Dieldrin; CASRN 60-57-1

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 Dieldrin

File First On-Line 09/07/1988

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<th>Category (section)</th>
<th>Assessment Available?</th>
<th>Last Revised</th>
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<td>09/07/1988</td>
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I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Dieldrin
CASRN — 60-57-1
Last Revised — 09/07/1988

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

<table>
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<tr>
<th>Critical Effect</th>
<th>Experimental Doses*</th>
<th>UF</th>
<th>MF</th>
<th>RfD</th>
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<td>Liver lesions</td>
<td>NOAEL: 0.1 ppm (0.005 mg/kg/day)</td>
<td>100</td>
<td>1</td>
<td>5E-5 mg/kg/day</td>
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<tr>
<td>2-Year Rat Feeding Study</td>
<td>LOAEL: 1.0 ppm (0.05 mg/kg/day)</td>
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<tr>
<td>Walker et al., 1969</td>
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</table>

*Conversion Factors -- 1 ppm = 0.05 mg/kg/day (assumed rat food consumption)

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


Walker et al. (1969) administered dieldrin (recrystallized, 99% active ingredient) to Carworth Farm "E" rats (25/sex/dose; controls 45/sex) for 2 years at dietary concentrations of 0, 0.1, 1.0, or 10.0 ppm. Based on intake assumptions presented by the authors, these dietary levels are approximately equal to 0, 0.005, 0.05 and 0.5 mg/kg/day. Body weight, food intake, and general health remained unaffected throughout the 2-year period, although at 10.0 ppm (0.5 mg/kg/day) all animals became irritable and exhibited tremors and occasional convulsions. No effects were seen in various hematological and clinical chemistry parameters. At the end of 2 years, females fed 1.0 and 10.0 ppm (0.05 and 0.5 mg/kg/day) had increased liver weights and liver-to-body weight ratios (p<0.05). Histopathological examinations revealed liver parenchymal cell changes including focal proliferation and focal hyperplasia. These hepatic lesions were considered to be characteristic of exposure to an organochlorine insecticide. The LOAEL was identified as 1.0 ppm (0.005 mg/kg/day) and the NOAEL as 0.1 ppm (0.005 mg/kg/day).
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)

Data considered for establishing the RfD:

1) 2-Year Feeding - rat: Principal study - see previous description

2) 2-Year Feeding (oncogenic) - dog: Systemic NOEL=0.005 mg/kg/day; LEL= 0.05 mg/kg/day (increased liver weight and liver/body weight ratios, increased plasma alkaline phosphatase, and decreased serum protein concentration) (Walker et al., 1969)

3) 2-Year Feeding - rat: Systemic LEL=0.5 ppm (approximately 0.025 mg/kg/day), (liver enlargement with histopathology); (Fitzhugh et al., 1964)

4) 2-Year Feeding (oncogenic) - mouse: Systemic LEL=0.1 ppm (0.015 mg/kg/day), (liver enlargement with histopathology); (Walker et al., 1972)

5) 25-Month Feeding - dog: Systemic NOEL=0.2 mg/kg/day; LEL=0.5 mg/kg/day, (weight loss and convulsions); (Fitzhugh et al., 1964)

6) Teratology - mouse: Teratogenic NOEL=6.0 mg/kg/day (HDT, gestational days 7-16); Maternal LEL=6.0 mg/kg/day (HDT, decrease in maternal weight gain); Fetotoxic LEL=6.0 mg/kg/day (HDT, decreased numbers of caudal ossification centers and increases in supernumerary ribs); (Chernoff et al., 1975). This study was not considered since 41% of the test dams died at the highest dose tested.

I.A.5. Confidence in the Oral RfD

Study — Low
Database — Medium
RfD — Medium

The principal study is an older study for which detailed data are not available and in which a wide range of doses was tested. The chronic toxicity evaluation is relatively complete and
supports the critical effect, if not the magnitude of effects. Reproductive studies are lacking. The 
RfD is given a medium confidence rating because of the support for the critical effect from other 
dieldrin studies, and from studies on organochlorine insecticides in general.

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


Other EPA Documentation — None

Agency Work Group Review — 04/16/1987

Verification Date — 04/16/1987

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 Dieldrin 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 — Dieldrin
CASRN — 60-57-1

Not available at this time.
II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Dieldrin
CASRN — 60-57-1
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 — B2; probable human carcinogen

Basis — Dieldrin is carcinogenic in seven strains of mice when administered orally. Dieldrin is structurally related to compounds (aldrin, chlordane, heptachlor, heptachlor epoxide, and chlorendic acid) which produce tumors in rodents.

II.A.2. Human Carcinogenicity Data

Inadequate. Two studies of workers exposed to aldrin and to dieldrin reported no increased incidence of cancer. Both studies were limited in their ability to detect an excess of cancer deaths. Van Raalte (1977) observed two cases of cancer (gastric and lymphosarcoma) among 166 pesticide manufacturing workers exposed 4-19 years and followed from 15-20 years. Exposure was not quantified, and workers were also exposed to other organochlorine pesticides (endrin and telodrin). The number of workers studied was small, the mean age of the cohort (47.7 years)
was young, the number of expected deaths was not calculated, and the duration of exposure and of latency was relatively short.

In a retrospective mortality study, Ditraglia et al. (1981) reported no statistically significant excess in deaths from cancer among 1155 organochlorine pesticide manufacturing workers [31 observed vs. 37.8 expected, Standardized Mortality Ratio (SMR) = 82]. Workers were employed for 6 months or more and followed 13 years or more (24,939 person-years). Workers with no exposure (for example, office workers) were included in the cohort. Vital status was not known for 112 or 10% of the workers, and these workers were assumed to be alive; therefore additional deaths may have occurred but were not observed. Exposure was not quantified and workers were also exposed to other chemicals and pesticides (including endrin). Increased incidences of deaths from cancer were seen at several specific sites: esophagus (2 deaths observed, SMR = 235); rectum (3, SMR = 242); liver (2, SMR = 225); and lymphatic and hematopoietic system (6, SMR = 147), but these site-specific incidences were not statistically significantly increased.

II.A.3. Animal Carcinogenicity Data

Sufficient. Dieldrin has been shown to be carcinogenic in various strains of mice of both sexes. At different dose levels the effects range from benign liver tumors, to hepatocarcinomas with transplantation confirmation, to pulmonary metastases.

The Food and Drug Administration (FDA) conducted a long-term carcinogenesis bioassay for dieldrin (Davis and Fitzhugh, 1962). Ten ppm dieldrin was administered orally to 218 male and female C3HeB/Fe mice for 2 years. The study was compromised by the poor survival rate, lack of detailed pathology, loss of a large percentage of the animals to the study, and failure to treat the data for males and females separately. A statistically significant increase in incidence of hepatomas was observed in the treated groups versus the control groups in both males and females. In FDA follow-up study, Davis (1965) examined 100 male and 100 female C3H mice which had been orally administered 10 ppm dieldrin. The same limitations as the previous study were reported. The incidence of benign hepatomas and hepatic carcinomas was significantly increased in the dieldrin group. A reevaluation of the histological material of both studies was done by Reuber in 1974 (Epstein, 1975a,b; 1976). He concluded that the hepatomas were malignant and that dieldrin was hepatocarcinogenic for male and female C3HeB/Fe and C3H mice.

Walker et al. (1972) conducted several studies of dieldrin in CF1 mice of both sexes. Dieldrin was administered orally at concentrations of 0, 0.1, 1.0, and 10 ppm. Treatment groups varied from 87 to 288 animals of each sex. Surviving animals were sacrificed during weeks 132-140. Incidence of tumors was related to the number of dose levels and the dose administered. Effects were detected at the lowest dieldrin level tested (0.1 ppm) in both male and female mice.
Dieldrin also produced significant increases (<0.05) in the incidence of pulmonary adenomas, pulmonary carcinomas, lymphoid tumors, and "other" tumors in female mice.

Diets containing 10 ppm dieldrin were fed to groups of 30 CF1 mice of both sexes for 110 weeks (Thorpe and Walker, 1973). The control group consisted of 45 mice of both sexes. A statistically significant increase (p<0.01) in incidence of liver tumors was found in both sexes of treated animals relative to controls. The liver tumors appeared much earlier in treated animals than controls.

Technical-grade dieldrin (>96%) was fed to B6C3F1 mice (50/sex/dose) at TWA doses of 0, 2.5, or 5 ppm for 80 weeks followed by an observation period of 10 to 13 weeks (NCI, 1978a). Matched control groups consisted of 20 untreated males and 10 untreated females. No significant difference in survival was noted. A significant dose-related increase in hepatocellular carcinoma was found in male mice when compared with pooled controls.

Tennekes et al. (1981) fed groups of 19 to 82 male CF1 mice control or dieldrin-supplemented (10 ppm) diets or control diets for 110 weeks. Dieldrin produced a statistically significant increased incidence of hepatocellular carcinomas in the treated group.

Dieldrin (>99%) was continuously fed in the diet for 85 weeks to 50 C3H/He, 62 B6C3Fl, and 71 C57Bl/6J male mice (Meierhenry et al., 1983). Controls were 50 to 76 males of each strain. Dieldrin produced a significant increase in the incidence of hepatocellular carcinomas compared with controls in all three strains.

Seven studies with four strains of rats fed 0.1 to 285 ppm dieldrin varying in duration of exposure from 80 weeks to 31 months did not produce positive results for carcinogenicity (Treon and Cleveland, 1955; Fitzhugh et al., 1964; Song and Harville, 1964; Walker et al., 1969; Deichmann et al., 1970; NCI, 1978a,b). Three of these studies used Osborne-Mendel rats, two studies used Carworth rats, and one each used Fischer 344 and Holtzman strains. Only three of the seven studies are considered adequate in design and conduct. The others used too few animals, had unacceptably high levels of mortality, were too short in duration, and/or had inadequate pathology examination or reporting.

II.A.4. Supporting Data for Carcinogenicity

Dieldrin causes chromosomal aberrations in mouse cells (Markaryan, 1966; Majumdar et al., 1976) and in human lymphoblastoid cells (Trepanier et al., 1977), forward mutation in Chinese hamster V79 cells (Ahmed et al., 1977), and unscheduled DNA synthesis in rat (Probst et al., 1981) and human cells (Rocchi et al., 1980). Dieldrin did not produce responses in 13 other mutagenicity tests. Negative responses were given in assays for gene conversion in S. cerevisiae,
back-mutation in S. marcesans, forward mutation (Gal Rz2 in E. coli), and forward mutation to streptomycin resistance in E. coli (Fahrig, 1974). Negative responses were produced in reverse mutation assays with six strains of S. typhimurium with or without metabolic activation (Bidwell et al., 1975; Marshall et al., 1976; Shirasu et al., 1976; Wade et al., 1979; Haworth et al., 1983). Majumdar et al. (1977), however, reported that dieldrin was mutagenic for S. typhimurium with and without metabolic activation.

Five compounds structurally related to dieldrin - aldrin, chlordane, heptachlor, heptachlor epoxide, and chlorondic acid - have induced malignant liver tumors in mice. Chlorendic acid has also induced liver tumors in rats.

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

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 1.6E+1 per (mg/kg) day

Drinking Water Unit Risk — 4.6E-4 per (ug/L)/day

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

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<th>Risk Level</th>
<th>Concentration</th>
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<tr>
<td>E-5 (1 in 100,000)</td>
<td>2E-2 ug/L</td>
</tr>
<tr>
<td>E-6 (1 in 1,000,000)</td>
<td>2E-3 ug/L</td>
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II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type: liver carcinoma
Test animals: mouse
Route: diet
Reference: see table

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<th>Sex/Strain</th>
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<td>Female, C3H</td>
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<td>Davis (1965), reevaluated by Reuber, 1974 (cited in Epstein, 1975a)</td>
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<td>Male, CF1</td>
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<td>Walker et. al. (1972)</td>
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<td>Walker et. al. (1972)</td>
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<td>7.1</td>
<td>Walker et. al. (1972)</td>
</tr>
<tr>
<td>Male, CF1</td>
<td>55</td>
<td>Thorpe and Walker (1973)</td>
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<tr>
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<td>26</td>
<td>Thorpe and Walker (1973)</td>
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<tr>
<td>Male, B63F1</td>
<td>9.8</td>
<td>NCI (1978a,b)</td>
</tr>
<tr>
<td>Male, CF1</td>
<td>18</td>
<td>Tennekes at al. (1981)</td>
</tr>
<tr>
<td>Male, C57B1/6J</td>
<td>7.4</td>
<td>Meierhenry et. al. (1983)</td>
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</tbody>
</table>
### II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The slope factor is the geometric mean of 13 slope factors calculated from liver carcinoma data in both sexes of several strains of mice. Inspection of the data indicated no strain or sex specificity of carcinogenic response.

The unit risk should not be used if the water concentration exceeds 20 ug/L, since above this concentration the unit risk may not be appropriate.

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

The individual slope factors calculated from 13 independent data sets range within a factor of 8.

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

#### II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 4.6E-3 per (ug/cu.m)

Extrapolation Method — Linearized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:
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<th>Risk Level</th>
<th>Concentration</th>
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<tr>
<td>E-4 (1 in 10,000)</td>
<td>2E-2 ug/cu.m</td>
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<tr>
<td>E-5 (1 in 100,000)</td>
<td>2E-3 ug/cu.m</td>
</tr>
<tr>
<td>E-6 (1 in 1,000,000)</td>
<td>2E-4 ug/cu.m</td>
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</tbody>
</table>

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Calculated from oral data in Section II.B.2.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

The unit risk should not be used if air concentrations exceed 2 ug/cu.m, since above this concentration the unit risk may not be appropriate.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

This inhalation risk estimate was based on oral data.

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

II.D.1. EPA Documentation


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

Agency Work Group Review — 03/05/1987

Verification Date — 03/05/1987
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 Dieldrin 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 — Dieldrin
CASRN — 60-57-1

VI.A. Oral RfD References


VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References


Reuber, M.D. 1974. Exhibit 42. Testimony at hearings on aldrin/dieldrin. (Cited in: Epstein, 1975a)


VII. Revision History

Substance Name — Dieldrin
CASRN — 60-57-1

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VIII. Synonyms

Substance Name — Dieldrin
CASRN — 60-57-1
Last Revised — 09/07/1988

- 60-57-1
- ALVIT
- COMPOUND 497
- DIELDREX
- Dieldrin
- DIEldrine
- DIEldrite
- 1,4:5,8-DIMETHANONAPHTHALENE, 1,2,3,4,10,10-HEXACHLORO-6,7-EPOXY-1,4,4a,5,6,7,8,8a-OCTAHYDRO, endo,exo-
- ENT 16,225
• HEOD
• HEXACHLOROEPoxyOCTAHYDRO-endo,exo-DIMETHANONAPHTHALENE
• 3,4,5,6,9,9-HEXACHLORO-1a,2,2a,3,6,6a,7,7a-OCTAHYDRO-2,7:3,6-
  DIMETHANONAPHTH(2,3-b)OXIRENE
• ILLOXOL
• NA 2761
• NCI-C00124
• OCTALOX
• PANORAM D-31
• QUINTOX
• RCRA WASTE NUMBER P037