Assure; CASRN 76578-14-8

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 Assure

File First On-Line 09/26/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/26/1988
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	06/01/1991

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Assure
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Last Revised — 09/26/1988

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
Liver cell enlargement **2-Year Rat Feeding Study** **du Pont, 1985**	NOEL: 25 ppm (0.9 mg/kg/day, males; 1.1 mg/kg/day, females) LEL: 100 ppm (3.7 mg/kg/day, males; 4.6 mg/kg/day, females)	100	1	9E-3 mg/kg/day

*Conversion Factors: Actual doses tested

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

E.I. du Pont de Nemours and Company, Inc. 1985. MRID No. 00146682. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Groups of CD-rats (50/sex/dose) were fed assure at nominal concentrations of 0, 25, 100, and 400 ppm (0, 0.9, 3.7, and 15.5 mg/kg/day, males; 0, 1.1, 4.6, and 18.6 mg/kg/day, females) for 104 weeks. Satellite groups of 35 rats/sex/dose were reserved for interim sacrifices which were carried out at weeks 26, 52, and 78. Ten rats/sex/dose were killed during each interim sacrifice except at week 78 at which time all surviving animals from the satellite groups were sacrificed. An increased incidence of hepatocyte enlargement was observed in high dose males and females, 15.5 and 18.6 mg/kg/day respectively, at interim and terminal sacrifices. A slight increase in the incidence of hepatocyte enlargement was also observed in 3.7 mg/kg/day males at interim and terminal sacrifices. The LEL was established at 3.7 mg/kg/day; the NOEL, 0.9 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) 2-Year Feeding (oncogenic) - rat: Principal study - see previous description; core grade guideline

2) 52-Week Feeding - dog: NOEL=400 ppm (10 mg/kg/day) (HDT; no compound related effects were observed); core grade minimum (Nissan Chemical Industries Ltd., 1985)

3) 2-Generation Reproduction - rat: Developmental NOEL=25 ppm (1.25 mg/kg/day); Developmental LEL=100 ppm (2.5 mg/kg/day) (increased liver weight and increased incidence of eosinophilic changes in the liver of offspring); Maternal NOEL=100 ppm (5 mg/kg/day); Maternal LEL=400 ppm (20 mg/kg/day) (decreased body weights of F0 and F1 males); core grade minimum (E.I. du Pont de Nemours and Co., Inc., 1985b)

4) Teratology - rat: Maternal NOEL=30 mg/kg/day; Maternal LEL=100 mg/kg/day (decreases in body weight and food consumption, increases in liver weights, and decrease in corpora lutea); Teratogenic NOEL=300 mg/kg/day (HDT); Teratogenic LEL=none; core grade minimum (E.I. du Pont de Nemours and Co., Inc., 1983a)

5) Teratology - rabbit: Maternal NOEL=60 mg/kg/day (HDT); Maternal LEL=none; Fetotoxic NOEL and LEL could not be determined because critical data on embryonic implantation and resorption were missing; core grade supplementary (E.I. du Pont de Nemours and Co., Inc., 1983b)

Other Data Reviewed:

1) 18-Month Study (oncogenic) - mouse: When groups of CD-1 mice were fed assure at dietary concentrations of 0, 2, 10, 80, and 320 ppm for 18 months, increased liver weight, changes in clinical chemistry parameters (albumin, alkaline phosphatase, and total protein) and in histomorphology were found. NOEL=10 ppm (1.5 mg/kg/day); LEL=80 ppm (12 mg/kg/day); core grade guideline (E.I. du Pont de Nemours and Co., Inc., 1985c)

2) 90-Day Feeding - rat: NOEL=40 ppm (2 mg/kg/day); LEL=128 ppm (6.4 mg/kg/day) (liver weight increases and liver lesions); core grade minimum (E.I. du Pont de Nemours and Co., Inc., 1982a)

3) 6-Month Feeding - dog: NOEL=100 ppm (2.5 mg/kg/day); LEL=400 ppm (10 mg/kg/day) (atrophy of seminiferous tubules, pylelitis and others); core grade guideline (E.I. du Pont de Nemours and Co., Inc., 1984)

4) 90-Day Feeding - mice: NOEL=none; LEL=100 ppm (15 mg/kg/day) (LDT; liver changes were seen at all dosage levels); core grade minimum (E.I. du Pont de Nemours and Co., Inc., 1982b)

Data Gap(s): Rabbit Teratology Study (A new study is currently under review)

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 studies are supportive and of good quality and therefore, the data base 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 — 01/21/1988

Verification Date — 01/21/1988

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 Assure 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 — Assure
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Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Assure
CASRN — 76578-14-8
Last Revised — 06/01/1991

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 — D; not classifiable as to human carcinogenicity

Basis — Based on no human data and inadequate animal data.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Inadequate. The carcinogenicity of Assure could not be adequately evaluated based on data obtained from mouse and rat studies. In a study conducted by Nissan Chemical Industries and reported by Hazleton Laboratories America (reviewed in U.S. EPA, 1987a,b), 70 CD-1 mice/sex/group were fed 0, 2, 10, 80 or 320 ppm Assure for 78 weeks. Groups of 10 mice/sex/group were killed at 26 and 52 weeks for interim evaluation. The incidence of an unusual luteoma of the ovary was 0/51 in the controls and 3/50 at the high dose. An additional granulosa cell tumor was also observed at the high dose only. The incidences of the luteoma and the combined incidences of luteoma and granulosa cell tumor were significantly elevated when compared with historical controls (0/196 for luteoma and 1/196 for the combined incidences of luteomas and granulosa) but they were not statistically different from the concurrent controls. In the livers of the high-dose male mice the incidence of adenomas, carcinomas and combined tumors were 5/68, 10/68 and 15/68, respectively; in the controls the incidences were 3/70, 4/70 and 7/70, respectively. For adenomas and carcinomas combined, there was no statistically significant trend and no significant pairwise difference by the Peto prevalevence test, which accounts for survival differences. The incidences of carcinomas increased with dose, but these data were not examined by the Peto prevalence test. Liver tumors were apparent in males killed at 26 and 52 weeks, suggesting a reduced latency. The highest dose tested in male mice exceeded the MTD as indicated by reduced survival (39% male mice survived compared with 59% for the controls), testicular atrophy and hepatotoxic effects.

In a 24-month rat oncogenicity study conducted by Huntingdon Research Centre (reviewed in U.S. EPA, 1987a,b), groups of 50 Charles River SD rats/sex/dose were fed Assure at 0, 25, 100 and 400 ppm in the diet. Assure produced a statistically significant positive trend for hepatocellular carcinomas in female rats, but the low increases in carcinomas were not considered biologically significant because no neoplastic lesions were observed and the increase did not exceed the historical control incidences for liver carcinomas reported by the test laboratory (U.S. EPA, 1987b).

II.A.4. Supporting Data for Carcinogenicity

Assure was not mutagenic in reverse mutation assays for Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 or for Escherichia coli WP-2. DNA damage assays in Bacillus subtilis strains M45 and H17, a chromosomal aberration assay in CHO cells and an

unscheduled DNA synthesis assay in rat hepatocytes were also negative. No materials structurally related to Assure have been found to be carcinogenic (reviewed in U.S. EPA, 1987a).

Radiolabeled Assure, when administered orally to rats, is readily absorbed from the gastrointestinal tract. The material is taken up in the blood and distributed to the liver and kidney. The biological half-life is 18-27 hours for blood and tissues of both sexes. In males, the major route of elimination is in the feces, whereas in females equal amounts of administered radioactivity are eliminated in the urine and feces. In fecal samples collected within 48 hours, unchanged parent compound accounted for approximately 23% of the high oral dose (160 mg/kg) and <7% of the low oral dose (1.5 mg/kg). The major metabolite is the corresponding acid of Assure (U.S. EPA, 1987b).

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

None.

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

None.

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

II.D.1. EPA Documentation

Source Document — Quest, 1988; U.S. EPA, 1987a,b

The Office of Pesticide Programs (Health Effects Division of U.S. EPA) peer reviewed the data pertaining to possible carcinogenicity of assure. (Memorandum from J. Quest to R. Taylor, Peer Review of Assure following SAP Meeting, March 17, 1988).

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

Agency Work Group Review — 01/21/1988, 09/22/1988

Verification Date — 09/22/1988

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 Assure 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.

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 — Assure
CASRN — 76578-14-8

VI.A. Oral RfD References

E.I. du Pont de Nemours and Company, Inc. 1982a. EPA Accession No. 250071. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

E.I. du Pont de Nemours and Company, Inc. 1982b. EPA Accession No. 250073. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

E.I. du Pont de Nemours and Company, Inc. 1983a. EPA Accession No. 250071. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

E.I. du Pont de Nemours and Company, Inc. 1983b. EPA Accession No. 073905. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

E.I. du Pont de Nemours and Company, Inc. 1984. EPA Accession No. 250553. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

E.I. du Pont de Nemours and Company, Inc. 1985a. MRID No. 00146682. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

E.I. du Pont de Nemours and Company, Inc. 1985b. EPA Accession No. 074017. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

E.I. du Pont de Nemours and Company, Inc. 1985c. EPA Accession No. 255982. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Nissan Chemical Industries Ltd. 1985. EPA Accession No. 073536. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Quest, J. 1988. U.S. EPA, Washington, DC. Memorandum to R. Taylor, U.S. EPA, Washington, DC. March 17. Peer Review of Assure following SAP Meeting.

U.S. EPA. 1987a. Peer Review of Assure. Office of Pesticides and Toxic Substances, Washington, DC. February 6.

U.S. EPA. 1987b. Second Peer Review of Assure. Office of Pesticides and Toxic Substances, Washington, DC. September 9.

VII. Revision History

Substance Name — Assure
CASRN — 76578-14-8

Date	Section	Description
09/26/1988	I.A.	Oral RfD summary on-line
06/01/1991	II.	Carcinogenicity assessment on-line
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Assure
CASRN — 76578-14-8
Last Revised — 09/26/1988

- 76578-14-8
- Assure
- 2-(4-((6-chloro-2-quinoxalinyl)oxy)phenoxy)propanoic acid ethyl ester
- DPX-Y 6202
- EXP 3864
- FBC 32197
- NC 302
- NCI 96683
- pilot
- propanoic acid, 2-(4-((6-chloro-2-quinoxalinyl)oxy)phenoxy)-, ethyl ester
- quinofop-ethyl
- quizalofop-ethyl
- terga