant metaphases in the chromosomes, which indicates clastogenic potential under in vitro conditions, this result was only observed with metabolic activation [cytogenicity study with V79 cells].

Importantly, the potential biological significance of this apparent chromosome damage observed in vitro only with metabolic activation, was evaluated in vivo using the mouse micronucleus assay. Testing in this in vivo micronucleus study with NMRI mice was conducted at a high dose level (2000 mg/kg b.w.), that demonstrated no clinical symptoms of toxicity but which represents the limit dose for this assay. No significant or dose-related increases in in vivo chromosomal damage were observed, indicating that the metabolite M 320I023 of metaflumizone does not cause chromosomal aberrations in intact animals.

Moreover, it has also been recognized by U.S. EPA that more weight should be placed on in vivo systems than in vitro systems as expressed in the Agency's weight-of-evidence for genotoxic evaluation of a chemical included in the "Guidelines for Mutagenicity Risk Assessment" (Federal Register, September 24, 1986, Vol. 51: 34006-34012). Thus, the negative in vivo results (non-clastogenicity for chromosomal aberrations) observed in the mouse micronucleus assay should override the positive results obtained in the in vitro assay only with metabolic activation. Furthermore, it has been noted that in vitro systems may simulate abnormal physiological conditions [Brusick, D.J. (editor) 1987. Genotoxicity Produced in Cultured Mammalian Cell Assay by Treatment Conditions. Mutation Research, Vol. 189, No.1: 1-69]. Additionally, it has been reported in the literature that S-9 metabolic activation does not often have adequate cofactors for activating detoxifying mechanisms found in the whole animal system [Ashby, J. 1983. The unique role of rodents in the detection of possible human carcinogens and mutagens. Mutation Research, Vol. 115: 117-213] [Galloway, S.M. 1994. Chromosome Aberrations Induced In Vitro: Mechanisms. Delayed Expression, and Intriguing Questions. Environmental and Molecular Mutagenesis, Vol. 23, Supplement 24: 44-

53]. Consequently, based on the weight-of-the-evidence presented above, the metabolite M 320I023 of metaflumizone does not pose a genotoxic concern.

Therefore, as indicated from the results of the mammalian toxicity studies as well as the mutagenicity assays, metabolite M 320I023 of metaflumizone does not demonstrate more adverse toxicity when compared to metaflumizone.

Toxicity Studies with the Z-Isomer of metaflumizone
(a) Acute Toxicity Study with Z-Isomer
The Z-isomer of metaflumizone demonstrates low acute toxicity via the oral route of exposure in the rat.
Oral LD50 > 5000 mg/kg b.w. (category IV).

(b) Subchronic Toxicity Study with Z-Isomer
In the Sprague-Dawley rat, treatment by oral gavage with the Z-isomer of metaflumizone for a subchronic (90-day) duration resulted in impaired body weight gain only in females at the mid-dose (300 mg/kg b.w./day) and the high-dose (1000 mg/kg b.w./day), as compared to controls. Several microscopic changes were observed in female animals at these two dose levels, but all morphologic changes were regarded to be indirect effects of the impaired body weight gain. Under the conditions of the study, the NOAEL for oral administration of the Z-isomer of metaflumizone for 90 days was 1000 mg/kg b.w./day (highest dose tested) in males and 100 mg/kg b.w./day (lowest dose tested) in females.

(c) Mutagenicity/Genotoxicity Study with Z-Isomer
In an in vitro mutagenicity assay with the Z-isomer of metaflumizone, there were no positive responses observed for increased revertant frequencies with and without metabolic activation [bacterial reverse mutation assay].

Therefore, as indicated from the results of the mammalian toxicity studies as well as the mutagenicity assay, the minor isomer of metaflumizone, namely the Z isomer, does not demonstrate more adverse toxicity when compared to metaflumizone.]

8. *Endocrine disruption.* [Data from the reproduction / developmental toxicity and short-and long-term repeated dose toxicity studies with metaflumizone in the rat, rabbit, mouse, or dog, do not suggest any endocrine disruption activity. This information is based on the absence of any treatment-related effects from the histopathological examination of reproductive organs as well as a low level of concern for possible effects on fertility, reproductive performance, or any other aspect of reproductive function, or on growth and development of the offspring.]

C. Aggregate Exposure

1. *Dietary exposure.*

i. *Food.* [

Metaflumizone and its metabolites (M320I04, M320I23) are expressed as the parent compound (metaflumizone). A dietary exposure analysis was conducted for grape, crop group 10 – citrus fruits group, crop group 14 – tree nuts group and all pending uses. The pending uses includes cotton, cottonseed oil, potential secondary residues in meat, fat, byproducts, milk, and eggs, potatoes, sweet potatoes, yams, leafy greens subgroup, leaf petioles subgroup, head & stem brassica subgroup, leafy brassica greens subgroup, fruiting vegetables except cucurbits, cotton.

Acute Dietary Food Exposure: The Health Effects Division (HED) of EPA has determined that there are no toxic effects attributable to a single dose of metaflumizone for the general populations including infants and children. Therefore, a quantitative acute dietary exposure and risk assessment for these sub-populations is not required. HED has set an aPAD for females 13 – 49 years old.

Acute dietary assessments were conducted to evaluate the potential risk due to acute dietary exposure to females 13 – 49 years old. The aRfd for metaflumizone is 1.0 mg/kg bw/day. The FQPA safety factor for metaflumizone has been set to 1. Therefore, the aPAD is 1.0 mg/kg bw/day. The tier 1 acute dietary exposure estimates were based on the proposed tolerance values, 100 percent crop treated values, concentration/processing factors and consumption data from the USDA Continuing Survey of Food Intake by Individuals (CSFII 1994 - 1996, 1998) and the EPA Food Commodity Ingredient Database (FCID) using Exponent's Dietary Exposure Evaluation Module (DEEM-FCID) software. Result exposure estimates were compared against the metaflumizone acute Population Adjusted Dose (cPAD) of 1.0 mg/kg b.w./day.

Exposure estimates for the metaflumizone acute dietary assessments were well below U.S. EPA's level of concern (See tables below). The estimated acute dietary exposure for females 13 – 49 years old was ? %. Additional refinements such as the use of anticipated residues and predicted percent crop treated would further reduce the estimated acute dietary exposure.

Table 1. Summary of Acute Dietary Exposure and Risk for Metaflumizone Considering Grape, Crop Group 10 – Citrus Fruits Group, Crop Group 14 – Tree Nuts Group, all pending, and Secondary Residues in Meat, Fat, Milk and Eggs

Population Subgroups	Exposure Estimate (mg/kg b.w./day)	%aPAD
Females (13-49 years old)	0.070633	7.06

aPAD = acute population adjusted dose (aPAD = 1.0 mg/kg bw/day)

Chronic Dietary Food Exposure:

A tier 1 dietary exposure assessment was conducted for all sub-populations including infants and children. The cRfd for metaflumizone is 0.12 mg/kg bw/day. The FQPA safety factor for metaflumizone has been set to 1. Therefore, the cPAD is 0.12 mg/kg bw/day. The tier 1 chronic dietary exposure estimates were based on the proposed tolerance values, 100 percent crop treated values,

concentration/processing factors and consumption data from the USDA Continuing Survey of Food Intake by Individuals (CSFII 1994 - 1996, 1998) and the EPA Food Commodity Ingredient Database (FCID) using Exponent's Dietary Exposure Evaluation Module (DEEM-FCID) software. Result exposure estimates were compared against the metaflumizone chronic Population Adjusted Dose (cPAD) of 0.12 mg/kg b.w./day.

Exposure estimates for the metaflumizone chronic dietary assessments were well below U.S. EPA's level of concern (See tables below. The most highly exposure sub-group was children 3 – 5 years old and the exposure accounted for ?% of the cPAD. Additional refinements such as the use of anticipated residues and predicted percent crop treated would further reduce the estimated chronic dietary exposure.

Table 2. Summary of Chronic Dietary Exposure and Risk for Metaflumizone Considering Grape, Crop Group 10 – Citrus Fruits Group, Crop Group 14 – Tree Nuts Group, all pending and Secondary Residues in Meat, Fat, Milk and Eggs

Population Subgroups	Exposure Estimate (mg/kg b.w./day)	%cPAD
U.S. Population	0.015792	13.2
All Infants (< 1 year old)	0.008408	7.0
Children (1-2 years old)	0.019314	16.1
Children (3-5 years old)	0.019165	16.0
Children (6-12 years old)	0.01567	13.1
Youth (13-19 years old)	0.013229	11.0
Females (13-49 years old)	0.016063	13.4
Adults (20-49 years old)	0.015845	13.2
Adults (50+ years old)	0.016113	13.4

cPAD = chronic population adjusted dose (cPAD = 0.12 mg/kg bw/day)]

ii. *Drinking Water.* [The estimated drinking water concentrations (EDWCs) used in this assessment were from the HED human health assessment of metaflumizone, January 24, 2006. The EDWCs used in this assessment included the total residue for metaflumizone and metabolite M320I23. The acute and chronic surface water EDWCs were 6.02 and 5.80 ppb, respectively. The acute and chronic ground water EDWC was 0.00717 ppb. The estimated drinking water exposure is shown in the table below. The acute drinking water exposure for females 13-49 years old accounts for less than 1% aPAD. The chronic drinking water exposure for all sub-populations including infants and children was less than 1% cPAD.

Table 3. Estimated Acute Drinking Water Exposure for Females Ages 13-49 Years Old for Metaflumizone.

Population sub-group	Acute Exposure (95th percentile)	% aPAD
US Population	NA	NA
All infants (< 1 year)	NA	NA
Children 1-2	NA	NA
Children 3-5	NA	NA
Children 6-12	NA	NA
Youth 13-19	NA	NA
Adults 20-49	NA	NA
Adults 50+ yrs	NA	NA
Females 13 - 49 yrs	0.000836	0.08

aPAD = acute population adjusted dose (aPAD = 1.0 mg/kg bw/day)

Table 4. Estimated Chronic Drinking Water Exposure for all Sub-populations including Infants and Children.

Population sub-group	Chronic Exposure	% cPAD
US Population	0.000122	0.1
All infants (< 1 year)	0.000401	0.3
Children 1-2	0.000182	0.2
Children 3-5	0.00017	0.1
Children 6-12	0.000117	0.1
Youth 13-19	0.000088	0.1
Adults 20-49	0.000114	0.1
Adults 50+ yrs	0.00012	0.1
Females 13 - 49 yrs	0.000114	0.1

cPAD = chronic population adjusted dose (cPAD = 0.12 mg/kg bw/day)]

2. *Non-dietary exposure.* [

Metaflumizone is registered for fire ant bait and spot-on treatment for pets. These two uses can result in residential exposure. The EPA HED has evaluated these uses and determined the exposure. The exposure and MOE values in the below tables are from the HED document January 24, 2006. The MOE values were calculated using the a short-term dermal NOAEL = 100 mg ai/kg bw/day and short-term incidential oral NOAEL = 20 mg ai/kg bw/day. The calculated MOEs for all homeowner and toddler exposures are greater than 100 and therefore do not exceed EPA's level of concern.

Table 5. Summary of Residential and Recreational Post-Application Exposure and Risks from use of Fire Ant Bait.

Fire Ant Bait	mg/kg bw/day	MOE
Toddler oral hand to mouth (turf grass)	0.000015	1333333
Toddler oral ingestion of granules	0.013	1538
Toddler oral object to mouth (turf)	0.00000093	21505376

Adult dermal pos-app (Res. Turf)	0.000232	431034
Toddler dermal post-app (Res. Turf)	0.00039	256410
Adult golfer dermal post-app (turf)	0.000016	6250000
Child golfer dermal post-app (turf)	0.0000272	3676471
Toddler oral (hand to mouth + object to mouth)	0.000016	1250000

Table 6. Summary of Post Application Exposure and Risk from Pet Spot-on Treatments.

Pet spot treatments	mg/kg bw/day)	MOE
Adult, dermal	0.29	345
Toddler, incidential oral ingestion	0.035	571
Toddler, dermal	0.16	625

3. Aggregate *exposure.*

[Acute Aggregate Risk:

No acute residential/recreational exposure are expected. The acute aggregate risk includes only exposure from food and water. The food and drinking water exposure accounts for 7.15% aPAD which is below HED's level of concern.

Short-Term Aggregate Risk:

There is the potential for short-term, non-dietary exposure of children and adults to metaflumizone from the use as fire ant bait and/or pet spot-on treatment of dogs and cats. Therefore, the short-term aggregate exposure includes residential/recreational, food and water exposure. The target MOE for metaflumizone aggregate risk is 100.

Table 7. Summary of Shor-Term Aggregate Risk from Fire Ant Bait Use.

	Food + water	Non-dietary oral	Dermal	Aggregate
Population Sub-Group	MOE	MOE	MOE	MOE
US population	1257	NA	431034	1253
All infants (< 1 yr old)	2270	1333333	256410	2247
Children 1-2	1026	1333333	256410	1021
children 3-5	1034	1333333	256410	1029
Children 6-12	1267	NA	3676471	1266
Youth 13-19	1502	NA	3676471	1501
Adults 20-49	1253	NA	431034	1250

Adults 50 + years	1232	NA	431034	1229

The aggregate MOE values are all greater than the HED level of concern which indicates that the aggregate use is below HED's level of concern.

Table 8. Summary of Shor-Term Aggregate Risk from Pet Spot-On Treatment use.

	Food + water	Non-dietary oral	Dermal	Aggregate
Population Sub-Group	MOE	MOE	MOE	MOE
US population	1257	NA	345	271
All infants (< 1 yr old)	2270	571	625	264
Children 1-2	1026	571	625	231
children 3-5	1034	571	625	232
Children 6-12	1267	NA	NA	1267
Youth 13-19	1502	NA	NA	1502
Adults 20-49	1253	NA	345	270
Adults 50 + years	1232	NA	345	269

The aggregate MOE values are all greater than the HED level of concern which indicates that the aggregate use is below HED's level of concern.

Chronic Aggregate Risk:

No chronic residential/recreational exposure are expected. The chronic aggregate risk includes only exposure from food and water. The chronic food and drinking water exposure for all sub-populations are below HED's level of concern.]

D. Cumulative Effects **[Section 408(b)(2)(D)(v) 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.**

The EPA is currently developing methodology to perform cumulative risk assessments. At this time, there is no available data to determine whether metaflumizone has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment.]

E. Safety Determination

1. *U.S. population.* [Using the conservative exposure assumptions described above and based on the completeness and the reliability of the toxicity data, BASF has estimated the aggregate exposure to metaflumizone are well below the EPA's level of concern.]

2. *Infants and children.* [All subpopulations based on age were considered.

Infants and children aggregate risk is well below remained below EPA's level of concern. BASF, considering a worst-case situation, concludes with reasonable certainty that no harm will result to infants or children from aggregate exposure to metaflumizone residues.]

F. International Tolerances

[No Maximum residue levels (MRLs) have been established for metaflumizone by the Codex Alimentarius Commision (CODEX) or in Canada and Mexico.]