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OFFICE OF
PREVENTION, PESTICIDES
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MEMORANDUM

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Subject: Sulfluramid: Human Health Risk Assessment for Sulfluramid
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1.0 Executive Summary

Sulfluramid (N-ethyl perfluorooctanesulfonamide; N-EtFOSA; GX-071, CAS# 4151-50-2) is a slow acting, but highly potent palatable insecticide that is effective on insects demonstrating social interactions. It is registered for use in a variety of termite, ant, and roach bait stations. Currently there are no registered food uses for sulfluramid.

Sulfluramid rapidly metabolizes to perfluorooctanesulfonate (PFOS) which accumulates in various organs (primarily in the liver), and recirculates enterohepatically. PFOS cannot be further metabolized, and excretion is extremely slow. It has a serum half-life of 1-4 years in humans. This poses a unique risk assessment concern because the consequence of even a single exposure is several years of systemic bioavailability. Sulfluramid's long-term toxicity and carcinogenicity have not yet been characterized.

This assessment addresses existing bait stations with time-limited registrations as well as proposed uses of granular baits in residential and forestry sites. The following products containing the active ingredient sulfluramid were evaluated: (1) ant/roach bait stations in child resistant packaging (CRP) for use inside homes; (2) termite bait stakes in CRP installed slightly below soil surface around the perimeter of homes; (3) termite bait stations in child resistant packaging fastened to infested wood and/or masonry of homes; (4) granular formulations applied to outdoor residential sites to control fire ants, harvest ants, and big headed ants; and (5) granular formulations applied to forestry sites to control Texas leaf-cutting ants or town ants.

There are no registered food uses for sulfluramid, so no acute or chronic dietary endpoints were selected. A short-term incidental oral NOAEL of 0.8 mg/kg/day from a developmental toxicity study in rats was selected based on reduced mean maternal body weight, mean body weight gain and reduced food consumption in rats at the Maternal LOAEL of 3.3 mg/kg/day. This endpoint is used to quantify the risk of children's oral exposure for a one to seven day period. The decrease in maternal body weight and body weight gain occurred during 10 days of exposure, which resembles a short-term exposure (1-7 days). The target MOE in a risk assessment is 300, which includes an extra UF of 3 to account for the unknown impact of systemic retention and enterohepatic recirculation.

An intermediate-term oral NOAEL of 0.45 mg/kg/day from a reproductive toxicity study in rats was selected based on reductions in body weight and body-weight gains, decreased adrenal and pituitary weights, and slightly increased liver weights in rats at the LOAEL of 1.34 mg/kg/day. This endpoint is used to quantify the risk of children's oral exposure for a 7-day to several month period. The target MOE in a risk assessment is 300, which includes an extra UF of 3 to account for the unknown impact of systemic retention and enterohepatic recirculation.

The short-term and intermediate-term endpoints for dermal and inhalation exposure are all based on a special developmental toxicity study in rabbits The oral Developmental LOAEL is 0.3 mg/kg/day (the lowest dose tested) based on decreased viability and lactation indices. The dose used in a dermal risk assessment is the developmental LOAEL adjusted by a 1% dermal absorption factor. The dose used in an inhalation risk assessment is the developmental LOAEL extrapolated to an estimated inhalation equivalent concentration using an oral:inhalation absorption ratio of 1. The target MOE in all dermal and inhalation risk assessments is 1000 which includes extra UFs of 3 each to account for: a.) the unknown impact of systemic retention

and enterohepatic recirculation, and b.) the use of a LOAEL. Long-term dermal and inhalation endpoints were not selected because long-term exposure is not expected.

Sulfluramid has very low acute toxicity. It is Toxicity Category III for oral toxicity and Toxicity Category IV for dermal and inhalation toxicity, and primary eye and skin irritation. It is not a sensitizer by the Buehler method.

Mutagenicity studies, including an Ames assay, a sister chromatid exchange in Chinese hamster ovary cells, and a rat primary hepatocyte unscheduled DNA synthesis assay, were negative. Requirements for chronic and carcinogenicity studies were previously waived on the assumption that bait stations preclude human exposure.

The Hazard Identification Assessment Review Committee (HIARC) noted evidence of qualitative and quantitative susceptibility in the developmental and reproductive toxicity studies. Because there are no registered food uses or tolerances for sulfluramid, this chemical is not subject to provisions of FQPA. Therefore, sulfluramid was not presented to the FQPA Safety Factor Committee for a determination of a safety factor to protect for infants and children and as a result an FQPA SF has not been applied to this assessment.

Occupational and non-occupational handler assessments for push type granular spreaders were based on surrogate unit exposures from two Outdoor Residential Exposure Task Force (ORETF) studies. Other occupational and non-occupational handler assessments were based on surrogate unit exposures from the Pesticide Handler Exposure Database (PHED) as presented in the PHED Surrogate Exposure Guide (8/98) and the draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments (12/18/97).

Non-occupational postapplication risk assessments are based on HED standard values as specified by the SOPs for Residential Exposure Assessments and recommended approaches by HED's Exposure Science Advisory Committee (ExpoSAC). Recent changes to the SOPs alter the residential postapplication scenario assumptions. These updated assumptions are expected to better represent residential exposure and are still considered to be high-end, screening level assumptions. HED management has authorized the use of these updated assumptions.

The MOE for a 15 kg child ingesting the contents of a single bait station is 0.6. In order to attain an MOE of 300, no more than 0.04 mg ai could be ingested by a 15 kg child (0.19 % of one bait station). Given the very limited accessibility of the termite bait stakes (installed slightly below soil surface), the use of child resistant packaging, and the estimated sulfluramid residue that can be released from the bait stakes by water, HED does not expect children to be exposed to residue levels that would result in MOEs below 300. Furthermore, adult's exposure when installing and removing bait stations is expected to be minimal. Limited accessibility of the bait stations when screwed to wood or masonry, and the use of child resistant packaging should also result in unlikely exposure to the contents of the termite bait stations.

For the proposed application of granules to outdoor residential sites, combined dermal/inhalation MOEs calculated for non-occupational handlers and postapplication exposure were greater than 1,000, the target MOE for this exposure scenario. MOEs calculated for children's hand-to mouth exposure were greater than 300, the target MOE for this exposure scenario. However, for children's ingestion of 0.55% ai granules, a screening level MOE of 7 was calculated. It was

assumed that a child would ingest 0.3 grams of granules in a day. It is not known the size range of granules for the proposed formulation. If the granules are somewhat small and not easily noticed by a child, the ingestion of 0.3 grams per day may be unlikely.

The short/intermediate-term MOEs calculated for professional lawn care workers applying granules were greater than the target 1,000. However for forestry workers applying granules, the short/intermediate-term MOEs ranged from 240 to 2,300 (assuming baseline clothing with additional layer of clothing, chemical-resistant gloves, and a respirator). The risk assessment for forestry workers may be further refined with additional data regarding the quantities of product handled per day.

Sulfluramid's carcinogenic potential is unknown. Therefore, cancer risk cannot be addressed at this time.

HED has identified the following major issues regarding the exposure and risk for the 5 types of products evaluated in this assessment

* An MOE of 0.6 was calculated for a child ingesting the contents of a single ant bait station. The results of the CRP testing data, as explained by RD (meeting with HED on 12/20/00), show that roughly 1% of small children will gain some access to the ant bait stations. However, the extent of access and ingestion for these children are not known.

* An MOE of 7 was calculated for a child ingesting granules applied in outdoor areas. The size of granules, which is not known for the proposed formulation, may effect the likelihood that a child will notice and ingest the granules.

* Except for the scenarios of a child ingesting the contents of a single ant bait station and a child ingesting granules applied in outdoor areas, all of the non-dietary MOEs are expected to be above target MOEs (300 for oral and 1,000 for dermal/inhalation routes). (see **Attachment 1** for summary of MOEs calculated).

* As expected for a chemical with acute effects that are not easily detected after exposure, a cursory analysis of incidence data does not show significant trends regarding reported acute health effects from children's exposure to baits containing sulfluramid.

* In rats, sulfluramid (N-ethyl perfluorooctanesulfonamide) is rapidly metabolized to PFOSA (perfluorooctane sulfonamide) and then to PFOS (perfluorooctanesulfonate) which accumulates in various organs, but primarily in the liver. PFOS cannot be metabolized because of the inherent stability of perfluorinated anions. It is resistant to physical, chemical, and biological degradation, and can only be degraded by combustion. There is considerable enterohepatic recirculation of PFOS, and excretion in the urine and feces is extremely slow.

* PFOS has a serum half-life of 1-4 years in humans. It is persistently bioavailable because it is neither excreted nor stored (e.g. in body fat). A single human sulfluramid exposure may elicit toxicity that persists for several years. Additional exposures may cause a cumulation of systemic dose (body burden) and increased toxicity, even if the exposures are spaced months or years apart. Thus, multiple daily exposures, as in a chronic toxicity

study, may not a prerequisite for long-term PFOS toxicity. No toxicity studies have been performed to investigate the impact of systemic persistence on long-term toxicity and carcinogenicity.

* The HIARC noted evidence of qualitative and quantitative susceptibility in the developmental and reproductive toxicity studies, however, since there are no food uses for sulfluramid, the uses in this assessment do not fall under the purview of FQPA. An FQPA Safety factor was not applied to this risk assessment.

* There is widespread potential exposure to PFOS, mostly from the use in food wrapping materials. Given recent provided information, it appears that PFOS exposure from pesticide products is a relatively small portion of the overall exposure to PFOS.

* Alternative bait station products containing the active ingredients fipronil, chlorpyrifos, avermectin, and propoxur would result in comparable MOE's (range of 0.04-28) if a child were to gain access and ingest the whole amount of bait (comparative acute dietary NOAELs and endpoints, and comparative MOEs for ingestion of these pesticides from different bait stations are listed in Attachments 2 and 3). Although HED has not researched this, it is likely that the active ingredients in alternative bait stations have much shorter half-lives in serum than PFOS metabolite of sulfluramid.

* Alternative application methods to these baits such as spraying would likely cause higher exposure to handlers by both the inhalation and dermal routes.

Data Gaps

The following have been identified as data gaps by the HIARC:

1. **Metabolism study in rats** - The HIARC did not have access to any pharmacokinetic data when it first considered sulfluramid on June 27, 2000, so a metabolism study in rats was identified as a significant data gap. A battery of pharmacokinetic studies was submitted in late January, 2001 which may satisfy this data gap. They were received too late to allow for a thorough review. Nevertheless, a cursory review confirms that sulfluramid exposure results in systemic retention that can span many years. Because the adequacy of these data cannot be assessed at this time, the Agency reserves the right to request further pharmacokinetic studies in the future.

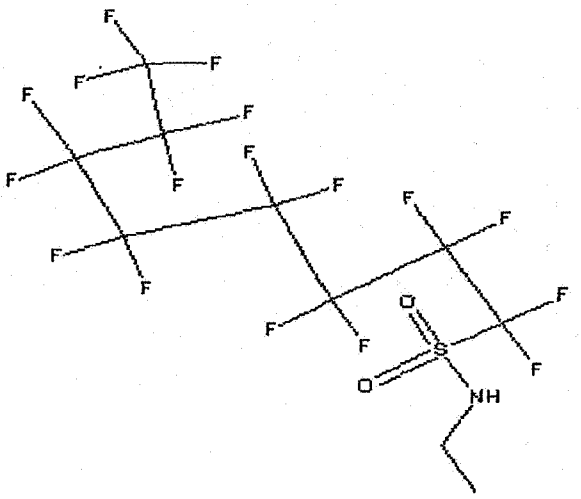
2. **Dermal absorption study** - Although this is a data gap, the HIARC determined that an absorption study is not required because it would not provide additional useful information.

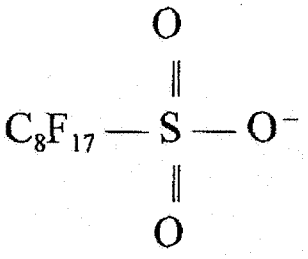
3. **Chronic/carcinogenicity study in rats** - Sulfluramid's chronic toxicity and carcinogenic potential are unknown. Requirements for chronic and carcinogenicity studies had previously been waived on the understanding that bait stations preclude human exposure. It is now recognized that human exposure can result from all sulfluramid uses (including bait stations), and that even a single exposure to sulfluramid can result in long-term systemic exposure. Thus, a chronic/carcinogenicity study in rats is required.

Given the extremely long serum half-life of the degradate, PFOS, the registrant is advised to consult with the Health Effects Division and with the Cancer Assessment Review Committee (CARC) in designing a study that reflects sulfluramid's incidental exposure scenarios.

A mouse carcinogenicity study is not required.

2.0 Physical/Chemical Properties Characterization

Names:	**Sulfluramid**, N-ethyl perfluorooctanesulfonamide; N-EtFOSA; GX-071
Chemical Structure:	
CAS:	4151-50-2
Empirical Formula:	$C_8F_{17}SO_2NHC_2H_5$
Chemical Class:	Sulfonated perfluorochemicals
Molecular Weight:	527 g/Mol
Physical State	Solid white crystals
Vapor Pressure:	5.7 x 10^{-8} kPa (4.3 x 10^{-7} mmHg) at 25°C
Odor:	None
Octanol/Water Partition Coefficient	P_{ow} = 3.10 (observed)
Solubility:	1.172 g/100 mL acetone 0.14 g/100 mL hexane 1.86 g/100 mL methylene chloride 7.09 g/100 mL 1-octanol 83.3 g/100 mL methanol <3 ppb in water
Mode of action for the ai:	Unknown

Names:	**PFOS**, perfluorooctanesulfonate
Chemical Structure:	
CAS:	anion - does not have a CAS number acid - 1763-23-1 ammonium (NH_4) salt - 29081-56-9 diethanolamine (DEA) salt - 70225-14-8 potassium (K^-) salt - 2795-39-3 lithium (Li^+) salt - 29457-72-5
Empirical Formula:	$C_8F_{17}SO_3^-$
Chemical Class:	Sulfonated perfluorochemicals
Molecular Weight:	498.98 g/Mol
Vapor Pressure:	3.31×10^{-7} kPa (2.48×10^{-6} mmHg) at 20°C
Octanol/Water Partition Coefficient	Cannot be determined due to surface-active properties.
Solubility:	Solubility of the salts in water ranges from slight to complete.
Bioconcentration:	Does not bioconcentrate in the lipid fraction in laboratory rats.

3.0 Hazard Characterization (HED's HIARC Report of 2-7-01, Attachment 4)

3.1 Hazard Profile

Toxicity Characterization: Human exposure was once considered to be nonexistent because sulfluramid was only used in child-resistant bait stations, so many toxicity data requirements were waived. It is now recognized that oral exposure can occur in children that gain access to bait station or consume loose bait spread on a lawn. Dermal exposure can occur in adults exposed when spreading loose bait onto residential lawns or during pine reforestation projects. In addition, new toxicity concerns have arisen given that sulfluramid metabolizes to PFOS which is extremely persistent in the body (human serum half-life of 1-4 years), and can be found in enterohepatic circulation. Consequently, the toxicity of sulfluramid is not fully characterized. In particular, no studies have been performed to investigate the impact of systemic persistence on long-term toxicity and carcinogenicity,

Acute Toxicity: Sulfluramid has very low acute toxicity. It is Toxicity Category III for oral toxicity and Toxicity Category IV for dermal and inhalation toxicity, and primary eye and skin irritation. It is not a sensitizer by the Buehler method.

Pharmacokinetics: In rats, a non-toxic dose of ^{14}C-radiolabeled sulfluramid (50 mg/kg orally;

labeled on the ethyl portion of the molecule) is slowly absorbed through the gut. Within 72 hours, 80% of sulfluramid is deethylated to PFOSA (perfluorooctane sulfonamide; i.e. the sulfonamide moiety remains attached to the perfluorooctyl group) with the majority of PFOSA tissue deposition occurring in the liver, kidneys, adrenals, and gonads.[1] PFOSA is progressively metabolized ($t_{½}$ = 6.2 days in the liver; faster in the serum) to PFOS which accumulates in the liver.[2]

PFOS cannot be further metabolized because of the inherent stability of perfluorinated anions.[3] It is resistant to physical, chemical, and biological degradation, and can only be degraded by combustion.[4] Excretion via the urine and feces is extremely slow. Rats dosed IV with ^{14}C-radiolabeled PFOS (the label was on the carbon to which the sulfonamide is attached) excreted 30.2% of the radiolabel via the urine, and 12.6% via the feces for a total excretion of 42.8% by 89 days. Residual levels of μg ^{14}C equivalents/g were liver: 20.6; plasma, 2.2; kidney, 1.1; lung, 1.1; spleen, 0.5; and bone marrow, 0.5. Lower concentrations were also measured in adrenals, skin, testes, muscle, fat, and eye. No radioactivity was detected in the brain. The radiolabel in liver and plasma represent 25% and 3% of the dose, respectively.[5] There is considerable enterohepatic circulation of PFOS.[6]

It is presumed that the metabolic pathway in humans resembles that in rats. Preliminary findings suggest that the serum half-life in humans is in the range of 1-4 years. In the absence of a dermal absorption study, dermal absorption is estimated to be 1% based on a comparison of oral (special rabbit developmental toxicity study) and dermal (rabbit 21-day dermal toxicity) LOAELs:

$$\frac{\textbf{3.0 } \textit{mg/kg/day (Rabbit Maternal Oral LOAEL)}}{\textbf{300 } \textit{mg/kg/day (Rabbit 21-Day Dermal LOAEL)}} = \textbf{0.01} = \textbf{1\%}$$

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[1] R.O. Manning, J.V. Bruckner, M.E. Mispagel, J.M. Bowen. **Metabolism and Disposition of Sulfluramid, a Unique Polyfluorinated Insecticide, in the Rat.** Drug Metabolism and Disposition. Volume 19. No. 1. 1991. Pages 205-211.

[2] A.M. Seacat and D.J. Luebker. **Toxicokinetic Study of Perfluorooctane Sulfonamide (PFOSA; T-7132.2) in Rats.** Unpublished Study. 3M Strategic Toxicology Laboratory. August 11, 2000.

[3] 3M. **Perfluorooctane Sulfonate: Current Summary of Human Sera, Health and Toxicity Data.** January 21, 1999. Page 34.

[4] 3M. **Sulfonated Perfluorochemicals in the Environment: Sources, Dispersin, Fate and Effects.** March 1, 2000. Page 39

[5] S.J. Gibson and J.D. Johnson. **Extent and Route of Excretion and Tissue Distribution of Total Carbon-14 in Rats after a Single Intravenous Dose of FC-95-^{14}C.** Unpublished Study. Riker Laboratories, Inc., Subsidiary of 3M. December 28, 1979.

[6] J.D. Johnson, S.J. Gibson, and R.E. Ober. **Cholestyramine-Enhanced Fecal Elimination of Carbon-14 in Rats after Administration of Ammonium [^{14}C] Perflurooctanoate or Potassium [^{14}C] Perfluorooctanesulfonate.** Fundamental and Applied Toxicology 4. 1984. Pages 972-976.

Cumulative Toxicity: A comparison of acute and repeated dosing studies reveals a marked cumulation of dose and toxicity that can be attributed to the protracted serum half-life of PFOS. Thus, a single sulfluramid exposure to a child or adult may result in a PFOS body burden that persists for several years, and any subsequent exposure may increase the body burden, even if the exposure occurs months or years later.

Subchronic Toxicity: Subchronic feeding studies were performed in the rat and dog. In the rat subchronic feeding study (MRID No. 41799405), the NOAEL was 0.5 mg/kg/day based on body weight, food consumption, hematology, clinical chemistry, organ weight, and histopathological anomalies at the LOAEL of 2.5 mg/kg/day. In the dog subchronic feeding study (MRID No. 41818401), the NOAEL was 0.825 mg/kg/day based on increased epididymal and testicular lesions at the LOAEL of 2.5 mg/kg/day. Sulfluramid appears to be a direct acting testicular toxin in dogs with a primary effect on the late spermatids and possibly Sertoli cells.

Neurotoxicity: No neurotoxicity studies have been performed. Nevertheless, there is no evidence of neurotoxicity in any of the available toxicity studies.

Developmental and Reproductive Toxicity: In a developmental toxicity study in rats (MRID No. 41799409), the developmental NOAEL (3.3 mg/kg/day) exceeded the maternal NOAEL (0.8 mg/kg/day). Maternal effects seen at the LOAEL included reduced body weight, body weight gain, and reduced food consumption. Developmental effects in the rat pups included reduced fetal weights and increased incidence of cleft palate, incomplete ossification of the 3rd and 4th sternebrae and skull, and an enlarged fontanelle at the LOAEL of 13.3 mg/kg/day.

The doses selected for a developmental toxicity study in rabbits (MRID No. 41799408) were insufficient to induce maternal or developmental toxicity (highest dose tested was 1.5 mg/kg/day), but were nevertheless justified by the range-finding studies (MRID No. 42633502).

In a reproductive toxicity study in rats (44341901), the parental and reproductive NOAELs were both 0.45 ♂ / 0.53 ♀ mg/kg/day, and the parental and reproductive LOAELs were 1.34 ♂ / 1.65 ♀ mg/kg/day. The parental LOAEL was based on reductions in body weight and body weight gains, decreased adrenal (F1 males and females) and pituitary weights (F1 females), and slightly increased liver weights (F0), and the reproductive LOAEL was based on reduced F1 and F2 pup body weights, reduced F2 pup postnatal survival, and slightly delayed physical development of both sexes (slight delays in balanopreputial separation in the F1 males and in vaginal opening in F1 females).

The discovery of epididymal and testicular lesions in the subchronic dog feeding study (MRID No. 41818401) prompted a special study of pre- and postnatal development, maturation, and fertility in rabbits (MRID No. 44257106) which assessed late gestation (*in utero*) and nursing-related sexual development of rabbits. The maternal NOAEL was 1.0 mg/kg/day and the maternal LOAEL was 3.0 mg/kg/day based on decreased body weight gain during gestation and decreased food consumption during lactation. The developmental LOAEL was 0.3 mg/kg/day, the lowest dose tested (a NOAEL was not determined), based on decreased viability and lactation indices. The developmental (post-weaning) NOAEL of 1.0 mg/kg/day was based on the fact that slight delays in preputial separation and vaginal opening, as well as a slight decrease in normal sperm, cannot be ruled out at 3.0 mg/kg/day (a developmental post-weaning LOAEL was not determined).

Chronic Toxicity/Carcinogenicity and Mutagenicity: Because PFOS has a protracted serum half-life (1-4 years in humans), the consequence of a single exposure to sulfluramid is systemic PFOS exposure which may persist for several years. Two or more exposures may cause a systemic cumulation even when exposures are spaced months or years apart. Thus, multiple daily exposures may not be required to cause long-term PFOS toxicity. No studies have been performed to investigate the impact of systemic PFOS persistence on long-term toxicity and carcinogenicity.

Sulfluramid's chronic toxicity and carcinogenic potential are unknown. Requirements for chronic and carcinogenicity studies had been waived on the understanding that bait stations, the only use at the time, preclude human exposure. It is now recognized that human exposure can result from all sulfluramid uses (including bait stations), and that even a single exposure to sulfluramid can result in long-term systemic exposure. Thus, a chronic/carcinogenicity study in rats is now required. A mouse carcinogenicity study is not required. Sulfluramid was not mutagenic in an Ames assay with and without metabolic activation (MRID No. 40863201), in a sister chromatid exchange in Chinese hamster ovary cells with and without metabolic activation (MRID Nos. 40612614, 40915801), or in a rat primary hepatocyte unscheduled DNA synthesis assay (MRID Nos. 41251002, 41505102).

Table 1. Toxicity Profile of Sulfluramid Technical

OPPTS No./Study Type	MRID	Results
870.1100 Acute Oral - Rat	40612602	LD_{50} = 607 mg/kg ♂ LD_{50} = 507 mg/kg ♀ LD_{50} = 543 mg/kg ♂+♀ **Toxicity Category III**
870.1200 Acute Dermal - Rabbit	40612608	LD_{50} >2000 mg/kg **Toxicity Category IV**
870.1300 Acute Inhalation - Rat	41799404	LC_{50} > 4.379 mg/L (4-hour) Levels tested: 0 (acetone aerosol control) and 4.379 (aerosol in acetone) mg/L gravimetric concentration. MMAD (SD) = 1.37 µm (0.13) **Toxicity Category IV**
870.2400 Primary Eye Irritation - Rabbit	40612609	Negative **Toxicity Category IV**
870.2500 Primary Skin Irritation - Rabbit	40612610	Mild skin irritation **Toxicity Category IV**
870.2600 Dermal Sensitization - Guinea Pig	41251001 41505101	Not a sensitizer by the Buehler method.

Table 1. Toxicity Profile of Sulfluramid Technical		
OPPTS No./Study Type	**MRID**	**Results**
870.3100 Subchronic Feeding - Rat	41799405	**NOAEL = 0.5 mg/kg/day** (10 ppm) **LOAEL = 2.5 mg/kg/day** (50 ppm) based on body weight, food consumption, hematology, clinical chemistry, organ weight, and histopathological data. Levels tested: 0, 10, 50, or 150 ppm (0, 0.5, 2.5, or 7.5 mg/kg/day)
870.3150 Subchronic Feeding - Dog	41818401	**NOAEL = 0.825 mg/kg/day** (33 ppm) **LOAEL = 2.5 mg/kg/day** (100 ppm) based on the increased epididymal and testicular lesions. Direct acting testicular toxin in dogs with primary effect on the late spermatids and possibly Sertoli cells. Levels tested: 0, 33, 100, 500, or 1500/800 ppm (0, 0.825, 2.5, 12.5, or 37.5/20 mg/kg/day) *The histopathologic findings in the testes prompted HED to request a pre- and postnatal developmental, maturation, and fertility study in rabbits.*
870.3200 21-Day Dermal - Rabbit	41799406	**NOAEL = 100 mg/kg/day** **LOAEL = 300 mg/kg/day** based on decreased body weight and food consumption, elevated BUN, bilirubin, and chloride, decreased calcium and sodium, tan striations in the liver, liver necrosis, and testicular and epididymal atrophy, aspermia in the epididymides, and seminal vesicle distension. Levels tested: 100, 300, 1000 mg/kg/day *Core Supplementary (stability data are missing)*
870.3700 Gavage Developmental Toxicity - Rat	41799409	**Maternal NOAEL = 0.8 mg/kg/day** **Maternal LOAEL = 3.3 mg/kg/day** based on reduced body weight, body weight gain, and reduced food consumption. **Developmental NOAEL = 3.3 mg/kg/day** **Developmental LOAEL = 13.3 mg/kg/day** based on reduced fetal weights and increased incidence of cleft palate, incomplete ossification of the 3rd and 4th sternebrae and skull, and an enlarged fontanelle Levels tested: 0, 0.8, 3.3, or 13.3 mg/kg/day
870.3700 Gavage Developmental Toxicity - Rabbit	41799408 42633502	**Maternal LOAEL >1.5 mg/kg/day** Although the doses used were inadequate to induce maternal or developmental effects, they were justified by the range-finding studies. Levels tested: 0, 0.1, 0.5, or 1.5 mg/kg/day

Table 1. Toxicity Profile of Sulfluramid Technical		
OPPTS No./Study Type	**MRID**	**Results**
870.3800 Feeding Reproductive Toxicity - Rat	44341901	**Parental NOAEL = 0.45♂ / 0.53♀ mg/kg/day** **Parental LOAEL = 1.34♂ / 1.65♀ mg/kg/day** based on reductions in body weight and body weight gains, decreased adrenal (F1 males and females) and pituitary weights (F1 females), and slightly increased liver weights (F0). **Reproductive NOAEL = 0.45♂ / 0.53♀ mg/kg/day** **Reproductive LOAEL = 1.34♂ / 1.65♀ mg/kg/day** based on reduced F1 and F2 pup body weights, reduced F2 pup postnatal survival, and slightly delayed physical development of both sexes (slight delays in balanopreputial separation in the F1 males and in vaginal opening in F1 females). Levels tested: 0, 2, 6, or 18 ppm (0, 0.15, 0.45, or 1.34 mg/kg/day in males; 0, 0.18, 0.53, or 1.65 mg/kg/day in females)
Special Study Gavage Pre- and Postnatal Development, Maturation, and Fertility - Rabbit	44257106	The discovery of epididymal and testicular lesions in a subchronic dog feeding study (MRID 41818401) prompted this study to assess late gestation and nursing-related sexual development of rabbits. Does were dosed during late gestation (G days 19 through 28) at 0, 0.3, 1.0, or 3.0 mg/kg/day. Pups may have been exposed on postnatal days 1 through 42 via lactation to their mothers' residual systemic doses. **Maternal NOAEL = 1.0 mg/kg/day** **Maternal LOAEL = 3.0 mg/kg/day** based on decreased body weight gain during gestation and decreased food consumption during lactation. **Developmental NOAEL = Not Determined** **Developmental LOAEL = 0.3 mg/kg/day** based on decreased viability and lactation indices. **Developmental (post-weaning) NOAEL = 1.0 mg/kg/day** based on the fact that slight delays in preputial separation and vaginal opening, as well as a slight decrease in normal sperm, cannot be ruled out at 3.0 mg/kg/day. **Developmental (post-weaning) LOAEL = Not Determined** Levels tested: 0, 0.3, 1.0, or 3.0 mg/kg/day
870.4100 Chronic Toxicity - Dog	–	Waived because bait stations preclude human exposure.

Table 1. Toxicity Profile of Sulfluramid Technical		
OPPTS No./Study Type	**MRID**	**Results**
870.4200 Carcinogenicity - Mouse (18 months)	–	Waived because bait stations preclude human exposure.
870.4300 Chronic Toxicity/Carcinogenicity-Rat	–	Waived because bait stations preclude human exposure.
870.5100 Bacterial Reverse Gene Mutation Test (Ames Assay)	40863201	Negative in five *Salmonella typhimurium* strains with and without activation.
870.5550 Unscheduled DNA Synthesis in Rat Hepatocytes	41251002 41505102	Negative
870.5900 *In Vitro* Sister Chromatid Exchange Assay	40612614 40915801	Negative
870.6200 Acute Neurotoxicity - Rats	–	Waived because bait stations preclude human exposure.
870.6200 Subchronic Neurotoxicity - Rats	–	Waived because bait stations preclude human exposure.
870.7485 Metabolism - Rat	–	Waived because bait stations preclude human exposure.

3.2 FQPA Considerations

Sulfluramid is not subject to FQPA since the current use pattern does not have or need tolerances or present exposure which results in a dietary risk due to use of the pesticide in or on food. Nevertheless, the HIARC considered fetal susceptibility following sulfluramid exposure and classified it quantitatively and qualitatively.

An evaluation of the potential for increased susceptibility of the developing organism to a specific pesticide is made by comparing the type and severity of the effects observed in the parental test animals to those observed in the fetuses or offspring. When similar adverse effects are seen at lower dose levels in the fetuses/offspring than in the parental animals, the result is described as **quantitatively increased susceptibility**. When adverse effects are seen at the same dose level in the fetuses/offspring as in the parental animals, but the effects in the fetuses/offspring are different from those seen in the parental animals and considered to be more severe, the result is described as

qualitatively increased susceptibility. [7]

Developmental Toxicity Study in Rats - Increased qualitative susceptibility was observed at the highest dose tested based on severity of effect. Although the developmental LOAEL (13.3 mg/kg//day) was higher than the maternal LOAEL (3.3 mg/kg/day), at the highest dose fetal effects (reduced fetal weights and increased incidence of cleft palate, incomplete ossification of the 3rd and 4th sternebrae and skull, and an enlarged fontanelle) were more severe than the maternal effects (reduced body weight, body weight gain, and reduced food consumption).

Developmental Toxicity Study in Rabbits - Susceptibility cannot be assessed because no maternal or developmental toxicity was observed in this study.

Special Developmental Toxicity Study in Rabbits - Increased quantitative and qualitative susceptibility were observed. The developmental LOAEL was 0.3 mg/kg/day which is lower than the maternal LOAEL of 3.0 mg/kg/day. While maternal effects were limited to a decrease in body weight gain and food consumption, developmental toxicity was manifested as decreased viability and lactation indices.

Reproductive Toxicity Study in Rats - Increased qualitative susceptibility was observed. While the LOAEL of 1.34 mg/kg/day was the same for parental and offspring toxicity, effects in the offspring (reduced F1 and F2 pup body weights, reduced F2 pup postnatal survival, and slightly delayed physical development of both sexes including slight delays in balanopreputial separation in the F1 males and in vaginal opening in F1 females) were severe compared to parental toxicity (reductions in body weight and body weight gains, decreased adrenal and pituitary weights, and slightly increased liver weights).

3.3 Dose Response Assessment

The doses and toxicological endpoints selected by the HIARC for various exposure scenarios are summarized in **Table 2** (Sulfluramid: Report of the Hazard Identification Assessment Review committee, March 2, 2001).

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[7] Brenda S. Tarplee and Edward Zager. **Current Approach to Recommending the FQPA Safety Factor for Use in Human Health Risk Assessment.** Health Effects Division, Office of Pesticide Programs, U.S. Environmental Protection Agency; Presented at the California Pesticide Residue Workshop, March 2000).

Table 2. Doses and Toxicological Endpoints			
EXPOSURE SCENARIO	**DOSE (mg/kg/day)**	**ENDPOINT**	**STUDY**
Acute Dietary	—	There is no potential for acute dietary exposure at this time.	—
	Acute RfD = N/A		
Chronic Dietary	—	There is no potential for chronic dietary exposure at this time.	—
	Chronic RfD = N/A		
Incidental Oral, Short-Term	Oral NOAEL = 0.8	Reduced mean maternal body weight, mean body weight gain and reduced food consumption at the Maternal LOAEL of 3.3 mg/kg/day. Target MOE = 300	Developmental Toxicity in Rats
Incidental Oral, Intermediate-Term	Oral NOAEL = 0.45	Reductions in body weight and body-weight gains, decreased adrenal and pituitary weights, and slightly increased liver weights at the LOAEL of 1.34 mg/kg/day. Target MOE = 300	2-Generation Reproduction in Rats
Dermal, Short-Term	Oral LOAEL = 0.3[a]	Decreased viability and lactation indices. Target MOE = 1000	Special Developmental Toxicity Study in Rabbits
Dermal, Intermediate-Term			
Dermal, Long-Term	—	Long-term exposure is not expected.	—
Inhalation, Short-Term	Oral LOAEL = 0.3[b]	Decreased viability and lactation indices. Target MOE = 1000	Special Developmental Toxicity Study in Rabbits
Inhalation, Intermediate-Term			
Inhalation, Long-Term	—	Long-term exposure is not expected.	—

[a] A 1% dermal absorption factor should be used in route-to-route extrapolations.
[b] An oral:inhalation absorption ratio of 1 should be used in route-to-route extrapolations.

Rationale for Not Requiring an Acute Dietary RfD:

The HIARC determined that an acute dietary risk assessment is not required at this time because there is no potential dietary exposure (non-food use).

Rationale for Not Requiring a Chronic Dietary RfD:

The HIARC determined that a chronic dietary risk assessment is not required at this time because there is no potential dietary exposure (non-food use).

Rationale for Selection of the Short-Term Oral Endpoint (1-7 Days):

This endpoint should be used to quantify the risk of a child eating the contents of a bait station or consuming loose bait scattered on a residential lawn on one to seven days. The decrease in maternal body weight and body weight gain occurred during 10 days of exposure, which resembles a short-term exposure (1-7 days).

The HIARC considers these endpoints to be protective of dose cumulation because systemic retention is similar whether exposure consists of a few high doses or numerous low doses. These endpoints are supported by comparable total doses in the subchronic feeding study in dogs and the 2-generation reproductive toxicity study in rats.

The subchronic feeding study in dogs and the special study of pre-and postnatal development, maturation, and fertility in rabbits were also considered in the selection of this endpoint. The NOAEL in the dog study was 0.825 mg/kg/day based on the increased epididymal and testicular lesions at the LOAEL of 2.5 mg/kg/day. The Post-Weaning Developmental NOAEL in the special rabbit study was 1.0 mg/kg/day based on the fact that slight delays in preputial separation and vaginal opening, as well as a slight decrease in normal sperm, cannot be ruled out at 3.0 mg/kg/day. Although the testicular effects in dogs are a primary concern, the rat developmental NOAEL of 0.8 mg/kg/day is considered protective.

The HIARC also considered using the developmental LOAEL of 0.3 mg/kg/day (lowest dose tested) in the special rabbit study based on decreased viability and lactation indices. These endpoints were not selected because they were most likely a consequence of *in utero* exposure, and therefore not relevant to oral exposure in children.

Rationale for Selection of the Intermediate-Term Oral Endpoint (7 Days to Several Months):

The treatment regimen in this study simulates the exposure period of concern (7-days to several months). The HIARC considered using the developmental LOAEL of 0.3 mg/kg/day (lowest dose tested) in the special rabbit study based on decreased viability and lactation indices. These endpoints were not selected because they were most likely a consequence of *in utero* exposure, and therefore not relevant to oral exposure in children.

Rationale for Selection of the Short-Term Dermal Endpoint (1-7 Days):

Although a 21-day dermal toxicity study was available, the HIARC selected an oral LOAEL from the special developmental toxicity study in rabbits in order to protect pregnant female applicators ages 13-60 years due to concerns over developmental effects (decreased viability and lactation) seen in rabbits following *in utero* and postnatal exposure.

Rationale for Selection of the Intermediate-Term Dermal Endpoint (7 Days to Several Months):

Although a 21-day dermal toxicity study was available, the HIARC selected an oral LOAEL from

the special developmental toxicity study in rabbits in order to protect pregnant female applicators ages 13-60 years due to concerns over developmental effects (decreased viability and lactation) seen in rabbits following *in utero* and postnatal exposure.

Rationale for Not Selecting a Long-Term Dermal Endpoint (Several Months to Lifetime):

Long-term dermal exposure to sulfluramid is not expected.

Rationale for Selection of the Short-Term Inhalation Endpoint (1-7 Days):[8]

The only inhalation toxicity study available, an acute study, is inadequate for endpoint selection. The HIARC selected an oral LOAEL from the special study in order to protect pregnant female applicators ages 13-60 years due to concerns over developmental effects (decreased viability and lactation) seen in rabbits following *in utero* and postnatal exposure. There is no way of knowing whether sulfluramid causes portal-of-entry effects in the respiratory tract.

Rationale for Selection of the Intermediate-Term Inhalation Endpoint (7 Days to Several Months):

The only inhalation toxicity study available, an acute study, is inadequate for endpoint selection. The HIARC selected an oral LOAEL from the special study in order to protect pregnant female applicators ages 13-60 years due to concerns over developmental effects (decreased viability and lactation) seen in rabbits following *in utero* and postnatal exposure. There is no way of knowing whether sulfluramid causes portal-of-entry effects in the respiratory tract.

Rationale for Not Selecting a Long-Term Inhalation Endpoint (Several Months to Lifetime):

Long-term inhalation exposure to sulfluramid is not expected.

Adequacy of the Data Base:

The following have been identified as data gaps by the HIARC:

1. **Metabolism study in rats** - The HIARC did not have access to any pharmacokinetic data when it first considered sulfluramid on June 27, 2000, so a metabolism study in rats was identified as a significant data gap. A battery of pharmacokinetic studies was submitted in late January, 2001 which may satisfy this data gap. They were received too late to allow for a thorough review. Nevertheless, a cursory review confirms that sulfluramid exposure results in systemic retention that can span many years. Because the adequacy of these data cannot be assessed at this time, the Agency reserves the right to request further pharmacokinetic studies in the future.

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[8] Aerosol inhalation of the granular formulations is highly unlikely due to the size of the granules and their resistance to attrition. Vapor exposure is extremely unlikely for all formulations because sulfluramid has a vapor pressure of 5.7×10^{-8} kPa (4.3×10^{-7} mmHg) at 25°C. Nevertheless, short and intermediate-term endpoints were selected because endpoints are routinely selected for all granular products.

2. **Dermal absorption study** - Although this is a data gap, the HIARC determined that an absorption study is not required because it would not provide additional useful information.

3. **Chronic/carcinogenicity study in rats** - Sulfluramid's chronic toxicity and carcinogenic potential are unknown. Requirements for chronic and carcinogenicity studies had previously been waived on the understanding that bait stations preclude human exposure. It is now recognized that human exposure can result from all sulfluramid uses (including bait stations), and that even a single dose of exposure to sulfluramid may result in long-term systemic exposure. Thus, a chronic/carcinogenicity study in rats is required.

   Given the extremely long serum half-life of the degradate, PFOS, the registrant is advised to consult with the Health Effects Division and with the Cancer Assessment Review Committee (CARC) in designing a study that reflects sulfluramid's incidental exposure scenarios.

   A mouse carcinogenicity study is not required.

3.4 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, sulfluramid may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Exposure Assessment

4.1 Summary of Registered and Proposed Uses

Sulfluramid (N-ethyl perfluorooctanesulfonamide; N-EtFOSA; GX-071, CAS# 4151-50-2) is a slow acting, but highly potent palatable insecticide that is effective on insects demonstrating social interactions. It is registered for use in a variety of termite, ant, and roach bait stations. Currently there are no registered food uses for sulfluramid. A loose granular formulation is being proposed for outdoor residential and forestry uses. **Table 3** summarizes all of the current and proposed end-use products containing sulfluramid.

Table 3. Current and Proposed End-use Products Containing Sulfluramid[1]				
Product Name	EPA REG. No.	% Active	Product Type	Status
Volcano Fire Ant Bait	1812-	0.55	Granular	Proposed
Volcano Leafcutter Ant Bait	1812-	0.5	Granular	Proposed
Firstline Termite Bait Station	279-3153	0.01	Bait Station	Registered
Fluorguard Ant Control Baits	279-3154	0.5	Bait Station	Registered
Firstline Termite Bait Tube Station	279-3170	0.01	Bait Station	Registered
Firstline Termite Bait Container Station	279-3171	0.01	Bait Station	Registered
Firstline Gt Plus Termite Bait Station	279-3196	0.01	Bait Station	Registered
Micro-Gen Ant Reactor	499-459	0.5	Bait Station	Registered
Pro-Control Roach Bait	499-460	1.0	Bait Station	Registered
Volcano Ant Bait	1812-348	0.5	Bait Station	Registered
Indoor Roach Bait	1812-354	1.0	Bait Station	Registered
Raid Max Roach Bait	4822-355	1.0	Bait Station	Registered
Raid Max Ant Bait	4822-356	0.5	Bait Station	Registered
Raid Double Control Ant Baits	4822-508	0.5	Bait Station	Registered
Chemsico Roach Control System CS	9688-131	1.0	Bait Station	Registered
Chemsico Insect Bait A	9688-134	0.01	Bait Station	Registered

[1]Based on labels provided by RD.

4.2 Dietary Exposure/Risk Pathway

There is no potential for dietary exposure at this time, hence acute and chronic RfDs have not been assigned.

4.3 Residential Exposure/Risk Pathway (for detailed discussion of non-occupational exposure and risk see HED memo of 3/19/01, S. Weiss, DP Barcode: D271985)

All currently registered sulfluramid products sold for home use are bait stations in child-resistant packaging (CRP) . However, a request for registration of a loose granular bait applied outdoors has been requested and is evaluated in this risk assessment

4.4.1 Bait Stations in Child Resistant Packaging (CRP)

4.4.1.1 Ant/roach Bait Stations for Use Inside Homes

Several bait stations containing 0.01% to 1% ai are currently registered for use inside homes for ants and roaches. These products are pre-filled and sold only in child-resistant packaging (CRP). Child-resistant packaging is designed to prevent most children under the age of five from gaining

access to the pesticide, or at least delay their access. It does not eliminate the potential for exposure.

In 1994 HED conducted an assessment for an 11.4 kg (25 lb) child ingesting the entire contents of a single ant bait station containing 21 mg of ai (HED memo, L. Taylor/HED to M. Mendelsohn/RD dated 10/21/94). Based on the currently registered products containing sulfluramid, this value still represents the worst case exposure for an 11.4 kg child ingesting all of the ai in a single bait station (1.8 mg/kg bw). Currently, HED uses a 15 kg body weight when assessing children's exposure. This body weight represents a 1 to 6 year old child.

The MOE for a 15 kg child ingesting the contents of a single bait station is 0.6. In order to attain an MOE of 300, no more than 0.04 mg ai could be ingested by a 15 kg child (0.19 % of one bait station).

4.4.1.2 Termite Bait Stakes Around the Perimeter of Homes

The sulfluramid product line of termite bait stations for application to the soil around perimeter of homes are clear plastic cylindrical stake containers that contain card-board material treated with 0.01% ai. The stakes have numerous holes on the sides and bottom for termites to enter and exit. These products are pre-filled and sold only in child-resistant packaging (CRP). Termites find the stakes and eat the bait inside. The foraging termites die.

Bait stations are sold in 0.125 and 1.0 oz sizes and contain 0.35 and 2.85 mg ai, respectively. Baits are placed 2-3 feet from foundation of the house and no more than 10 feet apart. A digging tool (provided with baits) is used create a hole. Each bait station is inserted into the ground slightly below the surface. The baits are checked every 1 to 3 months for termite activity. Baits are replaced if 50% or more of the bait has been eaten. The number of bait stations used around a home will range from 20 to 200.

The 1.0 oz station may be applied only by pest control operators (PCOs). The 0.125 oz station may be applied by PCOs or homeowners.

A study was conducted to quantify how much residue may be released from 0.125 oz bait stations after they are inserted into the soil. The study simulated potential transfer of sulfluramid by immersing bait stations into water. The highest concentration measured in the samples analyzed was 34 ppb (0.034 μg/mL). Based on this concentration and the 0.8 mg/kg/day NOAEL, a 15 kg child would need to ingest more than 0.31 gallons of water from 22.8 of the 0.125 oz bait stations to achieve an MOE of less than 300. A general summary of the study was provided to HED. The study and raw data were not reviewed by HED.

Given the very limited accessibility of the bait stakes (installed slightly below soil surface), the use of child resistant packaging, and estimated sulfluramid residue that can be released from the bait by water, HED does not expect children to be exposed to residue levels that would result in MOEs below 300 for either the 0.125 oz. or 1.0 oz bait products. Furthermore, adult's exposures when installing and removing bait stations are expected to be minimal.

4.4.1.3 Termite Bait Stations Fastened to Infested Wood and/or Masonry of Homes

Limited accessibility of the bait stations when screwed to wood or masonry, and the use of child resistant packaging should result in unlikely exposure to the contents of the termite bait stations.

4.4.2 Granular Formulation Applied to Outdoor Residential Sites

A granular/pellet type formulation containing 0.55 % ai is being proposed for use on turf and/or gardens to control fire ants. The product can be applied directly to the area around a mound (3 to 4 tablespoons per mound) or broadcast applied at rates up to 1 lb of product per acre.

4.4.2.1 Handlers

The following are the major potential handler exposure scenarios for the application of granular formulation to residential sites:

* applying granular formulation with hands
* loading/applying granular formulation using belly grinder
* loading/applying granular formulation using push-type spreader

The following assumptions were used in the handler assessment:

* Maximum application rate of 0.0055 lb ai/acre (1.0 lb product/acre)
* Treatment of up to 20,000 ft^2 (approximately 1/2 acre) for full lawn treatments and 1,000 ft^2 (0.023 acres) for spot treatments
* Unit exposures were based on the PHED version 1.1. as presented in the 12/18/97 draft SOPs for Residential Exposure Assessments and specific homeowner granular push-type spreader study (ORETF Study No. OMA003).

The short-term dermal/inhalation MOEs calculated for non-occupational handlers applying granular formulations were well above the target MOE of 1,000 (MOEs ranged from 5,600 to 850,000).

4.4.2.2 Postapplication

The following are the major exposure scenarios following the application of granular formulation to residential sites:

* dermal exposure via contact with treated turf-grass
* oral hand-to-mouth exposure via contact with treated turf-grass
* oral ingestion of granules

Screening-level assessments for these 3 scenarios were completed and are based on the draft 12/18/97 Standard Operating Procedures (SOPs) for Residential Exposure Assessments (with authorized changes by HED management).

4.4.2.2(a) Dermal Exposure via Contact with Turf-grass

The following assumptions were used to calculated dermal exposures and MOEs:

* The application rate was 0.0055 lb ai/acre
* The amount of residue available on day zero for dermal contact is 5% of the application rate.
* For short-term exposure, the dermal transfer coefficient for adults and children is 14,500 and 5,200 cm^2/hour, respectively. For intermediate-term exposure, the dermal transfer coefficient for adults and children is 7,300 and 2,600 cm^2/hour, respectively
* The exposure time is assumed to be 2 hours for adults and children.
* The body weights of adults and children are assumed to be 60kg and 15 kg, respectively.

The short dermal MOEs calculated for a 60 kg adult and 15 kg child on postapplication day '0' were 20,000 and 14,000, respectively. The intermediate-term dermal MOEs for a 60 kg adult and 15 kg child were 40,000 and 28,000, respectively.

4.4.2.2(b) Oral Hand-to-mouth Exposure from Turf-grass

The following assumptions were used to calculate **children's oral hand-to-mouth exposure** from treated turf:

* The fraction of ai that is available for hand-to-mouth contact on day '0' is assumed to be 0.05 (5% of maximum application rate).
* The maximum application rate of 0.0055 lb ai/acre was assumed.
* The surface area (SA) of hands inserted in child's mouth is assumed to be 20 cm^2/event (based on the palmer surface area of a child's 3 fingers being 20 cm^2).
* The saliva extraction factor (SEF) was assumed to be 0.5 (50%).
* The frequency (FQ) of hand-to-mouth activity was assumed to be 20 events/hour.
* The exposure time (ET) is 2 hours
* A body weight of 15 kg was assumed for children.
* The oral daily dose calculated for the post-application assessment was assumed to be a central to high-end value.

The short- and intermediate-term MOEs calculated for a 15 kg child were 9,800 and 5,500, respectively.

4.4.2.2(c) Oral Ingestion of Granules

The following assumptions were used to perform a screening-level estimate of episodic ingestion of granules by small children

* The ingestion rate (IgR) of dry formulation is 0.3 grams/day
* The fraction of ai in the formulation is 0.0055. This is based on the formulation with highest percentage of ai (0.55 % ai)
* The body weight of a small child is 15 kg

An MOE of 7 was calculated for a 15 kg child. It is not known the size range of granules of the proposed formulation. If the granules are somewhat small and not easily noticed by a child, the ingestion of 0.3 grams per day may be unlikely.

4.5 Occupational Exposure/Risk

(for detailed discussion of occupational exposure and risk see HED memo of 3/19/01, S. Weiss, DP Barcode: D271985)

4.5.1 Granular Formulation Applied to Outdoor Residential Sites

A granular/pellet type formulation containing 0.55 % ai is being proposed for use on turf and/or gardens to control fire ants. The product can be applied directly to the area around a mound (3 to 4 tablespoons per mound) or broadcast applied at rates up to 1 lb of product per acre.

4.5.1.1 Handlers

The following are the major potential handler exposure scenarios for the application of granular formulation to residential sites:

* Applying Granular Formulation with Hands
* Loading/applying Granular Formulation using Belly Grinder
* Loading/applying Granular Formulation using Push-type Spreader

The following assumptions were used in the handler assessment:

* Maximum application rate of 0.0055 lb ai/acre (1.0 lb product/acre)
* Professional lawn care operators (LCOs) were assumed to treat up to 5 acres per day
* Unit exposures were based on the PHED version 1.1. as presented in the August 1998 PHED Surrogate Exposure Guide and ORETF Study No. OMA001.

The baseline level of PPE for LCOs was assumed to be single layer clothing, no gloves and no respirator. The short- and intermediate-term MOEs calculated for occupational handlers applying granular formulations were well above the target MOE of 1,000 (short/intermediate-term MOEs ranged from 2,800 to 85,000)

4.5.1.2 Postapplication

There are no anticipated postapplication activities that will result in exposure to workers.

4.5.2 Granular Formulation Applied to Forestry Sites

4.5.2.1 Handlers

Volcano Leafcutter Ant Bait is 0.5% granular formulation that will applied directly to ant nests and mounds in pine forests.

The following assumptions were used in the handler assessment:

* The amount of ai handled per day was assumed to range from 0.125 to 1.2 lb ai/day.
* A belly grinder was the most likely method for application to forestry sites.
* Up to 5 acres will be treated per day

The short/intermediate-term MOEs calculated ranged from 93 to 890 at the baseline level and

from 240 to 2,300 at the maximum PPE level (assuming baseline clothing with additional layer of clothing, chemical-resistant gloves, and a respirator).

4.5.2.2 Postapplication

There are no anticipated postapplication activities that will result in exposure to workers.

5.0 Cancer Risk

PFOS has a serum half-life of 1-4 years in humans. It is persistently bioavailable because it is neither excreted nor stored (e.g. in body fat). A single human sulfluramid exposure may elicit toxicity that persists for several years. Additional exposures may cause a cumulation of systemic dose (body burden) and increased toxicity, even if the exposures are spaced months or years apart. Thus, multiple daily exposures, as in a chronic toxicity study, are not a prerequisite for long-term PFOS toxicity. Sulfluramid has not been evaluated for carcinogenicity, so it is impossible to perform a cancer risk assessment at this time. A chronic/carcinogenicity study in rats is required.

6.0 Human Incidence Data

Human incidence data for pesticide products may be useful to indicate trends in exposure especially when they contain active ingredients that have known acute health effects. Based on the protracted serum half-life of the PFOS metabolite, it is possible symptoms of sulfluramid exposure would be delayed and may not be readily associated with the exposure. If there were numerous reports of contact with bait products containing sulfluramid in the available incidence data, there would be some concern that would require additional investigation. However, as expected for a chemical with undetected effects, a cursory analysis of the incidence data conducted by HED for sulfluramid products indicated a relatively low number of reported exposures with adverse reactions. The lack of incidence reports for sulfluramid products does not indicate whether or not children have ingested/contacted sulfluramid in these products. Parents that have observed a child handling or even tampering with a bait station when there are no observable reactions may or may not report such occurrences to poison control centers. Thus, the use of incidence data provides only limited utility for determining whether exposures are occurring on a widespread basis.

7.0 Data Needs/label Requirements

7.1 Toxicology

The following have been identified as data gaps by the HIARC:

1. **Metabolism study in rats** - The HIARC did not have access to any pharmacokinetic data when it first considered sulfluramid on June 27, 2000, so a metabolism study in rats was identified as a significant data gap. A battery of pharmacokinetic studies was submitted in late January, 2001 which may satisfy this data gap. They were received too late to allow for a thorough review. Nevertheless, a cursory review confirms that sulfluramid exposure results in systemic retention that can span many years. This poses a unique risk assessment concern. Because the adequacy of these data cannot be assessed at this time, the Agency reserves the right to request further pharmacokinetic studies in the future.

2. **Dermal absorption study** - Although this is a data gap, the HIARC determined that an absorption study is not required because it would not provide additional useful information.

3. **Chronic/carcinogenicity study in rats** - Sulfluramid's chronic toxicity and carcinogenic potential are unknown. Requirements for chronic and carcinogenicity studies had previously been waived on the understanding that bait stations preclude human exposure. It is now recognized that human exposure can result from all sulfluramid uses (including bait stations), and that even a single dose of exposure to sulfluramid may result in long-term systemic exposure. Thus, a chronic/carcinogenicity study in rats is required.

   Given the extremely long serum half-life of the degradate, PFOS, the registrant is advised to consult with the Health Effects Division and with the Cancer Assessment Review Committee (CARC) in designing a study that reflects sulfluramid's incidental exposure scenarios.

   A mouse carcinogenicity study is not required.

7.2 Exposure

No additional exposure data are required.

Attachments:
1. Summary of MOEs for Sulfluramid Products
2. Acute Dietary NOAELs and Endpoints for Pesticides Used in Bait Stations
3. Comparative MOEs for different bait stations
4. 3/02/01 HIARC Report
5. ORE Assessment

cc: RAB2 RF, Y. Donovan, J. Whalan, S. Weiss.

Attachment 1- Summary of MOEs for Sulfluramid Products						
Exposure Scenario		Occupational or Non-Occupational	Exposure Route	Short-term MOE		Intermediate-term MOE
Handler	Applying Granular with Hands (Turf-grass/gardens)	Non-Occupational	Dermal + Inhalation	3,000		NA
	Loading/applying Granular using Belly Grinder (Turf-grass/gardens)	Non-Occupational	Dermal + Inhalation	5,600		NA
	Loading/applying Granular Formulation using Push-type Spreader (Turf-grass/gardens)	Non-Occupational	Dermal + Inhalation	850,000		NA
	Applying Granular with Hands (Turf-grass/gardens)	Occupational	Dermal + Inhalation	Baseline	2,800	2,800
	Loading/applying Granular using Belly Grinder (Turf-grass/gardens)	Occupational	Dermal + Inhalation	Baseline	20,000	20,000
	Loading/applying Granular Formulation using Push-type Spreader (Turf-grass/gardens)	Occupational	Dermal + Inhalation	Baseline	85,000	85,000
	Loading/applying Granular Formulation using Belly Grinder (Forestry)	Occupational	Dermal + Inhalation	**Baseline**	**93 to 890**	**93 to 890**
				Max PPE	**240 to 2,300**	**240 to 2,300**
Postapplication	**Children's Exposure to Bait Stations**	Non-Occupational	**Oral**	**0.6**		NA
	Hand-to-Mouth Exposure from treated Turf-grass	Non-Occupational	Oral	9,8700		5,500
	Adults on residential Turf-grass	Non-Occupational	Dermal	20,000		40,000
	Children on residential Turf-grass	Non-Occupational	Dermal	14,000		28,000
	Children's Incidental Ingestion of Granules/Pellets	Non-Occupational	**Oral**	7		NA

ATTACHMENT 2 - Acute Dietary NOAELs and Endpoints for Pesticides Used in Bait Stations

Insecticide [PC Code]	Acute Dietary NOAEL (mg/kg)	Endpoint	UF	Study
Abamectin [122804]	0.25	Mydriasis seen at week 1 of dosing.	100	Chronic toxicity - Dog
Boric acid [011001]	Not established[1]	–	–	–
Chlorpyrifos [059101]	0.5	40% plasma cholinesterase inhibition at peak time of inhibition (6 hours post exposure) at 1 mg/kg. Significant RBC ChE inhibition at 1.5 mg/kg. 4 hours post exposure	100	Blood Time Course Study (Mendrala and Brzak 1998) with support from Zheng et al. (2000)
Fipronil [129121]	2.0 mg/kg	LOAEL = 12 mg/kg based on decreases in locomotor activity as well as decreases in hindlimb splay and rectal temperature.	100	Acute neurotoxicity study - rat
Hydramethylnon [118401]	--	Hydramethylnon is a non-food use chemical. There is no reliable endpoint that can be attributed to an acute exposure. An acute dietary risk assessment is not required. (TES document; 1997)	–	–
Propoxur [047802]	0.15 mg/kg [Presumably a LOAEL]	Occurrence of 40% RBC ChE inhibition following five dosings of 0.15 mg/kg at half-hour intervals. The rationale behind dose and UF selection was not explained in the TES document (dated, April 4, 1996). The application of an extra UF of 3 suggests that 0.15 mg/kg is a LOAEL.	30	Acute oral toxicity - human *Bull. Wld. Hlth. Org.* 1971, *44*, 241-249.
Sulfluramid [128992]	There is no endpoint because there is no potential for acute dietary exposure at this time.[2]	--	--	–

[1] Boric acid has not been considered by the HIARC. A1995 RfD Committee document mentions a rat developmental NOAEL of 9.6 mg/kg/day.

[2] Sulfluramid does not have an acute dietary endpoint, but the HIARC selected a short-term oral incidental endpoint of 0.8 mg/kg/day based on reduced mean maternal body weight, mean body weight gain, and reduced food consumption at the Maternal LOAEL of 3.3 mg/kg/day. This NOAEL was used to calculate risk to children consuming the contents of a single bait station. The target MOE is 300.

ATTACHMENT 3 - Comparison of Other Pesticides Used in Bait Stations

	g product/ bait	% ai	mg ai/bait	Dose for 15 kg Child (mg/kg/day)	Observable Adverse Effect Level	MOE for 15 kg Child
sulfluramid	2.1	1	21	1.4	0.8	0.6
abamectin	1.5	0.05	0.75	0.05	0.25	5.0
boric acid	10.1	70	7070	471	not established	
chlorpyrofos (current)			150	10	0.5	0.05
chlorpyrofos (proposed)			5.7	0.4	0.5	1.3
fipronil	2.75	0.03	0.83	0.055	2	36
hydramethethylon	1	0.05	0.5	0.03	not established	
propoxur	2	2	40	2.67	0.15	0.06

Attachment

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

014491

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: March 2, 2001

MEMORANDUM

SUBJECT: **Sulfluramid** - Report of the Hazard Identification Assessment Review Committee.

FROM: John E. Whalan, Toxicologist 3-5-01
RAB2
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Elizabeth Doyle, Co-Chair E.A. Doyle 3/8/01
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Steven Weiss, Risk Assessor
Registration Action Branch 2
Health Effects Division (7509C)

PC Code: 128992

On June 27, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for sulfluramid with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to sulfluramid was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The HIARC met again on February 27, 2001 to review the recommendation of the Risk Assessment Review Committee (RARC) that all endpoints and target MOEs be reconsidered. This document is a summation of the HIARC's decisions at both meetings.

Committee Members in Attendance on June 27, 2000:

Members present were: Elizabeth Doyle, Pamela Hurley, Tina Levine, Elizabeth Mendez, Yung Yang, Jess Rowland, Brenda Tarplee (Executive Secretary), and Jonathan Chen.

Member(s) *in absentia*: William Burnam, Ayaad Assaad, and David Nixon.

Data evaluation prepared by: John E. Whalan, RAB2

Also in attendance were: Donna Davis (RAB2) and Linda Gerber (RD)

Committee Members in Attendance on February 27, 2001:

Members present were: Elizabeth Doyle, Pamela Hurley, Elizabeth Mendez, Ayaad Assaad, Yung Yang, Jess Rowland, Brenda Tarplee (Executive Secretary), and Jonathan Chen.

Member(s) *in absentia*: William Burnam and David Nixon.

Data evaluation prepared by: John E. Whalan, RAB2

Also in attendance was: George LaRocca (RD)

Data Evaluation / Report Presentation

John Whalan 3-5-01

John E. Whalan
Toxicologist

1. INTRODUCTION

On June 27, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for sulfluramid with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. Two exposure scenarios were considered by the HIARC–child exposure to ant and roach bait stations in the home, and worker exposure to loose bait (Volcano®) during reforestation. The potential for increased susceptibility of infants and children from exposure to sulfluramid was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996.

A risk assessment that considered bait station exposure to children and loose granule exposure to forestry workers was scheduled for August 10, 2000 review by the Risk Assessment Review Committee (RARC). RAB2 has since been asked to consider two additional exposure scenarios. On August 9, 2000, Registration Division asked RAB2 to include in its risk assessment a section 3 request for homeowner use of loose sulfluramid bait on residential lawns to kill fire ants. During a December 21, 2000 meeting with sulfluramid registrants, Registration Division asked RAB2 to also include termite bait stations.

A revised risk assessment was presented to the Risk Assessment Review Committee (RARC) on February 15, 2001. The RARC contested the HIARC's endpoints and target MOEs and recommended that they be reconsidered. The RARC made the following suggestions:

1. Although inhalation exposure to sulfluramid is unlikely, short and intermediate-term inhalation endpoints should be selected because endpoints are routinely selected for all granular products.

2. Consider using the Parental NOAEL from the reproductive toxicity study (0.45 mg/kg/day) for the short-term oral, dermal, and inhalation endpoints instead of the Maternal NOAEL from the rat developmental toxicity study (0.8 mg/kg/day). The rationale is that protracted systemic exposure to PFOS, even from a single exposure, is better represented by a study of longer duration than the developmental toxicity study.

3. Consider using the Developmental LOAEL of 0.3 mg/kg/day from the special study in rabbits for all oral, dermal, and inhalation endpoints because it is the most conservative value in any study.

4. Consider adding a 10x uncertainty factor (UF) to account for the lack of chronic and carcinogenicity studies, and to account for long-term exposure that can result from systemic retention.

When sulfluramid was first considered by the HIARC, an intermediate-term incidental oral endpoint was not needed because it is highly unlikely that a child would consume the contents of bait stations beyond a short-term duration. With the addition of loose baits applied to residential lawns in the risk assessment, however, an intermediate-term incidental oral endpoint is needed. Further, the HIARC was asked to reconsider how to deal with the lack of chronic toxicity and/or carcinogenicity studies with which to assess long-term hazard.

Sulfluramid was considered again by the HIARC on February 27, 2001. This document is a summation of the HIARC's decisions at both meetings.

Sulfluramid (N-ethyl perfluorooctanesulfonamide; N-EtFOSA; GX-071, CAS# 4151-50-2) is a slow acting, but highly potent palatable insecticide that is effective on insects demonstrating social interactions. Its mode of action is unknown. Sulfluramid is registered for use in a variety of termite, ant, and roach bait stations. There is a 24c (state registration) in Texas for Volcano™ Leafcutter Ant Bait use in pine reforestation. A section 3 registration is being considered for application of loose granules onto residential lawns to control fire ants.

A major concern with sulfluramid is the likelihood that children may be poisoned if they gain access to the contents of a bait station or consume loose bait scattered onto a residential lawn. Although sulfluramid does not meet the conventional acute endpoint triggers for child-resistant packaging (CRP) requirements, products containing sulfluramid were put into CRP due to concerns raised by a developmental study in rats. Because there are no food uses for sulfluramid, a number of toxicity studies were waived, and it had not been considered by the RfD, TES, or HIARC committees. Consequently, its toxicity is not well characterized.

In the mid-90's, it was determined that one of the registrant's bait stations was inadequate. This was because 1) the bait fell out of intact bait stations and 2) openings in the bait stations were large enough for little fingers to gain access. The company subsequently made changes to these stations. With the exception of Volcano™ Leafcutter Ant Bait, all registered products containing sulfluramid as the active ingredient are currently in CRP. It is important to note that the CRP designation means that a minimum of 80% of the children tested cannot access the contents of the bait station (as mandated by FIFRA 25 (c)(3)). Conversely, up to 20% of the children tested can access the contents.

Sulfluramid is a potential concern because it is an analog of perfluorooctanesulfonate (PFOS). On May 16, 2000, Minnesota, Mining, & Manufacturing (3M) notified the Office of Pollution Prevention and Toxics (OPPT) of its plan for phasing out the manufacture of products based on perfluorooctanyl chemistry. Human exposure to PFOS and its analogs comes mostly through indirect food exposure. They are used as defoamers in vegetable cooking oils, and as surfactants to impart oil and water resistance to paper and packaging used for fast food, pizza, and microwave popcorn. PFOS is also a component of three Scotchgard® products.

According to Bill Coyne, Senior Vice President for Research and Development at Minnesota Mining & Manufacturing (3M), "We have tested [PFOS] pretty widely--not only in this country but in other countries, as well--and it's found in very low levels everywhere we test. It is persistent and pervasive, and that is the reason we don't want to continue to add it to the environment." PFOS and its analogs are being lumped with other persistent and pervasive compounds such as DDT and PCB. Tens of ppb levels have been found in human serum of nonoccupationally exposed employees. It has been found in the livers of control rats fed diets containing fish meal.

In rats, sulfluramid is metabolized to PFOSA and then to PFOS which accumulates primarily in the liver. PFOS cannot be further metabolized because of the inherent stability of perfluorinated anions.[1] PFOS is resistant to physical, chemical, and biological degradation, and can only be degraded by combustion.[2] Excretion via the urine and feces is extremely slow. There is also considerable enterohepatic recirculation of PFOS. Essentially, sulfluramid toxicity is PFOS toxicity.

Preliminary findings in humans suggest that the PFOS serum half-life is in the range of 1-4 years, so dose cumulation may approach 100%. A single sulfluramid exposure to a child or adult results in a PFOS body burden that persists for several years, and any subsequent exposure increases the body burden, even if the exposure occurs months or years later.

PFOS caused the death of rat pups in a reproductive toxicity study. The Reproductive NOAEL for PFOS is 0.1 mg/kg/day, and the Reproductive LOAEL is 0.4 mg/kg/day based on decreased body weight and food consumption in parental animals; significant increases in pre-implantation losses and number of stillborn pups, reductions in number of implant sites, litter size, pup viability, growth, and survival.

Sulfluramid also caused rat pup death in a reproduction study. The Reproductive NOAEL for sulfluramid is 0.45-0.53 mg/kg/day and the Reproductive LOAEL is 1.34-1.65 mg/kg/day, so it is about one-fifth as potent as PFOS for reproductive effects.

2. HAZARD IDENTIFICATION

2.1 Acute Reference Dose (RfD)

An acute dietary risk assessment is not required because there is no potential for acute dietary exposure at this time.

2.2 Chronic Reference Dose (RfD)

A chronic dietary risk assessment is not required because there is no potential for chronic dietary exposure at this time.

2.3 Occupational/Residential Exposure

2.3.1 Short-Term (1-7 days) Incidental Oral Exposure

Study Selected: Developmental Toxicity in Rats §870.3700

MRID No.: 41799409

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[1] 3M. **Perfluorooctane Sulfonate: Current Summary of Human Sera, Health and Toxicity Data.** January 21, 1999. Page 34.

[2] 3M. **Sulfonated Perfluorochemicals in the Environment: Sources, Dispersin, Fate and Effects.** March 1, 2000. Page 39

Executive Summary: Since the average test article administered to the low-, mid, and high-dose group dose were -18%, -17%, and -13% less than the nominal concentrations of 1, 4, 16 mg/kg/day, the actual dose levels administered to rats were 0.8, 3.3, and 13.3 mg/kg/day for the low-, mid-, and high-dose groups, respectively.

According to the results of this study, administration of sulfluramid (96.6% linear and 3.4% branched isomeric mixture; Lot no. #AN-90247) at dose levels of 0.8, 3.3, and 13.3 mg/kg/day from day 6 to day 15 of gestation reduced the mean maternal body weight and mean body weight gain in the 3.3 and 13.3 mg/kg/day dose groups, and reduced food consumption in the 13.3 mg/kg/day dose group. Treatment-related maternal toxicity effects, flaccid body tone and piloerection, were noted in the 13.3 mg/kg/day group. A dose-related trend of increased incomplete ossification of the 3rd and 4th sternebrae and skull, and an enlarged fontanelle were noted in the high-dose group. The reduced fetal weights and increased incidence of cleft palate (3.5% of fetuses and 16.7% of litters in this study versus 0.02% fetuses in the fetal historical control) in the 13.3 mg/kg/day are other developmental toxicity effects.

The maternal toxicity NOAEL is determined to be 0.8 mg/kg/day, and the maternal toxicity LOAEL is 3.3 mg/kg/day based on reduced mean maternal body weight, mean body weight gain and the reduced food consumption. The developmental toxicity NOAEL is 3.3 mg/kg/day and the developmental toxicity LOAEL is 13.3 mg/kg/day based on reduced fetal weights and increased incidence of cleft palate, incomplete ossification of the 3rd and 4th sternebrae and skull, and an enlarged fontanelle.

Dose and Endpoint for Risk Assessment: The Maternal NOAEL is 0.8 mg/kg/day based on reduced mean maternal body weight, mean body weight gain, and reduced food consumption at the Maternal LOAEL of 3.3 mg/kg/day. The target MOE in a risk assessment is 300 which includes an extra UF of 3 to account for the unknown sequelae of systemic retention and enterohepatic recirculation.

Comments about Study/Endpoint: This endpoint should be used to quantify the risk of a child eating the contents of a bait station or consuming loose bait scattered on a residential lawn on one to seven days. The decrease in maternal body weight and body weight gain occurred during 10 days of exposure, which resembles a short-term exposure (1-7 days).

The HIARC considers these endpoints to be protective of dose cumulation because systemic retention is similar whether exposure consists of a few high doses or numerous low doses. These endpoints are supported by comparable total doses in the subchronic feeding study in dogs and the 2-generation reproductive toxicity study in rats.

The subchronic feeding study in dogs and the special study of pre-and postnatal development, maturation, and fertility in rabbits were also considered in the selection of this endpoint. The NOAEL in the dog study was 0.825 mg/kg/day based on the increased epididymal and testicular lesions at the LOAEL of 2.5 mg/kg/day. The Post-Weaning Developmental NOAEL in the special rabbit study was 1.0 mg/kg/day based on the fact

that slight delays in preputial separation and vaginal opening, as well as a slight decrease in normal sperm, cannot be ruled out at 3.0 mg/kg/day. Although the testicular effects in dogs are a primary concern, the rat developmental NOAEL of 0.8 mg/kg/day is considered protective.

The HIARC also considered using the developmental LOAEL of 0.3 mg/kg/day (lowest dose tested) in the special rabbit study based on decreased viability and lactation indices. These endpoints were not selected because they were most likely a consequence of *in utero* exposure, and therefore not relevant to oral exposure in children.

2.3.2 Intermediate-Term (7 Days to Several Months) Incidental Oral Exposure

Study Selected: 2-Generation Reproductive Toxicity in Rats §870.3800

MRID No.: 44341901

Executive Summary: In a 2-generation reproduction study (MRID 44341901) sulfluramid (99.4% a.i.) was administered in the diet to 30 Sprague Dawley Crl:CD BR rats/sex/dose at dose levels of 0, 2, 6, or 18 ppm (0, 0.15-0.18, 0.45-0.53, and 1.34-1.65 mg/kg/day). Exposure to F_0 rats (30/sex/dose) began at 6 weeks of age and lasted for 10 weeks prior to mating to produce F_1 pups. Upon weaning, F_1 pups (30/sex/dose) selected to become parents of the F_2 generation were fed sulfluramid in test diets at the same concentration their dam received. F_1 rats were given test diets for 10 weeks prior to mating. All rats were mated on a 1:1 ratio, and each generation was mated once.

There were no treatment-related mortalities or clinical signs of toxicity in either sex or generation. Body weights were comparable among the groups [both sexes] of F_0 rats throughout the premating period, but there were slight [non-significant] decreases in body-weight gains [males ↓6%-11%; females ↓5%-11%] at the 18 ppm dose level compared to control. During the first week of gestation, a slight decrease [↓5%] in body weight was noted at 18 ppm, and decreased body-weight gains were observed over the first 4 days of both gestation [↓17%] and lactation [↓48%] at this dose level. The mid-dose F_0 dams also displayed a significant decrease in body-weight gain [↓43%] during days 1-4 of lactation. At 18 ppm, treatment-related reductions in mean body weights of F_1 males (↓6%-12%) and females (↓9%-13%) were observed throughout the premating period. Reduced body-weight gains were also observed in 18 ppm F_1 females (↓17%-56%) during the premating period. Body weights of 18 ppm F_1 females remained reduced throughout gestation (↓10%-13%) and lactation (↓7%-12%). At necropsy, treatment-related decreases in terminal body weight were observed in both F_1 males and females (↓6%-12%). Both sexes of F_1 rat at the 18 ppm dose level displayed decreased pituitary and adrenal weights, and increased relative (to body) liver weights (↑8%-16%) were observed in the 18 ppm males and females of both generations. There were no treatment-related gross necropsy or microscopic findings for any treatment group in either the F_0 or F_1 generation.

Sulfluramid did not exhibit any treatment-related effects on reproductive parameters or function in rats administered dose levels up to 18 ppm. Mating, fertility, and gestation indices, days between pairing and coitus, regularity and duration of estrous, gestation length, parturition, number and size of litters, ovarian follicle counts, and spermatogenic endpoints [testicular and epididymal sperm numbers, sperm production rate, sperm motility, and sperm morphology] were not altered by treatment.

Neonatal toxicity of sulfluramid was observed at 18 ppm. F_1 and F_2 pup body weights were reduced in the 18 ppm groups throughout lactation (↓7%-15%). An increase in the number of pups dying between birth and postnatal day 4, with a resulting reduction in postnatal survival (% per litter), was observed in the 18 ppm F_2 pups (22 treated died vs 11 controls). There were slight delays in balanopreputial separation in the F_1 males and in vaginal opening in F_1 females at the high-dose level compared to the control and other treatment groups. There were no other treatment-related effects of sulfluramid on the indicators of physical and functional development and behavioral responses monitored in the selected F_1 pups.

The LOAEL for parental systemic toxicity is 18 ppm [1.34-1.65 mg/kg/day], based on reductions in body weight and body-weight gains, decreased adrenal [F_1 males and females] and pituitary [F_1 females] weights, and slightly increased liver [F_0 females] weights. The parental systemic NOAEL is 6 ppm [0.45-0.53 mg/kg/day].

The reproductive/offspring LOAEL is 18 ppm [1.34-1.65 mg/kg/day], based on reduced F_1 and F_2 pup body weights, reduced F_2 pup postnatal survival, and slightly delayed physical development of both sexes [slight delays in balanopreputial separation in the F_1 males and in vaginal opening in F_1 females]. The reproductive/offspring NOAEL is 6 ppm [0.45-0.53 mg/kg/day].

Dose/Endpoint for Risk Assessment: The Parental NOAEL is 0.45 mg/kg/day based on reductions in body weight and body-weight gains, decreased adrenal and pituitary weights, and slightly increased liver weights at the LOAEL of 1.34 mg/kg/day. The target MOE in a risk assessment is 300 which includes an extra UF of 3 to account for the unknown sequelae of systemic retention and enterohepatic recirculation.

Comments about Study/Endpoint: The treatment regimen in this study simulates the exposure period of concern (7-days to several months).

The HIARC also considered using the developmental LOAEL of 0.3 mg/kg/day (lowest dose tested) in the special rabbit study based on decreased viability and lactation indices. These endpoints were not selected because they were most likely a consequence of *in utero* exposure, and therefore not relevant to oral exposure in children.

2.3.3 Dermal Absorption

Dermal Absorption Factor: In the absence of a dermal absorption study, dermal absorption is estimated to be 1% based on a comparison of oral (special rabbit developmental toxicity study) and dermal (rabbit 21-day dermal toxicity) LOAELs:

$$\frac{\textbf{3.0 } \textit{mg/kg/day (Rabbit Maternal Oral LOAEL)}}{\textbf{300 } \textit{mg/kg/day (Rabbit 21-Day Dermal LOAEL)}} = \textbf{0.01} = \textbf{1\%}$$

By comparison, oral absorption of PFOS in rats is at least 95% over 24 hours. Occluded dermal PFOS dosings of rats and rabbits revealed traces of fluoride in rats serum, but no detectable levels in rabbit livers. If sulfluramid is pharmacokinetically similar to PFOS, a dermal absorption factor of 1% is probably conservative.

2.3.4 Short-Term Dermal (1-7 days) Exposure

Study Selected: Special Study - Gavage Pre- and Postnatal Development Maturation, and Fertility in Rabbits §870.xxxx

MRID No.: 44257106

Executive Summary: In a special developmental toxicity study (MRID 44257106) designed to determine the effect on sexual development of male rabbits after exposure to sulfluramid *in utero* during late gestation and potentially during nursing on postnatal days 1 through 42, sulfluramid (99.4% a.i.) in 1% carboxymethyl cellulose/0.1% polysorbate 80 was administered orally by gavage to 22 timed pregnant, litter-experienced, New Zealand White rabbits (9 months of age)/dose at nominal dose levels of 0, 0.3, 1.0, or 3.0 mg/kg/day. Exposure to the litter-experienced F0 does lasted from days 19 through 28 of gestation. Upon weaning (postnatal day 42), F_1 pups (22/sex/dose) were selected for evaluation of developmental landmarks of sexual maturity, including balanopreputial separation, vaginal perforation, spermatogenesis, and reproductive organ weights and histopathology.

There were no treatment-related effects noted on mortality, clinical signs, body weight, gross pathology, organ weights, or histopathological parameters in the treated maternal (F0) groups. Body-weight gain was reduced [42% of control] during the last 5 days of gestation at the high-dose level compared to the control and other treatment groups, and the overall body-weight gain during gestation was reduced [82% of control] at this dose level as well, although statistical significance was not attained. Food consumption was decreased at the high-dose level [3.0 mg/kg/day] throughout lactation (1-42 days; ↓23%) compared to the control but comparable to the control at the lower dose levels throughout the study.

There was a dose-related increase in the number of F_1 pups that were stillborn or found dead on postnatal day 0 (PND 0), a dose-related increase in the mean stillbirth litter size,

and a dose-related decrease in the live birth index. The lowest gestation survival index was noted at the high dose [81.8%] compared with the control and other treatment groups [95.5-100%]. However, the mean live litter size was only slightly reduced in the high-dose group compared to the controls (7.2 treated vs 8 controls). There was a dose-related increase in the number of dead pups during lactation (PND 1-42) [50, 71, 103, and 138] and a dose-related increase in the number of total litter losses [10%, 18%, 30%, and 55%] in the 0, 0.3, 1.0, and 3.0 mg/kg/day groups, respectively.

There were dose-dependent, statistically-significant [at all dose levels], decreases in the viability and lactation indices, with the majority of the pup deaths occurring during PND 1 and PND 7. The viability indices in the high-dose group were lower than the controls from the first day of lactation (PND 1; 82% treated vs 96.4% controls) to the last (PND 42; 39.1% treated vs 84.2% controls), although no deaths occurred in this group after PND 7. In the 1.0 mg/kg/day dose group, lower viability indices were observed from PND 4 (79% treated vs 89.9% controls) through to PND 42 (58% treated vs 84.2% controls). Similarly, in the 0.3 mg/kg/day dose group, lower viability indices were observed from PND 7 (77.3% treated vs 89.9% controls) through to PND 42 (69.2% treated vs 84.2%). The lactation indices in the 0, 0.3, 1.0, and 3.0 mg/kg/day groups were 87.5%, 73.9%, 59.7%, and 47.6%, respectively.

There were no treatment-related differences from controls in clinical observations, mean body weights/body weight gains, gross pathologic findings, organ weights, and histopathological findings in the F_1 generation.

There were no apparent, treatment-related, effects on the postweaning developmental parameters in any of the F_1 group rabbits examined (22/sex/dose). No significant differences in achievement of balanopreputial separation [days 71.73, 71.76, 72.95, 72.32] or vaginal perforation [days 29.07, 29.37, 30.06, 29.38 in the control, low-, mid-, and high-dose groups, respectively] were observed among the groups. All male pups were observed with balanopreputial separation by PNDs 79-88 and all females had vaginal opening by PNDs 38-41. However, due to the fact that the sample at the high-dose level for both sexes was truncated; i.e., there were half the number of litters available from which to select the pups and for the females the number of female pups available for assessment [24] was less than half the number assessed in the control [59] and other treatment groups [62 and 53], *no definitive statement regarding the lack of an effect on these parameters at the high-dose level can be made.* For both sexes, similar delays [slight] in preputial separation and vaginal opening were observed in the 2-generation reproduction study in rats. Similarly, during four weeks of spermatogenesis assessment, there were no treatment-related differences observed in mean number of ejaculated sperm, ejaculate volumes, percentages of motile sperm, numbers of ejaculated motile sperm, and morphology of ejaculated sperm among the F_1 males examined and their concurrent controls. However, due to the limited number of litters from which the high-dose males were taken, a definitive statement regarding a lack of effect at this dose level also cannot be made.

The maternal toxicity LOAEL is 3.0 mg/kg/day, based on decreased body-weight gain during gestation and decreased food consumption during lactation. The maternal toxicity NOAEL is 1.0 mg/kg/day.

The developmental toxicity LOAEL is 0.3 mg/kg/day, based on decreased viability and lactation indices. There is no developmental toxicity NOAEL.

The NOAEL for post-weaning developmental parameters is 1.0 mg/kg/day, based on the fact that slight delays in preputial separation and vaginal opening, as well as a slight decrease in normal sperm, cannot be ruled out at 3.0 mg/kg/day.

Dose and Endpoint for Risk Assessment: The oral Developmental LOAEL is 0.3 mg/kg/day based on decreased viability and lactation indices. The dose used in a risk assessment is the Developmental LOAEL adjusted by a 1% dermal absorption factor. The target MOE in a risk assessment is 1000 which includes extra UFs of 3 each to account for a.) the unknown sequelae of systemic retention and enterohepatic recirculation, and b.) the use of a LOAEL.

Comments about Study/Endpoint: Although a 21-day dermal toxicity study was available, the HIARC selected an oral LOAEL from the special study in order to protect pregnant workers 13-50 years due to concerns over developmental effects (decreased viability and lactation) seen in rabbits following *in utero* and postnatal exposure.

2.3.5 Intermediate-Term Dermal (7 Days to Several Months) Exposure

Study Selected: Special Study - Gavage Pre- and Postnatal Development Maturation, and Fertility in Rabbits §870.xxxx

MRID No.: 44257106

Executive Summary: See Short-Term Dermal (1-7 days) Exposure

Dose and Endpoint for Risk Assessment: The oral Developmental LOAEL is 0.3 mg/kg/day based on decreased viability and lactation indices. The dose used in a risk assessment is the Developmental LOAEL adjusted by a 1% dermal absorption factor. The target MOE in a risk assessment is 1000 which includes extra UFs of 3 each to account for a.) the unknown sequelae of systemic retention and enterohepatic recirculation, and b.) the use of a LOAEL.

Comments about Study/Endpoint: Although a 21-day dermal toxicity study was available, the HIARC selected an oral LOAEL from the special study in order to protect pregnant workers 13-50 years due to concerns over developmental effects (decreased viability and lactation) seen in rabbits following *in utero* and postnatal exposure.

2.3.6 Long-Term Dermal (Several Months to Life-Time) Exposure

Long-term dermal exposure to sulfluramid is not expected.

2.3.7 Short-Term Inhalation (1-7 days) Exposure[3]

Study Selected: Special Study - Gavage Pre- and Postnatal Development Maturation, and Fertility in Rabbits §870.xxxx

MRID No.: 44257106

Executive Summary: See Short-Term Dermal (1-7 days) Exposure

Dose and Endpoint for Risk Assessment: The oral Developmental LOAEL is 0.3 mg/kg/day based on decreased viability and lactation indices. The dose used in a risk assessment is the Developmental LOAEL extrapolated to an estimated inhalation equivalent concentration. Considering the pharmacokinetics of sulfluramid, it is likely that toxicity by the oral and inhalation routes is similar, so an oral:inhalation absorption ratio of 1 should be used during route extrapolations. The target MOE in a risk assessment is 1000 which includes extra UFs of 3 each to account for a.) the unknown sequelae of systemic retention and enterohepatic recirculation, and b.) the use of a LOAEL.

Comments about Study/Endpoint: The only inhalation toxicity study available, an acute study, is inadequate for endpoint selection. The HIARC selected an oral LOAEL from the special study in order to protect pregnant workers 13-50 years due to concerns over developmental effects (decreased viability and lactation) seen in rabbits following *in utero* and postnatal exposure. There is no way of knowing whether sulfluramid causes portal-of-entry effects in the respiratory tract.

2.3.8 Intermediate-Term Inhalation (7 days - Several Months) Exposure

Study Selected: Special Study - Gavage Pre- and Postnatal Development Maturation, and Fertility in Rabbits §870.xxxx

MRID No.: 44257106

Executive Summary: See Short-Term Dermal (1-7 days) Exposure

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[3] Aerosol inhalation of the granular formulations is highly unlikely due to the size of the granules and their resistance to attrition. Vapor exposure is extremely unlikely for all formulations because sulfluramid has a vapor pressure of 5.7×10^{-8} kPa (4.3×10^{-7} mmHg) at 25°C. Nevertheless, short and intermediate-term endpoints were selected because endpoints are routinely selected for all granular products.

Dose and Endpoint for Risk Assessment: The oral Developmental LOAEL is 0.3 mg/kg/day based on decreased viability and lactation indices. The dose used in a risk assessment is the Developmental LOAEL extrapolated to an estimated inhalation equivalent concentration. Considering the pharmacokinetics of sulfluramid, it is likely that toxicity by the oral and inhalation routes is similar, so an oral:inhalation absorption ratio of 1 should be used during route extrapolations. The target MOE in a risk assessment is 1000 which includes extra UFs of 3 each to account for a.) the unknown sequelae of systemic retention and enterohepatic recirculation, and b.) the use of a LOAEL.

Comments about Study/Endpoint: The only inhalation toxicity study available, an acute study, is inadequate for endpoint selection. The HIARC selected an oral LOAEL from the special study in order to protect pregnant workers 13-50 years due to concerns over developmental effects (decreased viability and lactation) seen in rabbits following *in utero* and postnatal exposure. There is no way of knowing whether sulfluramid causes portal-of-entry effects in the respiratory tract.

2.3.9 Long-Term Inhalation (Several Months to Life-Time) Exposure

Long-term inhalation exposure to sulfluramid is not expected.

2.3.10 Margins of Exposure for Occupational/Residential Risk Assessments

The target MOE in a risk assessment is 300 for short and intermediate-term incidental oral exposure, and 1000 for short and intermediate-term dermal and inhalation exposures. All target MOEs include an UF of 3 to account for the unknown sequelae of systemic retention and enterohepatic recirculation.

2.4 Recommendation for Aggregate Exposure Risk Assessments

Dermal and inhalation risk assessments may be aggregated because they are based on the same endpoints (decreased viability and lactation indices in an oral study). Oral ingestion should not be included in the aggregation because the endpoints are different (decreased body weight, body weight gain, and food consumption in an oral study).

3. CLASSIFICATION OF CARCINOGENIC POTENTIAL

3.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

A chronic study has not been performed in rats.

3.2 Carcinogenicity Study in Mice

A chronic study has not been performed in mice.

3.3 Classification of Carcinogenic Potential

Sulfluramid has not been evaluated for carcinogenicity. Long-term human exposure to sulfluramid is not expected to come from multiple daily exposures, but rather from one or a few exposures that are retained in the body over many years and recirculated enterohepatically.

4. MUTAGENICITY

Gene Mutation in Bacteria (Ames Assay)

The test article was negative for increasing revertants (i.e., nonmutagenic) in the standard set of five Ames strains of *Salmonella typhimurium* treated up to 10,000 μg/plate (a which dose heavy precipitation occurred), both in the absence and presence of metabolic activation. MRID No. 40863201.

Sister Chromatid Exchange in Chinese Hamster Ovary Cells

Under the conditions of this assay, GX-071 was found to be negative for induction of sister chromatid exchange in Chinese Hamster ovary cells, both with and without metabolic activation, at concentrations up to 1000 μg/mL. However, this top concentration did not result in at least a 50% reduction in the second mitosis, thus indicating that a higher dose should have been utilized. The study should be repeated using higher dose levels. MRID No. 40612614.

ADDENDUM: Corrected tables and information on solubility have been provided, so the study was upgraded to Acceptable. MRID No. 40915801

Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay

Under the conditions of the assay, four doses of sulfluramid (GX 071) (05, 0.75, 1.0, and 1.25 μg/mL) did not induce an appreciable increase in the net nuclear grain counts of treated rat hepatocytes. Cytotoxicity was clearly demonstrated at concentrations ≥1.5 μg/mL. It is concluded, therefore, that sulfluramid (GX 071) is not genotoxic in the primary rat hepatocyte unscheduled DNA synthesis (UDS) assay. However, the study was incomplete because information on test material purity and analytical data to verify actual test material concentrations used in the assay were not reported. MRID No. 41251002

ADDENDUM: Purity data have been provided, so the study was upgraded to Acceptable. MRID No. 41505102

5. FQPA CONSIDERATIONS

5.1 Adequacy of the Data Base

Developmental and reproductive hazard have been adequately characterized by developmental toxicity studies in rats and rabbits, a reproductive toxicity study in rats, and a special study of the effects of sulfluramid on pre-and postnatal development, maturation, and fertility in the rabbit. No neurotoxicity studies have been conducted.

5.2 Neurotoxicity

No neurotoxicity studies have been conducted. Nevertheless, there is no evidence of neurotoxicity in any of the available toxicity studies.

5.3 Developmental Toxicity

Developmental Toxicity in Rats

Since the average test article administered to the low-, mid, and high-dose group dose were -18%, -17%, and -13% less than the nominal concentrations of 1, 4, 16 mg/kg/day, the actual dose levels administered to rats were 0.8, 3.3, and 13.3 mg/kg/day for the low-, mid-, and high-dose groups, respectively.

According to the results of this study, administration of sulfluramid (96.6% linear and 3.4% branched isomeric mixture; Lot no. #AN-90247) at dose levels of 0.8, 3.3, and 13.3 mg/kg/day from day 6 to day 15 of gestation reduced the mean maternal body weight and mean body weight gain in the 3.3 and 13.3 mg/kg/day dose groups, and reduced food consumption in the 13.3 mg/kg/day dose group. Treatment-related maternal toxicity effects, flaccid body tone and piloerection, were noted in the 13.3 mg/kg/day group. A dose-related trend of increased incomplete ossification of the 3rd and 4th sternebrae and skull, and an enlarged fontanelle were noted in the high-dose group. The reduced fetal weights and increased incidence of cleft palate (3.5% of fetuses and 16.7% of litters in this study versus 0.02% fetuses in the fetal historical control) in the 13.3 mg/kg/day are other developmental toxicity effects.

The maternal toxicity NOAEL is determined to be 0.8 mg/kg/day, and the maternal toxicity LOAEL is 3.3 mg/kg/day based on reduced mean maternal body weight, mean body weight gain and the reduced food consumption. The developmental toxicity NOAEL is 3.3 mg/kg/day and the developmental toxicity LOAEL is 13.3 mg/kg/day based on reduced fetal weights and increased incidence of cleft palate, incomplete ossification of the 3rd and 4th sternebrae and skull, and an enlarged fontanelle.

Developmental Toxicity in Rabbits

Based on the results of this study, administration of Sulfluramid (96.6% linear and 3.4% branched isomeric mixture; Lot no. #AN-90247) at dose levels of 0.1, 0.5, and 1.5 mg/kg/day from day 6 to day 19 of gestation did not produce any treatment-related maternal and developmental toxicity.

Since no treatment-related maternal toxicity was evident in any dose group, it appears that adequate dosages were not used. Based on the data submitted, the maternal LOAEL is greater than 1.5 mg/kg/day. The developmental toxicity was not observed at any dosage. It was noted on p. 16 of the study report that the doses selected for this study were based on two Dose-Range-Finding studies (PH 329DR-GC-001-89 and PH 329DR-GC-001-90). These studies, however, were not submitted to this Agency. This study is not acceptable and it is classified as core-supplementary.

ADDENDUM: The range-finding studies (MRID 426335-02) justify the dose levels chosen for the study, based on reductions in body weight gain and food consumption deaths/abortions/premature deliveries at dose levels of 3.0 mg/kg/day and above. This study satisfies the guideline requirement for a developmental toxicity study in the rabbit.

Special Developmental Toxicity Study in Rabbits (Nonguideline study required for conditional registration)

In a special developmental toxicity study (MRID 44257106) designed to determine the effect on sexual development of male rabbits after exposure to sulfluramid *in utero* during late gestation and potentially during nursing on postnatal days 1 through 42, sulfluramid (99.4% a.i.) in 1% carboxymethyl cellulose/0.1% polysorbate 80 was administered orally by gavage to 22 timed pregnant, litter-experienced, New Zealand White rabbits (9 months of age)/dose at nominal dose levels of 0, 0.3, 1.0, or 3.0 mg/kg/day. Exposure to the litter-experienced F0 does lasted from days 19 through 28 of gestation. Upon weaning (postnatal day 42), F_1 pups (22/sex/dose) were selected for evaluation of developmental landmarks of sexual maturity, including balanopreputial separation, vaginal perforation, spermatogenesis, and reproductive organ weights and histopathology.

There were no treatment-related effects noted on mortality, clinical signs, body weight, gross pathology, organ weights, or histopathological parameters in the treated maternal (F0) groups. Body-weight gain was reduced [42% of control] during the last 5 days of gestation at the high-dose level compared to the control and other treatment groups, and the overall body-weight gain during gestation was reduced [82% of control] at this dose level as well, although statistical significance was not attained. Food consumption was decreased at the high-dose level [3.0 mg/kg/day] throughout lactation (1-42 days; ↓23%) compared to the control but comparable to the control at the lower dose levels throughout the study.

There was a dose-related increase in the number of F_1 pups that were stillborn or found dead on postnatal day 0 (PND 0), a dose-related increase in the mean stillbirth litter size, and a dose-related decrease in the live birth index. The lowest gestation survival index was noted at the high dose [81.8%] compared with the control and other treatment groups [95.5-100%]. However, the mean live litter size was only slightly reduced in the high-dose group compared to the controls (7.2 treated vs 8 controls). There was a dose-related increase in the number of dead pups during lactation (PND 1-42) [50, 71, 103, and 138] and a dose-related increase in the number of total litter losses [10%, 18%, 30%, and 55%] in the 0, 0.3, 1.0, and 3.0 mg/kg/day groups, respectively.

There were dose-dependent, statistically-significant [at all dose levels], decreases in the viability and lactation indices, with the majority of the pup deaths occurring during PND 1 and PND 7. The viability indices in the high-dose group were lower than the controls from the first day of lactation (PND 1; 82% treated vs 96.4% controls) to the last (PND 42; 39.1% treated vs 84.2% controls), although no deaths occurred in this group after PND 7. In the 1.0 mg/kg/day dose group, lower viability indices were observed from PND 4 (79% treated vs 89.9% controls) through to PND 42 (58% treated vs 84.2% controls). Similarly, in the 0.3 mg/kg/day dose group, lower viability indices were observed from PND 7 (77.3% treated vs 89.9% controls) through to PND 42 (69.2% treated vs 84.2%). The lactation indices in the 0, 0.3, 1.0, and 3.0 mg/kg/day groups were 87.5%, 73.9%, 59.7%, and 47.6%, respectively.

There were no treatment-related differences from controls in clinical observations, mean body weights/body weight gains, gross pathologic findings, organ weights, and histopathological findings in the F_1 generation.

There were no apparent, treatment-related, effects on the postweaning developmental parameters in any of the F_1 group rabbits examined (22/sex/dose). No significant differences in achievement of balanopreputial separation [days 71.73, 71.76, 72.95, 72.32] or vaginal perforation [days 29.07, 29.37, 30.06, 29.38 in the control, low-, mid-, and high-dose groups, respectively] were observed among the groups. All male pups were observed with balanopreputial separation by PNDs 79-88 and all females had vaginal opening by PNDs 38-41. However, due to the fact that the sample at the high-dose level for both sexes was truncated; i.e., there were half the number of litters available from which to select the pups and for the females the number of female pups available for assessment [24] was less than half the number assessed in the control [59] and other treatment groups [62 and 53], *no definitive statement regarding the lack of an effect on these parameters at the high-dose level can be made.* For both sexes, similar delays [slight] in preputial separation and vaginal opening were observed in the 2-generation reproduction study in rats. Similarly, during four weeks of spermatogenesis assessment, there were no treatment-related differences observed in mean number of ejaculated sperm, ejaculate volumes, percentages of motile sperm, numbers of ejaculated motile sperm, and morphology of ejaculated sperm among the F_1 males examined and their concurrent

controls. However, due to the limited number of litters from which the high-dose males were taken, a definitive statement regarding a lack of effect at this dose level also cannot be made.

The maternal toxicity LOAEL is 3.0 mg/kg/day, based on decreased body-weight gain during gestation and decreased food consumption during lactation. The maternal toxicity NOAEL is 1.0 mg/kg/day.

The developmental toxicity LOAEL is 0.3 mg/kg/day, based on decreased viability and lactation indices. There is no developmental toxicity NOAEL.

The NOAEL for post-weaning developmental parameters is 1.0 mg/kg/day, based on the fact that slight delays in preputial separation and vaginal opening, as well as a slight decrease in normal sperm, cannot be ruled out at 3.0 mg/kg/day.

5.4 Reproductive Toxicity

In a 2-generation reproduction study (MRID 44341901) sulfluramid (99.4% a.i.) was administered in the diet to 30 Sprague Dawley Crl:CD BR rats/sex/dose at dose levels of 0, 2, 6, or 18 ppm (0, 0.15-0.18, 0.45-0.53, and 1.34-1.65 mg/kg/day). Exposure to F_0 rats (30/sex/dose) began at 6 weeks of age and lasted for 10 weeks prior to mating to produce F_1 pups. Upon weaning, F_1 pups (30/sex/dose) selected to become parents of the F_2 generation were fed sulfluramid in test diets at the same concentration their dam received. F_1 rats were given test diets for 10 weeks prior to mating. All rats were mated on a 1:1 ratio, and each generation was mated once.

There were no treatment-related mortalities or clinical signs of toxicity in either sex or generation. Body weights were comparable among the groups [both sexes] of F_0 rats throughout the premating period, but there were slight [non-significant] decreases in body-weight gains [males ↓6%-11%; females ↓5%-11%] at the 18 ppm dose level compared to control. During the first week of gestation, a slight decrease [↓5%] in body weight was noted at 18 ppm, and decreased body-weight gains were observed over the first 4 days of both gestation [↓17%] and lactation [↓48%] at this dose level. The mid-dose F_0 dams also displayed a significant decrease in body-weight gain [↓43%] during days 1-4 of lactation. At 18 ppm, treatment-related reductions in mean body weights of F_1 males (↓6%-12%) and females (↓9%-13%) were observed throughout the premating period. Reduced body-weight gains were also observed in 18 ppm F_1 females (↓17%-56%) during the premating period. Body weights of 18 ppm F_1 females remained reduced throughout gestation (↓10%-13%) and lactation (↓7%-12%). At necropsy, treatment-related decreases in terminal body weight were observed in both F_1 males and females (↓6%-12%). Both sexes of F_1 rat at the 18 ppm dose level displayed decreased pituitary and adrenal weights, and increased relative (to body) liver weights (↑8%-16%) were observed in the 18 ppm males and females of both generations. There were no treatment-related gross necropsy or microscopic findings for any treatment group in either the F_0 or F_1 generation.

Sulfluramid did not exhibit any treatment-related effects on reproductive parameters or function in rats administered dose levels up to 18 ppm. Mating, fertility, and gestation indices, days between pairing and coitus, regularity and duration of estrous, gestation length, parturition, number and size of litters, ovarian follicle counts, and spermatogenic endpoints [testicular and epididymal sperm numbers, sperm production rate, sperm motility, and sperm morphology] were not altered by treatment.

Neonatal toxicity of sulfluramid was observed at 18 ppm. F_1 and F_2 pup body weights were reduced in the 18 ppm groups throughout lactation (↓7%-15%). An increase in the number of pups dying between birth and postnatal day 4, with a resulting reduction in postnatal survival (% per litter), was observed in the 18 ppm F_2 pups (22 treated died vs 11 controls). There were slight delays in balanopreputial separation in the F_1 males and in vaginal opening in F_1 females at the high-dose level compared to the control and other treatment groups. There were no other treatment-related effects of sulfluramid on the indicators of physical and functional development and behavioral responses monitored in the selected F_1 pups.

The LOAEL for parental systemic toxicity is 18 ppm [1.34-1.65 mg/kg/day], based on reductions in body weight and body-weight gains, decreased adrenal [F_1 males and females] and pituitary [F_1 females] weights, and slightly increased liver [F_0 females] weights. The parental systemic NOAEL is 6 ppm [0.45-0.53 mg/kg/day].

The reproductive/offspring LOAEL is 18 ppm [1.34-1.65 mg/kg/day], based on reduced F_1 and F_2 pup body weights, reduced F_2 pup postnatal survival, and slightly delayed physical development of both sexes [slight delays in balanopreputial separation in the F_1 males and in vaginal opening in F_1 females]. The reproductive/offspring NOAEL is 6 ppm [0.45-0.53 mg/kg/day].

5.5 Additional Information from Literature Sources (*if available*)

Supporting information is on file regarding PFOS and other organic fluorochemical analogs of sulfluramid.

5.6 Determination of Susceptibility

The HIARC has considered fetal susceptibility following sulfluramid exposure and classified it quantitatively and qualitatively:

Developmental Toxicity Study in Rats - Increased qualitative susceptibility was observed at the highest dose tested based on severity of effect. Although the developmental LOAEL (13.3 mg/kg//day) was higher than the maternal LOAEL (3.3 mg/kg/day), at the highest dose fetal effects (reduced fetal weights and increased incidence of cleft palate, incomplete ossification of the 3rd and 4th sternebrae and skull, and an enlarged fontanelle) were more severe than the maternal effects (reduced body weight, body weight gain, and reduced food consumption).

Developmental Toxicity Study in Rabbits - Susceptibility cannot be assessed because no maternal or developmental toxicity was observed in this study.

Special Developmental Toxicity Study in Rabbits - Increased quantitative and qualitative susceptibility were observed. The developmental LOAEL was 0.3 mg/kg/day which is lower than the maternal LOAEL of 3.0 mg/kg/day. While maternal effects were limited to a decrease in body weight gain and food consumption, developmental toxicity was manifested as decreased viability and lactation indices.

Reproductive Toxicity Study in Rats - Increased qualitative susceptibility was observed. While the LOAEL of 1.34 mg/kg/day was the same for parental and offspring toxicity, effects in the offspring (reduced F1 and F2 pup body weights, reduced F2 pup postnatal survival, and slightly delayed physical development of both sexes including slight delays in balanopreputial separation in the F1 males and in vaginal opening in F1 females) were severe compared to parental toxicity (reductions in body weight and body weight gains, decreased adrenal and pituitary weights, and slightly increased liver weights).

5.7 Recommendation for a Developmental Neurotoxicity Study

The HIARC determined that a developmental neurotoxicity study is not required because the evaluations of developmental landmarks in the special rabbit study addressed their primary concerns for fetal development from exposure to this chemical.

5.7.1 Evidence that suggest requiring a Developmental Neurotoxicity study:

Although there is no evidence of neurologic effects in the special rabbit study, the developmental LOAEL of 0.3 mg/kg/day (lowest dose tested; there is no developmental NOAEL), based on decreased viability and lactation indices, is lower than the maternal NOAEL of 1.0 mg/kg/day.

5.7.2 Evidence that **do not** support a need for a Developmental Neurotoxicity study:

In the standard required toxicity studies, there are no indications of neurotoxicity or neurodevelopmental effects.

According to information provided by Minnesota Mining & Manufacturing, the sulfluramid analog PFOS does not induce neurotoxicity or neurodevelopmental effects.

The sulfluramid developmental LOAEL in rats is 4-fold greater than the maternal LOAEL.

6. HAZARD CHARACTERIZATION

Toxicity Characterization: Because sulfluramid is used in child-resistant bait stations, exposure was once considered to be nonexistent, so many toxicity data requirements were waived. Consequently, the toxicity of sulfluramid is not fully characterized. It is now recognized that oral exposure can occur in children that gain access to the contents of a bait station or consume loose bait spread on a lawn. Dermal exposure can occur in adults exposed when spreading loose bait onto residential lawns or during pine reforestation. In addition, new toxicity concerns have arisen since the recent revelation that sulfluramid rapidly metabolizes to PFOS which is extremely persistent in the body (human serum half-life of 1-4 years), and can be found in enterohepatic circulation.

Acute Toxicity: Sulfluramid has very low acute toxicity. It is Toxicity Category III for oral toxicity and Toxicity Category IV for dermal and inhalation toxicity, and primary eye and skin irritation. It is not a sensitizer by the Buehler method. Sulfluramid does not meet the acute toxicity triggers for CRP requirements.

Pharmacokinetics: In rats, a non-toxic dose of ^{14}C-radiolabeled sulfluramid (50 mg/kg *per os*; labeled on the ethyl portion of the molecule) is slowly absorbed through the gut. Within 72 hours, 80% of sulfluramid is deethylated to PFOSA (perfluorooctane sulfonamide; i.e. the sulfonamide moiety remains attached to the perfluorooctyl group) with the majority of PFOSA deposition occurring in the liver, kidneys, adrenals, and gonads.[4] PFOSA is metabolized ($t_{½}$ = 5.2 days in the liver; faster in the serum) to PFOS which accumulates in the liver.[5]

PFOS cannot be further metabolized because biological systems lack the ability to break powerful fluoride bonds (organic fluorochemicals do not occur in nature), so excretion via the urine and feces is extremely slow. Rats dosed IV with ^{14}C-radiolabeled PFOS (the label was on the carbon to which the sulfonamide is attached) excreted 30.2% of the radiolabel via the urine, and 12.6% via the feces for a total excretion of 42.8% by 89 days. Residual levels of μg ^{14}C equivalents/g were liver, 20.6; plasma, 2.2; kidney, 1.1; lung, 1.1; spleen, 0.5; and bone marrow, 0.5. Lower concentrations were also measured in adrenals, skin, testes, muscle, fat, and eye. No radioactivity

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[4] R.O. Manning, J.V. Bruckner, M.E. Mispagel, J.M. Bowen. **Metabolism and Disposition of Sulfluramid, a Unique Polyfluorinated Insecticide, in the Rat.** Drug Metabolism and Disposition. Volume 19. No. 1. 1991. Pages 205-211.

[5] A.M. Seacat and D.J. Luebker. **Toxicokinetic Study of Perfluorooctane Sulfonamide (PFOSA; T-7132.2) in Rats.** Unpublished Study. 3M Strategic Toxicology Laboratory. August 11, 2000.

was detected in the brain. The radiolabel in liver and plasma represent 25% and 3% of the dose, respectively.[6] There is also considerable enterohepatic recirculation of PFOS.[7]

It is presumed that the metabolic pathway in humans resembles that in rats. Preliminary findings suggest that the serum half-life in humans is in the range of 1-4 years. In the absence of a dermal absorption study, dermal absorption of sulfluramid is estimated to be 1% based on a comparison of oral and dermal LOAELs.

Cumulative Toxicity: A comparison of acute and repeated dosing studies reveals a marked cumulation of toxicity due to a cumulation of daily doses. Because the human serum half-life for the metabolite PFOS is measured in years, dose cumulation may approach 100%. A single sulfluramid exposure to a child or adult results in a PFOS body burden that persists for several years, and any subsequent exposure increases the body burden, even if the exposure occurs months or years later.

Subchronic Toxicity: Subchronic feeding studies were performed in the rat and dog. In the rat subchronic feeding study (MRID No. 41799405), the NOAEL was 0.5 mg/kg/day based on body weight, food consumption, hematology, clinical chemistry, organ weight, and histopathological anomalies at the LOAEL of 2.5 mg/kg/day. In the dog subchronic feeding study (MRID No. 41818401), the NOAEL was 0.825 mg/kg/day based on increased epididymal and testicular lesions at the LOAEL of 2.5 mg/kg/day. Sulfluramid appears to be a direct acting testicular toxin in dogs with a primary effect on the late spermatids and possibly Sertoli cells.

Neurotoxicity: No neurotoxicity studies have been performed. Nevertheless, there is no evidence of neurotoxicity in any of the available toxicity studies.

Developmental and Reproductive Toxicity: In a developmental toxicity study in rats (MRID No. 41799409), the developmental NOAEL (3.3 mg/kg/day) exceeded the maternal NOAEL (0.8 mg/kg/day). Maternal effects seen at the LOAEL included reduced body weight, body weight gain, and reduced food consumption. Developmental effects in the rat pups included reduced fetal weights and increased incidence of cleft palate, incomplete ossification of the 3rd and 4th sternebrae and skull, and an enlarged fontanelle at the LOAEL of 13.3 mg/kg/day.

The doses selected for a developmental toxicity study in rabbits (MRID No. 41799408) were insufficient to induce maternal or developmental toxicity, but were nevertheless justified by the range-finding studies (MRID No. 42633502).

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[6] S.J. Gibson and J.D. Johnson. **Extent and Route of Excretion and Tissue Distribution of Total Carbon-14 in Rats after a Single Intravenous Dose of FC-95-^{14}C.** Unpublished Study. Riker Laboratories, Inc., Subsidiary of 3M. December 28, 1979.

[7] J.D. Johnson, S.J. Gibson, and R.E. Ober. **Cholestyramine-Enhanced Fecal Elimination of Carbon-14 in Rats after Administration of Ammonium [^{14}C] Perflurooctanoate or Potassium [^{14}C] Perfluorooctanesulfonate.** Fundamental and Applied Toxicology 4. Pages 972-976

In a reproductive toxicity study in rats (44341901), the parental and reproductive NOAELs were both 0.45 ♂ / 0.53 ♀ mg/kg/day, and the parental and reproductive LOAELs were 1.34 ♂ / 1.65 ♀ mg/kg/day. The parental LOAEL was based on reductions in body weight and body weight gains, decreased adrenal (F1 males and females) and pituitary weights (F1 females), and slightly increased liver weights (F0), and the reproductive LOAEL was based on reduced F1 and F2 pup body weights, reduced F2 pup postnatal survival, and slightly delayed physical development of both sexes (slight delays in balanopreputial separation in the F1 males and in vaginal opening in F1 females).

The discovery of epididymal and testicular lesions in the subchronic dog feeding study (MRID No. 41818401) prompted a special study of pre- and postnatal development, maturation, and fertility in rabbits (MRID No. 44257106) which assessed late gestation (*in utero*) and nursing-related sexual development of rabbits. The maternal NOAEL was 1.0 mg/kg/day and the maternal LOAEL was 3.0 mg/kg/day based on decreased body weight gain during gestation and decreased food consumption during lactation. The developmental LOAEL was 0.3 mg/kg/day, the lowest dose tested (a NOAEL was not determined), based on decreased viability and lactation indices. The developmental (post-weaning) NOAEL was based on the fact that slight delays in preputial separation and vaginal opening, as well as a slight decrease in normal sperm, cannot be ruled out at 3.0 mg/kg/day.

Chronic Toxicity/Carcinogenicity and Mutagenicity: Because PFOS has a protracted serum half-life (1-4 years in humans), the consequence of a single exposure to sulfluramid is systemic PFOS exposure which may persist for several years. Two or more exposures may cause a systemic cumulation even when exposures are spaced months or years apart. Thus multiple exposures may not be required to cause long-term PFOS toxicity and potential carcinogenicity. No studies have been performed to investigate the impact of systemic persistence on long-term toxicity and carcinogenicity.

Sulfluramid's chronic toxicity and carcinogenic potential are unknown because requirements for chronic and carcinogenicity studies were waived several years ago (when sulfluramid was used only in bait stations) on the understanding that bait stations preclude human exposure. Sulfluramid was not mutagenic in an Ames assay with and without metabolic activation (MRID No. 40863201), in a sister chromatid exchange in Chinese hamster ovary cells with and without metabolic activation (MRID Nos. 40612614, 40915801), or in a rat primary hepatocyte unscheduled DNA synthesis assay (MRID Nos. 41251002, 41505102).

7. DATA GAPS

The following have been identified as data gaps by the HIARC:

Metabolism study in rats - The HIARC did not have access to any pharmacokinetic data when it first considered sulfluramid on June 27, 2000, so a metabolism study in rats was identified as a significant data gap. A battery of pharmacokinetic studies was submitted in late January, 2001 which may satisfy this data gap. They were received too late to allow for a thorough review.

Nevertheless, a cursory review confirms that sulfluramid exposure results in systemic retention that can span many years. This poses a unique risk assessment concern. Because the adequacy of these data cannot be assessed at this time, the Agency reserves the right to request further pharmacokinetic studies in the future.

Dermal absorption study - Although this is a data gap, the HIARC determined that an absorption study is not required because it would not provide additional useful information.

Chronic/carcinogenicity study in rats - Sulfluramid's chronic toxicity and carcinogenic potential are unknown. Requirements for chronic and carcinogenicity studies had previously been waived on the understanding that bait stations preclude human exposure. It is now recognized that human exposure can result from all sulfluramid uses (including bait stations), and that even a single dose of exposure to sulfluramid can result in long-term systemic exposure. Thus, a chronic/carcinogenicity study in rats is required.

The OPPTS toxicity guidelines are inadequate for characterizing the toxicity of a chemical which has an extremely long serum half-life. The registrant is advised to consult with the Health Effects Division and with the Cancer Assessment Review Committee (CARC) in designing a study that reflects sulfluramid's incidental exposure scenarios. A mouse carcinogenicity study is not required.

8. ACUTE TOXICITY

Acute Toxicity of Sulfluramid

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
870.1100	Acute Oral	40612602	LD_{50} = 607 mg/kg ♂ LD_{50} = 507 mg/kg ♀ LD_{50} = 543 mg/kg ♂+♀	III
870.1200	Acute Dermal	40612608	LD_{50} >2000 mg/kg	IV
870.1300	Acute Inhalation	41799404	LC_{50} >4.379 mg/L (4-hour, gravimetric)	IV
870.2400	Primary Eye Irritation	40612609	Negative	IV
870.2500	Primary Skin Irritation	40612610	Mild skin irritation	IV
870.2600	Dermal Sensitization	41251001 41505101	Nonsensitizer (Buehler method)	–
870.6100	Acute Neurotoxicity	--	--	--

9. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	—	There is no potential for acute dietary exposure at this time.	—
	Acute RfD = N/A		
Chronic Dietary	—	There is no potential for chronic dietary exposure at this time.	—
	Chronic RfD = N/A		
Incidental Oral, Short-Term	Oral NOAEL = 0.8	Reduced mean maternal body weight, mean body weight gain and reduced food consumption at the Maternal LOAEL of 3.3 mg/kg/day. Target MOE = 300	Developmental Toxicity in Rats
Incidental Oral, Intermediate-Term	Oral NOAEL = 0.45	Reductions in body weight and body-weight gains, decreased adrenal and pituitary weights, and slightly increased liver weights at the LOAEL of 1.34 mg/kg/day. Target MOE = 300	2-Generation Reproduction in Rats
Dermal, Short-Term	Oral LOAEL = 0.3[a]	Decreased viability and lactation indices. Target MOE = 1000	Special Developmental Toxicity Study in Rabbits
Dermal, Intermediate-Term			
Dermal, Long-Term	—	Long-term exposure is not expected.	—
Inhalation, Short-Term	Oral LOAEL = 0.3[b]	Decreased viability and lactation indices. Target MOE = 1000	Special Developmental Toxicity Study in Rabbits
Inhalation, Intermediate-Term			
Inhalation, Long-Term	—	Long-term exposure is not expected.	—

[a] A 1% dermal absorption factor should be used in route-to-route extrapolations.
[b] An oral:inhalation absorption ratio of 1 should be used in route-to-route extrapolations.