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MEMORANDUM

SUBJECT: Trifluralin: Human Health Risk Assessment

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The following human health risk assessment for trifluralin has been prepared by the Health Effects Division for Phase One of the Tolerance Reassessment Eligibility Decision (TRED) process for trifluralin. Occupational risk assessment for trifluralin is not addressed in this document. Aggregate (food / drinking water / residential) risk assessment is based on the following memoranda:

Trifluralin: Report of the Hazard Identification Assessment Review Committee (R. Fricke memo, 5/2/03)

Trifluralin: Toxicology Disciplinary Chapter for the Tolerance Reassessment Eligibility Decision Document (R. Fricke memo, 10/2/03)

Trifluralin. Product Chemistry Chapter for the TRED Document (K. Dockter memo, 12/23/03)

Trifluralin: Residue Chemistry Chapter (R. Griffin memo, 3/4/04)

Trifluralin. Metabolism Assessment Review Committee Briefing Memorandum

(S. Piper memo, 1/6/04)

Trifluralin: Health Effects Division (HED) Metabolism Assessment Review Committee (MARC) Decision Document. (S. Piper memo, 3/9/04)

Trifluralin: Anticipated Residues, Acute, Chronic, and Cancer Dietary Exposure Assessments for the Reregistration Eligibility Decision (S. Piper memo, 4/12/04)

Trifluralin: Drinking Water Assessment for Tolerance Reassessment Eligibility Decision (S. Ramasamy memo, 12/11/03)

Residential Exposure Assessment and Recommendations for the Tolerance Reassessment Evaluation Decision (TRED) Document for Trifluralin (S. Recore memo, 5/6/04)

Review of Trifluralin Incident Reports (J. Blondell memo, 5/5/04)

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TABLES

1.0 SUMMARY

Trifluralin (2,6-dinitro-N,N-dipropyl-4-(trifluoromethyl)benzenamine) is a selective, pre-emergence, dinitroaniline herbicide registered for the control of annual grasses and certain broadleaf weeds. Trifluralin is primarily used in soybeans and cotton, but is also registered for use on a variety of food and feed crops including: alfalfa, asparagus, barley, Brassica vegetables, bulb vegetables, celery, citrus fruits, corn (field), cotton, cucurbit vegetables, endive, flax, fruiting vegetables, grapes, hops, legume vegetables, peanuts, peppermint, root and tuber vegetables, rapeseed (canola), safflower, sorghum, spearmint, stone fruits, sugarcane, sunflower, tree nuts, and wheat. Tolerances range from 0.05 ppm to 2.0 ppm and adequate enforcement methods are available for the determination of residues in/on plant commodities. Tolerances for residues of trifluralin in animal commodities have not been established. Non-agricultural uses include turf, ornamentals, and vegetable gardens.

The toxicity database is sufficient for tolerance reassessment. Technical trifluralin exhibits low acute toxicity in rats via the oral, dermal, and inhalation routes of exposure. In rabbit studies trifluralin is a slight eye irritant, but not a skin irritant; however it was found to be a dermal sensitizer in guinea pigs.

Subchronic oral studies in the rat and dog show that the liver and kidneys appear to be the principal target organs. Some blood effects such as lower hemoglobin levels and changes in clinical chemistry are reported. In a special urinalysis study in the male rat, tubular cytoplasmic hyaline droplets, increased total protein, aspartate amino-transferase (AST), and lactate dehydrogenase (LDH) were observed in the urine. Following electrophoresis, albumin, α1-globulin, and α2-globulin were identified in the urine. Histopathological findings included increased incidences of lesions of the renal proximal tubules, decreased corticomedullary mineralization, and hyaline droplets in the tubular epithelium in the rat. In the dog, multifocal cortical tubular cytoplasmic pigment deposition was observed.

Chronic toxicity to trifluralin was evaluated in the rat, mouse, and dog. Systemic toxicity in rats included decreases in body weight and body weight gains. Two 12-month oral toxicity studies were performed in the dog. In one study, increased frequency of abnormal stool, decreased body weights, decreased body weight gains, decreased erythrocytes and hemoglobin, and increased thrombocytes in males were observed, while increased absolute liver weights were observed in the other. Trifluralin does not appear to be an immunotoxicant. There were no signs of neurotoxicity in the trifluralin data base.

In a rat metabolism study many non-conjugated (20-30) and conjugated (10-20) urinary metabolites were observed with the majority present at 1-2% of the total urinary radioactivity. Four metabolic pathways were identified; (1) oxidative N-dealkylation of one or both propyl groups and metabolites which were hydroxylated on the propyl side chain; (2) reduction of one or both nitro groups to the corresponding amine; (3) cyclization reactions to give a variety of substituted and unsubstituted benzimidazole metabolites; and (4) conjugation reactions, including acetylation of the reduced nitro groups, sulfate, and glucuronic acid conjugates.

In developmental toxicity studies, maternal toxicity consisted of decreased body weight gain and food consumption, increased liver and spleen weights, increased incidence of resorptions and litters with total resorptions in the rat; and an increased number of abortions, macroscopic changes in the liver and lungs, and decreased food consumption in the rabbit. Reduced ossification of vertebrae and ribs were observed in both the rat and rabbit.

In reproduction studies kidney toxicity (acute renal failure, lesions of renal proximal tubule, increased relative liver) and uterine atrophy in females were observed. Offspring toxicity consisted of decreased pup weight and increased number of runts. Decreased fetal, neonatal, and litter viability, and decreased lactation index were also observed.

The toxicity database is adequate for FQPA consideration. The concern for qualitative susceptibility is low even though some effects seen in the rat developmental study indicate some susceptibility. The HIARC determined that since the dose response was well characterized, the developmental effects were only seen in the presence of materanal toxicity, and clear NOAELs were established for developmental and maternal toxicities, the concern for susceptibilty was low.

There are no residual uncertainties for pre-and post-natal toxicities since the doses selected for overall risk assessments will address the concerns seen in these studies. Based on the above data, no Special FQPA Safety Factor is needed (1x) since there are no residual uncertainties for pre- and/or post-natal toxicity.

The HIARC reviewed the trifluralin toxicity data and selected the appropriate studies, endpoints, and dose levels for human health risk assessment. An acute Population Adjusted Dose (aPAD) of 1.0 mg/kg/day was established for females of child-bearing age based on the No Observable Adverse Effect (NOAEL) of 100 mg/kg/day observed in the rat developmental study. A chronic Population Adjusted Dose (cPAD) of 0.024 mg/kg/day was established based on the NOAEL (2.4 mg/kg/day) of a chronic toxicity study in dogs. The endpoint(s) of concern is increased frequency of abnormal stool, decreased body weights, decreased body weight gains, decreased erythrocytes and hemoglobin, and *increased* thrombocytes in males at the

study LOAEL. The uncertainty factor is 100, based on 10x for inter-species extrapolation, 10x intra-species variability, and 1x for FQPA considerations.

Risk assessment by the Margin of Exposure (MOE) approach for short-term "incidental" oral exposure to children is based on the NOAEL (10 mg/kg/day) of the two-generation reproduction study in the rat. Risk assessment by the MOE approach for short-term inhalation exposure to residential applicators is based on the NOAEL (81 mg/kg/day) of the 30-day inhalation study in rats. Risk assessment by the MOE approach for short-term dermal exposure is not quantified based on no systemic toxicity observed at the limit dose in the dermal toxicity study. Intermediate- and long-term residential exposure is not expected for trifluralin and not assessed. The Agency considers a Margin of Exposure (MOE) of 100 to be adequately protective for each assessment.

On January 29 and February 27, 1986, the Carcinogenicity Peer Review Committee classified trifluralin as a Group C Carcinogen ("possible" human carcinogen), and recommended that, for the purpose of risk characterization, a low dose extrapolation model be applied to the experimental animal tumor data for quantification of human risk. The upper-bound potency factor (Q_1*) for trifluralin is 5.8 x 10^{-3} $(mg/kg/day)^{-1}$ based on male rat thyroid follicular cell combined adenoma, papillary adenoma, cystadenoma, and carcinoma tumors (converted from animals to humans by use of the 3/4's scaling factor). Extensive testing showed trifluralin is neither mutagenic nor genotoxic, and does not inhibit the polymerization of microtubules in mammalian cells.

The HED Metabolism Assessment Review Committee (MARC) reviewed trifluralin toxicology and metabolism data (2/4/04) and concluded that tolerances for enforcement (and dietary risk assessment for plant commodities) should be based on trifluralin *per se.* Also, dietary risk assessment for ruminant commodities should be based on trifluralin *per se* and all metabolites/degradates identified as total radioactive residue, or TRR, in a ruminant metabolism study. Risk assessment for drinking water contamination is based on estimates for trifluralin *per se* and 3 metabolites identified in metabolism and photolysis studies. All metabolites/degradates are considered toxicologically similar to parent.

Trifluralin is not acutely toxic and there is no expectation that single,or single-day high-end exposure, including aggregate exposure, will have an adverse effect. However, based on the toxicity observed in sub-chronic and chronic studies, trifluralin has been assessed for the following; 1) acute exposure from food and water (aPAD); 2) chronic exposure from food and water (cPAD); 3) chronic exposure from food and water (Q_1*); 4) short-term inhalation exposure to homeowner applicators (MOE); 5) combined inhalation and dermal exposure to homeowner applicators (Q_1*); 6) short-term oral exposure to children post-application on turf (MOE); and 7) dermal exposure to persons

(golfers, etc.) post-application on turf (Q_1*).

A *refined* chronic dietary risk assessment was conducted by comparing trifluralin dietary exposure, due to food uses and contaminated drinking water, to the trifluralin cPAD and secondly, by quantifying carcinogenic risk by the Q_1* approach. The dietary assessment relies on field trial, monitoring (PDP), and usage data (percent crop treated). Contamination estimates for drinking water are refined by PRZM-EXAMS modeling, incorporating percent cropped area (PCA) data. Food consumption data are from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII),1994-1996/1998, combined to form the Food Commodity Intake Database (FCID). For the cPAD dietary risk estimates, the assessment uses averaged consumption data for the general U.S. population and various population subgroups and for carcinogenic risk uses an overall average. Estimated chronic dietary risk estimates for all population subgroups are less than 1% of the trifluralin cPAD (0.005 mg/kg/day) and do not indicate a concern for this route of exposure. Carcinogenic risk for the general U.S. population, based on food and drinking water, is 10^{-7} and less than the level (10^{-6}) considered negligible by the Agency.

Trifluralin products are marketed for homeowner use on lawns, landscape ornamentals, and vegetable gardens. Trifluralin-containing products are also marketed for use by professional applicators on residential turf, on golf courses, other turf such as recreational/commercial areas, and on ornamental plantings. Based on these uses, trifluralin is assessed for the residential applicator (or "handler") and for post-application exposure that may occur from turf contact. For residential applicators, all estimated inhalation MOEs are above the target MOE of 100 and the carcinogenic risk estimate for typical turf applications is 10^{-8}.

Since a toxicological endpoint, based on dermal exposure, was not selected for trifluralin, only post-application incidental *oral* ingestion (i.e., soil, granule, and hand-to-mouth ingestion) exposures to children were calculated. Estimated MOEs for soil, granule, and hand-to-mouth exposures are above the target MOE of 100. However, carcinogenic risk has been estimated, based on dermal exposure during golfing or other activity, over a lifetime of exposure. These estimates are less than 10^{-8} and are again, considered upper-bound estimates.

The Agency remains concerned about *dermal sensitization* reactions to adults and children who are exposed to trifluralin in residential settings and recommends for labeling to this effect, on all products.

Acute dietary exposure based on both food and drinking water sources has been aggregated and the aPAD risk estimate is less than 1% for women of child-bearing age. Chronic dietary exposure based on both food and drinking water sources has been aggregated and the cPAD risk estimates are less than 1% for the general U.S.

population, and population sub-groups . Oral exposure estimates for 3 specific post-application activities of children on treated turf have been aggregated to form an upper-bound MOE risk estimate that is well above the target level of 100.

For trifluralin, chronic exposure from foods (0.000022 mg/kg/day) has been added to chronic exposure due to drinking water (0.000008 mg/kg/day) and this in turn is added to estimates of residential exposure to estimate carcinogenic risk. Since carcinogenic risk assessment attempts to reflect long-term exposure, the most appropriate exposure estimate would be based on the most common application method; the push-type spreader. The Lifetime Average Daily Dose estimated for this application method is negligible (0.0000006 mg/kg/day), and when added to the chronic dietary exposure the aggregate carcinogenic risk estimate is $2x10^{-7}$.

Although recognized as a member of the dinitroaniline group of pesticides, cumulative risk assessment has not been completed for trifluralin. HED has not initiated a comprehensive review to determine if other chemical substances have a mechanism of toxicity common to trifluralin.

Based on California incident data and the Agency's Incident Data System, it appears that the majority of reported trifluralin cases involved skin and eye illnesses. Poison Control Center data would tend to support these results, in that dermal and ocular effects were some of the most common effects reported. Appropriate protective clothing to protect the skin and eyes of applicators is recommended.

2.0 PHYSICAL / CHEMICAL PROPERTIES

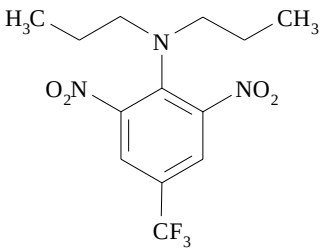
Table 1 Trifluralin Nomenclature	
Chemical structure	
Common name	Trifluralin
Molecular Formula	$C_{13}H_{16}F_3N_3O_4$
Molecular Weight	335.3
IUPAC name	α,α,α-trifluroro-2,6-dinitro-N,N-dipropyl-p-toluidine
CAS name	2,6-dinitro-N,N-dipropyl-4-(trifluoromethyl)benzenamine
CAS #	1582-09-8
PC Code	036101

Table 2 Physicochemical Properties of Trifluralin		
Parameter	Value	Reference
Melting point/range	42-49°C	Trifluralin Update 10/29/91
pH	5.9 ± 0.1 saturated aqueous solution	
Density or specific gravity (22 °C)	1.36 g/mL	D207577, 4/9/97, K. Dockter
Water solubility (25°C)	<1 ppm	D207577, 4/9/97, K. Dockter
Solvent solubility (25°C)	readily soluble in organic solvents such as acetone, acetonitrile, chloroform, dichloromethane, ethyl acetate, and toluene at >100 g/100 mL, and in hexane at 5-6.7 g/100 mL or methanol at 3.3-4 g/100 mL	D207577, 4/9/97, K. Dockter
Vapor pressure (25°C)	6.1×10^{-3} Pa	D207577, 4/9/97, K. Dockter
Dissociation constant (pK_a)	not required; does not dissociate	D207577, 4/9/97, K. Dockter
Octanol/water partition coefficient (log K_{ow}; 20°C)	4.83	D207577, 4/9/97, K. Dockter

Table 2 Physicochemical Properties of Trifluralin		
Parameter	Value	Reference
UV/vis absorption spectrum	not available	

3.0 TOXICOLOGY

3.1 Toxicity Profile

3.1.1 Acute Toxicity

Acute toxicity studies are available for technical trifluralin as well as manufactured products. Technical trifluralin shows low acute toxicity *via* the oral, dermal and inhalation routes of exposure (toxicity categories IV, III, and IV, respectively). Technical trifluralin showed some irritation in the eye (toxicity category III), but not in the skin (toxicity category IV). In the dermal sensitization assay trifluralin was found to be a dermal sensitizer. Although not required, an acute delayed neurotoxicity study was also performed with negative results. Acute toxicity studies are summarized in Table 3.

Table 3 Acute Toxicity

Guideline No.	Study Type	MRID No.	Results	Toxicity Category
870.1100	Acute Oral (Rat)	00157486 (1985) Acceptable/Guideline	LD50 > 5000 mg/kg	IV
870.1200	Acute Dermal (Rat)	00157482 (1985) Acceptable/Guideline	LD50 > 2000 mg/kg	III
870.1300	Acute Inhalation (Rat)	00155261 (1982) Acceptable/guideline	LC50 > 4660 mg/m^3, 4.66 mg/L	IV
870.2400	Primary Eye Irritation (Rabbit)	00157483 (1985) Acceptable/Guideline	Conjunctival redness at 24hr, cleared by 4 days	III
870.2500	Primary Skin Irritation	00157485 (1985) Acceptable/Guideline	Not an irritant	IV

870.2600	Dermal Sensitization	00157484 (1985) Acceptable/Guideline	Sensitizing agent	N/A

3.1.2 Subchronic Toxicity

The subchronic toxicity data base is complete. Trifluralin was evaluated in rat and mouse oral studies, in rat and rabbit dermal studies, in a rat inhalation study, and in a 6-month oral study in the dog. In the rat subchronic oral toxicity study, minor decreases in overall body weight gains and food consumption in males and females, decreased hemoglobin, alkaline phosphatase, and alanine aminotransferase in the males, and increased absolute and relative (to body) liver weights in males and females were observed at the LOAEL of 391 mg/kg/day. In the mouse subchronic oral toxicity study, no toxicity was observed at the highest dose tested of 375 mg/kg/day. In the dog 6-month oral study, increased absolute and relative (to body) liver weights, liver enlargement, discolored kidneys, decreased red cell indices, increased platelets in males; and increased alkaline phosphatase were observed at the LOAEL of 10 mg/kg/day.

A 21-day dermal toxicity study in the rat showed no systemic toxicity at the limit dose of 1,000 mg/kg/day (only dose tested). A 31-day dermal toxicity study in the rat showed no systemic toxicity at 1,000 mg/kg/day; dermal effects included sub-epidermal inflamation and ulcerations at 200 mg/kg/day. A rabbit 21-day dermal toxicity study with a formulation (35.8% trifluralin) also did not show any systemic toxicity at 1,000 mg/kg/day; dermal effects observed at the LOAEL (100 mg/kg/day) included erythema, edema, and/or scaling and fissuring. The systemic NOAELs (1,000 mg/kg/day) observed in the dermal toxicity studies are consistent with the dermal absorption factor of 3%. A 30-day inhalation exposure to rats at 1,000 mg/m^3 resulted in increased methemoglobin and bilirubin, as well as dyspnea and ruffled fur.

3.1.3 Chronic Toxicity

Chronic toxicity to trifluralin was evaluated in the rat, mouse, and dog. Systemic toxicity in rats exposed to 169/219 mg/kg/day (males/females) included decreases in body weight (NOAEL 40/53 mg/kg/day). In a 2-year mouse study no systemic toxicity was observed at the highest dose tested of 118 mg/kg/day. Two 12-month oral toxicity studies were performed in the dog. In one study increased frequency of abnormal stool, decreased body weights and body weight gains, decreased erythrocytes and hemoglobin, and increased thrombocytes in males were observed at the LOAEL of 40 mg/kg/day. In the other study increased absolute liver weights in males were observed at the LOAEL of 3.8 mg/kg/day.

3.1.4 Developmental / Reproductive Toxicity

Developmental toxicity of trifluralin in the rat and rabbit, as well as three 2-generation reproduction studies were evaluated. In all of these studies the NOAEL/LOAELs for parental toxicity were the same as, or lower, than the NOAEL/LOAELs for reproductive and developmental toxicity. In the developmental toxicity studies, maternal toxicity consisted of decreased body weight gain and food consumption, increased liver and spleen weights, increased incidence of resorptions and litters (with total resorptions observed in the rat); and increased abortions, macroscopic changes in the liver and lungs, and decreased food consumption in the rabbit. Reduced ossification of vertebrae and ribs were observed in both the rat and rabbit. In the reproduction studies kidney toxicity (acute renal failure, lesions of renal proximal tubule, increased relative liver weight) and uterine atrophy in females were observed. Offspring toxicity consisted of decreased pup weight including an increase in the number of runts. Decreased fetal, neonatal, and litter viability, and decreased lactation index were also observed.

3.1.5 Mutagenicity / Genotoxicity

Extensive testing showed that trifluralin is neither mutagenic nor genotoxic. There was no evidence of mutagenicity in rat dominant lethal, L5178Y mouse lymphoma, *Salmonella typhimurium*, *Saccharomyces cerevisiae*, and DNA repair assays, nor did it induce sister chromatid exchange in Chinese hamster ovary cells. These tests showed that trifluralin does not inhibit the polymerization of microtubules in mammalian cells.

3.1.6 Carcinogenicity

Two carcinogenicity studies by the National Cancer Institute (NCI) revealed hepatocellular carcinomas in both the rat and in the mouse. Subsequent analysis of the trifluralin used in these studies showed high concentrations of nitrosamine [N-dinitroso-di-n-propylamine NDPA] and the carcinomas were attributed to this contaminant. Subsequent carcinogenicity studies were conducted with purified trifluralin. On January 29 and February 27, 1986, the Carcinogenicity Peer Review Committee classified trifluralin as a Group C Carcinogen (“possible” human carcinogen), and recommended that, for the purpose of risk characterization, a low-dose extrapolation model be applied to the experimental animal tumor data for quantification of human risk. The upper-bound potency factor (Q_1*) for trifluralin is 5.8 x 10^{-3} $(mg/kg/day)^{-1}$ based on male rat thyroid follicular cell combined adenoma, papillary adenoma, cystadenoma, and carcinoma tumors (converted from animals to humans by use of the 3/4's scaling factor).

3.1.7 Immunotoxicity

Effects suggestive of immunotoxicity include thymic hypoplasia and decreased relative thymus weights in the rabbit developmental toxicity study and rat reproduction study, respectively, and increased spleen weights in a rat developmental toxicity study. No other indications of possible immunotoxicity were observed in the trifluralin data base.

3.1.8 Metabolism

In a rat metabolism study, ^{14}C-trifluralin was administered by gavage at 300 mg/kg/day to 5 rats/sex on three consecutive days. The objective of this study was to identify the urinary metabolites of trifluralin. There was no sex-dependent effect on metabolic profiles. A minimum of 20-30 non-conjugated metabolites and an additional 10-20 conjugated metabolites were present in the urine, but no parent compound was detected. No single metabolite accounted for more than 8-10% of the total urinary radioactivity, and the majority of the metabolites were present at 1-2% of the total urinary radioactivity. Thus, almost all of the metabolites were minor (<5% of the total radioactive dose). Four metabolic pathways were identified as follows; (1) oxidative N-dealkylation of one or both propyl groups and metabolites which were hydroxylated on the propyl side chain; (2) reduction of one or both nitro groups to the corresponding amine; (3) cyclization reactions to give a variety of substituted and unsubstituted benzimidazole metabolites; and (4) conjugation reactions, including acetylation of the reduced nitro groups, sulfate, and glucuronic acid conjugates.

3.1.9 Kidney Toxicity

The kidney appears to be a target organ for trifluralin. These findings are summarized in a peer review of trifluralin (April 11, 1986) and include the following observations; kidney and bladder tumors, decreased kidney weights, increased BUN, increases in total protein, aspartate aminotransferase and lactate dehydrogenase in the urine. Also, protein electrophoresis of urine samples showed α1-globulin and α2-globulin, tubular hyaline casts in the kidneys, minimal cortical tubular epithelial regeneration observed microscopically, and increased incidence of progressive glomerulonephritis.

A special rat urinalysis study included the presence of tubular cytoplasmic hyaline droplets, increased total protein, AST and LDH in the urine, albumin α1-globulin and α2-globulin observed by urine electrophoresis, and increased urinary volume. A two-generation reproduction study showed increased incidences of lesions of the renal proximal tubules, decreased corticomedullary mineralization, hyaline droplets in the tubular epithelium, and acute renal failure. A developmental toxicity

study in the rat demonstrated clear fluid in the renal pelvis, grey hollows on the kidney surface, and enlarged kidney with yellow calculi in the pelvis. In a chronic dog study, minimal to slight multifocal cortical tubular cytoplasmic pigment deposition was noted in the kidneys in males and females. A two-week range-finding study in the rat showed urinary triple phosphates.

3.2 FQPA Considerations

3.2.1 Database Summary Relative to FQPA

No significant toxicological data deficiency has been identified for trifluralin and the HED HIARC committee concluded that the toxicity data base is adequate for FQPA considerations. Acceptable rabbit and rat developmental toxicity studies were available in addition to two, acceptable, 2-generation reproduction studies in the rat. Also, the HIARC was able to conclude that additional developmental neurotoxicity data will not be required since there were no signs of neurotoxicity in the trifluralin data base.

3.2.2 Evidence of Quantitative / Qualitative Susceptibility

Evidence of increased susceptibility: The HIARC concluded that there is a concern for pre- and/or post-natal toxicity resulting from exposure to trifluralin. There was *qualitative* evidence of increased susceptibility in the rat developmental toxicity study where fetal developmental effects (increased resorptions and wavy ribs) occurred in the presence of less severe maternal effects (decreases in body weight gain, clinical signs, and changes in organ weights). Also qualitatively, there is an indication of increased sensitivity in the 2-generation reproduction study in the rat in that offspring effects (decreased fetal, neonatal and litter viability) were observed at a dose level where there was less severe maternal toxicity (decreased body weight, body weight gain and food consumption).

Degree of Concern Analysis and Residual Uncertainties: The HIARC concluded that concern is low for the qualitative susceptibility seen in the developmental rat study because the dose response was well characterized, the developmental effects were seen in the presence of maternal toxicity, and clear NOAELs/LOAELs were established for maternal and developmental toxicities. There is low concern for the qualitative susceptibility observed in the rat reproduction study since the dose-response was well characterized; there was a clear NOAEL/LOAEL for maternal and developmental toxicities; and the effects were seen at a high-dose level (295/337 mg/kg/day). Offspring viability was not adversely affected in two other 2-generation studies with trifluralin at dose levels up to 100 and 148 mg/kg/day. There are no residual uncertainties for pre- and postnatal toxicities since the doses selected for overall risk assessments will address the concerns seen in these studies. Also, the HIARC concluded that there is not a concern for developmental neurotoxicity resulting from

exposure to trifluralin since there were no signs of neurotoxicity in the trifluralin data base.

3.2.3. Special FQPA Safety Factor(s)

The HIARC concluded that the FQPA Safety Factor should be removed (equivalent to a 1x Safety Factor) based on a conclusion of no concern for qualitative susceptibility seen. The FQPA Safety Factor recommendation by the HIARC assumed that the exposure databases (food, drinking water, and residential) are complete and the risk assessment for each exposure scenario includes all metabolites and/or degradates of concern, and the assessment does not underestimate the potential risk for infants and children.

This criteria has been met in the aggregate risk assessment for trifluralin based on food, drinking water, and residential exposure. Specifically, the food exposure assessment is based on reliable residue, usage, and consumption data (including monitoring data) that does not underestimate actual trifluralin exposure. The drinking water assessment is based on an adequate environmental fate database for parent trifluralin and degradates, upper-bound modeling for parent trifluralin and degradates in water, and Agency estimates of daily drinking water consumption. Also, residential risk assessment for trifluralin is considered an upper-bound assessment since it is based (in general) on maximum use rates, the Agency's Residential SOPs (which tend to the high end), and more recent and reliable exposure data, including Outdoor Residential Exposure Task Force (ORETF) data.

3.3 Dose Response Assessment

Table 4 Toxicology Endpoint Selection

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* Target MOE	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age)	NOAEL = 100 mg/kg/day UF = 100 Acute RfD = 1.0 mg/kg/day	FQPA SF = 1 aPAD = 1.0 mg/kg/day	Developmental Toxicity Study - Rat LOAEL = 500 mg/kg/day based on increased total litter resorptions.
Acute Dietary (General population, including infants and children)	No appropriate single dose endpoint was selected		
Chronic Dietary (All populations)	NOAEL= 2.4 mg/kg/day UF = 100 Chronic RfD = 0.024 mg/kg/day	FQPA SF = 1 cPAD = 0.024 mg/kg/day	Chronic Toxicity (capsule) - Dog LOAEL = 40 mg/kg/day based on based on increased frequency of abnormal stool, decreased body weights and body weight gains, and on decreased erythrocytes and hemoglobin and increased thrombocytes in males
Short-Term Incidental Oral (1-30 days)	NOAEL= 10 mg/kg/day	MOE = 100	Two-generation Reproduction Study - Rat LOAEL = 32.5 mg/kg/day based on decreased pup weights in both generations
Intermediate-Term Incidental Oral (1- 6 months)	NOAEL= 10 mg/kg/day	MOE = 100	Special Urinalysis Study - Rat LOAEL = 40 mg/kg/day based on based on the presence of tubular cytoplasmic hyaline droplets; increased total protein, AST, and LDH in the urine; albumin α1-globulin and α2-globulin observed by urine electrophoresis; and increased urinary volume

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* Target MOE	Study and Toxicological Effects
Short-Term Dermal (1 to 30 days)	No quantification required since there was no systemic toxicity at the limit dose in the dermal toxicity study. There are no developmental toxicity concerns. The HIARC also recommends that the products containing trifluralin should be labeled as SENSITIZER		
Intermediate-Term Dermal (1 to 6 months)	Oral study NOAEL = 10 mg/kg/day (dermal absorption rate = 3 %)	Residential MOE = 100 Occupational MOE = 100	Special Urinalysis Study - Rat LOAEL = 40 mg/kg/day based on based on the presence of tubular cytoplasmic hyaline droplets; increased total protein, AST, and LDH in the urine; albumin α1-globulin and α2-globulin observed by urine electrophoresis; and increased urinary volume
Long-Term Dermal (>6 months)	Oral study NOAEL= 2.4 mg/kg/day (dermal absorption rate = 3 % when appropriate)	Residential MOE = 100 Occupational MOE = 100	Chronic Toxicity (capsule) - Dog LOAEL = 40 mg/kg/day based on based on increased frequency of abnormal stool, decreased body weights and body weight gains, and on decreased erythrocytes and hemoglobin and increased thrombocytes in males
Short-Term Inhalation (1 to 30 days)	Inhalation study NOAEL= 81 mg/kg/day	Residential MOE = 100 Occupational MOE = 100	30-Day Inhalation Study - Rat LOAEL = 270 mg/kg/day based on increased methemoglobin and bilirubin in females and incidences of dyspnea and ruffled fur in males and females
Intermediate-Term Inhalation (1 to 6 months)	Oral study NOAEL = 10 mg/kg/day (inhalation absorption rate = 100%)	Residential MOE = 100 Occupational MOE = 100	Special Urinalysis Study - Rat LOAEL = 40 mg/kg/day based on based on the presence of tubular cytoplasmic hyaline droplets; increased total protein, AST, and LDH in the urine; albumin α1-globulin and α2-globulin observed by urine electrophoresis; and increased urinary volume

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* Target MOE	Study and Toxicological Effects
Long-Term Inhalation (>6 months)	Oral study NOAEL= 2.4 mg/kg/day (inhalation absorption rate = 100%)	Residential MOE = 100 Occupational MOE = 100	Chronic Toxicity (capsule) - Dog LOAEL = 40 mg/kg/day based on based on increased frequency of abnormal stool, decreased body weights and body weight gains, and on decreased erythrocytes and hemoglobin and increased thrombocytes in males
Cancer (oral, dermal, inhalation)	$Q_1^* = 5.8 \times 10^{-3}$ $(mg/kg/day)^{-1}$ Group C ("Possible" Human Carcinogen)		

UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, NA = Not Applicable

3.4 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 recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife.

For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). In the available toxicity studies on trifluralin, the effects seen on the thyroid and kidney may possibly be endocrine related. When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, trifluralin may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.0 DIETARY / RESIDENTIAL EXPOSURE / RISK

4.1 Usage Summary

4.1.1 Agricultural Use

Trifluralin [2,6-dinitro-N,N-dipropyl-4-(trifluoromethyl)benzenamine] is a selective, pre-emergence (to the weed) herbicide registered for the control of annual grasses and certain broadleaf weeds. Trifluralin is one of the dinitroaniline family of herbicides that controls weeds by disrupting the growth process (preventing cell division) during germination, but does not control established weeds. The mode of action (MOA) is described as microtubule assembly inhibition.

Trifluralin is registered for use on a wide variety of food and feed crops including soybean, cotton, alfalfa, asparagus, barley, Brassica vegetables, bulb vegetables, celery, citrus fruits, corn (field), cotton, cucurbit vegetables, endive, flax, fruiting vegetables, grapes, hops, legume vegetables, peanuts, peppermint, root and tuber vegetables, rapeseed (canola), safflower, sorghum, spearmint, stone fruits, sugarcane, sunflower, tree nuts, and wheat. Trifluralin end-use products for food and feed crops include emulsifiable concentrates (EC, 36.4, 50.8% ai) and a granular formulation (G, 10% ai). These formulations may be applied using ground or aerial equipment, with the EC formulations being typically applied as aqueous dilutions. The application timing may be dormant, pre-plant, or pre-emergence; with application typically followed by mechanical or water-based soil incorporation.

Table 5 Registrations for Agricultural Use

Trifluralin Food / Feed Registrations			
Registrant EPA Reg. No.	Label Acceptance Date	Formulation Class	Product Name
Dow AgroSciences LLC			
62719-97	11/20/01	4 lb/gal EC	Treflan E.C. Weed and Grass Preventer
62719-131	12/4/01	10% G	Treflan TR-10
62719-222	2/16/99	3.4 lb/gal EC	Broadstrike + Treflan
62719-250	11/30/01	4 lb/gal EC	Treflan HFP
Industria Prodotti Chimici S.P.A.			
33660-31	1/15/99	5 lb/gal EC	Flutrix Five EC
33660-32	1/15/99	4 lb/gal EC	Flutrix 4 EC ATT
33660-33	1/25/99	4 lb/gal EC	Flutrix 4 EC
Agan Chemical Manufacturers Ltd.			
66222-46	10/24/02	4 lb/gal EC	Triflurex HFP

4.1.2 Residential / Commercial / Other Use

Trifluralin is also registered for weed control on ornamentals, field grown roses, cottonwood trees, turfgrass, christmas trees, non-bearing trees and vines, and root-barrier applications. Sites of usage include home lawns, home vegetable gardens, ornamental gardens (including planting beds, flowers, shrubs, and trees) and other public/private sites including golf courses, parkland, bike paths, and cemeteries. For residential and other non-agricultural uses, trifluralin is formulated as a granular (G 0.17 - 2.0 % ai) and an emulsifiable concentrate liquid (EC 43 % ai). For turf, trifluralin is typically applied once in Spring (March/April), prior to crabgrass germination. The predominant formulation for the above uses is granular, and granular is the only formulation used on turf. However, trifluralin may also be applied as a liquid to ornamentals and vegetable gardens.

4.1.3 Use Estimates

Based on 1997-2001 data, the Agency estimates that approximately 18,000,000 lbs of trifluralin ai is used per year for agricultural production in the United States. Usage data available for this assessment was limited and could not be used to predict the general trend of overall use, although data provided by the registrant(s) indicates a steady decline in trifluralin use on the two major uses, soybean and cotton. The top 6

uses include soybean, cotton, wheat, alfalfa, sunflowers, and dry beans/peas, and accounts for 93% of total trifluralin ai applied in the US. The label rate for for agricultural uses is 1 to 2 lbs ai/acre, with a maximum rate of 4 lbs ai/acre on sugarcane. However, the registrant reports that the typical use rate is 1 lb ai/acre, or less. The following are agency estimates of percent crop treated for trifluralin registrations. Other crops are estimated to be less than 10% treated (or lack data for a reliable estimate).

Use Estimates:

Crop	Pounds ai/Year	% Treated
Soybeans	8,200,000	15
Cotton	5,000,000	45
Sunflowers	800,000	30
Durum Wheat	600,000	35
Dry Beans	300,000	30
Sugarcane	200,000	10
Tomatoes	100,000	50
Beans, Green	70,000	35
Peanuts	60,000	10
Safflower	50,000	60
Carrots	50,000	55
Peas, Green	40,000	30
Cabbage	30,000	45
Asparagus	20,000	25
Peppers	20,000	25
Dry Peas	20,000	15
Watermelons	20,000	15
Cantaloupes	10,000	15
Broccoli	8,000	10
Collards	3,000	35
Cauliflower	3,000	10
Greens, Turnip	2,000	30
Greens, Mustard	2,000	25
Spinach	2,000	10
Kale	1,000	25
Celery	1,000	10
Okra	<500	20
Radishes	<500	10

4.2 Dietary Exposure / Food

4.2.1 Tolerance Summary

Trifluralin [2,6-dinitro-N,N-dipropyl-4-(trifluoromethyl)benzenamine] tolerances are established under 40 CFR §180.207 and are expressed in terms of trifluralin *per se* in/on the raw agricultural commodities (RACs) listed above under 4.1.1. Current tolerances range from 0.05 ppm to 2.0 ppm, with most tolerances established at the

enforcement method's "level of quantitation" (LOQ) of 0.05 ppm in plant matrices. At this time, tolerances for residues of trifluralin in livestock commodities have not been established. Adequate enforcement methods are available for the determination of trifluralin *per se* residues in/on plant commodities.

4.2.2 Tolerance Reassessment

In general, most trifluralin commodities will retain their current tolerance level of 0.05 ppm based on data indicating trifluralin *per se* at less than the level of detection, or LOD, in field trial studies. A proposed, but not final, registration for use on mung bean sprouts (at 2.0 ppm) as a growth regulator will be revoked, as well as a revocation of tolerance for upland cress. Other tolerance revocations and recommendations for new tolerances are made to conform to new guidance for crop group definitions.

Of greater significance however, is the tolerance increase from 0.2 ppm to 2.0 ppm for alfalfa hay and the new tolerance of 3.0 ppm for alfalfa forage, based on a revised use pattern allowing application during the growing season. In the residue chemistry chapter of the trifluralin Registration Eligibility Document (RED, 10/94), the data requirements for magnitude of trifluralin residues in livestock were waived (R. Perfetti memo, 2/4/93) based on the low levels of radioactive residues shown in the animal metabolism studies and the low trifluralin exposure estimated for cattle. The Agency concluded that tolerances for trifluralin in fat, meat, meat by-products, and milk were not necessary as there was no expectation for finite residues occurring in animal commodities [40 CFR 180.6(a)(3)]. In the recent alfalfa field trials, maximum trifluralin residues at the labeled 21-day PHI were 2.2 ppm in/on alfalfa forage and 1.6 ppm in/on alfalfa hay, and the highest average field trial (HAFT) residues were 2.0 ppm in/on alfalfa forage and 1.3 ppm in/on alfalfa hay. This estimated exposure to ruminants from alfalfa is significant enough to require additional data to both identify metabolites in meat products and milk, and to predict residue levels for tolerance and risk assessment.

4.2.3 Residue Data

As part of the "TRED" process, the Agency has re-examined the residue chemistry data submitted by the registrant(s) for trifluralin. These data include studies that support trifluralin's food uses in general, including metabolism in plants and livestock, analytical and multiresidue methods for enforcement, and studies with rotational crops. Studies have also been re-reviewed that support trifluralin commodities specifically, such as crop field trials, processing studies, and storage stability studies. This data is presented below as background to the dietary portion of the risk assessment.

4.2.4 Metabolism in Plants and Livestock

Plants: The qualitative nature of trifluralin residues in plants is adequately understood based on field corn and mustard green metabolism studies; supplemented with carrot, cotton, peanut, soybean, and sweet potato metabolism data. The residue of concern in plants is trifluralin *per se* and the current tolerance expression for plants is considered adequate. Trifluralin was the predominant residue in field corn and mustard greens. Smaller amounts of conjugates C1 (N-[2-Ethyl-1-propyl-5-(trifluoromethyl)-1H-benzimidazol-7-yl]-β-D-glucopyranosylamine) and C2 (N-[2-Ethyl-1-propyl-5-(trifluoromethyl)-1H-benzimidazol-7-yl]-α-D-glucopyranosylamine) as well as the metabolite TR-4 (α,α,α-trifluoro-5-nitro-N^4,N^4,-dipropyltoluene-3,4-diamine) were identified in corn forage. It was concluded that conjugates in corn plants were converted from nonpolar to polar compounds, and subsequently incorporated into insoluble forms including cell wall components.

Livestock: Trifluralin metabolism studies in ruminants and in poultry have been submitted to the Agency and are summarized below. Dietary risk assessment is based, in part, on the results of the ruminant metabolism study, even though the study is considered to be of low quality by current standards. To address this uncertainty in the dietary risk assessment, and to establish the appropriate tolerance expression and tolerance levels in ruminant commodities, the HED Metabolism Assessment Review Committee (2/4/04) concluded that a new metabolism study in ruminants must be submitted as well as a ruminant feeding study at 1x, 3x, and 10x (based on the reassessed tolerance of 3.0 ppm for alfalfa forage the revised maximum dietary exposure for cattle is ~6.0 ppm). In addition, an analytical method for determining trifluralin residues in ruminant fat, meat, meat by-products, and milk must be submitted for Agency review.

In the *available* ruminant metabolism study, two steers were dosed with uniformly ring-labeled [^{14}C]trifluralin at 0.88 ppm (0.15x the revised maximum exposure) and 8.8 ppm (1.5x) in the diet for 5 and 3 days, respectively. In addition, two dairy cows were dosed with uniformly ring-labeled [^{14}C]trifluralin at 1.7 ppm (0.3x) and 17 ppm (2.8x) in the diet for 5 and 3 consecutive days, respectively. For the steer dosed with [^{14}C]trifluralin at levels equivalent to 0.15x the (revised) maximum exposure for 5 days, total radioactive residues (TRR) were <0.001 ppm in muscle, 0.004 ppm in fat and kidney, and 0.014 ppm in liver. For the steer dosed with [^{14}C]trifluralin at levels equivalent to 1.5x the (revised) maximum exposure for 3 days, TRR were 0.003 ppm in muscle, 0.015 ppm in fat, 0.048 ppm in kidney, and 0.145 ppm in liver. Average TRR values in milk were 0.0016 ppm from the cow dosed at 0.3x and 0.011 ppm in milk from the cow dosed at 2.8x. Extracted ^{14}C-residues were fractionated and characterized by column chromatography, but residues in milk and tissues were not conclusively identified. Based on thin layer chromatography (TLC) data and comparison to metabolite fractions identified in urine, the following compounds were identified in milk and tissues:

Liver:	TR-14, TR-5, TR-6, TR-7, and desethyl TR-14
Kidney:	TR-42 or TR-44, and desethyl TR-15
Fat:	Trifluralin, TR-4, TR-6, and TR-14
Milk:	Trifluralin, TR-2, TR-6, TR-7 and TR-14

It should be noted that the HED Metabolism Committee concluded (2/4/04) that all trifluralin metabolites, including the above, must be considered toxicologically similar to trifluralin *per se.*

The maximum dietary exposure of trifluralin to poultry is 0.05 ppm based on a diet consisting of 80% field corn grain and 20% soybean. In the poultry metabolism study, laying hens were dosed with uniformly ring labeled [^{14}C]trifluralin at 0.05 ppm (1x) and 0.5 ppm (10x) in the diet for five consecutive days, or at 50 ppm (1,000x) for ten consecutive days. For the 1x dose group, TRR were nondetectable in muscle (<0.003 ppm), skin/fat (<0.003 ppm), and eggs (<0.001 ppm) and 0.004 ppm in liver. For the 10x dose group, TRR were nondetectable (<0.003 ppm) in muscle, 0.002 ppm in skin/fat, 0.014 ppm in liver, and $\leq$0.002 ppm in eggs. For the 1,000x dose group, TRR were 0.15 ppm in muscle, 0.47 ppm in skin/fat, 2.49 ppm in liver, and 0.032-0.53 ppm in eggs. ^{14}C-residues in eggs from the 1,000x dose group plateaued by 8 days. TRR in eggs and tissues from the 1,000x dose group were extracted and fractionated, but attempts at identifying metabolites were unsuccessful. However, given the low dietary exposure of trifluralin residues to poultry, the Agency has concluded that further characterization and identification of the residue in eggs and tissue is not required.

4.2.5 Residue Analytical Methods

Data Collection / Enforcement: The reregistration requirements for residue analytical methods are fulfilled for plant commodities. Adequate methods are available for data collection and enforcement of tolerances for residues of trifluralin *per se* in/on plant commodities. The Pesticide Analytical Manual (PAM, Vol. II, Section 180.207) lists four GC methods (designated as Methods I, II, III, and A) with electron capture detection (ECD) and a detection limit of 0.005-0.01 ppm, as available for determination of trifluralin *per se* in/on plant commodities. However, although the Agency previously (2/2/94) waived the requirement for an analytical method for animal commodities, an analytical method for determining trifluralin residues in fat, meat, meat byproducts, and milk is now required in conjunction with the required metabolism and feeding studies.

Multiresidue Methods: The FDA PESTDATA database (PAM Vol. I, Appendix II, 1/94) indicates that trifluralin is completely recovered (>80%) using multiresidue method PAM Vol. I Sections 302 (Luke method), 303 (Mills, Onley, Gaither method) and 304 (Mills Method; Protocol E, fatty foods).

4.2.6 Field Trial Data (“Magnitude of the Residue”)

Plants: Field trials determine the amount of residue in plant commodities at the time of harvest. Field trial data are used to set tolerance levels and are often used as the basis for dietary exposure estimates. Overall, adequate field trial data for trifluralin food/feed uses, based on the maximum registered use patterns, have been submitted and reviewed by the Agency. The residue chemistry chapter for the trifluralin RED (10/94) noted that, with a few exceptions, crop field trial data were available to support the registered uses of trifluralin. However, a substantial portion of the trifluralin crop field trials are older studies conducted 20 to 30 years ago and HED noted that samples stored at temperatures above freezing would be of particular concern because storage stability data indicated the potential for trifluralin residue instability in those cases. To address concerns pertaining to the storage stability of trifluralin residues, the Trifluralin Reregistration Standard, Science Chapter (7/85) and the Trifluralin Product and Residue Reregistration Update (10/91) required sample storage information to validate existing crop field trials. Although a substantial portion of the field trial residue database for trifluralin is still considered questionable, the Agency has determined that sufficient residue data are available for reassessment of trifluralin tolerances for most crops based on the following; (1) the early-season use pattern of trifluralin in most crops results in residues below the enforcement method LOQ (0.05 pm); (2) bridging studies from more recent field trials have residue levels that are similar to residue levels in the earlier field trials; (3) adequate residue data are available for some crops that can be readily translated to similar uses on related crops; and (4) numerous processing studies conducted at exaggerated rates indicate that trifluralin residues in various RACs are likely to be nondetectable (<0.01 ppm) following treatment at 1x the maximum labeled rate.

4.2.7 Residue Estimates for Risk Assessment

The HED MARC committee met on 2/4/04 and decisions were made concerning trifluralin residues for tolerance expression and residues for risk assessment. For dietary risk assessment, the residues of concern are trifluralin *per se* in plants; trifluralin *per se* and degradates TR-4, TR-6, and TR-15 in drinking water; and trifluralin *per se* and all degradates identified as total radioactive residue (TRR) in milk and meat(s) from the ruminant metabolism study. Note that the decision to use TRR is based, in part, on the MARC conclusion that lacking specific toxicological data, trifluralin metabolites/ degradates are considered to be similar to and not less toxic than trifluralin parent.

Plant Commodities: Trifluralin residues were not detected in crop field trials except for alfalfa, beets, cabbage, collards, cottonseed, flax seed, green onions, mint, radish, and one detection each in field corn and mustard greens. Also, monitoring data from the USDA Pesticide Data Program (PDP, 1997-2002) are available for the following commodities: asparagus, barley, green beans, broccoli, cantaloupe, carrots, celery, cherries, grapes, grape juice, oranges, orange juice, nectarines, oats, peaches,

peanut butter, potato, sweet peppers, sweet potato, tomatoes, winter squash, and wheat. Detectable residues of trifluralin were seen in barley (3 detects, 0.005 ppm), broccoli (1 detect, 0.007 ppm), carrots (889 detects, range of 0.01- 0.21 ppm) and canned tomato (range of 025 ppm to 0.002 ppm).

Livestock Commodities: Total radioactive residues (TRR) in tissue extracts and milk from cattle dosed with [^{14}C] trifluralin at levels equivalent to 1.5x to 2.8x the (revised) maximum expected exposure for 3 days, were 0.003 ppm in muscle, 0.015 ppm in fat, 0.048 ppm in kidney, 0.145 ppm in liver, and 0.011 ppm in milk. Based on the conclusions of the MARC (all metabolites are considered toxicologically similar to parent), the TRR measurements were used for dietary risk assessment.

4.2.8 Vegetable Gardens

Trifluralin is currently registered for use on home-grown vegetables; with a recommended rate equal to 4 lbs ai/acre. Based on field trial and monitoring data, the Agency expects that most vegetables, when eaten, would not have detectable trifluralin residues. However, since some crops have demonstrated detectable residues, at application rates less than 4 lbs ai/acre, the Agency cannot be certain that residential users will not be exposed to trifluralin from garden usage, or what that exposure would be. To mitigate the uncertainty (and risk) associated with this use, HED recommends that the label rate for vegetable garden use not exceed the label rate for agricultural uses.

4.3 Dietary Exposure / Water

A geographic information systems (GIS) analysis indicates trifluralin use is widespread across the United States. The highest trifluralin use areas (51 to 175 lbs of trifluralin/mile^2) are found in the Mississippi embayment, the Red River basin, northwestern Iowa, southwestern Minnesota, and the western panhandle of Texas. Moderate trifluralin use (11-50 lbs trifluralin/mile^2) can be found in most of the mid-western corn belt, the Great Plains, the central valley of California, the coastal plains of North Carolina and Georgia, and the Mississippi embayment. National Water Quality Assessment (NAWQA) surface and ground water sampling stations are located in the moderate to high trifluralin use regions. In these regions, the maximum trifluralin concentrations were greater than <0.02 ppb. The GIS analysis indicates the NAWQA sampling locations appear to reflect trifluralin use areas.

4.3.1 Residue Profile

Environmental Persistence: Trifluralin is moderately persistent in the environment. In laboratory soil metabolism studies, trifluralin degraded with half-lives of 116-201 days during aerobic conditions and 25-59 days during anaerobic conditions.

In field studies, trifluralin dissipated with half-lives ranging from 15-149 days. Trilfuralin is stable to hydrolysis in acidic, neutral, and basic conditions, but undergoes a rapid degradation by photolysis in aqueous conditions. The aqueous photolysis half-life for trifluralin is reported as 8.9 hours but photolyzes slowly in soil with a half-life of 41 days**.**

Mobility / Volatility: Trifluralin tends to bind to soil with greater affinity, with Kds ranging from 18 for sand to 156 for clay loam. In the field dissipation studies, trifluralin was rarely detected below 0-6" soil depth. Trifluralin is expected to be volatile, with vapor pressure measured as $1.1x10^{-4}$ Torr (mm Hg). In the laboratory volatility study using a trifluralin formulation incorporated in soil, up to 9% of the applied radioactivity was detected in volatiles at 30 days. The maximum volatility of trifluralin at day 1 was 0.0036 µg/cm^2/hour.

Environmental Metabolites / Degradates: The major degradates were reported in aqueous photolysis and anaerobic soil metabolism studies. The major degradates reported in aqueous photolysis study include: TR-6 (5-trifluoromethyl-3-nitro-1,2-benzenediamine) and TR-15 (2-ethyl-7-nitro-5-trifluromethylbenzimidazole). One major degradate, TR-4 (α,α,α,-trifluoro-5-nitro-N4,N4-dipropyl-toluene-3,4-diamine) was reported in the anaerobic soil metabolism study.

4.3.2 Surface Water

Monitoring Data: Surface water monitoring data for trifluralin were obtained from the USGS/NAWQA data and USGS/EPA pilot reservoir monitoring program data (Blomquist, et al. 2001). Trifluralin was detected in 15% (2,560 detections/17,637 sampled) of surface water samples, generally associated with watersheds with agricultural use patterns. The peak surface water concentration of trifluralin from the monitoring program is 1.74 ppb, from the San Joaquin Study Unit. The highest time-weighted annual mean concentration is 0.618 ppb, also from the San Joaquin Study Unit. Trifluralin was detected in the USGS/EPA pilot reservoir monitoring study at the CA, PA, LA, and SD reservoirs. Detection frequencies of trifluralin were low in both intake (2.8%) and treated (2.2%) water. A maximum of two detections were found in the intake water samples at the PA reservoir in 2000 and the LA reservoir in 1999.

Modeling: Modeling was completed for parent as well as combined trifluralin residues (i.e., trifluralin and its major environmental degradation products greater than 10% of application) observed in fate studies. Major degradation products include 5-trifluoromethyl-3-nitro-1,2-benzene diamine (TR-6), 2-ethyl-7-nitro- 5-trifluoromethyl benzimidazole (TR-15), and ααα-trifluoro-5-nitro- N4,N4-dipropyltoluene- 3,4,diamine (TR-4).

Tier I: Tier I (FIRST) modeling was conducted using the application rate for sugar cane (4.0 lbs ai/A); selected because it is the highest application rate for all

trifluralin agricultural uses. The daily peak concentration is not likely to exceed 66.9 ppb. The annual average concentration of trifluralin is not likely to exceed 6.6 ppb. For combined trifluralin residues (parent and degradation products), the peak daily and annual average concentrations are not likely to exceed 72.5 and 17.6 ppb, respectively.

Tier II: Since trifluralin is registered on several crops, Tier II modeling scenarios were selected to reflect crops with the highest use (soybeans, cotton), the maximum application rate (sugarcane), and availability of scenarios. GIS analysis indicates the selected scenarios generally represent moderate to high trifluralin use (i.e., $\geq$11 lbs ai/mi^2). Among the crops modeled (soybean, cotton, canola, tomatoes, wheat, carrots, cabbage, sugarcane, turf and ornamentals), the maximum environmental concentrations were obtained for sugarcane applied as a single aerial application at 4.0 lbs ai/acre. Trifluralin is a volatile pesticide (Henry Constant =1.62E^{-4} atm m^3/mole and vapor pressure=1.10E^{-4} Torr) and has been detected in both rain and air samples in environmental monitoring programs. Modeling of volatilization rates from soil, as modeled by PRZM, were assumed to be captured through the aerobic soil metabolism half-life. In the reservoir, volatilization was simulated using the Henry's Constant and vapor pressure.

For the sugarcane use, the 1 in 10 year daily peak concentration is not likely to exceed 38 ppb. The 1 in 10 year annual average concentration is not likely to exceed 1.9 ppb. The 30 year annual average concentration is not likely to exceed 1.3 ppb. For combined trifluralin residues, the concentration is not likely to exceed 38.4 ppb for the 1 in 10 year daily peak concentration, 2.0 ppb for the 1 in 10 year annual average concentration, and 1.4 ppb for the 30 year annual average concentration.

EEC Estimates for Risk Assessment: The two major agricultural uses of trifluralin are soybean and cotton. The Agency estimates that 15% of the soybean crop and 45% of the cotton crop is treated with trifluralin. Since a higher contamination of drinking water is expected with soybean use, the EEC estimates associated with soybean is used for risk assessement. The EECs for assessment are; 1) 7.0 ppb for acute; 2) 0.4 ppb for chronic endpoints; and 3) 0.3 ppb for assessing carcinogenic risk (note that the estimate for carcinogenic risk is intended to reflect *lifetime* exposure).

Table 6 Estimated Concentrations / Surface Water

Crop Scenarios	1 in 10 year Peak Concentration (ppb)		1 in 10 year Annual Daily Average Concentration (ppb)		30-year Annual Daily Average Concentration (ppb)	
	Trifluralin	Trifluralin + Degradates [1]	Trifluralin	Trifluralin+ Degradates [1]	Trifluralin	Trifluralin+ Degradates [1]
SoybeansMS 2.0lbs a.i./A, 1x	6.9	7.0	0.3	0.4	0.3	0.3
CottonMS 2.0lbs a.i./A, 1x	4.2	4.2	0.3	0.3	0.2	0.2
CanolaND 1.0 lb a.i./A, 1x	5.8	5.8	0.6	0.6	0.5	0.5
TomatoesFL 1.0 lb a.i./A, 1x	7.1	7.1	0.3	0.4	0.3	0.3
WheatND 1.0 lb a.i./A, 1x	4.1	4.1	0.4	0.5	0.4	0.4
CarrotsFL 1.0 lb a.i./A, 1x	7.3	7.3	0.3	0.4	0.3	0.3
CabbageFL 1.0 lb a.i./A, 1x	5.8	5.8	0.3	0.3	0.2	0.2
SugarcaneLA 4.0 lb a.i./A, 1x	38.1	38.4	1.9	2.0	1.3	1.4
SugarcaneLA 2.0 lb a.i./A, 2x, 180 days intervals	22.9	23.1	1.9	2.0	1.4	1.5
TurfFL 1.0 lb a.i./A, 2x 56 days intervals	16.9	17.0	0.6	0.6	0.4	0.4
TurfPA 1.0 lb a.i./A, 2x 56 days intervals	6.9	7.0	0.4	0.4	0.3	0.3
OrnamentalsOR 4.0 lb a.i./A, 1x	9.4	9.4	0.4	0.4	0.3	0.4
OrnamentalsOR 2.0 lb a.i./A, 2x 56 days intervals	4.9	5.0	0.4	0.5	0.4	0.4

[1] Degradates include TR-4 (α,α,α,-trifluoro-5-nitro-N4,N4-dipropyl toluene-3,4,diamine), TR-6 (5-trifluoromethyl-3-nitro-1,2-benzene diamine) and TR-15 (2-ethyl-7-nitro-5-trifluoromethylbenzimidazole)

The maximum daily peak concentration of trifluralin from PRZM/EXAMS simulation (38.1 ppb) is greater than the highest concentration in the USGS/NAWQA monitoring database (1.74 ppb). However, the maximum annual average trifluralin

concentration in surface water (1.9 ppb) is comparable to time weighted annual mean concentrations in USGS monitoring studies (0.62 ppb).

4.3.3 Ground Water

Monitoring Data: Ground water monitoring data for trifluralin were obtained from the USGS NAWQA database. Trifluralin was detected in 0.5% of 10,083 ground water samples (49 detections) with a peak ground water concentration of 0.15 ppb.

Modeling: SCI-GROW is a screening, or tier 1 model for pesticide concentrations in ground water. SCI-GROW modeling was based on sugarcane use because it represents the highest application rate (4.0 lbs ai/acre). The estimated shallow ground water concentration for trifluralin and trifluralin degradates is not likely to exceed 0.035 ppb. Predicted concentrations of trifluralin and combined trifluralin residues in ground water are the same because major degradation products of trifluralin were formed through degradation processes (e.g., photodegradation). Photodegradation is not considered in the SCI-GROW model. The maximum trifluralin concentration in shallow ground water (0.035 ppb), as predicted through SCI-GROW, is lower than concentrations in the NAWQA ground water monitoring database (0.15 ppb).

4.3.4 Data / Model Characterization

There are no aerobic aquatic degradation data for trifluralin. A default aerobic aquatic degradation half-life was calculated as twice the aerobic soil metabolism half-life. Submission of aerobic aquatic metabolism data is expected to reduce uncertainties in the aquatic metabolism of trifluralin. Volatilization of trifluralin was not directly modeled in the PRZM scenario, but because the aerobic soil metabolism half-life represents both degradation and volatilization, the aerobic soil metabolism half-life was used to jointly describe degradation and volatilization processes.

Trifluralin residue modeling accounted for only major degradation products (>10% of the applied radioactivity) identified in fate studies. The major degradation products were identified only in aqueous photolysis and in anaerobic soil metabolism studies. There were several degradation products identified in aerobic soil metabolism, but none of these are classified as major degradation products. The uncertainty in the predicted EECs arises from not including the minor degradation products (<10% of applied radioactivity) in the drinking water exposure assessment. Also, there may be uncertainty in the predicted EECs due to the application timing used for modeling since EECs are expected to vary according to the date of application. However, model simulations are based on a fixed application date of March 1st. Modeling was conducted using the maximum application rate for specific crops. The use of typical application rates on specific crops is expected to lower predicted concentrations.

Tier II EECs were adjusted for percent cropped area (PCA) in the watershed. For all crops modeled except soybean, cotton and wheat, a default percent cropped area factor of 0.87 was used. The crop specific PCA factors were available for soybean (0.46), cotton (0.2) and wheat (0.56). If specific PCA factors for other crops, such as canola, tomatoes, carrots, cabbage, sugarcane, turf, and ornamentals were available, it is likely to lower the predicted EECs for those specific crops.

No monitoring data for trifluralin degradation products are available to allow for a comparison of predicted concentrations and actual concentrations of combined trifluralin residues. Although the NAWQA monitoring stations appear to be located (based on county level data) in most of the high trifluralin use areas, the study design of NAWQA was not targeted to account for all trifluralin use areas, timing of application and other factors which may more accurately represent spatially and temporally dependent variables influencing runoff vulnerability.

4.3.5 Office of Water Health Advisory Values

Based on the 2002 drinking water standards and Health Advisories (HA), no MCL/MCLG is available for trifluralin. The one-day and 10-day health advisories for a 10 kilogram child are 80 ppb. The Lifetime HA is the concentration of a chemical in drinking water that is not expected to cause any adverse non-carcinogenic effects for a lifetime exposure. The Lifetime HA for trifluralin is 5 ppb and is based on the exposure of a 70 kg adult consuming 2 liters of water, per day. The Drinking Water Equivalent Level (DWEL) is reported as 300 ppb. DWEL is a lifetime exposure concentration protective of adverse, non-carcinogenic health effects that assumes all of the exposure to a contaminant is from drinking water. The Cancer Risk Health Advisory is reported as 500 ppb based on carcinogenic risk at the level of 10^{-4}.

4.4 Dietary (Food and Drinking Water) Risk Estimates

Acute Dietary Risk: An acute dietary assessment was not conducted for the general U.S. population or other population sub-groups because there was no appropriate single dose endpoint. The upper-bound risk estimate for females 13-49 years of age (designated in the HIARC report) is less than 1% of the aPAD at the 99.9^{th} exposure percentile. Results of the Lifeline analysis are fully consistent with DEEM-FCID results (<1% aPAD).

Chronic Dietary Risk: Based on the conclusions of the HED HIARC committee, dietary risk for trifluralin is assessed by comparing chronic dietary exposure estimates (in mg/kg/day) to the trifluralin cPAD, with dietary risk expressed as a percent of the cPAD. The cPAD is the chronic Population Adjusted Dose; the chronic Reference Dose (0.024 mg/kg/day) modified by the FQPA safety factor. The trifluralin cPAD is 0.024 mg/kg/day based on a RfD of 0.024 mg/kg/day (see Section 3.3.1, Endpoint

Selection Discussion), and incorporating the FQPA safety factor of 1x (no special factor) for the overall U.S. population or any population sub-groups.

The cPAD method of risk assessment is applicable to the oral exposure route and is used to assess both food and drinking water exposure. Exposure estimates that are less than 100% of the cPAD indicate a determination of safety can be concluded. The following summarizes the Agency's current method for determining exposure due to use on food commodities. Chronic dietary risk is estimated for the general U.S. population and population sub-groups defined by sex, age, region, and ethnicity. Durations of chronic exposure vary from one-year as represented by "all infants", to lifetime exposure as represented by the general U.S. population, which combines all population subgroups to form a mean exposure value. It should be noted that all parameters of chronic dietary exposure estimates are averaged values (i.e. average food consumption, average residue, etc.). The assessment is based on PDP, field trial and processing data. Dietary exposure estimates are also factored by the estimated weighted average usage, or "percent crop treated" data.

Carcinogenic dietary risk is based on the chronic exposure estimate for the general U.S. population derived from the same residue, percent use, and averaged consumption data summarized above for the cPAD method. Note that the consumption data for the general U.S. population represents all age groups, all geographic areas, all ethnic groups, and incorporates reports of no consumption (non-user). The final risk estimate is calculated by multiplying the average U.S. exposure estimate by the trifluralin *upper-bound* potency factor, or Q_1*. The risk estimate represents the probability of "excess" cancers attributable to trifluralin. In general, the Agency considers carcinogenic risk estimates of 10^{-6}, or less, to be negligible.

Consumption Data / DEEM / Lifeline: The trifluralin chronic dietary exposure assessment was conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 1.3) which incorporates consumption data from the USDA Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" are linked to EPA-defined food commodities using publicly available recipe translation files (developed jointly by USDA/ARS and EPA). For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population sub-groups, but are retained as individual consumption "events" for acute exposure assessment. Based on analysis of the 1994-96, 98 CSFII consumption data which took into account dietary patterns and survey respondents, HED concluded that it is appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old. Exposure estimates (Table 5) are expressed in mg/kg body weight/day and

as a percent of the cPAD.

Lifeline Model: Dietary exposure estimates were also conducted using the Lifeline™ model (Version 2.0) which is also based, in part, on CSFII, 1994 -1996 and 1998 consumption data with FCID. Lifeline™ models individual dietary exposures over a season by selecting a new CSFII diary each day from a set of similar individuals, based on age and season attributes. The Lifeline chronic dietary exposure estimate is based on an average daily exposure from a profile of 1,000 individuals over a one year period. Further information regarding the Lifeline™ model can be found at the following web site: www.theLifeline™group.org.

Chronic dietary risk estimates for all population sub-groups are less than 1% of the trifluralin cPAD (0.024 mg/kg/day) and concern for this route of exposure is not indicated. Carcinogenic risk is estimated to be 10^{-7} for the general U.S. population.

Table 7 Dietary Risk Estimates / Food and Water Combined

Acute / Chronic Dietary Exposure and Risk Estimates					
Population Subgroup	PAD, mg/kg/day	**DEEM-FCID**		**Lifeline**	
		Exposure, mg/kg/day	% PAD	Exposure, mg/kg/day	%PAD
Acute Dietary Estimates (99.9th Percentile of Exposure)					
Females 13-49 yrs	1	0.000262		0.000311	< 1
Chronic PAD Dietary Estimates					
U.S. Population	0.024	0.000030	< 1	0.000019	< 1
All infants (< 1 yr)	0.024	0.000062	< 1	0.000033	< 1
Children 1-2 yrs	0.024	0.000073	< 1	0.000051	< 1
Children 3-5 yrs	0.024	0.000062	< 1	0.000039	< 1
Children 6-12 yrs	0.024	0.000041	< 1	0.000024	< 1
Youth 13-19 yrs	0.024	0.000025	< 1	0.000016	< 1
Adults 20-49 yrs	0.024	0.000025	< 1	0.000017	< 1
Adults 50+ yrs	0.024	0.000025	< 1	0.000017	< 1
Females 13-49 yrs	0.024	0.000024	< 1	0.000017	< 1
Carcinogenic Risk Estimate					
U.S. Population	Q_1* 0.0058	0.000028	10^{-7}	0.000019	10^{-7}

4.5 Residential Exposure / Risk

Residential risk assessment considers all potential pesticide exposure, other than exposure due to residues in foods or in drinking water. Exposure may occur during and after application at homes; or after applications at golf courses, parks, schools, etc. Each route of exposure (oral, dermal, inhalation) is assessed, where

appropriate, and risk is expressed as a Margin of Exposure (MOE), which is the ratio of estimated exposure to an appropriate No-Observed-Adverse-Effect-Level (NOAEL) dose. For trifluralin, carcinogenic risk is also estimated by the Q_1* approach.

Trifluralin products are marketed for homeowner use on residential lawns, landscape ornamentals, trees, and vegetable gardens. Trifluralin containing products are also marketed for use by professional applicators (Pest Control Operators, or PCOs) on residential turf, on golf courses, other turf such as recreational/commercial areas, and on ornamental plantings. Based on these uses, trifluralin is assessed for the residential applicator (or "handler"), for children's post-application oral exposure that may occur from turf contact, and for post-application dermal contact.

4.5.1 Residential Applicator / Systemic Risk (MOE Approach)

Homeowners (or others) may be exposed to trifluralin while treating their lawns, ornamentals, or vegetable gardens. Trifluralin may be in a granular or liquid form, and applied at various rates from 3 lbs ai/A on turf, to 20 lbs ai/A on ornamental beds. HED has developed residential exposure scenarios for trifluralin based on the use sites, formulations, application rates, and the various equipment that may be used during applications. The quantitative exposure/risk assessment developed for residential handlers is based on these scenarios:

Granular formulation:	mix/load/apply with belly grinder spreader
Granular formulation:	mix/load/apply with push-type spreader
Granular formulation:	mix/load/apply with shaker can (by hand)
Liquid formulation:	mix/load/apply with hose-end sprayer
Liquid formulation:	mix/load/apply with low pressure handwand
Liquid formulation:	mix/load/apply with backpack sprayer
Other:	applying trifluralin impregnated fabric squares to soil

Residential risk estimates are also based on estimates (and assumptions) regarding the body weight of a typical homeowner/applicator, the area treated per application, and the seasonal duration (in days) of exposure. Note also that residential applicators are assumed to complete all elements of an application (mix/load/apply) without use of protective equipment (assessments are based on an assumption that individuals will be wearing short-sleeved shirts and short pants).

Trifluralin-specific data to assess the above exposure scenarios were not submitted to the Agency in support of reregistration. Instead, exposure estimates for these scenarios are taken from the Pesticide Handlers Exposure Database (PHED, Version 1.1 August 1998) which is routinely used to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available. In addition to PHED data, this risk assessment relies on data from the Outdoor

Residential Exposure Task Force (ORETF) and proprietary studies (see appendix for study descriptions).

Exposure Factors / Other Estimates: For risk assessment, the average body weight of an adult applicator is set at 70 kg and represents the general adult population (effects identified in the selected toxicity studies were not sex specific). Other factors used for the trifluralin assessment are taken from the HED Science Advisory Committee *Policy 12: Recommended Revisions To The Standard Operating Procedures For Residential Exposure Assessment* (2/22/01) and include the amount/area treated estimates of: 1) 5 gallons of liquid formulation per day when using a low-pressure handwand, or a backpack sprayer; 2) 1,000 ft^2 for ornamental and vegetable garden treatments, using liquid formulations, with a hose-end sprayer; 3) 0.5 acres for lawn and ornamental treatments, using granular formulations, with a bellygrinder spreader or push-type spreader; 4) 1,000 ft^2 for granular spot treatments to lawns with a belly grinder, spoon, measuring scoop, shaker can, or by hand; and 5) 1,000 ft^2 for granular treatments to flower or vegetable gardens with a belly grinder, spoon, measuring scoop, shaker can, or by hand.

The seasonal duration of trifluralin exposure to homeowner applicators is thought to be a day, or a few days, but well within the 30 day duration defined as *short-term* for the purposes of risk assessment. Dermal exposure at the time of application is typically assessed for pesticides, but in the case of trifluralin *systemic* toxicity was not observed at the limit dose of 1,000 mg/kg in the dermal toxicity study. However, inhalation exposure and associated systemic toxicity is assessed by comparing inhalation exposure estimates to the NOAEL (81 mg/kg/day) seen in the 30-day rat inhalation study. A margin of exposure of 100 (or more) is considered adequately protective for this route of exposure.

MOE estimates for applicator exposure scenarios are presented in Table 6 below.

Table 8. Residential Applicator Short-Term Inhalation Exposure / Risk						
Exposure Scenario (Scenario #)	Use Site	Inhalation Unit Exposure (μg/lb ai)[a]	Application Rate[b]	Amount Used or Area Treated per Day[c]	Daily Inhalation Dose (mg/day/day)[d]	Inhalation MOE[e]
MIXER/LOADER/APPLICATOR EXPOSURE						
Loading/applying granulars with a belly grinder (1)	ornamental (pre-plant)	62	20 lbs ai/acre	0.023 acres	4.10e-03	2.00e+05
	ornamental (post-plant)		4.0 lbs ai/acre	0.023 acres	8.20e-05	9.90e+05
	turf		3.0 lbs ai/acre	0.5 acres	1.30e-03	6.10e+04
	vegetable gardens		4.1 lbs ai/acre	0.023 acres	8.30e-05	9.70e+05
Loading/applying granulars with a push-type spreader (2)	ornamental (pre-plant)	0.88	20 lbs ai/acre	0.023 acres	5.80e-06	1.40e+07
	ornamental (post-plant)		4.0 lbs ai/acre	0.023 acres	1.20e-06	7.00e+07
	turf		3.0 lbs ai/acre	0.5 acres	1.90e-05	4.30e+06
	vegetable gardens		4.1 lbs ai/acre	0.023 acres	1.20e-06	6.90e+07
Loading/applying granulars using a spoon, measuring scoop, shaker can, or by hand(3)	ornamental (pre-plant)	45	20 lbs ai/acre	0.023 acres	3.00e-04	2.70e+05
	ornamental (post-plant)		4.0 lbs ai/acre	0.023 acres	5.90e-05	1.40e+07
	turf		3.0 lbs ai/acre	0.023 acres	4.40e-05	1.80e+06
	vegetable gardens		4.1 lbs ai/acre	0.023 acres	6.00e-05	1.30e+06
	rose bushes		0.00043 lbs ai/bush	50 bushes	1.40e-05	5.90e+06
Mixing/loading/applying liquids with a hose-end sprayer (4)	flowers, trees and shrubs	1.5	4.1 lbs ai/acre	0.023 acres	2.00e-06	4.00e+07
	vegetable gardens		4.1 lbs ai/acre	0.023 acres	2.00e-06	4.00e+07
Mixing/loading/applying liquids with low pressure hand wand (5)	flowers, trees, and shrubs	3.8	0.047 lbs ai/ gallon	5 gallons	1.30e-05	6.30e+06
	vegetable gardens		0.047 lbs ai/ gallon	5 gallons	1.30e-05	6.30e+06
Mixing/loading/applying liquids with back pack sprayer (6)	flowers, trees, and shrubs	30	0.047 lbs ai/ gallon	5 gallons	1.00e-04	8.00e+05
	vegetable gardens		0.047 lbs ai/ gallon	5 gallons	1.00e-04	8.00e+05
Applying trifluralin impregnated fabric squares to soil (7)	No data are available for this scenario.					

Footnotes below

Footnotes:

[a] Inhalation unit exposure values from PHED represent no respirator.[7]

[b] Application Rates are based on the maximum application rates listed on the trifluralin labels.

[c] Amount handled per day are from EPA estimates of acres treated, or square feet treated, in a single day based on the application method. For ready to use formulations, the whole container is assumed to be used in one day.

[d] Daily Inhalation dose (mg/kg/day) = (Inhalation Unit Exposure (μg/lb ai) x (1mg/1000 μg) Conversion Factor x Application Rate (lb ai/A or lb ai/gal or lb ai/bush) x Area Treated per day (acres, gallons, or bushes))/ body weight (70 kg).

[e] Short-term Inhalation MOE = Inhalation NOAEL (81 mg/kg/day)/Daily Inhalation Dose (mg/kg/day).

4.5.2 Residential Applicator / Carcinogenic Risk (Q_1* Approach)

Trifluralin has been classified as a Category C ("possible") human carcinogen with carcinogenic risk quantified by the Q_1* approach. The Agency considers all exposure to trifluralin, including the dermal and inhalation exposure expected for homeowners, to have an associated carcinogenic risk. Carcinogenic risk for homeowner applicators is assessed based on the rates and application methods outlined above. An (upper-end) assumption is made that the users assessed will apply trifluralin each season, as labeled, for 50 years of their life. Specific methods (or scenarios) of application (spreader, sprayer, etc.) are assessed to demonstrate the full range of exposure due to method and area treated, although users are not expected to use one method for 50 years. Carcinogenic risk for homeowner applicators is assessed by combining dermal exposure (adjusted for an estimated 3% absorption based on ethalfluralin data) and inhalation exposure (100% absorption), calculating this exposure on a per day basis ("Lifetime Average Daily Dose", in mg/kg/day), and then quantifying risk by multiplying the *upper-bound* carcinogenic potency factor (Q_1*) of 5.8 x 10^{-3} $(mg/kg/day)^{-1}$ by the combined exposure estimate.

For carcinogenic risk assessments, the Agency considers the typical application rate for a given use site, if known. The typical application rate is not known for most trifluralin applications in residential settings, therefore, with one exception, the maximum labeled application rate was used for carcinogenic risk assessment. However, since the labeled rate for established ornamentals is 2 to 4 lbs ai/A, the Agency has used 3 lbs ai/A for the assessment of this scenario.

Table 9. Residential Applicator Carcinogenic Risk

Exposure Scenario (Scenario #)	Use Site	Application Rate [a]	Area Treated	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (ug/lb ai)	Residential Handler Treatments /Year [b]	Daily Total Dose (mg/kg/day) [c]	Residential Handler Total LADD (mg/kg/day) [d]	Residential Handler Cancer Risk [e]	Combined Residential Handler Cancer Risk [f]
MIXER/LOADER/APPLICATOR EXPOSURE										
Loading/applying granulars with a belly grinder (1)	ornamental (pre)	20 lb ai/acre	0.023 acres	110	62	1	0.022	4.4E-05	2.5E-07	8.85E-07
	ornamental (post)	3 lb ai/acre	0.023 acres	110	62	1	0.0033	6.5E-06	3.8E-08	
	turf	3 lb ai/acre	0.5 acres	110	62	2	0.024	9.4E-05	5.4E-07	
	vegetable gardens	4.1 lb ai/acre	0.023 acres	110	62	1	0.0045	8.8E-06	5.1E-08	
Loading/applying granulars with a push type spreader (2)	ornamental (pre)	20 lb ai/acre	0.023 acres	0.67	0.88	1	0.00014	2.7E-07	1.6E-09	5.52E-09
	ornamental (post)	3 lb ai/acre	0.023 acres	0.67	0.88	1	0.000021	4.0E-08	2.3E-10	
	turf	3 lb ai/acre	0.5 acres	0.67	0.88	2	0.00015	5.9E-07	3.4E-09	
	vegetable gardens	4.1 lb ai/acre	0.023 acres	0.67	0.88	1	0.000028	5.5E-08	3.2E-10	
Loading/applying granulars using a spoon, measuring scoop, shaker can, or by hand(3)	ornamental (pre)	20 lb ai/acre	0.023 acres	3.5	45	1	0.00099	1.9E-06	1.1E-08	1.68E-08
	ornamental (post)	3 lb ai/acre	0.023 acres	3.5	45	1	0.00015	2.9E-07	1.7E-09	
	turf	3 lb ai/acre	0.023 acres	3.5	45	2	0.000049	1.9E-07	1.1E-09	
	vegetable gardens	4.1 lb ai/acre	0.023 acres	3.5	45	1	0.0002	3.9E-07	2.3E-09	
Mixing/loading/applying liquids with a hose-end sprayer (4)	flowers, trees, shrubs, vegetable gardens	4.1 lb ai/acre	0.023 acres	39	1.5	5	0.0016	1.5E-05	8.9E-08	
Mixing/loading/applying liquids with low pressure hand wand (5)	flowers, trees, shrubs, vegetable gardens	0.047 lb ai/gal	5 gallons	56	3.8	5	0.0057	5.5E-05	3.2E-07	
Mixing/loading/applying liquids with back pack sprayer (6)	flowers, trees, shrubs, vegetable gardens	0.047 lb ai/gal	5 gallons	100	30	5	0.01	1.0E-04	5.8E-07	
Applying trifluralin impregnated fabric squares to soil (7)	No data are available for this scenario.									

a Maximum application rates were utilized for all use sites except for the granular, post-plant application. The label rates for this use ranged from 2 to 4 lb ai/acre so the average rate of 3 lb ai/acre was utilized for the cancer assessment.
b The number of exposures per year are based on the label recommendations.
c Total Daily Dose (mg/kg/day) = Daily Dermal Dose (mg/kg/day) * Dermal Absorption (3%) + Daily Inhalation Dose (mg/kg/day).
d LADD (mg/kg/day) = Total Daily Dose (mg/kg/day) * (# days of exposure per year/365 days/year) * (50 years exposed/70 years in a lifetime).
e Cancer Risk = LADD (mg/kg/day) * Q1* (0.0058)
f Combined Cancer Risk by Equipment Type = Cancer risks for each crop in the equipment scenario added to one another.

4.5.3 Residential Post-Application / Systemic Risk (MOE Approach)

Exposure to trifluralin occurs in the residential environment following applications by professionals, or non-professionals, to lawns and ornamentals. Exposure to trifluralin also occurs following applications by professionals to private or public areas such as golf courses, parkland, etc. Although the type of site that trifluralin may be used on varies from golf courses to ornamental gardens, the scenario chosen for risk assessment (residential turf use) represents what the Agency considers the likely upper-end of possible exposure and risk. For this assessment, children are the population group of concern. Since *systemic* toxicity was not observed in a dermal toxicity study, up to a dose level of 1,000 mg/kg/day, the risk scenario addressed in this assessment is the possible oral exposure of small children from treated turf, or from treated soil (i.e., soil ingestion, granule ingestion, and hand-/object-to-mouth). A Margin of Exposure of 100 (or more) is considered adequately protective for this assessment.

Dose from hand-to-mouth activity from treated turf: Post-application dose among children from the “incidental” ingestion of pesticide residues on treated turf from hand-to-mouth transfer (i.e., those residues that end up in the mouth from a child touching turf and then putting their hands in their mouth);

Dose from object-to-mouth activity from treated turf: Post-application dose among children from incidental ingestion of pesticide residues on treated turf from object-to-mouth transfer (i.e., those residues that end up in the mouth from a child mouthing a handful of treated turf);

Dose from soil ingestion activity: Post-application dose among children from incidental ingestion of soil in a treated area;

Dose from ingestion of trifluralin granules from treated turf: Post-application dose among children from the “episodic” ingestion of pesticide granules picked up from treated turf. This assessment is not needed for trifluralin since an endpoint and dose for *acute* oral risk assessment for children was not identified by the HIARC and repeated exposure of this nature is not expected.

The term “episodic” is used to denote an event (granule ingestion) that is infrequent to very infrequent. The term “incidental” is used to denote the more likely oral ingestion that may occur following typical lawn treatments. Both terms are used to distinguish the seasonal and inadvertent oral exposure associated with lawn use, from the chronic exposure associated with treated foods, or from residue in drinking water. The exposure estimates of the oral ingestion scenarios (except granule ingestion) are combined to establish the *possible* (if not likely) upper-end of oral exposure from lawn (or similar) use.

Residue on Turf: The registrant submitted a “transferable” residue study of benefin and trifluralin on turf (*Dissipation of Transferable Residues of Benefin and Trifluralin on Turf Treated with a Formulation of the Pesticides*). This study measured surface residue available to be dermally or orally transferred, post-application. The study was conducted from June to September, 1997 at three geographical locations (California, Indiana, and Mississippi) that are said to be representative of the climatic and turf growing conditions expected in the intended use-areas. Turf was mowed to its normal cutting height prior to pesticide application and no irrigation, mowing, or maintenance chemical applications were performed for the duration of the study. A granular product containing 1.33% benefin and 0.67% trifluralin was applied to the turf in a single application at the maximum label rate of two pounds benefin active ingredient per acre and one pound trifluralin active ingredient per acre using a drop granule spreader, or an air-powered granular applicator. Samples were collected at days 0, 1, 2, 4, and 7 following application. For trifluralin, the study limit of detection (LOD) was 0.001 μg/cm^2 and the limit of quantitation (LOQ) was 0.003 μg/cm^2. Initial transferable residues of trifluralin were less than the LOQ and ranged from not-detectable to 0.002 μg/cm^2. The average transferable residues at day 0 were 0.0011 μg/cm^2, just slightly higher than the limit of detection. After day 0, no residues were detectable.

Exposure Factors / Other Estimates: 1) the turf transferable residue (TTR) value at day zero (0.0011 μg/cm^2) from the trifluralin-specific study was used in each scenario; 2) 3 year old children are expected to weigh an average 15 kg; 3) hand-to-mouth exposures are based on a frequency of 20 events/hour and a surface area per event of 20 cm^2 representing the palmar surfaces of three fingers; 4) saliva extraction efficiency is 50% (meaning that every time the hand goes in the mouth approximately ½ of the residues on the hand are removed); 5) object-to-mouth exposures are based on a 25 cm^2 surface area; 6) exposure durations are expected to be 2 hours based on information in the Agency’s *Exposure Factors Handbook*; and 7) soil residues are contained in the top centimeter.

Table 10 Oral Ingestion

Exposure Scenario	Route of Exposure	Application Rate[a]	Exposure mg/kg/day	MOE[b]
Hand to Mouth Activity on Turf[c]	Oral	3.0 lb ai/acre	0.000088	>100
Object to Mouth Activity on Turf[d]	Oral	3.0 lb ai/acre	0.0000055	>100
Incidental Soil Ingestion[e]	Oral	3.0 lb ai/acre	$1.5x10^{-8}$	>100

Footnotes:

[a] Application rates represent maximum label rates from current EPA registered labels (Granular rate is 3.0 lb ai/acre).

[b] MOEs calculated using residues which would be found on day of treatment. Short-term Oral MOE (S-T) = Short-term Incidental Oral NOAEL (10 mg/kg/day / short-term Oral Dose (mg/kg/day) with a target MOE of 100;

[c] Hand-to-mouth Dose Calculation: oral dose to child (1-6 year old) on the day of treatment (mg/kg/day**)** = TTR at day 0 normalized to application rate (0.0033 ug/cm^2) x median surface area for 1-3 fingers (20 cm^2/event) x hand-to-mouth rate (20 events/hour) x exposure time (2 hr/day) x 50% saliva extraction factor x 0.001 mg/µg] / bw (15 kg child).

[d] Object to Mouth Activity on - Turf Dose Calculation: oral dose to child (1-6 year old) on the day of treatment = TTR at day 0 normalized to application rate (0.0033 ug/cm^2) x median surface area for 1-3 fingers (25 cm^2/event) x hand-to-mouth rate (20 events/hour) x 0.001 mg/µg]] / bw (15 kg child).

[e] Incidental Soil ingestion - Dose Calculation**:** oral dose to child (1-6 year old) on the day of treatment (mg/kg/day) = [TTR at day 0 normalized to application rate (0.0033 ug/cm^2) x fraction of residue retained on uppermost 1 cm of soil (100% or 1.0/cm) x 0.67 cm^3/g soil conversion factor] x 100 mg/day ingestion rate x 1.0E-06 g/μg conversion factor] / bw (15 kg).

Table 11 Oral Ingestion / Combined Exposure

Exposure Scenario			Oral MOE	Combined Oral MOE
Child	Granules (3 lb ai/acre) on turf	Hand to Mouth	> 100	110,000
		Object to Mouth	> 100	
		Incidental Soil Ingestion	> 100	

4.5.4 Residential Post-Application / Carcinogenic Risk (Q_1* Approach)

Carcinogenic risk estimates are based, in part, on estimates of days per year, persons are exposed to treated areas following trifluralin use. Based on the transferable residue study, post-application exposure to residential turfgrass and golf course turfgrass will occur on the day of application (day zero) following two applications, each year. It is further estimated that the duration of exposure will be two hours (while exercising) on a treated lawn and four hours of exposure while playing golf. As with residential applicators, the assessment is based on 50 years of trifluralin use and exposure.

Exposure estimates are also based on data that measured the transfer of residue (any chemical) from the surface of treated turf to persons while doing specific activities. These estimates are termed “transfer coefficents” and are 7,300 for residential turf (while exercising) and 500 for golfing (this is the transfer coefficient in the *draft* standard operating procedure for golfer exposure assessment for adults and children, and used in other golfer exposure assessments). As in the post-application oral assessment, the transferable residue estimate (0.0033 ug/cm^2) is taken from the trifluralin-specific study and is the average transferable residues at day 0 (after day 0, no residues were detectable) and accounts for the higher rate (3lb ai/A) used on turf than used in the study (1lb ai/A). These estimates form the basis for the “Lifetime Average Daily Dermal Dose”, or LADD, used with the Q_1* to estimate (lifetime) carcinogenic risk for trifluralin users.

Table 12. Residential Post-Application Carcinogenic Risk								
Exposure Scenario	**Application Rate (lb ai/acre)[a]**	**TTR/DFR (μg/cm^2)[b]**	**Transfer Coefficient (Tc) (cm^2/hr)**	**Exposure Time (ET) (hrs/day)**	**ADD (mg/kg/day)[c]**	**Days of Exposure**	**LADD (mg/kg/day)[d]**	**Cancer Risk[e]**
Dermal contact with turf	3.0	0.0033 (at day 0)	7300	2	2.06×10^{-5}	2	8.08×10^{-8}	4.7×10^{-10}
Dermal contact with golf course turfgrass		0.0033 (at day 0)	500	4	2.83×10^{-6}	2	1.11×10^{-8}	6.4×10^{-11}

a Application rate for turf is the maximum label rate for turfgrass use patterns; application rate for vegetable gardens is maximum label rate for use on vegetable gardens.

b Turf transfer residue at day zero (μg/cm^2) = [AR (3 lbs ai/A) * TTR residue on day 0 from the trifluralin-specific study; Dislodgeable foliar residue for vegetable gardens at day zero (μg/cm^2) = [AR (4 lbs ai/A) *TTR residue on day 0 from the trifluralin-specific study;

c Average daily dermal dose (ADD) (mg/kg/day) = [DFR/TTR (μg/cm^2) * TC (cm^2/hr) * mg/1,000 μg * ET (hrs/day) * Dermal Absorption (3%)] / [BW (70 kg)]

d Lifetime average daily dose (LADD) = Average Daily Dermal Dose (mg/kg/day) * (number of days of exposure per year / 365 days/year) * (50 years exposed / 70 years in a lifetime).

e Cancer Risk = LADD (mg/kg/day) x Q1* (mg/kg/day) where Q1* = 0.00579.

4.5.5 Dermal Sensitization

The Agency is concerned about dermal sensitization reactions in adults and children due to trifluralin exposure in residential settings. At present, HED has no method for determining a quantitative endpoint for skin sensitization and, therefore, has no means of quantitatively assessing the risk resulting from trifluralin's sensitization potential. HED recommends a SENSITIZATION warning statement on all labels and a recommendation that contact with skin should be avoided. Note that the Agency's current policy is that it is not feasible to require personal protective equipment for homeowner pesticide users due to concerns about noncompliance.

4.5.6 Trifluralin Spray Drift

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, groundboom use can also be a source of exposure. 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 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.

5.0 AGGREGATE EXPOSURE / RISK ASSESSMENT

As part of the reregistration eligibility decision, the Agency is required by the Food Quality Protection Act to ensure *"that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there is reliable information."*

Trifluralin has been assessed for the following; 1) acute exposure from food and water by the aPAD approach; 2) chronic exposure from food and water by the cPAD approach; 3) chronic exposure from food and water by the Q_1* approach; 4) short-term inhalation exposure to homeowner applicators by the MOE approach; 5) 50-year combined inhalation and dermal exposure to homeowner applicators by the Q_1* approach; 6) short-term oral exposure to children post-application on turf by the MOE approach; and 7) 50-year (lifetime) dermal exposure to persons (golfers, etc.) post-

application on turf by the Q_1* approach. (Note that this assessment calculates trifluralin exposure due to drinking water *directly,* based on the consumption data of the USDA Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998).

Aggregate exposure assessment is based, in part, on the assumption that there is a predictable level of *chronic* pesticide exposure, attributable to food and drinking water, and this level is estimated on a per day basis (mg/kg/day) by using averaged estimates of residue, use, and consumption. This average, or "background" level of exposure is assumed to be constant, not seasonal, and residential or other exposures are additive to this background. For trifluralin, homewner use is highly seasonal (mostly early Spring) and this exposure will likely be acute (one day of golf) or short-term (multiple residential applications). The route of exposure may be oral (children on turf), dermal (at application or post-application), or by inhalation (at application).

The chronic dietary exposure and risk estimates presented in section 4.4 (above) for the general U.S. and population sub-groups, are aggregate estimates based on both food and drinking water sources. Also, the oral exposure estimates for 3 specific activities of children on treated turf have been aggregated to form an upper-bound estimate (in the interest of safety). Carcinogenic risk estimates for residential applicators have been aggregated to include dermal and inhalation exposure and to represent those making multiple applications to lawns, ornamentals, and gardens with a single type of application device. Also, residential applicator exposure has been aggregated with post-application exposure on turf (although it is thought this combination may exceed the upper-end of likely exposure).

Aggregate Short-Term Risk: The aggregate (3 specific exposure scenarios) incidental oral exposure estimate for children on turf is 0.00009 mg/kg/day. When combined with the estimated chronic dietary exposure (0.000051 mg/kg/day) for children 1-2 years old, the sum is 0.00014 mg/kg/day. Compared to the appropriate dose (10 mg/kg/day) for short-term incidental oral risk assessment, this aggregate exposure estimate is much greater than the target MOE of 100, and a conclusion of safety can be made.

Aggregate Carcinogenic Risk: When using the Q_1* approach to assess a pesticide, the Agency considers all exposure to be additive to aggregate carcinogenic risk, regardless of exposure route or exposure duration (per season). For trifluralin, this means that the chronic exposure from foods (0.000022 mg/kg/day) is added to chronic exposure due to drinking water (0.000008 mg/kg/day) and this in turn is added to exposure estimated for residential use. Based on this assumption, carcinogenic risk estimates are made for those applying trifluralin themselves, each season, throughout adulthood (50 years).

As seen in Table 7, the exposure and carcinogenic risk estimates for residential

applicators varies significantly depending on the application *method*, even if other inputs (rate and area treated) remain the same. Since carcinogenic risk assessment attempts to reflect long-term exposure, the most appropriate exposure estimate would be based on the most common application method; the push-type spreader. The Lifetime Average Daily Dose estimated for this application method is negligible (0.0000006 mg/kg/day), and when added to the chronic dietary (food and water) exposure the aggregate carcinogenic risk estimate is $2x10^{-7}$.

6.0 CUMULATIVE EXPOSURE ASSESSMENT

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

EPA does not have, at this time, available data to determine whether trifluralin has a common mechanism of toxicity with other substances. 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 trifluralin and any other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that trifluralin 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/.

7.0 HUMAN INCIDENT DATA REVIEW

Based on California data and the Incident Data System, it appears that the majority of cases involved skin and eye illnesses. Poison Control Center data would tend to support these results, dermal and ocular effects were some of the most common effects reported. Appropriate protective clothing to protect the skin and eyes of applicators is recommended. The following data bases have been consulted for the poisoning incident data on the active ingredient trifluralin.

OPP Incident Data System (IDS): Reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992. Reports submitted to the Incident Data System represent anecdotal reports or allegations only, unless otherwise stated. Typically no conclusions can be drawn implicating the pesticide as a cause of any of the reported health effects. Nevertheless, sometimes with enough cases and/or

enough documentation risk mitigation measures may be suggested. Of the 30 incidents listed in the IDS, nine involved hives, swelling, itching, shortness of breath, or asthma suggesting that trifluralin may cause an allergic reaction or asthmatic reaction in susceptible individuals. The other most common complaints were dermal effects such as rash.

Poison Control Centers: As the result of a data purchase by EPA, OPP received Poison Control Center data covering the years 1993 through 1998 for all pesticides. Most of the national Poison Control Centers (PCCs) participate in a national data collection system, the Toxic Exposure Surveillance System which obtains data from about 65-70 centers at hospitals and universities. PCCs provide telephone consultation for individuals and health care providers on suspected poisonings, involving drugs, household products, pesticides, etc.

Subgroup	Exposures	Outcome determined	Seen in Health Care Facility
Occupational: adults and older children	46	33	26
Non-occupational: adults and older children	90	56	27
Children under age six	64	35	4

In general, trifluralin is less likely to cause minor, moderate, or life-threatening symptoms than other pesticides except among non-occupational cases where moderate effects are more likely. There were no major or life-threatening cases or cases requiring hospitalization or intensive care except for one case involving a child that was hospitalized. The one case that was hospitalized involved an ingestion in a 2 year old that did not develop any symptoms. It appears likely this case was kept in the hospital overnight for observation. Symptoms most commonly reported in ten or more individuals were eye irritation/pain (25 reports), nausea (16 reports), vomiting (13 reports), and skin irritation/pain (10 reports). Of the symptomatic cases, one-quarter involved exposure to residue rather than direct spray or spill.

California Department of Pesticide Regulation: California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers. Information on exposure (worker activity), type of illness (systemic, eye, skin, eye/skin and respiratory), likelihood of a causal relationship, and number of days off work and in the hospital are provided.

The California data indicates that handlers (applicators and mixer/loaders) were associated with more exposures than any other category. These illnesses included symptoms of conjunctivitis, swollen arms, hand, and face and a rash, eye irritation, tearing and red eyes, headache, skin irritation, and abdominal pain. Effects to the skin, such as burning, itching, rash, appeared to be the most prevalent problems from exposure to trifluralin.

National Pesticide Information Center: On the list of the top 200 chemicals for which NPIC received calls from 1984-1991 inclusively, triflularin was ranked 53rd with 75 incidents in humans reported and 17 in animals (mostly pets).

Appendix A: Pesticide Handler Exposure Database (PHED) Version 1.1 (8/98)

PHED was designed by a task force of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide regulation, and member companies of the American Crop Protection Association. PHED is a software system consisting of two parts -- a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates)

Users select criteria to subset the PHED database to reflect the exposure scenario being evaluated. The subsetting algorithms in PHED are based on the central assumption that the magnitude of handler exposures to pesticides are primarily a function of activity (e.g., mixing/loading, applying), formulation type (e.g., wettable powders, granulars), application method (e.g., aerial, groundboom), and clothing scenarios (e.g., gloves, double layer clothing).

Once the data for a given exposure scenario have been selected, the data are normalized (i.e., divided by) by the amount of pesticide handled resulting in standard unit exposures (milligrams of exposure per pound of active ingredient handled). Following normalization, the data are statistically summarized. The distribution of exposure values for each body part (e.g., chest upper arm) is categorized as normal, lognormal, or "other" (i.e., neither normal nor lognormal). A central tendency value is then selected from the distribution of the exposure values for each body part. These values are the arithmetic mean for normal distributions, the geometric mean for lognormal distributions, and the median for all "other" distributions. Once selected, the central tendency values for each body part are composited into a "best fit" exposure value representing the entire body.

The unit exposure values calculated by PHED generally range from the geometric mean to the median of the selected data set. To add consistency and quality control to the values produced from this system, the PHED Task Force has evaluated all data within the system and has developed a set of grading criteria to characterize

the quality of the original study data. The assessment of data quality is based on the number of observations and the available quality control data. These evaluation criteria and the caveats specific to each exposure scenario are summarized in Appendix A, Table A1. While data from PHED provide the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. HED has developed a series of tables of standard unit exposure values for many occupational scenarios that can be utilized to ensure consistency in exposure assessments. Unit exposures are used which represent different levels of personal protection as described above. Protection factors were used to calculate unit exposure values for varying levels of personal protection if data were not available.

Appendix B: Outdoor Residential Exposure Task Force (ORETF) Handler Studies

A report was submitted by the ORETF (EPA MRID 44972201) that presented data in which the application of various products used on turf by homeowners and lawncare operators (LCOs) was monitored. All of the data submitted in this report were completed in a series of studies. The study that monitored homeowner exposure scenarios using a push-type spreader is summarized below.

Homeowner Push-Type Spreader (OMA003): A mixer/loader/applicator study was performed by the Outdoor Residential Exposure Task Force (ORETF) using Dacthal (active ingredient DCPA, dimethyl tetrachloroterephthalate) as a surrogate compound to determine "generic" exposures of individuals applying a granular pesticide formulation to residential lawns. A total of 30 volunteers were monitored using passive dosimetry (inner and outer whole body dosimeters, hand washes, face/neck wipes, and personal inhalation monitors). Each volunteer carried, loaded, and applied two 25-lb bags of fertilizer (0.89% active ingredient) with a rotary type spreader to a lawn covering 10,000 ft^2. The target application rate was 2 lb ai/acre (actual rate achieved was about 1.9 lbs ai/acre). The average application time was 22 minutes, including loading the rotary push spreader and disposing of the empty bags. Each replicate handled approximately 0.45 lbs ai. Dermal exposure was measured using inner and outer whole body dosimeters, hand washes, face/neck washes, and personal air monitoring devices with OVS tubes. The study results are normalized to kg ai handled. The US EPA HED typically assumes that residential applicators wear short pants and short-sleeved shirts, as described in the Residential SOPs (1997). Therefore, the table reports the dermal exposures for the short pants and short-sleeve shirt clothing scenario only.

Homeowner Hose-end and Hand-held Sprayer: (EPA MRID 44518501) Applications of Sevin Liquid® Carbaryl insecticide [RP-2 liquid (21%)] were made by

volunteers to two young citrus trees and two shrubs in each replicate that was monitored in the study. The test field was located only in Florida. Twenty (20) replicates were monitored using hose-end sprayer (Ortho® DIAL or Spray® hose end sprayer), and 20 replicates were monitored using hand held pump sprayers (low pressure handwands).

Each replicate opened the end-use product, added it to the hose-end sprayer or hand held pump and then applied it to the trees and shrubs. After application to two trees and two shrubs dosimeters were collected. Inhalation exposure was monitored with personal air sampling pumps with OVS tubes attached to the shirt collar in the breathing zone. Dermal exposure was assessed by extraction of carbaryl from inner and outer 100 percent cotton dosimeters. The inner and outer dosimeters were segmented into: lower and upper arms, lower and upper legs, front and back torso. No gloves were worn therefore hand exposure was assessed with 400 ml handwash with 0.01 percent Aerosol OT-75 sodium dioctyl sulfosuccinate (OTS). One hundred percent cotton handkerchiefs wetted with 25 ml OTS were used to wipe face and neck to determine exposure.

Field fortification recoveries for passive dosimeters averaged 88.3 percent for inner and 76.2 percent for outer dosimeters. Face and neck wipe fortifications average 82.5 percent. Handwash and inhalation OVS tube field fortification averaged >90 percent. Inner and outer dosimeter and face and neck wipe residues were adjusted for field fortification results. Handwash and inhalation residues were not adjusted.

Laboratory method validation for each matrix fell within the acceptable range of 70 to 120 percent. The limit of quantitation (LOQ) was 1.0 μg/sample for all media except the inhalation monitors where the LOQ was 0.01 μg/sample. The limit of detection (LOD) was 0.5 μg/sample for all media except the inhalation monitors where the LOQ was 0.005 μg/sample.

For use in reregistration documents, the dermal exposure was calculated by adding the values from the hand rinses, face/neck wipes to the outer dosimeter lower legs and lower arms plus the inner dosimeter front and rear torso, upper legs and upper arms. This accounts for the residential handler wearing short-sleeved shirt and short pants. The results for the low pressure handwand are summarized in Table 3 below.

The distribution of the unit exposure values is categorized as normal, lognormal, or "other" (i.e., neither normal nor lognormal). A central tendency value is selected from the distribution of the exposure values. These values are the arithmetic mean for normal distributions, the geometric mean for lognormal distributions, and the median for all "other" distributions. The dermal exposure had a lognormal distribution so the geometric mean value was used to determine dermal exposure to trifluralin. The inhalation exposure had neither a normal or lognormal distribution so the median was

used to determine inhalation exposure to trifluralin.

APPENDIX C: Proprietary Studies

Worker Exposure Study Durin/g Application of Regent 20GR In Banana Plantation (Fipronil): Handler exposure data from a proprietary granular mixer/loader/applicator study (MRID 45250702) in bananas using fipronil (Regent 20GR) were used in place of PHED data for the “loading/applying granulars using a spoon, measuring scoop, shaker can or by hand” scenario. This fipronil study is considered to be an appropriate source of surrogate handler exposure data for trifluralin because formulation types are similar (granular) and application methods are similar (applying granulars with a spoon). The study is considered to be of sufficient quality for use in risk assessment. Data compensation for these data should be determined.

Several factors should be considered when using fipronil data in the trifluralin exposure assessment. Protection factors used to calculate trifluralin dermal unit exposure values, based on the fipronil unit exposure values, include a standard 50% protection factor for the torso, a 10% protection factor for legs, based on shorts, and a 10% protection factor for arms, based on a short-sleeved shirt. These protection factors represent the typical attire assumed to be worn by a homeowner during pesticide application (shorts and short-sleeved shirt). The 10% protection factor for shorts and the 10% protection factor for a short-sleeved shirt are not standard protection factors used by the Agency; rather, these values are based on the best professional judgement of Agency scientists and are appropriate for calculating range-finding estimates only.