CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

FLURIDONE

Chemical Code # 2279, Tolerance # 420

Original: 8/20/87
Revised: 2/9/00

I. DATA GAP STATUS

Combined, rat :	No data gap; **possible adverse effect**
Chronic toxicity, dog:	No data gap; no adverse effect
Oncogenicity, mouse:	No data gap; possible adverse effect
Reproduction, rat:	No data gap; no adverse effect
Teratology, rat:	No data gap; no adverse effect
Teratology, rabbit:	No data gap; no adverse effect
Gene mutation:	No data gap; no adverse effect
Chromosome effects:	No data gap; no adverse effect
DNA damage:	No data gap; no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 154296 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T166658
Revised by Peter Leung, 2/9/00

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 015, 028; 44085, 64273; "Two-Year Chronic Dietary Toxicity Study of EL-171 (Fluridone) in the Rat." (G. S. Probst et. al., Toxicology Division, Lilly Research Lab., Greenfield, IN, R-1136 and R-1146 for 2-year report, R-1126 for 1-year report, 8/1980); Fluridone (Lot D36-Y25-091, 97.2 - 97.8% purity); fed at 0, 200, 650 or 2000 ppm in the diet to 60/sex/group for 2 years and 15/sex/group for 1 year**; possible adverse effect:** Glomerulonephritis at 2000 ppm in 1 year and at 650 and 2000 ppm in 2-year study. The study was initially evaluated as acceptable as an oncogenicity study only (Carlisle, 7/3/86) because of lack of interim data. Record 64273 contains the 1-year data and collectively with the 3-month studies, the studies are upgraded to **acceptable** as a combined feeding study. (Carlisle, 7/3/86 and Gee, 4/11/88).

CHRONIC TOXICITY, DOG

** 016; 44104; "A one-year chronic Toxicity Study of EL-171 Administered Orally to Beagle Dogs." (G.S.Probst et. al., Toxicology Division, Lilly Research Lab., Greenfield, IN, study D-3568, 6/1981); Fluridone (Lot # D36-Y93-107, 98.1% purity); doses of 0, 75, 150 or 400 mg/kg/day by capsule; animals of different ages (> 1 year differences), from different sources. all dogs survived the study; females from the 400 mg/kg/day dose group exhibited significant increases in absolute liver weight (males: 285.5 vs. 240.5, not significant; females: 296.7 vs. 230.9, $p < 0.05$) and elevated alkaline phosphatase activity which was first observed during the fifth week of ths study and persisted until termination; however, hepatic microsomal mixed function oxidase was not induced; NOEL = 150 mg/kg/day (increased liver weight and elevated alkaline phosphatase); **no adverse effect; acceptable**; (Carlisle, 6/30/86).

ONCOGENICITY, MOUSE

** 014, 028; 44090, 64272; "A Two-year Chronic Dietary Toxicity Study of EL-171 (Fluridone) in the Mouse." (G.S.Probst et. al., Toxicology Division, Lilly Research Lab., Greenfield, IN, studies M-9407, 9417 and M-9397, 12/81); Fluridone (97.2-97.8% purity); administered to ICR mice at 0, 33, 100 or 330 ppm in the diet equivalent to 0, 3.5, 10.9 or 30.7 mg/kg/day in males and 0, 4.0, 12.3 or 34.5 mg/kg/day in females; liver enzyme induction at high dose, borderline decrease in survival in the high dose group. **Possible adverse effect:** increased skin fibrosarcomas in high dose females. **acceptable**; 64272 is the 1-year report on 15/sex/group at the same concentrations in the diet. (Carlisle, 7/2/86 and Gee, 4/11/88).

REPRODUCTION, RAT

** 018, 042; 44095, 138394; "One-Generation Reproduction Bridging Study of Fluridone (EL-171, compound 112371) Administered in the Diet to Fischer 344 Rats (Studies R04090 and R21890)" submitted to support "A Multigeneration Reproduction Study with EL-171 in Rat (Studies R-338, R-888 and R-19)" (J. A. Hoyt, Toxicology Research Lab., Lilly Research Laboratories, Greenfield, IN, Study #s R04090 and R21890, 5/24/95); Dietary concentrations of fluridone (Lot# 117AS8, 99.5% purity): 0, 0.02, 0.065 or 0.2% administered daily to 30 rats/sex/dose in the F_7 generation for 10 weeks during premating, mating, gestation and lactation and in the F_7 generation throughout a 10 week postweaning growth period; two deaths in the F_7 generation (one male from the 0.065% group and one female from the 0.2% group) attributing to failure to adjust to ventilated caging were reported; no treatment-related effects on reproduction parameters; however, the live birth index was slightly depressed (92.74% of control, $p < 0.05$) in the 0.2% group as compared to control group; at 0.2%, 8/23 litters contained one or more offspring which were considered stillborn; in the F_7 and F_7 generations, males and females treated at the 0.2% level exhibited increased absolute kidney weight; minimal to slight bilateral chronic multifocal nephrosis detected in F_7 males of the 0.065% and 0.2% dose groups and in F_7 males and females of the 0.2% dose group; although dose related increases in absolute liver weight occurred in F_7 and F_7 generations in both sexes in the 0.065% and 0.2% dose groups, the liver weight increases were not accompanied by histopathological changes; **no adverse effects**; parental NOEL = 0.02% (based on bilateral chronic multifocal nephrosis and increased liver weight), developmental NOEL = 0.065% (depressed liver birth index); originally unacceptable and not upgradeable (Van Way and Parker, 7/18/86) and subsequently upgraded to **acceptable** (Leung, 8/3/95).

TERATOLOGY, RAT

019; 44093; "Teratology Study with EL-171 (Fluridone) in the Fischer 344 Rat." (G.S.Probst et. al., Toxicology Division, Lilly Research Lab., Greenfield, IN, study R-0018, 4/80); Fluridone (lot 367-Q52-59, 99.4% purity); 25/group given 0, 20, 65 or 200 mg/kg/day on days 6-15 of gestation; NOEL not established, > 200 mg/kg/day; No maternal toxicity or developmental toxicity; **unacceptable** (inadequate dose level selection) and **Not upgradeable**. (Gee, 7/1/86).

018; 44095; "Multi-generation Reproduction Study with EL-171 (Fluridone) in the Rat." (J.A. Hoyt, Toxicology Research Lab., Lilly Research Laboratories, Greenfield, IN, Studies, Lilly R-338, R-888 & R-19, 9/80); Fluridone, (Lilly compound 112371, Lot #X-29478, 99.5% purity) @ 0, 0.02, 0.065 or 0.2% in diet to 25/sex/dose group for 3 generations, the teratology conducted on the F_{3c} group; **unacceptable, not upgradeable**. No MTD. Few fetal findings described. Maternal and Developmental NOEL > 0.2% (HDT). (Gee, 7/1/86 and Parker, 7/16/86).

** 025 48849 "A Second Teratology Study of Fluridone (EL-171, Compound 112371) in Rats." (G.S.Probst et. al., Toxicology Division, Lilly Research Lab., Greenfield, IN, study R14285, 5/14/86); Fluridone (Lot 414DT4, 99.59% purity) tested at 0, 100, 300 or 1000 mg/kg/day, gavage on days 6-15 of gestation to 25 CD rats/dose level; no teratogenic effect; maternal NOEL = 100 mg/kg/day (decreased weight gain and food consumption); developmental NOEL = 300 mg/kg/day (decreased fetal weight).

Acceptable. (Parker, 1/6/87).

TERATOLOGY, RABBIT

** 019, 030; 44092, 44094, 68939; "Teratology Study with EL-171 (Fluridone) in the Dutch Belted Rabbit." (G.S.Probst et. al., Toxicology Division, Lilly Research Lab., Greenfield, IN, study B-7158, 4/80 and 6/88); Fluridone (Lot X-29478, 99.5% purity) given by oral gavage at 0, 125, 300 or 750 mg/kg/day on days 6-18 of gestation; 15/group; maternal deaths and abortions were observed at 300 and 750 mg/kg/day and an increased frequency of resorption at 750 mg/kg/day; no maternal toxicity or reproduction effects were noted at 125 mg/kg/day; NOEL = 125 mg/kg (maternal & developmental toxicity); 68939 contains a retrospective analysis of dosing solutions, stability data and copies of notebook pages for preparation of solutions. Initially evaluated as unacceptable but possibly upgradeable. With submission of 68939, the study is upgraded to **acceptable** status with **no adverse effects**. (Gee, 7/1/86 and 8/17/88).

GENE MUTATION

003, 017; 31921; "The Effect of Lilly Compound 112371, EL-171, upon Bacterial Systems Known to Detect Mutagenic Events." (J.C. Cline et. al., Lilly Research Laboratories, Greenfield, IN, 4/24/78); Fluridone (Lot D36-Y25-091, no purity stated); gradient plate method at 0.1-1, 1-10, 10-100 & 100-1000 ug/ml; strains include Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100, others and E. coli WP2 & WP2uvrA$^-$ ± S9 from rat liver; no evidence of cytotoxicity or mutagenicity; **Unacceptable, not upgradeable.** (Gee, 6/20/86).

017; 44099; "The Effect of Fluridone on the Induction of Bacterial Mutation using a Modification of the Ames Test." (C.Z. Thompson, Lilly Research Laboratories, Greenfield, IN, study 810413-GPA-574, 4/81); Fluridone (98% purity); gradient plate method at 0.1-1, 1-10, 10-100 or 100-1000 ug/ml; Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100, others and E. coli WP2 & WP2uvrA ± rat liver activation; 1 trial; no evidence of increased reversion rate; unacceptable. No repeat trial but see 44103; no justification for not using higher concentration and no evidence of diffusion in agar. (Gee 6/20/86).

017; 44100; "The Effect of Lilly Compound 125670 on the Induction of Bacterial Mutation using a Modification of the Ames Test." (C.Z. Thompson, Lilly Research Laboratories, Greenfield, IN, study 810413-GPA-1434, 4/81); Fluridone (hydroxy derivative, Lot # 462-710-1554, no purity given); Salmonella typhimurium TA1535, TA1537, TA1538. TA98, TA100 and others E. Coli WP2 and WP2uvrA$^-$; gradient plate method, 1 trial; 0.1-1000 ug/ml ± rat liver activation; no evidence of cytotoxicity or mutagenicity; Unacceptable and not upgradeable. no repeat trial. No evidence for diffusion, no justification for not using a higher concentration. See also 44103 and 44099. (Gee, 6/20/86).

** 017; 44103; "The Effect of Fluridone (EL-171), Compound 112371 on the Induction of Reverse Mutation in Salmomella typhimurium using the Ames Test." (G.S. Probst et. al., Toxicology Division, Lilly Research Lab., Greenfield, IN, Report # 840723AMS5740, 4/84); Fluridone (99.7% purity); Salmomella typhimurium TA1535, TA1537, TA1538, TA98 and TA100 ± rat liver activation; 125, 250, 500, 1000 or 2000 (ppt) ug/plate in triplicate, 1 trial (see other reports on Ames test); no

cytotoxicity; no increased reversion rate. **Acceptable**. (Gee, 6/20/86). Note: Although only one trial was run in this study, when several reports are examined together, there is sufficient evidence for the lack of mutagenicity of fluridone in the bacterial systems tested.

CHROMOSOME EFFECTS

003, 017; 31920; "A Dominant Lethal Study with EL-171 in the Rat." (G.S. Probst et. al., Toxicology Division, Lilly Research Lab., Greenfield, IN, 5/79); Fluridone (98.8% purity); 10 males were given 0 or 2 g/kg by oral gavage, one dosing and mated to one female for each 8 weekly periods; no evidence of toxicity or dominant lethal effect. **Unacceptable, not upgradeable**. No concurrent positive controls or historical data; single dose only with no evidence the MTD was approached; inadequate number of animals. No mortality, no clinical signs reported. (Gee, 6/20/86).

** 017; 44101; "The Effect of Fluridone (Lilly Compound 112371) on the In vivo Induction of Sister Chromatid Exchange in Bone Marrow of Chinese Hamsters." (G. S. Probst et. al., Toxicology Division, Lilly Research Lab., Greenfield, IN, Study CH810316, 4/1981); Fluridone (97.8% purity); 3 females/group were given 0, 62.5, 125, 250 or 500 mg/kg ip and sacrificed at 21 hours; Chinese hamsters; 2 vehicle controls and 1 positive control (cyclophosphamide); cytotoxicity at 500 > 250 mg/kg; no evidence for SCE formation. **Acceptable**. Initially reviewed as possibly upgradeable with justification of use of only females. Based on rebuttal in 420-026, #'s 56939 and 56940, the study was upgraded to acceptable status. Although there are some differences between the sexes in terms of lethality and the NOEL in a subchronic study in rats and incidence of fibrosarcomas of the skin in mice, these are considered minor differences in terms of genotoxicity effects. (Gee, 6/20/86 and 7/15/87).

DNA DAMAGE

** 017; 44098; "The Effect of Fluridone (Lilly Compound 112371) on the Induction of DNA Repair Synthesis in Primary Cultures of Adult Rat Hepatocytes." (G. S. Probst et. al., Toxicology Division, Lilly Research Lab., Greenfield, IN, Report 791120-247, 6/80); Fluridone (98% purity); Fischer 344 rat hepatocytes were exposed for 20 hours to 0, 0.5, 1, 5, 10, 50, 100, 500 or 1000 nmoles/ml; no evidence of UDS to toxic level at 1000 nmoles/ml; **acceptable**. (Gee, 6/20/86).

017; 44102; "The Effect of Lilly Compound 125670 on the Induction of DNA Repair Synthesis in Primary Cultures of Adult Rat Hepatocytes." (G.S. Probst et. al., Toxicology Division, Lilly Research Lab., Greenfield, IN, Study 810217-336-UDS, 6/81); Fluridone metabolite (no purity stated); primary Fischer 344 rat hepatocytes; unscheduled DNA synthesis by autoradiography; 20 hours with 0, 0.5, 1, 5, 10, 50, 100, 500 or 1000 nmoles/ml; cytotoxic at 500 and 1000 nmoles/ml; no increase in UDS. **Supplemental**; (Gee, 6/20/86).

NEUROTOXICITY

Not submitted and not required at this time.

None of the 6 studies submitted were acceptable; however, all will be considered adequate to fill the data gaps if the long-term studies they are intended to support are acceptable. Some are upgradeable.

SUBCHRONIC STUDIES

Oral, Dog

002/013; 31341; "A 3-Month Oral Toxicity Study of EL-171 in Beagle Dogs" (G.S. Probst, et. al., Toxicology Division, Lilly Research Laboratories, Greenfield, IN, Study D-4005, 4/78); dose selection for 44104; Fluridone, technical grade, (Lilly compound 112371, Lot #597-B29-20C, no purity statement) @ 0, 50, 100 or 200 mg/kg/day in gelatin capsules to 4/sex/dose group for 91-2 consecutive days; all dogs survived, and no adverse effects of treatment were noted; high dose dogs showed slightly decreased erythrocyte count, hemoglobin, hematocrit, slightly increased BUN and alkaline phosphatase values; NOEL $\geq$ 200mg/kg/day**; Unacceptable but possibly upgradeable** with purity statement. (Carlisle, 7/3/86; updated, Leung, 8/7/95).

002; 31342; "A 2-Week Pilot Oral Toxicity Study of EL-171 in Beagle Dogs" (G.S. Probst, et. al., Toxicology Division, Lilly Research Laboratories, Greenfield, IN, Study D-3635, 4/78); dose selection for subchronic #31341; 1/sex/dose @ 100 or 200 mg/kg/day in gelatin capsules for two weeks; all dogs survived the two week study; slight anorexia was observed in the females of both dose group; emesis and slight weight reduction observed in dogs from the 200/mg/kg groups. **Supplemental**; (Carlisle, 7/86; updated, Leung, 8/7/95).

Oral, Rat

003/013; 31345; "A 3-Month oral Toxicity Study of EL-171 in Rats" (G.S. Probst, et. al., Toxicology Division, Lilly Research Laboratories, Greenfield, IN, Study D-396, 4/78); dose selection for 44085; Fluridone (technical grade, (Lilly compound 112371, Lot #367-Q52-59, no purity statement) administered in diet at 0, 0.033, 0.056, 0.1, 0.14 or 0.2% to 15 SPF-CD Fischer 344 rats/sex/ dose/group for 85-87 days; all rats survived and no treatment-related effects were noted except for dose-related increases in liver and kidney weights; NOEL = 0.033% and 0.056% for male and female rats, respectively. **Unacceptable** (No purity statement, insufficient histopathology); (Carlisle, 7/3/86; updated, Leung, 8/7/95).

003/013; 31346; "A 3-Month Oral Toxicity Study of EL-171 in Rats" (J.G. page, et. al., Toxicology Division, Lilly Research Laboratories, Greenfield, IN, Study D-635, 4/78); dose selection for 44085; Fluridone (technical grade, Lilly compound 112371, Lot #367-Q52-59, no purity statement) administered in diet at 0, 2000, 4000 or 8000 ppm to 15 Wistar rats/sex/dose/group for 89-90 days; all rats survived; decreases in erythrocyte count, hemoglobin and hematocrit values in all treated males and increased liver

weights among all groups were noted. hepatic microsomal p-nitroanisole O-demethylase was elevated in males receiving 0.4 and 0.8% diets and in females receiving the 0.8% diet. NOEL < 2000 ppm; **Unacceptable and not upgradeable**. No purity statement. Carlisle, 7/3/86; updated, Leung, 8/7/95).
Oral, Mice

002/013; 31340; "A 3-Month Oral Toxicity Study of EL-171 in Mice" (G.S. Probst, et. al., Toxicology Division, Lilly Research Laboratories, Greenfield, IN, Study M-9175, 4/78); dose selection for 44090; Fluridone (technical grade, Lilly compound 112371, Lot #367-Q52-101C, no purity statement) administered in pelleted diet at 0, 0.2, 0.4 or 0.8% to 15/sex/dose/group for 90-91 days; all mice survived. Treatment-related effects on the liver were seen in all treated groups: increased relative and absolute liver weights, elevated microsomal p-nitroanisole O-demethylase activity, centrilobular hypertrophy, mild to moderate diffuse hepatitis with occasion focal necrosis and fatty metamorphosis in mid and high dose animals; NOEL < 0.2 % in diet, LTD; **Unacceptable, not upgradeable**. Hepatotoxicity at all levels tested, no purity statement, insufficient histopathology. (Carlisle, 7/3/86; updated, Leung. 8/7/95).

002/013; 31339; "A-Month Oral Toxicity Study of EL-171 in Mice" (G.S. Probst, et. al., Toxicology Division, Lilly Research Laboratories, Greenfield, IN, Study M-9116, 4/78); Fluridone (technical grade, Lilly compound 112371 Lot #D36-C106-250, no purity statement) administered in pelleted diet at 0, 0.033, 0.056, 0.100, 0.140 or 0.200% to 15 ICR/SPF Mice/sex/dose/group for 90-91 days; 1 female mouse from the 0.140% group died on day 94; treatment-related effects on the liver were noted in all treated groups: increased liver weights, elevated hepatic microsomal p-nitroanisole O-demethylase and increased incidence of hepatic centrilobular hypertrophy; **Unacceptable, not upgradeable**: No NOEL established because hepatic effects were noted at all dose levels, no purity statement, insufficient histopathology. (Carlisle, 7/17/86; updated, Leung, 8/7/95).

002/013; 31338; " A 3-Month Oral Toxicity Study of EL-171 in Mice" ((G.S. Probst, et. al., Toxicology Division, Lilly Research Laboratories, Greenfield, IN, Study M-9127, 4/78); dose selection 44090; Fluridone (technical grade, Lilly compound 112371, Lot #D36-Y25-091, no purity statement) administered in diet at 0, 0.0062, 0.011, 0.02, 0.033 or 0.056% to 15 ICR/SPFMice/sex/dose/ group for 91-93 days; 5 mice died; only treatment-related effect noted was hepatic centrilobular hypertrophy. Estimated NOEL = 0.0030% based on actual content in the diet. **Unacceptable, not upgradeable**; No purity statement, insufficient histopathology, poor dietary stability; Carlisle, 7/86; updated, Leung, 8/7/95)..

Dermal, rabbit

005 044036 "Subchronic (three week) dermal toxicity study in rabbits with an aqueous suspension containing 4 pounds per gallon fluridone, compound 112371, Study No. B-7300"; (Toxicology Division, Lilly Research Laboratories, Division of Eli Lilly and Company, 7/81); Dose levels of 2 ml/kg of water (5M/5F), 20% (6M/4F), 40% (5M/5F), and 80% (5M/5F) fluridone 4AS; (% 4AS doses = 192 [20%], 384 [40%], and 768 [80%] mg/kg fluridone); six hours exposure, occluded patch; dermal treatments were

performed five days a week for three consecutive weeks; moderate to severe erythema and slight edema, epidermal fissures, slight decrease in relative kidney weights in male treated rabbits; NOEL = 2 ml/kg of 20% fluridone 4AS; **Acceptable**; Berliner, 7-30-87

005; 044036; Subchronic (three week) dermal toxicity study in rabbits with an aqueous suspension containing 4 pounds per gallon fluridone, compound 112371 study B-7300; Toxicology Division, Lilly Research Laboratories, Division of Eli Lilly and Company, Greenfield, Indiana, 7/81; Dose levels 2 ml/kg of water (5M/5F), 20% (6M/4F), 40% (5M/5F), and 80% (5M/5F) fluridone 4AS; (% 4AS doses= 192 [20%], 384 [40%], and 768 [80%] mg/kg fluridone); six hours exposure, occluded patch; dermal treatments were performed five days a week for three consecutive weeks; moderate to severe erythema and slight edema, epidermal fissures, slight decrease in relative kidney weights in male treated rabbits; NOEL= 2 ml/kg of 20% fluridone 4AS; **Acceptable**; Berliner, 7-30-87

420-041; 138393; "Subchronic (21 Day) Dermal Toxicity Study in New Zealand White Rabbits with Technical Fluridone (EL-171, Compound 112371)", (Probst, G.S., et. al.; Study No. B01084; 7/85); 822; Rabbit; Toxicology Division, Lilly Research Lab., Greenfield, IN; Fluridone Technical (EL-171) (purity: 98.6%); 5 animals/sex/group; Doses: 0, 1000 mg/kg, 6 hours/day, applied under a damp gauze pad; No mortality; Clinical Observations: sign of mild erythema at application site, no treatment-related systemic signs or effect upon body weights or food consumption; No treatment-related effect upon hematology or serum chemistry; Necropsy: no treatment-related lesions or effect upon organ weights; Histopathology: no treatment-related lesions; No target organ indicated; No adverse effects; NOEL: 1000 mg/kg/day; Study **acceptable**. (Moore, 8/7/95)

METABOLISM STUDIES

012; 44017; "Radiocarbon Excretion from Fischer 344 Rats after Administration of a Single Oral Dose of ^{14}C-Fluridone" (G.S. Probst, et. al., Toxicology Division, Lilly Research Lab., Greenfield, IN, Studies R-977 & R-38, 9/81); Fluridone (technical grade, Lilly compound 112371, Lot #D36-C106-250, no purity statement) administered by oral gavage at 0, 10, 100, 250, 500 or 1000 mg/kg to 5/sex/dose/group, sampling at 24, 48 and 72 hours; 1 rat died at 4 hours; excretion occurred primarily in the feces, both males and females, and was dose-independent up to 500 mg/kg, then lower at 1000 mg/kg; **Unacceptable, not upgradeable** (No purity statement, less than 90% recovery in all groups at termination of study, only 2 of 4 required animal groups were used and no dose rationale); Hathaway, 7/86.

012; 44018; " Excretion of Radioactivity into Bile from Male Fischer 344 Rats after Administration of a Single Oral Dose of ^{14}C-Fluridone" (G.S. Probst, et. al., Toxicology Division, Lilly Research Lab., Greenfield, IN, Studies GP780208 and GP780912, 9/81); Fluridone (technical grade, Lilly compound 112371, Lot #D36-C106-250, no purity statement) suspended in acacia (10%, w/v) and administered by oral gavage to 13 male Fisher 344 rats at 100 mg/kg; bile excretion measured 24 and 48 hours after dosing; approximately 61.4% of the originally administered radioactivity was excreted in the bile by 48 hours. (No purity statement, dosage selection rationale, and justification of sex and number of animals); **Supplemental**; (Hathaway, 7/86).

012; 44019; "Distribution of Radioactivity into Tissues and Organs from Fischer 344 Rats after Administration of a Single Dose of ^{14}C-Fluridone" (G.S.Probst et. al., Toxicology Division, Lilly Research Lab., Greenfield, IN, Studies R-518 & R-618, 1981); Fluridone (technical grade, Lilly compound 112371, Lot #D36-C106-250, no purity statement) administered by oral gavage at 100 mg/kg to 15/sex, and tissues

measured (5/sex) at 4, 24 or 96 hours after dosing; approximately 90% of the radioactivity present in the tissues at 4 hours had cleared by 96 hours; No major trend toward the accumulation of fluridone in major tissues or organs was determined; No purity statement, dosage selection rationale; **Supplemental**; (Hathaway, 7/14/86).

420-049 154296 851 "Fluridone: Rat Metabolism Study" by R.A. Robinson, XenoBiotic Laboratories, Inc., Plainsboro, NJ (study #XBL 96061; 4/24/97). Preliminary study: Group A, 2M/2F exposed to a single oral dose of [^{14}C]fluridone (ABC lot #030196; radiopurity 99.8%; for test solutions [^{14}C]fluridone was mixed w/[^{12}C]fluridone, lot #AT93UU36, 100% purity; test substance was suspended in 1% sodium carboxymethyl cellulose [CMC]) at ~10 mg/kg. Group B, 1M/1F exposed to a single oral dose at ~1000 mg/kg. Urine, feces & cage rinses were collected daily for 7 days (because expired (trapped) $^{14}CO_2$ accounted for <1% of the dose after 24 hr, further $^{14}CO_2$ measurements were discontinued). Definitive study: Group C, vehicle controls, 2M/2F exposed to a single oral dose of 1% CMC. Group D, 5M/5F exposed to a single oral dose at ~7.4 mg/kg. Group E, 7M/7F exposed to ~10 mg/kg unlabeled fluridone once daily for 14 days, then 5M/5F exposed on day 15 to ~10 mg/kg [^{14}C]fluridone. Group F, 5M/5F exposed to a single oral dose at ~900 mg/kg. Urine, feces & cage rinses were collected twice daily for 2 days and daily for the next 5 days. After sacrifice, label was measured in a range of tissues. Extracts of urine and feces from both the Preliminary and Definitive studies were analyzed for metabolite identity by HPLC, TLC, radiochromatography, NMR & MS. Clinical signs (lack of mobility, abnormal & rapid head movement, squinting, loss of balance & cage biting) occurred only at the HD (Groups B & F), clearing w/I 24 hr. Results, Group A: by 7 days, 12.52%/12.89% (M/F) was excreted in urine and 72.76%/81.79% in feces. Group B: by 7 days 4.83%/3.43% was excreted in urine and 86.43%/86.31% in feces. Group D: by 24 hr 11.14%/10.44% was excreted in urine and 72.46%/77.72% in feces. By 7 days 11.61%/10.93% was excreted in urine and 79.19%/84.62% in feces. Combined excretion (including cage rinse) by 7 days was 92.93%/98.74%. Group E: by 24 hr 9.54%/8.51% was excreted in urine and 70.69%/69.90% in feces. By 7 days 10.11%/9.14% was excreted in urine and 79.80%/81.79% in feces. Combined excretion (including cage rinse) by 7 days was 92.81%/94.21%. Group F: by 24 hr 2.40%/2.43% was excreted in urine and 27.16%/27.18% in feces (thus, a relative delay in fecal excretion at the HD). By 7 days 8.30%/8.07% was excreted in urine and 91.58%/90.09% in feces. Combined excretion (including cage rinse) by 7 days was 101.02%/99.62%. Total tissue residues were always <1% of the dose (Groups D-F). Under all conditions, highest tissue levels occurred in the liver. The major metabolites were a variety of polar & non-polar compounds resulting from aromatic hydroxylations and heteroaromatic N-demethylation. The parent compound was the primary fecal component over the 1st 72 hr. **Acceptable**. (Rubin, 9/11/97)