p,p'-Dichlorodiphenyltrichloroethane (DDT); CASRN 50-29-3

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 DDT

File First On-Line 03/31/1987

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<th>Assessment Available?</th>
<th>Last Revised</th>
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<td>03/31/1987</td>
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<tr>
<td>Inhalation RfC (I.B.)</td>
<td>not evaluated</td>
<td></td>
</tr>
<tr>
<td>Carcinogenicity Assessment (II.)</td>
<td>yes</td>
<td>08/22/1988</td>
</tr>
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I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

IA Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — p,p'-Dichlorodiphenyltrichloroethane (DDT)
CASRN — 50-29-3
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 US 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>
<thead>
<tr>
<th>Critical Effect</th>
<th>Experimental Doses*</th>
<th>UF</th>
<th>MF</th>
<th>RfD</th>
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</thead>
<tbody>
<tr>
<td>Liver lesions</td>
<td>NOEL: 1 ppm diet (0.05 mg/kg bw/day)</td>
<td>100</td>
<td>1</td>
<td>5E-4 mg/kg/day</td>
</tr>
<tr>
<td>27-Week Rat Feeding Study</td>
<td>LOAEL: 5 ppm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laug et al., 1950</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Conversion Factors: Food consumption = 5% bw/day

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


Weanling rats (25/sex/group) were fed commercial DDT (81% P,P isomer and 19% O,P isomer) at levels of 0, 1, 5, 10 or 50 ppm for 15-27 weeks. The diet was prepared by mixing appropriate amounts of DDT in corn oil solution with powdered chow. No interference with growth was noted at any level. Females stored more DDT in peripheral fat than did males, but pathologic changes were seen to a greater degree in males. Increasing hepatocellular hypertrophy, especially centrilobularly, increased cytoplasmic oxyphilia, and peripheral basophilic cytoplasmic granules (based on H and E paraffin sections) were observed at dose levels of 5 ppm and above. The effect was minimal at 5 ppm (LOAEL) and more pronounced at higher doses. No effects were reported at 1 ppm, the NOEL level used as the basis for the RfD calculation. The authors believe the effect seen at 5 ppm "represents the smallest detectable morphologic effect, based on extensive observations of the rat liver as affected by a variety of chemicals."

DDT fed to rats for 2 years (Fitzhugh, 1948) caused liver lesions at all dose levels (10-800 ppm of diet). A LOAEL of 0.5 mg/kg bw/day was established. Application of a factor of 10 each for
uncertainty of estimating a NOEL from a LOAEL, as well as for interspecies conversion and protection of sensitive human subpopulations (1000 total) results in the same RfD level as that calculated from the critical study. DDT-induced liver effects were observed in mice, hamsters and dogs as well.

The Laug et al. (1950) study was chosen for the RfD calculation because: 1) male rats appear to be the most sensitive animals to DDT exposure; 2) the study was of sufficient length to observe toxic effects; and 3) several doses were administered in the diet over the range of the dose-response curve. This study also established a LOAEL and a NOEL, with the LOAEL (0.25 mg/kg/day) being the lowest of any observed for this compound.

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

UF — A factor of 10 each was applied for the uncertainty of interspecies conversion and to protect sensitive human subpopulations. An uncertainty factor for subchronic to chronic conversion was not included because of the corroborating chronic study in the database.

MF — None

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

In one 3-generation rat reproduction study (Treon and Cleveland, 1955), offspring mortality increased at all dose levels, the lowest of which corresponds to about 0.2 mg/kg bw/day. Three other reproduction studies (rat and mouse) show no reproductive effects at much higher dose levels.

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

The principal study appears to be adequate, but of shorter duration than that desired; therefore, confidence in the study can be considered medium to low. The database is only moderately supportive of both the critical effect and the magnitude, and lacks a clear NOEL for reproductive effects; therefore, confidence in the database can also be considered medium to low. Medium to low 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 — None

Agency Work Group Review — 12/18/1985

Verification Date — 12/18/1985

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 p,p’-Dichlorodiphenyltrichloroethane conducted in September 2002 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 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 — p,p’-Dichlorodiphenyltrichloroethane (DDT)
CASRN — 50-29-3

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — p,p’-Dichlorodiphenyltrichloroethane (DDT)
CASRN — 50-29-3
Last Revised — 08/22/1988

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 — Observation of tumors (generally of the liver) in seven studies in various mouse strains and three studies in rats. DDT is structurally similar to other probable carcinogens, such as DDD and DDE.

II.A.2. Human Carcinogenicity Data

Inadequate. The existing epidemiological data are inadequate. Autopsy studies relating tissue levels of DDT to cancer incidence have yielded conflicting results. Three studies reported that tissue levels of DDT and DDE were higher in cancer victims than in those dying of other diseases (Casarett et al., 1968; Dacre and Jennings, 1970; Wasserman et al., 1976). In other studies no such relationship was seen (Maier-Bode, 1960; Robinson et al., 1965; Hoffman et al., 1967). Studies of occupationally exposed workers and volunteers have been of insufficient duration to be useful in assessment of the carcinogenicity of DDT to humans.

II.A.3. Animal Carcinogenicity Data

Sufficient. Twenty-five animal carcinogenicity assays have been reviewed for DDT. Nine feeding studies, including two multigenerational studies, have been conducted in the following mouse strains: BALB/C, CF-1, A strain, Swiss/Bombay and (C57B1)x(C3HxAkR). Only one of these studies, conducted for 78 weeks, showed no indication of DDT tumorigenicity (NCI, 1978). Both hepatocellular adenomas and carcinomas were observed in six mouse liver tumor studies (Walker et al., 1973; Thorpe and Walker, 1973; Kashyap et al., 1977; Innes et al., 1969; Terracini et al., 1973; Turusov et al., 1973). Both benign and malignant lung tumors were observed in two studies wherein mice were exposed both in utero and throughout their lifetime.
(Shabad et al., 1973; Tarjan and Kemeny, 1969). Doses producing increased tumor incidence ranged from 0.15-37.5 mg/kg/day.

Three studies using Wistar, MRC Porton and Osborne-Mendel rats and doses from 25-40 mg/kg/day produced increased incidence of benign liver tumors (Rossi et al., 1977; Cabral et al., 1982; Fitzhugh and Nelson, 1946). Another study wherein Osborne-Mendel rats were exposed in this dietary dose range for 78 weeks was negative (NCI, 1978) as were three additional assays in which lower doses were given.

Tests of DDT in hamsters have not resulted in increased tumor incidence. Unlike mice and humans, hamsters accumulate DDT in tissue but do not metabolize it to DDD or DDE. Studies of DDT in dogs (Lehman, 1951, 1965) and monkeys (Adamson and Sieber, 1979, 1983) have not shown a carcinogenic effect. However, the length of these studies (approximately 30% of the animals’ lifetimes) was insufficient to assess the carcinogenicity of DDT. DDT has been shown to produce hepatomas in trout (Halver, 1967).

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

DDT has been shown to act as a liver tumor promoter in rats initiated with 2-acetylaminofluorene, 2-acetamidophenanthrene or trans-4-acetylaminostilbene (Peraino et al., 1975; Scribner and Mottet, 1981; Hilpert et al., 1983).

DDT has produced both negative and positive responses in tests for genotoxicity. Positive responses have been noted in V79 mutation assays, for chromosome aberrations in cultured human lymphocytes, and for sister chromatid exchanges in V79 and CHO cells (Bradley et al., 1981; Rabello et al., 1975; Preston et al., 1981; Ray-Chaudhuri et al., 1982). In one study, DDT was reported to interact directly with DNA; this result was not confirmed in the absence of a metabolizing system (Kubinski et al., 1981; Griffin and Hill, 1978).

DDT is structurally related to the following chemicals which produce liver tumors in mice: DDE, DDD, dicofol and chlorobenzilate.

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

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

Oral Slope Factor — 3.4E-1 per (mg/kg)/day

Drinking Water Unit Risk — 9.7E-6 per (ug/L)
Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-4 (1 in 10,000)</td>
<td>1E+1 ug/L</td>
</tr>
<tr>
<td>E-5 (1 in 100,000)</td>
<td>1E+0 ug/L</td>
</tr>
<tr>
<td>E-6 (1 in 1,000,000)</td>
<td>1E-1 ug/L</td>
</tr>
</tbody>
</table>

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

Tumor Type: Liver, benign and malignant (see table)
Test animals: mouse and rat (see table)
Route: diet
Reference: see table

<table>
<thead>
<tr>
<th>Species/Strain Tumor Type</th>
<th>Male</th>
<th>Female</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse/CF-1, Benign</td>
<td>0.80</td>
<td>0.42</td>
<td>Turusov et al., 1973</td>
</tr>
<tr>
<td>Mouse/BALB/C, Benign</td>
<td>0.082</td>
<td></td>
<td>Terracini et al., 1973</td>
</tr>
<tr>
<td>Mouse/CF-1, Benign, Malignant</td>
<td>0.52</td>
<td>0.81</td>
<td>Thorpe and Walker, 1973</td>
</tr>
<tr>
<td>Mouse/CF-1, Benign</td>
<td>1.04</td>
<td>0.49</td>
<td>Tomatis and Turusov, 1975</td>
</tr>
</tbody>
</table>
## II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The estimate of the slope factor did not increase in the multigeneration feeding studies (Terracini et al., 1973; Turusov et al., 1973) but remained the same from generation to generation. A geometric mean of the above slope factors was used for the overall slope factor of 3.4E-1. This was done in order to avoid excluding relevant data (note that the appropriateness of this procedure is currently under study by U.S. EPA). All tumors were of the liver; there were no metastases. A few malignancies were observed in the Turusov study; possible neoplasms were indicated in the Terracini and Tomatis studies. The Turusov study was carried out over six generations, the Terracini assay for two. The slope factor derived from data of Tarjan and Kemeny (1969) was not included in the calculation of the geometric mean because the tumors developed at different sites than in any other studies. In addition, there was a problem in this study with possible DDT contamination of the feed.

DDT is known to be absorbed by humans in direct proportion to dietary exposure; t(1/2) for clearance is 10-20 years.

The unit risk should not be used if the water concentration exceeds 1E+3 ug/L, since above this concentration the unit risk may not be appropriate.

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

Ten slope factors derived from six studies were within a 13-fold range. The slope factor derived from the mouse data alone was 4.8E-1 while that derived from the rat data alone was 1.5E-1. There was no apparent difference in slope factor as a function of sex of the animals. The geometric mean of the slope factors from the mouse and rat data combined was identical for the same tumor site as that for DDE [3.4E-1 per (mg/kg)/day], a structural analog.

### II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure
II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 9.7E-5 per (ug/cu.m)

Extrapolation Method — Linear multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

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<th>Risk Level</th>
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<tbody>
<tr>
<td>E-4 (1 in 10,000)</td>
<td>1E+0 ug/cu.m</td>
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<tr>
<td>E-5 (1 in 100,000)</td>
<td>1E-1 ug/cu.m</td>
</tr>
<tr>
<td>E-6 (1 in 1,000,000)</td>
<td>1E-2 ug/cu.m</td>
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</tbody>
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II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

The inhalation risk estimates were calculated from the oral data presented in Section II.B.2.

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

The unit risk should not be used if the air concentration exceeds 1E+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 calculated from the oral data presented in Section II.B.2.

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

II.D.1. EPA Documentation

The U.S. EPA risk assessment document on DDT is an internal report and has not received external review.

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


Verification Date — 06/24/1987

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 p,p'-Dichlorodiphenyltrichloroethane conducted in September 2002 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 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 — p,p'-Dichlorodiphenyltrichloroethane (DDT)
CASRN — 50-29-3

VI.A. Oral RfD References


VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References


VII. Revision History

Substance Name — p,p’-Dichlorodiphenyltrichloroethane (DDT)
CASRN — 50-29-3

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<th>Description</th>
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VIII. Synonyms
Substance Name — p,p'-Dichlorodiphenyltrichloroethane (DDT)
CASRN — 50-29-3
Last Revised — 03/31/1987

- 50-29-3
- AGRITAN
- ANOFEX
- ARKOTINE
- AZOTOX
- BENZENE, 1,1’-(2,2,2-TRICHLOROETHYLIDENE)BIS(4-CHLORO-)
- alpha,alpha-BIS(p-CHLOROPHENYL)-beta, beta-TRICHLORETHANE
- 1,1-BIS-(p-CHLOROPHENYL)-2,2,2-TRICHLOROETHANE
- 2,2-BIS(p-CHLOROPHENYL)-1,1,1-TRICHLOROETHANE
- BOSAN SUPRA
- BOVIDERMOL
- CHLOROPHENOTHAN
- CHLOROPHENOTHANE
- CHLOROPHENOTOXUM
- CITOX
- CLOFENOTANE
- DDT
- p,p'-DDT
- DEDELO
- DEOVAL
- DETOX
- DETOXAN
- DIBOVAN
- DICHLORODIPHENYLTRICHLOROETHANE
- 4,4'-DICHLORODIPHENYLTRICHLOROETHANE
- Dichlorodiphenyltrichloroethane, p,p'-
- DICOPHANE
- DIDIGAM
- DIDIMAC
- DIPHENYLTRICHLOROETHANE
- DODAT
- DYKOL
- ENT 1,506
- ESTONATE
- ETHANE, 1,1,1-TRICHLORO-2,2-BIS(p-CHLOROPHENYL)-
- GENITOX
- GESAFID
- GESAPON
- GESAREX
- GESAROL
- GUESAPON
- GUESAROL
- GYRON
- HAVERO-EXTRA
- HILDIT
- IVORAN
- IXODEX
- KOPSOL
- MICRO DDT 75
- MUTOXIN
- NA 2761
- NCI-C00464
- NEOCID
- PARACHLOROCIDUM
- PEB1
- PENTACHLORIN
- PENTECH
- PPZEIDAN
- R50
- RCRA WASTE NUMBER U061
- RUKSEAM
- SANTOBANE
- TECH DDT
  - 1,1,1-TRICHLOR-2,2-BIS(4-CHLOR FENYL)-ETHANE
  - 1,1,1-TRICHLOR-2,2-BIS(4-CHLOR-PHENYL)-AETHAN
  - 1,1,1-TRICHLORO-2,2-BIS(p-CHLOROPHENYL)ETHANE
  - TRICHLOROBIS(4-CHLOROPHENYL)ETHANE
  - 1,1,1-TRICHLORO-2,2-DI(4-CHLOROPHENYL)-ETHANE
  - 1,1,1-TRICLORO-2,2-BIS(4-CLORO-FENIL)-ETANO
  - ZEIDANE
  - ZERDANE