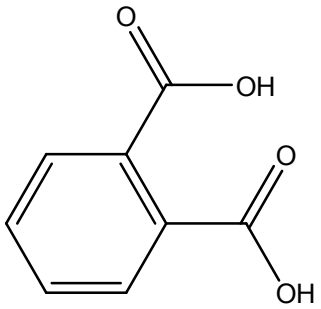
Update on the Toxicology of Eastman™ 168 (di-2-ethylhexyl terephthalate) Plasticizer

Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662-5280 U.S.A.

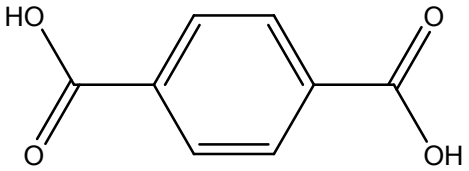
Di-2-ethylhexylterephthalate (DEHT)

- Despite the word “phthalate” in the name, DEHT is not considered a “phthalate ester”.

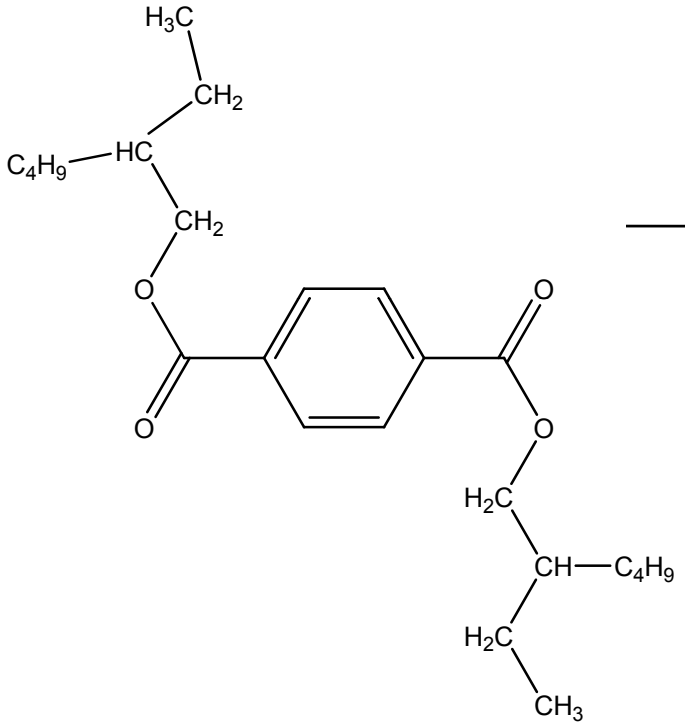
- Phthalate esters are based on *ortho*-phthalic acid

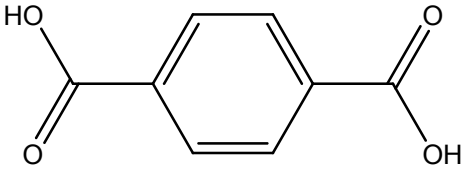


- DEHT is based on *para*-phthalic acid



Metabolism of Terephthalate Esters





+

(2) 2-Ethylhexanol

"In order for a phthalate ester to be metabolized to an active monoester, the ester groups must be in the *ortho* position. **DOTP**, which is isomeric with DEHP but reportedly not metabolized to MEHP, **was inactive** in the current study . . . "

Gray et al, *Toxicological Sciences*, 58, 350-365 (2000)

Terephthalate Acid (TPA) Ester Plasticizers

- Complete and rapid metabolism back to terephthalic acid and an alcohol
- Accordingly Terephthalate Plasticizers:
  - Do not demonstrate reproductive toxicity concerns
  - Do not demonstrate endocrine disruption concerns
  - Do not demonstrate peroxisome proliferation concerns
  - Do not demonstrate carcinogenicity concerns

Safety Data Base for Eastman™ 168

- Acute Toxicity
  - Oral LD50: >5,000 mg/kg (rat), >3,200 mg/kg (mouse)
  - Dermal LD50: >20 ml/kg
  - Dermal irritation: None – Slight
  - Ocular irritation: Slight - Mild
  - Sensitization: Negative
- Genotoxicity
  - Mutations: Negative
  - Chromosomal aberrations: Negative

Safety Data Base for Eastman™ 168

- Repeated Exposure
  - 3 – 104 weeks
  - NOAEL 1% (13 weeks); 79 mg/kg (104 weeks)
- Developmental Toxicity
  - NOAEL1% highest dose tested (rat)
  - NOAEL 0.7% highest dose tested (mouse)
- Reproductive Toxicity and Estrogenicity
  - 2-generation (rat) NOAEL 1%
  - Uterotrophic assay: NOAEL >2,000 mg/kg
- Carcinogenicity
  - No increase in tumors at a dietary level of 1.2%

Published and Peer Reviewed Data Manuscripts

- Sensitization (HRIPT)
- Metabolism
- Mutagenicity and chromosomal aberration
- Mutagenicity
- 3, 13, and 104 week toxicity studies
- Carcinogenicity
- Developmental toxicity
- Two-generation reproductive toxicity
- Endocrine (estrogenicity) activity: (Uterotrophic assay)

EASTMAN

Specific Comments: Review of Exposure and Toxicity Data for Phthalate Substitutes

- The current document states on page 12 (Table 2-1) that the BCF for DEHT is 1,400,000.
  - No reference provided for the source of this result
  - **Data from a BCF study conducted by Eastman Kodak indicates that the BCF value is only 393.**
  - Study was summarized as part of the OECD SIDS process where all data were reviewed by subject experts from the various regulatory agencies participating in the OECD SIDS program.
  - **TURI reported a BCF of 25 for DEHT.**
    - www.turi.org/library/turi_publications/five_chemicals_study/final_report/chapter_7_dehp#7.3

Eastman Chemical asks for this to be corrected.

Specific Comments: Review of Exposure and Toxicity Data for Phthalate Substitutes

- Skin Sensitization: page 60 “DEHT has been shown to act as a sensitizer in guinea pigs…”
  - The particular study that was cited in this report was deemed **invalid** in the context of the OECD review.
  - This study involved pilot plant material
  - No evidence of sensitization was seen in 2 subsequent studies in guinea pigs and in a human patch study with more representative production material
  - As a chemical class, terephthalate esters are not associated with such a potential and sensitization warnings are not present on the MSDS for Eastman™168.

Eastman Chemical asks for this to be corrected.

Testimony before Congress from EPA Toxicologist

Estimated Potencies of Various Plasticizers

	DEHP (DOP)	DBP	DIBP	BBP	DINP	DPP	DEP	DMP	DOtP
Estimated Relevant Potency	1	1	1	1	0.15	3	0	0	0

"*The estimated potencies describe the potential of each phthalate to disrupt testicular function and/or produce malformations in male rat offspring.*"

Testimony by Earl Gray, Jr., Ph. D., before the Committee on Energy and Commerce, Subcommittee on Commerce, Trade, and Consumer Protection, United States House of Representatives, June 10, 2008

Conclusions

- Eastman™ 168 (DEHT) is a very well studied material with a robust set of data.
  - All data are published or were peer reviewed by countries participating in the OECD SIDS program
- Terephthalate esters have little or no potential to form an active monoester. Terephthalate esters demonstrate rapid and almost complete metabolic hydrolysis back to TPA and the corresponding alcohol.
- Terephthalate esters do not possess the same toxicological issues as *ortho*-phthalate esters

Update on the Worldwide Regulatory Clearances of Eastman™ 168 (di-2-ethylhexyl terephthalate) Plasticizer

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Eastman™ 168 (Di-2-ethylhexylterephthalate)

- Food Contact Notification
  - *Eastman 168 may be lawfully used in accordance with FCN 770; 21 CFR 176.180 Components of paper and paperboard in contact with dry food; 21 CFR 175.105 Adhesive and 21 CFR 175.125 Pressure-sensitive adhesives. It is also permitted as a component of closure-sealing gaskets for food containers under 21 CFR 177.1210 subject to certain limitations on food type and conditions of use as described in tables 1 and 2 of 21 CFR 176.170.*

- European Food Safety Authority (EFSA)
  - Included in EC No. 975/2009

Eastman™ 168 (Di-2-ethylhexylterephthalate)

- RIVM (Rijksinstituut voor Volsgezondheid en Milieu) NE
  - *Risk Assessment non-phthalate plasticizers in toys*, P. Janssen, H. J. Bremmer

Table 1: Results migration experiments (VWA 2009)

Name plasticizer	Abbreviation	CAS nr	Mean migration [µg / (min x 10 cm^2)]	Maximum migration [µg / (min x 10 cm^2)]
2,2,4-trimethyl-1,3-pentanediol diisobutyrate	TXIB	6846-50-0	0.87	2.25
diethylhexyl terephthalate	DEHT	6422-86-2	0.27	0.48
diisononyl cyclohexanate	DINCH	166412-78-8	0.41	0.86

The very low migration of DEHT is in accordance with the results obtained by the CPSC.
Memo: Phthalates and Phthalate Substitutes in Children's Toys. 3/31/2010

Eastman™ 168 (Di-2-ethylhexylterephthalate)

- RIVM (Rijksinstituut voor Volsgezondheid en Milieu) NE

Table 2: Margins of safety, scenario 1; exposure due to mouthing

	Internal exposure [mg/kg bw/day]	External NOAEL [mg/kg bw/day]	Internal NOAEL[mg/kg bw/day]	MoS
TXIB	0.041	30	24	580
DEHT	0.0066	79	48	7300
DINCH	0.0095	100	50	5300

Table 3: Margins of safety, scenario 2; exposure due to dermal contact

	Internal exposure [mg/kg bw/day]	NOAEL [mg/kg bw/day]	Internal NOAEL[mg/kg bw/day]	MoS
TXIB	0.14	30	24	170
DEHT	0.0040	79	48	12000
DINCH	0.0098	100	50	5100

"The calculated margins of safety for DEHT and DINCH are very high, leading to the conclusion that these compounds are not expected to pose any health risk for toy-users at the migrated levels."

Eastman™ 168 (Di-2-ethylhexylterephthalate)

- EU Medical Devices
  - Commercialized in 2010
  - Based on Thorough Risk Assessment by an Independent Toxicologist
  - Very low extraction due to extremely low water solubility
  - Full Testing of the Final Medical Device

- U.S. Drug Master File (DMF) Available
  - Under test by Major Medical Device Manufacturers

Comment on Benzoate Esters as Alternatives to Phthalates in toys and Childcare Items

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Benzoate Esters

- Reviewed by COWI for the ECHA
- Focused on replacement of BBP, DBP and DEHP
- Recommended DPG (Dipropyleneglycol Dibenzoate)
  - As replacement for BBP
  - As replacement for DBP

Thank you!

Questions?