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OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES
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MEMORANDUM

SUBJECT: FLURIDONE: Toxicology Chapter for RED and Updating Executive Summaries for 11 Studies

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Attached are the Toxicology Chapter of the RED for Fluridone and updated executive summaries for 11 studies. The executive summaries of many studies were found to be different from the current format and they were appropriately modified to reflect the current policy and guidelines of the Agency. The attached studies are listed as follows:

Developmental Toxicity - Rat (MRID 00159963)
90-Day Oral Toxicity [Feeding] - Dog (MRID 00082344)
Combined chronic toxicity/carcinogenicity [diet]-[rat] (MRID 00103305; MRID 00103251)
Carcinogenicity - mice (MRID 00103252; MRID 00103335)
Metabolism - Rat (MRID 00103262; MRID 00103261)
21-Day Dermal Toxicity - Rabbit (MRID 00103299)
Developmental Toxicity - Rabbit (MRID 00103302)
Reproduction and Teratology Study - Rat (MRID 00103304)
Chronic toxicity [feeding] - dog (MRID 00159963)
90-Day Oral Toxicity [Feeding] - Rat (MRID 00135209)
Developmental Toxicity - Rat (MRID 00103336)

Fluridone: TOXICOLOGY CHAPTER FOR RED

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1.0 HAZARD CHARACTERIZATION

The available toxicity data indicated that acute oral, dermal, inhalation, and primary dermal irritation toxicity of fluridone to be in toxicity categories III and IV. Fluridone was shown to cause slight to moderate corneal dullness, iritis, and conjunctivitis, and it was toxicity category II for primary eye irritation. Fluridone was not a dermal sensitizer or a skin irritant.

The results of the subchronic dietary feeding studies showed that fluridone increased incidence of hepatic centrilobular hypertrophy in mice and increased absolute and relative liver weights and relative kidney weights in rats. It produced no effects in subchronic dietary feeding study in dogs at 200 mg/kg/day, the highest doses tested.

In developmental toxicity studies, maternal toxicity such as increased incidence of abortions and slight decreases in the body weight and food consumption were seen in rabbits at 300 mg/kg/day or above. In the rats, maternal toxicity such as decreased body weight gains and food consumption were seen at 300 mg/kg/day. Developmental toxicity such as decreased fetal weight, increased incidences of rudimentary ribs, and delayed ossification in sternbrae and pelvic girdle were seen at 1000 mg/kg/day.

In a 3-generation reproduction study in rats, no maternal toxicity was seen at any dose levels. Also, the test chemical did not significantly affect any of the reproductive parameters. For the offspring, there was a decrease in pup weight on lactation day 21 at 112 mg/kg/day.

In the combined chronic toxicity/carcinogenicity study in rats, there was no treatment-related increase in tumor incidence in any treated groups when compared to controls. Chronic toxicity consisted of decreased body weights, decreased eosinophil counts, decreased absolute and relative liver and kidney weights at 81 mg/kg/day. In addition, fluridone at 81 mg/kg/day also caused an increased incidence of small testes, ocular keratitis and pale or granular kidneys.

In a chronic toxicity study in dogs, significant increases in absolute liver weights and increases in alkaline phosphatase activity in female dogs were seen at the highest dose-tested (400 mg/kg/day).

Carcinogenicity study in mice showed no treatment-related increase in tumor incidence in any treated groups when compared to controls. Increase in alkaline phosphatase activity and increased incidence of hepatocellular hyperplasia were seen at 50 mg/kg/day.

No neurotoxicity was reported in any of the studies.

Fluridone was negative for inducing mutations in all guideline studies of the standard battery of mutagenicity tests.

In an oral metabolism study in rats, fluridone was rapidly and almost completely absorbed into the systemic circulation and eliminated in both the male and female rats within 3 days. The total radioactivity recovered within 3 days after dosing in the urine and feces were 78-90% and 87-

97% of administered dose in males and females, respectively. Majority of the radioactivity was eliminated via feces (approximately 70%). No tissue accumulation was observed. The major components in the feces were fluridone and fluridone metabolites produced primarily by ring hydroxylation and N-demethylation.

2.0 REQUIREMENTS

The requirements (CFR 158.340) for food and non-food uses for Fluridone are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

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

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

¹Either 870.4300 or 870.4100 can fulfil this requirement.

3.0 DATA GAP(S)

No data gaps have been identified.

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The data base for acute toxicity for Fluridone is considered complete. No additional studies are required at this time. The available toxicity data indicated that acute oral, dermal, inhalation, and primary dermal irritation toxicity of fluridone to be in toxicity categories III and IV. Fluridone was shown to cause slight to moderate corneal dullness, iritis, and conjunctivitis, and it was toxicity category II for primary eye irritation. Fluridone was not a dermal sensitizer or a skin irritant.

The acute toxicity data on Fluridone is summarized as shown in Table 2 .

Table 2: Summary of Acute Toxicity Data for Fluridone

Guideline No.	Study Type	MRID No./ TXR No.	RESULTS	TOXICITY CATEGORY
81-1	Acute Oral -Rat	/000824	LD ₅₀ = 10 g/kg	IV
81-2	Acute Dermal - Rabbit	/000824*	LD ₅₀ > 2 g/kg	III
81-3	Acute Inhalation - Rat	/000824	LC ₅₀ > 2.13 mg/L	IV
81-4	Eye Irritation- Rabbit	/000824	slight to moderate corneal dullness, iritis, and conjunctivitis with clearing by 4 days.	II
81-5	Dermal Irritation- Rabbit	41424102/ 008947**	No dermal effects	IV
81-6	Dermal sensitization - Guinea pig	41424105/ 008947**	Not a skin sensitizer	N/A

* Fluridone 50% WP

** Sonar 5P (a formulation containing 5% a.i.)

4.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The data base for subchronic toxicity is considered complete. No additional studies are required at this time. The results of the subchronic dietary feeding studies showed that fluridone affected increased incidence of hepatic centrilobular hypertrophy in mice and increased absolute and relative liver weights and relative kidney weights in rats. It produced no effects in subchronic dietary feeding study in dogs at 200 mg/kg/day, the highest doses tested. The 21-day dermal toxicity study in rabbits showed a decrease in kidney weight at 768 mg/kg/day. No additional treatment related effects were found.

870.3100a 90- Day Oral Toxicity - Rat MRID # 00135209

EXECUTIVE SUMMARY:

In a 90-day oral toxicity study (MRID 00135209), fluridone (98.6% a.i.; Lot # 367-Q52-59) was administered to 15 SPF-CD Fischer 344 rats/sex/dose in the diet at concentrations of 0, 330, 560, 1000, 1400, or 2000 ppm (equivalent to 0, 30, 54, 106, 139, or 178.4 mg/kg/day for males and 0, 34, 53, 94, 126, or 202 mg/kg/day for females based on initial food consumption). The dosages in mg/kg/day were further corrected because stability study of fluridone in diets showed that only 81.9% of the theoretical concentration of fluridone in the 330 ppm (30 mg/kg/day) diet was present in the feed sample after 1 week storage. The corrected dosages administered were 25, 44, 87, 114, or 146 mg/kg/day for males.

There were no treatment-related effects on survival, clinical signs, body weights, food consumption, and hematology or clinical chemistry parameters.

Treatment related effects were limited to statistically significant increases in absolute and relative liver and kidney weights in both the male and female animals. In male rats receiving the 560 ppm diets, absolute and relative liver weights (112-113% of controls) and relative kidney weights (106% of controls) were significantly increased.

In both males and females receiving the 1000 ppm diets and above, absolute and relative liver and kidney weights were significantly increased (105-124% of controls). In this study, only tissues from liver and kidneys were examined microscopically because the high doses of fluridone (2000, 4000, and 8000 ppm diets) had been shown to produce alterations in only liver and kidney in the previous study (MRID No: 135208). Histological alterations were limited to liver centrilobular hypertrophy in male rats in the two highest doses groups (0/15 of control, 330, 560, and 1000 ppm groups, 1/15 of 1400 ppm and 12/15 of 2000 ppm groups).

As stated above, stability study of fluridone in diets showed that only 81.9% of the theoretical concentration of fluridone in the 330 ppm (30 mg/kg/day) diet was present in the feed sample after 1 week storage. The recovery of 81.9% of the test compound necessitated estimating a NOAEL for this study. The estimated NOAEL is 81.9% of 30 mg/kg/day or 25 mg/kg/day. Also, the estimated LOAEL is 81.9% of 54 mg/kg/day (560 ppm) or 44 mg/kg/day.

The LOAEL for fluridone in rats is 44 mg/kg/day based on increased absolute and relative liver weights and relative kidney weights. The NOAEL is 25 mg/kg/day.

This 90-day oral toxicity study is classified Acceptable/Guideline and satisfies the guideline requirements for a 90-day oral toxicity study in the rat (OPPTS 870.3100; OECD 408).

870.3100a 90- Day Oral Toxicity - Mice MRID #00082342

EXECUTIVE SUMMARY:

In a 90-day oral toxicity study (MRID No. 00082342), fluridone (97.8% a.i.; Lot # D36-Y25-091) was administered to 15 ICR/SPR mice/sex/dose in the diet at concentrations of 0, 62, 110, 200, 330 or 560 ppm (equivalent to 0, 9.3, 16.5, 30, 49.5 or 84 mg/kg/day based on 1 ppm = 0.15 mg/kg/day). The dosages in mg/kg/day were further corrected because stability study of fluridone in diets showed that approximately 50% of the theoretical concentration of fluridone was present in the feed sample after 3 months storage. The corrected dosages administered were 4.6, 8.3, 15, 25, and 42 mg/kg/day.

There were no treatment-related effects on appearance, behavior, body weights or liver weights. Four males (2, 1, and 1 death in the 110, 200, and 330 ppm groups, respectively) and one female (in the 62 ppm group) died during the study but none of the deaths were attributed to treatment. Treatment related effects were limited to increased incidence of hepatic centrilobular hypertrophy with increasing dose of fluridone in the male mice. The incidence of this lesion seen in the males was 1/28, 1/29, 3/29, or 6/30 in 110, 200, 330 or 560 ppm groups, respectively. The dose related findings of this lesion was also observed in other 90-day study with fluridone (MRID No. 00082341) with the incidence of 5/30, 8/30, or 26/30 in 330, 560, or 1400 ppm groups, respectively.

As stated above, stability study of fluridone in diets showed that approximately 50% of the theoretical concentration of fluridone was present in the feed samples after 3 months storage. Therefore, the recovery of 50% of the test compound necessitated estimating a NOAEL for this study. The estimated NOAEL is 50% of 30 mg/kg/day (200 ppm diet) or 15 mg/kg/day. Also, the estimated LOAEL is 50% of 49.5 mg/kg/day (330 ppm diet) or 25 mg/kg/day.

The LOAEL for fluridone in mice is 25 mg/kg/day based on increased incidence of hepatic centrilobular hypertrophy. The NOAEL is 15 mg/kg/day.

This 90-day oral toxicity study is classified Acceptable/Guideline and satisfies the guideline requirements for a 90-day oral toxicity study in the mouse (OPPTS 870.3100; OECD 408). The study was reported in 1978. The diet analysis indicated that the concentration of the test compound in treatment diet decreased overtime. The report did not show how rapidly the concentration of the test diet deteriorated. Using the decrease found at 3 month (50% drop) was a conservative approach. In addition, the report did not indicate how frequently diet was prepared and how long it was stored prior to offering to the test mice.

870.3150b 90- Day Oral Toxicity - Dog MRID # 00082344

EXECUTIVE SUMMARY:

In a 90-day oral toxicity study (MRID No. 00082344), 4 beagle dogs/sex/dose were orally administered by capsules at doses of 0, 50, 100, or 200 mg/kg/day of fluridone (purity unspecified; Lot # 597-B29-200C) for 90 days. There were no treatment-related effects on survival, clinical signs, body weights, urinalysis, and organ weights. In the dogs receiving the 2000 mg/kg/day, erythrocyte count, hemoglobin, and hematocrit values were lower than controls and alkaline phosphatase and BUN values were slightly higher than controls. However, these values for hematology or clinical chemistry parameters were within normal ranges and these alterations were not supported by either gross or microscopic examination. Therefore, these alterations were not considered toxicologically significant.

The LOAEL for fluridone in dogs is not established and the NOAEL is equal or greater than 200 mg/kg/day (HDT).

This 90-day oral toxicity study is classified unacceptable/Guideline and does not satisfy the guideline requirements for a 90-day oral toxicity study in the dog [OPPTS 870.3150 (§82-1b)]. Although the results reported were valid for the doses tested, the study is classified unacceptable because no clear cut dose related toxicity was established in the highest dose (200 mg/kg/day) in this study. However, another 90-day guideline non-rodent study is not required at this time because the toxicological data requirements are satisfied by the 1-year feeding study in dogs (MRID No. 00103336). In the chronic toxicity study, 4 beagle dogs/sex/dose were orally administered in gelatin capsules at doses of 0, 75, 150, or 400 mg/kg/day for 52 weeks (TXR No.: 0052046). The LOAEL was 400 mg/kg/day based on significant increases in absolute liver weights and increases in alkaline phosphatase activity in female dogs. The NOAEL was 150 mg/kg/day. In the original DERs (TXR Nos. 004039 and 004448), the LOAEL was estimated at 150 mg/kg/day based on the slight weight loss in males and the trend towards increased alkaline phosphatase activity (120-170% of the control values) in females.

[NOTE: This study was classified as minimum (acceptable) in the previous review (TXR No. 000824).]

870.3200 21-Day Dermal Toxicity

EXECUTIVE SUMMARY:

In a 21-day dermal toxicity study (MRID No. 00103299), groups of New Zealand white rabbits (5/sex/dose group) received Fluridone 4AS (Lot No.: #X-36339; purity: 44.5% a.i.) by dermal application at doses of 0, 192, 384 or 768 mg/kg/day for 21 days (6 hours/day and 5 days/week).

One control male died during the treatment period, but no signs of toxicity were observed in any

other rabbit. No differences from controls in body weights or food consumption were recorded. Dose-related dermal irritation occurred in all dose groups as follows:

Animals in the 192 mg/kg/day group (20% formulation) showed transient, slight erythema in 9/10 animals, accompanied by slight desquamation.

Animals in the 384 mg/kg/day group (40% formulation) showed moderate, well-defined erythema, slight edema and mild desquamation, and epidermal fissures in 3/10 rabbits.

Animals in the 768 mg/kg/day group (80% formulation) showed moderate to severe erythema with epidermal fissures in 8/10 rabbits, accompanied by slight edema.

Differences in the dermal response between abraded and non-abraded skin were not significant.

At low- and mid-doses, no evidence of systemic toxicity and no unusual clinical chemistry findings were observed. Hematological changes observed were slight increase in MCV and MCH in low-dose males and a slight increase in terminal monocyte count in mid-dose females.

In high-dose males, significant decreased relative kidney weights (85% of controls; $p < 0.05$) was observed in the absence of any abnormal histopathological findings or clinical chemistry. In addition, there was a slight increase in terminal monocyte count in high-dose males, however, this finding is not considered biologically relevant to fluridone treatment in the absence of clear dose-response.

The LOAEL for systemic toxicity was 768 mg/kg/day based on the kidney findings (decreased relative kidney weights) and the NOAEL was 384 mg/kg/day.

Based on the dermal findings (transient, slight erythema in 9/10 animals accompanied by slight desquamation) at 192 mg/kg/day (LDT), the NOAEL/LOAEL for dermal toxicity was not established.

This 21-day dermal toxicity study is classified acceptable/guideline and satisfies the guideline requirement for a 21-day dermal toxicity study (82-2) in the rabbit.

4.3 Prenatal Developmental Toxicity

Adequacy of data base for Developmental Toxicity: The data base for prenatal developmental toxicity is considered complete. No additional studies are required at this time. In developmental toxicity studies, maternal toxicity such as increased incidence of abortions and slight decreases in the body weight and food consumption were seen in rabbits at 300 mg/kg/day or above. In the rats, maternal toxicity such as decreased body weight gains and food consumption were seen at 300 mg/kg/day. Developmental toxicity such as decreased fetal weight, increased incidences of rudimentary ribs, and delayed ossification in sternbrae and pelvic girdle were seen at 1000 mg/kg/day.

870. 3700a Prenatal Developmental Toxicity Study- Rat MRID #00159963

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID No. 00159963), 25 presumed pregnant CrI:CD[®] (SD) rats per group were administered Fluridone (purity: 99.5%; batch/lot No.: 414DT4) by oral gavage in 10% acacia solution at doses of 0, 100, 300, or 1000 mg/kg/day on gestation days (GD) 6-15, inclusive. On GD 20, dams were sacrificed and necropsied, and gravid uterine weights and the numbers of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. All fetuses were weighed, sexed, and subjected to external examination followed by fresh dissection. Approximately one-half of the fetuses from each litter terminated on GD 20 were fixed in Bouin's solution for visceral examination, and the remaining fetuses were eviscerated and processed for skeletal examination.

Maternal Toxicity

One dam (#2061) on 300 mg/kg/day was found dead on GD 10 (after receiving 4 doses) apparently as a consequence of an injury during dosing. Autopsy revealed dark-red, collapsed lungs, surrounded by fibrin and fluid. There were 15 implantation sites *in utero*.

In mid- and high-dose groups, dose-related significant decreases in the body weight gain and food consumption were recorded during the first half of the treatment period (days 6 to 10), but weight gain rebounded during the latter half (days 11 to 15) of the treatment period.

In the high-dose group, adjusted overall net weight gain (minus gravid uterine weight) during the post-treatment period remained significantly depressed (20% less than controls). In addition, higher incidences of alopecia was observed only in the 1000 mg/kg/day group (5 rats vs. 0, 1, and 1 rat at 0, 100, and 300 mg/kg/day, respectively).

Necropsy findings in sacrificed dams (hydronephrosis, empty stomach and gastrointestinal tract, infantile uterine horn, etc.) were evenly distributed and of low incidence in all groups with no compound relationship.

Therefore, the LOAEL for maternal toxicity was 300 mg/kg/day based on reduced body weight gains and food consumption; NOAEL for maternal toxicity was 100 mg/kg/day.

Developmental Toxicity

There were no differences between the control group and the all treated groups for number of females pregnant, corpora lutea, number of implant per pregnancy, % of live fetuses or % resorptions. No dead fetuses were observed in any group.

At 1000 mg/kg/day, mean fetal weight (males = 3.25 g; females = 3.04 g) was significantly decreased as compared with controls (male= 3.66 g; females 3.53 g). In female fetuses at 1000

mg/kg/day, rudimentary ribs (T-13, T-14, L-1) in seven litters and delayed ossification of sternebrae and pelvic girdle in two litters were observed.

Renal cavitation and ureter dilatation were reported at a higher incidence than controls in the mid- and high-dose groups, but these fetal variations have been observed in higher incidences in controls from other studies conducted by the same laboratory. One high-dose fetus had a shortened right hindlimb (micromelia) and associated skeletal defects, while two high-dose fetuses from a separate litter had hernias and one of these had hypoplastic lungs.

Therefore, the LOAEL for developmental toxicity was 1000 mg/kg/day based on decreased fetal weight, increased incidences of rudimentary ribs, and delayed ossification in sternebrae and pelvic girdle; NOAEL for developmental toxicity was 300 mg/kg/day.

This study is classified as Acceptable/Guideline and satisfies the requirements for a developmental toxicity study [OPPTS: 870.3700a (83-3a)] in rats.

870. 3700b Prenatal Developmental Toxicity Study- Rabbit MRID # 00103302

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID No. 00103302), fluridone (lot no.:X-29478; purity: 99.5% a.i.) in 10% acacia solution was administered daily by oral gavage to pregnant female Dutch Belted rabbits (15/sex/dose) on days 6-18 of gestation at dose levels of 0, 125, 300, or 750 mg/kg/day. The rabbits were observed for signs of toxicity and body weight and food consumption values were recorded. On day 28 of gestation, the rabbits were sacrificed and necropsied and the numbers of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. The fetuses were removed, weighed, sexed, and examined for external anomalies. They were then processed for visceral or skeletal evaluation.

Maternal Toxicity

No deaths were observed in the control and 125 mg/kg/day (LDT) groups. One female in the 300 mg/kg/day group was found dead on day 23 of gestation. An acute upper respiratory tract infection and focal acute pneumonia were observed at necropsy. Two animals were found dead on day 23 in the 750 mg/kg/day group. No diagnosis was reported for one; the other female was diagnosed as having an acute upper respiratory tract infection and acute pneumonia. No other signs of toxicity were observed in any of the surviving animals during the study.

There were no differences between the control group and low-dose group for the body weight gain and mean food consumption during the treatment period.

In the mid-dose group, a slight loss in the body weight, the body weight gain, and mean food consumption during the treatment period were slightly reduced when compared to the controls, however, the difference was not statistically significant. At the mid- and high-dose levels,

increased incidence of abortions was also seen (detailed below).

The mean body weight changes during the treatment period at high dose-level was significantly reduced (-2.3%; $p < 0.05$) when compared to the controls (+4.9%). Mean food consumption during the treatment period and post-treatment period of the high-dose animals were 62% and 77% of the control values, respectively.

In addition, treatment related increased incidences of abortions was observed at both the mid- and high-doses. Since maternal toxicity was also observed at these doses (reduced body weight and food consumption), the increased incidence of abortions seen at mid- and high-dose levels was considered to be secondary to the maternal effects.

Therefore, the LOAEL for maternal toxicity was 300 mg/kg/day based on increased incidence of abortions and slight decreases in the body weight and food consumption; NOAEL for maternal toxicity was 125 mg/kg/day.

Developmental Toxicity

No dead fetuses were observed in any group and the mean fetal body weights of all treatment groups were comparable to the control group. A dose-related decrease in the ratio of live fetuses to implantation sites was evident. The ratios were 0.96, 0.95, 0.80, and 0.65 for control, low-, mid- and high-dose groups, respectively.

The reproduction findings showed that 4 of 14 mid-dose and 6 of 11 high-dose pregnant rabbits aborted between days 20 and 25 of gestation. The number of high-dose rabbits successfully maintaining pregnancy until day 28 of gestation was reduced by deaths and abortions when compared to the control group. Thirteen of the 13 control rabbits reached day 28 of gestation, whereas, only 5 of the 11 high-dose rabbits were still pregnant by day 28 of gestation. The mean number of resorptions/litter was increased two and one half fold when the mid-dose (1.5) was compared to the controls (0.6), however, this difference was not statistically significant. At high-dose, the mean number of resorptions/litter (3.0) was significantly increased ($p < 0.05$) when compared to the controls (0.6).

One control and one high-dose fetus each had multiple abnormalities, however, these abnormalities were considered spontaneous and not related to fluridone. In addition, the control fetus was observed to have hair lip, omphalocelle, and absent forepaws and hindlimbs. The high-dose fetus was observed to have exencephally, omphalocele, rudimentary ear, and rudimentary forelimbs without digits. No visceral abnormalities were observed in either the control or treatment groups. An increase in the percentage of fetuses with 13th ribs was observed in the high-dose level as compared to controls, however, the percentage of fetuses with 13th ribs was comparable to the historical controls. There were increased incidences of unidentified thickened rib and sternebral variations in the high-dose level.

Therefore the LOAEL for developmental toxicity was 300 mg/kg/day based on increased incidences of abortions; NOAEL for developmental toxicity was 125 mg/kg/day.

This study is classified as Acceptable/Guideline and satisfies the requirements for a developmental toxicity study [OPPTS: 870.3700b (83-3b)] in rabbits.

4.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is considered complete. No additional studies are required at this time. In a 3-generation reproduction study in rats, no maternal toxicity was seen at any dose levels. Also, the test chemical did not significantly affect any of the reproductive parameters. For the offsprings, there was a decreased pup weight on lactation day 21 at 112 mg/kg/day.

870. 3800 Reproduction and Fertility Effects Study MRID # 00103304

EXECUTIVE SUMMARY:

In a 3-generation reproduction study (MRID 00103304), fluridone (99.5% a.i., lot # X-29478) was administered to 25 Fischer 344 rats/sex/dose in the diet at concentrations of 0, 200, 650, or 2000 ppm. The mean calculated intake of fluridone during the growth phases over the 3 generations were 10.6-11.1, 35.5-36.6, or 111.9-112.3 mg/kg/day for males and 12.4-13.2, 40.4-44, or 128-131.4 mg/kg/day for females. Two litters were produced by each generation, and the animals were administered test or control diet continuously for at least 10 weeks prior to mating, throughout mating, gestation, lactation, and until necropsy. The F₂ generation parents were mated three times and histopathologic examination was conducted on selected F_{3b} progeny and the teratology phase of the study was conducted on the F_{3c} litters. The F_{3a} pups were terminated at weaning because of poor viability in all treatment groups, however, the report stated that “No cause was determined for the loss of significant numbers of F_{3a} pups between days 1 and 7 postpartum.”

For low- and mid-dose F₀ females, there were two deaths resulting from the room temperature reaching 38°C. One control F₂ female died, but cause of death was not evident. There were no treatment-related effects on body weights and food consumption during the growth phase in any of the three generations. Also, fluridone did not produce clinical signs of toxicity in the animals in any of the generation. The absence of parental toxicity indicates that optimal dietary levels of the test material were not used, thus compromising the sensitivity of the test.

The maternal body weights and body weight gains of the fluridone-treated females were comparable to those of the control females on days 0 to 20 of gestation and on day 21 of lactation during all generations (F₁, F₂, F_{3a}, and F_{3b}). Also, in the teratology phase (F_{3c}) of the study, no dose-related differences were observed in the body weights at days 0, 7, 14, and 20 of gestation, nor were any observed for the weight gains from day 0 to day 20 of gestation. The LOAEL for maternal toxicity was not determined; NOAEL for maternal toxicity was equal or greater than 2000 ppm (112 mg/kg/day, HDT).

The test chemical did not significantly affect any of the reproductive parameters. Therefore, the NOAEL for reproductive toxicity is equal to or greater than 2000 ppm (112 mg/kg/day, HDT)

and the LOAEL is not established.

Fluridone significantly depressed the body weights (90.7% of controls; $p < 0.05$) on lactation day 21 of the 2,000 ppm F₂ pups. A comparison of the pup weight gain from day 1 to day 21 of lactation indicated a dose-related trend toward decreased weight gain among the fluridone-treated pups, however, the differences were not statistically significant. Therefore, the NOAEL for offspring toxicity is 650 ppm (36 mg/kg/day) and the LOAEL is 2000 ppm (112 mg/kg/day, HDT) based on decreased pup weight (on lactation day 21).

For developmental toxicity phase of the study, F_{3c} developmental toxicity data shows that there were no evidence of embryolethality, altered fetal growth, or developmental alteration. Therefore, the LOAEL for developmental toxicity was not determined; NOAEL for developmental toxicity was equal or greater than 2000 ppm (112 mg/kg/day, HDT).

This study is classified as Acceptable/Guideline and satisfies the guideline requirements for a 2-generation reproductive study in the rat (OPPTS 870.3800; OECD 416). However, the teratology phase of the study is classified as unacceptable/guideline and does not satisfy the requirements for a developmental toxicity study [OPPTS: 870.3700 (83-3a)] in rats because the highest dietary level failed to produce maternal toxicity.

The results of this study show increased quantitative susceptibility of offspring to fluridone based on reduced pup weight (90.7% controls; $p < 0.05$) on lactation day 21. However, considering the overall toxicity profile and the doses and endpoints selected for risk assessment for fluridone, the degree of concern for the effects observed in this study was considered as low, noting that the study was well-conducted, clear NOAELs/LOAELs were established, and the dose response for the observed effects are well characterized. In addition, the NOAEL of 8 mg/kg/day identified to established the chronic RfD is more than 4 times less than that of 36 mg/kg/day for offspring toxicity. Therefore, no residual uncertainties were identified for pre- and/or postnatal toxicity.

In another one-generation reproduction bridging study (MRID No. 43701901), the parental toxicity NOAEL was 15 mg/kg/day and the LOAEL was 49 mg/kg/day based on nephrotoxicity (increased kidney weight and nephrosis). The reproductive toxicity was 49 mg/kg/day and the LOAEL was 159 mg/kg/day based on slight depression in live birth index. However, this study is not appropriate to use for risk assessment because this study was not a guideline study.

4.5 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete. No additional studies are required at this time. In the combined chronic toxicity/carcinogenicity study in rats, there was no treatment-related increase in tumor incidence in any treated groups when compared to controls. Chronic toxicity consisted of decreased body weights, decreased eosinophil counts, decreased absolute and relative liver and kidney weights at 81 mg/kg/day. In addition, fluridone at 81 mg/kg/day also caused an increased incidence of small testes, ocular keratitis and pale or granular kidneys. In a chronic toxicity study in dogs, significant

increases in absolute liver weights and increases in alkaline phosphatase activity in female dogs were seen at the highest dose-tested (400 mg/kg/day).

870.4100b Chronic Toxicity Study- Dog MRID # 00103336

EXECUTIVE SUMMARY:

In a chronic toxicity study (MRID No. 00103336), 4 beagle dogs/sex/dose were orally administered in gelatin capsules at doses of 0, 75, 150, or 400 mg/kg/day of fluridone (98.1% a.i.; Lot # D36-Y93-107) for 52 weeks.

There were no deaths during the study and no treatment-related ophthalmic findings were noted at the termination of the study. No differences that could be attributed to compound administration were evident in any of the urinalysis, hematologic parameters, and gross or histopathologic examinations. Also, fluridone did not induce hepatic mixed-function oxidase activity. Dose-related emesis occurred in females only (0/4 controls, 2/4 low-dose, 3/4 mid-dose, and 4/4 high-dose), however, sporadic occurrence of this finding precludes assessment of its biological significance.

No treatment-related effects were found in the low-dose animals.

In the 150 mg/kg/day group, body weight gain was slightly lower (4-6%; statistically not significant) in males as compared to the controls over the last two months of the study.

In the 400 mg/kg/day group, body weight gain was slightly lower (6-10%; statistically not significant) in males and females as compared to the controls over the last two months of the study. Also, alkaline phosphatase activity in female dogs was statistically significantly elevated (approximately 2-3 times of control) beginning at the 5th week and continuing to the study termination. No increase in alkaline phosphatase activity was found in the males. Additional findings in the high-dose females were significantly increased absolute liver weights (118% of controls, $p < 0.05$) and increase in the relative liver weights (not statistically significant). A potential hepatotoxic effect of fluridone in this study is consistent with previous findings: elevated alkaline phosphatase activity was observed at 200 mg/kg (HDT) in a 3-month oral toxicity study in dogs and elevated alkaline phosphatase activity and increased relative liver weights were observed at 400 mg/kg (HDT) in a 2 week oral pilot study in dogs.

The LOAEL is 400 mg/kg/day based on significant increases in absolute liver weights and increases in alkaline phosphatase activity in female dogs. The NOAEL is 150 mg/kg/day. (In the original DER, the LOAEL was conservatively estimated at 150 mg/kg/day based on the slight weight loss in males and the trend towards increased alkaline phosphatase activity (120-170% of the control values) in females.

This chronic study in the dog is classified Acceptable/Guideline and satisfies the guideline requirement for a chronic oral study in the dog [OPPTS 870.4100b; OECD 452].

870.4300 Combined Chronic Toxicity/Carcinogenicity - Rat MRID # 00103305 and 00103251

EXECUTIVE SUMMARY:

There were three studies conducted concurrently and reported as combined chronic/carcinogenicity study (MRID Nos. 00103305 and 00103251). For these three studies fluridone (Lot No: D36-Y25-091; purity: 97.2% a.i.) was administered to Fischer 344 rats (75/sex/dose) in the diet at levels of 0, 200, 650, or 2000 ppm. Corresponding daily intake of test material for the two-year studies were 0, 7.65, 25.15, or 80.80 mg/kg/day in males and 0, 9.17, 30.11, or 97.00 mg/kg/day in females. The first study was a one year study consisting of 15 rats/sex/dose and the other two studies were 2-year study each consisting of 30 rats/sex/dose/study. The 3 studies were evaluated together in this DER.

The mortality rate through week 77 was 10% or less for all test groups. However, from week 78 (18 months) through the remainder of the study, increase in mortality occurred in high-dose males (87% vs 20-32% in the other male groups). Mortality rates among female groups were similar to the control until the last month of the study, when an increase in mortality occurred among high-dose females (37% vs 23% in the controls).

No treatment-related effect was seen at 200 ppm (7.65 mg/kg/day).

The mid-dose males (25.15 mg/kg/day) at final sacrifice exhibited decreased body weights (92% of controls; $p < 0.05$), decreased eosinophil counts, and increased absolute and relative liver and kidney weights as compared to controls.

In the high-dose animals (80.8 mg/kg/day), treatment related toxicity observed includes decreased body weights and food consumption and pale eyes and thin appearance in both sexes, increased incidences of chromorrhinorrhea, anorexia, and cloudy eyes in males.

At final sacrifice, the mean erythrocyte counts, hemoglobin, mean corpuscular hemoglobin concentration and hematocrit values from high-dose males were significantly lower ($p < 0.05$) than control values. The high-dose males also had increased levels of nucleated erythrocytes and neutrophil count and a decreased levels of lymphocyte and eosinophil counts when compared to controls at study termination. Total leukocyte count, BUN and creatinine levels in both sexes were significantly higher when compared to controls.

Necropsy findings observed at final sacrifice were increased incidence of small testes noted in the high-dose group. The mean testes weight of high-dose males was lower than control values. In addition, there was an increased dose-related trends in number of enlarged, pale and/or granular kidneys (in both sexes). In addition, there was increased number of opaque, cloudy, pale, red, or ulcerated eyes (in males) and increased number of skin nodules or masses (in females).

Both absolute and relative liver and kidney weights and relative spleen weights (in both sexes) were significantly higher than controls. Examination of the renal cortex by electron microscopy showed necrosis in albumin precipitate in 1/4 high-dose male and necrosis in 2/4 high-dose females.

Histopathologic findings showed that incidence of atrophy of the testes and ocular keratitis were increased in high-dose males. Incidences of epidermal inclusion cysts (non-neoplastic retention of keratin in the skin) were increased in treated animals of both sexes. Also the incidences of skin papillomas were increased in treated animals of both sexes, however, the skin papillomas do not represent an oncogenic response to fluridone treatment because of the following reasons:

- 1) statistical analyses were conflicting;
- 2) skin papillomas do not represent a life-threatening lesion;
- 3) the majority of "masses" grossly identified in this study were minute in size ("wart-like"); and
- 4) there is no hint these could have undergone malignant transformation.

The NOAEL for systemic toxicity was 200 ppm (7.65 in males and 9.17 mg/kg/day in females). The LOAEL for systemic toxicity was 650 ppm (80.8 in males and 97 mg/kg/day in females) based on decreased body weights, decreased eosinophil counts, and decreased absolute and relative liver and kidney weights.

The tumor issue of this study was peer reviewed by the HED Cancer Assessment Review Committee (TXR 007726, July 15 and October 7, 1985). The committee evaluated the available data concluded that the data did not provide evidence for the carcinogenicity of fluridone in rats.

Dosing was considered adequate in this study based on increased mortality, decreased body weight and food consumption, increased absolute and relative liver and kidney weights, changes in hematology parameters, changes in clinical chemistry parameters (increased BUN, creatinine, bilirubin), increased incidence of chromorrhoea, anorexia, and cloudy and pale eyes observed at high-dose (80.8 mg/kg/day). In addition, there were changes in morphology of erythrocytes (increased incidences of nucleated erythrocytes, leukocyte and neutrophil counts), changes in total and differential leukocyte counts (increased leukocyte counts and decreased lymphocyte and eosinophil counts). Also, fluridone treatment at high-dose resulted in increased incidences of small testes and enlarged, pale and/or granular kidneys. Also increased incidences of opaque, cloudy, pale, red, or ulcerated eyes, skin nodules or masses, atrophy of testes, ocular keratitis, and epidermal inclusion cyst observed at high-dose.

This study is classified as Acceptable/Guideline and satisfies the Subdivision F guideline requirements for a combined chronic toxicity/carcinogenicity study (83-5) in rats.

4.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity is considered complete. No additional studies are required at this time. The HED Cancer Assessment Review

Committee (TXR 007726, July 15 and October 7, 1985) evaluated the available data and concluded that the data did not provide evidence for the carcinogenicity of fluridone in either rats or mice.

870.4200a Carcinogenicity Study - rat

See two-year combined chronic toxicity/carcinogenicity study described above.

870.4200b Carcinogenicity Toxicity - Mice MRID # 00103335 and 00103252

There were three studies conducted concurrently and reported as carcinogenicity study (MRID Nos. 00103335 and 00103252). In these 3 studies, fluridone (Lot No: D36-Y25-091; purity: 97.2% a.i.) was administered to ICR mice (120/sex/dose in controls; 80/sex/dose in treated groups) in the diet at levels of 0, 33, 100, or 330 ppm (equivalent to 0, 5, 15 or 50 mg/kg/day based on a conversion factor of 1 ppm = 0.15 mg/kg/day). The first study was a one year study consisting of 15 mice/sex/dose. In the 2 two-year studies, the control groups consisted of 60 mice/sex/study and each of the dosed groups consisted of 40 mice/sex/study.

Mortality among the control and dosed animals in the one- and two-year studies were similar.

No treatment-related effect was seen at 33 (low-dose) and 100 (mid-dose) ppm.

Overall, no dose-related changes in hematology parameters were apparent for 300 (high-dose) ppm males and females. For high-dose females of the first 2-year study (M-9407), hematology data showed statistically significant decreases in hemoglobin, packed cell volume, and monocyte counts compared to controls. For high-dose males, a significant decrease in the lymphocyte counts and a significant increase in the neutrophil counts were observed. However, these parameters were not reduced in the second 2-year study (M-9417).

The high-dose males showed statistically significant increases in alkaline phosphatase (134 and 209% of controls at 12 and 24 months, respectively) (study M-9407). The combined data from 2 two-year studies indicated a significant increase (157% of controls) in alkaline phosphatase activity in the high-dose group males as compared to controls.

Absolute organ weights for males and females showed no compound-related effects at interim and final sacrifices. In the high-dose females, relative liver weights were significantly higher than controls at interim sacrifice but this was not supported by the absolute liver weights.

Gross examination showed no compound related effects in any tissue. Histopathological examination at final sacrifice showed a slight but significant ($p < 0.05$) increase in hepatocellular hyperplasia for the high-dose males (2, 2, 4, and 6 cases in control, low-, mid-, and high-doses). A slight increase in hepatic focal atypia (not defined in the final study report) was also noted for high-dose females (0, 1, 2, and 2 cases in control, low-, mid-, and high-doses).

The report indicated an increased incidence of fibrosarcomas of the skin in the high-dose females.

The tumor issue of this study was peer reviewed by the HED Cancer Assessment Review Committee (TXR 007726, July 15 and October 7, 1985). The committee concluded that the available data did not provide evidence for the carcinogenicity of fluridone in mice.

The NOAEL for systemic toxicity was 100 ppm (15 mg/kg/day). The LOAEL for systemic toxicity was 330 ppm (50 mg/kg/day) based on increase in alkaline phosphatase activity and increased incidence of hepatocellular hyperplasia.

There was not a treatment-related increase in tumor incidence in any treated groups when compared to controls.

Dosing was considered adequate in this study based on increase in alkaline phosphatase activity and increased incidence of hepatocellular hyperplasia for the high-dose males.

This study is classified as Acceptable/Guideline and satisfies the Subdivision F guideline requirements for a carcinogenicity study (83-2) in mice.

4.7 Mutagenicity

Adequacy of data base for Mutagenicity: The data base for mutagenicity is considered adequate based on 1991 mutagenicity guidelines and no further testing is required at this time.

Fluridone was negative for inducing mutations in all acceptable guideline studies of the standard battery of mutagenicity tests except for the following three assay systems. Based on the database, fluridone was not mutagenic in a microbial mutagenicity assay (Ames assay) and in sister chromatid exchange assay in Chinese hamsters, and fluridone did not induce unscheduled DNA synthesis in primary rat hepatocytes. Accordingly, the acceptable studies satisfy the pre-1991 FIFRA mutagenicity guidelines.

In a microbial mutagenicity assay (MRID 255339), five *Salmonella typhimurium* strains were exposed to fluridone (Lot no. X-035479; purity 99.7% a.i.) in DMSO with and without S-9 metabolic activation at test levels up to the solubility of 2,000 µg/plate. S9 homogenates for metabolic activation were made from Aroclor induced rat livers. Fluridone was negative for the induction of gene mutations. The positive control substances induced marked increases in revertant colonies in their respective strains. The study is classified as Acceptable/guideline and satisfies the requirements for FIFRA Test Guideline 84-2 for a bacterial gene mutation assay.

In a first *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocyte (MRID 070942), fluridone (Lot No. D35-Y25-91; purity 98.1% a.i.) was assayed at eight concentrations ranging from 0.5 to 1,000 nmoles/ml. The cytotoxicity was produced at the highest concentration tested (1,000 nmoles/ml). The test was negative with fluridone at any concentration from 0.5 to 100 nmoles/ml. The study is classified as Acceptable/guideline and satisfies the requirements for FIFRA Test Guideline 84-2 for a UDS assay.

In another *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocyte (MRID

070942), fluridone (Lot No. 462-710-155H; unspecified purity) was assayed at eight concentrations ranging from 0.5 to 1,000 nmoles/ml. The cytotoxicity was produced at the two highest concentrations tested (500 and 1,000 nmoles/ml). The test was negative with fluridone at any concentration from 0.5 to 100 nmoles/ml. The study is classified as Acceptable/guideline and satisfies the requirements for FIFRA Test Guideline 84-2 for a UDS assay.

In an *in vivo* Chinese hamster bone marrow sister chromatid exchange (SCE) assay (MRID 070942), tablets of BrdU were implanted into the abdomen and five hours later fluridone (Lot No. D36-Y25-91; purity 97.8% a.i.; solubilized in DMSO and diluted in corn oil) was administered in a single intraperitoneal injection. The dosages of fluridone were 62.5, 125, 250 and 500 mg/kg. The bone marrow was harvested from both femurs of each animal. Twenty-five metaphases per hamster were evaluated for SCE. The cytotoxicity was produced at the two highest concentrations tested (250 and 500 mg/kg). The test chemical did not induce sister chromatid exchanges in Chinese hamster bone marrow cells as compared to the solvent control in this study. The study is classified as Acceptable/guideline and satisfies the requirements for FIFRA Test Guideline for a sister chromatid exchange (SCE) assay.

4.8 Neurotoxicity

Adequacy of data base for Neurotoxicity:

The available data base indicated that this chemical does not induce neurotoxicity.

870.6100 Delayed Neurotoxicity Study - Hen

No delayed neurotoxicity study in hens is available nor is one required.

870.6200 Acute Neurotoxicity Screening Battery

No acute neurotoxicity screening battery study is available nor is one required.

870.6300 Developmental Neurotoxicity Study

No developmental neurotoxicity study in rats is available nor is one required.

4.9 Metabolism

Adequacy of data base for metabolism: The data base for metabolism is considered to be complete. No additional studies are required at this time.. The details are presented below.

870.7485 Metabolism Study

In an oral metabolism study in rats (MRID Nos. 00103261 and 00103262), fluridone is rapidly and almost completely absorbed into the systemic circulation and eliminated in both the male and

female rats within 3 days. The total radioactivity recovered within 3 days after dosing in the urine and feces were 78-90% and 87-97% of administered dose in males and females, respectively. Majority of the radioactivity eliminated via feces (approximately 70%). No tissue accumulation was observed. In another metabolism study in rats (MRID No.44265101), the major components in the feces were identified as fluridone and fluridone metabolites produced primarily by ring hydroxylation and N-demethylation.

870.7600 Dermal Absorption - Rat

Dermal absorption study with Fluridone is not available.

5.0 HAZARD ENDPOINT SELECTION

The proposed relevant toxicity endpoints and doses for risk assessment for various exposure conditions are shown in Table 3. These endpoints were selected by the risk assessment team of RRB1.

5.1 Endpoint Selection Table for Use in Human Risk Assessment (see Table 3)

Table 3 Summary of Toxicological Dose and Endpoints for Fluridone for Use in Human Risk Assessment Proposed by RRB1

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Dietary Risk Assessments			
Acute Dietary (Females 13-50 years of age)	Dev. NOAEL = 125 mg/kg/day UF = 100 Acute RfD = 1.25 mg/kg/day	FQPA SF = 1X aPAD = $\frac{\text{acute RfD}}{\text{FQPA SF}}$ = 1.25mg/kg/day	Developmental Toxicity - Rabbit LOAEL = 300 mg/kg/day based on increased incidences of abortions
Acute Dietary (General population including infants and children)	NOT APPLICABLE. A dose and endpoint were not selected for this population group because there were no effects observed in oral toxicology studies including maternal toxicity in the developmental toxicity studies in rats and rabbits that are attributable to a single exposure (dose).		
Chronic Dietary (All populations)	NOAEL= 15 mg/kg/day UF =100 Chronic RfD = 0.15 mg/kg/day	FQPA SF = 1X cPAD = $\frac{\text{chronic RfD}}{\text{FQPA SF}}$ = 0.15 mg/kg/day	2-year cancer study in mice LOAEL =25 mg/kg/day based on increased alkaline phosphatase activity and increased incidence of hepatocellular hyperplasia
Non-Dietary Risk Assessments			
Short-term exposures dermal (a), inhalation (b), and incidental oral	NOAEL= 15 mg/kg/day MOE=100	FQPA SF = 1X	2-year cancer study in mice (See as above)
Intermediate-term exposures dermal (a), inhalation (b), and incidental oral	NOAEL= 15 mg/kg/day MOE=100	FQPA SF = 1X	2-year cancer study in mice (See as above)
Long-term exposures dermal, inhalation, and incidental oral	The endpoint is not applicable because use pattern does not indicate long term exposure.		
Dermal absorption factor	39% - Estimated from the ratios of LOAELs of a 21 day dermal toxicity study and a developmental toxicity study in rabbits.		
Cancer	Classification: Not likely to be carcinogenic to humans		

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

a = Since an oral NOAEL was selected, a dermal absorption factor of 39% should be used in route-to-route extrapolation.

b = Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) should be used in route-to-route extrapolation.

Acute Dietary

(Females 13-50 years of age)

The maternal NOAEL of 125 mg/kg/day was selected based on increased incidences of abortions at 300 mg/kg/day (LOAEL) from the developmental rabbit toxicity study for the assessment of the *acute dietary* exposure. After reviewing all the toxicity studies in the fluridone database, the use of the developmental rabbit toxicity study to establish an *acute dietary* endpoint is the most conservative and appropriate approach.

Acute Dietary

(General population including infants and children)

A dose and endpoint were not selected for this population group because there were no effects observed in oral toxicology studies including maternal toxicity in the developmental toxicity studies in rats and rabbits that are attributable to a single exposure (dose).

Chronic Dietary

(All populations)

The NOAEL of 15 mg/kg/day was selected based on increased alkaline phosphatase activity and increased incidence of hepatocellular hyperplasia at 25 mg/kg/day (LOAEL) from a 2-year carcinogenicity study for the assessment of the *chronic dietary* exposure. A 2-year chronic/carcinogenicity toxicity study in rats, a subchronic toxicity study in mice, and a subchronic toxicity study in rats were also available for consideration (see Table 4 below). However, the 2 year cancer study in mouse was selected. This endpoint is conservative because only minor effects were observed in 90 day studies. The minor effects include centrilobular hypertrophy and increased liver and kidney weights and they were observed at LOAELs of 25 mg/kg/day in mice and 44 mg/kg/day in rats with NOAELs of 15 mg/kg/day in mice and 25 mg/kg/day in rats.

In addition, the LOAEL (25 mg/kg/day) based on decreased body weights and increased liver and kidney weights (minimal effects) from the chronic rat support the data in the 2 year cancer study in mouse which was used to establish the LOAEL of 25 mg/kg/day based on increased alkaline phosphatase activity and increased incidence of hepatocellular hyperplasia. Therefore, the

NOAEL in the 2 year cancer study in mouse study maybe a better indicator of the true NOAEL.

Incidental Oral Exposure: Short-Term (1-30 day)

The NOAEL of 15 mg/kg/day was selected based on increased alkaline phosphatase activity and increased incidence of hepatocellular hyperplasia at 25 mg/kg/day (LOAEL) from a 2-year carcinogenicity study for the assessment of the short-term incidental oral exposure. This endpoint is appropriate for short term (1 to 30 days) exposure scenario and population (toddlers).

Incidental Oral Exposure: Intermediate-Term (1-6 months)

The NOAEL of 15 mg/kg/day was selected based on increased alkaline phosphatase activity and increased incidence of hepatocellular hyperplasia at 25 mg/kg/day (LOAEL) from a 2-year carcinogenicity study for the assessment of the intermediate-term incidental oral exposure. This endpoint is appropriate for intermediate term (1-6 months) exposure scenario and population.

Dermal Absorption

An acceptable dermal absorption study is not available. However, a dermal absorption factor of 39% was estimated from the results of a 21 day dermal toxicity study and a developmental toxicity study in rabbits. This 39% value is extrapolated by comparing LOAELs of oral and dermal studies. In the 21-day dermal toxicity study in rabbits (MRID No.00 103299), the LOAEL was 768 mg/kg/day based on decreased relative kidney weights. In the developmental toxicity study in rabbits (MRID No.00103302), the LOAEL for maternal toxicity was 300 mg/kg/day based on abortion and reduced body weight and food consumption. A ratio of the LOAELs based on these endpoints in the same species indicated an approximate dermal absorption factor of 39%. It is recognized, however, a common toxicity was not present in these two studies. Under the current conditions, this comparison is probably the best we can propose.

Table 4. Comparison of a 2-year chronic/carcinogenicity toxicity study in rats, a 2-year carcinogenicity study in mice, and subchronic toxicity studies in rats and mice

Study	Dose (mg/kg/day) and effects					
2-year chronic/carcinogenicity-rat		8 (NOAEL)		25 (LOAEL) ↓ body wts ↑ liver & kidney weights (no histopathologic finding)		80 severe adverse effects

2-year carcinogenicity –mouse	5		15 (NOAEL)			50 (LOAEL) ↑ hyperplasia of liver	
90-day oral toxicity-mouse	4.6	8.3	15 (NOAEL)	25 (LOAEL) ↑ hypertrophy of liver	42 ↑ hypertrophy of liver		
90-day oral toxicity-rat				25	44 ↑ liver & kidney wts (↑ 13%)		87 ↑ hypertrophy of liver

Dermal Exposure: Short-Term (1- 30 days) Exposure

The NOAEL of 15 mg/kg/day was selected based on increased alkaline phosphatase activity and increased incidence of hepatocellular hyperplasia at 25 mg/kg/day (LOAEL) from a 2-year carcinogenicity study for the assessment of the short-term dermal exposure. This endpoint is appropriate for short term (1 to 30 days) exposure scenario and population.

Dermal Exposure: Intermediate-Term (1 - 6 Months)

The NOAEL of 15 mg/kg/day was selected based on increased alkaline phosphatase activity and increased incidence of hepatocellular hyperplasia at 25 mg/kg/day (LOAEL) from a 2-year carcinogenicity study for the assessment of the intermediate-term dermal exposure. This endpoint is appropriate for intermediate term (1-6 months) exposure scenario and population.

Dermal Exposure Long-Term (> 6 Months)

The endpoint is not applicable because use pattern does not indicate long term exposure.

Inhalation Exposure: Short -Term (1- 30 days)

The NOAEL of 15 mg/kg/day was selected based on increased alkaline phosphatase activity and increased incidence of hepatocellular hyperplasia at 25 mg/kg/day (LOAEL) from a 2-year carcinogenicity study for the assessment of the short-term inhalation exposure. This endpoint is appropriate for short term (1 to 30 days) exposure scenario and population (toddlers). Since an oral endpoint was selected for inhalation exposure, therefore, absorption via the inhalation route is assumed to be equivalent to oral absorption (100% default value).

Inhalation Exposure: Intermediate-Term (1- 6Months)

The NOAEL of 15 mg/kg/day was selected based on increased alkaline phosphatase activity and

increased incidence of hepatocellular hyperplasia at 25 mg/kg/day (LOAEL) from a 2-year carcinogenicity study for the assessment of the intermediate-term inhalation exposure. This endpoint is appropriate for intermediate term (1-6 months) exposure scenario and population. Since an oral endpoint was selected for inhalation exposure, therefore, absorption via the inhalation route is assumed to be equivalent to oral absorption (100% default value).

Inhalation Exposure: Long-Term (> 6 Months)

The endpoint is not applicable because use pattern does not indicate long term exposure.

5.2 Dermal Absorption

Dermal Absorption Factor: 39%

See under 5.0 HAZARD ENDPOINT SELECTION

5.3 Classification of Carcinogenic Potential

5.3.1 Conclusions

The carcinogenicity data showed that Fluridone did not produce an increase in tumor incidence in any treated groups when compared to controls in the combined chronic/carcinogenicity study in rats and in carcinogenicity study in mice.

5.3.2 Classification of Carcinogenic Potential

The HED Cancer Assessment Review Committee (TXR 007726, July 15 and October 7, 1985) concluded that Fluridone be classified as a Group E carcinogen "not likely to be carcinogenic to humans". This classification is based on the lack of evidence of carcinogenicity in mice and rats.

5.3.3 Quantification of Carcinogenic Potential

No quantification is needed.

6.0 FQPA CONSIDERATIONS

6.1 Special Sensitivity to Infants and Children

The special FQPA Safety Factor can be removed (1X) because:

- 1) acceptable developmental and reproduction studies have been submitted and reviewed;
- 2) there is no evidence (quantitative or qualitative) of susceptibility following *in utero* exposure to rats;

3) there is low level of concern and no residual uncertainties for the effects seen in the developmental toxicity study in rabbits and in the 2-generation reproduction studies after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment.

NOTE: The recommended Special FQPA Safety Factor assumes that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

6.2 Recommendation for a Developmental Neurotoxicity Study

The available toxicity data on fluridone showed no neurotoxicity or offspring toxicity in a reproduction study which would warrant a recommendation for requiring a developmental neurotoxicity.

7.0 OTHER ISSUES

Currently there are no other issues.

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9.0 APPENDICES
Tables for Use in Risk Assessment

9.1 Toxicity Profile Summary Tables

9.1.1 Acute Toxicity Table - See Section 4.1

9.1.2 Subchronic, Chronic and Other Toxicity Tables

DER #	STUDY TYPE– DOSE LEVELS	NOAEL m/k/d	LOAEL m/k/d	EFFECTS
1	<p>2-year combined chronic/carcinogenicity (1980) –RAT</p> <p>0, 200, 650, 2000 ppm for 2 years (0,7.65, 25.15, 80.8 mg/kg/day in males and 9.17, 30.11, 97.00 mg/kg/day in females)</p> <p>MRID103305 and 103251</p>	<p>7.65</p> <p>ADI = 8 mg/kg/d</p>	25.15	<p>↓ body weights (92% of controls; p<0.05)</p> <p>↑ absolute and relative liver and kidney weights</p> <p>Treatment related increase in tumor incidence was not found.</p> <p>At 80.8 mg/kg/day (HDT)</p> <p>↑ mortality (87% in ♂; 37% in ♀)</p> <p>↑ chromorhinorrhea, anorexia, cloudy eyes, pale eyes</p> <p>↓ body weight (59-66% in ♂; 81-89% in ♀)</p> <p>↓ food consumption</p> <p>↓ RBC counts, Hb, hematocrit, MCV, MCH</p> <p>↓ lymphocyte and eosinophil counts</p> <p>↑ nucleated erythrocytes, leukocyte and neutrophil counts</p> <p>↑ total leukocyte count</p> <p>↑ BUN, creatinine, bilirubin</p> <p>↑ small testes, dose-related trends in number of enlarged, pale and/or granular kidneys; opaque, cloudy, pale, red, or ulcerated eyes; and skin nodules or masses.</p> <p>↑ absolute and relative liver and kidney weights</p> <p>↑ atrophy of testes, ocular keratitis, epidermal inclusion cyst</p>

DER #	STUDY TYPE– DOSE LEVELS	NOAEL m/k/d	LOAEL m/k/d	EFFECTS
2	2-year carcinogenicity –mouse (1981-1982) 0, 33, 100, or 330 ppm for 2 years (equivalent to 0, 5, 15 or 50 mg/kg/day) MRID No.103252 & 103335	15	50	↑ alkaline phosphatase activity (209% of controls) ↑ incidence of hepatocellular hyperplasia (2, 2, 4, and 6 cases in control, low-, mid-, and high-doses) Treatment related increase in tumor incidence was not found.
3	1-year chronic study in dog (1981) of 0, 75, 150, or 400 mg/kg/day MRID No. 103336	150	400	↑ absolute liver weights ↑ alkaline phosphatase activity (in female dogs)
4	Developmental toxicity–rats (1986) CD rats 0, 100, 300, or 1000 mg/kg/day by oral gavage on gestation days 6 through 15 inclusive MRID 159963	maternal 100 developmental 300	maternal 300 developmental 1000	↓ body weight gain and food consumption ↓ fetal body weight, ↑ rudimentary ribs ↑ delayed ossification in sternebrae and pelvic girdle
5	Developmental toxicity–rabbits (1980) Dutch Belted rabbits (15/sex/dose) on days 6-18 of gestation at dose levels of 0, 125, 300, or 750 mg/kg/day MRID 103302	maternal 125 developmental 125	maternal 300 developmental 300	↓ body weight and food consumption ↑ incidences of abortions (4/14 aborted between days 20 and 25 of gestation) ↑ incidences of abortions (see above) At 750 mg/kg/day, 6/11 aborted between days 20 and 25 of gestation

DER #	STUDY TYPE– DOSE LEVELS	NOAEL m/k/d	LOAEL m/k/d	EFFECTS
6	<p>3-generation reproduction study—rat (1980)</p> <p>0, 200, 650, or 2000 ppm. calculated intake of fluridone during the growth phases over the 3 generations were 10.6-11.1, 35.5-36.6, or 111.9-112.3 mg/kg/day for males and 12.4-13.2, 40.4-44, or 128-131.4 mg/kg/day for females.</p> <p>MRID 103304</p>	<p>parental toxicity >112, HDT</p> <p>offspring toxicity</p> <p>36</p> <p>Reproductive toxicity >112, HDT</p> <p>Developmental toxicity</p> <p>>112, HDT</p>	<p>parental toxicity >112</p> <p>offspring toxicity</p> <p>112</p> <p>Reproductive toxicity >112</p> <p>Developmental toxicity >112</p>	<p>↓ pup weight (90.7% of controls; p<0.05; on lactation day 21)</p>

DER #	STUDY TYPE– DOSE LEVELS	NOAEL m/k/d	LOAEL m/k/d	EFFECTS
7a	Metabolism study–RAT (1981) ¹⁴ C-labeled Fluridone (¹⁴ C labeled in the 4-position of the pyridinone ring) 10, 100, 250, 500 or 1000 mg/kg MRID 103261 & 103262			Readily absorbed and eliminated. Total recovery of dosed radioactivity = 78-90% (3 days) 4-19 % (urine) 68-85 % (feces) Negligible% (tissues and carcasses) 66% (bile) Component in urine and feces–not identified Major component (37% of dose) in bile–not identified Minor component in bile: Fluridone (8% of dose) 4-hydroxyphenyl fluridone (6% of dose)
7b	Metabolism study–RAT (1997) ¹⁴ C-labeled Fluridone 10 or 1000 mg/kg MRID 44265101			Eight (8) metabolites were identified from feces. Fluridone was extensively metabolized primarily through ring hydroxylation and N-demethylation.
8	21-Day Dermal Toxicity - Rabbit (1981) 0, 192, 384 or 768 mg/kg/day for 21 days (6 hours/day and 5 days/week). MRID No. 103299	systemic 384 dermal toxicity lower than 192 (LDT)	systemic 768 dermal toxicity lower than 192 (LDT)	decreased relative kidney weights (85% of controls, p<0.05) transient, slight erythema in 9/10 animals accompanied by slight desquamation at 192 mg/kg (LDT)

DER #	STUDY TYPE– DOSE LEVELS	NOAEL m/k/d	LOAEL m/k/d	EFFECTS
9	<p>90-day oral toxicity-mice (1978) 0, 62, 110, 200, 330, or 560 ppm (equivalent to 0, 9.3, 16.5, 30, 49.5 or 84 mg/kg/day based on 1 ppm = 0.15 mg/kg/day) MRID 82342</p> <p>NOTE: 50% of the theoretical concentration was present in the feed sample after 3 months storage. Therefore, corrected doses administered are 4.6, 8.3, 15, 25, and 42 mg/kg/day.</p>	<p>15 –see note under study type</p>	<p>25 –see note under study type</p>	<p>↑ centrilobular hypertrophy of the liver (incidences of centrilobular hypertrophy of the liver were 0/30, 1/28, 2/29, 3/29, and 6/30 cases in control, low-, mid-, high- and highest-doses)</p> <p>NOTE: The dose related findings of this lesion was also observed in other 90-day mouse study with fluridone (MRID No. 82341)</p>
10	<p>90-day oral toxicity-rat (1978) 0, 330, 560, 1000, 1400, or 2000 ppm (males: 0, 30, 54, 106, 139, or 178.4; females: 0, 34, 53, 94, 126, or 202 mg/kg/day based on initial food consumption) MRID 135209</p> <p>NOTE: 81.9% of the theoretical concentration was present in the feed sample after 1 week storage. Therefore, corrected doses administered are 25, 44, 87, 114, or 146 m/k/d for males.</p>	<p>25 –see note under study type</p>	<p>44 –see note under study type</p>	<p>↑ absolute and relative liver (112-113% of controls) and relative kidney weights (106% of controls) (males only)</p> <p>In males at 2 highest doses (114 and 146 m/k/d) ↑ centrilobular hypertrophy of the liver (1/15 of 114 m/k/d group) (12/15 of 146 m/k/d group)</p>

DER #	STUDY TYPE– DOSE LEVELS	NOAEL m/k/d	LOAEL m/k/d	EFFECTS
11	90-day oral toxicity-dog (1978) 0, 50, 100, or 200 mg/kg/day (oral capsules) MRID: 82344	>250 (HDT)	not establishe d	
12	dermal absorption rat			not available
13	Microbial mutagenicity assay (Ames assay) MRID 255339			not mutagenic
14	<i>In Vivo</i> Mammalian Cytogenetics - Sister Chromatid Exchange assay in Chinese hamsters MRID 070942			Not mutagenic
15	Unscheduled DNA damage/repair MRID 070942			Not mutagenic
16	Unscheduled DNA damage/repair MRID 070942			Not mutagenic