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Endrin (CASRN 72-20-8)

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Reference Dose for Chronic Oral Exposure (RfD)

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Endrin; CASRN 72-20-8

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Endrin

File First On-Line 09/07/1988

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	04/01/1991
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	07/01/1993

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name -- Endrin
 CASRN -- 72-20-8
 Last Revised -- 04/01/1991

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

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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
Mild histological lesions in liver, occasional convulsions	NOEL: 1 ppm in diet (0.025 mg/kg/day)	100	1	3E-4 mg/kg/day
Dog Chronic Oral Bioassay	LOAEL: 2 ppm in diet (0.05 mg/kg/day)			
Velsicol Chemical Corporation, 1969				

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

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

Velsicol Chemical Corporation. 1969. MRID. No. 00030198. Available from EPA. Write FOI, EPA, Washington, DC. 20460.

Groups of 3 to 7 dogs/sex were fed diets containing 0.1, 0.5, 1.0, 2.0 or 4.0 ppm endrin for 2 years. Dogs receiving 2 or 4 ppm experienced occasional convulsions, slightly increased relative liver weights, and mild histopathological effects in the liver (slight vacuolization of hepatic cells). No adverse effects on these parameters or on growth, food consumption, behavior, serum chemistry, urine chemistry or histological appearance of major organs occurred at 1 ppm (NOEL) or less. The 2 ppm level is the LOAEL. The authors provided data concerning actual endrin consumptions as weekly averages, but no overall averages were calculated. Visual inspection of these data indicated that application of the standard food factor of 2.5% bw/day would closely approximate actual consumption. Therefore, the 1 ppm NOEL was equivalent to an endrin intake of 0.025 mg/kg/day.

An earlier study (Treon et al., 1955) established a dietary NOEL of 1 ppm for both dogs and rats for long-term feeding (18 months - 2 years). LOAELs of 3 ppm and 5 ppm were reported for dogs and rats, respectively. The primary target organs were the kidney and the liver. Dogs are judged to be more sensitive than rats to long-term exposure to endrin because of the lower food consumption of dogs (than rats) and because of the much shorter duration of exposure (in this study) relative to lifetime for dogs as compared to rats.

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

UF -- The UF of 100 allows for uncertainty in the extrapolation of dose levels from laboratory animals to humans (10A) and uncertainty in the threshold for sensitive humans (10H).

MF -- None

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

Acute lethality data suggest that rabbits and monkeys are much more sensitive to

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endrin than rats (Treon et al., 1955). Long-term studies have not been conducted with species other than rats or dogs. Conflicting evidence exists as to the developmental toxicity of endrin. Developmental effects have been observed to occur at dose levels much greater than those associated with chronic toxicity; these studies are discussed in U.S. EPA (1987).

__I.A.5. Confidence in the Oral RfD

Study -- Medium
Database -- Medium
RfD -- Medium

The principal study was of average quality and is given medium confidence. The database is assigned medium confidence because, although the chronic data is supportive, information on reproductive effects is lacking. Medium confidence in the RfD follows.

__I.A.6. EPA Documentation and Review of the Oral RfD

Source Document -- U.S. EPA, 1987, 1985

Other EPA Documentation -- None

Agency Work Group Review -- 05/20/1985, 08/13/1987, 10/15/1987, 04/20/1988

Verification Date -- 04/20/1988

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 Endrin conducted in November 2001 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).

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__I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name -- Endrin
CASRN -- 72-20-8

Not available at this time.

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__II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name -- Endrin
CASRN -- 72-20-8
Last Revised -- 07/01/1993

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 carcinogenicity for humans

Basis -- Oral administration of endrin did not produce carcinogenic effects in either sex of two strains of rats and three strains of mice. An NCI bioassay was suggestive of responses in male and female rats although NCI reported a no evidence conclusion. The inadequacies of several of the bioassays call into question the strength of the reported negative findings. These inadequacies and the suggestive responses in the NCI bioassay do not support a Group E classification; rather a Group D classification best reflects the equivocal data.

__II.A.2. Human Carcinogenicity Data

Inadequate. Ditraglia et al. (1981) conducted a retrospective cohort study to examine the mortality of workers employed in the manufacture of organochlorine pesticides including endrin. No statistically significant excesses or deficits in mortality for any specific cancer site were noted. Limited follow-up time (12 years), lack of exposure data, and few deaths give this study low power.

__II.A.3. Animal Carcinogenicity Data

Inadequate. The potential carcinogenic effects of endrin have been evaluated following oral exposure to 1-100 ppm endrin in the diet of Carworth Farm rats, (Treon et al., 1955), Osborne-Mendel rats (Deichmann et al., 1970; NCI, 1979), C57Bl/6J mice (Witherup et al., 1970), C3D2F1/J mice (Witherup et al., 1970) and B6C3F1 mice (NCI, 1979). There was no evidence of carcinogenicity in any of these studies. Treon et al., (1955) also failed to note any increase in tumorigenesis in dogs exposed up to 18.7 months at the maximum tolerated dose. The length of this study was insufficient to provide for the expected latency period in dogs.

The NCI (1979) bioassay was done in Osborne-Mendel rats (50/sex/group) and B6C3F1 mice (50/sex/group); matched control groups included 10 animals/sex/species. Since the number of animals in the matched-control groups was small, pooled-control groups from concurrent pesticide bioassays were used for statistical

evaluation.

Endrin was administered daily in the diet for 80 weeks. Rats were observed for an additional 31 to 34 weeks and mice were observed for an additional 11 weeks. The initial doses for male rats and all mice were 2.5 or 5 ppm and for female rats were 5 or 10 ppm. Because of subsequent toxic effects, the doses for the female rats and male mice were reduced during the course of the studies. High-dose male mice were fed treatment and control diets on alternate weeks for 10 weeks. The resulting time-weighted average dose fed in the diets of treated animals was reported as follows: 2.5 or 5 ppm for male rats, 3 or 6 ppm for female rats, 1.6 or 3.2 ppm for male mice, and 2.5 or 5 ppm for female mice.

When compared with pooled controls, a statistically significant increase in hemangioma was observed in low-dose male rats (0/49, 5/46, 3/47), and a significant increase in adrenal adenoma or carcinoma was seen in high-dose male rats (2/44, 4/46, 8/44). Islet-cell carcinoma incidence in male rats showed a significant positive trend but the pairwise comparisons were not significant. A statistically significant increase in pituitary adenoma was observed in the high-dose female rats (4/44, 11/47, 13/45) and a significant increase in adrenal adenoma or carcinoma was observed in the low-dose female rats (4/46, 14/49, 7/47).

Although NCI concluded from the bioassays that endrin was not carcinogenic, the responses noted above cannot be totally ignored. A primary reviewer for NCI noted that the negative findings could be a reflection of the high toxicity of endrin, which only permitted the administration of relatively low chronic doses. Furthermore, the reviewer observed that an accidental overdose among low-dose male mice resulted in the early death of several animals in this treatment group. The study was marred by a small number (10) of matched controls; however, this deficiency was compensated by the use of pooled controls.

Reuber (1978) reported positive carcinogenic effects of endrin had been observed in a FDA bioassay (Bierbower, 1965). Male and female Osborne-Mendel rats were exposed to 0.1 to 25 ppm endrin in the diet. At the 0.1 ppm dose, incidence of hyperplastic nodules and malignant tumors of the liver was significantly increased in female rats and in male and female rats combined. A variety of other tumors were observed including mammary gland, uterine, and thyroid tumors in females and thyroid and adrenal cortex tumors in males.

Reuber (1979) independently reevaluated several endrin carcinogenicity studies including the NCI (1979) study and the FDA (Bierbower, 1965) study and determined that a significant increase in tumor incidence was present. It is difficult to draw conclusions from Reuber's findings, however, since his criteria for classifying lesions as tumorigenic appear to differ from those of other investigators. Reuber did not provide slide by slide tabulation of his findings nor did he distinguish between primary and/or metastatic tumors in the liver (Albert, 1977).

__II.A.4. Supporting Data for Carcinogenicity

Maslansky and Williams (1981) showed that endrin (10⁻³ and 10⁻⁴ M) was not genotoxic in the hepatocyte primary culture (HPC)/DNA repair assay using hepatocytes from male Fischer F344 rats, male CD-1 mice, and male Syrian hamsters. DNA repair was observed in response to a positive control in all three systems. Endrin was not mutagenic in microbial systems with or without metabolic activation (Moriya et al., 1983; Probst et al., 1981; Glatt et al., 1983), and endrin exposure did not significantly affect sister-chromatid exchange frequencies in a human lymphoid cell line (Sobti et al., 1983). Endrin is also structurally related to aldrin, dieldrin, chlordane, chlorendic acid, and heptachlor which are known to be carcinogenic in animals.

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

Not available.

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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, 1987a,b

The 1988 Carcinogenicity Assessment for Endrin has had Agency review.

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

Agency Work Group Review -- 03/23/1988, 10/19/1988

Verification Date -- 10/19/1988

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 Endrin conducted in November 2001 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).

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III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name -- Endrin
CASRN -- 72-20-8
Last Revised -- 07/01/1993

VI.A. Oral RfD References

Treon, J.F., F.P. Cleveland and J. Cappel. 1955. Toxicity of endrin for laboratory animals. *Agric. Food Chem.* 3(10): 842-848.

U.S. EPA. 1987. Health Effects Assessment for Endrin. Final Draft. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-H089.

U.S. EPA. 1985. Drinking Water Criteria Document for Endrin. Final Draft. Environmental Criteria and Assessment Office, Cincinnati, OH. NTIS PB86- 117967.

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VI.B. Inhalation RfC References

None

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VI.C. Carcinogenicity Assessment References

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Bierbower, G.W. 1965. Final report on pathological study of rats fed endrin or dieldrin. Prepared as a memo to A.J. Lehman. Food and Drug Administration. (Cited in: Reuber, 1978)

Deichmann, W.B., W.E. MacDonald, E. Blum, et al. 1970. Tumorigenicity of aldrin, dieldrin and endrin in the albino rat. *Ind. Med.* 39: 426-434.

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Glatt, H., R. Jung and F. Oesch. 1983. Bacterial mutagenicity investigation of epoxides: Drugs, drug metabolites, steroids and pesticides. *Mutat. Res.* 11: 99-118.

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NCI (National Cancer Institute). 1979. Bioassay of endrin for possible carcinogenicity. *Carcinogenesis Technical Report Series 12, NCR-CG-TR-12. Publ. No. (NIH) 79-812.*

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Reuber, M.D. 1979. Carcinogenicity of endrin. *Sci. Total Environ.* 12: 101-135.

Sobti, R.C., A. Krishan and J. Davies. 1983. Cytokinetic and cytogenetic effect of agricultural chemicals on human lymphoid cells in vitro. II. Organochlorine pesticides. *Arch. Toxicol.* 52: 221-231.

Treon, J.F., F.P. Cleveland and J. Cappel. 1955. Toxicity of endrin for laboratory animals. *J. Agric. Food Chem.* 3: 842-848.

U.S. EPA. 1987a. Drinking Water Criteria Document for Endrin. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. (External Review Draft)

U.S. EPA. 1987b. Health Effects Assessment for Endrin. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. (Final Draft)

Witherup, S., K.L. Stemmer, P. Taylor and P. Bietsch. 1970. The incidence of neoplasms in two strains of mice sustained on diets containing endrin. *Kettering Lab., Univ. Cincinnati, Cincinnati, OH.*

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_VII. Revision History

Substance Name -- Endrin
CASRN -- 72-20-8

Date	Section	Description
09/07/1988	I.A.	Oral RfD summary on-line
04/01/1989	V.	Supplementary data on-line
08/01/1989	VI.	Bibliography on-line

10/01/1989	II.	Carcinogen summary on-line
10/01/1989	VI.C.	Carcinogen references added
04/01/1991	I.A.	Secondary contact changed
04/01/1991	II.	Primary contact changed
01/01/1992	IV.	Regulatory Action section on-line
07/01/1993	II.D.1.	EPA Documentation clarified
07/01/1993	VI.C.	EPA references clarified
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

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_VIII. Synonyms

Substance Name -- Endrin
CASRN -- 72-20-8
Last Revised -- 09/07/1988

72-20-8
Endrin
mendrin, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4(a)5,6,7,8,8a-octahydro-endo

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