PB89-215818

Information Profiles on Potential Occupational Hazards Phthalates

Syracuse Research Corp., NY

Prepared for:

National Inst. for Occupational Safety and Health, Rockville, MD

Mar 82

PB89-215818

SRC TR 82-520

SECOND DRAFT

Information Profiles on Potential Occupational Hazards: Phthalates

Center for Chemical Hazard Assessment
Syracuse Research Corporation
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Syracuse, New York 13210-4080

Contract No. 210-79-0030

March 1982

Prepared for:

National Institute for Occupational Safety and Health
5600 Fisher Lane
Rockville, Maryland 20857

PB82-101

REPORT DOCUMENTATION PAGE	1. REPORT NO.	2.	3. Recipient's Accession No. PB89 215818/AS
4. Title and Subtitle Information Profiles on Potential Occupational Hazards: Phthalates			5. Report Date 82/03/00 6.
7. Author(s) Anonymous			8. Performing Organization Rept. No. SRC TR 82-520
9. Performing Organization Name and Address Center for Chemical Hazard Assessment, Syracuse Research Corporation, Syracuse, New York			10. Project/Task/Work Unit No. 11. Contract (C) or Grant(G) No. (C) 210-79-0030 (G)
12. Sponsoring Organization Name and Address			13. Type of Report & Period Covered 14.

15. Supplementary Notes

16. Abstract (Limit: 200 words) Information profiles were presented for the following phthalates deemed to be significant based on their annual production quantities: butyl-benzyl-phthalate (85687), diallyl-phthalate (131179), di-n-butyl-phthalate (84742), di-2-ethylhexyl-phthalate (117817), diethyl-phthalate (84662), diisodecyl-phthalate (26761400), diisononyl-phthalate (28553120), dimethyl-phthalate (131113), ditridecyl-phthalate (119062), and diundecyl-phthalate (3648202), N-hexyl-N-decyl-phthalate (25724587) and mixed dialkyl (C7 to C11) phthalates. In general the phthalates had a low order of acute toxicity. Histological damage to the lungs, liver and kidneys was associated with acute oral and/or intraperitoneal exposures to some of the compounds. Others have caused slight skin and eye irritation. Repeated oral exposure to many of the esters resulted in liver and/or kidney damage. Butyl-benzyl-phthalate and di-2-ethylhexyl-phthalate induced development of leukemia in rats and hepatocellular carcinomas in mice, respectively. Ingestion of di-n-butyl-phthalate in humans caused nausea, dizziness, photophobia, lacrimation and conjunctivitis. Patients receiving blood stored in polyvinyl-chloride bags that contained residual di-2-ethylhexyl-phthalate suffered a respiratory distress syndrome called shock lung. Neurological effects have been reported in workers exposed to a mixture of phthalate esters in production vapors. Epidemiological studies of di-2-ethylhexyl-phthalate showed no adverse health effects.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms NIOSH-Publication, NIOSH-Contract, Contract-210-79-0030, Plasticizers, Coatings, Adhesives, Insecticides, Resins, Solvents, Toxic-effects, Carcinogens, Occupational-exposure, Epidemiology

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages 17
	22. Security Class (This Page)	22. Price

(See ANSI-Z39.18) *See Instructions on Reverse*

OPTIONAL FORM 272(4-77)
(Formerly NTIS-35)
Department of Commerce

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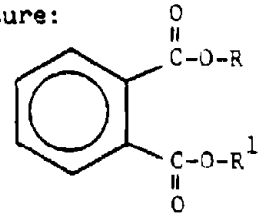
I. SCOPE OF DOCUMENT AND SUMMARY OF MAJOR FINDINGS

A. CLASS IDENTIFICATION

Phthalates are a class of chemical compounds characterized by the following chemical structure:



R and R' can be identical or different functional groups. The functional groups considered in this class definition are composed solely of carbon, hydrogen, and/or oxygen, or of metallic ions such as barium, potassium, lead, or sodium.

Appendix A contains a list of all the phthalates identified by the above definition.

B. CHEMICALS TO BE ADDRESSED

Individual profiles have been prepared for the following phthalates:

Butyl benzyl phthalate
Diallyl phthalate
Di-n-butyl phthalate
Di-2-ethylhexyl phthalate
Diethyl phthalate
Diisodecyl phthalate
Diisononyl phthalate
Dimethyl phthalate
Ditridecyl phthalate
Diundecyl phthalate
n-Hexyl n-decyl phthalate
Mixed dialkyl (C_7-C_{11}) phthalates

Individual profiles were prepared for the above phthalates because all, with the exception of diallyl phthalate, are produced in annually quantities in excess of ten million pounds. Diallyl pthalate is the only phthalate produced in million pound annual quantities which is not primarily used as a plasticizer.

Collectively, the above phthalate account for roughly 95% of the total volume (1.29 billion pounds) of all phthalates annually produced in the United States.

C. SUMMARY OF BIOLOGICAL ACTIVITY

A vast amount of information concerning the biological effects of phthalates in animals has been generated in recent years. Most of the investigators have centered on the effects of exposure to diallyl, di-n-butyl, diethyl, di-2-ethylhexyl, dimethyl, and butyl benzyl phthalates, but limited toxicity data is available for the diisodecyl, diisononyl, ditridecyl, diundecyl, n-hexyl-n-decyl, and mixed diallkyl (C_7-C_{11}) compounds. Although it is apparent that the biological effects of many of the profiled phthalates need to be clarified in specific areas, the currently available information does not suggest that any member of the phthalate ester series considered here produced unique toxicological effects.

The phthalates have a very low order of acute toxicity; rodent oral LD50 values generally range from approximately 4 g/kg (butyl benzyl and di-n-butyl phthalates) to >50 mg/kg (diisodecyl and n-hexyl-n-decyl phthalates). Diallyl phthalate is the most acutely toxic of the phthalate esters considered in these profiles (rat oral LD50's range from 0.77 to 0.97 g/kg). Histological damage to the lungs, liver and kidneys has been associated with acute oral and/or intraperitoneal exposure to diallyl, di-n-butyl, di-2-ethylhexyl, diethyl, and dimethyl phthalates. Intradermal and/or topical application and ocular instillation of many of the profiled phthalates resulted in slight skin and eye irritation.

Liver and/or kidney effects appear to be the primary result of repeated oral exposure to many of the esters (butyl benzyl, diallyl, di-n-butyl, di-2-ethylhexyl, diethyl, diisonomyl, dimethyl, and mixed dialkyl C_7 to C_{11} phthalates). NCI carcinogenicity bioassays have shown that butyl benzyl and

di-2-ethylhexyl phthalate can induce development of, respectively, leukemia (rats) and hepatocellular carcinomas (mice). Many of the profiled phthalates were tested for mutagenicity in bacteria (particularly Ames and rec assays) and found to be negative; di-2-ethylhexyl phthalate was additionally found to be negative in several mammalian cell assays, although positive results were elicited in a dominant lethal assay with mice. Rodent studies with di-n-butyl, di-2-ethylhexyl, and dimethyl phthalates indicate that these compounds produce embryotoxic effects, skeletal abnormalities, and some gross malformations at high levels of administration. Butyl benzyl, di-n-butyl, and di-2-ethylhexyl phthalates have further been reported to produce testicular effects.

There is a paucity of information on the effects of phthalate exposure in humans. Ingestion of di-n-butyl phthalate reportedly caused symptoms of nausea, dizziness, photophobia, lacrimation, and conjunctivitis. A respiratory distress syndrome ("shock lung") has been observed in patients that have received transfused blood that was stored in polyvinyl chloride bags tha contained residual di-2-ethylhexyl phthalate. Worker exposure to a mixture of phthalate esters in production vapors has been reported to produce neurological effects, but it is not known if one or more of the phthalates are responsible. Epidemiological studies of di-2-ethylhexyl phthalate showed no adverse health effects attributable to exposure, but human exposure to heated vapors of diethyl phthalate may produce transient mucous membrane irritation.

II. DATA FOR COMMERCIALLY IMPORTANT CHEMICALS NOT INDIVIDUALLY PROFILED

Other phthalate compounds that have some commerical importance are presented in Tables 1-4; these compounds were not treated in individual profiles. Table 1 lists synonyms, CAS numbers, RTECS numbers, and chemical structures; Table 2 presents chemical and physical properties; Table 3 lists production volumes and uses, and summarizes manufacturing processes; and Table 4 lists manufacturers.

Table 1. Compounds in Phthalate Class

Compound and Synonyms	CAS Number	RTECS Number	Chemical Structure
Barium phthalate Phthalic acid, barium salt	15656-86-7	---	
Benzyl alkyl (mixed) phthalates Phthalic acid, benzyl alkyl esters	68515-40-2	---	
Butyl carbobutoxymethyl phthalate Butoxycarbonylmethyl butyl ester, phthalic acid Phthalic acid, butyl ester, ester with butyl glycolate Phthalic acid, butoxycarbonylmethyl butyl ester 1,2-Benzenedicarboxylic acid, 2-butyoxy-2-oxoethyl butyl ester	85-70-1	TI0525000	
Butyl cyclohexyl phthalate Phthalic acid, butyl cyclohexyl ester 1,2-Benzenedicarboxylic acid, butyl cyclohexyl ester	84-64-0	---	
Butyl decyl phthalate Phthalic acid, butyl decyl ester Plasticizer DBP PX114 Decyl butyl phthalate Benzenedicarboxylic acid, butyl decyl ester	89-19-0	TI0527000	

Table 1. Compounds in Phthalate Class (Cont'd)

Compound and Synonyms	CAS Number	RTECS Number	Chemical Structure
Butyl octyl phthalate Butylethylhexyl phthalate Phthalic acid, butyl octyl ester 1,2-Benzenecarboxylic acid, butyl 2-ethylhexyl ester	85-69-8	---	
Di(2-butoxyethyl) phthalate Phthalic acid, bis(2-butoxyethyl)ester Bis(2-butoxyethyl) phthalate beta-Butoxyethyl phthalate Butyl 'Cellosolve' phthalate Butyl glycol phthalate Dibutyl 'Cellosolve' phthalate Dibutyl glycol phthalate Ethanol, 2-butoxy-, phthalate (2:1) Kesscoflex Kronisol Benzenedicarboxylic acid, bis(2-butyoxyethyl) ester	117-83-9	TI0175000	
Dicapryl phthalate bis(2-Octyl)phthalate 1,2-Benzenedicarboxylic acid, bis(1-methylheptyl)ester Dicapryl 1,2-benzene dicarboxylate Monoplex DCP Phthalic acid, dicapryl ester Phthalic acid, bis(1-methylheptyl)ester	131-15-7	TI0360000	
Dicyclohexyl phthalate Phthalic acid dicyclohexyl ester 1,2-Benzenedicarboxylic acid, dicyclohexyl ester	84-61-7	---	

Table 1. Compounds in Phthalate Class (Cont'd)

Compound and Synonyms	CAS Number	RTECS Number	Chemical Structure
Didecyl phthalate Phthalic acid, dedecyl ester Di-n-decyl phthalate 1,2-Benzenedicarboxylic acid, didecyl ester DDP	64-77-5	TI0900000	
Didodecyl phthalate Phthalic acid, didodecyl ester 1,2-Benzenedicarboxylic acid, diddodecyl ester	2432-90-8	---	
Diheptyl phthalate Phthalic acid, diheptyl eser 1,2-Benzenedicarboxylic acid, diheptyl ester	3648-21-3	---	
Dihexyl phthalate Phthalic acid, dihexyl ester 1,2-Benzenedicarboxylic acid, dihexyl ester	84-75-3	TI1100000	
Diisobutyl phthalate Phthalic acid, diisobutyl ester Hexaplas M/1B 1,2-Benzenedicarboxylic acid, bis(2-methylpropyl)ester	84-69-5	TI1225000	
Diisohexyl phthalate Phthalic acid, diisohexyl ester 1,2-Benzenedicarboxylic acid, diisohexyl ester	146-50-9	---	

Table 1. Compounds in Phthalate Class (Cont'd)

Compound and Synonyms	CAS Number	RTECS Number	Chemical Structure
Diisooctyl phthalate Phthalic acid, diisoctyl ester 1,2-Benzenedicarboxylic acid, diisooctyl ester	27554-26-3	---	
Dimethoxyethyl phthalate Phthalic acid, di(methoxyethyl)ester 1,2-Benzenedicarboxylic, bis(2-methoxyethyl)ester	117-82-8	TI1400000	
Dinonyl phthalate Dinonyl ester phthalic acid Bisoflex 91 Dinonyl 1,2-benzenedicarboxylate Di-n-nonyl phthalate Benzenedicarboxylic acid, dinonyl ester	84-76-4	TI1800000	
Dioctadecyl phthalate Phthalic acid, dioctadecyl ester 1,2-Benzenecarboxylic acid, dioctadecyl ester	14117-96-5		
Di-n-octyl phthalate Dioctyl ester phthalic acid o-Benzenedicarboxylic acid, dioctyl ester Celluflex DOP Dioctyl o-benzenedicarboxylate Dioctyl phthalate n-Dioctyl phthalate Octyl phthalate Plasticizer 162; PX-138	117-84-0	TI1925000	

Table 1. Compounds in Phthalate Class (Cont'd)

Compound and Synonyms	CAS Number	HTECS Number	Chemical Structure
Diphenyl phthalate Phthalic acid, diphenyl ester 1,2-Benzenedicarboxylic acid, diphenyl ester	84-62-8	---	
Isodecyl octyl phthalate Phthalic acid, isodecyl octyl ester 1,2-Benzenedicarboxylic acid, isodecyl octyl ester	1330-96-7	---	
Isooctyl benzyl phthalate 1,2-Benzenedicarboxylic acid, isooctyl benzyl ester	---	---	
Isooctyl isodecyl phthalate Phthalic acid, isooctyl isodecyl ester 1,2-Benzenedicarboxylic acid, isodecyl isooctyl ester	42343-35-1	---	
Lead Phthalate, dibasic Phthalic acid, lead salt, dibasic	17976-43-1	---	$2PbO \cdot Pb(O_2C)_2C_6H_4 \cdot 1/2H_2O$
Mixed alkyl (C_7-C_{11}) phthalates Phthalic acid, alkyl esters (C_7-C_{11})	68648-91-9	---	
Monobutyl phthalate 1,2-Benzenedicarboxylic acid, monobutyl ester	131-70-4	---	

Table 1. Compounds in Phthalate Class (Cont'd)

Compound and Synonyms	CAS Number	RTECS Number	Chemical Structure
Monodecyl phthalate 1,2-Benzenedicarboxylic acid, monodecyl ester	24539-60-4	---	
Monopotassium phthalate 1,2-Benzenedicarboxylic acid, monopotassium salt	877-24-7	---	
n-Octyl n-decyl phthalate Phthalic acid, n-octyl n-decyl ester 1,2-Benzenedicarboxylic acid, decyl octyl ester Decyl octyl phthalate Dinopol 235 Octyl decyl phthalate Polycizer 532 Polycizer 562 Staflex 500	119-07-3	TI0550000	

Table 2. Phthalate Compounds: Chemical and Physical Properties

Compound	Description	Boiling Point (°C)	Melting Point (°C)	Vapor Pressure	Water Solubility	Specific Gravity	Molecular Weight
Barium phthalate	---	---	---	---	---	---	301.44
Benzyl alkyl (mixed) phthalates	---	---	---	---	---	---	variable
Butyl carbobutoxy methyl phthalate	---	---	---	---	---	---	320.37
Butyl cyclohexyl phthalate	clear liquid	189-222 (5 mm Hg)	---	---	---	1.076 (25°C)	304.4
Butyl decyl phthalate	liquid	220 (5 mm Hg)	-50	---	---	0.991 (25°C)	352.46
Butyl octyl phthalate	water-white liquid	225 (5 mm Hg)	<-50	---	---	0.993 (25°C)	334.44
Di(2-butoxyethyl) phthalate	colorless liquid	270	-55	---	---	1.06 (20°C)	366.50
Dicapryl phthalate	nearly colorless, viscous liquid	227-234 (4.5 mm Hg)	---	---	insol.	0.965	390.62
Dicyclohexyl phthalate	white granular solid	212-218 (5 mm Hg)	58-65	---	insol.	1.148 (20°C)	330.4
Didecyl phthalate	light colored liquid	261 (5 mm Hg)	---	0.3 mm Hg (200°C)	insol.	0.9675 (20°C)	446.66
Didodecyl phthalate	---	---	---	---	---	---	498.74
Diheptyl phthalate	---	---	---	---	---	---	362.6
Dihexyl phthalate	pale yellow liquid	350 (735 mm Hg)	---	---	---	1.01	33..50
Diisobutyl phthalate	liquid	327	---	---	---	1.040 (20°C)	278.38
Diisohexyl phthalate	---	---	---	---	---	---	334.50

Table 2. Phthalate Compounds: Chemical and Physical Properties (Cont'd)

Compound	Description	Boiling Point (°C)	Melting Point (°C)	Vapor Pressure	Water Solubility	Specific Gravity	Molecular Weight
Diisooctyl phthalate	nearly colorless, viscous liquid	370	<-50	---	insol.	0.986 (20°C)	390.62
Dimethoxyethyl phthalate	oily liquid	340	-45	---	---	1.172 (20=C)	282.32
Dinonyl phthalate	colorless liquid	205-220 (1 mm Hg)	---	---	---	0.979 (25°C)	418.68
Dioctadecyl phthalate	---	---	---	---	---	---	671.10
Di-n-octyl phthalate	liquid	220-248 (4 mm Hg)	-25	<0.2 torr (150°C)	3 mg/l (25°C)	0.978 (20°C)	390.62
Diphenyl phthalate	yellow-white powder	405	68-80	---	insol.	1.28 (20°C)	318.3
Isodecyl octyl phthalate	---	---	---	---	---	---	418.61
Isooctyl benzyl phthalate	---	---	---	---	---	---	380.47
Isooctyl isodecyl phthalate	clear liquid	235-248 (4 mm Hg)	-49	---	---	0.967 (25°C)	418.61
Lead phthalate (dibasic)	white crystalline powder	---	---	---	insol.	4.6	826. 87
Mixed alkyl (C_7-C_{11}) phthalates	---	---	---	---	---	--	variable
Monobutyl phthalate	solid	---	73-74	---	---	---	222.24
Monodecyl phthalate	---	---	---	---	---	---	305.38
Monopotassium phthalate	---	---	---	---	---	---	204.21
n-Octyl n-decyl phthalate	clear, oily liquid	250 (5 mm Hg)	-28	---	---	0.970 (25°C)	418.68

Table 3. Iron Compounds: Production, Use, and Manufacturing Methods

Compound	Production	Use	Manufacturing Methods
Barium phthalate	1977: 1-10 thousand lb (U.S. EPA, 1980)	Not available	From phthalic anhydride
Benzyl alkyl (mixed) phthalates	1977: 1-10 million lb (U.S. EPA, 1980)	Plasticizer	Similar to process in Appendix B.
Butyl carbobutoxy methyl phthalate	1977: 1-10 million lb (U.S. EPA, 1980)	Plasticizer for cellulose acetates styrenes.	Reaction of phthalic anhydride, butyl alcohol, and ammonia, followed by heating with $ClCH_2CO_2Bu$ (Umemura and Maniwa, 1952).
Butyl cyclohexyl phthalate	1977: 0.1-1.0 million lb (U.S. EPA, 1980)	Plasticizer for polymers and elastomers; nitrocellulose lacquers (Hawley, 1977).	Similar to process in Appendix B.
Butyl decyl phthalate	Not available	Plasticizer for PVC and copolymer resins (Hawley, 1977)	Similar to process in Appendix B.
Butyl octyl phthalates	1973: 7.4 million lb (USITC, 1975) 1977: 2.1-21 million lb (U.S. EPA, 1980)	Plasticizer for vinyl resins (Hawley, 1977)	Similar to process in Appendix B.
Di(2-butoxyethyl)phthalate	1977: 20-200 thousand lb (U.S. EPA, 1980)	Plasticizer for PVC, polyvinyl acetate, and other resins (Hawley, 1977).	From phthalic anhydride
Dicapryl phthalate	1977: 10-100 thousand lb (U.S. EPA, 1980)	Monomeric plasticizer for vinyl and cellulose resins (Hawley, 1977).	See Appendix B.
Dicyclohexyl phthalate	1977: >1 million lb (U.S. EPA, 1980) 1979 import: 0.396 million lb 1978 import: 0.311 million lb (USITC, 1980b, 1979b)	Specialty plasticizer in nitrocellulose lacquers and adhesives (Frey, 1976).	See Appendix B.

Table 3. Iron Compounds: Production, Use, and Manufacturing Methods (Cont'd)

Compound	Production	Use	Manufacturing Methods
Didecyl phthalate	1977: 1-10 million lb (U.S. EPA, 1980)	Plasticizer, especially for vinyl resins (Hawley, 1977).	See Appendix B.
Didodecyl phthalate	1977: 10-100 thousand lb (U.S. EPA, 1980)	Plasticizer	See Appendix B.
Diheptyl phthalate	Not available--but is a Monsanto's component of Monsanto's Mixed Dialkyl Phthalates esters (see individual profile).	Plasticizer	See Appendix B.
Dihexyl phthalate	1977: 0.2-2 million lbs (U.S. EPA, 1980) 1974 import: 26 thousand lb (USITC, 1976)	Plasticizer for plastisols and carpet backcoatings (Frey, 1976).	See Appendix B.
Diisobutyl phthalate	1977: >1 million lb (U.S. EPA, 1980)	Plasticizer (Hawley, 1977).	See Appendix B.
Diisohexyl phthalate	Not available	Plasticizer	See Appendix B.
Diisooctyl phthalate	1977: 1-10 million lb (U.S. EPA, 1980)	Plasticizer for vinyl, cellulosic, and acrylate resins and synthetic rubber (Hawley, 1977).	See Appendix B.
Dimethoxyphthalate	1977: 1-10 million lb (U.S. EPA, 1980)	Plasticizer, especially for cellulose acetate; solvent (Hawley, 1977).	See Appendix B.
Dinonyl phthalate	Not available--but is a component of Monsanto's Mixed Dialkyl Phthalate esters (see individual profile).	General-purpose low-volatile plasticizer for vinyl resins; pure grade as stationary liquid phase in chromatography (Hawley, 1977).	See Appendix B.
Dioctadecyl phthalate	1977: 1-10 million lb (U.S. EPA, 1980)	Plasticizer	See Appendix B.
Di-n-octyl phthalate	1977: 1-10 million lb 1977 import: 4-40 thousand lb (U.S. EPA, 1980)	Plasticizer	See Appendix B.

Table 3. Iron Compounds: Production, Use, and Manufacturing Methods (Cont'd)

Compound	Production	Use	Manufacturing Methods
Diphenyl phthalate	1977: 0.1 to 1.0 million lb (U.S. EPA, 1980)	General-purpose plasticizer which which has uses in speciality acrylics and cellulosics (Touchette, 1978).	See Appendix B.
Isodecyl octyl phthalate	1977: 1-10 million lb (U.S. EPA, 1980)	Plasticizer	Similar to process in Appendix B.
Isooctyl benzyl phthalate	Not available	Plasticizer	Similar to process in Appendix B.
Isooctyl isodecyl phthalate	Not available	Plasticizer (Hawley, 1977).	Similar to process in Appendix B.
Lead phthalate	Not available	Stabilizer in PVC wire insulation (Towle et al., 1968)	From phthalatic anhydride
Mixed alkyl (C_7-C_{11}) phthalates	1977: 1-10 million lb (U.S. EPA, 1980)	Plasticizers	Similar to process in Appendix B.
Monobutyl phthalate	1977: 10-100 thousand lb (U.S. EPA, 1980)	Captive use by manufacturer (U.S. EPA, 1980).	Similar to process in Appendix B.
Monodecyl phthalate	1977 import: 10-100 thousand lb (U.S. EPA, 1980)	Not available	Similar to process in Appendix B.
Monopotassium phthalate	1977: >10 thousand lb (U.S. EPA, 1980)	Not available	From phthalic anhydride
n-Octyl n-decyl phthalate	1977: 1.1-11 million lb (U.S. EPA, 1980)	Plasticizer for PVC and other vinyls (Hawley, 1977).	Similar to process in Appendix B.

Table 4. Manufacturers
(U.S. EPA, 1980; SRI International, 1980; USITC, 1980a)

Compound	Manufacturer (Location)
Barium phthalate	Witco Chemical Corp. (Brooklyn, NY)
Benzyl alkyl (mixed) phthalates	Monsanto Co. (Bridgeport, NJ)
Butyl carbobutoxymethyl phthalate	Monsanto Co. (St. Louis, MO)
Butyl cyclohexyl phthalate	CPS Chem. Co. (Old Bridge, NJ)
Butyl decyl phthalate	Reichhold Chem. (Carteret, NJ)
Butyl octyl phthalate	Hatco Chem. (Fords, NJ) Tennessee Eastman (Kingsport, TN) Reichhold Chem. (Carteret, NJ) U.S. Steel Chem. (Neville Island, PA)
Di(2-butoxyethyl)phthalate	C.P. Hall Co. (Chicago, IL) Reichhold Chem. (Carteret, NJ) Armak Ind. Chem. (Philadelphia, PA)
Dicapryl phthalate	Union Camp Corp. (Dover, OH)
Dicyclohexyl phthalate	Monsanto Co. (Everette, MA) Pfizer (Greensboro, NC) Stepan Chem. Co. (Elwood, IL) LOF Plastics Inc. (Auburn, ME)
Didecyl phthalate	Eastman Kodak (Rochester, NY) Monsanto (Texas City, TX) Tenneco (Chestertown, MD) Continental Oil Co. (Aberdeen, MS)
Didodecyl phthalate	Eastman Kodak (Rochester) U.S. Steel Chem. (Pittsburg, PA)
Diheptyl phthalate	Monsanto Co. (Texas City, TX) Tenneco (Chestertown, MD)
Dihexyl phthalate	Interstab Chem. (New Brunswick, NJ) U.S. Steel Chem. (Neville Island, PA)
Diisobutyl phthalate	Hatco Chem. (Fords, NJ) Ashland Chem. (Mapleton, IL)
Diisohexyl phthalate	Exxon Chem. (Baton Rouge, LA)

Table 4. Manufacturers (Cont'd)
(U.S. EPA, 1980; SRI International, 1980; USITC, 1980a)

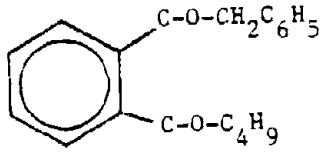
Compound	Manufacturer (Location)
Diisooctyl phthalate	Reichhold Chem. (Carteret, NJ) Teknor Apex (Hebronville, MA) U.S. Steel Chem. (Neville Island, PA) Tenneco (Chestertown, MD) Hatco Chem. (Fords, NJ)
Dimethoxyethyl phthalate	Tennessee Eastman (Kingsport, TN)
Dinonyl phthalate	Monsanto (Texas City, TX) Eastman Kodak (Rochester, NY) Tenneco (Chestertown, MD)
Dioctadecyl phthalate	Henkel Inc. (importer) (Teaneck, NJ)
Di-n-octyl phthalate	Eastman Kodak (Rochester, NY) Monsanto (Texas City, TX) U.S. Steel Chem. (Pittsburg, PA) Tenneco (Chestertown, MD)
Diphenyl phthalate	Monsanto (St. Louis, MO)
Isodecyl octyl phthalate	U.S. Steel Chem. (Pittsburg, PA)
Isooctyl benzyl phthalate	Monsanto (Bridgeport, NJ)
Isooctyl isodecyl phthalate	Reichhold Chem. (Carteret, NJ)
Lead phthalate	Not available
Mixed alkyl (C_7-C_{11}) phthalates	Tenneco (Chestertown, MD)
Monobutyl phthalate	Eastman Kodak (Rochester, NY) DuPont (Toledo, OH)
Monodecyl phthalate	DSM-U.S.A (Importer) (Atlanta, GA)
Monopotassium phthalate	Eastman Kodak (Rochester, NY) Fisher Scientific (Fairlawn, NJ) G. Fredrick Smith Chem. (Columbus, OH)
n-Octyl n-decyl phthalate	Reichhold Chem. (Carteret, NJ) Teknor Apex (Hebronville, NJ) U.S. Steel Chem. (Neville Island, PA) Monsanto (Texas City, TX) Tenneco (Chestertown, MD)

III. INFORMATION PROFILES

A. BUTYL BENZYL PHTHALATE

1. Chemical Name: Butyl Benzyl Phthalate

2. Chemical Structure:



3. Synonyms: Benzyl butyl phthalate
1,2-Benzene carboxylic acid, butyl phenylmethyl ester
NCI-C54375
Palatinol BB
Phthalic acid, butyl benzyl ester
Santicizer 160
Sicol 160
Unimoll BB

4. Chemical Abstracts Service (CAS) Number: 85-68-7

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

TH9990000

6. Chemical and Physical Properties:

Description:	clear, oily liquid
Molecular Weight:	312.40
Boiling Point:	370°C
Melting Point:	greater than -35°C
Vapor Pressure:	---
Solubility:	2.9 mg/l in water
Specific Gravity:	1.111 (25°C)
Stability:	combustible; Flash point: 390°F

7. Production

In 1974, an estimated 110 million pounds of butyl benzyl phthalate were manufactured (Frey, 1976).

In 1974, 1.1 million pounds of butyl benzyl phthalate were imported (USITC, 1976).

Data available from the U.S. EPA (1980a) regarding producers of butyl benzyl phthalate and production volumes are presented in Table 5.

According to Modern Plastics (1978), butyl benzyl phthalate can be expected to increase its share of the phthalate plasticizer market because the manufacturer (Monsanto) has recently increased plant capacity.

8. Use

Butyl benzyl phthalate is used predominantly as a plasticizer in vinyl flooring, often in combination with dioctyl phthalate. It is also used in vinyl foams, coatings, polyvinyl acetate adhesives, and acrylic caulking compounds (Frey, 1976). It has minor uses as a chemical intermediate (Hawley, 1977).

9. Manufacturers and Distributors

Butyl benzyl phthalate is manufactured and distributed by the following company (SRI International, 1980):

Monsanto Co.	Sauget, IL Bridgeport, NJ

It is also distributed by (1980-81 OPD Chemical Buyers Director, 1980; Chem Sources--USA, 1980):

Chem Services	Pfaltz and Bauer
Helm NY	Polysciences
ICN/K and K	Sattva Trading Co.
	Union Chemical

10. Manufacturing Processes

Butyl benzyl phthalate is manufactured from butyl alcohol, benzyl chloride (hydrolyzed to benzyl alcohol), and phthalic anhydride (Ringk, 1978). The reaction is typical of the esterification that produces the dialkyl

Table 5. Producers of Butyl Benzyl Phthalate and Production Ranges (U.S. EPA, 1980a)

Producer	Type of Production	1977 Production Range
Monsanto Co.		
Bridgeport, NJ	Manufacturer	100-500 million lb
Sauget, IL	Manufacturer	1-10 million lb
ICI Americas		
Wilmington, DE	Importer	confidential

phthalates. The process operations are also similar to the dialkyl phthalate operations shown in Appendix B.

For phthalates in general, the anhydride is reacted with an alcohol under relatively mild conditions to produce the monoester, which may be transferred to another vessel for conversion to the diester. If a mixed diester such as butyl benzyl is desired, remnants of the first alcohol will be removed from the monoester before reaction with the second alcohol. Usually an excess of alcohol is used and the unreacted portion is recycled. Water formed by the second esterification is removed from the system to drive the reaction to completion (Thompson, 1977).

11. Impurities or Additives

There is no evidence in the literature searched to indicate the presence of impurities or deliberate additives in commercially produced butyl benzyl phthalate.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 68,488 workers are potentially exposed to butyl benzyl phthalate.

13. Control Technology and Work Practice

Specific factors that may contribute to or prevent employee exposure to butyl benzyl phthalate were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute lethal effects of butyl benzyl phthalate are summarized in Table 6. Oral and intraperitoneal administration of the compound indicate a relatively low level of toxicity in comparison to other phthalates.

Table 6.

Acute Lethal Effects of Butyl Benzyl Phthalate

Route	Species	Dose (g/kg)	Response	Reference
oral	rat	18	LD50	Shibko and Blumenthal, 1973
oral	rat	2.33	LD50	NTP, 1981a
oral	mice (male)	6.16	LD50	NTP, 1981a
oral	mice (female)	4.17	LD50	NTP, 1981a
i.p.	mice	3.16	LD50	Calley et al., 1966

i.p. = intraperitoneal

Intradermal injection of 20 mg butyl benzyl phthalate into rabbits caused a mild inflammatory response at the injection site (Calley et al., 1966). A Russian abstract has reported that the compound produces skin irritation, but not sensitization, when applied topically to mice and rats (Statsek, 1974).

(2) Subchronic Exposures

Two subchronic feeding studies were conducted by the NTP (1981a) to determine the concentrations of butyl benzyl phthalate to be used in a carcinogenesis bioassay (Section 14.a.4). In a 14-day study, groups of 5 male and 5 female rats (F344) and mice (B6C3F1) were administered the compound in the feed at concentrations ranging from, respectively, 12,500-100,000 ppm and 1,600-25,000 ppm. In the second study, diets containing 1,600-25,000 ppm butyl benzyl phthalate were fed for 13 weeks to similarly sized groups of rats and mice of each sex. The results of these studies are summarized in Table 7.

Dietary administration of butyl benzyl phthalate to rats for 90 days has also been reported to produce increased liver weights at levels of 1.0, 1.5, and 2.0% of the compound, but no histopathological effects were observed (Monsanto, 1972). Similar studies with dogs did not show adverse hematopoietic system or liver and kidney function tests, or gross or histopathological tissue changes at dietary levels of 1.0, 2.0 or 5.0% butyl benzyl phthalate (Erikson, 1965; Monsanto, 1972). Based on the Erikson (1965) study, the FDA has estimated a no-effect level for subacute feeding of butyl benzyl phthalate to be 250 mg/kg/day for dogs (Shibko and Blumenthal, 1973).

Daily interperitoneal injection of 500 mg/kg butyl benzyl phthalate into mice for 6 weeks was reported to cause peritonitis and extramedullary hematopoiesis in the liver and spleen, and periportal hepatitis (Calley et al., 1966).

Table 7. Subchronic Feeding Studies of Butyl Benzyl Phthalate in Rats and Mice (NTP, 1981a)

Species	Dose	Response
14-day Study[a]		
Rats	100,000 ppm	weight loss, thymic atrophy
	50,000 or 100,000 ppm	testicular atrophy
	≥25,000 ppm	depressed weight gain in both sexes
Mice	1,600-25,000 ppm	depressed weight gain (not dose related), no compound-related effects at necropsy
13-week Study[b]		
Rats	25,000	depressed weight gain and testicular testicular degeneration in males, no compound related effects in females
	1,600-12,500 ppm	no compound-related effects at necropsy
Mice	1,600-25,000 ppm	depressed weight gain; no other compound related effects

[a]Doses of 0, 12,500, 50,000 and 100,000 ppm were administered to groups of 5 rats and 5 mice of each sex; no significant mortality.

[b]Doses of 0, 1600, 3100, 6300, 12,500, and 25,000 ppm were administered to groups of 5 rats and 5 more of each sex; no significant mortality.

(3) Chronic Effects

No information was found in the literature searched.

(4) Carcinogenicity

The NTP has recently completed a carcinogenesis bioassay of butyl benzyl phthalate (NTP, 1981a). In this study, groups of 50 F344 rats and 50 B6C3F1 mice of each sex were exposed to 6,000 and 12,000 ppm levels of the compound by lifetime feeding (28-103 weeks). Results indicated that under the conditions of the bioassay, butyl benzyl phthalate was probably carcinogenic for the female rats at the 12,000 ppm level, causing an increased incidence of myelomonocytic leukemias. The male rat study was considered inadequate for evaluation due to compound-related toxicity and mortality (due to internal hemorrhaging). Butyl benzyl phthalate was not carcinogenic for mice of either sex.

(5) Mutagenicity

Butyl benzyl phthalate did not induce reverse mutation in S. typhimurium, and was negative in differential growth inhibition assays with wild and DNA repair-deficient strains of E. coli and B. subtilis (Table 8).

Butyl benzyl phthalate has been scheduled for mutagenicity testing in Salmonella by the NTP (1980).

(6) Teratogenicity

Injection of ≈50 mg of butyl benzyl phthalate into fertilized eggs failed to produce malformations or general toxicity in developing chick embryos (Bower et al., 1970).

(7) Reproductive Effects

Two of the subchronic studies summarized in Section 14.a.3.indicated that testicular atrophy resulted in rats from exposure to high (≥25,000 ppm) dietary levels of butyl benzyl phthalate (NTP, 1981a).

Table 8. Mutagenicity of Butyl Benzyl Phthalate

Type of Assay	Organism	Strain	Activation	Dose	Result	Reference
Reverse Mutation	S. typhimurium	TA98	±	1000 µg/plate	-	Rubin et al., 1979
		TA100	±	1000 µg/plate	-	Rubin et al., 1979
Reverse Mutation	E. coli	wild	-	30 mg/plate	-	Kurata, 1975
		uvr A^-	-	30 mg/plate	-	Kurata, 1975
DNA damage/repair	B. subtilis	rec A^-	-	30 mg/plate	-	Kurata, 1975
	E. coli	uvr A^-	-	30 mg/plate	-	Kurata, 1975
		Pol A^-	-	30 mg/plate	-	Kurata, 1975
		rec A^-	-	30 mg/plate	-	Kurata, 1975

(8) Other Relevant Information

Butyl benzyl phthalate was eliminated primarily unchanged (87-91%) in the feces of dogs following oral administration (Erickson, 1965).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of butyl benzyl phthalate were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for butyl benzyl phthalate were found.

17. Sources of Additional Relevant Information

Comprehensive reviews of phthalate esters have been completed by Peakall (1975), Daniel (1978), Lawrence (1978), Thomas et al. (1978), Lawrence and Tuell (1979), and the U.S. EPA (1980b).

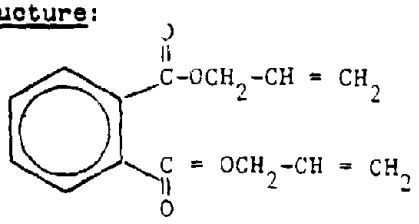
18. Other Pertinent Data

No other information that would aid in the assessment of butyl benzyl phthalate as an occupational hazard was found in the literature searched.

B. DIALLYL PHTHALATE

1. Chemical Name: Diallyl Phthalate

2. Chemical Structure:



3. Synonyms: 1,2-Benzene dicarboxylic acid, di-2-propenyl ester
DAP
Dapon R
Dapon 35
NCI-C50657
Phthalic acid, diallyl ester

4. Chemical Abstracts Service (CAS) Number: 131-17-9

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

CZ4200000

6. Chemical and Physical Properties:

Description:	nearly colorless, oily liquid
Molecular Weight:	246.30
Boiling Point:	290°C (160°C at 4 mm Hg)
Melting Point:	-70°C
Vapor Pressure:	---
Solubility:	insoluble in water; limited solubility in gasoline, mineral oil, glycerin, glycols, and certain amines; soluble in most other organic liquids
Specific Gravity:	1.120^{20}_{20}
Stability:	combustible; Flash point: 330°F

7. Production

Production of diallyl phthalate in 1974 was estimated to be about 5 million pounds (Blackford, 1975).

Importation of diallyl phthalate in recent years is as follows (USITC, 1980b, 1978b, 1977b):

Year	Importation (in millions of pounds)
1979	0.040
1977	1.121
1976	0.992

Data available from the U.S. EPA (1980a) regarding producers of diallyl phthalate and production volumes are presented in Table 9.

8. Use

Diallyl phthalate is one of the few commercially produced phthalate esters that is not used primarily as a plasticizer. It is a monomer chiefly used as a cross-linking agent in the manufacture of unsaturated polyester resins; it is also used as such to make molded articles (particularly for the electronics industry) and to make insulating varnishes (Blackford, 1975). Diallyl phthalate also has minor use as a dye carrier (Wannemacher and Demaria, 1979).

9. Manufacturers and Distributors

SRI International (1980) lists the following as manufacturers of diallyl phthalate:

Ethyl Corp. Hardwicke Chem. Co.	Elgin, SC
FMC Corp.	Baltimore, MD

Distributors include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Allied Chem.	GLS Chem.
Anachemia Chem.	The C.P. Hall Co.
Ashland Chem.	Helm NY
Atomergic Chemetals	Lachat Chem.
Chemisphere Corp.	MCB Reagents
Chem Services	Monomer-Polymer and Dajac
Durez Div. Hooker	Pfaltz and Bauer
Eastman Kodak	Polysciences
EM Lab	Miki Sangyo (USA)
Fehr Bros. Inc.	Solchem
Fisher Sci.	Tridom Chem.

Table 9. Producers of Diallyl Phthalate and Production Ranges (U.S. EPAμ 1980)

Producer	Type of Production	1977 Production Range
FMC Corp.		
Baltimore, MD	Manufacturer	1-10 millionlb
Monsanto Co.		
Miamisburg, OH	Manufacturer	1-10 thousand lb
St. Louis, lMO	Manufacturer	none
Haven Chemical		
Philadelphia, PA	Manufacturer	confidential
Hardwicke Chemical Corp.		
Elgin, SC	Manufacturer	0.1-1.0 million lb
Lonza Inc.		
Fairlawn, NJ	Importer	confidential
Nichimen Co.		
New York City, NY	Importer	under 1000 lb
Rhone-Poulenc		
New York City, NY	Importer	none

10. Manufacturing Processes

Diallyl phthalate is manufactured by the esterification reaction of allyl alcohol and phthalic anhydride. The process operations are similar to those for the dialkyl phthalates.

Appendix B diagrams the typical process by which all commercial dialkyl phthalates are made. Plants are designed to allow any of the phthalate esters to be made in the same equipment, giving flexibility to production. While many plants produce phthalates by batch methods, other newer plants operate continuously and are highly automated (Lowenheim and Moran, 1975).

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 11,451 workers are potentially exposed to diallyl phthalate.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to diallyl phthalate were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute lethal and irritant effects of diallyl phthalate are summarized in Table 10. Oral administration and intraperitoneal injection of the compound into mice has demonstrated that this compound is the most acutely toxic of the phthalate esters. Following oral administration of a single lethal dose of compound (970 mg/kg) to rats, liver, lung, and intestinal lesions were noted at necropsy (Carter et al., 1978). These lesions represented

Table 10. Acute Lethal and Irritant Effects of Diallyl Phthalate

Route	Species	Dose (g/kg)	Response	Reference
oral	rats	1.68	LDLo	McOmie, 1946
oral	rats	0.77	LD50	Hagen et al., 1949
oral	rats	0.97	LD50	Carter et al., 1978
oral	rabbits	1.68	LDLo	McOmie, 1946
i.p.[a]	mice	0.67	LD50	McOmie, 1949
s.c.[b]	rabbit	1.12	LDLo	McOmie, 1946
dermal	rabbits	3.36	LD50	McOmie, 1949
dermal	rabbits	3.14	LDLo	McOmie, 1946
ocular	rabbits	0.1 ml undiluted (0.11 g)	mild and transient conjunctivitis	McOmie, 1946
ocular	rabbits	0.5 ml undiluted (0.56 g)	mild irritation	Carpenter and Smyth, 1946

[a] i.p. = intraperitoneal.

[b] s.c. = subcutaneous

hemorrhage in the lungs, liver, and intestinal tract, congestion of the liver, and edema of the lungs.

Two rabbits died after 3 and 5 applications respectively of 4256 mg/kg to the shaved back skin (approximately 14% of the body surface) (McOmie, 1946); autopsies revealed mild skin inflammation in the exposed area, hepatitis and lung congestion. Two other rabbits survived without apparent effect 12 exposures to 1792 mg/kg on approximately 5% of the body surface. One guinea pig died after 7 topical applications of 6160 mg/kg, but 3 others survived 12 exposures ranging from 2352-448 mg/kg. It should be noted that the frequency of exposures in the aforementioned experiments (McOmie, 1946) were not stated.

Instillation of undiluted diallyl phthalate (≈0.1-0.56 g) into the conjunctival sacs of rabbits caused mild irritation (Carpenter and Smyth, 1946; McOmie, 1946).

(2) Subchronic Exposures

Repeated oral dosing (schedule not specified) of rats with diallyl phthalate at 250 to 300 mg/kg levels has been reported to produce decreases in liver enzyme activity (ethyl morphine demethylase, P-450), microsomal protein content, and increases in liver weight (Carter et al., 1978). The liver weight increase was due to fluid accumulation, and the lungs were also found to have an increased fluid content.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

Diallyl phthalate has been scheduled for mutagenicity testing in Salmonella by the NTP (1980).

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

A long-term carcinogenesis bioassay of diallyl phthalate administered by gavage to rats and mice is currently underway (NTP, 1981b).

16. Exposure Standards

No recommended or promulgated occupational exposure standards for diallyl phthalate were found.

17. Sources of Additional Relevant Information

Comprehensive reviews of phthalate esters have been completed by Peakall (1975), Daniel (1978); Lawrence (1978), Thomas et al. (1978), Lawrence and Tuell (1979), and the U.S. EPA (1980b).

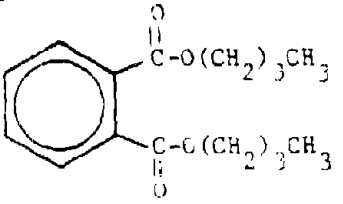
18. Other Pertinent Data

No other information that would aid in the assessment of diallyl phthalate as an occupational hazard was found in the literature searched.

C. Di-n-BUTYL PHTHALATE

1. Chemical Name: Di-n-Butyl Phthalate

2. Chemical Structure:



3. Synonyms: Benzene-o-dicarboxylic acid, di-n-butyl ester
Celluflex DBP
DBP
Dibutyl phthalate
Elaol
Genoplast B
Hexaplas M/B
Palatinol C
Phthalic acid, dibutyl ester
Polycizer DBP
PX 104
o-Benzene dicarboxylic acid, dibutyl ester Staflex DBP
Unimoll DB
Witcizer 300

4. Chemical Abstracts Service (CAS) Number: 84-74-2

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

TI0875000

6. Chemical and Physical Properties:

Description:	colorless, oily liquid
Molecular Weight:	278.35
Boiling Point:	340°C (76 mm Hg)
Melting Point:	-35 to -40°C
Vapor Pressure:	0.01 mm Hg (20°C)
Solubility:	13 mg/l (25°C) water; very soluble in acetone, benzene, alcohol, ether; soluble in most organic solvents and oils
Specific Gravity:	1.047_4^{20}
Stability:	combustible; Autoignition temperature: ≈750°F, Flash point (COC): 340°F

7. Production

Recent production figures for di-n-butyl phthalate are as follows (USITC, 1980a, 1979a, 1978a, 1977a):

Year	Production (in millions of pounds)
1979	17.2
1978	16.9
1977	16.6
1976	13.7

Data available from the U.S. EPA (1980a) regarding producers of dibutyl phthalate and production volumes are presented in Table 11.

Recent data regarding importation of di-n-butyl phthalate are as follows (USITC, 1980b, 1979b, 1978b, 1977b):

Year	Production in Millions of Pounds
1979	1.004
1978	0.931
1977	1.645
1976	0.205

8. Use

Di-n-butyl phthalate is used primarily as a plasticizer in polyvinyl acetate emulsions; small amounts are consumed in specialized vinyl compounds (Frey, 1976).

Di-n-butyl phthalate is used in nail polish removers; a typical nail polish remover formula is ethyl acetate 40%, acetone 30%, carbitol 19%, dibutyl-n-phthalate 10%, sesame oil 1% (Isacoff, 1979).

Di-n-butyl phthalate can also be used as an insect repellent; it is usually impregnated into clothing as a chigger repellent (Spencer, 1968; Meister, 1976). This use of the chemical is minor. Other minor uses of di-n-butyl phthalate include solid rocket propellents, solvent for perfume oils,

Table 11. Producers of Di-n-Butyl Phthalate and Production Ranges (U.S. EPA, 1980a)

Producer	Type of Production	1977 Production Range
Hatco Chemical Div. Fords, NJ	Manufacturer	confidential
Haven Chemical Philadelphia, PA	Manufacturer	confidential
Monsanto Co. St. Louis, MO	Manufacturer	none
Tennessee Eastman Kingsport, TN	Manufacturer	1-10 million lb
U.S. Steel Corp. Pittsburg, PA	Manufacturer	10-50 million lb
Sherwin-Williams Co. Chicago, IL	Manufacturer	1-10 million lb
Tenneco Chem. Chestertown, MD	Manufactuer	none
Morganton Plant Morganton, NC	Manufacturer	10-100 thousand lb
Hooker Chemical North Tonawanda, NY	Manufacturer-Not distributed	10-100 thousand lb
Reichhold Chemical Carteret, NJ	Manufacturer	1-10 million lb
IMC Chemical Terre Haute, IN	Manufacturer	none
Henkel Inc. Teaneck, NJ	Importer	under 1000 lb
Cellofilm Corp. Wood-Ridge, NJ	Importer	none
Fayette Chemical WoodRidge, NJ	Importer	none
Fallek Chemical New York City, NY	Importer	none
BASF Wyandotte Parsippany, NJ	Importer	none

Table 11. Producers of Di-n-Butyl Phthalate and Production Ranges (U.S. EPA, 1980a) (Cont'd)

Producer	Type of Production	1977 Production Range
DuPont Wilmington, DE	Importer	under 1000 lb
Thorson Chemical New York City, New York	Importer	under 1000 lb
Synarome Corp. New York City, NY	Importer	under 1000 lb
Proprietary Perfumes Limited Maywood, NJ	Importer	10-100 thousand lb

perfume fixative, textile lubricating agent, safety glass, insecticides, printing inks, resin solvent, paper coatings, adhesives, lipsticks and cosmetics, and dilutent in elastomers for dental materials (Hawley, 1977; Isacoff, 1965; Freeman, 1965; Paffenbarger and Rupp, 1979).

9. Manufacturers and Distributors

The following companies manufacture di-n-butyl phthalate (SRI International, 1980):

Eastman Kodak (Tennessee Eastman)	Kingsport, TN
The C.P. Hall Co.	Chicago, IL
Hatco Chem. Corp.	Fords, NJ
IMC Chem. Corp.	Terre Haute, IN
Reichhold Chem.	Carteret, NJ
J.T. Baker Chem.	Phillipsburg, NJ
Sherwin-Williams	Chicago, IL
Union Camp Corp.	Dover, OH
USS Chem.	Neville Island, PA
BASF Wyandotte	Kearny, NJ

The many distributors of di-n-butyl phthalate include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Aldrich Chem.	Gallard-Schlesinger
Alfa Products	Helm NY
Alltech Assoc.	Jobin Chem.
Alpha International	Lachat Chem.
Amerchem.	LaPine Sci.
Anachemica Chem.	Lux Chem.
Ashland Chem.	MCB Reagents
Atomergic Chemetals	Mallinckrodt
Bentley Chem.	Mitsibushi Gas Chem.
Bio-Clinical Lab.	Pfaltz and Bauer
CPS Chem.	Phillip Bros. Chem.
CTC Organics	Pioneer Salt and Chem.
Chem Services	Signo Trading
Chemical Dynamics	Star, Milton M. Chem.
Chemical Industries	Suburban Chem.
Chemisphere Corp.	Thompson-Hayward Chem.
Chemtech Industries	Tridom Chem.
Crest Chem.	Joseph Turner and Co.
EM Lab	Union Chem.
Eastern Chem.	Unitex Chem.

Fisher Sci.	Velco Enterprises
GRL Chem.	Worth Chem.

10. Manufacturing Processes

The dialkyl phthalates, including di-n-butyl phthalate, are produced by esterifying phthalic anhydride with the appropriate alcohols in the presence of catalytic amounts of sulfuric acid. The process is essentially the same for all the lower aliphatic alcohols, and modifications are necessary only in the alcohol-recovery and product-purification systems (Lowenheim and Moran, 1975). In the case of di-n-butyl phthalate, the esterification is done with phthalic anhydride and n-butyl alcohol.

Appendix B diagrams the typical process by which all commercial dialkyl phthalates are made. Plants are designed to allow any of the phthalate esters to be made in the same equipment, giving flexibility to production. While many plants produce phthalates by batch methods, other newer plants operate continuously and are highly automated (Lowenheim and Moran, 1975).

The production process begins by charging phthalic anhydride and the appropriate alcohol into a reactor that is actually the still of a distillation column. The reactor is equipped with an efficient agitator and internal steam coils for heating. A stoichiometric excess of alcohol is normally utilized. A 1% solution of concentrated sulfuric acid is added as a catalyst. The reactor is heated to such a temperature that the azeotrope of water and alcohol distills at the column-head. The distillate is cooled and separated by decantation. The alcohol-rich layer is recycled to the column, while the water-rich layer is either wasted or sent to recovery. When the optimum amount of water has been removed from the reactor, the residual crude phthalate (still bottoms) is discharged to an alkali washer that neutralizes the sulfuric acid content with sodium carbonate. This neutralizing operation is followed by a

water-washing operation. The crude phthalate is then stripped in a vacuum column to separate the volatile products such as olefins, alcohol, and other impurities. When economically feasible, the alcohol is recovered for reuse. The phthalate can be further purified by decolorizing with activated charcoal (Lowenheim and Moran, 1975; Sittig, 1967).

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 905,227 workers are potentially exposed to di-n-butyl phthalate.

13. Control Technology and Work Practices

It was noted in an abstract from the Russian literature that filters of polypropylene fibers (8-10 μm in diameter) were effective in removing a large percentage of dibutyl phthalate from waste gases, although this material had a high aerodynamic resistance which increased during the test (Shkarupa and Myagkov, 1976). Better results were obtained with filtering materials of lavsan fibers (diameter 15-20 μm), which had a comparatively low resistance and gave 98% purification with a linear gas stream speed of 1.42 m/sec. Filters of polypropylene fibers (diameters of 22 and 48 μm) and of lavsan fiber (60 μm diameter) had a low aerodynamic resistance, but did not acceptably filter dibutyl phthalate from the air.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute lethal and irritant effects of di-n-butyl phthalate are summarized in Table 12. Pulmonary congestion, edema and petechial hemorrhages, lymphocyte fragmentation in the spleen, and renal tubular

Table 12. Acute Lethal and Irritant Effects of Di-n-Butyl Phthalate

Route	Species	Dose (g/kg)	Response	Reference
oral	rats	4.0	0/3 died	Smith, 1953
oral	rats	8.0	4/9 died	Smith, 1953
oral	rats	16.0	6/6 died	Smith, 1953
oral	rats	8-16	LD50	Shibko and Blumenthal, 1973
oral	rats	10.42[b]	LD50	Bornmann et al., 1956
inhalation	rats	61.5-79 ppm	LD50	Spasovski, 1964
inhalation	rats	saturated air x 7.5 min	0/6 died	Shaffer et al., 1945
inhalation	rats	saturated air x 15 min	6/6 died	Shaffer et al., 1945
i.p.[a]	rats	3.18	LD50	Singh et al., 1972
i.p.	rats	3.57	LD50	Lawrence et al., 1975
i.p.	mice	4.14	LD50	Karel et al., 1947
i.p.	mice	5.5	LD50	Hodge et al., 1942
i.p.	mice	4.0	LD50	Calley et al., 1966
i.p.	mice	1.4	1 of 3 died	Nematollahi et al., 1967
s.c.	rats	<6.2	LD50	Kowalski and Bassendowsa, 1965
intradermal	mice	5.2	no dermal or visceral organ irritation	Lawrence et al., 1975
ocular	rabbits	not stated	no irritation	Lawrence et al., 1975

[a] i.p. = intraperitoneal; s.c. = subcutaneous.

[b] The toxicity for rabbits and dogs was reported to be the same as that found for rats.

degeneration were observed in mice within 72 hours of injection of intraperitonal median lethal doses of di-n-butyl phthalate (Karel et al., 1947).

Intradermal injection of di-n-butyl phthalate (5.2 g/kg) into mice was non-irritating to the skin, and there was no histological damage to the peritoneal organs (Lawrence et al., 1974). Instillation of undiluted compound (volume not stated) into the eyes of rabbits did not result in grossly observable irritation (Lawrence et al., 1975).

(2) Subchronic Exposures

Oral administration of di-n-butyl phthalate to rats at a level of 2.5 mg/kg/day for 6 months has been reported to produce no toxic effects (Maslenko, 1968). Three-month studies with the compound fed at 0.12 and 1.20 g/kg/day levels produced a significant increase in the liver weight of rats, but no histologic evidence of changes in any of the tissues examined (Nikonorow et al., 1973).

Repeated intraperitoneal injection (5 days/week for 25 weeks) of di-n-butyl phthalate into mice produced a progressive decrease in the calculated LD50 value (Lawrence et al., 1974); the authors suggested that this represents a cumulative effect. A nearly 3-fold change in the LD50 value was observed, but this decrease is smaller than that observed for either di-2-ethylhexyl or dioctyl phthalates.

3. Chronic Exposures

Dietary administration of di-n-butyl phthalate to rats at concentrations of 0.01, 0.05, or 0.25% for 1 year did not affect growth, survival, hematologic parameters or organ histology, although 1.25% levels did cause 50% mortality (Smith, 1953). Results similar to these (i.e., no observable toxic effects) were also found with rats following oral exposure to 500 and 1000 mg/kg (twice weekly, gavage) for 1 year (Bornmann et al., 1956), 0.125%

(diet) for 1 year (Nikonorow et al., 1973), 0.01 and 0.03% (dietary) for 21 months (LeBreton, n.d.), or 0.05% (diet) for 15 months (LeBreton, n.d.).

Based on data from 1 year feeding studies, the FDA has estimated a no-effect level of 125 mg/kg/day for di-n-butyl phthalate in rats, and 18 mg/kg/day for the compound in dogs (Shibko and Blumenthal, 1973).

(4) Carcinogenicity

A carcinogenicity investigation of di-n-butyl phthalate was conducted at the Villejuif Cancer Institute in France (LeBreton, n.d.) and summarized by LeFaux (1968). Wistar rats were maintained for 21 months on diets containing 100 and 300 ppm di-n-butyl phthalate, and for 15 months on a diet containing 500 ppm. It was concluded that di-n-butyl phthalate was not carcinogenic under these conditions, but it should be noted that additional information on the experimental design was not presented in the LaFaux (1968) summary.

(5) Mutagenicity

Di-n-butyl phthalate was negative in reverse mutation assays with S. typhimurium, E. coli and S. cerevisiae, and in differential growth inhibitor assays with wild and DNA repair-deficient strains of E. coli and B. subtilis (Table 13). Yagi et al. (1976a) has indicated in a preliminary report that the moncester metabolite, mono-n-butyl-phthalate, showed some activity at a level of 10 mg/disk in the rec-assay with B. subtilis.

(6) Teratogenicity

Oral administration of di-n-butyl phthalate to rats throughout pregnancy at doses of 120 and 600 mg/kg/day failed to produce teratogenic effects, but increased resorptions and decreased fetal weights were caused by the higher dose (Nikonorow et al., 1973). When di-n-butyl phthalate was fed to pregnant mice at dietary concentrations of 1.0% (approximately

Table 13. Mutagenicity of Di-n-Butyl Phthalate

Type of Assay	Organism	Strain	Activation	Dose	Result	Reference
Reverse Mutation	S. typhimurium	TA98	+	10 mg/plate	-	Kurata, 1975
		TA100	+	10 mg/plate	-	Kurata, 1975
	S. typhimurium	TA98	±	1000 µg/plate	-	Rubin et al., 1979
		TA100	±	1000 µg/plate	-	Rubin et al., 1979
	S. typhimurium	n.a.	n.a.	n.a.	-	Yagi et al., 1976a
	E. coli	WP-2	n.a.	n.a.	-	Yagi et al., 1976a
	S. cerevisiae	XV185-14C	±	n.a.	-	Shahin and von Borsted, 1978
DNA damage/repair	E. coli	uvr A^-	-	10 mg/plate	-	Kurata, 1975
		Pol A^-	-	10 mg/plate	-	Kurata, 1975
		rec A^-	-	10 mg/plate	-	Kurata, 1975
	B. subtilis	rec A^-	-	10 mg/plate	-	Kurata, 1975
	B. subtilis	rec A^-	n.a.	n.a.	-	Yagi et al., 1976a
Chromosome damage	Cultured Chinese Hamster fibroblasts	CHL	n.a.	0.03 mg/ml	±	Ishidate and Odashima, 1977

2100 mg/kg) throughout pregnancy, however, marked embryotoxicity and a marginally significant increase in exencephaly was observed (Shiota et al., 1980); treatment at this dose level also resulted in marked embryotoxicity (fetal resorptions and dead fetuses).

Skeletal abnormalities have been reported in the offspring of rats injected (intraperitoneal) with di-n-butyl phthalate at levels of ≈300-1000 mg/kg on days 5, 10, and 15 gestation. At the highest level administered, a significant increase in fetal resorption was also noted (Singh et al., 1972). Injection of rats with 2.1 and 4.2 mg/kg dibutyl phthalate on days 3, 6, and 9 of gestation markedly reduced the number of implants and the number of pups weaned per litter (Peters and Cook, 1973).

Injection of ≈104 mg dibutyl phthalate into fertilized eggs failed to produce malformations in developing chick embryos (Bower et al., 1970).

(7) Reproductive Effects

Adverse reproductive effects were not observed in rats administered di-n-butyl phthalate orally at levels of 500 or 1000 mg/kg (twice weekly) for 1 year (Bornmann et al., 1956), 300 or 500 ppm/day (diet) for 3 generations (LeBreton, n.d.), or 100 ppm (diet) for 5 generations (LeBreton, no date). Dietary administration of the compound at levels of 10 and 100 mg/kg/day to mice for 3 generations has, however, been reported to increase the formation of renal cysts in the F_1 and F_2 generations (Onda et al., 1974).

Intubation of di-n-butyl phthalate to young male rats (2000 mg/kg/day for 4 days) produced testicular atrophy which was demonstrable by morphological damage and loss in organ weight (Cater et al., 1977). There was also an increase in the urinary excretion of zinc with a decrease in testicular zinc content.

(8) Other Relevant Information

Animal studies indicate that di-n-butyl phthalate is metabolized rapidly, primarily to the monoester form, and excreted in the urine. Tissue retention and accumulation of the compound appear to be low (Albro and Moor, 1974; Williams and Blanchfield, 1975; Tanaka et al., 1978).

b. Human Studies

(1) Pharmacokinetics

Systemic levels of compound following ingestion of food containing di-n-butyl phthalate indicate that absorption from the gastrointestinal tract occurs (Tomita et al., 1977); blood levels of di-n-butyl phthalate were reported to exceed those measured in ingested food.

Measurable quantities of di-n-butyl phthalate (0.-144 μg/mg lipid) were found in the triglyceride fractions of cortical and medullary tissues from 4 of 15 kidneys obtained from autopsies (Overturf et al., 1979). Two of the kidneys were histologically normal and two were nephrosclerotic, and none of the 15 kidneys were obtained from donors with recent histories of medical or occupational exposure to phthalates.

(2) Health Effects

A clinical report of a single incident in which a chemical worker swallowed 10 g of di-n-butyl phthalate described symptoms of nausea, dizziness, photophobia, lacrimation, and conjunctivitis; recovery was rapid (Cagianut, 1954).

Widespread topical use of the compound during World War II as an insect repellent did not result in overt toxicity (ACGIH, 1979).

Two studies of workers in phthalate plasticizer manufacturing or use plants have reported symptoms of motor and motor-sensory polyneuropathies in exposed populations. Exposure was shown to involve primarily di-n-butyl phthalate, but also a variety of other phthalate esters, at levels (total phthalates) of up to 70 mg/m^3 (Gilioli et al., 1978; Milkov et al., 1969). The incidence of neurological symptoms was reported in both studies to increase with increasing duration of employment. Abstracts of two Russian studies indicate that efforts are being made to correlate occupational exposure to di-n-butyl phthalate with neurological symptoms; however, these articles were not available for evaluation (Milkov and Aldyreva, 1979; Turbin, 1979).

(3) Target Organ Toxicity

The previously cited reports of Gilioli et al. (1978) and Milkov et al. (1969) indicate peripheral nervous system effects of the compound.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of di-n-butyl phthalate were found.

16. Exposure Standards

The ACGIH (1981) currently recommends and OSHA (1976) has promulgated a Time-Weighted Average (TWA) exposure limit of 5 mg/m^3 for occupational exposure to di-n-butyl phthalate; a Short-Term Exposure Limit (STEL) of 10 mg/m^3 has also been recommended by the ACGIH.

17. Sources of Additional Relevant Information

The abstracts of two Russian studies (Milkov and Aldyreva, 1979; Turbin, 1979) discussed in the Health Effects section indicate that those articles may provide epidemiologic information for di-n-butyl phthalate.

A health hazard evaluation/toxicity determination relating to dibutyl phthalate has been conducted at Jeffery Bigelow Design Group, Inc., an acrylic furniture manufacturing plant in Washington, D.C. (HEE No. 76-92-363).

Comprehensive reviews of phthalate esters have been completed by Peakall (1975), Daniel (1978), Lawrence (1978), Thomas et al. (1978), Lawrence and Tuell (1979), and the U.S. EPA (1980b).

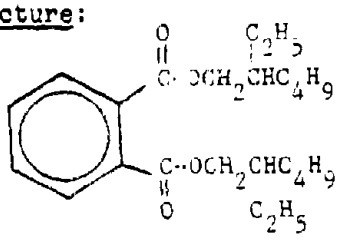
18. Other Pertinent Data

No other information that would aid in the assessment of di-n-butyl phthalate as an occupational hazard was found in the literature searched.

D. DI-2-ETHYLHEXYL PHTHALATE

1. Chemical Name: Di-2-Ethylhexyl Phthalate

2. Chemical Structure:



3. Synonyms: bis(2-ethylhexyl)ester
1,2-Benzenecarboxylic acid,
bis(2-Ethylhexyl)ester, phthalic acid
bis(2-2-Ethylhexyl)phthalate
Bisoflex 81
Bisoflex DOP
Compound 889
DEHP
DOP
Di(2-ethylhexyl)orthophthalate
Dioctyl phthalate
Di-sec-octyl phthalate
Eviplast 80, 81
Fleximel
Flexol DOP
Herco Flex 260
Kodaflex DOP
Octoil
Palatinol AH
Pittsburg PX--138
RC Plasticizer D>P
Sicol 150
Staflex DOP
Truflex DOP
Vestinol AH
Vinicizer 80
Witcizer 312

4. Chemical Abstracts Service (CAS) Number: 117-81-7

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number: TI0350000

6. Chemical and Physical Properties:

Description:	Nearly colorless viscous liquid
Molecular Weight:	390.54
Boiling Point:	384°C
Melting Point:	-46°C to - 50°C
Vapor Pressure:	1.2 mm Hg (200°C)

Solubility:	0.4 mg /l (25°C)water; soluble in most organic solvents; virtually insoluble in glycerol and glycols
Specific Gravity:	0.986^{20}_{20}
Stability:	combustible; Flashpoint: 425°F.

7. Production

Recent production figures for di-2-ethylhexyl phthalate are as follows (USITC, 1980a, 1979a, 1978a, 1977a):

Year	Production (in Million of Pounds)
1979	300.6
1978	408.6*
1977	388.5
1976	296.7

*Figure includes other dioctyl phthalates in addition to DEHP

Data available from the U.S. EPA (1980a) regarding producers of di-2-ethylhexyl phthalate and production volumes are presented in Table 14.

Dioctyl phthalates--di-2-ethylhexyl phthalate in particular--account for approximately one-third of all phthalate production. Future growth of the dioctyl phthalate (DOP) market can probably be expected to be less than the general phthalate market due to the availability of low-cost imports and a pressure on suppliers to find alternatives to DOP (Modern Plastics, 1978).

Recent import data for di-2-ethylhexyl phthalate (and other dioctyl phthalates) follow (USITC, 1980b, 1979b, 1978b):

Year	Importation in Millions of Pounds
1979	3.246
1978	11.290
1977	0.57[illegible]

Table 14. Producers of Di-2-ethylhexyl Phthalate and Production Ranges (U.S. EPA, 1980a)

Producer	Type of Production	1977 Production Range
Ashland Chemical Dublin, OH	Importer	none
BASF Wyandotte Kearny, NJ	Manufacturer	50 to 100 million lb
BF Goodrich Chemical Avon Lake, OH	Manufacturer	10 to 50 million lb
A. Campbell and Co. Cleveland, OH	Importer	confidential
Cellofilm Corp. Woodridge, NJ	Importer	none
Continental Oil Co. Aberdeen, MS	Manufacturer	1 to 10 million lb
Fayette Chemical Woodridge, NJ	Importer	none
Hatco Chemical Division Fords, NJ	Manufacturer	confidential
Haywood Co. Brownsville, TN	Manufacturer	1 to 10 million lb
JSR America New York, NY	Importer	under 1000 lb
Lilly Industrial Coatings Indianapolis, IN	Importer	none
Mobay Chemical Pittsburg, PA	Importer	under 1000 lb
Reichhold Chemical Carteret, NJ	Manufacturer	10 to 50 million lb
Teknon Apex Co. Atterbow, MA	Manufacturer	1 to 10 million lb
Tenneco Chemical Chestertown, MD	Manufacturer	confidential
Tennessee Eastman Kingsport, TN	Manufacturer	50 to 100 million lb
U.S. Steel Corporation Pittsburg, PA	Manufacturer	50 to 100 million lb

8. Use

Di-2-ethylhexyl phthalate is the most widely used general-purpose plasticizer for polyvinyl chloride. It is used in products such as automobile vinyls and plastics, wire and cable insulations, and a wide variety of consumer goods and home furnishings (Frey, 1976).

Di-2-ethylhexyl phthalate is also used as a dielectric fluid component in capacitors as a replacement for PCBs (Versar, 1976). The volume of di-2-ethylhexyl phathalate consumed annually for capacitor applications is on the order of 1 million pounds (SRC estimate). This is a minor use compared to the plasticizer uses, which consume nearly 300-400 million pounds annually.

9. Manufacturers and Distributors

The following companies manufacture di-2-ethylhexyl phthalate (SRI International, 1980; USITC, 1980a):

BASF Wyandotte Corp.	Kearny, NJ
Continental Oil Co.	Aberdeen, MS
Eastman Kodak (Tennessee Eastman)	Kingsport, TN
BF Goodrich	Avon Lake, OH
Hatco Chem. Corp.	Fords, NJ
Monsanto	Texas City, TX
Reichhold Chem.	Carteret, MA
Teknor Apex Co.	Hebronville, MA
USS Chemical	Neville Island, PA

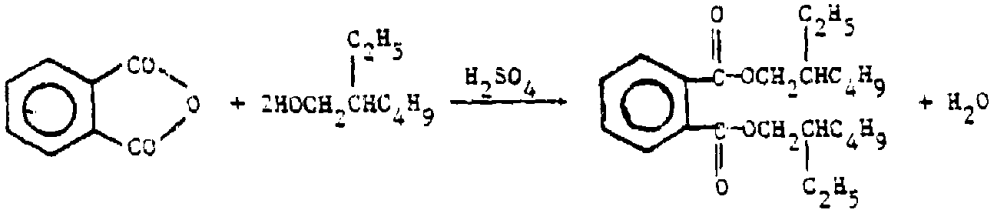
Hatco Chem. is the largest volume producer of the chemical, followed by USS Chemical, BASF Wyandotte, and Tennessee Eastman. Combined, these four companies produce on the order of 85% of all di-2-ethylhexyl phthalate (Frey, 1976).

The distributors of di-2-ethylhexyl phthalate include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Alltech Assoc.	GRL Chem.
Anachemia Chem.	The C.P. Hall Co.
Ashland Chem.	ICN/K and K
Chemisphere Corp.	MCB Reagents
Chem Service	Mitsubishi Gas Chem.
Eastern Chem.	Pfaltz and Bauler
Fallek Chem.	Polysciences
Fehr Bros. Chem.	Star, Milton M. Chem.

10. Manufacturing Processes

The dialkyl phthalates, including di-2-ethylhexyl phthalate, are produced by esterifying phthalic anhydride with the appropriate alcohols in the presence of catalytic amounts of sulfuric acid. The process is essentially the same for all the lower aliphatic alcohols, and modifications are necessary only in the alcohol-recovery and product-purification systems (Lowenheim and Moran, 1975). In the case of di-2-ethylhexyl phthalate, the esterification is done with phthalic anhydride and 2-ethylhexyl alcohol as follows:



Appendix B diagrams the typical process by which all commercial dialkyl phthalates are made. Plants are designed to allow any of the phthalate esters to be made in the same equipment, giving flexibility to production. While many plants produce phthalates by batch methods, other newer plants operate continuously and are highly automated (Lowenheim and Moran, 1975).

The production process begins by charging phthalic anhydride and the appropriate alcohol into a reactor that is actually the still of a distillation column. The reactor is equipped with an efficient agitator and internal steam coils for heating. A stoichiometric excess of alcohol is normally utilized. A 1% solution of concentrated sulfuric acid is added as a catalyst. The reactor is heated to such a temperature that the azeotrope of water and alcohol distills at the column-head. The distillate is cooled and separated by decantation. The alcohol-rich layer is recycled to the column, while the water-rich layer is either wasted or sent to recovery. When the optimum amount of water has been removed from the reactor, the residual crude phthalate (still bottoms) is discharged to an alkali washer that neutralizes the sulfuric acid content with sodium carbonate. This neutralizing operation is followed by a water-washing operation. The crude phthalate is then stripped in a vacuum column to separate the volatile products such as olefins, alcohol, and other impurities. When economically feasible, the alcohol is recovered for reuse. The phthalate can be further purified by decolorizing with activated charcoal (Lowenheim and Moran, 1975; Sittig, 1975).

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 612,106 workers are potentially exposed to di-2-ethylhexyl phthalate.

13. Control Technology

Specific factors that may contribute to or prevent employee exposure to di-2-ethylhexyl phthalate were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute lethal and irritant effects of di-2-ethylhexyl phthalate are summarized in Table 15. As indicated, di-2-ethylhexyl phthalate has been demonstrated to produce a low level of acute toxicity, particularly when compared with other phthalates. Histological examination of rats following single lethal oral doses of di-2-ethylhexyl phthalate revealed cloudy swelling of the liver and kidneys accompanied by granular secretion in the tubules (Shaffer et al., 1945). Single non lethal oral doses (2 g/kg) caused an increase in liver and brain weight in rats after 7 days, but the weights and gross pathology of other organs, hepatic microsomal enzyme activity and hematological indices were not affected by exposure (Chu et al., 1981).

Inhalation exposure of rats to a mist containing high levels of di-2-ethylhexyl phthalate (exact concentration unknown) has been reported to produce fatalities in 4 hours; animals exposed for 2 hours showed no lethal effects (Shaffer et al., 1945).

Intradermal injection of undiluted di-2-ethylhexyl phthalate (4.93 g/kg) to mice was non-irritating to the skin, although there was some histological evidence of transient irritation to the peritoneal organs (Lawrence et al, 1974). Instillation of 0.5 ml of undiluted di-2-ethylhexyl phthalate (=0.49 g) into the conjunctival sacs of rabbits has resulted in slight eye irritation (Shaffer et al., 1945; Carpenter and Smyth, 1946).

(2) Subchronic Exposures

Ten days to three-month feeding of di-2-ethylhexyl phthalate to rats at a dietary level of 0.2 to 5.0% has caused liver enlargement and related histological and biochemical changes (Table 16).

Table 15. Acute Lethal and Irritant Effects of Diethylhexyl Phthalate

Route	Species	Dose (g/kg)	Response	Reference
oral	rats	30.6	LD50	Shaffer et al., 1945
oral	rats	79.5	8/10 died	Shaffer et al., 1945
oral	rabbits	33.9	LD50	Shaffer et al., 1945
inhalation	rats	saturated atmosphere X 2 hrs.	0/6 died	Shaffer et al., 1945
inhalation	rats	saturated atmosphere X 4 hrs.	6/6 died	Shaffer et al., 1945
i.p.[a]	mice	14.2	LD50	Calley et al., 1966
i.p.	mice	37.8	LD50	Lawrence et al., 1975
i.p.	rats	>49.3	LD50	Singh et al., 1972
i.p.	rats	30.7	LD50	Shaffer et al., 1945
i.v.[b]	rats	0.3	LDLo	Shaffer et al., 1945
intradermal	mice	4.9	no dermal irritation, but slight transient irritation to the peritoneal organs.	Lawrence et al., 1975
dermal	rabbits	24.6	LD50	Shaffer et al., 1945
dermal	guinea pigs	10.0	LD50	Krauskopf, 1973
ocular	rabbits	0.5 ml undiluted	transient congestion of the lids	Shaffer, et al., 1945
ocular	rabbits	0.5 ml undiluted	slight irritation	Carpenter and Smyth, 1946
ocular	rabbits	not stated	no irritation	Lawrence et a., 1975

[a] i.p. = intraperitoneal

[b] i.v. = intravenous

Table 16. Effects of Subchronic Exposure to Di-2-Ethylhexyl Phthalate

Route	Species	Exposure	Principle Findings	Reference
oral (diet)	rats	0.375, 0.75, 1.5 and 3.0% for 90 days (0.2, 0.4, 0.9 and 1.9 g/kg/day, respectively	Retarded growth at the three highest doses. No effect on hematology or micropathology of heart, liver, kidney or spleen, but testicular degeneration was noted.	Shaffer et al., 1945
oral (gavage)	rats	0.34 and 3.40 g/kg/day for 90 days	Increased liver weights at 0.34 g/kg; 15/20 deaths in 3.4 g/kg group; effects included congestion of the small intestine, loss of mucosa in the stomach and parts of the intestine, purulent pneumonia and endometritis. No histopathologic alterations in the liver, spleen or kidneys in either group.	Nikonorow, et al., 1973
oral (diet)		0.25 and 2.5% for 3 months	Increase in the weight of the kidneys and formation of renal cysts.	Ohta et al., 1973
oral		1,4 and 10 g/kg for 3 weeks	Increased liver weight at 4 g/kg. At 10 g/kg, significant increase in mortality and liver weight, with a proliferation of the bile duct and Kupffer's cells	Yamada, 1974

Table 16. Effects of Subchronic Exposure to Di-2-Ethylhexyl Phthalate (Cont'd)

Route	Species	Exposure	Principle Findings	Reference
oral (diet)	rats	0.5 and 2.5% for 21 weeks	Enlarged livers, elevated serum alkaline phosphatase, cloudy swelling and necrosis liver cells and renal tubule epitheleal cells, and absence of spermatogenesis in both groups.	Yamada et al., 1974
oral (diet)	rats	0.2, 1, and 5% for 3 months	Increased liver weight and drug metabolism enzyme activities (not specified) in all groups. Atrophy of testes in the 5% group.	Yamada et al., 1975
oral (intubation)	rats	2 g/kg/day for 21 days	Progressive liver enlargement, hypoactivity of proliferated smooth endoplasmic reticulum, and diminished enzyme activity resulting from mitochondrial changes	Lake et al., 1975
oral (diet)	rats	0.5% for 10 days	Liver enlargement and a significant increase in hepatic phospholipids	Yanagita et al., 1978
inhalation	mice	saturated air for 2 hrs/day, 3 days/week for 4 to 16 weeks	No compound-related histological alterations in lung or other tissues.	Lawrence et al., 1975
i.v.	dogs	0.5, 0.75, and 1.4 mg/kg/day (in canine plasma) for 21 days	No effect on behavior, hematology, clinical chemistry, body or organ weights or histomorphology	Rutter, 1975
i.p.	mice	250 mg/kg/day for 6 weeks	Nearly all organs showed cloudy sedimentation, adhesions of the diaphram, liver and intestines.	Calley, et al., 1966

Repeated intraperitoneal injection (5 days /week for 12 weeks) of the compound into mice has resulted in a significantly lowered LD50 value (approximately 20-fold) (Lawrence et. al., 1974); the investigators believe that this reflects an ability of di-2-ethylhexyl phthalate to accumulate.

(3) Chronic Exposures

Long-term feeding studies (1-2 years' duration) in several species with di-2-ethylhexyl phthalate (0.1 to 0.5% dietary levels) have indicated that the compound may produce liver and kidney effects as indicated by increased weights of those organs (Carpenter et al., 1953; Lefaux, 1968; Nikonorow et al., 1973). Based on these chronic studies, the FDA has estimated no-effect levels for di-2-ethylhexyl phthalate to be 60 mg/kg/day for rats and 65 mg/kg/day for dogs (Shibko and Blumenthal, 1973).

(4) Carcinogenicity

Two-year NCI carcinogenicity bioassays of di-2-ethylhexyl phthalate with B6C3F1 mice and F344 rats have been completed, but the report is currently in review (NTP, 1981b). Fifty animals/sex/dose were tested, and preliminary results (NCI, 1980) indicated that the administration of 3000 and 6000 ppm dietary levels of di-2-ethylhexyl phthalate to mice of both sexes produced a marked increase in the incidence of hepatocellular carcinomas. Rats fed dietary levels of 6000 ppm di-2-ethylhexyl phthalate also showed an increase in hepatocellular carcinomas. Statistical evaluation of these results was not available in the preliminary report.

A carcinogenicity investigation of di-2-ethylhexyl phthalate was conducted at the Villejuif Cancer Institute in France and summarized by LeFaux (1968). In this study, rats were apparently maintained on

diets containing 500 ppm of the compound for a period of 21 months. It was concluded that the phthalate was innocuous and noncarcinogenic under these conditions, but it should be noted that additional information regarding experimental design was not presented in the Lefaux (1968) summary.

(5) Mutagenticity

Reverse mutation and differential growth inhibition (DNA damage/repair) assays of di-2-ethylhexyl phthalate with bacteria were negative, and the compound failed to produce increased aberrations in cultured Chinese hamster fibroblasts, human leokocytes or human fetal lung cells (Table 17). Singh et al. (1974) have, however, reported positive mutagenic effects in the dominant lethal assay following a single intraperitoneal injection of di-2-ethylhexyl phthalate into mice at 1/3, 1/2, or 2/3 of the LD50 level (12.5, 19 and 25 mg/kg, respectively).

Di-2-ethylhexyl phthalate has been schedule for mutagenicity testing in Drosophila by the NTP (1980).

(6) Teratogenicity

Embryotoxic and teratogenic effects have been observed following oral and intraperitoneal administration of di-2-ethylhexyl phthalate to rats and mice (Table 18).

Injection of 0.05 ml (0.49 g) undiluted di-2-ethylhexyl phthalate into the yolk sacs of 3-day old developing chicken eggs resulted in marked embryolethality (51%), but no evidence of gross malformations (Lee et al., 1974). Teratogenic effects (clubbed feet, neuromuscular disorders) were observed, however, following injection of 0.05 ml of chick Ringer's solution that was saturated with di-2-ethylhexyl phthalate.

Table 17. Mutagenicity of Di-2-Ethylhexyl Phthalate

Type of Assay	Organism	Strain	Activation	Dose	Result	Reference
Reverse mutation	S. typhimurium	TA 98, TA 100	±	1000 µg/plate	-	Rubin et al., 1979
	S. typhimurium	TA 98, TA 100, TA 1535, TA 1537	±	n.a.	-	NTP, 1980
	S. typhimurium	n.a.	n.a.	n.a.	-	Yagi et al., 1976a
	E. coli	WP-2	n.a.	n.a.	-	Yagi et al., 1976a
DNA damage/ repair	B. subtilis	rec A⁻	n.a.	n.a.	-	Yagi et al., 1976a
Chromosome damage	Cultured Chinese hamster fibroblasts	CHL	n.a.	0.16 mg/ml	-	Odashima and Ishidate, 1975
	Cultured human leukocytes	n.a.	---	0.6 to 60 µg/ml	-	Peterson et al., 1975
	Cultured human fetal lung cells	n.a.	---	6.0 µg/ml	-	Peterson et al., 1975
Dominant lethal	mice	Harlan/ICR Swiss albino	+	12.7 to 25.3 mg/kg, single dose, i.p.	+	Singh et al., 1974

Table 18. Embryotoxic and Teratogenic Effects of Di-2-Ethylhexyl Phthalate

Species	Route	Exposure	Principal Findings	Reference
rats	oral (diet)	0.05, 0.13 and 0.4% for 2 years	No effect upon total number of pups born, mean number of litters, mean size of litters, or incidence of stillborns	Carpenter et al., 1953
rats	oral (gavage)	0.34 or 1.70 g/kg/day for 3 months prior to conception	Decreased fetal and placental weights and increased number of resorptions; no gross abnormalities observed.	Nikonorow et al., 1973
rats	oral	2.5 or 5 mg/kg/day on days 7-13 of gestation.	Increased fetal mortality and resorptions.	Nakayama, 1968
mice	oral	2.5 to 10 g/kg/day on days 6-10 of gestation	Unspecified external and skeletal malformations in offspring of mice exposed to 7.5 g/kg on day 8, but no other details reported	Yagi et al., 1976a, 1976b
mice	oral (diet)	0.05, 0.1, 0.2, 0.4 and 1.0 wt% throughout gestation (ca. 70, 190, 400 830 and 2200 mg/kg, respectively)	Marginally significant increase in malformations (primarily exencephaly and spina bifida) at 0.2%; all implanted ova died in utero at 0.4 and 1.0%	Shiota et al., 1980

Table 18. Embryotoxic and Teratogenic Effects of Di-2-Ethylhexyl Phthalate (Cont'd)

Species	Route	Exposure	Principal Findings	Reference
mice	oral	0.05, 0.1, or 1.0 g/kg on day 7 of gestation	Fetal mortality at 0.1 and 1.0 g/kg. Gross and skeletal abnormalities at 1.0 g/kg (elongated and fused ribs, absence of tail bones, abnormal or incomplete skull bones, incomplete or missing leg bones)	Nakamura et al., 1979
rats	i.p.	ca. 5 and 10 mg/kg/day on days 5, 10 and 15 of gestation	hemangiomas and twisted hind legs at 10 mg/kg. Resorptions at both doses but no dead fetuses	Singh et al., 1972
rats	i.p.[a]	2 and 4 g/kg/day on days 3, 6, and 9 of gestation	Adversely affected implantation and parturition.	Peters and Cook, 1973
rats	i.v.[b]	1.3, 4.7, and 5.3 mg/kg day[c] on days 6 to 15 of gestation	No effect on numbers of live and resorbed fetuses, fetal weights and sizes, or the incidence of gross external skeletal and visceral malformations	Lewandowski et al., 1980

[a] intraperitoneal

[b] intravenous

[c] Polyvinyl chloride (PVC) plastics which contained DEHP as a plasticizer were extracted with rat plasma to yield the administered concentrations of DEHP; PVC bags are widely used to collect and store blood and parenteral solutions.

(7) Reproductive Effects

Oral and intraperitoneal exposure to high levels of di-2-ethylhexyl phthalate have produced tubular changes in the testes, testicular atrophy and impaired spermatogensis in rats (Table 19).

Results of a three-generation reproduction study conducted with rats maintained on diets containing di-2-ethylhexyl phthalate have shown a lowered mating index in females exposed to 1500 ppm levels of the compound (Industrial Biotest, 1978). Normal reproduction, parturition and nursing were reported in rats exposed to 500 ppm di-2-ethylhexyl phthalate for 4 generations (LeFaux, 1968).

Di-2-ethylhexyl phthalate has been selected for testing for effects on reproductive function by the NTP (1980).

(8) Other Relevant Information

The i.v. administration of di-2-ethylhexyl phthalate (≈ 200 to 300 mg/kg), solubilized in non-ionic detergents, resulted in immediate respiratory distress and subsequent death due to pulmonary edema in male rats (Schulz et al., 1975; Rubin and Chang, 1976). The pulmonary pathology was characterized by an inflammatory state commonly referred to as "shock lung" (edematous thickening of the interalveolar septa and marked engorgement of the pulmonary vasculature with polymorphonuclear leukocytes). The syndrome was not elicited when di-2-ethylhexyl phthalate was injected without solubilizer, although more recent results confirm the pulmonary toxicity in rats when the compound is solubilized directly in plasma without the addition of a detergent (Rubin and Chang, 1978).

Di-2-ethylhexyl phthalate is extensively metabolized to the corresponding monoester, mono-2-ethylhexyl phthalate, and to the acid, alcohol and ketone resulting from the side chain oxidation of the monoester

Table 19. Reproductive Effects of Di-2-Ethylhexyl Phthalate

Species	Route	Exposure	Principal Findings	Reference
rats	oral (diet)	0.375, 0.75, 1.5 and 3.0% for 90 days (0.2, 0.4, 0.9 and 1.9 g/kg/day, respectively)	Tubular atrophy and degeneration in the testes	Shaffer et al, 1945
rats	oral (diet)	0.5 and 2.5% for 21 weeks	Absence of spermatogenesis in both groups	Yamada et al., 1974
rats	oral (diet)	0.2, 1, and 5% for 90 days	Atrophy of the testes in the 5% group	Yamada et al., 1975
rats	oral (diet)	0.2, 1.0 and 2.0% for 17 weeks	Severe seminiferous tubular atrophy and cessation of spermatogenesis at 1.0 and 2.0%; evidence of decreased spermatogenesis at 0.2%	Gray et al., 1977
rats	oral (diet)	0.2 and 1.0% for 90 days	Testicular atrophy; damage produced in 2 weeks at 1.0%	Cater et al., 1977
rats	oral (intubation)	2.8 g/kg/day for 10 days	Reversible age-dependent seminiferous tubular atrophy; effect most pronounced at 4 weeks; no damage in 15 week old rats	Gray and Butterworth, 1980

Table 7. Reproductive Effects of Di-2-Ethylhexyl Phthalate (Cont'd)

Species	Route	Exposure	Principal Findings	Reference
rats	oral (diet)	2% (≈1.2 g/kg/day for 10 days	Testicular effects not influenced by simultaneous administration of testosterone or follicle stimulating hormone	Gray and Butterworth, 1980
rats	i.p.[a]	5 g/kg on days 1, 5, and 10 of the study; rats sacrificed on day 22	Degenerated seminiferous tubules in males No apparent histopathologic alterations in ovaries	Seth et al., 1976
rats	i.p.	1.25 g/kg/day for 5 days	Decrease in resting and human chorionic gonadotropoin-stimulated testosterone plasma levels	Oishi and Hiraga, 1979

[a] i.p. = intraperitoneal

(Albro et al., 1973; Daniel and Bratt, 1974; Lake et al., 1975). Both di- and mono-2-ethylhexyl phthalate are rapidly metabolized and excreted after oral or intravenous administration in rats, and high levels of administered di-2-ethylhexyl phthalate may saturate the liver clearance capability in this species (Schulz and Rubin, 1973; Daniel and Bratt, 1974; Chu et al., 1978).

Distribution studies following the i.p. injection of radiolabeled di-2-ethylhexyl phthalate into pregnant rats have indicated that the compound crosses the placental barrier (Singh et al., 1975); the disappearance half-life for the compound was estimated to be 2.33 days.

b. Human Studies

(1) Pharmacokinetics

Reports on the accidental ingestion of large doses (5 g, 10 g) of di-2-ethylhexyl phthalate (Shaffer et al., 1945) and systemic levels of di-2-ethylhexyl phthalate following ingestion of food containing the compound (Tomita et al., 1977) indicate that absorption from the gastrointestinal tract occurs. Neurological symptoms in workers exposed to phthalate plasticizers indicate that phthalate esters may be absorbed through the respiratory tract (Milkov, 1969; Gilioli et al., 1978).

Di-2-ethylhexyl phthalate residues have been detected in plasma, liver, kidney, spleen, lung, and abdominal fat samples at autopsy (Jaegar and Rubin, 1972; Napier, 1976; Overturf et al., 1979). An increased incidence of positive samples has been reported in patients receiving blood transfusions (Napier, 1976; Hillman et al., 1975), but residues have also been detected in tissues of individuals with no known transfusion history (Miripol et al., 1975).

Lewis et al. (1978) have reported that following elevation of blood levels of compound during patient hemodialysis,

di-2-ethylhexyl phthalate was cleared rapidly from the blood within 5 to 7 hours. A blood half-life of 28 minutes has been estimated for di-2-ethylhexyl phthalate in patients that have received transfusions (Rubin and Schiffer, 1976).

In two patients who swallowed 5 to 10 g of di-2-ethylhexyl phthalate, about 4.5% of the dose was recovered in the urine as phthlate equivalents in 24 hours (Shaffer et al., 1945). Two leukemia patients given platelets stored in vinyl plastic bags excreted 60% and 90% of the infused dose of di-2-ethylhexyl phthalate as unchanged compound, and as phthalate metabolites in the urine within 24 hours of transfusion (Rubin and Schiffer, 1976).

(2) Health Effects

Di-2-ethylhexyl phthalate has been shown to cause pulmonary reactions leading to respiratory distress in animals (Section 14.a.8); this response may relate to "shock lung" syndrome observed in some patients that have received transfused blood (Thomas et al., 1978) that was stoed in polyvinyl chloride bags that contained residues of the compound. Respiratory distress may result from increased platelet aggregation produced by di-2-ethylhexyl phthalate (Petersen et al., 1975) or from effects of the compound on histamine release and metabolism (Chang and Rubin, 1979).

When undiluted di-2-ethylhexyl phthalate was applied to the backs of 23 subjects during patch tests, left in contact for 7 days and reapplied on the same spots 10 days later, no erythema or other dermal reaction was observed (Shaeffer et al., 1945).

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

A morbidity study of 101 worker exposed to very low atmospheric levels (0.0006 to 0.01 ppm) of di-2-ethylhexyl phthalate for an

average of 12 years revealed no significant health effects (neurological abnormalities, premature births or miscarriages) and no increase in chromosomal aberrations (Thiess et al., 1978). Workers were exposed for periods of 4 months to 35 years in a di-2-ethylhexyl phthalate production plant.

Two epidemiological studies of workers exposed to di-2-ethyhexyl phthalate as well as several other phthalate esters (dibutyl, butyl benzyl, diisooctyl) have indicated an increased incidence of polyneuropathies of both the sensory and motor-sensory types (Milkov et al., 1969; Gilioli et al., 1978). The Italian study (Gilioli et al., 1978) indicated that 12 of 23 phthalate plasticizer workers exposed to atmospheric levels of phthalates ranging from 1 mg/m^3 to 60 mg/m^3 suffered neurological disturbances. Workers exposed for 2 to 3 years showed symptoms in 25% of the cases examined, while those exposed for longer than 3 years showed symptoms in 46.6% of the cases investigated. Exposure of the Russian workers (Mikov et al., 1969) in an artificial leather and film production plant involved atmospheric levels that ranged from 1.7 mg/m^3 to 60 mg/m^3. The incidence of subjective symptoms increased from 57% in those employed 6 to 10 years to 82% in those employed for more than 10 years.

15. Ongoing Studies

The distribution, biotransformation, and elimination characteristics of di-2-ethylhexyl phthalate in primates (including man) are currently being studied by Peck and Odom (1981).

16. Exposure Standards

The ACGIH (1981) currently recommends and OSHA (1976) has promulgated a Time-Weighted Average (TWA) exposure limit of 5 mg/m^3 for occupational exposure to di-2-ethylhexyl phthalate; a Short-Term Exposure Limit (STEL) of 10 $mg/^3$ has also been recommended by the ACGIH.

17. Sources of Additional Relevant Information

Comprehensive reviews of phthalate esters have been completed by Peakall (1975), Daniel (1978); Lawrence (1978); Thomas et al. (1978), Lawrence and Tuell (1979), and the U.S. EPA (1980b).

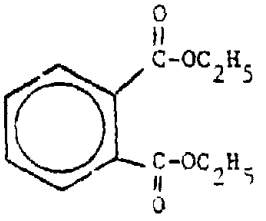
18. Other Pertinent Data

No other information that would aid in the assessment of di-2-ethylhexyl phthalate as an occupational hazard were found in the literature searched.

E. DIETHYL PHTHALATE

1. Chemical Name: Diethyl Phthalate

2. Chemical Structure:



3. Synonyms: Anozol
1,2-Benzenedicarboxylic acid, diethyl ester
DEP
Diethyl E
Diethyl o-phthalate
Ethyl phthalate
Neantine
Palatinol A
Phthalic acid, diethyl ester
Phthalol
Placidol E
Solvanol
Unimoll DA

4. Chemical Abstracts Service (CAS) Number: 84-66-2

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

TI1050000

6. Chemical and Physical Properties:

Description:	water-white, odorless liquid
Molecular Weight:	222.24
Boiling Point:	296-298°C
Melting Point:	-40.5°C
Vapor Pressure:	1 mm Hg (108.8°C)
Solubility:	896 mg/l (25°C) water; soluble in acetone, benzene; miscible with alcohol; soluble in all proportions of ether
Specific Gravity:	1.118
Stability:	combustible; Flash point: 325°F (O.C.)

7. Production

Recent production figures for diethyl phthalate are as follows (USITC, 1980a, 1979a, 1978a, 1977a):

Year	Production (in millions of pounds)
1979	--
1978	22.3
1977	17.5
1976	16.1

Data available from the U.S. EPA (1980a) regarding producers of diethyl phthalate and production volumes are presented in Table 20.

Recent import figures are as follows (USITC, 1980a,b, 1979b, 1978b, 1977b):

Year	Importation in Millions of Pounds
1979	0.131
1978	0.010
1977	0.270
1976	0.161

8. Use

The major use of diethyl phthalate is as a plasticizer; in this application, it is used almost entirely for cellulose ester plastics, with small amounts used in polyurethane casting compounds (Frey, 1976).

Minor uses of diethyl phthalate include use as a dye carrier, solvent for cellulosics, wetting agents, insecticidal sprays, camphor substitutes, perfumery, alcohol denaturant, mosquito repellents, and elastomer diluent in dental materials (Wannemacher and DeMaria, 1979; Hawley, 1977; Freeman, 1965; Gontz and Ellis, 1965).

9. Manufacturers and Distributors

Diethyl phthalate is manufactured by the following companies (SRI International, 1980; USITC, 1980a):

Table 20. Producers of Diethyl Phthalate and Production Ranges (U.S. EPA, 1980a)

Producer	Type of Production	1977 Production Range
Allied Resins Conneaut, OH	Manufacturer	10-100 thousand lb
Kay-Freis Chemicals Stony Point, NY	Manufacturer	confidential
Fritzsche Dodge and Olcott East Hanover, NJ	Manufacturer	none
Pfizer Inc. Greensboro, NC	Manufacturer	0.1-1.0 million lb
Polak's Frutal Works Middletown, NY	Manufacturer	confidential
Monsanto Co. St. Louis, MO	Manufacturer	1-10 million lb
Tennessee Eastman Kingsport, TN	Manufacturer	1-10 million lb
Nickstadt-Moeller Ridgefield, NJ	Manufacturer	confidential
Finetex Inc. Elmwood, NJ	Manufacturer	confidential
Polyesther Corp. Southhampton, NY	Importer	none
EM Laboratories Elmsford, NY	Importer	confidential
Ungerer and Co. Totowa, NJ	Importer	1-10 thousand lb
Syrarome Corp. New York City, NY	Importer	under 1000 lb
Solchem. Inc. New York City, NY	Importer	confidential
V. Mane Fils Inc. Fairfield, NJ	Importer	confidential
Roure Bertrand DuPont Inc. Teaneck, NJ	Importer	confidential
Proprietary Perfumes Ltd Maywood, NJ	Importer	1-10 thousand lb
Dragoco Inc. Totowa, NJ	Importer	1-10 thousand lb

Eastman Kodak (Tennessee Eastman)	Kingsport, TN
Kay-Fries, Inc.	Stony Point, NY
Monsanto	St. Louis, MO
Pfizer	Greensboro, NC
Sybron (Tanatex)	Lyndhurst, NJ

The distributors of diethyl phthalate include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Aldrich Chem.	GRL Chem.
Alfa Prod.	Gallard-Schlesinger
Anachemia Chem.	Haarmann and Reimer
Ashland Chem.	LaPine Sci.
Atomergic Chemetals	Lachat Chem.
J.T. Baker Chem.	Lux Chem.
Berje Chem.	MCB Reagents
Bio-Clinical Labs	Mallinckrodt
CPS Chem.	Pfaltz and Bauer
CTC Organics	Philipp Bros. Chem.
Chem Services	Pioneer Salt and Chem.
Davos Chem.	Polyesther Corp.
EM Labs	Polysciences
Eastern Chem.	Solchem
Fallek Chem.	Thompson-Hayward Chem.
Fehr Bros. Chem.	Tridom Chem.
Fisher Sci.	Unichema International
	Union Chem.

10. Manufacturing Processes

The dialkyl phthalates, including diethyl phthalate, are produced by esterifying phthalic anhydride with the appropriate alcohols in the presence of catalytic amounts of sulfuric acid. The process is essentially the same for all the lower aliphatic alcohols, and modifications are necessary only in the alcohol-recovery and product-purification systems (Lowenheim and Moran, 1975). In the case of diethyl phthalate, the esterification is done with phthalic anhydride and ethyl alcohol.

Appendix B diagrams the typical process by which all commercial dialkyl phthalates are made. Plants are designed to allow any of the phthalate esters to be made in the same equipment, giving flexibility to production.

While many plants produce phthalates by batch methods, other newer plants operate continuously and are highly automated (Lowenheim and Moran, 1975).

The production process begins by charging phthalic anhydride and the appropriate alcohol into a reactor that is actually the still of a distillation column. The reactor is equipped with an efficient agitator and internal steam coils for heating. A stoichiometric excess of alcohol is normally utilized. A 1% solution of concentrated sulfuric acid is added as a catalyst. The reactor is heated to such a temperature that the azeotrope of water and alcohol distills at the column-head. The distillate is cooled and separated by decantation. The alcohol-rich layer is recycled to the column, while the water-rich layer is either wasted or sent to recovery. When the optimum amount of water has been removed from the reactor, the residual crude phthalate (still bottoms) is discharged to an alkali washer that neutralizes the sulfuric acid content with sodium carbonate. This neutralizing operation is followed by a water-washing operation. The crude phthalate is then stripped in a vacuum column to separate the volatile products such as olefins, alcohol, and other impurities. When economically feasible, the alcohol is recovered for reuse. The phthalate can be further purified by decolorizing with activated charcoal (Lowenheim and Moran, 1975; Sittig, 1967).

Manufacture of diethyl phthalate is normally done by batch esterification. Benzene is usually introduced into the reactor column to reduce the partial pressure of the alcohol; therefore, the distillate is a ternary mixture of water, alcohol, and benzene. The benzene is separated from the water-alcohol mixture by decantation. The benzene is recycled to the column; the alcohol and water are rectified to recover the alcohol for reuse (Lowenheim and Moran, 1975).

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 889,365 workers are potentially exposed to diethyl phthalate.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to diethyl phthalate were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute lethal and irritant effects of diethyl phthalate are summarized in Table 21. Pulmonary congestion, edema and petechial hemorrhages, lymphocyte fragmentation in the spleen, and renal tubular degeneration were observed in mice within 72 hours of injection of intraperitoneal median lethal doses of diethyl phthalate (Karel et al., 1947).

Intradermal injection of undiluted diethyl phthalate into mice (2.24 g/kg) produced irritation, but no histological damage to the peritoneal organs (Lawrence et al., 1975). Instillation of 0.1 ml undiluted diethyl phthalate (≈0.1 g) into the conjunctival sac of rabbits has been reported to cause mild irritation (Draize et al., 1944).

(2) Subchronic Exposures

Dietary administration of diethyl phthalate to rats at 5.0% levels for 16 weeks has been reported to increase liver and kidney weights in both sexes. Histologic examination demonstrated fatty degeneration and

Table 21. Acute Toxicity of Diethyl Phthalate

Route	Species	Dose (g/kg)	Response	Reference
oral	rats	9.68	LD50	Tyson, 1972
oral	rabbits	1.0	LD50	Fassett, 1967
i.p.[a]	mice	2.75	LD50	Karel et al., 1947
i.p.	mice	3.22	LD50	Lawrence et al., 1975
i.p.	mice	2.8	LD50	Calley et al., 1966
i.p.	rats	5.66	LD50	Singh et al., 1972
intradermal	mice	2.24	dermal irritation, but no visceral organ irritation	Lawrence et al., 1975
ocular	rabbits	0.1 ml undiluted (=0.1 g)	mild irritation	Draize et al., 1944
ocular	rabbits	not stated	no irritation	Lawrence et al., 1975

[a] i.p. = intraperitoneal

slight vacuolization of the liver, and pyelonephritis and lymphocytic infiltration of the kidney (Brown et al., 1978).

Repeated intraperitoneal injection (5 days/week for 14 weeks) of mice with diethyl phthalate resulted in a progressive decrease in observed LD50 values over this period (≈2-fold) (Lawrence et al., 1974). The authors suggest that this effect is related to cumulative toxicity of the compound; the diethyl ester shows a much smaller change in LD50 than that observed for either di-2-ethylhexyl or the di-n-octyl phthalates (Lawrence et al., 1975).

(3) Chronic Exposures

Oral administration of diethyl phthalate to rats at a level of 1250 mg/kg for 2 years has been reported to produce no significant toxic effects; a similar lack of toxicity was reported in a 1-year study with dogs maintained orally at 625 mg/kg levels of diethyl phthalate (Shibko and Blumenthal, 1973).

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

Diethyl phthalate has been reported to be mutagenic to S. typhimurium TA100 when tested without metabolic activation at a dose of 1000 µg/plate (Rubin et al., 1979), but testing in strain TA100 with activation at this dose and in other strains at lower doses was negative (Table 22). The compound was also negative in reverse mutation testing with E. coli (no activation) and in differential growth inhibition assays with wild and DNA repair-deficient strains of E. coli and B. subtilis. Addition of diethyl phthalate at concentrations up to 0.25 mg/ml to cultured Chinese Hamster cells did not produce an increase in chromosome gaps or breaks (Odashima and Ishidate, 1975).

Table 22. Mutagenicity of Diethyl Phthalate

Type of Assay	Organism	Strain	Activation	Dose	Result	Reference
Reverse Mutation	S. typhimurium	TA98	+	1000 µg/plate	-	Rubin et al., 1979
			-	1000 µg/plate	-	Rubin et al., 1979
		TA100	+	1000 µg/plate	-	Rubin et al., 1979
			-	1000 µg/plate	+	Rubin et al., 1979
	S. typhimurium	TA98	±	667 µg/plate	-	Florin et al., 1980
		TA100	±	667 µg/plate	-	Florin et al., 1980
		TA1535	±	667 µg/plate	-	Florin et al., 1980
		TA1537	±	667 µg/plate	-	Florin et al., 1980
	S. typhimurium	TA98	+	10 mg/plate	-	Kurata, 1975
		TA100	+	10 mg/plate	-	Kurata, 1975
	E. coli	wild	-	10 mg/plate	-	Kurata, 1975
		uvr A^-	-	10 mg/plate	-	Kurata, 1975
DNA damage/ repair	E. coli	uvr A^-	-	10 mg/plate	-	Kurata, 1975
		Pol A^-	-	10 mg/plate	-	Kurata, 1975
		rec A^-	-	10 mg/plate	-	Kurata, 1975
	B. subtilis	rec A^-	-	10 mg/plate	-	Kurata, 1975
Chromosome damage	Cultured Chinese Hamster fibroblasts	CHL	n.a.	0.25 mg/ml	-	Odashima and Ishidate, 1975

Diethyl phthalate has been scheduled for mutagenicity testing in Salmonella by the NTP (1980).

(6) Teratogenicity

Intraperitoneal injection of diethyl phthalate on days 5, 10, and 15 of gestation have produced teratogenic effects in rats at levels of 1,130 mg/kg and 560 mg/kg. Skeletal abnormalities such as elongated and fused ribs were observed. The lower dose of the compound also produced a significant increase in the number of fetal resorptions (Singh et al., 1972).

Diethyl phthalate produced a low incidence (1/10) of teratogenic effects in developing chick embryos following a single injection of 28 mg of compound into fertile eggs (Bower et al., 1970). The congenital defect observed involved malrotation of the left leg.

(7) Reproductive Effects

Oral intubation of diethyl phthalate into rats at a level of 1.6 g/kg/day for 4 days had no effect on testis weight, testis pathology or urinary excretion of zinc (Foster et al., 1980).

(8) Other Relevant Information

Distribution studies following the i.p injection of radiolabeled diethyl phthalate into pregnant rats have indicated that the compound passes across the placental barrier (Singh et al., 1975); the disappearance half-life for the compound was estimated to be 2.2 days.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

A preliminary report from Eastman Kodak, reported by ACGIH (1979), has indicated that 150 to 250 workers exposed to a mixture of

phthalates including diethyl phthalate at vapor levels of 1-5 ppm showed no phthalates in blood and no evidence of peripheral polyneuritis. Human exposure to heated vapors of the compound may produce some transient irritation of the nose and throat (ACGIH, 1979).

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

A carcinogenesis bioassay of diethyl phthalate has been started by the NTP (1981b), preclronic testing is currently in progress. The compound is being administered to rats and mice in the fee

16. Exposure Standards

The ACGIH (1981) currently recommends an 8-hour Time-Weighted Average (TWA) limit of 5 mg/m^3 for occupational exposure to diethyl phthalate; the recommended Short-Term Exposure Limit (STEL) is 10 mg/m^3.

17. Sources of Additional Relevant Information

Comprehensive reviews of phthalate esters have been completed by Peakall (1975), Daniel (1978), Lawrence (1978), Thomas et al. (1978), Lawrence and Tuell (1979), and the U.S. EPA (1980b).

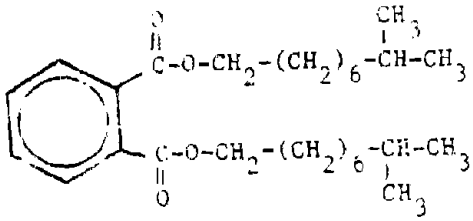
18. Other Pertinent Data

No other information that would aid in the assessment of diethyl phthalate as an occupational hazard was found in the literature searched.

F. DIISODECYL PHTHALATE

1. Chemical Name: Diisodecyl Phthalate

2. Chemical Structure:



3. Synonyms: 1,2-Benzenedicarboxylic acid, diisodecyl ester
Phthlaic acid, dissodecyl ester

4. Chemical Abstract Service (CAS) Number: 26761-40-0

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number: Not listed

6. Chemical and Physical Properties:

Description:	liquid
Molecular Weight:	446.7
Boiling Point:	255°C (5mm Hg)
Melting Point:	-48°C
Vapor Pressure:	<10 mmHg (25°C)
Solubility:	insoluble in water
Specific Gravity:	0.966^{25}
Stability:	combustible; Flash point 430°F

7. Production

Domestic production in recent years is as follows (USITC, 1980a, 1979a, 1978a, 1977a):

Year	Production (in million lbs)
1979	174.8
1978	170.8
1977	160.6
1976	143.1

Data available from the U.S. EPA (1980a) regarding producers of diisodecyl phthalate and production volumes are presented in Table 23.

8. Use

Diisodecyl phthalate is used as a plasticizer for films and calendered goods, building wires, appliance wires, and communication wire (Frey, 1976).

9. Manufacturers and Distributors

Commercial manufacturers include (SRI International, 1980; USITC, 1980a):

BASF Wyandotte	Kearny, NJ
Continental Oil Co.	Aberdeen, MS
Exxon Corp.	Baton Rouge, LA
Hatco Chem.	Fords, NJ
Reichhold Chem.	Carteret, NJ
Teknor Apex Co.	Hebronville, MA
Tenneco Chem.	Chestertown, MD
US Steel Corp.	Neville Island, PA

Also see Table 23.

Other distributors include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem. Sources--USA, 1980):

American Can (Inolex)	Americhem.
Alltech Assoc.	Ashland Chem.
Chem Services	CRL Chem.
ICN/K and K	MCB Reagents
Pfaltz and Bauer	Pfizer
Pioneer Salt and Chem.	Polysciences
PVO International	Rohm and Haas

10. Manufacturing Processes

Diisodecyl phthalate is made by the esterification reaction of phthalic anhydride with isodecyl alcohol. Appendix B outlines the general manufacturing operations.

11. Impurities or Additives

No data available from the literature searched.

Table 23. Producers of Diisodecyl Phthalate and Production Ranges (U.S. EPA, 1980a)

Producers	Type of Production	1977 Production Range
Continental Oil Co. Aberdeen, MS	Manufacturer	1 to 10 million lb
C.P. Hall Co. Chicago, IL	Manufacturer	under 1000 lb
Hatco Chemical Fords, NJ	Manufacturer	confidential
Haywood Co. Brownsville, TN	Manufacturer	0.1 - 1.0 million lb
Reichhold Chemical Carteret, NJ	Manufacturer	none
Teknon Apex Co. Atterbow, MA	Manufacturer	1 to 10 million lb
Tenneco Chem Chestertown, MD	Manufacturer	10 to 50 million lb
U.S. Steel Corp. Pittsburg, PA	Manufacturer	10 to 50 million lb

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 40,164 workers are potentially exposed to diisodecyl phthalate.

13. Control Technology

Specific factors that may contribute to or prevent employee exposure to diisodecyl phthalte were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute lethal and irritant effects of diisodecyl phthalate are summarized in Table 24. As indicated, the available data indicates that this phthalate is not highly toxic.

Intradermal injection of undiluted diisodecyl phthalate (concentration not stated) into mice was non-irritating to the skin, and did not cause histologic damage to the peritoneal organs (Lawrence et al., 1975). Instillation of undiluted compound (volume not stated) into the eyes of rabbits did not result in grossly observable irritation.

(2) Subchronic Exposures

A 14-week feeding study with rats and dogs established a no-effect level of 0.1 g/kg of body weight for both species (Dewey and Alma, 1968). Livers were markedly heavier than those of controls in rats maintained on 1% diets, but no histological changes were observed. A slightly elevated liver/body weight ratio was noted in dogs fed a similar concentration of diisodecyl phthalate, but pathological examination of the livers revealed swollen and vacuolated hepatocytes. Additional details on the experimental design of this study and results were not available for review.

Table 24. Acute Toxicity of Diisodecyl Phthalate

Route	Species	Dose (g/kg)	Response	Reference
oral	rat	29	All survived	Younger, 1961
oral[a]	rat	>6.2	LD50	Smyth et al., 1962
oral	rat	64	LD50	Shibko and Blumenthal, 1973
oral	rabbit	21.7	minimum lethal dose	Younger, 1961
i.p.[b]	mouse	>100	LD50	Lawrence et al., 1975
intradermal	mouse	undiluted, volume not stated	no dermal or visceral organ irritation	Lawrence et al., 1975
ocular	rabbit	undiluted, volume not stated	no irritation	Lawrence et al., 1975

[a] di-(decyl)ester tested; isomer not stated

[b] i.p. = intraperitoneal

(3) Chronic exposure

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

Diisodecyl phthalate did not inhibit the growth of DNA-repair deficient strains of B. subtilis and E. coli, and did not induce reverse mutations in S. typhimurium or E. coli (Table 25).

(6) Teratogenicity

Injection of 0.05 ml undiluted diisodecyl phthalate (0.048 g) into the yolk sacs of 3-day old developing chicken eggs resulted in marked embryolethality (63%), but no evidence of gross malformations (Lee et al., 1974). Teratogenic effects were observed, however, following injection of 0.05 ml chick Ringer's solution that was saturated with diisodecyl phthlate; twisting or "clubbing" of one or both feet and neuromusculur disorders were the commonest abnormalities observed in hatched chicks.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

Table 25. Mutagenic Activity of Diisodecyl Phthalate

Type of Assay	Organism	Strain	Activation	Dose	Result	Reference
Reverse Mutation	S. typhimurium	TA 100	yes	10 mg/plate	-	Kurata, 1975
	S. typhimurium	TA 98	yes	10 mg/plate	-	Kurata, 1975
	E. coli	wild	no	10 mg/plate	-	Kurata, 1975
	E. coli	uvr A^-	no	10 mg/plate	-	Kurata, 1975
DNA damage/ repair	B. subtilis	rec A^-	no	10 mg/plate	-	Kurata, 1975
	E. coli	uvr A^-	no	10 mg/plate	-	Kurata, 1975
	E. coli	Pol A^-	no	10 mg/plate	-	Kurata, 1975
	E. coli	rec A^-	no	10 mg/plate	-	Kurata, 1975

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No information was found in the literature searched.

16. Exposure Standards

No information was found in the literature searched.

17. Sources of Additional Relevant Information

Comprehensive reviews of phthalate esters have been completed by Peakall (1975), Daniel (1978), Lawrence (1978), Thomas et al. (1978), Lawrence and Tuell (1979), and the U.S. EPA (1980b).

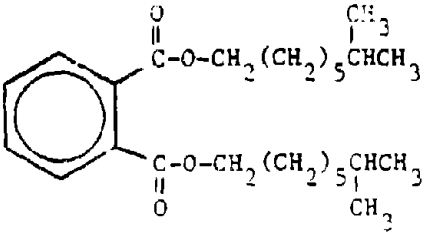
18. Other Pertinent Data

No information was found in the literature searched.

G. DIISONONYL PHTHALATE

1. Chemical Name: Diisononyl Phthalate

2. Chemical Structure:



3. Synonyms: 1,2 - Benzenedicarboxylic acid, diisononyl ester
   Phthalic acid, diisononyl ester

4. Chemical Abstract Service (CAS) Number: 28553-12-0

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

6. Chemical and Physical Properties:

Description:	---
Molecular Weight:	418.6
Boiling Point:	---
Melting Point:	---
Vapor Pressure:	---
Solubility	---
Specific Gravity:	---
Stability:	combustible

7. Production

Production of diisononyl phthalate in 1974 was about 100 million pounds (Frey, 1976).

Production ranges are not available from the U.S. EPA (1980).

In 1976, 3.3 million pounds were imported (USITC, 1977b).

8. Use

Diisononyl phthalate is used as a general-purpose plasticizer (Inchalik and Rubin, 1975).

It has a minor use as a dielectric fluid in capacitors as a replacement for PCB's (Versar, 1976).

9. Manufacturers and Distributors

Commercial manufacturers include (SRI International, 1980; USI[illegible] 1980a):

Exxon Corp.	Baton Rouge, LA
U.S. Steel Corp.	Neville Island, PA

Distributors include (1980-81 OPD Chemical Buyers' Directory, 1980; Chem Sources-[illegible] 1980):

Ashland Chemical
[illegible] Services

10. Manufacturing Processes

Diisononyl phthalate is made by the esterification reaction of phthalic anhydride with isononyl alcohol. Appendix B outlines the general manufacturing operations.

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 15,022 workers are potentially exposed to diisononyl phthalate.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to diisononyl phthalate were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

An oral LD50 of >10 g/kg has been reported for rats (Livingston, 1971). The only symptom noted following administration of single oral doses of 5 or 10 g/kg to rats was oily fur.

(2) Subchronic Exposures

Oral administration of 500 mg/kg/day diisononyl phthalate for 13 weeks caused an increase in liver weights and a slight loss in body weight gain in rats of both sexes (Livingston, 1971). Doses of 50 mg/kg/day or 150 mg/kg/day were apparently without effect.

Increased liver weights, decreased body weights, and histologic changes in the liver, gall bladder, spleen and kidney were induced in 4 dogs by the dietary administration of diisononyl phthalate (Livingston, 1971). In this experiment, 2% levels of the compound were fed for 8 weeks; the dose was subsequently increased to 4% for 9 to 13 weeks. Administration of 0.5% diisonoyl phthalate in the diet for 13 weeks caused a liver weight increase, but 0.125% of the compound had no observable toxic effect.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of diisononyl phthalate were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for diisononyl phthalate were found.

17. Sources of Additional Relevant Information

Comprehensive reviews of phthalate esters have been completed by Peakall (1975), Daniel (1978), Lawrence (1978), Thomas et al. (1978), Lawrence and Tuell (1979), and the U.S. EPA (1980b).

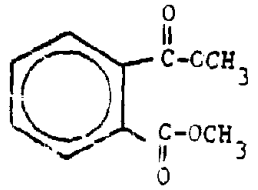
18. Other Pertinent Data

No other information that would aid in the assessment of diisononyl phthalate as an occupational hazard was found in the literature searched.

H. DIMETHYL PHTHALATE

1. Chemical Name: Dimethyl Phthalate

2. Chemical Structure:



3. Synonyms: Avolin
1,2-Benzene dicarboxylic acid, dimethyl ester
Dimethyl 1,2-benzene dicarboxylate
Dimethyl benzene orthodicarboxylate
DMP
Methyl phthalate
Phthalic acid, methyl ester

4. Chemical Abstracts Service (CAS) Number: 131-11-3

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number: TI1575000

6. Chemical and Physical Properties:

Description:	colorless, odorless liquid
Molecular Weight:	194.18
Boiling Point:	282°C
Melting Point:	0°C-5.5°C
Vapor Pressure:	<0.01 mm Hg (20°C); 1mm Hg (100.3°C)
Solubility:	0.5 g/100 ml water (20°C); miscible with alcohol, ether, chloroform; practically insoluble in petroleum ether and paraffin hydrocarbons
Specific Gravity:	1.192
Stability:	combustible; Autoignition temperature: 1032°F, Flash point: 300°F

7. Production

Recent production figures for dimethyl phthalate are as follows (USTIC, 1980a, 1979a, 1978a, 1977a):

Year	Production (in millions of pounds)
1979	10.5
1978	9.6
1977	9.9
1976	8.8

Data available from the U.S. EPA (1980a) regarding producers in dimethyl phthalate and production volumes are presented in Table 26.

8. Use

The major use of dimethyl phthalate is as a plasticizer; in this application, it is used almost entirely for cellulose ester plastics (Frey, 1976). Dimethyl phthalate is a commercially used dye carrier (Wannemacher and DeMaria, 1979).

Dimethyl phthalate is also used in relatively small amounts as an insect repellent. It is effective as a fly repellent for horses and cows and as a biting-insect repellent for humans; it can be incorporated into creams or combined with other chemicals for military use (Spencer, 1968; Meister, 1976). Other minor uses of dimethyl phthalate include solid rocket propellents, lacquers, coating agents for polyvinylidene fluoride polymers, safety glass, molding powders, and perfumery (Hawley, 1977; The Merck Index, 1976; Barnhart and Hall, 1966).

9. Manufacturers and Distributors

Dimethyl phthalate is manufactured by the following companies (SRI International, 1980):

Eastman Kodak (Tennessee Eastman)	Kingsport, TN
Kay-Fries Inc.	Stony Point, NY
Monsanto	St. Louis, MO
Pfizer	Greensboro, NC
Sybron (Tanatex)	Lyndhurst, NJ

Table 26. Producers of Dimethyl Phthalate and Production Ranges (U.S. EPA, 1980a)

Producer	Type of Production	1977 Production Range
Carroll Products Wood River Junction, RI	Importer	none
A. Campbell and Co. Cleveland, OH	Importer	confidential
Dragco Inc. Totowa, NJ	Importer	under 1000 lb
GAF Corp. Rensselaer, NY	Manufacturer	none
Kay-Fries Chemicals Stony Point, NY	Manufacturer	confidential
D.H. Litter and Co. New York, NY	Importer	1 to 10 thousand lb
Monsanto Co. St. Louis, MO	Manufacturer	1 to 10 million lb
Pfizer Inc. Greensboro, NC	Manufacturer	0.1 to 1.0 million lb
Soltex Polymer Corp. Deer Park, TX	Importer	under 1000 lb
Sybron Corp. Lyndhurst, NJ	Manufacturer	0.1 to 1.0 million lb
Synarome Corp. New York, NY	Importer	under 1000 lb
Tennessee Eastman Kingsport, TN	Manufacturer	1 to 10 million lb

The distributors of dimethyl phthalate include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chemical Sources--USA, 1980):

Alfa Prod.	Fallek Chem.
Aldrich Chem.	Fisher Sci.
Anachemia Chem.	GRL Chem.
Ashland Chem.	Gallard-Schelsinger
Atomergic Chemetals	Haarmann and Reimer Corp.
J&T& Baker Chem.	LaChat Chem.
Bentley Chem.	LaPine Sci.
Bio-Clinical Lab.	Lux Chem.
Carroll Products	Mallinchrodt
Chem. Services	MCB Reagents
CPS Chem.	Pfaltz and Bauer
Crest Chem.	Pioneer Salt and Chem.
Davos Chem.	Polysciences
EM Lab	Solchem Inc.
Electron Microscopy Sci. Star,	Milton M. Chem.
	Tridom Chem.

10. Manufacturing Processes

The dialkyl phthalates, including dimethyl phthalate, are produced by esterifying phthalic anhydride with the appropriate alcohols in the presence of catalytic amounts of sulfuric acid. The process is essentially the same for all the lower aliphatic alcohols, and modifications are necessary only in the alcohol-recovery and product-purification systems (Lowenheim and Moran, 1975). In the case of dimethyl phthalate, the esterification is done with phthalic anhydride and methyl alcohol.

Appendix B diagrams the typical process by which all commercial dialkyl phthalates are made. Plants are designed to allow any of the phthalate esters to be made in the same equipment, giving flexibility to production. While many plants produce phthalates by batch methods, other newer plants operate continuously and are highly automated (Lowenheim and Moran, 1975).

The production process begins by charging phthalic anhydride and the appropriate alcohol into a reactor that is actually the still of a distillation

column. The reactor is equipped with with an efficient agitator and internal steam coils for heating. A stoichiometric excess of alcohol is normally utilized. A 1% solution of concentrated sulfuric acid is added as a catalyst. The reactor is heated to such a temperature that the azeotrope of water and alcohol distills at the column-head. The distillate is cooled and separated by decantation. The alcohol-rich layer is recycled to the column, while the water-rich layer is either wasted or sent to recovery. When the optimum amount of water has been removed from the reactor, the residual crude phthalate (still bottoms) is discharged to an alkali washer that neutralizes the sulfuric acid content with sodium carbonate. This neutralizing operation is followed by a water-washing operation. The crude phthalate is then stripped in a vacuum column to separate the volatile products such as olefins, alcohol, and other impurities. When economically feasible, the alcohol is recovered for reuse. The phthalate can be further purified by decolorizing with activated charcoal (Lowenheim and Moran, 1975; Sittig, 1967).

Manufacture of dimethyl phthalate is usually done by batch esterification. Benzene is usually introduced into the reactor column to reduce the partial pressure of the alcohol; therefore, the distillate is a ternary mixture of water, alcohol, and benzene; the benzene is separated from the water-alcohol mixture by decantation. The benzene is recycled to the column, while the alcohol and water are rectified to recover the alcohol for reuse. (Lowenheim and Moran, 1975).

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 53,096 workers are potentially exposed to dimethyl phthalate.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to dimethyl phthalate were not found in the literature searched.

14. Biological Effects

A. Animal Studies

1. Acute Exposures

The acute lethal and irritant effects of dimethyl phthalate are summarized in Table 27. Pulmonary congestion and atelectasis, lymphocyte fragmentation in the spleen and lymph nodes, and renal tubular necrosis were observed in mice within 72 hours of injection of i.p. median lethal doses of dimethyl phthalate (Karel et al., 1947).

Intradermal injection of undiluted dimethyl phthalate produced irritation, but no histological damage to the peritoneal organs (Lawrence et al., 1975). When 0.1 ml (Draize et al., 1944) or 0.5 ml (Carpenter and Smyth, 1946) undiluted dimethyl phthalate (=0.12 and 0.6 g, respectively) was instilled into conjunctival sacs of rabbits, mild irritation was observed.

2. Subchronic Exposure

Repeated intraperitoneal injection (5 days/week for 18 weeks) with dimethyl phthalate produced a progressive decrease in the calculated LD50 value in mice (Lawrence et al., 1974); the authors suggested that this represents a cumulative effect. The nearly 3-fold change in the LD50 value is smaller than that observed for di-2-ethylhexyl phthalate (Lawrence et al., 1974).

A Russian report has indicated that daily inhalation (5 hrs/day) of dimethyl phthalate at levels of 0.5 and 2.0 mg/m^3 (=0.06 and 0.25 ppm, respectively) produced nervous system effects, liver effects, and blood changes in unspecified experimental animals (Timofievskaya and Aldyrwa, 1972).

Table 27. Acute Lethal and Irritant Effects of Dimethyl Phthalate

Route	Species	Dose (g/kg)	Response	Reference
oral	rats	≈2.86	LD50	Hodge et al., 1942
oral	rats	8.22	LD50	Draize et al., 1948
oral	mice	8.58	LD50	Draize et al., 1948
oral	guinea pigs	2.86	LD50	Draize et al., 1948
oral	rabbits	5.25	LD50	Draize et al., 1948
i.p.[a]	rats	4.02	LD50	Singh et al., 1972
i.p.	mice	3.6	LD50	Karel et al., 1947
i.p.	mice	1.58	LD50	Calley et al., 1966
i.p.	mice	3.98	LD50	Lawrence et al., 1975
intradermal	mice	not stated	skin irritation but no visceral organ irritation	Lawrence et al., 1975
dermal	rabbits	11.9	LD50	Draize et al., 1948
ocular	rabbits	0.1 ml undiluted (0.12 g)	mild irritation	Draize et al., 1944
ocular	rabbits	0.5 ml undiluted (0.6 g)	mild irritation	Carpenter and Smyth, 1946
ocular	rabbits	not stated	no irritation	Lawrence et al., 1975

Daily application of 4.0 ml/kg (=4.8 g/kg) dimethyl phthalate to the clipped intact skin of rabbits for 90 days has been reported in a brief summary to cause pulmonary edema and slight kidney damage, but not dermatitis (Draize et al., 1948).

(3) Chronic Exposures

Two-year feeding studies with 8% dimethyl phthalate in the diet produced significant kidney damage in rats. Administration of the compound at 4% dietary levels produced a slight reduction in growth, while 2% levels of compound did not result in overt toxicity (Autian, 1973). Oral administration of 1000 mg/kg/day for 103 weeks has been reported to produce no significant toxic effects in rats (Lehman, 1955).

Based on 2-year feeding studies in rats, the FDA has estimated a no-effect level of 1000 mg/kg/day for dimethyl phthalate in rats (Shibko and Blumenthal, 1973).

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

Rubin et al. (1979) have reported that dimethyl 100, without metabolic activation, at levels up to 1000 µg/plate; testing in strain TA 100 with activation and in strain TA 98 with or without activation was negative.

It was noted in a Russian abstract (Yurchenko, 1977) that repeated application of dimethyl phthalate to rat skin produced mutag nic effects in hepatocytes, but no other details of this study were provided.

(6) Teratogenicity

Intraperitoneal injection of pregnant rats on days 5, 10, and 15 of gestation with dimethyl phthalate at 400 to 1300 mg/kg levels has been reported to produce teratogenic effects. Congenital anomalies included missing tails, missing eyes, and skeletal abnormalities (fused ribs, incomplete ribs, and incomplete skulls). At the lowest and highest doses of the compound embryotoxic effects were also noted (Singh et al., 1972). A slight effect on implantation was observed in rats following intraperitoneal injections of 600 to 2400 mg/kg of compound on days 3, 6, and 9 of gestation (Peters and Cook, 1973).

Injection of 0.05 ml (=0.06 g) dimethyl phthalate into the yolk sacs of 3-day old developing chick eggs resulted in marked embryolethality (69%), but no evidence of gross malformations (Lee et al., 1974). Teratogenic effects were observed, however, following injection of 0.05 ml chick Ringer's Solution that was saturated with dimethyl phthalate; twisting or "clubbing" of one or both feet and neuromuscular disorders were the commonest abnormalities observed in hatched chicks.

(7) Reproductive Effects

Oral intubation of dimethyl phthalate into rats at a level of 1.6 g/kg/day for 4 days had no effect on testis weight, testis pathology or urinary excretion of zinc (Foster et al., 1980).

(8) Other Relevant Information

Following oral administration of dimethyl phthalate to rats, significant amounts of unchanged compound were detected in the urine (Albro and Moore, 1974).

b. Human Studies

(1) Pharmacokinetics

A Russian abstract has indicated that following dermal application of dimethyl phthalate to human volunteers, the compound was absorbed and then rapidly eliminated from the body (Gleiberman et al., 1978).

(2) Health Effects

Repeated inhalation of the vapor of dimethyl phthalate may cause irritation of the nasal mucous membrane and upper respiratory tract. Prolonged inhalation may lead to central nervous system depression and eventual paralysis (Autian, 1973). The compound does not exist in the vapor state, however, unless heat is applied (ACGIH, 1979).

Use of the compound dermally as an insect repellent has not been reported to produce skin irritation or sensitization; some skin absorption may occur (ACGIH, 1979).

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of dimethyl phthalate were found.

16. Exposure Standards

The ACGIH (1981) currently recommends and OSHA (1976) has promulgated a Time-Weighted Average (TWA) exposure limit of 5 mg/m^3 for occupational exposure to dimethyl phthalate; a Short-Term Exposure Limit (STEL) of 10 mg/m^3 has also been recommended by the ACGIH.

17. Sources of Additional Relevant Information

Comprehensive reviews of phthalate esters have been completed by Peakall (1975), Daniel (1978), Lawrence (1978), Thomas et al. (1978), Lawrence and Tuell (1979), and the U.S. EPA (1980b).

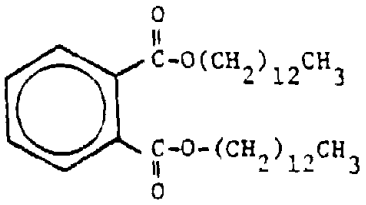
18. Other Pertinent Data

No other information that would aid in the assessment of dimethyl phthalate as an occupational hazard was found in the literature searched.

I. DITRIDECYL PHTHALATE

1. Chemical Name: Ditridecyl Phthalate

2. Chemical Structure:



3. Synonyms: 1,2-Benzenedicarboxylic acid, ditridecyl ester
DTDP
Phthalic acid, ditridecyl ester
Polycizer 962-BPA
Staflex DTDP
1-Tridecanol, phthalate
Truflex DTDP

4. Chemical Abstract Service (CAS) Number: 119-06-2

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number: TI1950000

6. Chemical and Physical Properties:

Description:	liquid
Molecular Weight:	530.92
Boiling Point:	>285°C at 5 mm Hg
Melting Point:	-37°C (pour point)
Vapor Pressure:	---
Solubility:	---
Specific Gravity:	0.951^{20}_{20}
Stability:	combustible; Flash point: 460°F

7. Production

Production in recent years is as follows (USITC, 1980a, 1978a, 1977a):

Year	Production (in Million Pounds)
1979	27.4
1978	---
1977	23.3
1976	10.5

Data available from the U.S. EPA (1980a) regarding producers of ditridecyl phthalate and production volumes are presented in Table 28.

8. Use

Ditridecyl is used as a plasticizer in high-temperature wire and cable (Inchalik and Rubin, 1975; Frey, 1976).

9. Manufacturers and Distributors

Commercial manufacturers include (SRI International, 1980; USITC, 1980a):

Exxon Corp.	Baton Rouge, LA
Hatco Chemical	Fords, NJ
Reichhold Chem.	Carteret, NJ
Teknor Apex Co.	Hebronville, MA
Tenneco Chemical	Chestertown, MD
U.S. Steel Corp.	Neville Island, PA

Other distributors include (Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Ashland Chem.
Chem Services
The C.P. Hall Co.
Hooker Chemical, Ruco Div.
Polysciences
Union Chem.

10. Manufacturing Process:

Ditridecyl phthalate is made by the esterification reaction of pthalic anhydride and ditridecyl alcohol. Appendix B outlines the general manufacturing operations.

11. Impurities or Additives

No information was found in the literature searched.

Table 28. Producers of Ditridecyl Phthalate and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Diamond Shamrock Cleveland, OH	Importer	none
Finetex Inc. Elmwood Park, NJ	Manufacturer	confidential
Hatco Chemical Fords, NJ	Manufacturer	confidential
Haywood Co. Brownsville, TN	Manufacturer	0.1 to 1.0 million lb
Mobil Chemical Edison, NJ	Manufacturer	10 to 100 thousand lb
Reichhold Chemical Carteret, NJ	Manufacturer	0.1 to 1.0 million lb
Teknon Apex Co. Atterbow, MA	Manufacturer	0.1 to 1.0 million lb
Tenneco Chemical Chestertown, MD	Manufacturer	1 to 10 million lb
U.S. Steel Corp. Pittsburg, PA	Manufacturer	1 to 10 million lb

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 25,215 workers are potentially exposed to ditridecyl phthalate.

13. Control Technonology

Specific factors that may contribute to or prevent employee exposure to ditridecyl phthalate were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The only toxicity information for ditridecyl phthalate that was found in the literature searched was reported by Smyth et al. (1962). This data is summarized in Table 29.

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

Table 29. Acute Lethal and Irritant Effects of Ditridecyl Phthalate

Route	Species	Dose (g/kg)	Response	Reference
oral	rat	>60.9	LD50	Smyth et al., 1962
dermal	rabbit	>19	LD50	Smyth et al., 1962
dermal	rabbit	0.01 ml, uncovered (≈0.01 g)	slight irritation	Smyth et al., 1962
ocular	rabbit	0.5 ml (0.48 g)	mild corneal necrosis	Smyth et al., 1962

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of ditridecyl phthalate were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for ditridecyl phthalate were found.

17. Sources of Additional Relevant Information

Comprehensive reviews of phthalate esters have been completed by Peakall (1975), Daniel (1978), Lawrence (1978), Thomas et al. (1978), Lawrence and Tuell (1979), and the U.S. EPA (1980b).

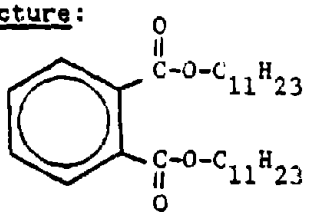
18. Other Pertinent Data

No other information that would aid in the assessment of ditridecyl phthalate as an occupational hazard was found in the literature searched.

J. DIUNDECYL PHTHALATE

1. Chemical Name: Diundecyl Phthalate

2. Chemical Structure:



3. Synonyms: 1,2-Benzene dicarboxylic acid, diundecyl ester
Phthalic acid, diundecyl ester
Santicizer 711

4. Chemical Abstract Service (CAS) Number: 3648-20-2

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number: TI1980000

6. Chemical and Physical Properties:

Description:	---
Molecular Weight:	424.3
Boiling Point:	---
Melting Point:	---
Vapor Pressure:	---
Solubility:	---
Specific Gravity:	---
Stability:	combustible

7. Production

Data available from the U.S. EPA (1980a) regarding producers of diundecyl phthalate and production volumes are presented below:

Monsanto Co. (Texas City, TX)
Manufacturer
1977 Production: 10 to 50 million lbs.

Tenneco Chem Inc. (Chestertown, MD)
Manufacturer
1977 Production: under 1000 lbs.

8. Use

Diundecyl phthalate is used as a plasticizer in high-temperature wire and cable (Inchalik and Rubin, 1975).

9. Manufacturers and Distributors

The manufacturers are listed above in the production section.

Chem Services is a distributor (Chem Sources--USA, 1980).

10. Manufacturing Processes

Diundecyl phthalate is made by the esterification reaction of phthalic anhydride and diundecyl alcohol. Appendix B outlines the general manufacturing operations.

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 5,214 workers are potentially exposed to diundecyl phthalate.

13. Control Technology

Specific factors that may contribute to or prevent employee exposure to diundecyl phthalate were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute lethal and irritant effects of diundecyl phthalate are summarized in Table 30.

Monsanto (1975) exposed male rats to an atmosphere that was nearly saturated with diundecyl phthalate vapor heated to 149°C (nominal vapor concentration of 1.85 mg/l (≈107 ppm). After 4 hours the animals appeared slightly lethargic, but all rats survived a 6 hour exposure and a subsequent 10 day observation period.

Table 30. Acute Lethal and Irritant Effects of Diundecyl Phthalate

Route	Species	Dose (g/kg)	Response	Reference
oral	rats	15.8	not lethal	Monsanto, 1975
inhalation	rats	1.85 mg/l (≈107 ppm) 6 hours	no observable effects except lethargy after 4 hours	Monsanto, 1975
i.p.	mice	2.1	0/3 died	Nematollahi, et al., 1967
i.p.	mice	>100	LD50	Lawrence et al., 1975
intradermal	mice	undiluted, volume not stated	no dermal or visceral organ irritation	Lawrence et al., 1975
dermal	rabbits	7.9	not lethal	Monsanto, 1975
ocular	rabbits	undiluted, volume not stated	slight irritation (see text)	Monsanto, 1975
ocular	rabbits	undiluted, volume not stated	no irritation	Lawrence et al., 1975

Intradermal injection of undiluted diundecyl phthalate (volume not stated) into mice was non-irritating to the skin and did not cause histologic damage to the peritoneal organs (Lawrence et al., 1975).

Instillation of undiluted diundecyl phthalate into the conjunctival sacs of rabbits was reported by one source (Monsanto, 1975) to cause a slight degree of irritation 1 hour after treatment (maximum score of 4.0 on a scale of 110.0), but all eyes regained a normal appearance 48 hours after dosing. Lawrence et al. (1975) found that instillation of undiluted compound into the eyes of rabbits did not result in grossly observable irritation.

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

No information was found in the literature searched.

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of diundecyl phthalate were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for diundecyl phthalate were found.

17. Sources of Additional Relevant Information

Comprehensive reviews of phthalate esters have been completed by Peakall (1975), Daniel (1978), Lawrence (1978), Thomas et al. (1978), Lawrence and Tuell (1979), and the U.S. EPA (1980b).

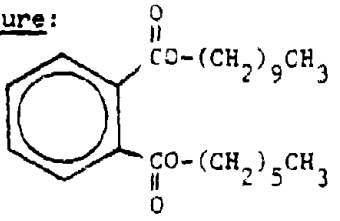
18. Other Pertinent Data

No other information that would aid in the assessment of diundecyl phthalate as an occupational hazard was found in the literature searched.

K. N-HEXYL N-DECYL PHTHALATE

1. Chemical Name: n-Hexyl n-Decyl Phthalate

2. Chemical Structure:



3. Synonyms: 1,2-Benzenedicarboxylic acid, decyl hexyl ester
Phthalic acid, n-hexyl n-decyl ester

4. Chemical Abstract Service (CAS) Number: 25724-58-7

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

TI0545000

6. Chemical and Physical Properties:

Description:	---
Molecular Weight:	366.60
Boiling Point:	---
Melting Point:	---
Vapor Pressure:	---
Solubility:	---
Specific Gravity:	---
Stability:	combustible

7. Production

Production in recent years is as follows (USITC, 1979a, 1978a, 1977a):

Year	Production (in million pounds)
1978	15.6
1977	15.2
1976	19.8

Data available from the U.S. EPA (1980a) regarding producers of n-hexyl n-decyl phthalate and production volumes are presented in Table 31.

Table 31. Producers of n-Hexyl n-Decyl Phthalate and Production Ranges (U.S. EPA, 1980a)

Producer	Type of Production	1977 Production Range
Monsanto Co. Texas City, TX	Manufacturer	none
Reichhold Chemical Carteret, NJ	Manufacturer	none
Tenneco Chemical Chestertown, MD	Manufacturer	under 1000 lb
U.S. Steel Corp. Pittsburgh, PA	Manufacturer	10 to 50 million lb

8. Use

n-Hexyl n-decyl phthalate is used as a plasticizer. Specific applications were not encountered.

9. Manufacturers and Distributors

In addition to the manufacturers listed by the U.S. EPA (1980) in Table 31, USITC (1980a) lists Continental Oil Co. and Teknor Apex Co. as manufacturers.

Chem Services is a distributor (Chem Sources--USA, 1980).

10. Manufacturing Processes

n-Hexyl n-decyl phthalate is made by the esterification reactions of phthalic anhydride with n-hexyl alcohol and n-decyl alcohol. Appendix B describes the general manufacturing operations for dialkyl phthalates; the operations for n-hexyl n-decyl phthalate may require an extra step as the phthalic anhydride is first reacted with only one alcohol and then the other.

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to n-hexyl n-decyl phthalate.

13. Control Technology

Specific factors that may contribute to or prevent employee exposure to n-hexyl n-decyl phthalate were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The only toxicity information for n-hexyl n-decyl phthalate that was found in the literature searched was reported by Smyth et al. (1969). This data is summarized in Table 32.

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

No information was found in the literature searched.

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

Table 32. Acute Lethal and Irritant Effects of n-Hexyl n-Decyl Phthalate

Route	Species	Dose	Response	Reference
oral	rat	49.4 ml/kg	LD50	Smyth et al., 1969
inhalation	rat	concentrated vapor x 8 hrs	maximum time for no death	Smyth et al., 1969
dermal	rabbit	>20 ml/kg	LD50	Smyth et al., 1969
dermal	rabbit	0.01 ml, uncovered	slight irritation	Smyth et al., 1969
ocular	rabbit	0.5 ml	slight corneal necrosis	Smyth et al., 1969

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of n-hexyl n-decyl phthalate were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for n-hexyl n-decyl phthalate were found.

17. Sources of Additional Relevant Information

Comprehensive reviews of phthalate esters have been completed by Peakall (1975), Daniel (1978), Lawrence (1978), Thomas et al. (1978), Lawrence and Tuell (1979), and the U.S. EPA (1980b).

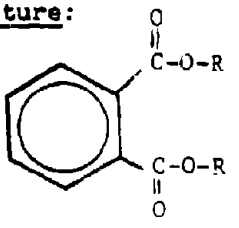
18. Other Pertinent Data

No other information that would aid in the assessment of n-hexyl n-decyl phthalate as an occupational hazard was found in the literature searched.

L. MIXED DIALKYL (C_7 to C_{11}) PHTHALATES

1. Chemical Name: Mixed Dialkyl (C_7 to C_{11}) Phthalates

2. Chemical Structure:



where R varies from C_7H_{15} through $C_{11}H_{23}$

3. Synonyms: Phthalic acid, dialkyl esters

4. Chemical Abstract Service (CAS) Number:

Dialkyl phthalate esters C_7-C_9: 68515-41-3
Dialkyl phthalate esters C_7-C_{11}: 68515-42-4
Dialkyl phthalate esters C_9-C_{11}: 68515-43-5
Dialkyl phthalate esters C_7: 68515-44-6
Dialkyl phthalate esters C_9: 68515-45-7

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Not listed

6. Chemical and Physical Properties:

Description:	---
Molecular Weight:	variable
Boiling Point:	---
Melting Point:	---
Vapor Pressure:	---
Solubility:	---
Specific Gravity:	---
Stability:	combustible

7. Production

Data available from the U.S. EPA (1980a) regarding producers of mixed dialkyl phthalates and production volumes are presented in Table 33.

In 1977, an estimated 330 million pounds of mixed linear phthalates based on C_7-C_{11} and C_6-C_{10} alcohols were manufactured (Frey, 1976).

Table 33. Producers of Mixed Dialkyl Phthalates and Production Ranges (U.S. EPA, 1980a)

Producer	Type of Production	1977 Production Range
Monsanto Co. Texas City, TX	Manufacturer	for CAS No. 68515-41-3 50 to 100 million lb
Monsanto Co. Texas City, TX	Manufacturer	for CAS No. 68515-42-4 50 to 100 million lb
Monsanto Co. Texas City, TX	Manufacturer	for CAS No. 68515-43-5 10 to 50 million lb
Monsanto Co. Texas City, TX	Manufacturer	for CAS No. 68515-44-6 10 to 50 million lb
Monsanto Co. Texas City, TX	Manufacturer	for CAS No. 68515-45-7 10 to 50 million lb

8. Use

Mixed dialkyl phthalates are heavily used as plasticizers for automotive vinyls. They are also used for other calendered and extruded products and are widely used in dispersion coatings (Frey, 1976).

9. Manufacturers and Distributors

From Table 33, Monsanto can be identified as the primary commercial manufacturer. Monsanto's product is mainly based on C_7, C_9, and C_{11} alcohols. Continental Oil Co. also makes mixed dialkyl phthalates, but from C_6, C_8, and C_{10} alcohols (Frey, 1976).

10. Manufacturing Processes

Mixed dialkyl phthalates are made by the esterification reaction of phthalic anhydride with a proprietary mixture of C_7 to C_{11} or C_6 to C_{10} alcohols. Appendix B outlines the general manufacturing operations.

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to mixed dialkyl (C_7-C_{11}) phthalate.

13. Control Technology

Specific factors that may contribute to or prevent employee exposure to mixed dialkyl phthalates were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute lethal and irritant effects of mixed dialkyl (C_7 to C_{11}) phthalates are summarized in Table 34. These phthalate mixtures have a

Table 34. Acute Lethal and Irritant Effects of Mixed Dialkyl (C_7 - C_{11}) Phthalates[a]

Mixture	Route	Species	Dose	Response	Reference
C_7-C_9	oral	rat	>70-80 ml/kg	LD50	Elizarova, 1961
C_7-C_9	oral	rat	20 g/kg	no deaths	Gaunt et al., 1968
C_7-C_9	oral	rat	19.3 g/kg	no deaths	Brown et al., 1970
C_7-C_9	oral	mouse	>44 ml/kg	LD50	Elizarova, 1961
C_7-C_9	oral	mouse	20 g/kg	no deaths	Gaunt et al., 1968
C_7-C_9	oral	mouse	19.3 g/kg	no deaths	Brown et al., 1970
C_7-C_9	i.p.	rat	20 g/kg	no deaths	Gaunt et al., 1968
C_7-C_9	i.p.	mouse	20 g/kg	no deaths	Gaunt et al., 1968
C_7-C_9	s.c.	guinea pig	0.1% (volume not stated), 3 days/week for 3 weeks followed by challenge 10 days later	no sensitization, but some primary irritation	Brown et al., 1970
C_7-C_9	dermal	guinea pig	0.1% (volume not stated), 3 days/week for 3 weeks followed by challenge 10 days later	no sensitization	Brown et al., 1970
C_7-C_9	dermal	rabbit	1.0 ml, 6 hrs/day for 3 days, covered	no irritation	Brown et al., 1970
C_7-C_9	ocular	rabbit	0.1 ml	no irritation	Brown et al., 1970

Table 34. Acute Lethal and Irritant Effects of Mixed Dialkyl (C_7 - C_{11}) Phthalates (Cont'd)

Mixture	Route	Species	Dose	Response	Reference
C_8, C_{10}	oral	rat	45.2 ml/kg	LD50	Smyth et al., 1969
C_8, C_{10}	inhalation	rat	concentrated vapor for 8 hours	maximum time for no death	Smyth et al., 1969
C_8, C_{10}	dermal	rabbit	>20 ml/kg	LD50	Smyth et al., 1969
C_8, C_{10}	dermal	rabbit	0.01 ml	slight irritation	Smyth et al., 1969
C_8, C_{10}	ocular	rabbit	0.5 ml	slight corneal necrosis	Smyth et al., 1969
C_7, C_9, C_{11}	oral	rat	20 g/kg	no effect	Birch, 1969
C_9-C_{11}	oral	rat	19.7 g/kg	no deaths	Brown et al., 1970
C_9-C_{11}	oral	mouse	19.7 g/kg	no deaths	Brown et al., 1970
C_9-C_{11}	s.c.	guinea pig	0.1% (volume not stated), 3 days/wk for 3 weeks followed by challenge 10 days later	no sensitization, but some primary irritation	Brown et al., 1970
C_9-C_{11}	dermal	guinea pig	0.1% (volume not stated), 3 days/wk for 3 weeks followed by challenge 10 days later	no sensitization	Brown et al., 1970
C_9-C_{11}	ocular	rabbit	0.1 ml	no irritation	Brown et al., 1970

[a] n-Hexyl n-decyl phthalate addressed in a separate profile.

very low order of toxicity; signs of intoxication in rats and mice following oral and i.p. administration of high concentrations of C_7 to C_9 dialkyl phthalates included diarrhea and wet hair (Gaunt et al., 1968; Brown et al., 1970).

These phthalates are non-irritating to the skin and eyes of rabbits. Repeated subcutaneous injection (Table 34) did result in some primary irritation at the sight of injection in guinea pigs, but subcutaneous and dermal administration did not sensitize guinea pigs (Brown et al., 1970).

(2) Subchronic Exposures

Oral administration of mixtures of phthalate esters (5 ml/kg) containing 7 to 9 and 9 to 11 carbon atoms to rats (8/sex/group) for 7 consecutive days did not result in overt signs of toxicity other than "general depression" (Brown et al., 1970). Histological examinations following sacrifice on the eighth day revealed periportal cytoplasmic vacuolation in the livers of some of the rats.

When dialkyl 79 phthalate (C_7 to C_9 mixture) was fed to rats at dietary levels of 0, 0.125, 0.5, and 1.0% for 90 days, significant growth retardation was observed in males fed at 1.0%, and a slight anemia was found at all but the lowest level of feeding (Gaunt et al., 1968). Test groups consisted of 15 male and 15 female weanling rats. Kidney and liver weights were elevated in both sexes at the 0.5 and 1.0% dose levels. Male rats on the 1.0% diet also failed to concentrate the urine properly, and showed renal casts and an increased number of cells in the urine. No gross changes were seen at autopsy and histological examination showed only an increase of hemosiderin in the spleen at the highest level (1.0%) in both sexes.

It was indicated in an abstract by Levinskas et al. (1975) that inhalation of di($C_7C_9C_{11}$-alkyl)phthalate at a level of 5 or 20 mg/m^3,

5 hours a day for a total of 130 days over a 6 month period, was not toxic to monkeys, rats or guinea pigs of either sex. Although sizes of the test groups and additional experimental design information (or results) were not published, it was noted that no treatment related deaths occurred among any of the tested animals.

In a skin irritation study, Brown et al. (1970) applied C_7 to C_9 and C_9 to C_{11} dialkyl phthalate mixtures to the uncovered back skin of rabbits (1 ml/day) and guinea pigs (0.5 ml/day) for 5 days per week for 3 weeks. A daily visual assessment of gross skin damage was made, and on the day after the 15th application of test material blocks of skin were removed for histopathologic examination. Results showed that both phthalate mixtures did not irritate the skins of rabbits, and that in guinea pigs, the uncovered exposures caused slight epidermal thickening and some sloughing of the surface layers of the epidermis.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

Di-n-octyl-n-decyl phthalate (C_8,C_{10}) reportedly did not inhibit the growth of DNA-repair deficient strains of B. subtilis and E. coli, and did not induce reverse mutation in E. coli (Table 35).

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

Table 35. Mutagenic Activity of Di-n-Octyl-nDecyl Phthalate

Type of Assay	Organism	Strain	Activation	Dose	Result	Reference
Reverse mutation	E. coli	wild	no	30 mg/plate	-	Kurata, 1975
	E. coli	uvrA$^-$	no	30 mg/plate	-	Kurata, 1975
DNA damage/repair	B. subtilus	rec M$^-$	no	30 mg/plate	-	Kurata, 1975
	E. coli	uvrA$^-$	no	30 mg/plate	-	Kurata, 1975
	E. coli	PolA$^-$	no	30 mg/plate	-	Kurata, 1975
	E. coli	recA$^-$	no	30 mg/plate	-	Kurata, 1975

b. Human Studies

No information was found in the literature searched.

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of mixed dialkyl (C_7 to C_{11}) phthalates were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for mixed dialkyl (C_7 to C_{11}) phthalates were found.

17. Sources of Additional Relevant Information

Comprehensive reviews of phthalate esters have been completed by Peakall (1975), Daniel (1978), Lawrence (1978), Thomas et al. (1978), Lawrence and Tuell (1979), and the U.S. EPA (1980b).

18. Other Pertinent Data

No other information that would aid in the assessment of mixed dialkyl (C_7 to C_{11}) phthalates as an occupational hazard was found in the literature searched.

Appendix A--Phthalates

The following list includes all of the phthalates considered under the class definition. The compounds in the list were identified primarily from the following sources: U.S EPA TSCA list and U.S. EPA (1980a), SRI International (1980), USITC (1980a, 1980b), Hawley (1977), Chem Sources--USA, (1980), and the Kirk-Othmer Encyclopedia of Chemical Technology.

CAS numbers are given, where available, as these types of organic compounds may be known by a variety of synonyms.

Compound	CAS Number
Barium phthalate	15656-86-7
Benzyl alkyl (mixed) phthalates	68515-40-2
Bis(1,3-dimethylbutyl) phthalate	84-63-9
Bis(2,3-epoxypropyl) phthalate	7195-45-1
Bis[2-(2-ethoxyethoxy)]ethyl phthalate	117-85-1
Bis(2-ethoxyethyl) phthalate	605-54-9
Bis(2-ethylbutyl) phthalate	7299-89-0
Bis(2-hydroxyethyl) phthalate	84-73-1
Bis(8-methylnonyl) phthalate	89-16-7
Butyl benzyl phthalate	85-68-7
Butyl carbobutoxymethyl phthalate	85-70-1
Butyl cyclohexyl phthalate	84-64-0
Butyl decyl phthalate	89-19-0
Butyl isodecyl phthalate	42343-36-2
Butyl isohexyl phthalate	89-14-5
Butyl 8 methylheptyl phthalate	89-18-9
Butyl octyl phthalate	84-78-6
Butyl octyl phthalate	85-69-8
Calcium phthalate	5793-85-1
Calcium phthalate	5793-86-2
Copper phthalate	Not readily accessible
Cyclic hexamethylene phthalate	16709-50-5
Cyclic oxydiethylene phthalate	13988-26-6
Decyl hexyl phthalate	25724-58-7
Decyl pentyl phthalate	7493-81-4
Diallyl phthalate	131-17-9
Dibenzyl phthalate	523-31-9
Di-n-butyl phthalate	84-74-2
Dicapryl phthalate	131-15-7
Di(2-butoxyethyl) phthalate	117-83-9
Dicyclohexyl phthalate	84-61-7
Didecyl phthalate	84-77-5

Didodecyl phthalate	2432-90-8
Diethyl phthalate	84-66-2
Di-2-ethylhexyl phthalate	117-81-7
Diheptyl phthalate	3648-21-3
Dihexyl phthalate	84-75-3
Diisobutyl phthalate	84-69-5
Diisodecyl phthalate	26761-40-0
Diisohexyl phthalate	146-50-9
Diisononyl phthalate	28553-12-0
Diisooctyl phthalate	27554-26-3
Diisopentyl phthalate	605-50-5
Diisopropyl phthalate	605-45-8
Dimethoxyethyl phthalate	117-82-8
Dimethyl phthalate	131-11-3
Dinonyl phthalate	84-76-4
Di-n-octyl pthalate	117-84-0
Dioctadecyl phthalate	14117-96-5
Dipentyl phthalate	131-18-0
Diphenyl phthalate	84-62-8
Dipropyl phthalate	131-16-8
Disodium phthalate	15968-01-1
Ditridecyl phthalate	119-06-2
Diundecyl phthalate	3648-20-2
Ethyl carbethoxymethyl phthalate	84-72-0
Ethylene dimethyl phthalate	2055-00-7
2-Ethylhexyl 8-methylnonyl phthalate	89-13-4
Hexyl isodecyl phthalate	61702-81-6
Hexyl isooctyl phthalate	Not readily accessible
Hexyl sec-octyl phthalate	29590-41-8
n-Hexyl n-octyl n-decyl phthalate	Not readily accessible
Isobutyl 6-methylheptyl phthalate	89-11-2
Isobutyl 8-methylnonyl phthalate	89-12-3
Isodecyl octyl phthalate	1330-96-7
Isodecyl tridecyl phthalate	61886-60-0
Isooctyl benzyl phthalate	Not readily accessible
Isooctyl isodecyl phthalate	42343-35-1
Isooctyl tridecyl phthalate	Not readily accessible
Lead phthalate	6838-85-3
Magnesium dihydrate phthalate	6150-90-9
5-Methylheptyl 8-methylnonyl phthalate	89-15-6
6-Methylheptyl 8-methylnonyl phthalate	119-05-1
Mixed alkyl (C_7 to C_{11}) phthalates	68648-91-9
Mixed alkyl (C_9 to C_{11}) phthalates	68648-92-0
Mixed dialkyl (C_7 to C_9) phthalates	68515-41-3
Mixed dialkyl (C_7 to C_{11}) phthalates	68515-42-4
Mixed dialkyl (C_9 to C_{11}) phthalates	68515-43-5
Mixed dialkyl (C_7) phthalates	68515-44-6
Mixed dialkyl (C_9) phthalates	68515-45-7
Monobutyl phthalate	131-70-4

Monodecyl phthalate	24539-60-4
Mono(dimethylcyclohexyl) phalates	1322-94-7
Mono(1-ethyl-1-methyl-2-propynl) phthalate	131-67-9
Mono(1-ethyl-1-methyl-2-propynl) phthalate, sodium salt	16509-28-7
Mono[2-(2-hydroxyethyoxy)ethyl] phthalate	2202-98-4
Monopotassium phthalate	877-24-7
Monosodium phthalate	827-27-0
n-Octyl n-decyl phthalate	119-07-3
Oxydiethylene phthalate	7447-67-8

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