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MEMORANDUM

Date: 28-JULY-2009

Subject: **Flucarbazone-Sodium. Human-Health Risk Assessment for Application to Turf, Tree Nurseries, and Christmas Tree Farms, Golf Courses and Other Non-food Use Sites.**

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RD of the Office of Pesticide Programs (OPP) requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from all registered and proposed uses of flucarbazone-sodium (referred to as flucarbazone from this point forward in this memorandum). A summary of these findings is provided in this document.

HED has determined that potential exposure could occur via the dietary (drinking water), residential and occupational pathways. HED determined that there is reasonable certainty that no harm will result to the general population or to infants and children from aggregate exposure resulting from the proposed uses.

The occupational and residential exposure assessment and the human-health risk assessment were conducted by Mary Clock-Rust of RAB1; the dietary exposure assessment was provided by Julie Van Alstine of RAB1; the toxicological review was provided by Robert Mitkus of RAB1; and the drinking water assessment was provided by Stephanie Syslo of the Environmental Fate and Effects Division (EFED).

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1.0 EXECUTIVE SUMMARY

Background
Flucarbazone is a selective herbicide registered for use in burndown application and post-emergence control of broadleaf weeds in wheat. The registrant of flucarbazone, Arysta LifeScience, has requested an amended registration for the product Everest®/Prepare™ to be used on non-food use sites (turf and tree nurseries) under the alternate name, Flucarbazone 70 WDG (EPA Reg # 66330-49).

This memorandum addresses human-health risk resulting from the proposed uses and the currently registered food use. The most recent human-health risk assessment for flucarbazone was performed in August of 2000 (Memo, D257851, J. Rowell *et. al*, 8/31/2000). For details on the physical and chemical properties of flucarbazone, please refer to the 2000 risk assessment cited above.

Two flucarbazone products, Prepare™ (pre-emergent use) and Everest® (post-emergent use; EPA Reg. No. 66330-49), are registered for weed control in wheat. Both are water-dispersible granulars (WDG) containing 70% ai flucarbazone. The registrant proposes the uses on residential, public, and commercial turf sites (including golf courses and schools) and tree farms and nurseries.

Hazard Assessment
The toxicological database for flucarbazone is complete. All required toxicity studies have been submitted, including a subchronic inhalation toxicity study that was requested in the last risk assessment for flucarbazone (Memo, D257851, J. Rowell *et al.*, 8/31/2000).

Technical flucarbazone is of low acute toxicity by oral, dermal, and inhalation routes of exposure. It is slightly irritating to the eye, non-irritating to the skin and is not a dermal sensitizer. All acute studies are in Toxicity Category IV, except the eye irritation study which is Toxicity Category III.

There were no adverse treatment-related findings in the 28-day or 90-day dietary studies in mice. In a 2-year carcinogenicity study in mice, retarded body weight development in both sexes and increased food consumption (males) were observed at the limit dose of 7,000 ppm. In the rat, there was reversible vacuolation of the fore-stomach squamous epithelium at the limit dose of 20,000 ppm in both sexes in the 90-day study believed to be due to an irritative effect. In the 2-year study in the rat, at the limit dose (1,000 mg/kg/day), there was an increased incidence of thickened mucosa of the glandular stomach (both sexes), inflammatory infiltrates (males), and vacuolation of the squamous epithelium in the fore-stomach (females). Based on negative results from five immunotoxicity studies in rodents, flucarbazone is not considered an immunotoxic chemical.

Induction of microsomal liver enzymes (Phase I and Phase II) was observed in both sexes in the 28-day and 90-day dietary studies but not in the 1-year dietary study in the dog. Decreased thyroxine (T4) levels and increased thyroxine-binding capacity (TBC) were also observed in both sexes in the 28-day and 90-day dietary studies in the dog at 50,000 and 5,000 ppm, respectively. The changes in T4 levels and TBC were most likely associated with induction of microsomal liver enzymes, especially p-nitrophenol uridine 5'-diphosphate glucuronyl transferase (UDPGT).

Increases in N-demethylase in both sexes and a transient decrease in T4 levels in females were observed in the 1-year dietary study in the dog at 5,000 ppm. However, in the absence of any changes in other thyroid biomarkers (triiodothyronine [T3], TBC and thyroid-stimulating hormone), the transient decrease in T4 in females was not attributed to a primary effect on the thyroid, but rather to hepatic clearance. Other findings in the 90-day dog study indicative of a treatment-related effect on the liver include changes in clinical chemistry, increased liver weights and histopathological findings in one or both sexes. Gross pathological and histopathological findings in the stomach observed in this study suggest that the test substance may cause local irritation in both sexes at the higher doses.

There were no maternally or developmentally toxic effects in rats up to the limit dose. In rabbits, developmental delays (decreased fetal body weight and delayed ossification) occurred in the presence of maternal toxicity (clinical signs and decreased food consumption). In the 2-generation reproduction study in rats, there were no effects on reproductive function in males (sperm measurements) and females (estrous cycling), or reproductive and litter parameters at any treatment level in the F0 or F1 parental animals. Offspring effects occurred at the highest dose tested in the presence of parental systemic toxicity and included decreased body weight at lactation days 21 and 28 (F1), decreased liver weight (F2), marbled liver surface (F1/F2), and air-filled stomach (F1). Liver weight was decreased in F1 adult males and an increased incidence of cecal enlargement in F1and reduced uterus weights in F0 and F1 adult females were also seen at the highest dose tested. There was no indication of offspring susceptibility in the developmental and reproductive toxicity studies.

There were no neurotoxicological effects at any dose level tested in either the acute or subchronic neurotoxicity study, and a developmental neurotoxicity study is not required. The HIARC (2000) concluded that flucarbazone was negative for carcinogenic potential in mice and rats and in accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999) classified flucarbazone as "not likely to be carcinogenic to humans" by all routes of exposure; therefore, a cancer risk assessment was not performed. Flucarbazone was non-mutagenic in a standard battery of genotoxicity assays.

Dose-Response

The PoD chosen for acute dietary exposure assessment for females 13-49 years of age is based on the results of the developmental toxicity study in rabbits in which decreased fetal body weight and delayed ossification were observed at the developmental lowest-observed adverse-effect level (LOAEL) of 500 mg/kg/day [the no-observed adverse-effect level (NOAEL) is 300 mg/kg/day]. The acute dietary reference dose (RfD) and population-adjusted dose (PAD) are 3.0 mg/kg/day. The PoD chosen for chronic dietary risk assessment (all populations) is based on the results of the one-year feeding study in dogs in which decreased body weight gain, decreased thyroxine, increased N-demethylase, and increased liver weight were observed at the LOAEL of 183 mg/kg/day (the NOAEL is 35.9 mg/kg/day). The chronic RfD and PAD are 0.36 mg/kg/day.

Since June, 2001, short-term exposure is defined as 1-30 days (see: memo, M. Stasikowski, 6/4/2001) as opposed to 1-7 days as in the last risk assessment. As a result, for this risk assessment, PoDs were updated for the current risk assessment in order to include all exposure scenarios (since residential uses are proposed), as well as current definitions of "short-" and "intermediate-term" exposure. The PoD chosen for assessment of short- and intermediate-term incidental oral and dermal risk is based on the results of the 90-day feeding study in dogs in

which decreased thyroxine, increased thyroxine-binding capacity, induction of microsomal liver enzymes, gross pathology and histopathology in the stomach, and histopathology in the liver observed at the LOAEL of 162 mg/kg/day (NOAEL=33.8 mg/kg/day). The occurrence of the decreased T4 levels beginning at week 2 and the timeframe of other toxic effects observed in this 13-week dog study correspond to current definitions of short- and intermediate-term durations of exposure in HED. In addition, a requested subchronic inhalation toxicity study has been submitted since the last risk assessment, and this study was determined by RAB1 toxicologists to be the most relevant for the inhalation exposure scenarios. The PoD chosen for short- and intermediate-term inhalation risk assessment is based on the results of the subchronic inhalation toxicity study in rats in which eosinophilic globules (nasal cavity) and squamous cell metaplasia (larynx) in males and females were observed at the LOAEL of 0.18 mg/L (48.8 mg/kg/day). The NOAEL is 0.03 mg/L (8.1 mg/kg/day).

In 2000, the HIARC and the FQPA Safety Factor Committee (SFC) evaluated the potential for increased susceptibility of infants and children from exposure to flucarbazone. RAB1 toxicologists re-evaluated the toxicological database for this risk assessment and reaffirmed the previous conclusion that the FQPA SF should be reduced to 1X.

Drinking Water

EFED provided a drinking water assessment of flucarbazone based on the registered use on wheat at the 0.027 lb ai/acre application rate (Memo, S. Syslo, 8/14/00, D257866). EFED determined that the proposed use on non-food use sites will not result in an increase in drinking water concentrations of flucarbazone (email message from I. Abdel-Saheb to E. Kraft, 5/26/09). Estimates of exposure for the parent alone and the total residues containing the sulfonamide moiety were calculated. The estimated environmental concentration (EEC) (parent and metabolites) for soil porewater is 50 ppb. Residues in ground water are expected to be much lower due to dispersion during leaching through the soil. The estimated drinking water concentrations (EDWCs; parent and metabolites of concern) for surface water [from the Generic Estimated Environmental Concentration (GENEEC) model] are 1.45 ppb for the acute (peak) concentration and 0.48 ppb for the 60-day value (with a 3x adjustment factor). Drinking water estimates were incorporated directly into the dietary exposure analysis.

Dietary (food and water) Exposure and Risk Assessment

Although no new food uses are proposed in the current action, an assessment of dietary risk resulting from potentially contaminated drinking water was performed. The most recent risk assessment for flucarbazone (memo, D257851, J. Rowell, *et. al,* 8/31/2000) included a dietary exposure analysis but did not incorporate drinking water. Therefore, for the current assessment, updated acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments were conducted for the existing use on wheat. The analysis was performed using the Dietary Exposure Evaluation Model DEEM-FCID™, Version 2.03 which uses food consumption data from the U.S. Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998.

The acute and chronic assessments utilized anticipated residues (ARs) for wheat and tolerance-level residues for all remaining commodities, and assumed DEEM™ (ver. 7.81) default processing factors and 100% crop treated (CT) for all commodities. Estimated drinking water residues were provided by EFED.

The acute analysis was conducted for females 13-49 years old, the only population subgroup of

concern. At the 95th percentile, the acute dietary risk estimate for females 13-49 years old accounted for <1.0% of the acute population-adjusted dose (aPAD). The chronic analysis was conduced for the general U.S. population and several population subgroups. The chronic dietary risk estimates are <1.0% of the chronic population-adjusted dose (cPAD) for the general U.S. population, and 1.0% of the cPAD for infants <1 year, the mostly highly exposed population subgroup. The acute and chronic dietary risk estimates are below HED's level of concern. A cancer dietary assessment was not conducted because flucarbazone was classified as "not likely to be carcinogenic to humans."

Residential and Non-Occupational Exposure and Risk Assessment
In the current action, uses are proposed on residential lawns, golf courses and other areas involving potential non-occupational exposure (dermal, inhalation and incidental oral exposure). A conservative assessment of residential exposure for handlers treating home lawns and post-application exposure for adults and children spending time on treated lawns or golf courses was performed. The level of concern (LOC) for residential scenarios is 100 (10X to account for inter-species extrapolation to humans from the animal test species and another factor of 10X to account for intra-species sensitivity). The results of the residential assessment indicate that risks are not of concern for any population, including children [i.e., margins of exposure (MOEs) ≥100].

Aggregate Exposure and Risk Assessment:
Since are proposed on residential areas, aggregate risk was assessed by combining exposure from all potential exposure pathways. Short-term aggregate risk was estimated for all potential populations. For adults, residential handler exposure (dermal and inhalation) was combined with dietary exposure. For children, post-application dermal and incidental oral exposure was combined with dietary exposure. The results of the aggregate risk assessment indicate that risks are not of concern for any population subgroup. All aggregate MOEs are at least 1,500 (LOC=100).

Occupational Exposure and Risk Assessment
Occupational handler exposure involves mixing/loading and applying flucarbazone using aerial and ground application equipment as well as hand-held sprayers. Chemical-specific data are not available with which to assess potential exposure to pesticide handlers. The estimates of exposure in this document are based upon surrogate study data available in the Pesticide Handler's Exposure Database (PHED) (v. 1.1, 1998). For pesticide handlers, estimates of dermal exposure were presented for individuals wearing a single layer of work clothing (i.e., long pants, long-sleeved shirt and shoes plus socks) without the use of protective gloves.

HED performed a conservative assessment of occupational handler risk using standard assumptions for handler exposure. While an exact match for the proposed formulation (WDG) was not possible for all exposure scenarios with the available data, reasonable surrogate data were used to estimate occupational handler exposure. The results of the occupational handler exposure and risk assessment indicate that risks are not of concern with a single layer of clothing.

Post-application activities for the proposed uses include sod and golf course mowing, golf course maintenance, and hand harvesting Christmas trees. HED's assessment can be considered a screening level, conservative assessment of occupational post-application exposure and risk because standard assumptions are used. The results indicate that risks are not of concern for

occupational post-application exposure for all exposure scenarios.

Restricted-Entry Interval (REI)
A 12-hour REI is stated on the proposed Flucarbazone 70 WDG label. Based on the acute toxicity of the ai (Toxicity Category IV for all acute toxicity categories, except eye irritation which is Toxicity Category III) the REI is in compliance with the Worker Protection Standard (WPS).

Review of Human Research
This risk assessment relies in part on data in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies have been reviewed and have been determined to be ethical.

Environmental Justice Considerations
Potential areas of environmental justice concerns, to the extent possible, were considered in this human-health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.hss.energy.gov/nuclearsafety/env/guidance/justice/eo12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under CSFII and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Recommendations for Registration
The proposed uses on turf and tree farms are all non-food use sites. Therefore, no new tolerances are necessary. However, the tolerance expression in 40 CFR §180.562 is incorrect. It should read: "Tolerances are established for residues of flucarbazone-sodium, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only flucarbazone-sodium, 4,5-dihydro-3-methoxy-4-methyl-5-oxo-*N*-[[2-(trifluoromethoxy)phenyl]sulfonyl]-1*H*-1,2,4-triazole-1-carboxamide, sodium salt, and its metabolite *N*-desmethyl flucarbazone-sodium (4,5-dihydro-3-methoxy-5-oxo-*N*-[[2(trifluoromethoxy)phenyl]sulfonyl]-1*H*-1,2,4-triazole-1-carboxamide), calculated as the stoichiometric equivalent of flucarbazone-sodium."

2.0 Ingredient Profile/Structure and Nomenclature

Details about flucarbazone are available in the last risk assessment (memo, J. Rowell, *et al.*, D275851; 8/31/2000) and are summarized here.

Chemical Name:4,5-dihydro-3-methoxy-4-methyl-5-oxo-*N*-[[2(trifluoromethoxy)phenyl] sulfonyl]-1*H*-1,2,4-triazole 1-carboxamide, sodium salt

Common Name:	Flucarbazone-sodium
Synonym:	MKH-6562
Chemical Type:	Herbicide
Trade Name:	Everest®
PC Code Number:	114009
CAS Registry No.:	181274-17-9
Empirical Formula:	$C_{12}H_{10}F_3N_4NaO_6S$
Molecular Weight:	418.29
Appearance:	Colorless crystalline powder
Odor:	Odorless
Melting Point:	200°C (under decomposition)
Density:	1.59 g/mL at 20°C
Vapor Pressure:	$<1x10^{-9}$ at 20°C
Solubility in Water:	44g/L in neutral, acidic, and alkaline conditions at 20°C
n-Octanol/water Partition Coefficient:	

pH	Log K_{ow}
Unbuffered	-2.85
4	-0.89
7	-1.84
9	-1.88

Dissociation Constant: 1.9 for free acid

2.1 Summary of Registered Uses

Flucarbazone is a selective herbicide for burndown application and post-emergence control of many broadleaf weeds in wheat. Two flucarbazone products, Everest® and Prepare™ (EPA Reg. No. 66330-49), are registered for weed control in wheat. Both are WDGs containing 70% active ingredient flucarbazone. Prepare™ is used to control weeds pre-emergence and Everest® is used to control weeds post-emergence.

2.2 Summary of Proposed Uses

The registrant of flucarbazone, Arysta LifeScience, has requested an amended registration for the product Everest®/Prepare™ to be used on non-food use sites (turf and tree nurseries) under the alternate name, Flucarbazone 70 WDG.

Table 2.2: Proposed Use Pattern for Flucarbazone.

Formulation and Product	% AI	Methods of Application	Application Timing	Maximum Number of Applications per Season	PHI (days)	Use Sites	Application Rate (seasonal maximum)
Water Dispersible Granular (WDG) Flucarbazone 70 WDG Reg. No. 66330-49	70%	**Occupational:** Groundboom sprayer, Aerial sprayer, handgun sprayer, low pressure handwand; **Non-Occupational:** hose-end sprayer, low pressure handwand, backpack.	Ground application only, applied post-emergence	1	N/A (non-food uses)	Turf, Tree Nurseries, Golf courses, Sod Farms	0.6 fl oz product, or 0.027 lb ai/acre (0.027 lb ai/acre)

ai = active ingredient

3.0 HAZARD ASSESSMENT

Technical flucarbazone is of low acute toxicity by oral, dermal, and inhalation routes of exposure. It is slightly irritating to the eye, non-irritating to the skin and is not a dermal sensitizer. All acute studies are in Toxicity Category IV, except the eye irritation study which is Toxicity Category III. See Attachment 1 for the relevant toxicity profiles for flucarbazone.

In the mouse, there were no adverse treatment-related findings in the 28-day or 90-day dietary studies. In a 2-year carcinogenicity study, retarded body weight development in both sexes and increased food consumption (males) were observed at the limit dose of 7,000 ppm. In the rat, there was reversible vacuolation of the fore-stomach squamous epithelium at the limit dose of 20,000 ppm in both sexes in the 90-day study believed to be due to an irritative effect. In the 2-year study, at the limit dose (1,000 mg/kg/day), there was an increased incidence of thickened mucosa of the glandular stomach (both sexes), inflammatory infiltrates (males), and vacuolation of the squamous epithelium in the fore-stomach (females).

In rats, immunological changes were observed in both sexes in the 28-day and 90-day dietary studies (reversible) and in males in the 2-year dietary study at the 1-year interim sacrifice, but not at 2 years. Because the toxicology database did not show clinical evidence of immunotoxicity (no increase in clinical signs, sickness, mortality or tumors), the significance and relevance of these immunological findings in rats was unclear. Therefore, the immunotoxic potential of flucarbazone in rats was investigated in more detail in five immunotoxicity studies, including antibody plaque-forming cell assays and in assays examining cell-mediated immune response (anti-CD-3 T-cell proliferation assay), splenic T-cells, B-cells, and natural killer (NK) cells at doses up to and including 1,000 mg/kg bw/day, the limit dose, according to accepted EPA guidelines. In each of these guideline studies, the immunotoxic potential was negative up to and

including 1,000 mg/kg/day. Therefore, the immunological findings in the rat studies are considered to represent slight or moderate nonspecific toxicity rather than immunotoxicity, and flucarbazone is not considered an immunotoxic chemical.

In the dog, induction of microsomal liver enzymes (Phase I and Phase II) was observed in both sexes in the 28-day and 90-day dietary studies but not in the 1-year dietary study. Decreased thyroxine (T4) levels and increased thyroxine-binding capacity (TBC) were also observed in both sexes in the 28-day and 90-day dietary studies at 50,000 and 5,000 ppm, respectively. The changes in T4 levels and TBC were most likely associated with induction of microsomal liver enzymes, especially UDPGT. Increases in N-demethylase in both sexes and a transient decrease in T4 levels in females were observed in the 1-year dietary study at 5,000 ppm. However, in the absence of any changes in other thyroid biomarkers (triiodothyronine [T3], TBC and thyroid-stimulating hormone), the transient decrease in T4 in females was not attributed to a primary effect on the thyroid, but rather to hepatic clearance. Other findings in the 90-day dog study indicative of a treatment-related effect on the liver include changes in clinical chemistry, increased liver weights and histopathological findings in one or both sexes. Gross pathological and histopathological findings in the stomach observed in this study suggest that the test substance may cause local irritation in both sexes at the higher doses.

There were no maternally or developmentally toxic effects in rats up to the limit dose of 1,000 mg/kg/day. In rabbits, developmental effects (decreased fetal body weight and delayed ossification) occurred at the LOAEL of 500 mg/kg/day in the presence of maternal toxicity (clinical signs and decreased food consumption). In the 2-generation reproduction study in rats, there were no effects on reproductive function in males (sperm measurements) and females (estrous cycling), or reproductive and litter parameters at any treatment level in the F0 or F1 parental animals up to 12,000 ppm. Offspring effects, which occurred at 12,000 ppm in the presence of parental toxicity, included decreased body weight at lactation days 21 and 28 (F1), decreased liver weight (F2), marbled liver surface (F1/F2), and air-filled stomach (F1). Liver weight was decreased in F1 adult males and an increased incidence of cecal enlargement in F1and reduced uterus weights in F0 and F1 adult females was seen at 12,000 ppm. The NOAEL for parental animals and offspring was 4,000 ppm. There was no indication of quantitative or qualitative extra-sensitivity in fetuses or pups in comparison to adult animals in the developmental and reproductive toxicity studies.

In the acute neurotoxicity study, both sexes had transient decreases in motor activity and locomotor activity and an increase in the incidence of low levels of activity in the open field at the limit dose (2000 mg/kg bw/day). In the subchronic neurotoxicity study, body weight, body-weight gain and food consumption were reduced in males at doses that were above the limit dose. There were no neurotoxicological effects at any dose level tested. In addition, there were no treatment-related histopathological findings in the central or peripheral nervous system at any dose level tested in either the acute or subchronic study. Based on a weight-of-the-evidence analysis, there is no requirement for a developmental neurotoxicity study in rats.

The Hazard Identification and Assessment Review Committee (HIARC, 2000) concluded that flucarbazone was negative for carcinogenic potential in mice and rats up to or above the limit doses of 2066-3121 mg/kg/day in mice and 1,000 mg/kg/day in rats. In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the HIARC classified flucarbazone as not likely to be carcinogenic to humans by all routes of exposure based upon lack

of evidence of carcinogenicity in rats and mice, therefore, a cancer risk assessment is not necessary. The genotoxic potential is negative based on negative results in *in vitro* bacterial (Ames assay) and mammalian cells (V79 HGPRT (Rob: Please spell) gene mutation assay), in the *in vitro* V79 cells chromosome aberration assay with or without metabolic activation, in an *in vitro* UDS assay and an *in vivo* mouse micronucleus assay.

3.1 FQPA Assessment

In 2000, the HIARC and the FQPA Safety Factor Committee (SFC) evaluated the potential for increased susceptibility of infants and children from exposure to flucarbazone. RAB1 toxicologists re-evaluated the toxicological database for this risk assessment and reaffirmed the previous conclusion that the FQPA SF should be reduced to 1X based on the following:

➢ The toxicology database is complete for FQPA assessment.

➢ No increased quantitative or qualitative susceptibility was seen following pre and/or post natal exposures. There were no developmental findings in rats up to the limit dose of 1,000 mg/kg/day. In the rabbit developmental toxicity study, the effects seen in fetuses (decreased fetal body weight and delayed ossification) are at dose levels equal to or greater than doses where maternal toxicity (increased clinical signs and decreased food consumption) were observed. In a 2-generation reproductive toxicity study in rats, the effects seen in offspring were at dose levels equal to or greater than doses where parental toxicity was seen.

➢ There was no evidence of neurotoxicity in either the acute or subchronic neurotoxicity study.

➢ A developmental neurotoxicity (DNT) study is not required.

➢ The residential exposure assessment will not underestimate the potential exposures for infants and children from the use of flucarbazone.

➢ The drinking water assessment was based on screening-level models (Tier I) and is not expected to over-estimate drinking water exposure.

3.2 Dose-Response Assessment

A summary of the doses and points of departure (PoDs) chosen for human health risk assessment is found in Table 3.2. PoDs have been updated since the last risk assessment (2000) in order to include all current HED exposure scenarios. The acute and chronic RfDs remain the same as in the last risk assessment. Effects observed in the 90-day feeding study in the dog were determined to be relevant for short- and intermediate-term incidental oral and dermal exposures. Decreased thyroxine levels in both sexes first appeared at week 2 and persisted until the end of the study (13 weeks). The occurrence of the decreased T4 levels beginning at week 2 and the timeframe of other toxic effects observed in this 13-week dog study correspond to current definitions of short- and intermediate-term durations of exposure in HED. In addition, a requested subchronic inhalation toxicity study has been submitted since the last risk assessment, and this route-specific study was determined by RAB1 toxicologists to be the most relevant for the inhalation exposure scenarios.

Table 3.2. Summary of Toxicological Doses and Endpoints for Use in Human-Health Risk Assessment.

Exposure Scenario	Point of Departure, Uncertainty/FQPA Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (females 13-49 years of age)	NOAEL = 300 mg/kg/day UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	aRfD = aPAD = 3.0 mg/kg/day	Developmental Toxicity Study - Rabbit Developmental LOAEL = 500 mg/kg/day based on decreased fetal body weight and delayed ossification
Chronic Dietary (all populations)	NOAEL = 35.9 mg/kg/day UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	cRfD = cPAD = 0.36 mg/kg/day	One year feeding study - Dog LOAEL = 183 mg/kg/day based on decreased body weight gain, decreased thyroxine, increased N-demethylase, and increased liver weight
Incidental oral Short- and Intermediate-term (1-30 days and 1-6 months)	NOAEL = 33.8 mg/kg/day UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	LOC for MOE = 100 (Residential)	90-Day Feeding Study - Dog LOAEL = 162 mg/kg/day based on decreased thyroxine, increased thyroxine-binding capacity, induction of microsomal liver enzymes, gross pathology and histopathology in the stomach, and histopathology in the liver
Dermal Short- and Intermediate-term (1-30 days and 1-6 months)	NOAEL = 33.8 mg/kg/day UF_A = 10X UF_H = 10X UF_{FQPA} = 1X (Dermal absorption = 25%)	LOC for MOE = 100 (Occupational) LOC for MOE = 100 (Residential)	90-Day Feeding Study - Dog LOAEL = 162 mg/kg/day based on decreased thyroxine, increased thyroxine-binding capacity, induction of microsomal liver enzymes, gross pathology and histopathology in the stomach, and histopathology in the liver
Dermal Long-Term (>6 months)	NOAEL = 35.9 mg/kg/day UF_A = 10X UF_H = 10X UF_{FQPA} = 1X (Dermal absorption = 25%)	LOC for MOE = 100 (Occupational) LOC for MOE = 100 (Residential)	One year feeding study - Dog LOAEL = 183 mg/kg/day based on decreased body weight gain, decreased thyroxine, increased N-demethylase, and increased liver weight
Inhalation Short-, Intermediate-, and Long-Term (1-30 days, 1-6 months, >6 months)	NOAEL = 0.03 mg/L (8.1 mg/kg bw/day[1]) UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	LOC for MOE = 100 (Occupational) LOC for MOE = 100 (Residential)	Subchronic inhalation toxicity study - Rat LOAEL = 0.18 mg/L (48.8 mg/kg/day) based on eosinophilic globules (nasal cavity) and squamous cell metaplasia (larynx) in males and females
Cancer (oral, dermal, inhalation)	Not likely to be carcinogenic to humans (2000).		

1. Calculated as follows: 0.03 mg/L * 45.2 L/hr/kg * 6 hr/day = 8.1 mg/kg/day.

3.3 Endocrine Disruption

EPA is required under the 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 the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, 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. When the appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disrupter Screening Program (EDSP) have been developed and vetted, flucarbazone sodium may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 DIETARY EXPOSURE AND RISK

An assessment of dietary exposure and risk for the proposed uses was provided in an HED memorandum (memo, J. Van Alstine, D366918, 7/28/2009). Acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments were conducted using the DEEM-FCID™, Version 2.03 which uses food consumption data from the USDA's CSFII from 1994-1996 and 1998. Updated acute and chronic dietary (food and drinking water) exposure and risk assessments are necessary because the most recent dietary risk assessment for flucarbazone (J. Rowell, *et al.,* 17-AUG-2000; D267413) did not incorporate drinking water residues into the assessment.

4.1 Drinking Water Residue Profile

The drinking water residues used in the dietary risk assessment were provided by EFED (memo, (S. Syslo, D257866, 8/14/2000) and were incorporated directly into this dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources."

Groundwater and surface water monitoring data were not available to EFED for flucarbazone. Tier I screening models were used to determine estimated concentrations for the parent flucarbazone in groundwater and surface water following use on wheat (memo, S. Syslo, D257866, 8/14/2000). The Generic Estimated Environmental Concentration (GENEEC) Model was used for predicting surface water concentrations and Screening Concentration in Ground Water (SCI-GROW) Model was used for predicting ground water concentrations. Estimates of exposure for the parent alone and the total residues containing the sulfonamide moiety were calculated. EDWCs could not be calculated for the degradate of flucarbazone, N-desmethyl flucarbazone, because this compound was not observed in the environmental fate studies.

EDWCs Parent Only: Results from the SCI-GROW screening model predict that the maximum acute and chronic concentration of parent flucarbazone in shallow groundwater is not expected to exceed 0.2 µg/L for the proposed use on wheat. This EDWC is well below the LOQ for the

analytical method (LOQ in water = 1.0 μg/L = 1000 ng/L). Based on the Tier I GENEEC modeling results, flucarbazone EDWCs in surface water are not likely to exceed 1.42 ppb for the acute (peak) concentration and 1.25 ppb for the chronic (60-day) concentration from maximum aerial spray application of 0.027 lb ai/acre per year.

EDWCs-Total Flucarbazone Residues: Because degradates of flucarbazone are so resistant to aerobic metabolism in soil, they lie outside the range of environmental characteristics from which SCI-GROW was developed. It was therefore not appropriate in this case to use the model to estimate EDWCs. Instead, a value for the concentration of total flucarbazone residues in the soil pore water of the top 1-foot of soil immediately post-application was estimated, assuming that this value would be a maximum upper limit to the amount of chemical that could be found. The following assumptions were made:

- The application rate was 0.027 lb/A.
- The volume of pore water would be 20% of the total volume of soil.
- The compound is not sorbed to soil particles (Koc = 11), so all of the chemical will be found in the pore water.

For an acre of soil 1 foot deep, one has 43,560 ft^3 x 0.2 = 8712 ft^3 of pore water. If 0.027 lb of the chemical is diluted into 8712 ft^3 of pore water, and the appropriate conversion factors are applied, one would expect a maximum concentration in the soil pore water in the upper 1-foot of soil to be 50 ppb. This number would be an upper limit to the amount of chemical that could be found in the soil pore water. Residues reaching groundwater would be of lower concentration due to dispersion during leaching through the soil. However, repeated applications would result in accumulation over time.

Based on the Tier I GENEEC modeling results, total flucarbazone EDWCs in surface water are not likely to exceed 1.45 ppb for the acute (peak) concentration and 1.44 ppb for the chronic (60-day) concentration from maximum aerial spray application of 0.027 lb ai/acre per year.

Since 50 ppb is the highest estimate of concentration of total flucarbazone residues in water, it was used to assess acute and chronic aggregate risk for this dietary assessment.

4.2 Dietary Exposure and Risk

Residues of Concern
On January 30, 2001, the HED Metabolism Assessment Committee (MARC) reviewed and discussed the material in the 23-JAN-2001 flucarbazone Issues Memorandum (J. Tyler *et al.*; D272091) (memo, J. Tyler, D273561, 3/21/2001). The MARC concluded that the appropriate tolerance expression for wheat is the parent flucarbazone-sodium and N-desmethyl flucarbazone-sodium. However, the Committee recommended that MKH 6562 sulfonamide and its conjugates, in addition to the parent and N-desmethyl flucarbazone-sodium, be included in the risk assessment for wheat. The Committee recommended that sulfonamide and its conjugates be excluded from the tolerance expression due to the absence of an analytical enforcement method to measure them and the ability of the parent and the N-desmethyl metabolite to serve as a measure of misuse.

On July 27, 2000, the HED MARC recommended that the parent and the sulfonamide metabolite

and its conjugates should be included in the tolerance expression and risk assessment for livestock commodities (memo, J. Rowell, *et al.,* D267418; 8/14/2000).

Wheat RACs
Results of a submitted crop field trial study on wheat (MRID#44848823) were reviewed by HED. However, to account for the metabolites of concern in wheat, calculation of the anticipated total residues (parent and metabolites) to be used in the dietary exposure assessment was necessary. Using the ratio of the sulfonamide metabolites to the sum of the parent and N-desmethyl metabolite observed in the wheat metabolism study, and the results from the crop field trial study, the following anticipated total residues (parent and metabolites) expected to be in wheat were determined: 0.92 ppm in wheat forage, 0.904 in wheat hay, 0.84 ppm in wheat straw and 0.24 ppm in wheat grain (memo, J. Rowell, D267412, 8/23/2000).

Livestock Commodities
The anticipated total residues (parent and metabolites) in wheat and the result of the submitted ruminant feeding study were used to calculate the maximum theoretical dietary burden (MTDB) and appropriate total residue levels (parent and metabolites) to be used in the risk assessment for ruminants (memo, J. Rowell, 23-AUG-2000; D267412).

Processed Commodities
The results of the processed food/feed study indicated that flucarbazone will not concentrate in processed wheat commodities (memo, J. Rowell, D273561, 3/21/2001).

Dietary Exposure Analysis
The acute analysis was performed for females 13-49 years old, the population of concern. The aPAD for females 13-49 years old is 3 mg/kg/day. The acute food plus water risk estimates are not of concern to HED (<100% aPAD) at the 95th percentile for females 13-49 years old (<1.0% aPAD).

The chronic analysis was performed for the general U.S. population and several population subgroups. The cPAD for the general U.S. population and all regulated population subgroups is 0.36 mg/kg/day. The results reported in Table 4.2 are for the general U.S. population, all infants (<1 year old), children 1-2 years old, children 3-5 years old, children 6-12 years old, youth 13-19 years old, adults 20-49 years old, adults 50+ years old, and females 13-49 years old. The resulting chronic food and drinking water risk estimates are not of concern to HED (≤100% cPAD). The general U.S. population utilizes <1.0% of the cPAD; all infants <1 year old are the most highly exposed population subgroup and utilizes 1.0% of the cPAD. A cancer dietary assessment was not conducted because flucarbazone was classified as not likely to be carcinogenic to humans.

Table 4.2. Dietary (Food and Drinking Water) Exposure and Risk for Flucarbazone[1].

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	NA	NA	0.001514	<1.0
All Infants (< 1 year old)			**0.003710**	**1.0**
Children 1-2 years old			0.002736	<1.0
Children 3-5 years old			0.002602	<1.0
Children 6-12 years old			0.001795	<1.0
Youth 13-19 years old			0.001215	<1.0
Adults 20-49 years old			0.001343	<1.0
Adults 50+ years old			0.001342	<1.0
Females 13-49 years old	0.002923	<1.0	0.001327	<1.0

[1] The value for the highest exposed population for the chronic risk assessment is bolded.

The acute and chronic assessments utilized ARs for wheat and tolerance-level residues for all remaining commodities, and assumed DEEM™ (ver 7.81) default processing factors and 100% CT all commodities. Estimated drinking water residues were provided by EFED. The current acute and chronic analyses could be further refined through the use of percent CT data, preparation/cooking factors, and/or ARs for meat and milk commodities; however, refinement is not needed at this time.

5.0 RESIDENTIAL EXPOSURE AND RISK

Flucarbazone is proposed for use on residential turf and recreational sites such as schools, parks and golf courses. The proposed label (Flucarbazone 70 WDG) does not prohibit application by home-owners; therefore, short-term residential (non-occupational) handler exposure and post-application exposure were evaluated. Based on the proposed use pattern, intermediate- and long-term exposure is not expected. An assessment of residential and occupational exposure has been completed for the proposed uses (memo, M. Clock-Rust, D367458, 7/28/09).

5.1 Residential Handler Exposure and Risk

Residential application methods include low-pressure handwand, hose-end sprayer, and backpack sprayer.

HED's Draft SOPs for Residential Exposure Assessments, and Recommended Revisions (HED Policy Number 11, revised 22 Feb 2001), were used as the basis for all residential handler exposure calculations and assumptions. Data from the ORETF (MRID # 44972201) were used in this assessment in place of PHED data for the garden hose-end sprayer scenario, which provided more confidence in the exposure estimate than PHED.

Since exposure data for WDG formulations are not available, it is HED policy to use exposure data for wettable powders and liquids as reasonable surrogates.

Assumptions for Residential Handler Assessment

- ½ acre lawn is treated or, 5 gallons per day (treated area/amount handled);
- Handlers are adults;

- Applicators wear short-sleeved shirt, and long pants (and gloves for hose-end sprayer scenario);
- 25% dermal absorption factor, 100% inhalation absorption factor; and
- Adult body weight is 70 kg.

A summary of handler exposure and risk is provided in Table 5.1.

Table 5.1. Handler Exposure and Risk Estimates for Residential Lawn Applicators Treating Turf.

Residential Handler Scenario	Application Rate[1] (lb ai/A or lb ai/gal)	Area Treated[2] (acres/ Day or gal/day)	Dermal Unit Exposure[3] (mg/lb ai)	Inhalation Unit Exposure[3] (mg/lb ai)	Daily Dose[4] (mg/kg/ day)	Short-Term MOE[5]	Combined MOE[6]
Mixing/loading wettable powders and applying using low-pressure handwand sprayer (ORETF)	0.0019 lb ai/gallon	5 gallons	38	0.0027	Dermal: 0.0013	Dermal: 26,000	26,000
					Inhal: 0.0000003	Inhal: 27,000,000	
Mixing/loading liquids and applying using garden hose-end sprayer (ORETF)	0.027	0.5	11	0.017	Dermal: 0.00053	Dermal: 64,000	63,000
					Inhal: 0.0000032	Inhal: 2,500,000	
Mixing/loading liquids and applying using backpack sprayer (PHED)	0.027	0.5	5.1	0.03	Dermal: 0.00025	Dermal: 140,000	130,000
					Inhal: 0.0000057	Inhal: 1,400,000	

1. Application rate is based on maximum values found in proposed label: Flucarbazone 70WDG (EPA Reg. No. 66330-49).
2. Area treated is based on the area that can be reasonably treated in a single day based on the application method (standard EPA/OPP/HED values).
3. Inhalation unit exposure values represent no respirator. Dermal unit exposure values represent individuals wearing short-sleeved shirt, short pants and no gloves. Values for backpack sprayer are reported in the PHED Surrogate Exposure Guide dated August 1998, and that for hose-end sprayer and low-pressure handwand were obtained from the ORETF data.
4. Daily Dose (mg/kg/day) = [Unit Exposure * Application rate * Absorption Rate (dermal: 25%, inhalation: 100%) *Area treated] / 70 kg.
5. Short-Term Dermal MOE = NOAEL (33.8 mg/kg/day) / Daily Dose. Short-term inhalation MOE = NOAEL (8.1 mg/kg/day) / Daily Dose. The LOC is 100.
6. Combined MOE: $MOE_{combined} = \frac{1}{\frac{1}{MOE_{INHALATION}} + \frac{1}{MOE_{DERMAL}}}$

Exposure and risk estimates for residential handlers for all scenarios are not of concern (MOEs are above the LOC of 100).

5.2 Residential Post-application Exposure

Residential post-application exposure for adults is composed of dermal exposure only. Post-application inhalation exposure is expected to be negligible given the low volatility of flucarbazone (<1 x 10^{-9} Pa @ 20°C) and the outdoor setting. For children, potential risk pathways include incidental oral exposure as well as dermal exposure from treated residential and public turfgrass.

An assessment of short-term exposure and risk was performed. Intermediate-term exposure is not expected as only one or two applications per year are expected. The short-term assessment is conservative in that the duration of exposure is likely an over-estimate of actual time spent on treated turf. Further, the endpoint for short-term dermal risk assessment is protective of intermediate-term risk as both are based on the same study and dose level.

5.2.1 Residential Dermal Post-application Exposure Assessment

Post-application dermal exposure is based on the assumption that pesticide residues are transferred to the skin of adults and children who spend time on treated lawns (turf) or golf courses.
An assessment of short-term residential post-application risk was performed. Intermediate-term exposure is not expected as only one or two applications per year are proposed. The short-term assessment is conservative in that the duration of exposure for residential post-application is likely an over-estimate of actual time spent on treated turf (2 hours/day) and standard assumptions are built into the assessment. Further, the endpoint for short-term dermal risk assessment is protective of intermediate-term risk as both are based on the same study and dose level (90-day feeding study in dogs, NOAEL/PoD = 33.8 mg/kg/day).

Assumptions for Dermal Post-application Exposure Assessment

- Post-application exposure was assessed using a residue based on "day zero" (after sprays have dried);
- Transfer coefficients (TCs) were used to assess short-term post-application dermal exposure for adults on treated lawns (14,500 cm^2/hour), golfing (500 cm^2/hour);
- Short-term TCs for children on treated lawns: 5,200 cm^2/hour.
- Adult body weight is 70 kg;
- Child's body weight is 15 kg;
- Duration of exposure on lawns: 2 hours per day;
- Duration of exposure on golf courses: 4 hours per day;
- 25% dermal absorption factor.

Note Regarding Golf Course Exposure
Risk assessments for children golfing are very difficult to complete because of the increased uncertainties associated with extrapolation of adult dermal exposure data and because of the increased likelihood of other behaviors that might contribute to exposure, such as mouthing contaminated hands or golf balls. Therefore, the risk associated with children in a golfing scenario is addressed qualitatively below:

Five-year-old children are assumed to be the age group for children in a golfing scenario since younger children are not considered to be a realistic population for the purposes of assessing risk for golfing scenarios. Therefore, the risk associated with children in a golfing scenario is based on the surface area to body weight ratio (SA/BW) for male children 5 years of age (i.e., the difference is larger for males compared to female making the value more protective) was calculated by using the 95th percentile body surface area and the 50th percentile for body weight. This skewed SA/BW for children was compared to that of the average adult, and found to be approximately 70 percent greater. Based on this parameter alone, the child's exposure could be almost twice that of the adult golfer, however, it should be noted that a child is not expected to use the golf course for the same length of time as an adult. While an adult is likely to play a full round of golf (i.e., 18 holes), which takes approximately 4 hours, a child would probably only spend about 2 hours (i.e., the 75th percentile for time spent playing on grass by children aged 1-4 years and 5-11 years) on the course. Thus, the child's shorter duration on the golf course offsets the higher SA/BW, and therefore, the child golfer's exposure is likely to be similar to that of the adult golfer. [Note: The values used to calculate SW/BW and estimate time spent playing on

grass were obtained from the EPA Exposure Factors Handbook (1997)]. Therefore, a separate assessment for youth/children golfing was not conducted.

TCs for residential post-application exposure on lawns and golf courses are standard values established by HED's ExpoSAC.

For adults and children, residential post-application dermal exposure and risk resulting in MOEs greater than or equal to 100 are not of concern to HED. Table 5.2.1 provides a summary of the short-term dermal exposures and risks for adults and children. Residential post-application dermal risk estimates are not of concern (i.e., all MOEs are above 100).

Table 5.2.1. Residential Post-application Dermal Exposure and Risk for Adults and Children from Residential Lawns and Golf Courses Treated with Flucarbazone.

Population	Application Rate (lb ai/A)	Fraction of ai Transferrable from the Foliage	Turf Transferable Residue [1] ($\mu g/cm^2$)	Transfer Coefficient (cm^2/hr)	Body Weight (kg)	Exposure Time (hr)	Daily Dose[2] (mg/kg/day)	Short-term Dermal MOE[3]
Residential Lawns								
Adults	0.027	0.05	0.015	14,500	70	2	0.0016	22,000
Children	0.027	0.05	0.015	5,200	15	2	0.0026	13,000
Golf courses								
Adults	0.027	0.05	0.015	500	70	4	0.00011	320,000

[1] Turf Transferrable Residue ($\mu g/cm^2$) = Application rate (lb ai/A) * Fraction of ai Transferrable from the Foliage * 4.54E+8 $\mu g/lb$ * 2.47E-8 A/cm^2
[2] Daily Dose = (Turf Transferrable Residue ($\mu g/cm^2$) * TC (cm^2/hr) * Exposure Time (hrs) * Dermal Abs. Factor (25%) * 0.001 mg/μg / [Body Weight (kg)]
[3] Dermal MOE = NOAEL/Daily Dose; where Short-term NOAEL = 33.8 mg/kg/day.

5.2.2 Children's Incidental Oral Exposure Assessment

Incidental oral exposure for children consists of oral hand-to-mouth exposure, object-to-mouth exposure and incidental soil ingestion.

Assumptions

- On the day of application, 5% of the application rate is available on turf grass as transferable residue;
- Incidental oral post-application exposure was estimated using day zero assumption for the initial fraction of residues available;
- Surface area of a child's hand that is mouthed is 20 cm^2;
- The rate of hand-to-mouth activity is 20 times/hour for short-term exposure;
- The saliva extraction factor is 50%;
- Child's body weight is 15 kg;
- Duration of exposure for children is assumed to be 2 hours per day.
- On the day of application, it may be assumed that 20% of the application rate is available to be ingested;

- Grass ingestion rate for children is 25 cm^2/day;
- On the day of application, it is assumed that 100% of the application rate is located within the uppermost 1 cm of soil;
- Soil ingestion rate for children is 100 mg/day;

For children, residential post-application incidental oral exposure and risk resulting in MOEs greater than or equal to 100 are not of concern to HED. Tables 5.2.2a through 5.2.2c provide a summary of the short-term incidental oral exposures and risks for children. Residential post-application incidental oral risk estimates are not of concern (i.e., all MOEs are above 100).

Table 5.2.2a. Post-application Oral Hand-to-Mouth Exposure and Risk for Children from Treated Lawns.

Application Rate (lb ai/A)	Fraction of ai Transferrable from Foliage	Turf Transferable Residue [1] (µg/cm^2)	Hand Surface Area (cm^2/event)	Saliva Extraction Factor	Frequency (events/ hour)	Daily Dose[2] (mg/kg/day)	Short-term Oral MOE[3]
0.027	0.05	0.015	20	50%	20	0.00040	84,000

[1] Turf Transferrable Residue $_{\text{Post-application day}}$ (µg/cm^2) = Application rate (lb ai/A) * Fraction of ai transferrable from foliage * 4.54E+8 µg/lb * 2.47E-8 A/cm^2
[2] Daily Dose = [Turf Transferrable Residue (µg/cm^2) * Hand Surface Area (cm^2/event) * Saliva extraction factor * Frequency (events/hr) * 0.001 mg/µg * Exposure time (2 hrs/day)] / [Body Weight (15 kg)]
[3] Oral MOE = Oral NOAEL/Daily Dose; where Short-term NOAEL = 33.8 mg/kg/day.

Table 5.2.2b. Post-application Oral Object-to-Mouth Exposure and Risk for Children from Treated Lawns

Application Rate (lb ai/A)	Fraction of ai Transferrable from Foliage	Grass/Object Residue [1] (µg/cm^2)	Ingestion Rate (cm^2/day)	Body Weight (kg)	Daily Dose[2] (mg/kg/day)	Short-term Oral MOE[3]
0.027	0.2	0.061	25	15	0.0001	330,000

[1]Grass/Object residue $_{\text{Post-application day}}$ (µg/cm^2) = Application rate (lb ai/A) * Fraction of ai transferrable from foliage * 4.54E+8 µg/lb * 2.47E-8 A/cm^2
[2] Daily Dose = [Grass residue (µg/cm^2) * Ingestion rate (cm^2/day) * 0.001 mg/µg] / [Body Weight (kg)]]
[3]Oral MOE = Oral NOAEL / Daily Dose; where Short-term NOAEL = 33.8 mg/kg/day.

Table 5.2.2c. Post-application Incidental Soil Ingestion Exposure and Risk for Children from Treated Lawns

Application Rate (lb ai/A)	Fraction of ai Retained in the Soil	Soil Residue [1] (µg/g)	Ingestion Rate (mg/day)	Body Weight (kg)	Daily Dose[2] (mg/kg/day)	Short-term Oral MOE[3]
0.027	1	0.20	100	15	0.0000013	26,000,000

[1] Soil residue (µg/cm^2) = Application rate (lb ai/A) * Fraction of ai retained on soil * (4.54E+8 µg/lb * 2.47E-8 A/cm^2 * 0.67 cm^3/g soil)
[2] Daily Dose = [Soil residue (µg/g) * Ingestion rate (mg/day) * 0.000001 g/µg] / [Body Weight (kg)]]
[3] Oral MOE = Oral NOAEL/Daily Dose; where Short-term NOAEL = 33.8 mg/kg/day.

The combined scenarios for children resulted in MOEs greater than the LOC (LOC = MOE >100) and, therefore, children's incidental oral risk is not of concern to HED. Table 5.2.2d provides a summary of the combined MOEs for subpopulations to flucarbazone.

Table 5.2.2d. Children's Combined Incidental Oral Exposure and Risk Estimates from Residential Lawns

Children's Exposure Scenarios	TTR/GR/SR$_0$ (ug/cm^2 or g)[1]	Daily Dose (mg/kg/day)[2]	Short-Term MOE[3]	Total Short-Term MOE[4]
(1) Hand-to-Mouth	0.015	0.00040	84,000	Oral: 67,000 Dermal+Oral: 11,000
(2) Object-to-Mouth	0.061	0.0001	330,000	
(3) Soil Ingestion	0.20	0.0000013	26,000,000	
(4) Dermal	0.015	0.0026	13,000	

1. TTR = turf transferable residue; GR = grass residue; SR=soil residue.
2. Daily Dose = potential dose rate.
3. MOE = NOAEL/PDR; where Short-term NOAEL = 33.8 mg/kg/day (for dermal and oral exposures).
4. Total MOE = NOAEL/[summed daily dose from all scenarios (mg/kg/day)].

As a conservative, health-protective measure, HED estimated residential risk for children from all possible sources of oral and dermal post-application sources of flucarbazone residues. The estimates provided in Table 5.2.2d are expected to be overestimates of exposure and risk as it is unlikely that one individual would experience dermal, hand-to-mouth, object-to-mouth and soil ingestions exposure concurrently. The combined scenarios for children resulted in MOEs greater than the LOC (LOC = MOE >100) and therefore, children's incidental oral risk is not of concern to HED.

5.3 Non-occupational Off-Target Exposure

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for flucarbazone. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT® computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate. Note that flucarbazone is directly applied to residential turf and does not result in exposures of concern. It is unlikely that spray drift would result in a higher potential for risk of exposure than the scenarios already assessed.

6.0 AGGREGATE RISK ASSESSMENT

In general, aggregate exposures are calculated by summing dietary (food and water) and residential exposures (residential or other non-occupational exposures). Based on the anticipated residential exposure scenarios and since cancer risk assessments are not necessary, acute (food and water), short-term (residential, food, and water) and chronic (food and water) aggregate exposure assessments were conducted.

An assessment of short-term residential risk was performed. Intermediate-term exposure is not expected as only one or two applications per year are proposed. The short-term assessment is conservative in that the duration for residential post-application exposure is likely an over-estimate of actual time spent on treated turf (2 hours/day). Further, the endpoint for short-term dermal risk assessment is protective of intermediate-term risk as both are based on the same study and dose level (90-day feeding study in dogs, NOAEL/PoD=33.8 mg/kg/day).

Acute Aggregate Risk: Since there are no registered/proposed uses which result in acute residential exposures, the acute (females 13-49 years old only) aggregate exposure assessment consists of exposure from food and water. Therefore, the dietary exposure estimates presented in Section 4.2 represent aggregate acute exposure.

Short-Term Aggregate Risk Assessment: Short-term incidental oral exposures to toddlers are anticipated from the registered turf application scenarios and short-term exposure to residential handler applicators is anticipated for the proposed home turf application scenario.

The incidental oral, dermal and inhalation exposures were combined with chronic dietary (food and water) exposure for determination of aggregate short-term exposure. HED uses chronic dietary exposure to represent the dietary exposure component of aggregate assessments as it has been determined that this will more accurately reflect exposure from food over the HED defined short-term interval (1-30 days) than will acute exposure. The LOC for short-term dermal, inhalation and incidental oral risk assessment is 100. For short-term aggregate risk assessment, chronic dietary exposure is added to short-term inhalation exposure and short-term dermal exposure for adults and incidental oral exposure for children. This total exposure can then be compared to the respective PoDs for aggregate risk assessment. A combined MOE is calculated by summing the MOEs. Table 6.0 is a summary of the short-term aggregate exposures and risk estimates for adults and children. Since the aggregate MOEs are ≥100, short-term aggregate exposure to flucarbazone is not of concern to HED.

Table 6.0. Short-Term Aggregate Risk Calculations.

Population	Chronic Dietary Exposure (mg/kg/day)[1]	Residential Oral Exposure[2]	Oral + Dietary MOE[3]	Residential Inhalation MOE[4]	Residential Dermal MOE[4]	Aggregate MOE (food, water, and residential)[5]
All Infants (< 1 year old)	0.001514	0.0005013	17,000	N/A	13,000	7,400
Children 1-2 years old	0.003710		8,000			5,000
Children 3-5 years old	0.002736		10,000			5,700
Children 6-12 years	0.002602		11,000			6,000
Youth 13-19 years old	0.001795	N/A	19,000			7,700
Adults 20-49 years old	0.001215		28,000	3,800	2,800	1,500
Adults 50+ years old	0.001343		25,000			1,500
Females 13-49 years	0.001342		25,000			1,500

1. From Table 4.2 of this document.
2. For children only, from Table 5.2.2d.
3. Using the PoD for incidental oral exposure assessment (33.8 mg/kg/day).
4. For adults, dermal handler risk from Table 5.1 (low pressure handwand scenario) was used since handler exposure is higher than post-application dermal exposure (Table 5.2.1). For children, dermal post-application risk is from Table 5.2.1.
5. Aggregate MOE = $\dfrac{1}{\dfrac{1}{MOE_{DIETARY+ORAL}} + \dfrac{1}{MOE_{INHALATION}} + \dfrac{1}{MOE_{DERMAL}}}$

Chronic Aggregate Risk: Since there are no registered/proposed uses which result in chronic residential exposures, the chronic aggregate exposure assessment consists of exposure from food and water. Therefore, the dietary exposure estimates presented in Section 4.2 represent aggregate chronic exposure. Chronic dietary risk is not of concern to HED (exposure comprises <1.0% of the cPAD).

7.0 CUMULATIVE RISK

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 flucarbazone sodium and any other substances and flucarbazone sodium 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 flucarbazone sodium 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/.

8.0 OCCUPATIONAL EXPOSURE AND RISK

Individuals who handle flucarbazone (WDG formulation) may be exposed when they mix, load and/or make applications. Workers who perform post-application activities in areas where flucarbazone has been used may be exposed. Use sites include agricultural crops and non-agricultural/crop use sites (see Section 3.0 for the proposed use pattern). Application methods include groundboom sprayer, aerial sprayer, handgun sprayer, and high- and low-pressure handwand. The formulation, WDG, is a low-dust dry granule that is mixed with water and sprayed as a liquid. The Flucarbazone 70WDG product labels direct applicators and other handlers to wear long-sleeve shirt and long pants, chemical-resistant gloves (Category A), shoes plus socks.

One or two applications are proposed to be made per season. For this reason, HED expects that most exposures will be short-term in duration (1-30 days); intermediate-term exposure is not expected. However, since the dose levels and endpoints for short- and intermediate-term dermal and inhalation risk assessments are the same (see Table 3.2), the short-term assessment is protective of intermediate-term risk. Long-term exposure is not expected.

HED performed conservative assessments for handlers of flucarbazone and for workers exposed to flucarbazone residues from treated areas (memo, M. Clock-Rust, D367458, 7/28/09). Standard assumptions were used for area treated per day, gallons handled per day, body weight, and the level of PPE to assess handler exposures. For handlers, unit exposure values were obtained from standard HED sources (PHED, ORETF). For occupational post-application exposure, HED assumed that workers engaged in high-contact activities, resulting in health-protective/conservative risk estimates.

8.1 Handler Exposure and Risk

Exposure assessments were conducted for workers wearing a single layer of clothing consisting of long sleeved shirt, long pants, shoes and socks, and no gloves. Inhalation exposure was not corrected for a respirator.

No chemical-specific handler exposure data were submitted in support of this Section 3 registration. In accordance with HED's Exposure Science Advisory Council (ExpoSAC) policy, exposure data from PHED Version 1.1, as presented in PHED Surrogate Exposure Guide (Dated 8/98) were used.

There are no unit exposure data in PHED to assess mixing/loading the WDG formulation. Also, for the handheld application equipment (handwands, backpack, etc.), unit exposure data for the WDG were not available. Therefore, as a reasonable surrogate for WDG, unit exposure values from PHED for other formulations (dry flowables, wettable powders and liquids) were used.

<u>Handler Exposure Scenarios</u>

<u>Mixer/Loader:</u>
(1a) Open mixing/loading WDG for aerial application (sod farms);
(1b) Open mixing/loading WDG for groundboom application (golf courses, sod farms, tree farms);

Applicator:
(2a) Applying sprays using aerial applications (sod farms);
(2b) Applying sprays using groundboom applications (golf courses, sod farms and tree farms);

Mixer/Loader/Applicator:
(3a) Open mixing/loading/applying dry flowable using handgun sprayer (turf, golf courses);
(3b) Open mixing/loading/applying wettable powder using low-pressure handwand (turf, golf courses); and
(3c) Open mixing/loading/applying liquid using backpack sprayer (turf, golf courses).

Daily dermal or inhalation handler exposures are estimated for each applicable handler task with the application rate, the area treated per day (or amount handled per day), and the applicable dermal or inhalation unit exposure.

Table 8.1. Summary of Occupational Exposure and Risk for Flucarbazone Handlers.

Exposure Scenario (Scenario #)	Unit Exposure (mg/lb ai)[1]	Use Site	Application Rate (lb ai/A) or as noted[2]	Area Treated (A/day) or as noted	Daily Dose (mg/kg/day)[3]	Short-Term MOE[4]
Mixer/Loader						
(1a) Open Mixing/Loading Dry Flowables for Aerial Application (PHED); PPE: Single layer, no gloves, no respirator.	Derm: 0.066 Inhal: 0.0008	Sod Farms	0.027	1200	Derm: 0.0076 Inhal: 0.00037	Derm: 4,500 Inhal: 22,000 Comb: 3,700
(1b) Open Mixing/Loading Dry Flowables for Groundboom application (PHED); PPE: Single layer, no gloves, no respirator.		Sod Farms, Golf Courses, Tree Farms		40	Derm: 0.00025 Inhal: 0.000012	Derm: 140,000 Inhal: 660,000 Comb: 120,000
Applicator						
(2a) Applying Sprays with Sprays with Fixed-wing Aircraft (PHED); PPE: Single layer, no gloves, no respirator.	Derm: 0.005 Inhal: 0.00007	Sod Farms	0.027	1200	Derm: 0.00058 Inhal: 0.000031	Derm: 58,000 Inhal: 260,000 Comb: 48,000
(2b) Applying Sprays with Open Cab Groundboom (PHED); PPE: Single layer, no gloves, no respirator.	Derm: 0.014 Inhal: 0.00074	Sod Farms, Golf Courses, Tree Farms		40	Derm: 0.000054 Inhal: 0.000011	Derm: 630,000 Inhal: 72,000 Comb: 65,000

Exposure Scenario (Scenario #)	Unit Exposure (mg/lb ai)[1]	Use Site	Application Rate (lb ai/A) or as noted[2]	Area Treated (A/day) or as noted	Daily Dose (mg/kg/day)[3]	Short-Term MOE[4]
Mixer/Loader/Applicator						
(3a) Mixing/Loading Dry Flowables and Applying with Handgun Sprayer (ORETF); PPE: Single layer, gloves, no respirator.	Derm: 0.50 Inhal: 0.0019	Turf, Golf Courses	0.027	5	Derm:0.00024 Inhal: 0.0000036	Derm: 140,000 Inhal: 2,300,000 Comb: 130,000
(3b) Mixing/Loading Wettable Powders and Applying with Low-Pressure Handwand (ORETF); PPE: Single layer, no gloves, no respirator.	Derm: 38 Inhal: 0.0027		0.0019 lb ai/gal	40 gal/day	Derm: 0.0003 Inhal: 0.0000029	Derm: 3,300 Inhal: 2,700,000 Comb: 3,300
(3c) Mixing/Loading Liquid and Applying with Backpack Sprayer (PHED); PPE: Single layer, gloves, no respirator.	Derm: 2.5 Inhal: 0.03		0.0019 lb ai/gal	40 gal/day	Derm: 0.00068 Inhal: 0.000033	Derm: 50,000 Inhal: 250,000 Comb: 42,000

1. Values are reported in the PHED Surrogate Exposure Guide dated August 1998, except for hose-end sprayer and low-pressure handwand, which were obtained from ORETF. Derm=Dermal; Inhal=Inhalation.
2. Application rates are based on maximum values presented in proposed Flucarbazone 70WDG label (EPA Reg. No. 66330-49).
3. Daily Dose (mg/kg/day) = (Unit exposure * Application rate * Absorption rate * Area treated) / 70 kg
4. MOE = NOAEL / Daily Dose; where the short-term dermal PoD is 33.8 mg/kg/day and the short-term inhalation PoD is 8.1 mg/kg/day. The LOC is 100. Combined MOE (Comb): $MOE_{combined} = \frac{1}{\frac{1}{MOE_{INHALATION}} + \frac{1}{MOE_{DERMAL}}}$

Risk estimates for all occupational handler exposure scenarios are not of concern for handlers wearing baseline PPE, or baseline PPE with gloves (i.e., MOEs >100).

8.2 Occupational Post-Application Exposure and Risk

The proposed use involves application to golf courses, parks, sod farms, commercial and residential lawns, and tree farms. Dermal exposure is possible for workers performing activities in treated areas such as mowing/maintaining turf on sod farms and golf courses and performing tasks on tree farms.

HED assumes that inhalation exposures are minimal following outdoor applications of an active ingredient with low vapor pressure. Since flucarbazone is applied only in outdoor settings and has a low vapor pressure (<1 x 10^{-9} Pa @ 20°C), post-application inhalation exposures and risks were not assessed.

As can be seen in Table 8.2, risk estimates for occupational post-application exposure to flucarbazone are not of concern on the day of application (i.e., all MOEs are greater than 100).

Table 8.2 Occupational Post-application Exposure and Risk to Flucarbazone.

Exposure Scenario	TC[1] cm^2/hour	DFR[2] ug/cm^2 dat = 0	Daily Dose[3] mg/kg/day	Short-term MOE[4]
Sod Farm and Golf Course Mowing	3,400	0.015	0.0015	23,000
Golf Course Maintenance (hand weeding, transplanting)	500	0.015	0.00021	160,000
Hand Harvesting Christmas Trees	8,000	0.061	0.014	2,400

1. TC (cm^2/hr) = transfer coefficients and associated activities from ExpoSAC Policy Memo #003.1 "Agricultural Transfer Coefficients", 8/7/2000.
2. Surrogate DFR_0 = AR * 20% available as dislodgeable residue (5% for turf) * 4.54E8 ug/lb * 2.47E-8 A/cm^2
3. Daily dose = (DFR * TC * ET (8 hrs/day) * 0.001 mg/ug /BW (70 kg)) * %DA (25% dermal absorption).
4. MOE = NOAEL/dose; Short-term NOAEL = 33.8 mg/kg/day.

HED performed a conservative, health-protective assessment of occupational post-application exposure and risk. Risk estimates provided in Table 8.2 are based on standard assumptions recommended by HED's ExpoSAC. Some of these standard assumptions are very conservative. As can be seen above in Table 5.2, risk estimates for occupational post-application exposure to flucarbazone are not of concern (i.e., all MOEs are greater than 100).

REI

The proposed Flucarbazone 70 WDG label has a 12-hour REI stated on it. Based on the acute toxicity of the active ingredient, the REI is in compliance with the Worker Protection Standard.

9.0 DEFICIENCIES / DATA NEEDS

The tolerance expression in 40 CFR §180.562 is incorrect. It should read: "Tolerances are established for residues of flucarbazone-sodium, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only flucarbazone-sodium, 4,5-dihydro-3-methoxy-4-methyl-5-oxo-*N*-[[2-(trifluoromethoxy)phenyl]sulfonyl]-1*H*-1,2,4-triazole-1-carboxamide, sodium salt, and its metabolite *N*-desmethyl flucarbazone-sodium (4,5-dihydro-3-methoxy-5-oxo-*N*-[[2(trifluoromethoxy)phenyl]sulfonyl]-1*H*-1,2,4-triazole-1-carboxamide), calculated as the stoichiometric equivalent of flucarbazone-sodium."

Attachment 1: Toxicology Profile for Flucarbazone.

M. Clock-Rust: S10947:PY1: (703)308-2718:7509P.

Attachment 1: Toxicology Profile for Flucarbazone.

Table A.1. Acute Toxicity of Flucarbazone.

Guideline No./Study Type	MRIDs	Results	Tox Category
870.1100 Acute Oral	44848716	LD_{50} > 5000 mg/kg (M) LD_{50} > 5000 mg/kg (F)	IV
870.1200 Acute Dermal	44848717	LD_{50} > 5000 mg/kg (M & F)	IV
870.1300 Acute Inhalation	44848718	LC_{50} > 5.13 mg/L	IV
870.2400 Primary Eye Irritation	44848719	Slight irritation, cleared by 72 hours	III
870.2500 Primary Skin Irritation	44848719	No erythema after 24 hours	IV
870.2600 Dermal Sensitization	44848720	Not a sensitizer	NA

Table A.2. Subchronic and Chronic Toxicity of Flucarbazone

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 28-Day oral toxicity in rodents (rats)	44848732 (1996) Acceptable/nonguideline 0, 100, 250, 2500, or 10,000 ppm M: 0, 10.3, 27, 266, or 1134 mg/kg/day F:0, 10.8, 25, 251, or 1150 mg/kg/day	NOAEL = 27 mg/kg/day in males and 25 mg/kg/day in females. LOAEL = 266 mg/kg/day in males and 251 mg/kg/day in females based on immunological changes in both sexes.
870.3100 90-Day oral toxicity in rodents (rats)	44848727, 44848728 (1998) Acceptable/guideline 0, 250, 1000, 4000 or 20,000 ppm M: 0, 17.6, 73.5, 287, or 1,669 mg/kg/day F: 0, 21.4, 102, 358, or 2314 mg/kg/day	NOAEL = 73.5 mg/kg/day in males and 102 mg/kg/day in females LOAEL = 287 mg/kg/day in males and 358 mg/kg/day in females based on immunological findings in both sexes
870.3100 28-Day oral toxicity in rodents (mice)	44848733 (1998) Acceptable/nonguideline 0, 100, 1000, or 10,000 ppm M: 0, 45.2, 472, or 4,554 mg/kg/day F: 0, 61.2, 603, or 6,429 mg/kg/day	NOAEL = >4,554 mg/kg/day in males and 6,429 mg/kg/day in females. LOAEL >4,554 mg/kg/day in males and 6,429 mg/kg/day in females. There were no signs of toxicity attributable to treatment at any dose level.
870.3100 90-Day oral toxicity in rodents (mice)	44848725, 44848726 (1998) Acceptable/guideline 0, 260, 780, 2340, or 7,000 ppm M: 0, 77, 209, 696, or 2,083 mg/kg/day F: 0, 115, 337, 1038, or 3,051 mg/kg/day	NOAEL = > 2,083 mg/kg/day in males and 3,051 mg/kg/day in females. LOAEL > 2,083 mg/kg/day in males and 3,051 mg/kg/day in females. There were no signs of toxicity attributable to treatment at any dose level.
870.3150 28-Day oral toxicity in nonrodents (dogs)	44848735, 44848736 (1996) Acceptable/nonguideline 0, 1000, 5000, or 50,000 ppm M: 0, 33.1, 164, or 1,614 mg/kg/day F: 0, 36.1, 171, or 1,319 mg/kg/day	NOAEL = 164 mg/kg/day in males and 171 mg/kg/day in females. LOAEL = 1,614 mg/kg/day in males and 1,319 mg/kg/day in females based on decreased body weight gain, decreased food consumption, decreased T4 levels and increased thyroxine-

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
		binding capacity, induction of microsomal enzymes, increased liver weight and liver histopathology in both sexes.
870.3150 90-Day oral toxicity in nonrodents (dogs)	44848737, 44848733 (1998) Acceptable/guideline 0, 1000, 5000, or 50,000 ppm M: 0, 33.8, 162, or 1,674 mg/kg/day F: 0, 35.2, 170, or 1,750 mg/kg/day	NOAEL = 33.8 mg/kg/day in males and 35.2 mg/kg/day in females with the occurrence of slight, adaptive induction of hepatic microsomal enzymes. LOAEL = 162 mg/kg/day in males and 170 mg/kg/day in females based on decreased T4 levels, increased thyroxine-binding capacity, induction of microsomal enzymes, gross pathology and histopathology in the stomach, and histopathology in the liver in both sexes.
870.3200 21/28-Day dermal toxicity in rabbits	44848734 (1996) Acceptable/guideline M & F: 0, or 1,000 mg/kg/day	NOAEL ≥1,000 mg/kg/day for both sexes. LOAEL >1,000 mg/kg/day There were no signs of toxicity attributable to treatment at any dose level.
870.3250 90-Day dermal toxicity in rats	NA	NA
870.3465 90-Day inhalation toxicity in rats	46168501 (2003) Acceptable/non-guideline 0, 5.0, 30.0, 180, or 500 mg/m^3 (0, 0.005, 0.03, 0.18, or 0.5 mg/L) for 28 days	LOAEL = 0.18 mg/L based on eosinophilic globules (nasal cavity) and squamous cell metaplasia (larynx) in males and females NOAEL = 0.03 mg/L
870.3700a Prenatal developmental toxicity in rats 870.3700b Prenatal developmental toxicity in rabbits	44848748, 44848749, 44848750, 44848751, 44848752 (1998) Acceptable/guideline F: 0, 100, 300, or 1,000 mg/kg/day 44848753, 44848801, 44848802 (1997) Acceptable/guideline F: 0, 100, 300, 500, or 1,000 mg/kg/day	**Maternal** NOAEL = > 1,000 mg/kg/day LOAEL > 1,000 mg/kg/day **Developmental** NOAEL = > 1,000 mg/kg/day LOAEL > 1,000 mg/kg/day **Maternal** NOAEL = 100 mg/kg/day LOAEL = 300 mg /kg/day based on decreased food consumption and increased clinical signs **Developmental** NOAEL = 300 mg/kg/day LOAEL = 500 mg/kg/day based on decreased fetal weight and increased incidence of delayed fetal ossification
870.3800 Reproduction and fertility effects in rats	44848745, 44848746, 44848747 (1998) Acceptable/guideline 0, 50, 4000, 20,000/12,000 ppm (dose reduced in week 6) F_0 M: 3.5, 287 or 800 mg/kg/day, F_0 F: 4.2, 340, or 991 mg/kg/day F_1 M: 4.2, 346 or 1,059 mg/kg/day F_1 F: 5.5, 453, or 1,249 mg/kg/day	**Parental/Systemic** NOAEL = 287 mg/kg/day for males and 340 mg/kg/day for females with a slight, increased incidence of moderate cecal enlargement occurring as an adaptive response to treatment. LOAEL = 800 mg/kg/day for males based decreased liver weight and 991 mg/kg/day for females based on decreased uterine weight and

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
		increased incidence of severe cecal enlargement. **Reproductive/Offspring** NOAEL = 287 mg/kg/day for males and 340 mg/kg/day for females LOAEL = 800 mg/kg/day for males and 991 mg/kg/day for females based on reduced pup weights, decreased liver weight in male pups, marbled liver, air filled stomach
870.4100b Chronic toxicity in dogs	44848729, 44848730, 44848731 (1998) Acceptable/guideline 0, 200, 1000, or 5,000 ppm M: 0, 6.7, 35.9, or 183 mg/kg/day F: 0, 7.43, 37.1, or 187 mg/kg/day	NOAEL = 35.9 mg/kg/day in males and 37.1 mg/kg/day in females. LOAEL = 183 mg/kg/day in males and 187 mg/kg/day in females based upon body weight gain depression and increased N-demethylase levels in both sexes, decreased T4 levels and marginally increased liver weight in females.
870.4300 2-Year Chronic toxicity/carcinogenicity in rats	44848739, 44848743, 44848744 (1998) Acceptable/guideline M/F: 0, 2.5, 7.5, 125, or 1,000 mg/kg/day	NOAEL = 125 mg/kg/day in males and females LOAEL = 1,000 mg/kg/day in males and females based on decreased body weight and increased food consumption in females, thickened mucosa of the glandular stomach in both sexes, inflammatory infiltrates (males), vacuolation of the squamous epithelium in the fore-stomach (females) and immunological effects in males. **No evidence of carcinogenicity.**
870.4200b 2-Year Carcinogenicity in mice	44848740, 44848741, 44848742 (1998) Acceptable/guideline 0, 50, 1000, or 7,000 ppm M: 0, 12.2, 275, or 2,066 mg/kg/day F: 0, 22.6, 459, or 3,212 mg/kg/day	NOAEL = 275 mg/kg/day in males and 459 mg/kg/day in females LOAEL = 2,066 mg/kg/day in males and 3,212 mg/kg/day in females based on decreased body weight in both sexes and increased food consumption in males. **No evidence of carcinogenicity.**
Gene Mutation 870.5100 reverse gene mutation assay in bacteria	44848803 (1993) Acceptable/guideline	There was *no evidence* of induced mutant colonies over background.
Gene Mutation 870.5100 reverse gene mutation assay in bacteria	44848705 (1999) Acceptable/guideline MKH 10868, an animal, plant, and soil metabolite	There was *no evidence* of induced mutant colonies over background.
870.5300 gene mutation assay in V79 cultured mammalian cells	44848804 (1996) Acceptable/guideline	No increase in mutant frequency above that of negative controls up to the limit dose.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Cytogenetics 870.5375 *in vitro* mammalian cytogenetics assay	44848805 (1996) Acceptable/guideline	No increases in aberrant metaphases were observed up to the limit dose.
870.5395, bone marrow micronucleus assay	44848806 (1996) Acceptable/guideline	There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow at 2000 mg/kg.
Other Genotoxicity 870.5550, Unscheduled DNA synthesis in primary rat hepatocytes	44848807 (1996) Acceptable/guideline	There was no evidence of unscheduled DNA synthesis up to cytotoxic levels.
870.6200a Acute neurotoxicity screening battery in rats	44848809 (1998) Acceptable/guideline M & F: 0, 125, 500 or 2000 mg/kg/day	NOAEL = 500 mg/kg/day for males and females LOAEL = 2000 mg/kg/day based on increased incidence of perianal staining in males, decreased motor activity and locomotor activity in both sexes and increase in the incidence of animals exhibiting low levels of activity in open field in both sexes.
870.6200b Subchronic neurotoxicity screening battery in rats	44848808 (1998) Acceptable/guideline 0, 250, 2000, or 20,000 ppm M: 0, 18.5, 147, or 1,482 mg/kg/day F: 0, 21.9, 174, or 1,736 mg/kg/day	NOAEL = 147 mg/kg/day in males and 1,736 mg/kg/day in females LOAEL = 1,482 mg/kg/day based on decreased body weight, decreased body weight gain, and decreased food consumption in males. LOAEL > 1,736 mg/kg/day in females.
870.6300 Developmental neurotoxicity in rats	NA	NA
870.7800 Antibody Plaque-forming cell assay in male rats	44848703 (1999) 0, 15, 150, or 1,000 mg/kg/day	NOAEL = >1,000 mg/kg/day LOAEL >1,000 mg/kg/day
870.7800 Antibody Plaque-forming cell assay in female rats	44848707 (1999) 0, 15, 150, or 1,000 mg/kg/day	NOAEL = >1,000 mg/kg/day LOAEL >1,000 mg/kg/day
870.7800 Splenic T-cells, B-cells, and NK-cell assay in male rats	44848704 (1999) 0, 15, 150, or 1,000 mg/kg/day	NOAEL = >1,000 mg/kg/day LOAEL >1,000 mg/kg/day
870.7800 Splenic T-cells, B-	44848709 (1999) 0, 15, 150, or 1,000 mg/kg/day	NOAEL = >1,000 mg/kg/day LOAEL >1,000 mg/kg/day

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
cells, and NK-cell assay in female rats		
870.7800 Plaque-Forming cell assay in rats	44848810, 44848811, 44848812 (1998) 0, 1000, 5000, or 20,000 ppm M: 0, 107, 510, or 2,205 mg/kg/day F: 0, 115, 612, or 2,556 mg/kg/day	NOAEL = 2,205 mg/kg/day in males and 2,556 mg/kg/day in females LOAEL >2,205 mg/kg/day in males and 2,556 mg/kg/day in females
870.7485 Metabolism in rats	44848830 (1998) Acceptable/guideline M & F: 17.5 mg/kg of phenyl-C^{14}; M: 398.5 mg/kg of phenyl-C^{14}; M: Repeat 14 days of unlabeled followed by 17.6 mg/kg of phenyl-C^{14}. Also, bile fistula, plasma concentration and expired air studies were conducted.	There were no sex-related differences in the absorption, distribution, metabolism or excretion. Based on urinary excretion, absorption was 15-30% and maximum plasma concentrations were achieved within 30 minutes. At sacrifice, tissues and carcass contained less than 1% of radioactivity. The highest residue in the tissues was in the liver. Greater than 90% of the administered dose was eliminated within 24 hours. The major component in urine and feces was unchanged parent which represented 90-95% of the administered dose.
870.7485 Metabolism in rats	44848831 (1998) Acceptable/nonguideline together with 44848830 M: 17.7 mg/kg of triazolinone-3-C^{14}	Major component in urine and feces was unchanged parent which represented 94% of the administered dose. Less than 1% of the administered dose was recovered in the carcass, tissues, expired air, or cage wash. Highest residue was in the liver.
870.7485 Metabolism in rats	44848833 (1998) Acceptable/guideline M: 5.13 mg/kg of phenyl-UL-C^{14} MKH 6562 sulfonamide lactate (plant metabolite of MKH 6562)	Metabolized via two pathways. One pathway involved the oxidative decarboxylation of sulfonamide lactate to form sulfonamide acetate. The other pathway involved the hydrolysis of sulfonamide lactate and sulfonamide acetate to give sulfonamide.
870.7485 Mteabolism in rats	44848832 (1998) Acceptable/guideline M: 5 mg/kg of phenyl-C^{14} MKH 6562 sulfonamide alanine (a plant metabolite of MKH 6562)	Approximately 70% absorption and elimination with 98% recovery in urine and feces. Several metabolites in addition to parent (17%). Less than 1% of the administered dose was recovered in the carcass, tissues, expired air, or cage wash. Highest residue was in the liver.
870.7600 Dermal penetration	NA	NA

NA - Not applicable.

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Chemical Name: Flucarbazone-sodium

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