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## **Acephate; CASRN 30560-19-1**

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 Acephate

**File First On-Line 09/07/1988**

Category (section)	Assessment Available?	Last Revised
<b>Oral RfD (I.A.)</b>	yes	05/01/1989
<b>Inhalation RfC (I.B.)</b>	not evaluated	
<b>Carcinogenicity Assessment (II.)</b>	yes	09/07/1988

### **I. Chronic Health Hazard Assessments for Noncarcinogenic Effects**

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

Substance Name — Acephate

CASRN — 30560-19-1

Last Revised — 05/01/1989

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
<b>Inhibition of brain ChE</b>	NOEL: None	30	1	
<b>90-Day Rat Feeding Study</b>	LEL: 2 ppm (0.12/0.15 mg/kg/day, M/F)			4E-3 mg/kg/day
<b>Chevron Chemical Co., 1987a</b>				

\*Conversion Factors -- Actual dose tested

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

Chevron Chemical Company. 1987a. MRID No. 40504819. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Five groups of 60 Sprague-Dawley rats (30 male and 30 female) were dosed with nominal dietary concentrations of 0, 2, 5, 10, and 150 ppm (Males: 0, 0.12, 0.28, 0.58, 8.90 mg/kg/day; Females: 0, 0.15, 0.36, 0.76, 11.48 mg/kg/day) acephate for 13 weeks. The rats were approximately 45 days old at the start of dosing.

Although there was still some statistically significant brain cholinesterase inhibition at 13 weeks at 2 ppm (0.12 mg/kg/day in males and 0.15 mg/kg/day in females), it was concluded that this level essentially represented a threshold i.e., the dose response curve in this area was very flat becoming essentially parallel to the x-axis. At 150 ppm (8.9 mg/kg/day in males and 11.48 in females), in both the brain and RBC ChE there was statistically significant inhibition. Plasma ChE determinations varied widely and only one subset showed statistical significance (females after 13 weeks of dosing with the 150 ppm diet). The NOEL for RBC and plasma ChE is 10 ppm (0.58 mg/kg/day in males and 0.76 in females). A NOEL for brain cholinesterase inhibition was not found in this study.

Human subjects were dosed with graded levels of Monitor: Acephate mixtures (1:4, 1:9) at 0.1, 0.2, 0.3 or 0.4 mg/kg/day for a total of 37 to 73 days. No effects on erythrocyte ChE activity, hematology, blood chemistry, blood pressure, pulse rate, pupil size, light reflex, eye accommodation, chest sound, muscle tone, knee jerk, tongue tremor, and finger tremor were observed. Plasma ChE activities were inhibited significantly in the 1:4 and 1:9 groups. The inhibition in the 1:4 group was first noted at the 0.2 mg/kg/day level after 16 days of dosing and occurred in all subjects studied. The depression was greater than 2 standard deviations below mean pretest activity for consecutive determinations. The first significant inhibition in the 1:9 group was observed at the 0.3 mg/kg/day level after 21 days of dosing and only in males subjects. At the 0.4 mg/kg/day level, 2 out of 3 female subjects tested exhibited a significant ChE depression after 10 days of dosing. All inhibited ChE activities returned to the pretreatment levels during the 7-day recovery periods (Chevron Chemical Co., 1973).

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

UF — The human study and the comparative in vitro studies were considered by the RfD Work Group when evaluating the database for acephate. The human study was not found to be adequate as the basis for the RfD because it was 1) carried out by IBT and 2) because brain ChE inhibition seems a more sensitive endpoint than RBC or plasma ChE for acephate, and brain ChE was not measured in the human study. In vitro studies on the affinity of acephate to human brain, RBC and plasma ChE, show differences of less than 10-fold. Upon reconsideration and discussion the Agency concluded that both the human study and the in vitro data could be used to support a modification of the customary 100-fold uncertainty factor used for brain cholinesterase inhibition. This 100-fold factor was reduced to 10 (e.g., the 10-fold factor from animal to man was not considered necessary). Furthermore, a 3-fold factor was used because a NOEL was not determined in the critical study. This intermediate factor of 3 was considered as more appropriate than 10 because the LEL dose was concluded to represent a threshold dose. Finally, the 10-fold factor normally used to estimate an RfD using subchronic data was not considered necessary, since the results after subchronic exposure are similar in both severity and magnitude as for chronic studies.

MF — None

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

Data Considered for Establishing the RfD

1) 13-Week Feeding - rat: Principal study - see previous description; core grade acceptable

2) Subchronic Feeding - human: Plasma ChE NOEL=0.1 mg/kg/day; ChE LEL= 0.2 mg/kg/day; see previous description; core grade supplementary (Chevron Chemical Co., 1973)

3) 28-Month Feeding (oncogenic) - rat: ChE NOEL=not established; ChE LEL=5 ppm (0.25 mg/kg/day) (inhibition of ChE activities in brain, plasma, and RBC); Systemic NOEL=50 ppm (2.5 mg/kg/day); Systemic LEL=700 ppm (35 mg/kg/day) (HDT; weight loss in male rats); core grade minimum (Chevron Chemical Co., 1981)

4) 2-Year Feeding - dog: NOEL=30 ppm (0.75 mg/kg/day); LEL=100 ppm (2.5 mg/kg/day) (HDT; brain, plasma, and RBC ChE activity); Systemic LEL=100 ppm (2.5 mg/kg/day); core grade minimum (Chevron Chemical Co., 1972)

5) 2-Generation Reproduction - rat: Maternal NOEL=50 ppm (2.5 mg/kg/day); Maternal LEL=500 ppm (25 mg/kg/day) [decreased body weight gain for adults and pups; increases in food consumption relative to body weight in adults; clinical signs in males (alopecia and loose stools); decreases in litter size (25-30%) for 4 of the 5 litter groups]; Reproductive NOEL=50 ppm (2.5 mg/kg/day); Reproductive LEL=500 ppm (25 mg/kg/day) (decreased viability index); core grade guideline (Chevron Chemical Co., 1987b)

6) Teratology - rat: Teratogenic NOEL=200 mg/kg/day [slightly more resorption sites per female at 200 mg/kg/day level than in controls; less weight gain at 100 mg/kg/day level (25%) and 200 mg/kg/day (29%) by female during gestation]; core grade minimum (Chevron Chemical Co., 1971)

7) Teratology - rabbit: Teratogenic and Fetotoxic NOEL=10 mg/kg/day (HDT); Maternal NOEL=3 mg/kg/day; Maternal LEL=10 mg/kg/day (HDT; increase in nasal discharge and 2/16 abortions); core grade guideline (Chevron Chemical Co., 1980)

#### Other Data Reviewed:

1) 2-Generation Reproduction - rat: Reproductive NOEL=not established; Various reproductive effects (fetal losses, decreased litter weights) were observed at 50 ppm (2.5 mg/kg/day) (LDT); Systemic NOEL=not established; Weight loss by females and decreased food utilization by males and females was observed at 50 ppm; core grade minimum (Chevron Chemical Co., 1983)

Data Gap(s): None

### **I.A.5. Confidence in the Oral RfD**

Study — Medium

Database — High

RfD — High

The critical study is of adequate quality and is given a medium confidence rating. Additional studies are also 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**

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

Other EPA Documentation — Pesticide Registration Files

Agency Work Group Review — 04/08/1986, 11/25/1986, 01/18/1989

Verification Date — 01/18/1989

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 acephate 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](mailto: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](mailto:hotline.iris@epa.gov) (internet address).

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

Substance Name — Acephate

CASRN — 30560-19-1

Not available at this time.

## II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Acephate

CASRN — 30560-19-1

Last Revised — 09/07/1988

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 — The classification is based on increased incidence of hepatocellular carcinomas and adenomas in female mice.

#### II.A.2. Human Carcinogenicity Data

None.

#### II.A.3. Animal Carcinogenicity Data

Limited. Technical grade acephate was administered in the diet of Charles River CD-1 mice (75/sex/dose) at 0, 50, 250 and 1000 ppm for 105 weeks (Chevron Chemical, 1982a). Ten male and female mice of each dose group were killed at 52 weeks and necropsies were performed; the remaining mice were killed at 105 weeks. There was a statistically significant increase in

incidence of hepatocellular carcinomas and adenomas (15/61) and hyperplastic nodules (15/61) in the high-dose female group at terminal sacrifice, as compared to controls (1/62 and 2/62). There were no such increases in the lower-dose female groups nor were there increased tumor incidences in any of the male groups. There was no increase in tumor incidence observed at the 52-week sacrifice. Survival was not affected by the occurrence of tumors. There were toxic effects at the mid-dose, and the MTD may have been exceeded at the high dose.

Technical grade acephate was fed in the diet of Charles River (CD) Sprague-Dawley rats (75 rats/sex/dose) at 0, 5, 50 and 700 ppm for 28 months (Chevron Chemical, 1981). Although the incidence of pheochromocytomas was elevated above the controls in the treated males, there was no evidence of a dose-dependent increase. Furthermore, the incidence of pheochromocytomas was within the range of historical incidences reported for controls in the testing laboratory and in the literature for the strain tested. There was no evidence of either increased malignancy of lesions or decreased latency in the treated males and the pheochromocytoma incidence in acephate-treated female rats was the same or lower than that observed in controls. The U.S. EPA (1985) thus concluded that the observed increase in pheochromocytomas was not indicative of a true carcinogenic effect in rats. These conclusions were in agreement with those of a consulting veterinary pathologist based on histopathologic reevaluation of the tissue.

#### **II.A.4. Supporting Data for Carcinogenicity**

Acephate was mutagenic for *Salmonella*, *Escherichia coli* and *Saccharomyces cerevisiae*. Generally weak responses were noted (Simmon, 1979; Moriya et al., 1983; Mortelmans et al. 1980). Acephate has been reported to produce mutations in mouse lymphoma cells, sister chromatid exchange in CHO cells and mitotic recombination in *Saccharomyces* (Chevron Chemical, 1982b; Jotz and Mitchell, 1980; Evans and Mitchell, 1980; Mortelmans et al., 1980). No metabolism studies are available for mice, but one study did indicate that rats excreted acephate largely in the urine and in an unchanged form. Acephate is structurally related to methamidophos.

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

### **II.B.1. Summary of Risk Estimates**

Oral Slope Factor —  $8.7E-3/\text{mg}/\text{kg}/\text{day}$

Drinking Water Unit Risk —  $2.5E-7/\text{ug}/\text{L}$

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	4E+2 ug/L
E-5 (1 in 100,000)	4E+1 ug/L
E-6 (1 in 1,000,000)	4 ug/L

**II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)**

Tumor Type — liver adenomas and carcinomas

Test animals — mouse/CD-1, female

Route — diet

Reference — Chevron Chemical, 1982a

Administered Dose (ppm)	Human Equivalent Dose (mg/kg)/day	Tumor Incidence
0	0	1/62
50	0.63	3/61
250	3.33	0/62
1000	13.3	15/61

**II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)**

Twelve of 15 tumors in the high-dose group were carcinomas. The slope factor of 6.6E-3 presented in a 1984 Health and Environmental Effects Profile was based on carcinomas only and was not corrected for early mortality.



The unit risk should not be used if the water concentration exceeds 4E+4 ug/L, since above this concentration the slope factor may differ from that stated.

#### **II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)**

Adequate numbers of animals were treated and observed for a period approximating the natural lifespan. It should be noted that oncogenic effects were significantly elevated only at the high dose although toxic effects were observed in the mid-dose group as well.

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

Not available.

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

##### **II.D.1. EPA Documentation**

Source Document — U.S. EPA, 1985

The Toxicology Branch Peer Review Committee Office of Pesticide Programs, reviewed data on acephate.

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

Agency Work Group Review — 02/24/1988, 03/23/1988

Verification Date — 03/23/1988

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 acephate 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](mailto: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](mailto:hotline.iris@epa.gov) (internet address).

**III. [reserved]**

**IV. [reserved]**

**V. [reserved]**

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## **VI. Bibliography**

Substance Name — Acephate

CASRN — 30560-19-1

### **VI.A. Oral RfD References**

Chevron Chemical Company. 1971. MRID No. 00014695. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Chevron Chemical Company. 1972. MRID No. 00014699. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Chevron Chemical Company. 1973. MRID No. 00015160. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Chevron Chemical Company. 1980. MRID No. 00069684. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Chevron Chemical Company. 1981. MRID No. 00084017. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Chevron Chemical Company. 1983. MRID No. 00129508. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Chevron Chemical Company. 1987a. MRID No. 40504819. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Chevron Chemical Company. 1987b. MRID No. 40323401. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

## **VI.B. Inhalation RfD References**

None

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## **VI.C. Carcinogenicity Assessment References**

Chevron Chemical Corporation. 1981. MRID No. 00084017. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Chevron Chemical Corporation. 1982a. MRID No. 00105197. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Chevron Chemical Corporation. 1982b. (Cited in Acephate Assessment of Chronic and Oncogenic Effects Summary, OPP, March, 1984, p. 28)

Evans, E. and A. Mitchell. 1980. Science Research Institute (SRI) at Louisiana State University (LSU). Study no. 7558. (Cited in Acephate Assessment of Chronic and Oncogenic Effects Summary, OPP, March, 1984)

Jotz, M. and A. Mitchell. 1980. Science Research Institute (SCI) at Louisiana State University (LSU). Study no. 7558-21. (Cited in Acephate Assessment of Chronic and Oncogenic Effects Summary, OPP, March, 1984)

Moriya, M., T. Ohta, K. Watanabe, T. Miyazawa, K. Kato and Y. Shirasu. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. *Mutat. Res.* 116(3-4): 185-216.

Mortelmans, K. et al. 1980. Science Research Institute (SCI) at Louisiana State University (LSU). Study no. 7558-20. (Cited in Acephate Assessment of Chronic and Oncogenic Effects Summary, OPP, March, 1984)

Simmon, V.F. 1979. In vitro microbiological mutagenicity and unscheduled DNA synthesis studies of eighteen pesticides. p. 177. EPA 600/1-79-041. NTIS PB 80-133226. (CA 93:108605k)

U.S. EPA. 1985. Toxicology Branch Peer Review Committee, Memorandum on acephate 05/08/1985.

## VII. Revision History

Substance Name — Acephate  
CASRN — 30560-19-1

Date	Section	Description
09/07/1988	II.	Carcinogen summary on-line
05/01/1989	I.A.	Oral RfD 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 — Acephate  
CASRN — 30560-19-1  
Last Revised — 09/07/1988

- 30560-19-1
- 75 SP
- ACEPHAT
- Acephate
- ACETYLPHOSPHORAMIDOTHIOIC ACID O,S-DIMETHYL ESTER
- CHEVRON RE 12,420
- ENT 27822
- N-(METHOXY(METHYLTHIO)PHOSPHINOYL)ACETAMIDE
- ORTHENE
- ORTHENE-755
- ORTHO 12420
- ORTRAN
- ORTRIL
- O,S-DIMETHYLACETYLPHOSPHOROAMIDOTHIOATE
- PHOSPHORAMIDOTHIOIC ACID, N-ACETYL-, O,S-DIMETHYL ESTER
- RE 12420