Di(2-ethylhexyl)adipate; CASRN 103-23-1

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 Di(2-ethylhexyl)adipate

File First On-Line 10/01/1989

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	07/01/1992
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	08/01/1991

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Di(2-ethylhexyl)adipate
CASRN — 103-23-1
Primary Synonym — Hexanedioic acid
Last Revised — 07/01/1992

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
Changes in body weight and liver weight increased liver weight of male and female parents; reduced ossification and slightly dilated ureters in fetuses; reduced offspring weight gain, total litter weight, and litter size **Rat Teratogenicity Feeding Study** **ICI, 1988a** **One-generation Rat Reproductive Study** **ICI, 1988b**	NOAEL: 1800 ppm (170 mg/kg/day) LOAEL: 12000 ppm (1080 mg/kg/day)	300	1	6E-1 mg/kg/day

*Conversion Factors: Doses were calculated based on actual body weight and food consumption.

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

ICI (ICI Central Toxicology Laboratory). 1988a. Di-(2-ethylhexyl)adipate: Teratogenicity study in the rat. Report CTL/P/2119 (unpublished study).

ICI (ICI Central Toxicology Laboratory). 1988b. Di-(2-ethylhexyl)adipate (DEHA) fertility study in rats. Report CTL/P/2229 (unpublished study).

The oral RfD is based on two studies that used dietary administration of di(2-ethylhexyl)adipate (DEHA) to rats; one assessed the effects of DEHA on gestating females and their developing fetuses (ICI, 1988a) and the other study examined effects on fertility, reproductive outcome and gross and histological parameters in parents of both sexes (ICI, 1988b).

In the developmental toxicity study, Wistar-derived pregnant rats (24/dose) were fed diets containing 0, 300, 1800 or 12,000 ppm DEHA (corresponding to doses of 0, 28, 170 or 1080 mg/kg/day) on gestational days 1-22 (ICI, 1988a). At the high dose, slight reductions in maternal body weight gain and food consumption were observed, and reduced ossification and kinked or dilated ureters were found in the fetuses.

In a companion one-generation reproductive study (ICI, 1988b), groups of Wistar-derived rats (15 males/dose; 30 females/dose) were administered DEHA in their diets at the same levels (0, 28, 170, or 1080 mg/kg/day). After 10 weeks on the diet, the animals were mated to produce one-generation of offspring that was reared to day 36 post partum. Test diets were fed continuously throughout the study (approximately 18-19 weeks of exposure). No effects were seen on male or female fertility. However, at the highest dose, there was a reduction in the body weight gain of the dams during gestation; an increase in liver weight in both male and female parents; and reductions in offspring weight gain, total litter weight, and litter size. The NOAEL and LOAEL for this study were also 170 and 1080 mg/kg/day, respectively.

Other studies that were considered include the NTP (1982) 2-year bioassays in rats and mice. In a 91-day range-finding feeding study, DEHA was administered to rats and mice of both sexes at 0, 1600, 3100, 6300, 12500, or 25000 ppm in feed, corresponding to doses of 0, 100, 200, 400, 700, or 1500 mg/kg/day for the rat and 0, 400, 700, 1300, 2800 or 7000 mg/kg/day for the mouse, based on food consumption and body weight data. Decreased body weight gain was observed in both species and sexes at the 2 highest doses (8-18% decrease in female and male rats, respectively; and 13-25% decrease in female and male mice, respectively). No gross or microscopic lesions were noted at any dose tested.

The two highest doses, 12500 and 25000 ppm, corresponding to approximately 700 and 1500 mg/kg/day in the rat, and 2800 and 7000 mg/kg/day in the mouse, were then used in a 2-year

feeding study. In the rat, survival was not adversely affected by treatment with DEHA. At 105-107 weeks, survival was 68%, 68%, and 80% for control, low-dose, and high-dose male rats, respectively, and 58%, 78%, and 88% for females. Both species and sexes showed a dose-related suppression of weight gain. Most non-neoplastic lesions were observations in single animals; some frequently observed lesions were not dose-related or were inversely dose-related. For example, the incidence of nephrosis was 45/49 (92%), 42/50 (84%), and 41/50 (82%) in male rats in control, low-dose, and high-dose groups, respectively, and 29/50 (58%), 31/50 (62%), and 20/50 (40%) in female rat groups. The LOAEL for mild depression of weight gain in rats was 1500 mg/kg/day and the NOAEL was 700 mg/kg/day.

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

UF — The uncertainty factor of 300 includes the standard uncertainty factor of 10 for interspecies and 10 intrahuman-variability and an additional uncertainty factor of 3 for database deficiencies including the lack of a multi-generation reproductive study and the lack of data in species other than rodents.

MF — None

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

The 2-year NTP study was not used to calculate the RfD, because the sensitive effects on fetal development, reproductive outcome, and other parameters in the ICI (1988a,b) studies were seen at a lower concentration of DEHA.

Singh et al. (1975) investigated dominant-lethal mutations by administering DEHA by single intraperitoneal injection to male Harlan/ICR albino Swiss mice (10/dose) (8-10 weeks old; 25-30 grams) at doses of 0, 0.45, 0.9, 4.6, or 9.2 g/kg body weight, followed by caging with 2 different female mice each week for 8 weeks. On day 15 of gestation, the pregnant mice were killed by an overdose of ether, and the uterine horns and ovaries were examined for corpora lutea, total implantations, preimplantation losses, early and late fetal deaths, and viable fetuses. DEHA was associated with a dose- related decrease in fertility (mean percentage of pregnancies: 82, 81, 76, 76, and 67, from control to high-dose group, respectively), and a dose-related increase in dominant-lethal mutations as measured by early fetal deaths (mean incidence of early fetal deaths per prepregnancy: 0.29, 0.39, 0.48, 0.74, and 0.96, from control to high-dose group, respectively). Both pre-meiotic and post-meiotic effects were inferred by the investigators. The lowest dose tested, 0.45 g/kg (450 mg/kg), appeared to be a LOAEL in this study. This study was not used as the basis for the RfD, because the single bolus intraperitoneal injection is less relevant to human exposure than is oral exposure.

Singh et al. (1973) injected (i.p.) groups of 5 pregnant rats on days 5, 10, and 15 of gestation with DEHA at 1, 5, or 10 mL/kg (0.9, 4.6, or 9.2 g/kg). There was no increase in embryolethality, but reduced fetal weight was statistically significant at the two highest doses. One skeletal abnormality was reported at the low dose, but one skeletal abnormality was also found in the blunt-needle control group; the specific skeletal abnormalities were not described. The NOAEL in this study for "embryonic-fetal toxicity and teratogenic effects" was 0.9 g/kg (900 mg/kg).

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

The level of confidence in the critical studies is medium. Results are obtained from a short-term (22-day exposure) developmental study (ICI, 1988a) and a companion one-generation (18-19 week exposure) reproductive study assessed an even broader spectrum of toxicological parameters (ICI, 1988b). However, a multi-generation reproductive study and a toxicity study in a second species are lacking. Thus, the database can be considered medium to low. Confidence in the RfD can also be considered medium to low.

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

Source Document — U.S. EPA, 1992

The 1992 Drinking Water Criteria Document for Di-(2-ethylhexyl) adipate received extensive Agency and public review.

Other EPA Documentation — U.S. EPA, 1991

Agency Work Group Review — 02/16/1989, 03/21/1989, 07/16/1991

Verification Date — 07/16/1991

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 — Di(2-ethylhexyl)adipate
CASRN — 103-23-1
Primary Synonym — Hexanedioic acid

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Di(2-ethylhexyl)adipate
CASRN — 103-23-1
Primary Synonym — Hexanedioic acid
Last Revised — 08/01/1991

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 — C; possible human carcinogen

Basis — Based on an absence of human data and increased incidence of liver tumors in female mice. Except for a positive dominant lethal assay, there was no evidence of genotoxicity; this

compound does, however, exhibit structural relationships to other nongenotoxic compounds classified as probable and possible human carcinogens.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited. There was an increased incidence of a single type of tumor in female mice. In an NTP (1982) (see also Kluwe et al., 1985; Kluwe, 1986) bioassay 50 B6C3F1 mice/sex/dose were fed 0, 12,000 or 25,000 ppm di(2- ethylhexyl)adipate (DEHA) in their diet for 104 weeks and observed for 106 weeks. The two DEHA preparations used were 98.1 and 99.7% pure. The estimated doses for female mice were 0, 3222 and 8623 mg/kg/day in the control, low- and high-dose groups, respectively, and for male mice were 0, 2659 and 6447 mg/kg/day, respectively. An MTD was achieved in the high-dose group of both sexes. There was a significant dose-related decrease in the mean body weights of both dose groups in each sex. The survival rate in female mouse groups was 84, 78 and 73% in the control, low- and high-dose groups, respectively, and in the male groups 72, 64 and 82%, respectively.

In females there was a statistically significant positive trend with dose for the hepatocellular carcinoma incidence; the incidences were 1/50, 14/50 and 12/49, for the control, low- and high-dose groups, respectively. The combined hepatocellular carcinoma or adenoma incidences also showed a statistically significant trend test; the incidences were 3/50, 19/50 and 18/49 in the control, low- and high-dose groups, respectively. Time-to-tumor analysis showed that the development time of carcinomas and adenomas in the dosed groups was significantly shorter (by pair-wise comparison test) than their development in the control group. In this laboratory the incidence of combined hepatocellular adenomas and carcinomas in the historical control was 31/397 (7.8%) for female mice of this strain.

In male mice a statistically significant positive trend was seen in the incidences of hepatocellular adenomas and carcinomas combined. The incidences of hepatocellular adenomas were 6/50, 8/49 and 15/49 in the control, low- and high-dose groups, respectively, and the combined hepatocellular adenoma and carcinoma incidences were 13/50, 20/49 and 27/49 in the control, low- and high-dose groups, respectively. It should be noted that the combined incidence of hepatocellular adenomas and carcinomas of the high-dose group does not differ greatly from the male B6C3F1 historical control incidence (116/398) in this laboratory. Furthermore, the time-to-tumor analysis did not show significant differences between the control and dose groups in males.

In a companion study, F344 rats (50/sex/dose) were fed 0, 12,000 or 25,000 ppm DEHA in a powdered diet for 103 weeks and observed for 106 or 107 weeks (NTP, 1982). (The two DEHA preparations used were 98.1 and 99.7% pure.) The estimated intake for female rats was 0, 860 and 1674 mg/kg/day in the control, low- and high-dose groups, respectively, and for male rats was 0, 697 and 1509 mg/kg/day in the control, low- and high-dose groups, respectively. Mean body weights in the high-dose groups of both sexes were lower than those of the respective control groups. The MTD appeared to be achieved in the high-dose groups. The survival rates in the female rat groups were 58, 78 and 88% in the control, low- and high-dose groups, respectively, and in male rat groups 68, 68 and 88% in the control, low- and high-dose groups, respectively. No differences attributable to DEHA administration, were observed in the incidences or types of tumors seen in this study. A statistically significant increase in interstitial cell tumors in the testes of high-dose male rats was discounted because incidences of this tumor type normally approach 100% in aging F344 males.

Hodge et al. (1966) investigated the carcinogenicity of DEHA for mice, rats and dogs in a series of assays which proved to be of limited value. A single subcutaneous injection of trioctinonin (control) or 0.1 mg DEHA in trioctinonin was administered to 50 C3H/Anf mice/sex/group. No carcinogenic activity was attributed to the DEHA injections; a breast tumor (fibromyxoma) was, however, reported in one DEHA-dosed male. In a skin-painting study, 50 C3H/Anf mice/sex/group were treated once weekly with either 0.1 mg DEHA in 20 mL acetone or 10 mg DEHA in 50 mL of acetone (for maximum total doses of 8.8 and 920 mg in males and 9.8 and 1010 mg in females, respectively). No gross or microscopic evidence of application site tumors was observed in any of the groups. In an unpublished study reported by Hodge et al. (1966) unknown numbers of rats and dogs were fed DEHA. Rats were fed 0, 0.1, 0.5 or 2.5% DEHA in the diet for 2 years. A total of 33 tumors was reported; however, the incidences for each group were not reported. Tumor incidence was reportedly not related to dietary treatment. Groups of 2 to 4 dogs were fed 0, 0.7, 0.15 or 0.2% DEHA in the diet for 1 year; no tumors were observed. It was not stated if an MTD was achieved in any of these studies.

II.A.4. Supporting Data for Carcinogenicity

DEHA was negative in a variety of genetic toxicity assays. DEHA with hepatic homogenates added for metabolism was not mutagenic at 5 ug/plate or the lowest dose giving a toxic response in a reverse mutation assay in Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 (Barber et al., 1985; Simmon et al., 1977; Zieger et al., 1982). DEHA was also negative in a mouse lymphoma L5178Y genotoxicity assay, an unscheduled DNA synthesis assay in rat hepatocytes, and a mouse micronucleus assay (Barber et al., 1985).

DEHA did not increase transformation frequencies in mouse BALB/3T3 cells at concentrations of up to 12.5 ug/mL (U.S. EPA, 1981, 1984a,b; Barber et al., 1985). Von Daniken et al. (1984)

reported that DEHA did not covalently bind to female mouse liver DNA. Oral dosing with DEHA by gavage did not increase the mutagenicity of rat urine for Salmonella strains TA98, TA100, TA1535, TA1537 and TA1538 (DiVincenzo et al., 1985).

DEHA was administered through a single i.p. injection to 10 male Harlan/ICR albino Swiss strain mice/dose at doses of 0, 0.5, 1.0, 5.0 and 10.0 mL/kg. Immediately after injection each male was mated to two virgin females; two new virgin females were exchanged once/week for each of the next 7 weeks. In the high-dose group there was a significant increase in early fetal deaths (Singh et al., 1975).

In structure-activity relationship studies based upon NTP data, four compounds containing the 2-ethylhexyl moiety (di(2-ethylhexyl)phthalate, tris(2-ethylhexyl)phosphate, 2-ethylhexyl sulfate and DEHA) exhibited some evidence of liver carcinogenicity in rats and/or mice (Kluwe et al., 1985; Kluwe, 1986). Peroxisome production and induction of peroxisome-associated enzymes in the livers of rodents exposed to DEHA, di(2-ethylhexyl)phthalate, tris(2-ethylhexyl)phosphate and 2-ethylhexyl sulfate have been extensively studied (Reddy et al., 1986; Kawashima, 1983a,b; Moody and Reddy, 1978). The induction of peroxisomes is associated with a several-fold increase in the activity of the peroxisomal fatty acid beta-oxidation system and a 2-fold increase in catalase activity (Kawashima et al., 1983b). In addition, long- term exposure to these peroxisome proliferators results in the induction of hepatocellular carcinomas in rats and mice. The lack of mutagenicity of these agents, combined with consistent findings of proliferation of hydrogen peroxide-generating peroxisomes, indicates that persistent proliferation of peroxisomes serves as an endogenous initiator of neoplastic transformation by enhancing oxidative stress. In a comparative peroxisome proliferation assay (U.S. EPA, 1987; Lin, 1987), the relative potency of several phthalate compounds, as well as DEHA, was measured in rats. Criteria used in this assay differed from those in the previous assay. DEHA was found to be the least potent peroxisome proliferator tested.

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

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 1.2E-3 per(mg/kg)/day

Drinking Water Unit Risk — 3.4E-8 per(ug/L)

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	3E+3 ug/L
E-5 (1 in 100,000)	3E+2 ug/L
E-6 (1 in 1,000,000)	3E+1 ug/L

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

Tumor Type — combined hepatocellular adenomas and carcinomas
Test Animals — mouse/B6C3F1, female
Route — diet
Reference — NTP, 1982

----------- Dose -----------		
Administered (ppm)	Human Equivalent (mg/kg)/day	Tumor Incidence
0	0	3/50
12,000	255	19/50
25,000	625	18/49

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Animal doses were calculated as time-weighted averages using measured body weights and food consumption. Human equivalent doses were calculated using a human body weight of 70 kg and animal body weights of 0.028 and 0.037 kg for the high- and low-dose groups, respectively; the length of the exposure was 103 weeks for both treated groups, and the length of the experiment

and lifespan of the animals were 105 and 105.5 weeks for the high- and low-dose groups, respectively.

The unit risk should not be used if the water concentration exceeds 2.9E+5 ug/L, since above this concentration the unit risk may not be appropriate.

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

An adequate number of animals was observed in a lifetime study. The mice were group housed in this study and fed powdered food. There was a possibility of spillage of the powdered food, suggesting the estimated food consumption may be an overestimate. Overestimating consumption would lead to an underestimate of the risk.

The female mouse data for combined hepatocellular adenomas and carcinomas was selected as the basis for the oral quantitative estimate. The results of the likelihood ratio test indicated that these combined incidences of hepatocellular carcinomas and adenomas data sets for both male and female mice should not be combined to derive the oral quantitative estimate. In addition, there are some biological concerns about using the male mice data for quantitation (e.g., adenoma incidence within historical control range).

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 — U.S. EPA, 1992

The Drinking Water Criteria Document for Di(2-ethylhexyl)adipate has received Program Office and external review.

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

Agency Work Group Review — 03/07/1991, 04/04/1991

Verification Date — 04/04/1991

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 — Di(2-ethylhexyl)adipate
CASRN — 103-23-1
Primary Synonym — Hexanedioic acid

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

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VII. Revision History

Substance Name — Di(2-ethylhexyl)adipate
CASRN — 103-23-1
Primary Synonym — Hexanedioic acid

Date	Section	Description
10/01/1989	I.A.	Oral RfD summary on-line
08/01/1991	I.A.	Withdrawn; new oral RfD verified (in preparation)
08/01/1991	II.	Carcinogenicity assessment now on-line
07/01/1992	I.A.	Oral RfD summary replaced; new RfD and new studies

VIII. Synonyms

Substance Name — Di(2-ethylhexyl)adipate
CASRN — 103-23-1
Primary Synonym — Hexanedioic acid
Last Revised — 10/01/1989

- 103-23-1
- ADIPIC ACID, BIS(2-ETHYLHEXYL) ESTER
- ADIPOL 2EH
- BEHA

- BIS(2-ETHYLHEXYL) ADIPATE
- BIS-(2-ETHYLHEXYL)ESTER KYSELINY ADIPOVE (CZECH)
- BISOFLEX DOA
- DEHA
- DI-2-ETHYLHEXYL ADIPATE
- DIOCTYL ADIPATE
- DOA
- EFFEMOLL DOA
- EFFOMOLL DOA
- ERGOPLAST ADDO
- FLEXOL A 26
- FLEXOL PLASTICIZER 10-A
- FLEXOL PLASTICIZER A-26
- HEXANEDIOIC ACID, BIS(2-ETHYLHEXYL) ESTER (9CI)
- HEXANEDIOIC ACID, DIOCTYL ESTER
- KEMESTER 5652
- KODAFLEX DOA
- MOLLAN S
- MONOPLEX DOA
- NCI-C54386
- OCTYL ADIPATE
- PLASTOMOLL DOA
- PX-238
- REOMOL DOA
- RUCOFLEX PLASTICIZER DOA
- SICOL 250
- STAFLEX DOA
- TRUFLEX DOA
- UNIFLEX DOA
- VESTINOL OA
- WICKENOL 158
- WITAMOL 320