

## Warfarin; CASRN 81-81-2

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 Warfarin

**File First On-Line 03/31/1987**

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

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Warfarin

CASRN — 81-81-2

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
<b>Increased prothrombin time</b>	NOAEL: none	100	1	3E-4 mg/kg/day
<b>Human Clinical Studies</b>	LOAEL: 2.0 mg/day converted to 0.029 mg/kg/day			
<b>Huff, 1985</b>				

\*Conversion Factors and Assumptions: Dose divided by the Reference Value for human body weight (70 kg)

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

Huff, B.B., Ed. 1985. Physicians Desk Reference, 39th ed. Medical Economics Co., Inc., Oradell, NJ.

Warfarin is an oral anticoagulant used therapeutically for a variety of embolic and venous thrombotic problems. Huff (1985) has recommended a maintenance dose range of 2-10 mg/day or 0.029-0.14 mg/kg/day. The maintenance dose in humans is that level which, when given therapeutically, will elevate prothrombin times to values of 150-250% of control levels. The half-life of this compound in humans is 2.5 days; therefore, daily (chronic) administration of therapeutic levels requires close monitoring and dose adjustment. The use of warfarin during pregnancy has been contraindicated (Huff, 1985). Because of marked differences in the susceptibility of different species to the effects of warfarin, it would be inappropriate to derive an RfD from studies on lower animals. However, the lower recommended maintenance dose of 2 mg/day (Huff, 1985) can be used as the basis for derivation of an RfD for warfarin. Since this level has been associated with increased prothrombin time, this effect would be considered adverse for the general population, although under controlled therapeutic conditions it would not be considered adverse to certain individuals under life-threatening medical situations and the 2 mg/day dose level would, therefore, be considered a LOAEL.

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

UF — An uncertainty factor of 100 was applied: 10 to account for the use of a LOAEL and 10 to protect for sensitive individuals in the population.

MF — None

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

In a comprehensive retrospective study of pregnancies (women therapeutically treated with warfarin), doses generally ranging from 2.5-12.5 mg/day have been found to be teratogenic (Hall et al., 1980). A critical exposure period of 6- 9 weeks of gestation has been reported for chondrodysplasia punctata, the most consistently reported malformation. Hall et al. (1980) also described CNS effects, eye disorders and developmental retardation, which appeared independently of the critical exposure period described previously.

Other investigators have associated specific doses of warfarin with malformations during pregnancy. Chondrodysplasia punctata has been observed in neonates born to mothers taking daily warfarin dosages of 6-7 mg (Abbott et al., 1977), 10 mg/kg (Whitfield, 1980) and 2.5-5 mg/kg (Shaul et al., 1975). In the Shaul et al. (1975) study, however, the concomitant intake of alcohol and diazepam may have dislodged warfarin from its plasma-binding sites, thereby increasing its apparent toxicity. In all of these cases dosing was maintained at least through the first trimester. There are a number of cases (Bemiller et al., 1970; Bloomfield and Rubinstein, 1969) in which first- trimester warfarin at maintenance dose levels did not disrupt the course of pregnancy. Of 15 pregnant women with circulatory problems requiring warfarin therapy of 4-11 mg/day during the second and third trimesters, no infants were born with either osteologic or neurologic dysfunction (Pridmore et al., 1975). Although no NOEL for teratogenicity in humans has been established, the RfD established is approximately 100-500 times smaller than the warfarin doses which are associated with teratogenicity (0.03-0.14 mg/kg/day).

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

Study — Low

Database — Low

RfD — Low

A low confidence rating has been given the critical study because it is based on a retrospective study of therapeutic doses administered to patients of varying susceptibilities and problems. The database was given a low rating because of the lack of supporting chronic toxicity studies as well as reproductive studies. Therefore, the RfD was given a low confidence rating.

### **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 — None

Agency Work Group Review — 05/15/1986

Verification Date — 05/15/1986

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 warfarin conducted in August 2003 identified one or more significant new studies. IRIS users may request the references for those studies from 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 — Warfarin

CASRN — 81-81-2

Not available at this time

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## II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Warfarin  
CASRN — 81-81-2

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

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III. [reserved]

IV. [reserved]

V. [reserved]

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## VI. Bibliography

Substance Name — Warfarin  
CASRN — 81-81-2

### VI.A. Oral RfD References

Abbott, A., J.R. Sibert and J.B. Weaver. 1977. Chondrodysplasia punctata and maternal warfarin treatment. *Br. Med. J.* 1(6077): 1639-1640.

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Bloomfield, D.K. and L.I. Rubinstein. 1969. Mitral-valve prosthesis, warfarin anticoagulation, and pregnancy. *Lancet.* Aug: 290-291.

Hall, J.G., R.M. Pauli and K.M. Wilson. 1980. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am. J. Med.* 68: 122-140.

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Shaul, W.L., H. Emery, and J.G. Hall. 1975. Chondrodysplasia punctata and maternal warfarin use during pregnancy. *Am. J. Dis. Child.* 129(3): 360-362.

Whitfield, M.F. 1980. Chondrodysplasia punctata after warfarin in early pregnancy. *Arch. J. Dis. Child.* 55: 139-180.

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### VI.B. Inhalation RfC References

None

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### VI.C. Carcinogenicity Assessment References

None

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## VII. Revision History

Substance Name — Warfarin

CASRN — 81-81-2

Date	Section	Description
10/28/2003	I.A.6	Screening-Level Literature Review Findings message has been added.

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## VIII. Synonyms

Substance Name — Warfarin

CASRN — 81-81-2

Last Revised — 03/31/1987

- 81-81-2
- 3-(ACETONYLBENZYL)-4-HYDROXYCOUMARIN

- 3-(alpha-ACETONYLBENZYL)-4-HYDROXYCOUMARIN
- ARAB RAT DETH
- ATHROMBINE-K
- ATHROMBIN-K
- 2H-1-BENZOPYRAN-2-ONE, 4-HYDROXY-3-(3-OXO-1-PHENYLBUTYL)-
- BRUMOLIN
- COMPOUND 42
- d-CON
- CO-RAX
- COUMADIN
- COUMAFEN
- COUMAFENE
- COUMARIN, 3-(alpha-ACETONYLBENZYL)-4-HYDROXY-
- COUMEFENE
- COV-R-TOX
- DETHMOR
- DETHNEL
- EASTERN STATES DUOCIDE
- FASCO FASCRAT POWDER
- 1-(4'-HYDROXY-3'-COUMARINYL)-1-PHENYL-3-BUTANONE
- 4-HYDROXY-3-(3-OXO-1-FENYL-BUTYL) CUMARINE
- 4-HYDROXY-3-(3-OXO-1-PHENYLBUTYL)-2H-1-BENZOPYRAN-2-ONE
- 4-HYDROXY-3-(3-OXO-1-PHENYL-BUTYL)-CUMARIN
- 4-IDROSSI-3-(3-OXO-)-FENIL-BUTIL)-CUMARINE
- KUMADER
- KUMADU
- KYPFARIN
- LIQUA-TOX
- MAR-FRIN
- MARTIN'S MAR-FRIN
- MAVERAN
- MOUSE PAK
- (PHENYL-1 ACETYL-2 ETHYL) 3-HYDROXY-4 COUMARINE
- 3-(alpha-PHENYL-beta-ACETYLAETHYL)-4-HYDROXYCUMARIN
- 3-(1'-PHENYL-2'-ACETYLETHYL)-4-HYDROXYCOUMARIN
- 3-(alpha-PHENYL-beta-ACETYLETHYL)-4-HYDROXYCOUMARIN
- PROTHROMADIN
- RAT-A-WAY
- RAT-B-GON
- RAT-GARD
- RAT-KILL
- RAT-MIX
- RAT-O-CIDE #2
- RAT-OLA
- RATOREX

- RATOX
- RATOXIN
- RATRON
- RATRON G
- RATS-NO-MORE
- RAT-TROL
- RATTUNAL
- RAX
- RCRA WASTE NUMBER P001
- RODAFARIN
- RO-DETH
- RODEX
- RODEX BLOX
- ROSEX
- ROUGH and READY MOUSE MIX
- SOLFARIN
- SPRAY-TROL BRAND RODEN-TROL
- TEMUS W
- TOX-HID
- TWIN LIGHT RAT AWAY
- VAMPIRINIP II
- VAMPIRINIP III
- W.A.R.F. 42
- WARAN
- WARFARAT
- Warfarin
- WARFARINE
- WARFARIN PLUS
- WARFARIN Q
- WARF COMPOUND 42
- WARFICIDE
- ZOOCOUMARIN