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Flurprimidol; CASRN 56425-91-3

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Flurprimidol

File First On-Line 07/01/1989

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	07/01/1989
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Flurprimidol
CASRN — 56425-91-3
Primary Synonym — Cutlass
Last Revised — 07/01/1989

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of

substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Increased incidence of hepatocellular changes including fatty change and vacuolation (M); increased susceptibility to stress factors (F) 2-Generation Rat Reproduction Study Eli Lilly and Co., 1986a	NOEL: 25 ppm (1.8 mg/kg/day) LEL: 100 ppm (7.3 mg/kg/day)	100	1	2E-2 mg/kg/day

*Conversion Factors: Calculated from time weighted averages of food consumption and body weight

I.A.2. Principal and Supporting Studies (Oral RfD)

Eli Lilly and Company. 1986a. MRID No. 00162770. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Three week old Crl:CD(SD) rats, 25/sex/dose, weighing 148 and 125 grams for F0 males and females, respectively, were administered 0, 25, 100, and 1000 ppm (0, 1.8, 7.3, and 74 mg/kg/day) flurprimidol (100% pure) for 70 days prior to mating (about 15 weeks of age). They were then bred to obtain the F1a litters. These progeny were raised until weaning age [Postpartum (PP) day 21]. The F0 rats were then mated again producing the F1b litters. Following a 70 day feeding period (15 weeks of age) the F1a rats were bred to obtain the F2a

litters. After the F2a litters were weaned, the F1 parents (about 26 weeks old) were mated again to produce the F2b litters.

No parental systemic toxicity was observed at 25 ppm (1.8 mg/kg/day) whereas an increased incidence of altered hepatocellular histology was observed in both generations of males at 100 ppm (7.3 mg/kg/day), as well as the high-dose females. Hepatocellular changes included fatty change, vacuolation and centrilobular hypertrophy (HDT only). Increased susceptibility to stress factors was observed in the first generation females. (Note: stress observed in the females was the result of being transferred to delivery cages.) The increased evidence of stress at 100 and 1000 ppm was indicated by signs of toxicity (pallor and weakness) prior to death. Thus the NOEL and LEL for parental systemic toxicity is 25 ppm (1.8 mg/kg/day) and 100 ppm (7.3 mg/kg/day), respectively.

The NOEL for reproductive toxicity is 100 ppm (7.3 mg/kg/day) and the LEL is 1000 ppm (74 mg/kg/day) based on decreased fertility (male and female) and gestation survival with an associated decrease in litter size. Although these effects occurred in both generations, they were more pronounced in the second generation. The reproductive cycle in the female was altered, characterized by prolonged vaginal estrous and absence of corpora lutea. A decrease in neonatal survival and depressed neonatal body weight was also observed at 1000 ppm.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 100 was used to account for the inter- and intraspecies differences.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

Data Considered for Establishing the RfD

- 1) 2-Generation Reproduction - rat: Principal study - see previous description; core grade minimum
- 2) 2-Year Feeding (oncogenic) - rat: NOEL=90 ppm (3.6 mg/kg/day); LEL=300 ppm (12.1 mg/kg/day) (hepatocellular changes in males including enzyme induction, fatty change, hepatocellular eosinophilic change, and focal atypia); At 1000 ppm (41.2 mg/kg/day) there was also a transient body weight and weight gain decrease (males), increased cholesterol and triglycerides (males and females), increased hepatic enzyme induction and liver weight, fatty

change and hepatocellular eosinophilic change (females); core grade minimum for chronic feeding (Eli Lilly and Co., 1987a)

3) 1-Year Feeding - dog: NOEL=7 mg/kg/day; LEL=30 mg/kg/day [HDT; adrenal changes including decreased plasma cortisol response to ACTH stimulation (males), decreased relative and absolute adrenal weight (males) and degenerative changes to the zona fasciculata of the adrenal cortex which was characterized by eosinophilic degeneration, vacuolation and cortical atrophy; slight increase in hepatic p-nitroanisole O-demethylase activity (males)]; core grade minimum (Eli Lilly and Co., 1987b)

4) Teratology - rat: Maternal NOEL=10 mg/kg/day; Maternal LEL=45 mg/kg/day (decreased body weight gain and food consumption); At 200 mg/kg/day there was increased mortality, stained perigenital area and snout, chromodacryorrhea, decreased muscle tone, hypoactivity, and alopecia); Developmental NOEL=10 mg/kg/day; Developmental LEL=45 mg/kg/day (decreased fetal weight, increased incidence of hydronephrosis, hydroureter, and numerous developmental skeletal anomalies); The 200 mg/kg/day group also had a reduction in the proportion of live fetuses, and an increase in the incidence of resorptions and runts; core grade minimum (Eli Lilly and Co., 1987c)

5) Teratology - rabbit: Maternal NOEL=9 mg/kg/day; Maternal LEL=45 mg/kg/day (decreased body weight and food consumption); Developmental NOEL=45 mg/kg/day; Developmental LEL=none; core grade minimum (Eli Lilly and Co., 1987d)

Other Data Reviewed:

1) Chronic Feeding (oncogenic) - rat: NOEL=none (LDT; hepatocellular changes in males and females including increased absolute and relative organ weight, fatty change, hepatocellular eosinophilic change and focal atypia; transient body weight and weight gain decrease in males); core grade supplementary for chronic feeding; (Eli Lilly and Co., 1987e)

2) 2-Year Feeding (oncogenic) - mouse: NOEL=10 ppm (1.4 mg/kg/day); LEL=80 ppm (10.5 mg/kg/day) (increased absolute and relative liver weight in females; At 600 ppm (79.9 mg/kg/day) there was an increase in liver weight in males); core grade supplementary (Eli Lilly and Co., 1987f)

3) 90-Day Feeding - rat: NOEL=1.68/1.98 mg/kg/day (M/F); LEL=6.04/7.13 mg/kg/day (M/F) (increased p-nitroanisole O-demethylase activity); core grade minimum (Eli Lilly and Co., 1982)

4) 90-Day Feeding - dog: NOEL=2 mg/kg/day; LEL=10 mg/kg/day (adrenal cortical vacuolation, decreased adrenal weight, increased hepatic enzyme induction, males only); At 80

mg/kg/day (HDT) there was increased hepatic enzyme induction for females, testicular atrophy or depressed spermatogenesis in males (and possibly at 10 mg/kg/day), accompanied by inactive prostates; core grade minimum (Eli Lilly and Co., 1986a)

5) 90-Day Feeding - dog: NOEL=1.5 mg/kg/day; LEL=30 mg/kg/day [HDT; adrenal changes (M&F) including decreased plasma cortisol response to ACTH stimulation, decreased relative and absolute organ weight and degenerative changes of the adrenal cortex; The adrenal histopathology was limited to the zona fasciculata and zona reticularis of the adrenal cortex, characterized by eosinophilic degeneration, vacuolation, and cortical atrophy]; core grade minimum (Eli Lilly and Co., 1986b)

6) 90-Day Feeding - mouse: NOEL=100 ppm (15 mg/kg/day); LEL=450 ppm (67.5 mg/kg/day) (increased incidence of hepatocellular hypertrophy in the males); At 2000 ppm there was evidence of enzyme induction, increased liver weight, as well as hepatocellular hypertrophy in both males and females; core grade guideline (Eli Lilly and Co., 1985)

Data Gap(s): None

I.A.5. Confidence in the Oral RfD

Study — Medium

Database — High

RfD — High

The critical study is of good quality and is given a medium confidence rating. Comparison of LELs from the subchronic and chronic rat and mouse studies indicate that the rat is the most sensitive species; therefore, the chronic rat study is the appropriate study upon which to base the RfD. Additional studies are supportive and of good quality and therefore the database is given a high confidence rating. High confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — Pesticide Registration Standard, June 1988; Pesticide Registration Files

Agency Work Group Review — 04/20/1989

Verification Date — 04/20/1989

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Flurprimidol conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Flurprimidol
CASRN — 56425-91-3
Primary Synonym — Cutlass

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Flurprimidol
CASRN — 56425-91-3
Primary Synonym — Cutlass

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Flurprimidol

CASRN — 56425-91-3

Primary Synonym — Cutlass

VI.A. Oral RfD References

Eli Lilly and Company. 1982. MRID No. 00117945. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Eli Lilly and Company. 1985. MRID No. 00162767. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Eli Lilly and Company. 1986a. MRID No. 00162770. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Eli Lilly and Company. 1986b. MRID No. 00158239. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Eli Lilly and Company. 1986c. MRID No. 00162769. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Eli Lilly and Company. 1987a. MRID No. 40486003. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Eli Lilly and Company. 1987b. MRID No. 40486001. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Eli Lilly and Company. 1987c. MRID No. 40396601, 00147301. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Eli Lilly and Company. 1987d. MRID No. 40396602, 00141300. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Eli Lilly and Company. 1987e. MRID No. 40486002. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Eli Lilly and Company. 1987f. MRID No. 40513701. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Flurprimidol

CASRN — 56425-91-3

Primary Synonym — Cutlass

Date	Section	Description
07/01/1989	I.A.	Oral RfD summary on-line
12/03/2002	I.A.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Flurprimidol

CASRN — 56425-91-3

Primary Synonym — Cutlass

Last Revised — 07/01/1989

- 56425-91-3
- CUTLASS
- CUTLESS

- EL 500
- FLURPRIMIDOL
- alpha-(1-METHYLETHYL)-alpha-(4-TRIFLUOROMETHOXY)PHENYL)-5-PYRIMIDINEMETHANOL
- 5-PYRIMIDINEMETHANOL, alpha-(1-METHYLETHYL)-alpha-(4-TRIFLUOROMETHOXY)PHENYL)-

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