Haloxyfop-methyl; CASRN 69806-40-2

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 Haloxyfop-methyl

File First On-Line 05/01/1990

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	05/01/1990
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 — Haloxyfop-methyl
CASRN — 69806-40-2
Primary Synonym — Verdict
Last Revised — 05/01/1990

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
Reduced relative kidney weights in F0, F1, and F2b adults; Reduced fertility in the F1/F2b generation **3-Generation Rat Reproduction Study** **Dow Chemical U.S.A., 1985a**	NOEL: 0.005 mg/kg/day LEL: 0.05 mg/kg/day	100	1	5E-5 mg/kg/day

*Conversion factors: Actual dose tested

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

Dow Chemical U.S.A. 1985a. MRID No. 00147518. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Male and female CDF Fischer rats, 30/sex/dose, were offered standard rat chow diets containing 0, 0.005, 0.05, or 1.0 mg/kg/day of haloxyfop-methyl throughout the study beginning 102 days prior to breeding (F0 generation). F0 females were mated one on one with treated males to produce the F1a generation. The F0 females were rested for 1 week following weaning, then rebred with the same male to produce the F1b litter. The F0 adults were necropsied following weaning of the F1b litters. The F1b litters were maintained on test diets for 137 days, then bred as the initial matings to produce the F2a, F2b, and F2c litters.

The F2b animals were bred to produce the F3a and F3b litters. Each litter was produced by two consecutive 7-day matings with different males. The F2c females were bred with untreated males

and the males were each bred to two untreated females. The females from these matings were then killed at mid to late term in gestation and uterine contents examined for numbers of corpus lutea, implantations, and resorption sites. The uterus from nonpregnant animals was removed and stained with 10% sodium sulfide solution for evidence of early resorptions. The reproductive LEL is 0.05 mg/kg/day based on reduced fertility indices in the F2b generation. Reduced fertility indices was also noted at the HDT. Therefore, the reproductive NOEL is 0.005 mg/kg/day. However, the decrease in fertility observed in the F2 generation was not apparent in the F3 generation or when the F2c treated males and females were cross-mated with untreated male and female rats.

Signs of toxicity in parental rats at 1 mg/kg/day level were reduced body weight gain and reduced food consumption without increased mortality or obvious toxicity to the offspring. In addition, a significant increase in relative liver weight and enlarged livers were observed, however this finding was more frequent in males than females. A significant decrease in relative kidney weight was observed at 0.05 and 1 mg/kg/day, but it again occurred more frequently in the F0, F1, and F2b adult male rats. Renal pigmentation was also reported at 1 mg/kg/day for male and female adult rats after the gross and histopathological examinations. Based on decreases in relative kidney weights, the LEL for systemic toxicity is 0.05 mg/kg/day. The NOEL for systemic toxicity is 0.005 mg/kg/day.

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) 3-Generation Reproduction - rat: see previous description; core grade guideline (Dow Chemical U.S.A., 1985a)

2) 2-Generation Reproduction - rat: Dietary levels tested: 0, 0.01, 0.65, and 1.0 mg/kg/day; Groups Sprague-Dawley rats (30/sex/dose) were administered haloxyfop-methyl. The F0 generation was dosed for 8 weeks and the F1 generation for 11 weeks after each generation was mated. The only apparent effect was reduced body weights of the offspring in the F1a litters at weaning, at 21 days in all treatment groups, and in the 1 mg/kg/day groups of the F1b males and females and F2a males. Although statistically significant, the reductions are not large, amount to

10% or less. It is questionable whether this is a true toxic effect in all exposure groups, since it was not seen in subsequent litters except at the high-dose. No organ weights or histopathological examinations were performed. No maternal or reproductive toxicity was observed at any dose tested. The LEL for developmental toxicity is 1 mg/kg/day based on reduced weanling weight in F1a, F1b, and F2a litters. The NOEL for developmental toxicity is 0.065 mg/kg/day; core grade supplementary (Dow Chemical U.S.A., 1985b)

3) 1-Year Feeding - dog: Dietary levels tested: 0, 0.05, 0.5, and 5.0 mg/kg/day; Beagle dogs (6/sex/dose) were administered haloxyfop-methyl in the diet for 1 year. A significant increase in the serum glucose levels of males fed the 5.0 mg/kg/day level were reported for the 6 and 9-month intervals, but not at the termination of the study. Cholesterol level were significantly depressed for males of the 5.0 mg/kg/day level at 1, 3, 6, 9, and 12-month intervals with an observed effect on the triglyceride values. At the high- dose level, females showed significant increases in alanine transaminase at 9 months and aspartate transaminase at 12 months. At the 9- and 12-month intervals, males fed the 0.5 mg/kg/day showed a significant decrease in packed cell volume (PCV) and Hgb values. An increase in male and female relative live weights were observed at the high dose level. The LEL for systemic toxicity is 0.5 mg/kg/day based on significant decrease in PCV and Hgb values reported at the 9 and 12-month intervals for males. The NOEL for systemic toxicity is 0.05 mg/kg/day; core grade minimum (Dow Chemical U.S.A., 1984a)

4) 2-Year Feeding (carcinogenicity) - rat: Dietary levels tested: Male: 0, 0.01, 0.03, 0.065, and 0.1 mg/kg/day; Female: 0, 0.01, 0.03, 0.065, and 1.0 mg/kg/day; CDF Fischer 344 rats (50/sex/dose) were administered haloxyfop- methyl in the diet for 2 years. No effects were observed in the male at any dose tested. The LEL for systemic toxicity is 1 mg/kg/day based on a significant decrease in female absolute (8%) and relative (9%) kidney weights accompanied by a significant increase in the incidence (24/50) in renal pigmentation reported for females of this level. Kidney function was not impaired as the urinalysis parameters between test and control values were comparable. The NOEL for systemic toxicity is 0.065 mg/kg/day; core grade guideline for chronic toxicity (Dow Chemical U.S.A., 1984b)

5) Developmental toxicity - rat: Dose levels tested: 0, 0.1, 1.0, 7.5, 10, and 25 mg/kg/day; Groups of pregnant Fischer 344 rats (10/dose) were administered haloxyfop-methyl orally during days 6 through 15 of gestation. At the 7.5 mg/kg/day dose a decrease in weight gain and food consumption accompanied by an increase in water intake during gestation was observed. Additional maternal toxicity was observed at 10 and 25 mg/kg/day, including a decrease in weight gain and food consumption accompanied by an increase in liver weight. An increase in the incidence of resorptions was also observed at 10 and 25 mg/kg/day. At 7.5 mg/kg/day, a significant incidence of delayed ossification of the centra of the thoracic vertebra was observed. The NOEL and LEL for maternal toxicity are 1 and 7.5 mg/kg/day, respectively. The NOEL and

LEL for developmental toxicity are 1 and 7.5 mg/kg/day, respectively; core grade guideline (Dow Chemical U.S.A., 1983a)

6) Developmental toxicity - rabbit: Dose levels tested: 0, 3, 7.5, and 15 mg/kg/day; Inseminated New Zealand White rabbits (Dams: 27, 28, 30, and 25 for the control, low-, mid-, and high-dose, respectively) were administered haloxyfop-methyl by gavage on days 6 through 18 of gestation. No evidence of developmental toxicity was observed at any dose tested. At the 7.5 mg/kg/day dose level reduced body weight gain on days 6 to 18 was observed. Therefore the NOEL and LEL for maternal toxicity is 3 and 7.5 mg/kg/day, respectively; core grade minimum (Dow Chemical Co., 1985)

7) Developmental toxicity - rabbit: Dose levels tested: 0, 1.0, 7.5, and 20 mg/kg/day; Inseminated New Zealand White rabbits (30/dose) were administered haloxyfop-methyl orally on days 6 through 18 of gestation. At 20 mg/kg/day, 4/31 pregnant animals died between days 18 and 24 of gestation with 1/31 pregnant animals dead on day 8 of gestation. A decrease in weight gain was also observed at 20 mg/kg/day. Body weight gain at the 7.5 mg/kg/day was comparable to controls. At 20 mg/kg/day, a significant increase in the incidence of resorbed implantations was reported. The LEL for maternal toxicity is 20 mg/kg/day based on dam mortality and decreased weight gain. The NOEL for maternal toxicity is 7.5 mg/kg/day. The LEL for fetotoxicity is 20 mg/kg/day based on the increase in resorptions. The NOEL for fetotoxicity is 7.5 mg/kg/day; core grade guideline (Dow Chemical U.S.A., 1983b)

Other Data Reviewed:

1) 2-Year Feeding (carcinogenicity) - mouse: Dietary levels tested: 0, 0.03, 0.065, and 0.6 mg/kg/day; B6C3F1 mice (50/sex/dose) were administered haloxyfop-methyl in the diet for 24 months. High-dose males exhibited a reduced body weight gain, elevated alkaline phosphatase levels, and an increase in relative liver weights. Histopathological observations of the livers from high-dose males and females were characterized by an alteration of the tinctorial staining properties of the hepatocytes. Based on the above effects the LEL for systemic toxicity is 0.6 mg/kg/day. The NOEL for systemic toxicity is 0.065 mg/kg/day; core grade minimum (Dow Chemical U.S.A., 1985c)

2) 13-Week Feeding - dog: Dietary levels tested: 0, 2, 5, and 20 mg/kg/day; Beagle dogs (4/sex/dose level) were administered haloxyfop-methyl in the diet for 13 weeks. A statistically significant decrease in serum cholesterol values was reported for males fed 2 mg/kg/day. A statistically significant decrease in serum cholesterol values was reported for males and females fed 5 mg/kg/day. A significant decrease in male and female triiodothyronine and free thyroxine values was accompanied by a significant decrease in male and female relative thyroid/parathyroid weights. Hepatic peroxisomal fatty acid beta-oxidation was increased in

males and females fed 5 mg/kg/day. Histological changes reported at this level were hepatocellular enlargement with increased glycogen content, decrease in follicular size and hypertrophy of the follicular epithelial cells of the thyroid, and decrease size of the testicular tubules. The LEL for systemic toxicity is 2 mg/kg/day, the lowest dose tested, based on decreases in serum cholesterol values in males. A NOEL for systemic toxicity was not established; core grade minimum (Dow Chemical Co., 1987a)

3) 13-Week Feeding - monkey: Dietary levels tested: 0, 2, 10, and 30 mg/kg/day; Cynomolgus monkeys (4/sex/dose level) were administered haloxyfop- methyl by nasogastric intubation for 13 weeks. A statistically significant decrease in triglyceride values was reported for males and females dosed at 2 mg/kg/day. The statistically significant decrease in triglyceride values in males and females dosed at 10 mg/kg/day was accompanied by a nonsignificant decrease (15%) in cholesterol values for females at this level. Female livers appeared pale with an accentuated lobular pattern. Slight hepatocellular hypertrophy was observed for male and females at this level. Relative kidney weights were significantly increase for males and females by 12 and 37%, respectively. The LEL for systemic toxicity is 2 mg/kg/day, the lowest dose tested, based on a statistically significant decrease in triglyceride values in males and females. A NOEL for systemic toxicity was not established; core grade minimum (Dow Chemical Co., 1987b)

4) 16-Week Feeding - rat: Dietary levels tested: 0, 0.002, 0.02, 0.2, and 2 mg/kg/day; CDF Fischer 344 rats (15/sex/group) were administered haloxyfop- methyl in the diet for 16 weeks. A significant dose-related increase in relative liver weight was reported for male rats of the 0.002, 0.02, 0.2, and 2.0 mg/kg/day levels by 4, 5, 11, and 44%, respectively. Female relative liver weights were increased significantly (4%) at the 2.0 mg/kg/day levels. Males fed the 0.2 and 2.0 mg/kg/day levels showed enlarged hepatocytes and increased cytoplasmic homogeneity. An increase in hepatocellular cytoplasmic homogeneity was reported for females at 2.0 mg/kg/day. A significant decrease in relative testes weight (5%) accompanied by atrophy of the seminiferous tubules were reported for males fed the 2.0 mg/kg/day level. The LEL for systemic toxicity is 0.002 mg/kg/day, the lowest dose tested, based on a dose related increase in relative liver weight in males. A NOEL for systemic toxicity was not established; core grade minimum (Dow Chemical U.S.A., 1982a)

5) 37-Week Feeding - rat: Dietary levels tested: 0, 0.02, and 2.0 mg/kg/day; CDF Fischer 344 rats (12/sex/group) were administered haloxyfop-methyl in the diet for 37 weeks. An 8% increase in female SGPT values was observed at 0.02 mg/kg/day level. A significant increase in relative liver weight at the 2 mg/kg/day level was reported for males (23%) and females (5%). Enlarged hepatocytes in males and increased hepatocellular cytoplasmic homogeneity were reported for males and females at 2 mg/kg/day. The LEL for systemic toxicity is 0.02 mg/kg/day, the lowest dose tested, based on an increase in female SGPT values. The NOEL for systemic toxicity was not established; core grade minimum (Dow Chemical U.S.A., 1982b)

6) 13-Week Feeding - mouse: Dietary levels tested: 0, 0.002, 0.02, 0.2, and 2 mg/kg/day; B6C3F1 mice (10/sex/group) were administered haloxyfop-methyl in the diet for 3 months. A significant decrease in body weight gain and food consumption in females, a significant increase in alkaline phosphatase (25%) in males and a significant increase in relative liver weight for males (14%) and females (23%) were reported for the 2.0 mg/kg/day level. Enlarged hepatocytes, increased cytoplasmic homogeneity and increased eosinophilia were also observed at this level. Based on the above effects, the LEL for systemic toxicity is 2.0 mg/kg/day. The NOEL for systemic toxicity is 0.2 mg/kg/day; core grade minimum (Dow Chemical U.S.A., 1982c)

7) 36-Week Feeding - mouse: Dietary levels tested: 0, 0.02, and 2.0 mg/kg/day; B6C3F1 mice (10/sex/group) were administered haloxyfop-methyl in the diet for 9 months. A significant increase in serum alkaline phosphatase was reported for males at the 2.0 mg/kg/day level with a slight increase in serum alkaline phosphatase for females. The liver was slightly enlarged and darkened for both males and females at 2.0 mg/kg/day. A significant increase in the liver absolute weight and organ-to-body weight ratio of both males and females fed 2.0 mg/kg/day was observed. Males also exhibited a significant decrease in kidney and heart weights compared with the control organ weight. Livers of males and females at the 2.0 mg/kg/day dose exhibited an enlargement of centrilobular hepatocytes cells with an increase cytoplasmic homogeneity and increased eosinophilia. Kidneys of males fed 2.0 mg/kg/day showed a decrease of cytoplasmic vacuolation of the proximal convoluted tubular cells. Based on the above effects, the LEL for systemic toxicity is 2.0 mg/kg/day. The NOEL for systemic toxicity is 0.02 mg/kg/day; core supplementary (Dow Chemical U.S.A., 1982d)

Data Gap(s): None

I.A.5. Confidence in the Oral RfD

Study — High
Database — High
RfD — High

The critical study is of good quality and is given a high confidence rating. Additional data are of adequate quality and supportive of the critical study. 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 Files

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

Other EPA Documentation — Pesticide Registration Files

Agency Work Group Review — 02/21/1990

Verification Date — 02/21/1990

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 Haloxyfop-methyl conducted in August 2003 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 — Haloxyfop-methyl
CASRN — 69806-40-2
Primary Synonym — Verdict

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Haloxyfop-methyl
CASRN — 69806-40-2
Primary Synonym — Verdict

Not available at this time.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Haloxyfop-methyl
CASRN — 69806-40-2
Primary Synonym — Verdict

VI.A. Oral RfD References

Dow Chemical Company. 1985. MRID No. 00147517, 40441101, 40887901. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical Company. 1987a. MRID No. 40244704. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical Company. 1987b. MRID No. 40244706. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical U.S.A. 1982a. MRID No. 00148213. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical U.S.A. 1982b. MRID No. 00148213. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical U.S.A. 1982c. MRID No. 00114118, 001258454, 00147513. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical U.S.A. 1982d. MRID No. 00114118, 001258454, 00147513. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical U.S.A. 1983a. MRID No. 00128817. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical U.S.A. 1983b. MRID No. 00128817. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical U.S.A. 1984a. MRID No. 00132073, 00147516. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical U.S.A. 1984b. MRID No. 00132072, 00147515. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical U.S.A. 1985a. MRID No. 00147518. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical U.S.A. 1985b. MRID No. 00132075, 00147519. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical U.S.A. 1985c. MRID No. 00148214. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Haloxyfop-methyl
CASRN — 69806-40-2
Primary Synonym — Verdict

Date	Section	Description
05/01/1990	I.A.	Oral RfD summary on-line
10/28/2003	I.A.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Haloxyfop-methyl
CASRN — 69806-40-2
Primary Synonym — Verdict
Last Revised — 05/01/1990

- 69806-40-2
- Propanoic acid, 2-(4-((3-chloro-5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)-, methyl ester
- Dowco 453
- Dowco 453ME
- Haloxyfop methyl ester
- Haloxyfop-methyl
- Methyl 2-(4-((3-chloro-5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propanoate
- Verdict