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Fosetyl-al; CASRN 39148-24-8

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 Fosetyl-al

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	03/31/1987
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	08/22/1988

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Fosetyl-al

CASRN — 39148-24-8

Primary Synonym — Aliette

Last Revised — 03/31/1987

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
Slight testicular degeneration	NOEL: 10,000 ppm (diet) (250 mg/kg/day)	100	1	3E+0 mg/kg/day
2-Year Dog Feeding Study	LEL: 20,000 ppm (diet)			
Rhone-Poulenc, 1981a				

*Conversion Factors: 1 ppm = 0.025 mg/kg/day (assumed dog food consumption)

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

Rhone-Poulenc Chemical Company. 1981a. MRID No. 00098340. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Twenty-four male and 24 female purebred Beagle dogs, approximately 3-4 months old, were randomly assigned to one of three treatment groups or to the control group (6 animals/sex/dose). Fosetyl-Al was administered to the dogs at the following concentrations in the diet for 2 years: 10,000, 20,000 and 40,000 ppm. Observed effects included a slight degenerative effect on the testes of 2/6 animals.

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

UF — Based on a chronic exposure study, 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)

None

Data Considered for Establishing the RfD:

- 1) 2-Year Feeding - dog: Principal study - see previous description; core grade minimum
- 2) 3-Generation Reproduction - rat: NOEL=6000 ppm (300 mg/kg/day); LEL=12,000 ppm (600 mg/kg/day) (lower weight gains of F2b generation, lower litter and mean weight in late lactation, urinary tract changes in occasional adults and 1/10 weanling males of F3b generation); core grade minimum (Rhone-Poulenc, 1981b)
- 3) 2-Year Feeding (oncogenic) - rat: Systemic NOEL = 2000 ppm (100 mg/kg/day); Systemic LOEL = 8000 ppm (400/mg/kg/day); core grade minimum (Rhone-Poulenc, 1981c)
- 4) Teratology - rat: NOEL=1000 mg/kg/day; LEL=4000\mg/kg/day (5/20 pregnant rats died, retarded maternal weight gain, litter and mean fetal weights reduced, total resorptions increased, delayed ossification); core grade minimum (Rhone-Poulenc, 1977)
- 5) Teratology - rabbit: NOEL=500 mg/kg (HDT); LEL=none; core grade minimum (Rhone-Poulenc, 1976)

Other Data Reviewed:

- 1) 2-Year Feeding (oncogenic) - mice: Systemic NOEL=20,000 ppm (HDT); Systemic LEL=none; core grade minimum (Rhone-Poulenc, 1981d)

Data Gap(s): None

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — High
RfD — High

The critical study appears to be of good quality and is given a medium confidence rating. Additional studies are of good quality; 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

Pesticide Registration Files

Agency Work Group Review — 09/29/1986

Verification Date — 09/29/1986

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 Fosetyl-al 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 — Fosetyl-al
CASRN — 39148-24-8
Primary Synonym — Aliette

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Fosetyl-al
CASRN — 39148-24-8
Primary Synonym — Aliette
Last Revised — 08/22/1988

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day.

The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — C; possible human carcinogen.

Basis — Increased incidence of urinary bladder tumors (adenomas/carcinomas combined) in male rats. No increase in tumor incidence occurred in female rats or in mice of either sex.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited. Alette was administered for a period of 2 years in the diet of male and female Charles River CD rats, 80/sex/dose, at dosages of 0, 2000, 8000 and 40,000 ppm (changed to 30,000 ppm after week 2 due to red coloration of the urine and staining of the fur) (IRDC, 1981). Survival in the several groups was comparable within each sex. A significantly ($p < 0.05$) elevated incidence of urinary bladder tumors (adenomas/carcinomas combined) of 15/80 (19%) was observed in the male rats fed the high dosage as compared to 2/80 (2.5%) in the control males. Tumor diagnosis was independently confirmed by a second pathologist who examined all slides blindly. An elevated incidence of pheochromocytomas (adenomas/carcinomas combined) was also initially reported for the male rats fed the mid and high dosages, but this diagnosis was not confirmed by two other independent pathologists. The high dose approximated an MTD based on urinary bladder hyperplasia.

Alette caused no increase in tumor incidence in female Charles River CD rats, or in Charles River CD-1 mice of either sex (60/group) which were fed Alette in the diet at 0, 2500, 10,000 or 30,000 ppm for 2 years (IRDC, n.d.). When monosodium phosphite, the urinary metabolite of

aliette, was fed in the diet of CD-1 rats, 60/sex/dose, at dosages of 0, 2000, 8000 and 32,000 ppm for 27 months, there was no evidence of oncogenic response in the urinary bladder, the adrenal medulla, or at any other site (IRDC, n.d.).

Aliette was fed in the diet to six dogs/sex/dosage at 0, 10,000, 20,000 or 40,000 ppm for 2 years, without increasing tumor incidence at any dosage (IRDC, n.d.).

II.A.4. Supporting Data for Carcinogenicity

Aliette was not mutagenic for five strains of Salmonella (Benazet and Cartier, 1977; Bouanchaud and Cartier, 1981). It was negative for bacteriophage induction (Inductest) (Institute Pasteur, 1978; Bouanchaud and Cartier, 1981) and DNA repair in *E. coli*, mitotic recombination in *Saccharomyces cerevisiae* (Bouanchaud and Cartier, 1981) and did not produce erythrocyte micronuclei in either Swiss or CD-1 mice (Siou, 1977; Cordier and Fournier, 1981).

Metabolism studies in Sprague-Dawley rats following oral administration of ¹⁴C-aliette at 250 mg/kg/day for 7 days indicated the compound was rapidly metabolized mainly to carbon dioxide (60%) while 26% was found in the urine as unchanged Aliette or as the monosodium phosphite derivative.

No structure/activity data were available.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1986

The Toxicology Branch Peer Review Committee reviewed data on aliette.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 05/04/1988, 06/08/1994

Verification Date — 05/04/1988

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Fosetyl-al 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.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

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).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Fosetyl-al

CASRN — 39148-24-8

Primary Synonym — Aliette

VI.A. Oral RfD References

Rhone-Poulenc Chemical Company. 1981a. MRID No. 00098340. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Rhone-Poulenc Chemical Company. 1981b. MRID No. 00098348. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Rhone-Poulenc Chemical Company. 1981c. MRID No. 00098339, 00098352, 00126757, 00128233, 00128535. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Rhone-Poulenc Chemical Company. 1977. MRID No. 00114091. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Rhone-Poulenc Chemical Company. 1976. MRID No. 00098340. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Rhone-Poulenc Chemical Company. 1981d. MRID No. 00098353. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Benazet, F. and M. Cartier. 1977. Mutagenic activity of LS 74, 783 (32,545 R.P.) in *Salmonella typhimurium*. Unpublished report prepared by Rhone-Poulenc, Direction des Recherches et du Development, Centre Nicolas Grillet, 94400 Vitry-sur-Seine, France. (Data Evaluation Record).

Bouanchaud, D.H. and J.R. Cartier. 1981. Supplementary studies of mutagenesis in microorganisms. (Data Evaluation Record).

Cordier, A. and E. Fournier. 1981. Fosetyl-Al (32 545 R.P., Aluminium salt), micronucleus test in the mouse by the oral route. Unpublished report prepared by Rhone-Poulenc Industries, Centre Nicolas Grillet, Department of Toxicology, 13, Quai Jales Guesde, 94400 Vitry-sur-Seine, France. (Data Evaluation Record).

Institute Pasteur. 1978. Inductests on phosphorous acid and LS 74, 783. Unpublished report prepared by Institute Pasteur, Paris, France. January 2. (Data Evaluation Record).

IRDC (International Research and Development Corporation. 1981. Fosetyl-AL (LS 74-783). Chronic toxicity (2-year) and carcinogenicity study in rats. Report No. 347-016. March 27. (Cited in U.S. EPA, 1986)

IRDC (International Research and Development Corporation). n.d. (Cited in U.S. EPA, 1986)

Siou, G. 1977. Investigation of the possible mutagenic activity of "Aliette" and or hydrated monosodium phosphite. Unpublished report prepared by Cabinet d'Etudes et de Recherches en Toxicologic Industrielle, Histopathology and Cytopharmacology Laboratory, December 23. (Data Evaluation Record).

U.S. EPA. 1986. Toxicology Branch Peer Review Committee memorandum on aliette.

VII. Revision History

Substance Name — Fosetyl-al
CASRN — 39148-24-8
Primary Synonym — Aliette

Date	Section	Description
08/22/1988	II.	Carcinogen summary on-line
10/28/2003	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Fosetyl-al

CASRN — 39148-24-8

Primary Synonym — Aliette

Last Revised — 03/31/1987

- 32545 RP
- 39148-24-8
- Aliette
- ALUMINUM TRIS(O-ETHYL PHOSPHONATE)
- EFOSITE-AL
- EPAL
- Fosetyl-al
- LS 74783
- PHOSETHYL
- PHOSETHYL AL
- PHOSPHONIC ACID, MONOETHYL ESTER, ALUMINUM SALT