AMBIENT WATER QUALITY CRITERIA FOR

PHTHALATE ESTERS

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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PHTHALATE ESTERS

CRITERIA

Aquatic Life

The available data for phthalate esters indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 940 and 3 μg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

The available data for phthalate esters indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 2,944 μg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of phthalate esters to sensitive saltwater aquatic life but toxicity to one species of algae occurs at concentrations as low as 3.4 μg/l.

Human Health

For the protection of human health from the toxic properties of dimethyl phthalate ingested through water and contaminated aquatic organisms, the ambient water criterion is determined to be 313 mg/l.

For the protection of human health from the toxic properties of dimethyl phthalate ingested through contaminated aquatic organisms alone, the ambient water criterion is determined to be 2.9 g/l.

For the protection of human health from the toxic properties of diethyl phthalate ingested through water and contaminated aquatic organisms, the ambient water criterion is determined to be 350 mg/l.

For the protection of human health from the toxic properties of diethyl phthalate ingested through contaminated aquatic organisms alone, the ambient water criterion is determined to be 1.8 g/l.

For the protection of human health from the toxic properties of dibutyl phthalate ingested through water and contaminated aquatic organisms, the ambient water criterion is determined to be 34 mg/l.

For the protection of human health from the toxic properties of dibutyl phthalate ingested through contaminated aquatic organisms alone, the ambient water criterion is determined to be 154 mg/l.

For the protection of human health from the toxic properties of di-2-ethylhexyl phthalate ingested through water and contaminated aquatic organisms, the ambient water criterion is determined to be 15 mg/l.

For the protection of human health from the toxic properties of di-2-ethylhexyl phthalate ingested through contaminated aquatic organisms alone, the ambient water criterion is determined to be 50 mg/l.

INTRODUCTION

Phthalic acid esters (PAEs), or "phthalate esters," represent a large family of chemicals widely used as plasticizers, primarily in the production of polyvinyl chloride (PVC) resins (U.S. Int. Trade Comm., 1978). Table 1 lists the major esters with their production figures. Phthalates are esters of the ortho form of benzenedicarboxylic acid, also referred to as ortho-phthalic acid. Two other isomeric forms of phthalic acid esters are also produced. These include the meta form (or isothalate esters) and the para form (or terephthalate esters). Both of these isomers have a number of important commercial applications such as starting materials for plastics and textiles. In this document, however, consideration will be given only to the ortho-phthalate esters.

The annual production of phthalic acid esters in the United States in 1977 amounted to approximately 1.2 billion pounds. Since 1945, the cumulative total production (up to 1972) of these esters reached a figure of 12.5 billion pounds (Peakall, 1975). On a worldwide scale, three to four billion pounds are produced annually.

The most widely used phthalate plasticizer is di-2-ethylhexyl phthalate (DEHP), which accounted for an estimated 32 percent of the total phthalate esters produced in 1977 (U.S. Int. Trade Comm., 1978). In addition to DEHP, other phthalates produced included other dioctyl phthalates, butylbenzyl phthalate (BBP), diisodecyl phthalate, dibutyl phthalate (DBP), diethyl phthalate (DEP), dimethyl phthalate (DMP), di-tridecyl phthalate, and n-hexyl n-decyl phthalate (U.S. Int. Trade Comm., 1978).

TABLE 1

Production of Individual Phthalic Acid Esters in U.S. in 1977*

Ester	Production in Pounds (1,000 pounds)
Dibutyl	16,592
Diethyl	17,471
Diisodecyl	160,567
Dimethyl	9,887
Dioctyl	
Di-2-ethylhexyl	388,543
Other dioctyl phthalates	11,664
Di-tridecyl	23,278
n-Hexyl n-decyl	15,182
All other phthalate esters	559,229
Total	1,202,413

*Source: United States International Trade Commission, 1978

PVC resins are used in such diverse industries as construction (high temperature electrical wire, cable insulation, and flooring), home furnishings (furniture upholstery, wall coverings), transportation (upholstery and seat covers), apparel (footwear), and food and medical packaging materials. Phthalates also have non-plasticizer uses in pesticide carriers, cosmetics, fragrances, munitions, industrial oils, and insect repellants (U.S. Int. Trade Comm., 1978). Table 2 illustrates the variety of uses for esters with an estimate of the amount of the esters used in the specific categories.

PAE plasticizers can be present in concentrations up to 60 percent of the total weight of the plastic. The plasticizers are loosely linked to the plastic polymers and are easily extracted (Mathur, 1974).

For the most part, the esters are colorless liquids, have low volatility, and are poorly soluble in water but soluble in organic solvents and oils. Table 3 lists several of the physical properties of these esters.

The phthalate esters can be prepared by reaction of phthalic acid with a specific alcohol to form the desired esters. In industry, however, the esters are manufactured from phthalic anhydride rather than from the acid. For the most part, manufactured esters will not be completely pure, having various isomers and contaminants present. These esters, however, can be prepared with a purity of greater than 99 percent even though most of these esters are not sold with this high degree of purity.

Evidence also is available suggesting that certain plants and animal tissue may synthesize phthalic acid esters (Peakall, 1975). However, to what extent this occurs in nature is not known.

The ease of extraction of phthalate esters and their widespread use either alone or in PVC account for their ubiquity. PAEs have been detected in soil (Ogner and Schnitzer, 1970), water (Ewing and Chian, 1977; Corcoran,

TABLE 2

Uses of Phthalate Esters in the United States*

A. As Plasticizers	
Building and Construction	
Wire and cable	185
Flooring	150
Swimming pool liners	20
Miscellaneous	32
Subtotal	387
Home Furnishings	
Furniture upholstery	90
Wall coverings	38
Houseware	30
Miscellaneous	45
Subtotal	203
Cars (upholstery, tops, etc.)	114
Wearing apparel	72
Food wrapping and closures	25
Medical tubing and intravenous bags	21
Total as Plasticizers	922
B. As Nonplasticizers	
Pesticide Carriers	—
Oils	—
Insect repellent	—
Total as Nonplasticizers	50
Grand Total	972

*Source: Graham, 1973

TABLE 3

Physical and Chemical Properties of Phthalate Esters

Compound	Molecular Weight	Specific Gravity	BP, °C	Solubility in H_2O, g/100 ml
Dimethyl phthalate	194.18	1.189	282	0.5
Diethyl phthalate	222.23	1.123	296.1	Insoluble
Diallyl phthalate	246.27	1.120	290	0.01
Diisobutyl phthalate	278.3	1.040	327	Insoluble
Dibutyl phthalate	278.34	1.0465	340	0.45 (25°C)
Dimethoxyethyl phthalate	282.0	1.171	190–210	0.85
Dicyclohexyl phthalate	330.0	1.20	220–228	Insoluble
Butyl octyl phthalate	334.0	--	340	--
Dihexyl phthalate	334.0	0.990	--	Insoluble
Butylphthalyl butyl glycolate	336.37	1.097	219*	0.012%
Dibutoxyethyl ethyl phthalate	366.0	1.063	210	0.03
Di-2-ethylhexyl phthalate	391.0	0.985	386.9*	Insoluble
Diisooctyl phthalate	391.0	0.981	239*	Insoluble
Di-n-octyl phthalate	391.0	0.978	220*	Insoluble
Dinonyl phthalate	419.0	0.965	413	Insoluble

*Measured at 5 mm Hg

1973; Hites and Bieman, 1972), fish (Mayer, 1976; Stalling, 1973), air (Mathur, 1974) and animal and human tissues (Nazir, et al. 1971; Rubin and Shiffer, 1976; Jaeger and Rubin, 1970). Their detection in certain vegetation, animals and minerals (Mathur, 1974; Graham, 1973), and in areas remote from industrial sites (Carpenter and Smith, 1972) have raised questions about possible natural origins of PAEs. PAEs found in greatest frequencies in an EPA monitoring survey of U.S. surface waters (Ewing and Chian, 1977) were DEHP (132/204) and DEP (84/204). Other esters detected in the EPA survey were diethyl phthalate, disobutyl phthalate, and diocyl phthalate.

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Aquatic Life Toxicology*

INTRODUCTION

Phthalate esters are a large group of chemical agents (esters of ortho benzene dicarboxylic acid) used primarily as plasticizers.

A limited number of applicable reports were found having effects data on individual phthalate esters to freshwater aquatic life. More information is available for butylbenzyl and di-2-ethylhexyl phthalate than for the other esters.

Toxicity test data for saltwater organisms are available for six phthalate esters. Tests have provided some acute and plant effects of butylbenzyl phthalate, diethyl phthalate, and dimethyl phthalate. Limited information is also available on di-n-propyl, di-n-butyl, and di-2-ethylhexyl phthalates. These data indicate great differences in toxicity among esters.

EFFECTS

Acute Toxicity

All freshwater acute values were determined with static procedures and the test concentrations were unmeasured. Data for five phthalate esters can be found in Table 1. Values for four of the esters were from tests with both fish and invertebrate species.

Tests with butylbenzyl, diethyl, and dimethyl phthalate were conducted with bluegill, fathead minnow, and *Daphnia magna* (U.S. EPA, 1978; Gledhill, et al. 1980). The acute values ranged from 1,700 to 98,200 µg/l.

Gledhill, et al. (1980) reported butylbenzyl phthalate LC_{50} values for three fish and one invertebrate species. The values ranged from 1,700 to

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of the appropriate table are calculations for deriving various measures of toxicity as described in the Guidelines.

5,300 μg/l (Table 1). The two fathead minnow acute values represent two water hardness levels. Their LC_{50} values for Daphnia magna and bluegills were about 25 times less than reported by the U.S. EPA (1978).

Di-n-butyl phthalate tests were conducted with four fish and two invertebrate species. The LC_{50} values varied from 730 to 6,470 μg/l or a difference of about nine times. Bluegills were the most sensitive fish and the scud the most sensitive invertebrate species tested with this ester. An additional acute datum for a crayfish species and this ester is included in Table 6, but the LC_{50} value exceeded the highest test concentration (10,000 μg/l).

Only one acute value was obtained with di-2-ethylhexyl phthalate and was derived from a test with Daphnia magna. Additional acute data for this ester are shown in Table 6, and the LC_{50} values for the midge, scud, and bluegill exceeded the highest concentrations tested. The LC_{50} range for Daphnia magna (Monsanto, 1978) represents the 50 percent mortalities obtained in two of the six concentrations.

Acute effects of only three phthalate esters (butylbenzyl phthalate, diethyl phthalate, and dimethyl phthalate) on two saltwater species, mysid shrimp and sheepshead minnow, have been reported (Table 1). All of the eight data were based on static test procedures with unmeasured concentrations. For the effects of butylbenzyl phthalate, there was a great difference between the two values for the mysid shrimp (900 and 9,630 μg/l) and also between those for the sheepshead minnow (3,000 and 445,000 μg/l). The tests were conducted by the same laboratory, but the lower values were obtained in tests using a solvent (Gledhill, et al. 1980) and the higher values represent tests not using a solvent (U.S. EPA, 1978). Undoubtedly, much of the chemical was not available to the test animals when a solvent was not used. Less than full solubility of the chemical may also have occurred for the data on diethyl phthalate (7,590 μg/l for mysid shrimp; 29,600 μg/l for sheepshead minnow) and dimethyl phthalate (73,700 µg/l for mysid shrimp; 58,000 µg/l for sheepshead minnow) generated without use of solvents (U.S. EPA, 1978), although there are no comparable data obtained using solvents.

Chronic Toxicity

Freshwater data were found for two phthalate esters and the results are presented in Table 2. An early life stage test with a fish and a life-cycle *Daphnia magna* test were conducted for each ester.

The butylbenzyl phthalate chronic values reported for the fathead minnow and *Daphnia magna* were 220 and 440 µg/l, respectively. The corresponding acute-chronic ratios were determined to be 17 and 42. The chronic values and acute-chronic ratios for this ester were within a factor of about 2 for the fish and invertebrate species.

A di-2-ethylhexyl phthalate test was conducted with rainbow trout. The chronic value was 8.4 µg/l. No acute-chronic ratio could be calculated because of the absence of a 96-hour LC_{50} value. Mayer and Sanders (1973) conducted a chronic test with di-2-ethylhexyl phthalate and *Daphnia magna*. Significant reproductive impairment was found at 3 µg/l. Since this value was at the lowest test concentration, the adverse effects on reproduction were less than 3 µg/l. This concentration represents the lowest toxicity value reported for the phthalate esters.

Species mean acute values and acute-chronic ratios are summarized in Table 3.

No saltwater fish or invertebrate species have been tested in a chronic toxicity study.

Plant Effects

The adverse effects of three phthalate esters on freshwater algal species are summarized in Table 4. Similar EC_{50} values with *Selenastrum capricornutum* were found for cell numbers and chlorophyll *a* for each ester tested by the

U.S. EPA (1978). By comparison, the butylbenzyl phthalate EC_{50} value found by Gledhill, et al. (1980) with this alga was about 3 times higher, and the alga, Microcystis aeruginosa, was shown to be resistant to this ester. The lowest EC_{50} values for diethyl and dimethyl phthalate were 85,600 and 39,800 µg/l, respectively. A much lower EC_{50} value of 110 µg/l was obtained with butylbenzyl phthalate, and represents a lower value than found for fish and invertebrate species (Table 1).

Data on the toxicity of five phthalate esters to one or two species of saltwater algae are listed in Table 4. Butylbenzyl phthalate and dimethyl phthalate were more toxic to a saltwater alga, Skeletonema costatum, than to the tested fish and invertebrate species.

The various phthalates showed a wide range of toxicity to the same species of alga. Thus, butylbenzyl phthalate was very toxic to Skeletonema costatum with a chlorophyll a EC_{50} value of 170 µg/l; however, the chlorophyll a EC_{50} of diethyl phthalate for the same species was 65,500 µg/l. In addition, the lowest EC_{50} of di-n-butyl phthalate for Gymnodinium breve was 3.4 µg/l and the lowest EC_{50} of dimethyl phthalate for the same species was 54,000 µg/l. Some of these wide ranges in toxicity could be due to EC_{50} values reported that may surpass the solubility limits of the compounds tested or to relatively large differences reported for replicate tests, particularly those of Wilson, et al. (1978).

Residues

Freshwater bioconcentration factors for five phthalate esters are reported in Table 5. Mayer (1976) measured both the actual concentrations and ^{14}C-labeled di-2-ethylhexyl phthalate in a test system and found the difference was less than two times after equilibrium in fathead minnows. The bioconcentration factors for di-2-ethylhexyl phthalate with fish and invertebrate species ranged from 54 to 2,680. Tests with di-n-butyl phthalate performed with two invertebrate species gave equilibrium bioconcentration factors of 400 and 1,400. Bioconcentration factors for ^{14}C-labeled butylbenzyl, diethyl, and dimethyl phthalate with bluegills were 663, 117, and 57, respectively, after a 21-day exposure (U.S. EPA, 1978). The half-life of these three phthalate esters was between 1 and 2 days. Bioaccumulation data with di-*n*-octyl phthalates by Sanborn, et al. (1975) in a static model ecosystem are given in Table 6. Their water concentrations rapidly decreased with time and do not permit comparisons with values in Table 5.

Since no maximum permissible tissue levels exist for phthalate esters, no Residue Limited Toxicant Concentration could be calculated for any phthalate ester.

No data are available for bioconcentration of phthalate esters by any saltwater species.

Miscellaneous

Additional freshwater toxicity data for phthalate esters are given in Table 6. Many of these data have already been discussed and were not lower than the acute or chronic values (Tables 1 and 2). Mayer, et al. (1977) exposed rainbow trout embryos to di-2-ethylhexyl phthalate for 90 days and found concentrations of 14 to 54 µg/l significantly increased total protein catabolism 24 days after hatching. This concentration range is similar to the lowest adverse test concentration found with this ester in the embryo-larval test (Table 2). Birge, et al. (1978) performed tests with several fish species using di-isononyl and di-*n*-octyl phthalate. The tests were started with 7-hour-old fertilized embryos and continued through four days post-hatch; because of the test duration and endpoints measured, the data for these two esters were listed in Table 6. Also listed in this table is a diet study with the guppy using di-2-ethylhexyl phthalate which resulted in an increase in aborted young.

Saltwater data for effects (Table 6) not listed in the other tables suggest no more sensitive effects than those already presented. The only toxicity data available for di-2-ethylbutyl phthalate indicated that 1,000 µg/l had no significant effect on the entire larval development of the grass shrimp, and that only a high concentration (EC_{50} = 3.1%) affected growth rate of the alga, Gymnodinium breve (Wilson, et al. 1978).

Summary

Acute freshwater test results were available for five phthalate esters, and these were conducted with a relatively small diverse group of freshwater fish and invertebrate species. The acute values, with one exception, all exceeded 1,000 µg/l. Sensitivity differences were generally similar for the tested freshwater species. No final acute values are calculable for any ester since the minimum data base requirements were not met.

Chronic freshwater test results were available for two phthalate esters. The chronic values for butylbenzyl phthalate were 220 and 440 µg/l with the calculated acute-chronic ratios being 17 and 42. The chronic values for di-2-ethylhexyl phthalate were 3 and 8.4 µg/l and no acute-chronic ratios were calculable. No final chronic values could be determined.

Plant test results were available for three phthalate esters. The plant values for diethyl and dimethyl phthalate were similar to the acute results for these phthalates and invertebrate species. A wide variation was found in the EC_{50} values for butylbenzyl phthalate, which values ranged from 110 to 1,000,000 µg/l.

Residue test results were available for five phthalate esters. A wide variation was found for bioconcentration values for both the invertebrate (14-2,680) and fish (42-886) species. More residue data were available for di-2-ethylhexyl phthalate than for the other esters.

Additional freshwater toxicity results were available with four phthalate esters. None of these data showed toxicity values lower than those already discussed.

Acute saltwater test results were available for three phthalate esters with one invertebrate and one fish species. The lowest concentrations at which acute effects were observed were 900 µg/l for butylbenzyl phthalate and 7,590 µg/l for diethyl phthalate, both for mysid shrimp, and 58,000 µg/l for dimethyl phthalate with the sheepshead minnow. There were no saltwater chronic or residue test results for any phthalate ester. Effects of phthalate esters on saltwater algal species were reported at concentrations as low as 3.4 µg/l.

CRITERIA

The available data for phthalate esters indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 940 and 3 µg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

The available data for phthalate esters indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 2944 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of phthalate esters to sensitive saltwater aquatic life but toxicity to one species of algae occurs at concentrations as low as 3.4 µg/l.

Table 1. Acute values for phthalate esters

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
		FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	S, U	Butylbenzyl phthalate	92,300	-	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	Butylbenzyl phthalate	3,700	18,500	Gledhill, et al. 1980
Cladoceran, *Daphnia magna*	S, U	Diethyl phthalate	52,100	52,100	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	Dimethyl phthalate	33,000	33,000	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	di-2-ethylhexyl phthalate	11,100	11,100	U.S. EPA, 1978
Scud, *Gammarus pseudolimnaeus*	S, U	di-n-butyl phthalate	2,100	2,100	Mayer & Sanders, 1973
Midge, *Chironomus plumosus*	S, U	di-n-butyl phthalate	4,000	4,000	Streufert, 1977
Rainbow trout, *Salmo gairdneri*	S, U	Butylbenzyl phthalate	3,300	3,300	Gledhill, et al. 1980
Rainbow trout, *Salmo gairdneri*	S, U	di-n-butyl phthalate	6,470	6,470	Mayer & Sanders, 1973
Fathead minnow, *Pimephales promelas*	S, U	Butylbenzyl phthalate	5,300	-	Gledhill, et al. 1980
Fathead minnow, *Pimephales promelas*	S, U	Butylbenzyl phthalate	2,100	3,300	Gledhill, et al. 1980
Fathead minnow, *Pimephales promelas*	S, U	di-n-butyl phthalate	1,300	1,300	Mayer & Sanders, 1973
Bluegill, *Lepomis macrochirus*	S, U	Butylbenzyl phthalate	43,300	-	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	Butylbenzyl phthalate	1,700	8,600	Gledhill, et al. 1980

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Bluegill, *Lepomis macrochirus*	S, U	Diethyl phthalate	98,200	98,200	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	Dimethyl phthalate	49,500	49,500	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	di-n-butyl phthalate	730	-	Mayer & Sanders, 1973
Bluegill, *Lepomis macrochirus*	S, U	di-n-butyl phthalate	1,200	940	U.S. EPA, 1978
Channel catfish, *Ictalurus punctatus*	S, U	di-n-butyl phthalate	2,910	2,910	Mayer & Sanders, 1973
		SALTWATER SPECIES			
Mysid shrimp, *Mysidopsis bahia*	S, U	Butylbenzyl phthalate	9,630	-	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	S, U	Butylbenzyl phthalate	900	2,944	Gledhill, et al. 1980
Mysid shrimp, *Mysidopsis bahia*	S, U	Diethyl phthalate	7,590	7,590	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	S, U	Dimethyl phthalate	73,700	73,700	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	Butylbenzyl phthalate	445,000	-	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	Butylbenzyl phthalate	3,000	36,538	Gledhill, et al. 1980
Sheepshead minnow, *Cyprinodon variegatus*	S, U	Diethyl phthalate	29,600	29,600	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	Dimethyl phthalate	58,000	58,000	U.S. EPA, 1978

* S = static, U = unmeasured

Table 2. Chronic values for phthalate esters

Species	Method*	Chemical	Limits (µg/l)	Species Mean Chronic Value (µg/l)	Reference
		FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	LC	Butylbenzyl phthalate	260-760	440	Gledhill, et al. 1980
Cladoceran, *Daphnia magna*	LC	di-2-ethylhexyl phthalate	<3	<3	Mayer & Sanders, 1973
Rainbow trout, *Salmo gairdneri*	ELS	di-2-ethylhexyl phthalate	5-14	8.4	Mehrle & Mayer, 1976
Fathead minnow, *Pimephales promelas*	ELS	Butylbenzyl phthalate	140-360	220	U.S. EPA, 1978

* ELS = early life stage, LC = partial life cycle or full life cycle

Acute-Chronic Ratios

Species	Chemical	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Cladoceran, *Daphnia magna*	Butylbenzyl phthalate	18,500	440	42
Cladoceran, *Daphnia magna*	di-2-ethylhexyl phthalate	11,100	<3	-
Rainbow trout, *Salmo gairdneri*	di-2-ethylhexyl phthalate	-	8.4	-
Fathead minnow, *Pimephales promelas*	Butylbenzyl phthalate	3,300	220	15

Table 3. Species mean acute values and acute-chronic ratios for phthalate esters

Rank*	Species	Chemical	Species Mean Acute Value (µg/l)	Acute-Chronic Ratio
		FRESHWATER SPECIES		
16	Bluegill, *Lepomis macrochirus*	Diethyl phthalate	98,200	-
15	Cladoceran, *Daphnia magna*	Diethyl phthalate	52,100	-
14	Bluegill, *Lepomis macrochirus*	Dimethyl phthalate	49,500	-
13	Cladoceran, *Daphnia magna*	Dimethyl phthalate	33,000	-
12	Cladoceran, *Daphnia magna*	Butylbenzyl phthalate	18,500	42
11	Cladoceran, *Daphnia magna*	di-2-ethylhexyl phthalate	11,100	-
10	Bluegill, *Lepomis macrochirus*	Butylbenzyl phthalate	8,600	-
9	Rainbow trout, *Salmo gairdneri*	di-n-butyl phthalate	6,470	-
8	Midge, *Chironomus plumosus*	di-n-butyl phthalate	4,000	-
7	Fathead minnow, *Pimephales promelas*	Butylbenzyl phthalate	3,300	15
6	Rainbow trout, *Salmo gairdneri*	Butylbenzyl phthalate	3,300	-
5	Channel catfish, *Ictalurus punctatus*	di-n-butyl phthalate	2,910	-
4	Scud, *Gammarus pseudolimnaeus*	di-n-butyl phthalate	2,100	-
3	Fathead minnow, *Pimephales promelas*	di-n-butyl phthalate	1,300	-

Table 3. (Continued)

Rank*	Species	Chemical	Species Mean Acute Value (µg/l)	Acute-Chronic Ratio
2	Bluegill, *Lepomis macrochirus*	di-n-butyl phthalate	940	-
1	Rainbow trout, *Salmo gairdneri*	di-2-ethylhexyl phthalate	-	-
		SALTWATER SPECIES		
6	Mysid shrimp, *Mysidopsis bahia*	Dimethyl phthalate	73,700	-
5	Sheepshead minnow, *Cyprinodon variegatus*	Dimethyl phthalate	58,000	-
4	Sheepshead minnow, *Cyprinodon variegatus*	Butylbenzyl phthalate	36,538	-
3	Sheepshead minnow, *Cyprinodon variegatus*	Diethyl phthalate	29,600	-
2	Mysid shrimp, *Mysidopsis bahia*	Diethyl phthalate	7,590	-
1	Mysid shrimp, *Mysidopsis bahia*	Butylbenzyl phthalate	2,944	-

* Ranked from least sensitive to most sensitive based on species mean acute value.

Table 4. Plant values for phthalate esters

Species	Chemical	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES		
Alga, *Selenastrum capricornutum*	Butylbenzyl phthalate	96-hr EC50 chlorophyll *a*	110	U.S. EPA, 1978
Alga, *Selenastrum capricornutum*	Butylbenzyl phthalate	96-hr EC50 cell number	130	U.S. EPA, 1978
Alga, *Selenastrum capricornutum*	Butylbenzyl phthalate	96-hr EC50 cell number	400	Gledhill, et al. 1980
Alga, *Selenastrum capricornutum*	Diethyl phthalate	96-hr EC50 chlorophyll *a*	90,300	U.S. EPA, 1978
Alga, *Selenastrum capricornutum*	Diethyl phthalate	96-hr EC50 cell number	85,600	U.S. EPA, 1978
Alga, *Selenastrum capricornutum*	Dimethyl phthalate	96-hr EC50 chlorophyll *a*	42,700	U.S. EPA, 1978
Alga, *Selenastrum capricornutum*	Dimethyl phthalate	96-hr EC50 cell number	39,800	U.S. EPA, 1978
Alga, *Microcystis aeruginosa*	Butylbenzyl phthalate	96-hr EC50 cell number	1,000,000	Gledhill, et al. 1980
Alga, *Navicula pelliculosa*	Butylbenzyl phthalate	96-hr EC50 cell number	600	Gledhill, et al. 1980
		SALTWATER SPECIES		
Alga, *Skeletonema costatum*	Butylbenzyl phthalate	96-hr EC50 chlorophyll *a*	170	U.S. EPA, 1978
Alga, *Skeletonema costatum*	Butylbenzyl phthalate	96-hr EC50 cell number	190	U.S. EPA, 1978
Alga, *Skeletonema costatum*	Butylbenzyl phthalate	96-hr EC50 cell number	600	Gledhill, et al. 1980
Alga, *Skeletonema costatum*	Diethyl phthalate	96-hr EC50 chlorophyll *a*	65,500	U.S. EPA, 1978

Table 4. (Continued)

Species	Chemical	Effect	Result (µg/l)	Reference
Alga, *Skeletonema costatum*	Diethyl phthalate	96-hr EC50 cell number	85,000	U.S. EPA, 1978
Alga, *Skeletonema costatum*	Dimethyl phthalate	96-hr EC50 chlorophyll *a*	26,100	U.S. EPA, 1978
Alga, *Skeletonema costatum*	Dimethyl phthalate	96-hr EC50 cell number	29,800	U.S. EPA, 1978
Alga, *Gymnodinium breve*	Diethyl phthalate	96-hr EC50 chlorophyll *a*	6,100	Wilson, et al. 1978
Alga, *Gymnodinium breve*	Diethyl phthalate	96-hr EC50 chlorophyll *a*	3,000	Wilson, et al. 1978
Alga, *Gymnodinium breve*	Diethyl phthalate	96-hr EC50 cell number	33,000	Wilson, et al. 1978
Alga, *Gymnodinium breve*	Dimethyl phthalate	96-hr EC50 chlorophyll *a*	96,000	Wilson, et al. 1978
Alga, *Gymnodinium breve*	Dimethyl phthalate	96-hr EC50 chlorophyll *a*	54,000	Wilson, et al. 1978
Alga, *Gymnodinium breve*	Dimethyl phthalate	96-hr EC50 cell number	125,000	Wilson, et al. 1978
Alga, *Gymnodinium breve*	Dimethyl phthalate	96-hr EC50 cell number	185,000	Wilson, et al. 1978
Alga, *Gymnodinium breve*	di-n-butyl phthalate	96-hr EC50 chlorophyll *a*	200	Wilson, et al. 1978
Alga, *Gymnodinium breve*	di-n-butyl phthalate	96-hr EC50 chlorophyll *a*	3.4	Wilson, et al. 1978
Alga, *Gymnodinium breve*	di-n-butyl phthalate	96-hr EC50 cell number	600	Wilson, et al. 1978
Alga, *Gymnodinium breve*	di-n-butyl phthalate	96-hr EC50 cell number	20	Wilson, et al. 1978

Table 4. (Continued)

Species	Chemical	Effect	Result (µg/l)	Reference
Alga, *Gymnodinium breve*	di-n-propyl phthalate	96-hr EC50 chlorophyll *a*	2,400	Wilson, et al. 1978
Alga, *Gymnodinium breve*	di-n-propyl phthalate	96-hr EC50 chlorophyll *a*	900	Wilson, et al. 1978
Alga, *Gymnodinium breve*	di-n-propyl phthalate	96-hr EC50 cell number	6,500	Wilson, et al. 1978
Alga, *Gymnodinium breve*	di-n-propyl phthalate	96-hr EC50 cell number	1,300	Wilson, et al. 1978
Alga, *Dunaliella tertiolecta*	Butylbenzyl phthalate	96-hr EC50 cell number	1,000	Gledhill, et al. 1980

Table 5. Residues for phthalate esters

Species	Tissue	Chemical	Bioconcentration Factor*	Duration (days)	Reference
		FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	Whole body	di-n-butyl phthalate	400	14	Mayer & Sanders, 1973
Scud, *Gammarus pseudolimnaeus*	Whole body	di-n-butyl phthalate	1,400	14	Mayer & Sanders, 1973
Scud, *Gammarus pseudolimnaeus*	Whole body	di-2-ethylhexyl phthalate	54-2,680**	14-21	Sanders, et al. 1973
Sowbug, *Asellus brevicaudus*	Whole body	di-2-ethylhexyl phthalate	14-50**	21	Sanders, et al. 1973
Rainbow trout, *Salmo gairdneri*	Whole body	di-2-ethylhexyl phthalate	42-113	36	Mehrle & Mayer, 1976
Fathead minnow, *Pimephales promelas*	Whole body	di-2-ethylhexyl phthalate	155-886	56	Mayer, 1976
Fathead minnow, *Pimephales promelas*	Whole body	di-2-ethylhexyl phthalate	91-569***	56	Mayer, 1976
Bluegill, *Lepomis macrochirus*	Whole body	Butylbenzyl phthalate	663	21	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	Whole body	Diethyl phthalate	117	21	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	Whole body	Dimethyl phthalate	57	21	U.S. EPA, 1978

* Based on total ^{14}C radioactivity accumulated.

** Conversion from dry to wet weight.

***Based on measured concentrations of di-2-ethylhexyl phthalate.

Table 6. Other data for phthalate esters

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES			
Alga, *Oedogonium cardiacum*	di-n-octyl phthalate	33 days	Model ecosystem* 28,500X bioconcentration	-	Sanborn, et al. 1975
Cladoceran, *Daphnia magna*	di-2-ethylhexyl phthalate	48 hrs	LC50	1,000-5,000	Monsanto, 1978
Cladoceran, *Daphnia magna*	di-n-octyl phthalate	33 days	Model ecosystem* 2,600X bioconcentration	-	Sanborn, et al. 1975
Midge, *Chironomus plumosus*	di-2-ethylhexyl phthalate	48 hrs	LC50	>18,000	Streufert, 1977
Scud, *Gammarus pseudolimnaeus*	di-2-ethylhexyl phthalate	96 hrs	LC50	>32,000	Sanders, et al. 1973
Mosquito (larva), *Culex pipens quinquefasciatus*	di-n-octyl phthalate	33 days	Model ecosystem* 9,400X bioconcentration	-	Sanborn, et al. 1975
Snail, *Physa* sp.	di-n-octyl phthalate	33 days	Model ecosystem* 13,600X bioconcentration	-	Sanborn, et al. 1975
Crayfish, *Orconectes nais*	di-n-butyl phthalate	96 hrs	LC50	>10,000	Mayer & Sanders, 1973
Rainbow trout, *Salmo gairdneri*	di-2-ethylhexyl phthalate	24 days	Significant increase in total body protein catabolism	14-54	Mayer, et al. 1977
Rainbow trout (early life stage), *Salmo gairdneri*	di-n-octyl phthalate	26 days	LC50	139,500	Birge, et al. 1978
Rainbow trout, *Salmo gairdneri*	di-n-octyl phthalate	26 days	LC50	149,200	Birge, et al. 1978

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Guppy, *Poecilia reticulata*	di-2-ethylhexyl phthalate	90 days	Increase in aborted young	fed 100 µg/g in diet	Mayer & Sanders, 1973
Bluegill, *Lepomis macrochirus*	di-2-ethylhexyl phthalate	96 hrs	LC50	>770,000	U.S. EPA, 1978
Redear sunfish (early life stage), *Lepomis microlopus*	di-isononyl phthalate	7-8 days	LC50	4,670	Birge, et al. 1978
Redear sunfish, (early life stage), *Lepomis microlopus*	di-n-octyl phthalate	7-8 days	LC50	6,180	Birge, et al. 1978
Mosquitofish, *Gambusia affinis*	di-n-octyl phthalate	33 days	Model ecosystem* 9,400X bioconcentration	-	Sanborn, et al. 1975
Channel catfish (early life stage), *Ictalurus punctatus*	di-isononyl phthalate	7 days	LC50	420	Birge, et al. 1978
Channel catfish (early life stage), *Ictalurus punctatus*	di-n-octyl phthalate	7 days	LC50	690	Birge, et al. 1978
Largemouth bass (early life stage), *Micropterus salmoides*	di-n-octyl phthalate	7-8 days	LC50	42,100	Birge, et al. 1978
Largemouth bass (early life stage), *Micropterus salmoides*	di-n-octyl phthalate	7-8 days	LC50	32,900	Birge, et al. 1978
		SALTWATER SPECIES			
Alga, *Gymnodinium breve*	di-2-ethylhexyl phthalate	96 hrs	Growth rate EC50 = 3.1% vol/vol	-	Wilson, et al. 1978

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Grass shrimp (larva), *Palaemonetes pugio*	di-2-ethylhexyl phthalate	Entire larval development	None on survival and developmental rate	1,000	Laughlin, et al. 1978
Grass shrimp (larva), *Palaemonetes pugio*	Dimethyl phthalate	Entire larval development	Significant decrease in survival; increased intermolt and developmental periods	100,000	Laughlin, et al. 1978
Mud crab (larva), *Rhithropanopeus harrisii*	Dimethyl phthalate	Entire larval development	None on development	1,000	Laughlin, et al. 1977
Mud crab (larva), *Rhithropanopeus harrisii*	di-n-butyl phthalate	Entire larval development	None on development	1,000	Laughlin, et al. 1977

* Based on actual concentrations of di-n-octyl phthalate accumulated

Lowest Freshwater Value: di-isononyl phthalate = 420 µg/l
di-2-ethylhexyl phthalate = 14-54 µg/l
di-n-butyl phthalate = >10,000 µg/l
di-n-octyl phthalate = 690 µg/l

Lowest Saltwater Value: dimethyl phthalate = 100,000 µg/l

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Mammalian Toxicology and Human Health Effects

INTRODUCTION

The annual production of phthalic acid esters in the United States in 1977 amounted to approximately 1.2 billion pounds. Since 1945, the cumulative total production (up to 1972) of these esters reached a figure of 12.5 billion pounds (Peakall, 1975). On a worldwide scale, 3 to 4 billion pounds are produced annually.

When the term "phthalate esters" is used, it indicates the ortho form of benzenedicarboxylic acid. Two other isomeric forms of benzenedicarboxylic acid esters are also produced. These include the meta form (or isothalate esters) and the para form (or terephthalate esters). Both of these isomers have a number of important commercial applications such as starting materials for plastics and textiles. In this document, however, consideration will be given only to the "ortho" esters.

Pthalic acid esters have a large number of commercial uses, the largest being as plasticizers for specific plastics such as polyvinyl chloride. Other uses for these esters include: defoaming agents in the production of paper, in cosmetic products as a vehicle (primarily diethyl phthalate) for perfumes, in lubricating oils, and in other industrial and consumer applications.

Dioctyl phthalate (includes di-2-ethylhexyl phthalate and other dioctyl phthalates) accounts for approximately 42 percent of the esters produced in this country, followed by diisodecyl phthalate. Dioctyl phthalate (DOP) and di-2-ethylhexyl phthalate (DEHP) are often used synonymously even though it should be clear that they are not the same, one being an isomer of the other.

The extremely large production of phthalates and the variety of uses for these esters have led to the presence of these esters in water sources, food, consumer products, air (industrial settings, automobiles having vinyl furnishings), and in medical devices such as tubings and blood bags. Esters can thus enter the environment and biological species, including man, through a variety of sources.

Therefore, man is exposed to phthalates from a variety of routes such as: (1) ingestion from water, (2) ingestion from food, (3) inhalation, (4) dermal, and (5) parenteral administration (via blood bags and tubes in which the ester is extracted by a parenteral solution including blood).

EXPOSURE

Ingestion from Water

In the early seventies, a great deal of attention began to focus on chemical contaminants in surface water and adjacent ocean regions. One of the first reports published on the presence of phthalic acid esters was presented by Corcoran (1973). He indicated that a level of approximately 0.6 ppm DEHP was present at the mouth of the Mississippi River. He further calculated that approximately 350 million pounds of the ester enter the Gulf of Mexico from the Mississippi River each year. As pointed out by Peakall (1975), the 350 million pounds stated by Corcoran must be in error and may be due to an error in the analytical procedure or to an abnormal local concentration. Corcoran also indicated the presence of DEHP (or its equivalent) in the Gulf near Pensacola, Florida and in the clear blue waters of the Gulf Stream, but the levels of the esters were much less than at the mouth of the Mississippi.

Hites (1973) studied chemical contaminants in the Charles and Merrimack Rivers in Massachusetts. He reported that approximately 7 miles from the mouth of the Charles River the level of phthalate was 1.8 to 1.9 ppb. As the water approached the mouth of the river, the level was reduced. For example, three miles from the mouth, the level was 1.1 ppb while at one mile from the mouth, the level ranged from 0.88 to 0.98 ppb.

A review of various EPA reports shows that surface waters do contain phthalate esters in parts per billion, with the levels being higher at sites close to industrial centers.

Ingestion from Food

A number of packaging materials and tubings used in the production of foods and beverages are polyvinyl chloride contaminated with phthalic acid esters, primarily DEHP. These esters migrate from the packaging to the food or beverages. The extent of migration depends upon a number of factors such as temperature, surface area contact, lipoidal nature of the food, and length of contact. Peakall (1975) refers to reports on the migration of plasticizers from tubings used in milk production. Extracted levels for the dinonyl phthalate ester (in PVC tubing) were found to be 4.6 mg/100 ml/day at 38°C and 7.0 mg/100 ml/day at 56°C. The rate for DEHP was 2.0 mg/100 ml/day at 38°C and 3.1 mg/100 ml/day at 56°C. The tubing was 1 meter in length and 100 ml of milk was the extracting medium. Peakall suggests that in actual practice approximately 40 mg of DEHP could be extracted over a 15 day period from tubings in contact with milk, but indicated that the actual levels in milk are not known. A German report (Pfab, 1967) indicates that cheese and lard placed experimentally in contact with two plastic films (one containing dibutyl and the other dicyclohexyl phthalates) extracted less than one percent of the esters after one month at 25°C. The concentrations in the food were reported as less than 2 ppm.

Food and Drug Administration (FDA) surveys indicate that several of the phthalate esters are present in food and fish which have had contact with plastic packaging systems such as polyvinyl chloride (PVC). Some data on the residue of the esters in Japanese foods have also been reported. Table 1, taken from the study by Tomita, et al. (1977) shows the amounts of several agents migrating to selected Japanese foods packaged in plastics, laminated films, paper, and aluminum foil. As will be noted, levels above 600 ppm and even higher than 3,000 ppm of total phthalates migrated to certain foods.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

An average measured steady-state bioconcentration factor of about 330 was obtained for di-2-ethylhexyl phthalate using fathead minnows (Mayer,

TABLE 1

Migration of Phthalic Acid Esters from Packaging Film to Foodstuffs*

Foodstuffs		Time after Manufacture (months)	Packaging Materials (ppm)				Foodstuffs (ppm)		
			Materials**	DNBP	DEHP	Total	DNBP	DEHP	Total
Tempura (frying) powder	A	3	Pl-l	70.28	3,675.0	3,745.28	14.70	68.08	82.78
	B	4	Pl-L	6.29	2.30	8.59	0.39	0.11	0.50
Instant cream soup	A	14	P-Al-Pl	23.17	1.35	24.52	1.73	0.04	1.77
	B	?	P-Al-Pl	586.16	58.92	647.08	60.37	2.15	62.52
	C	?	P-Al-Pl	588.75	58.93	647.08	51.79	3.01	54.80
Instant soybean soup		?	P-Pl	2.75	1.85	4.60	nd	nd	nd
Soft margarine		4	Pl	1.29	1.44	2.73	nd	nd	nd
Fried potato cake	A	1	P-PL	10.86	385.85	396.91	1.11	0.05	1.16
	B	?	P-PL	10,66	1.28	11.94	nd	nd	nd
	C	?	P-PL	22.98	11.80	34.78	1.21	9.06	10.27
Orange juice		1	P-Pl	1.52	0.74	2.26	0.35	0.05	0.40
Red ginger pickles		?	Pl	7.24	2.75	9.99	nd	nd	nd
Table salt		?	P-Pl	5.18	2.58	7.76	nd	nd	nd

*Source: Tomita, et al. 1977

**Pl indicates plastic, L indicates laminated film, P indicates paper, Al indicates aluminum foil.

1976). Similar fathead minnows contained an average of 7.6 percent lipids (Veith, 1980). An adjustment factor of 3.0/7.6 = 0.395 can be used to adjust the measured BCF from the 7.6 percent lipids of the fathead minnow to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for di-2-ethylhexyl phthalate, and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 330 x 0.395 = 130.

Measured steady-state bioconcentration factors of 57, 117, and 663 were obtained for dimethyl, diethyl, and butylbenzyl phthalates, respectively, using bluegills (U.S. EPA 1980). Similar bluegills contained an average of 4.8 percent lipids (Johnson, 1980). An adjustment factor of 3.0/4.8 = 0.625 can be used to adjust the measured BCF from the 4.8 percent lipids of the bluegill to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factors for dimethyl, diethyl, and butylbenzyl phthalates, and the edible portion of all freshwater and estuarine organisms consumed by Americans are calculated to be 36, 73, and 414, respectively.

No measured steady-state bioconcentration factor with an appropriate percent lipids is available for dibutyl phthalate. However, log BCF is nearly proportional to log P (Veith, et al. 1979). Thus, using values for log P (Hansh and Leo, 1979) and the weighted average BCF values of 73 and 130 derived above for diethyl and di-2-ethylhexyl phthalates, respectively, the weighted average bioconcentration factor for dibutyl phthlate and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is estimated to be 89.

Inhalation

This route may be a significant portal of entrance for esters of phthalic acid, at least to selected populations at risk. The presence of the esters in air for relatively short periods of time most likely is due to the incineration of PVC items. In closed spaces such as automobiles having PVC furnishings, the ester can volatilize and the persons inside the vehicle will inhale the vapors.

In closed rooms which have PVC tiles, levels of esters may reach 0.15 to 0.26 mg/m^3 (Peakall, 1975). Mens'shikova (1971) reported the presence of dibutyl phthalate (DBP) from ship quarters furnished with PVC tile, decorative laminated plastics and pavinols (assumed to be PVC plastics). He reported that even after three years, the level of DBP in the air of the rooms contained from 0 to 1.22 mg/m^3 of the ester.

Milkov, et al. (1973) reported that vapors or aerosols of phthalate esters ranged from 1.7 to 40 mg/m^3 at one working site where mixing was done, and a level of 10 to 66 mg/m^3 at another working site in a company manufacturing artificial leather and films of PVC.

American published reports regarding levels of esters in the working environment are rare. Thus, insufficient data are available to judge what levels of these esters are present in various working sites manufacturing the esters or using the esters for consumer products.

It seems reasonable to assume that certain workers will be exposed to the phthalic acid esters in the form of the vapor or as mists. Depending upon the hygiene standard maintained, these workers could inhale sufficient concentrations of the ester to lead to health problems.

Dermal

The phthalate esters can be absorbed through the skin and this route may thus become an important portal of entrance. Many cosmetic products may contain small concentrations of the lower molecular weight phthalate esters such as diethyl phthalate, and thus, application to the skin could introduce the ester to humans through the skin. Because dimethyl phthalate is used as a mosquito repellent, dermal absorption can occur. Swimming pools lined with PVC could also release the phthalate esters to the water and, in turn, swimmers would be exposed to very minute concentrations of the plasticizer (phthalate esters) which could then be absorbed through the skin. As with the other routes, lack of available data prevents even a very crude projection of the levels of esters which could enter man through the skin.

Because a number of medical devices such as blood bags, infusion containers, collection and administration tubings, and catheters are prepared from plasticized (generally DEHP) polyvinyl chloride, a parenteral route of entrance into a selected human population becomes a possibility. In fact, it is possible that the parenteral route contributes the greatest quantity of the esters to selected groups under medical care in hospitals. These medical devices have been introduced into medical practice since Walter (1951) first introduced the polyvinyl chloride blood bag in 1950, and thus, "many millions of persons have been exposed to phthalate esters by the parenteral route."

The total number of renal hemodialyses performed each year in the United States has reached close to six million. A single five-hour dialysis will expose these patients to approximately 150 mg of DEHP. In open heart surgery, extra corporeal pump oxygenators are used. Approximately 360,000 such operations are performed each year. Under these conditions, a patient may be exposed to an average of 33 mg of DEHP during the surgery.

As early as 1960, a report appeared by Meyler, et al. (1960) that certain medically used PVC tubings released toxic ingredients to solutions passed through them. Isolated heart experiments were used to detect toxic ingredients released from PVC. Since these specific "toxic" tubings contained an organotin stabilizer, the authors surmised that the toxic component was the stabilizer and not the phthalate ester.

Braun and Kummel (1963) reported that PVC containers used for storage of blood and transfusion solutions did release phthalate esters as well as other additives to an extracting medium (water).

A report by Guess, et al. (1967) revealed that a number of American PVC blood bags containing an anticoagulant solution (ACD) were contaminated by the presence of small amounts of DEHP, 2-ethylhexanol, phthalic anhydride, phthalic acid, and some unidentified chemicals.

Jaeger and Rubin (1970) reported the release of phthalate esters from PVC blood bags and tubings, and further identified these plasticizers in tissues and organs of two deceased patients who previously were transfused with blood from PVC blood bags.

Hillman, et al. (1975) identified the presence of DEHP in neonatal tissues after the insertion of umbilical catheters. It was interesting to note that three infants who died of necrotizing enterocolitis had significantly higher DEHP values in the gut than infants not having this disorder. There was generally an increase in DEHP content of tissue if the specific patient had also received blood products. Residue levels were measured in both heart and gastrointestinal tissues. The average level of DEHP in heart tissue was 1.27 µg/g. In the gut of the three patients having died of gastrointestinal disorders, the levels ranged from 0.016 to 0.63 µg/g.

It is now well recognized that plasticized PVC medical devices will release the plasticizers to tissue and to solutions in contact with the object. Extraction of a plasticizer such as DEHP with water is extremely small with the present PVC blood bags and infusion containers, but if lipoidal solutions such as blood and blood fractions are used, the extent of release becomes significant.

The quantity of di-2-ethylhexyl phthalate released into stored blood at 4°C for 21 days ranges from 5 to 7 mg/100 ml (Jaeger and Rubin, 1972).

Kevy, et al. (1978) have done extensive studies on DEHP and found the plasticizer to be extracted from PVC storage containers into blood and blood components. A summary of some of their extract results is shown in Table 2.

Needham and Luzzi (1973) and Needham and Jones (1978) indicated that when PVC infusion containers containing normal saline were agitated, DEHP would occur in colloidal form in the saline. Even under this condition, however, the total concentration of the colloidal particles came to 0.1 ppm (Darby and Ausman, 1974). The presence of ethyl alcohol in the solution will increase the level of DEHP in the solution. A 10 percent solution will increase the DEHP content to 6 ppm, while a concentration of 40 percent will increase the DEHP in the solution to 30 ppm (Corley, et al. 1977).

The total quantity of DEHP that a transfused patient may receive parenterally will, of course, depend upon the number of units of blood or blood products administered to him. Patients undergoing chronic transfusions with whole blood, packed cells, platelets, and plasma stored in PVC containers

TABLE 2

Extraction Data of DEHP from PVC Containers*

1.	Normal whole blood stored at 4°C contains 0.19 mg percent DEHP on collection and 5.84 mg percent after 21 days of storage.
2.	Cryoprecipitate which is prepared and stored at -30°C contains low levels of DEHP (1.05 to 2.6 mg percent).
3.	The level of DEHP in stored platelets maintained at 4°C and 22°C after 72 hours is 10.85 mg percent and 43.21 mg percent, respectively.

*Source: Kevy, et al. 1978

may receive a total of approximately 70 mg of DEHP. There are cases, however, when a patient may receive as many as 63 units of blood containing approximately 600 mg of DEHP (Jaeger and Rubin, 1972).

PHARMACOKINETICS

Absorption

The phthalic acid esters and/or their metabolites are readily absorbed from the intestinal tract, the intraperitoneal cavity, and the lungs. There is also evidence indicating that these esters can be absorbed through the skin. As will be pointed out, the vehicle can play an important role in the absorption, distribution, and elimination of the ester.

Schulz and Rubin (1973) administered orally to rats ^{14}C-DEHP in corn oil and found that approximately 13 percent of the administered dose was found in the organic solvent extracts of urine, feces, and contents of the large intestine. The urine contained about 62 percent in water extracts. Daniel and Bratt (1974) injected a single oral dose of ^{14}C-DEHP in rats and found 42 percent and 57 percent of the dose in the urine and feces, respectively, in seven days. They also pointed out that a significant amount of the dose is excreted in bile. In studies by Wallin, et al. (1974) rats were orally administered ring or side chain-labeled DEHP. Twenty-four hours after the dose was given, approximately 50 percent of the recovered radioactivity was found in the feces and in the gastrointestinal tract contents. The remaining radioactive substance was recovered in the urine. The authors also indicated that "a portion of the radioactivity recovered from the feces undoubtedly had been absorbed but returned to the gut in the bile."

Lake, et al. (1975) have suggested that orally administered phthalic acid esters are absorbed in the gut primarily as monoesters. Wallen, et al. (1974) however, found from their studies that a significant amount of orally administered DEHP is absorbed in the gastrointestinal tract as the intact compound. From the present data, it appears clear that the diester phthalates can be hydrolyzed to the monoester in the gut and thus be absorbed as the monoester. Further studies are needed to clarify the ratio of intact diester to monoester which would be absorbed in the gut under various conditions in several species of animals.

Information on the absorption of the phthalic acid esters in man is limited. As early as 1945, however, Shaffer, et al. (1945) reported that a single oral dose of 10 g DEHP in a human subject was recovered as a phthalate equivalent in the urine after 24 hours. The amount recovered was 4.5 percent of the original dose. In another subject, 5 g DEHP was taken orally and 2.0 percent of the original dose (as phthalate equivalent) was found in the urine 24 hours later. Tomita, et al. (1977) reported the presence of phthalate esters in the blood of individuals having ingested food which had been in contact with flexible plastics having the phthalic acid esters. DEHP and di-n-butyl phthalate (DNBP) levels detected in the blood after meals were much higher than prior to eating the foods in the plastic packaging system. In 13 individuals who were included in the study, DEHP and DNBP in the blood ranged from 0.13 to 0.35 ppm when compared to an average value of 0.02 ppm prior to the meals.

Dillingham and Pesh-Imam detected nine percent in urine 24 hours after labeled DEHP had been applied to rabbit skin. After 48 hours, the levels in the urine had increased to 14 percent and within 72 hours the radioactivity had increased to 16 to 20 percent of the originally administered dose.

Distribution

Absorbed esters of phthalic acid esters (or their metabolites) distribute quite rapidly to various organs and tissues both in animals and humans.

Again, it must be kept in mind that, depending upon the route and the physical form of the ester (true solution, colloid, emulsion), the distribution of the esters (metabolites) can vary. Jaeger and Rubin (1970) studied the distribution of DEHP in human tissues of two deceased patients having had large volumes of blood (stored in PVC blood bags) transfused into them. They detected the presence of DEHP in the spleen, liver, lung, and abdominal fat with concentrations ranging from 0.025 mg/g in spleen to 0.270 mg/g in abdominal fat.

Radio-labeled DEHP (emulsified in oleic acid) administered intravenously (i.v.) as a single dose was found to disappear rapidly from the blood and approximately 60 to 70 percent of the total dose was detected in the liver and lungs within two hours of the dose (Daniel and Bratt, 1974). In studies in which rats were maintained on diets containing DEHP, there was a progressive increase in the amount of the compound in the liver and abdominal fat of the animals but within a short time a steady state concentration was achieved (Daniel and Bratt, 1974).

Waddell, et al. (1977) examined the distribution of ^{14}C-DEHP (serum solubilized) after a single i.v. injection in rats using whole body autoradiography techniques. Results from the study revealed that a rapid accumulation of radioactivity in the kidney and the liver had occurred followed by rapid excretion into urine, bile, and intestine. No accumulation of the compound was found (up to 168 hours after the injection) in the spleen and lung, but significant radioactivity was detected in the lumen of the intestine which the authors surmised occurred because of the secretion of the compound by the liver into the bile.

Tanaka, et al. (1975) administered ^{14}C-DEHP solubilized in Tween 80® orally to groups of rats. The concentrations in the liver and kidney tissues and organs. A study by Jacobson, et al. (1977), in which nonhuman primates were transfused with blood containing DEHP following a procedure of treatment common to humans, revealed the presence of DEHP (or metabolites) in trace amounts even up to 14 months post-transfusion. As pointed out by Daniel and Bratt, (1974), there probably is a steady state concentration which is reached after which the esters (or metabolites) are then rapidly eliminated from the organs or tissues through various routes, thus preventing significant accumulation over long periods of exposure.

Metabolism

Albro, et al. (1973) have identified the metabolites of DEHP after oral feeding to rats. These authors conclude that the first step in the metabolism is the conversion of the diester to monoester (mono-2-ethylhexyl phthalate). By ω- and (ω-1) oxidation, the side chain of the monoester forms two different alcohol intermediates. Further oxidation of the alcohols leads to the corresponding carboxylic acid or ketone and, in turn, the acid may be further oxidized (β-oxidation). Figure 1 shows a number of products which can be formed from metabolism of orally ingested DEHP (in rats). Lack of detailed data on the metabolism of other esters in various species of animals and in humans prevents a clear understanding of what metabolic products are formed in other species. It seems clear, however, that for DEHP a significant biotransformation can take place in the gut (DEHP to the monoester) and thus the same possibility may also be true in other higher orders of animals and in man. The absorbed intact DEHP and/or the monoester is then further metabolized in the liver.

Excretion

For the most part, the esters of phthalic acid in animals and man are excreted readily in urine and feces. For example, Lake, et al. (1975) found

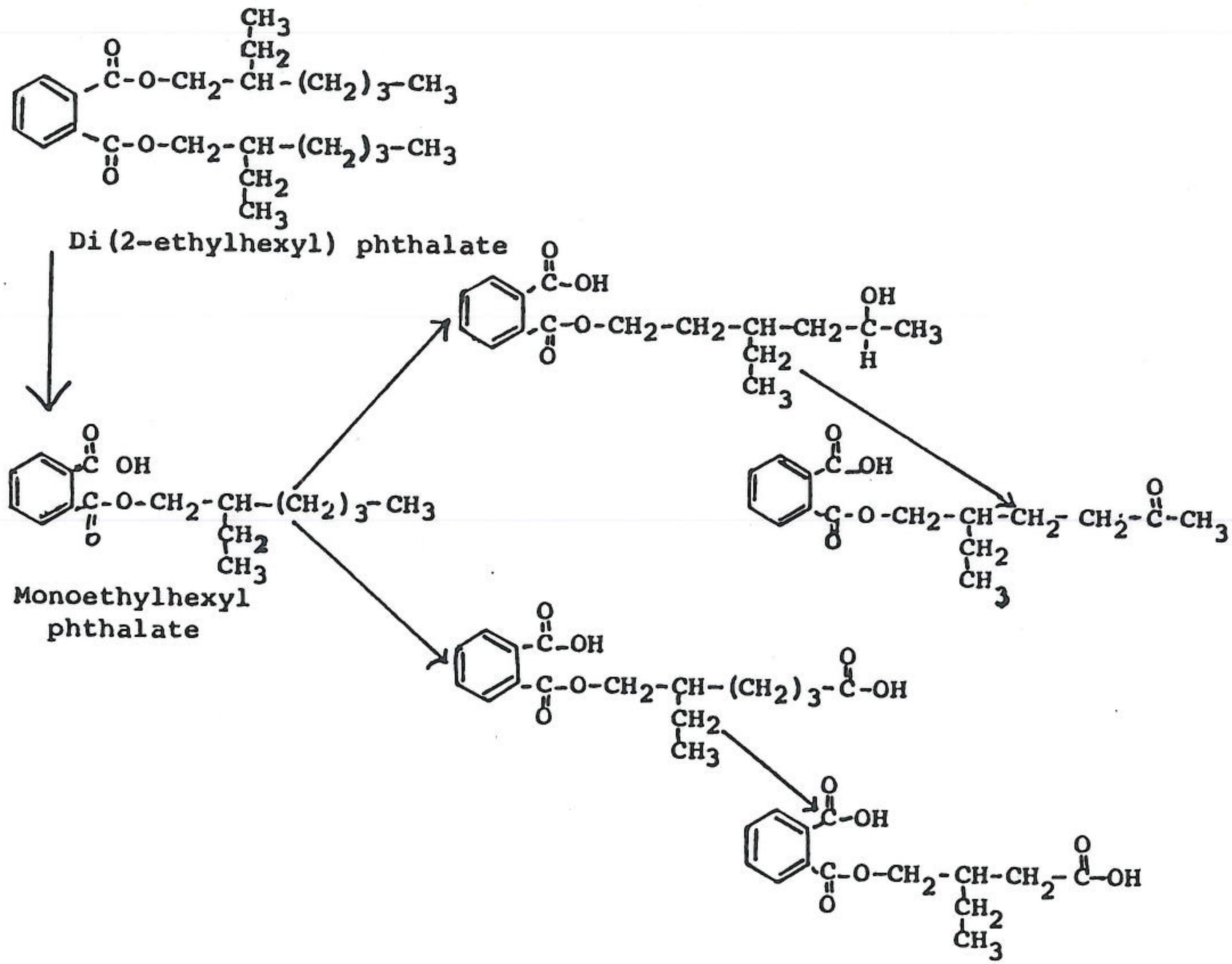

FIGURE 1

Routes of Metabolism of Di(2-ethylhexyl) Phthalate

Source: Albro, et al. 1973

that a single oral dose of labeled DEHP was practically all excreted in urine and feces within a four day period, leaving less than 0.1 percent of the radioactivity in the organs and tissues. Rats pretreated with DEHP for 6 and 13 days also showed a similar elimination rate upon the administration of labeled DEHP. Excretion into bile also appears to be a significant route of excretion increasing the content of DEHP (or metabolites) in the intestine.

Schulz and Rubin (1973) intravenously administered labeled DEHP to groups of rats and then monitored the radioactivity in blood versus time. They noted a bi-phasic curve when the data were plotted as log DEHP vs. time. The initial slope led to a half-life in blood of nine minutes while the second slope gave a half-life of 22 minutes. Within one hour, 8 percent of the total injected DEHP was found in water-soluble metabolites, primarily in the liver, intestinal contents and urine. Twenty-four hours after injection, 54.6 percent of the initial dose was recovered as water-soluble metabolites primarily in the intestinal tract, excreted feces, and urine. Only 20.5 percent was recovered in organic extractable form.

Dillingham and Pesh-Imam studied the excretion in the urine of mice of labeled DEHP administered i.p. (as pure ester) and i.v. (as saturated saline solution), (Autian, 1973). They noted that 68 percent and 63 percent, respectively, of the total initial dose was excreted in seven days.

Tanaka, et al. (1975) reported about 80 percent of the original labeled DEHP given orally or by i.v. to rats was excreted in the urine and feces in five to seven days. These authors also pointed out that, upon a single oral administration of DEHP, the intact diester could not be identified in the urine. On the other hand, repeated oral administration of 500 mg/kg in rats for 20 days revealed the presence of intact DEHP in the urine. They concluded that "repeated administration of DEHP may lead to its accumulation in the body until a steady state is reached between the rates of absorption and elimination." After steady state is reached, DEHP as the unchanged molecule, would appear in the urine.

As Thomas, et al. (1978) have expressed in their review article on biological effects of DEHP, pharmacokinetic data in animals and humans support the thesis that DEHP is absorbed from the gastrointestinal tract and widely distributed to various tissues following either the oral or i.v. routes of administration. DEHP is then rapidly metabolized to a number of derivatives of mono-2-ethylhexyl phthalate which are, in turn, excreted mainly in the urine. The half-life of elimination from tissues and the body is short.

EFFECTS

Acute, Subacute, and Chronic Toxicity

One of the first comprehensive reviews on the toxicity of phthalate esters was presented by Autian in 1973. A much more detailed review of the phthalate esters was given by Peakall in 1975 and the most recent one on this subject was published by Thomas, et al. in 1978. The potential health threats of phthalic acid esters in the early seventies led to a national conference on the subject in 1972. The papers presented at this meeting were published in the January 1973 issue of Environmental Health Perspectives. As will become evident, most of the detailed toxicological studies have centered primarily on DEHP since this specific ester accounts for approximately 40 percent of the phthalates which are used commercially.

From the accumulated data on acute toxicity in animals, the phthalate esters may be considered as having a rather low order of toxicity. It is now thought that the toxic effect of the esters is most likely due to one of the metabolites in particular to the monoester. This appears to be the case for DEHP since this ester has been studied more extensively than the others. Table 3 is taken from Autian's 1973 review and lists the LD_{50} of the esters. Oral acute toxicity for the lower molecular weight esters is greater in animals than for the higher molecular weight esters such as DEHP. Other routes of administration such as i.p. and dermal do not significantly increase the acute toxicity (Autian, 1973).

The toxicity of DEHP by the i.v. route is quite important since, as has been indicated previously, PVC administration devices will leach the plasticizer into blood and lipo-protein-containing solutions. Since DEHP has a very limited solubility in water, other means of administering the agent in experimental animals have been used to study the toxic effects when administered i.v. Preparation of emulsions or dispersion of DEHP in various vehicles may induce toxic responses when injected i.v. which may not occur when DEHP is solubilized by having the ester migrate from PVC into blood. Studies by Stern, et al. (1977) have indicated that the pharmacokinetic pattern for DEHP will be different depending upon the vehicle which is used and they make the suggestion that i.v. studies should be performed on the extracted DEHP which will take place when the blood product is placeed in contact with a PVC device. Since DEHP will have a limited solubility in blood and blood products, the total dose given to animals will be relatively small and, in general, no acute toxicity would be expected. Rubin (1976), however, has suggested the possibility of "shocked lungs" when DEHP is administered i.v. and has presented experimental evidence in rats to support this contention. This is discussed in a subsequent section of this report. The low volatility of most of the esters precludes them from presenting an acute toxic response by inhalation. Generally, at least for the higher molecular weight

TABLE 3

Acute Toxicity of Phthalate Esters: LD_{50} in Animals*

Compound	Animal	Route	LD_{50} g/Kg
Dimethyl phthalate	Mouse	oral	7.2
	Mouse	i.p.	3.6
	Mouse	i.p.	1.58
	Rat	oral	2.4
	Rat	i.p.	3.38a
	Guinea pig	oral	2.4
	Rabbit	dermal	10.0a
Diethyl phthalate	Mouse	i.p.	2.8
	Mouse	i.p.	2.8
	Rat	i.p.	5.06a
	Rabbit	oral	1.0
Dimethoxyethyl phthalate	Mouse	oral	3.2-6.4
	Mouse	i.p.	2.51
	Rat	oral	4.4
	Rat	i.p.	3.7
	Guinea pig	oral	1.6-3.2
	Guinea pig	dermal	10.0
Diallyl phthalate	Mouse	i.p.	0.7
	Rat	oral	1.7
	Rabbit	oral	1.7
	Rabbit	dermal	3.4a
Dibutyl phthalate	Mouse	i.p.	4.0
	Rat	i.p.	3.05a
	Rat	i.m.	8.0
	Rabbit	dermal	20.0a
Diisobutyl phthalate	Mouse	oral	12.8
	Mouse	i.p.	4.50
	Rat	i.p.	3.75a
	Guinea pig	dermal	10.0a
Butyl carbobutoxy methyl phthalate	Rat	oral	14.6a
	Rat	i.p.	6.89

TABLE 3 (cont.)

Compound	Animal	Route	LD_{50} g/Kg
Dihexyl phthalate	Rat	oral	30.0
	Rabbit	dermal	20.0a
Dioctyl phthalate	Mouse	oral	13.0
	Rat	i.p.	50.0a
	Guinea pig	dermal	5.0a
Di-2-ethyhexyl phthalate	Mouse	i.p.	14.2
	Rat	oral	26.0
	Rat	i.p.	50.0a
	Rabbit	oral	34.0
	Guinea pig	dermal	10.0
Butylbenzyl phthalate	Mouse	i.p.	3.16
Dicapryl phthalate	Mouse	i.p.	14.2
Dinonyl phthalate	Rat	oral	2.00
Dibutyl (diethylene glycol bisphthalate)	Mouse	oral	11.2
	Mouse	i.p.	11.2
	Rat	oral	11.2
	Rat	i.p.	11.2
Dialkyl phthalate	Mouse	oral	20.00
	Rat	i.p.	20.00

*Source: Autian, 1973

[a]LD_{50} in ml/kg

phthalic acid esters, only through heating will there be sufficient vapor concentration to carry out an adequate inhalation study.

Even though the phthalate esters have been in commercial production for nearly 50 years, relatively few long-term toxicity studies appear in the literature. As would be expected, subacute (or subchronic) studies are more plentiful but even these are few when one considers the large production of these agents every year. Perhaps the meager toxicological data can be attributed to the long use of these esters with relatively few episodes of ill effects among the general population. Also, it is possible that a number of these esters have been studied in more toxicological detail by industry without the results appearing in published form. A general indication of long-term toxicity of phthalate esters can be seen in Table 4 in which Krauskopf (1973) has summarized the maximum no-effect dose for several esters.

Dimethyl Phthalate: Dimethyl phthalate is used as an effective mosquito repellent. In human experience, few toxic effects from this ester have been noted. Two-year feeding studies in female rats by Draize, et al. (1948) at levels of 2 and 8 percent in the diet produced only a minor growth effect at the 4 and 8 percent levels. At the 8 percent level, some indication of nephritic involvement was detected. Dose levels less than 8 percent showed no such effect. A 90-day study in which the ester was applied to the skin of rabbits led to an LD_{50} of greater than 4 ml/kg. The ester does not produce primary irritation on the skin nor has it been found to act as a sensitizing agent.

Diethyl Phthalate: This ester has been used as a plasticizer for cellulose materials and as a perfume carrier. Nearly 50 years ago, Smith (1924) reported that rats could tolerate up to 0.5 percent of their body weight of

TABLE 4

Calculated Allowable Daily Intake (ADI) for Various Phthalate Esters*

Ester	Species	Period Days	Maximum No-Effect Level (mg/kg/day)
Di-2-ethylhexyl	Rat	365	400
	Rat	730	80
	Dog	98	100
	Rat	90	200
	Dog	98	100
	Rat	365	60-200
	Guinea pig	365	60
	Dog	365	60
Dibutyl	Rat	365	350-110
	Rat	450	4.3
Diisonyl	Rat	91	150
	Dog	91	37
Heptyl nonyl	Rat	90	60
	Mouse	90	60

*Source: Krauskopf, 1973

this ester without death occurring. Rabbits could be fed 3 ml/kg/day without significant toxic response (Blickensdorfer and Templeton, 1930).

In a two year study (Food Research Laboratories, Inc., 1955) groups of 30 rats (15 of each sex) were fed either 0.5, 2.5, or 5.0 percent diethyl phthalate in the diet. No effects were observed at levels of 0.5 or 2.5 percent. Diethyl phthalate at 5.0 percent resulted in a small but significant decrease in the growth rate of the rats without any effect on food consumption. Thus, 5.0 percent diethyl phthalate appeared to affect the efficiency of food conversion. Also in this study, dogs were fed diethyl phthalate at levels of 0.5, 1.5, 2.0, and 2.5 percent for one year. Problems were encountered with palatability of diethyl phthalate in the diet. As a result, the dogs received varying exposures to diethyl phthalate before each dog attained stabilization at the highest dietary level that could be tolerated. Accordingly, three dogs were maintained at 0.5 percent, one each at 1.5 and 2.0 percent, and three at the 2.5 percent level. The average weekly intakes of diethyl phthalate were computed and found to be 0.8, 2.4, 3.5, and 4.4 g/kg/week in order corresponding to increasing dietary level. No effects were noted at any of these levels.

Diethyl phthalate does not act as a primary irritant when applied to the skin nor has it induced allergic responses in humans who have contact with it. Heated vapors may produce slight irritancy in mucous membranes of the nasal passages and may also irritate the upper respiratory tract.

Even though diethyl phthalate is not generally used as a plasticizer in PVC tubings, Neergaard, et al. (1975) reported that this ester was present in tubings used in hemodialysis equipment and that the use of these tubings led to hepatitis in several patients. When other tubings, presumably without diethyl phthalate, were used the hepatitis did not occur. It seems unlikely that the ester was responsible for the hepatitis and the cause may have been related to another additive in the tubing.

Dibutyl Phthalate: Smith (1953) studied the effects of feeding dibutyl phthalate to groups of rats. At concentrations of 0.01, 0.05, and 0.25 percent of dibutyl phthalate in food, no adverse effects were noted after one year. When the dose level was increased to 1.25 percent, approximately half of the animals died in the first week but the remaining animals grew normally as compared to the untreated controls.

Spasovski (1964) conducted an inhalation study lasting 93 days during which mice were exposed for six hours a day to different concentrations of the ester. The concentrations ranged from 0.017 to 0.42 mg/m^3. Unfortunately, during the study, the same animals received various exposure concentrations rather than specific concentrations for the whole time period and thus interpretation of the results is difficult even though Spasovski proposed a permissible standard concentration (PSC) of 1 mg/m^3. Dvoskin, et al. (1961) exposed groups of rats to 0.2 and 0.4 mg/m^3 for 2.5 months. Some weight loss was noted and an increase of gamma globulin was reported for the animals receiving the higher exposure during the fourth and sixth weeks of the experiments. The same group of animals also demonstrated alterations in the phagocytic activity of neutrophils after one month; these returned to normal. It is difficult to conclude from this study the significance of the results in regard to the toxic potential of dibutyl phthalate when inhaled.

A much more detailed study on the inhalation of dibutyl phthalate has been reported by Men'shikova (1971). Rats were exposed continuously for 93 days at chamber concentrations of 0.098, 0.256 and 0.98 mg/m^3. No behavioral changes were noted nor any weight loss discerned. The important finding was that gamma globulin was increased and appeared to be dose related. In humans, Men'shikova (1971) found an olfactory threshold value ranging from 0.26 to 1.47 mg/m^3. Atmospheric concentrations of 0.12 and 0.15 mg/m^3 resulted in abnormal encephalographic responses in the three human subjects in the study. When the level was reduced to 0.093 mg/m^3 no conditioned reflex was noted. Men'sikova recommends a PSC value of 0.1 mg/m^3.

Carter, et al. (1977) described a study on dibutyl phthalate and the resultant testicular atrophy which occurred. In the study, the ester was dissolved in corn oil and administered orally (by intubation) for a period of time. The dose administered was 2,000 mg/kg while control animals received corn oil in a volume of 5 ml/kg. The initial effect noted was a progressive reduction in weight of the testes. In 14 days, the reduction amounted to 60 to 70 percent of the original weight. Since there was also a decrease in body weight, the authors used "relative testes weight" and found that even in this manner of reporting there was still a significant loss (testes weight). Histopathological methods on testes tissue demonstrated morphological damage. Further investigations by these authors revealed that the ester apparently influenced zinc metabolism with an increase in the excretion of zinc in urine. It was visualized that after oral administration, dibutyl phthalate is metabolized by nonspecific esterases in the gastrointestinal tract to the monobutyl phthalate prior to absorption into the bloodstream. Results from the various experiments have led the authors to suggest that the monoester or another metabolite of dibutyl phthalate may be acting as a chelating agent by removing the zinc from the testes. The deficiency of zinc in testes tissues is, according to the authors, the causative factor leading to the atrophized organ.

Milkov, et al. (1973) reported in 1969 that a group of esters in an industrial environment produced various degrees of toxic polyneuritis. These investigators studied 147 persons (87 women and 60 men), the majority of whom were not more than 40 years old. These industrial workers were exposed primarily to dibutyl phthalate but other esters apparently were also present but in much lower concentrations. These included dioctyl, diisooctyl and benzyl butyl phthalates. Also, in some instances there were small amounts of sebacates, adipates, and tricresyl phosphate.

Until more occupational studies are performed, the report by Milkov, et al. (1973) must be taken with some reservation because of the presence of other chemical agents such as tricresyl phosphate, an agent known for inducing polyneuritis.

Dibutyl (diethylene glycol bisphthalate) (DDGB): Hall, et al. (1966) studied the toxicity of DDGB. They used a commercial sample which also contained 15 percent dibutyl phthalate and 5 percent (diethylene glycol) phthalate. The oral LD_{50} of this product in rats was found to be greater than 11.2 g/kg and the i.p. LD_{50} approximately 11.2 g/kg. A 12-week toxicity study was conducted on the product using rats as the test animals. Diets in different groups of rats contained 0, 0.25, 1.0, and 2.5 percent of the product, respectively. Over the period of the study, there was a marked reduction of growth in the treated animals as compared with the control group. Also evident were enlargements of the liver and heart at the 1.0 and 2.5 percent levels in male rats and enlarged brain in both male and female animals. At the 2.5 percent level, oxaluria and hematuria were found in both sexes, the oxaluria being assumed to be a direct consequence of the *in vivo* liberation of diethylene glycol (a known producer of oxalate stones in the bladder).

Ethylphthalyl ethyl glycolate (EPEG): Hodge, et al. (1953) conducted a chronic oral toxicity study with EPEG in rats for two years and dogs for one year. Groups of 50 rats (25 of each sex) were fed either 0, 0.05, 0.5, or 5.0 percent EPEG in the diet. No effects were observed at levels of 0.05 or 0.5 percent. EPEG at 5.0 percent resulted in decreased growth and survival. Kidney damage was also observed at 5.0 percent EPEG. This consisted of mottled granular kidneys, sometimes swollen and pale yellow. The pelvis of the kidney was usually dilated, and frequently a hard, stag-horn calculus, a fine sand, or both were seen. In the study performed with dogs, dose levels of 0, 0.01, 0.05, and 0.25 gm/kg/day were used with two male dogs per dose level. No effects were observed at any of these levels.

Butylphthalyl butyl glycolate (BPBG): Information on the chronic toxicity of BPBG comes from two unpublished reports to the FDA.

Sovler, et al. (1950) conducted a two-year feeding study in rats (10 per exposure group) at levels of 0.02, 0.2, or 2.0 percent BPBG in the diet. Sovler, et al. reported that there was no evidence of toxicity or retardation of growth at any of the levels of BPBG. In the second study (Hazleton Laboratories, 1950) groups of 20 rats were fed average daily doses of either 4, 40, or 389 mg/kg/day in order corresponding to 0.02, 0.2, and 2.0 percent BPBG in the dietary levels of BPBG.

Butyl benzyl phthalate: Mallette and Von Hamm (1952) administered both orally (1.8 g/kg) and i.p. (4 g/kg) butyl benzyl phthalate to groups of rats. Animals died after four to eight days and histopathological studies demonstrated toxic splenitis and degeneration of central nervous system tissue with congestive encephalopathy. Further, myelin degeneration and glial proliferation were reported.

Dialkyl 79 phthalate: This product contains a mixture of phthalate esters of alcohols having chain lengths of seven to nine carbons. In a 90-day feeding study in rats by Gaunt, et al. (1968) no demonstrable adverse effects were noted at diet levels of 0.125 percent, but at the 0.5 and 1.0 percent levels, increased liver weights were observed even though histopathological changes were not seen. The authors concluded that a 60 kg adult could ingest 36 mg/day without any apparent harm.

Di-2-ethylhexyl phthalate (DEHP): As has been indicated a number of times, this ester is the most used phthalate and for this reason more toxicological data are available on it than any of the other esters. It should be remembered that DEHP is often used synonymously with the dioctyl phthalate and, even though they are isomers, they have slightly different biological properties. The acute oral toxicity for rodents ranges from 14.2 to greater than 50 g/kg. Dermal absorption occurs but in rabbits approximately 25 ml/kg must be applied to the skin to cause death.

In 1945, Shaffer, et al. (1945) reported a 90-day subacute toxicity study in rats. Groups of animals were given in feed 0.375, 0.75, 1.5, and 3.0 percent of the ester which approximates daily intakes of 0.2, 0.4, 0.9, and 1.9 g DEHP/kg per rat in the four treated groups while the fifth group served as a control (no phthalate). At the three higher levels (0.75, 1.5, 3.0), a slight decrease in growth was noted when compared to the control animals. At the 1.5 and 3.0 percent doses, tubular atrophy and degeneration in the testes were observed. No deaths occurred in any of the treated animals while blood cell counts, hemoglobin concentrations and differential white cell counts remained normal. The authors concluded that no adverse effect from oral administration would occur at approximately 0.2 g/kg/day or less while only a slight retardation in growth may occur when the dose is increased to 0.4 g/kg/day.

Carpenter, et al. (1953) conducted a study on chronic oral toxicity of DEHP using rats, guinea pigs, and dogs. In the rat study, parental (P_1) generation rats received daily diets containing 0.04, 0.13, and 0.4 percent of DEHP for a maximum period of two years. In addition, a group of filial generation (F_1) rats were given in feed 0.4 percent of DEHP for one year. Control groups of rats were maintained on the same basic diet without the ester. The investigators examined the following signs and symptoms of toxicity: mortality, life expectancy, body weight, food consumption, liver and kidney weights, micropathological changes, neoplasm, hematology and fertility.

Over the two-year period for the P_1 group and over a one-year period for the F_1 group, a number of deaths occurred. However, these deaths were not attributed to the ester since they were also noted in the control animals.

The mean liver and kidney weights, as percentage of body weights, were found to be increased over those of the controls in both the initial group (P_1) and their offspring (F_1) which had received the diet containing 0.4 percent DEHP. The results were statistically significant. Histopathological examination of the liver and kidney tissues of treated animals did not reveal statistically significant differences from organs of control animals. The authors did suggest that even though pathological changes in the two organs of treated groups were not different from control animals, the increase in size of the organs may indicate a toxic response. Results from comparisons of life expectancy, body weight, food consumption, neoplasia, hematology and fertility in the treated animals were found not to differ significantly from controls.

In another study by the same investigators (Carpenter, et al. 1953), groups of guinea pigs were administered in diet 0.04 and 0.13 percent DEHP for one year. Similar criteria, with the exception of hematology and fertility, as used in the rat study were employed. Liver weights, as percentage of body weights, were found to be statistically higher in the treated groups than in the control animals. The authors pointed out that the effect was not related to the concentrations since both treated groups appeared to be about the same in regard to liver weight. The other parameters studied were found not to be significantly different from control animals. A "no effect" dose for DEHP in guinea pigs (for one year) was estimated to be 0.06 g/kg/day.

A one-year study was also reported by Carpenter, et al. (1953). In this study, dogs were administered capsules with 0.013 ml/kg/day DEHP, five days a week, for the first 19 doses and then 0.06 ml/kg/day until 240 doses had been administered. No statistically significant adverse effects were seen. The authors concluded that a "no effect" dose in dogs would be approximatley 0.06 g/kg/day.

Harris, et al. (1956) published a paper which, in effect, confirmed the results of Carpenter, et al. (1953). A chronic oral toxicity study in male and female rats was conducted in which groups of animals received in their feed 0, 0.1 and 0.5 percent DEHP. At various time periods, rats were sacrificed and food consumption records, body weight, and liver, testes, kidneys, lungs, brain, stomach, heart and spleen weights examined. Histopathological studies were also conducted on selected tissues and organs. The study was terminated after 24 months. Significant increases in liver and kidney weights were noted at the 0.5 percent dose level for the three and six-month sacrifices. At the one and two year periods, no real differences in the liver and kidney weights were apparent in any of the groups, but the authors point out that this may have been due to the small number of rats remaining after these longer periods. No unusual pathology was noted in the tissues and organs prepared for microscopic examination which could be attributed to the ester. Slight body weight reduction was seen at the 0.4 and 0.5 percent dose. Food consumption was decreased at the 0.5 percent level when compared to the control animals.

In a dog study, Harris, et al. (1956) reported a mild toxic effect within three months when a dog was administered 5 g/kg/day of DEHP but not with 0.1 g/kg/day. The small number of dogs in this study (two) and relatively short period of study (14 weeks) do not permit a valid conclusion to be made of the chronic effects of DEHP on dogs. However, this data considered with the data of Carpenter, et al. (1953) suggests that a no-effect dose in dogs is approximately 0.1 g/kg/day.

Lawrence, et al. (1975) studied the subchronic toxicity of a number of phthalate esters to determine the chronic LD_{50} by the i.p. route. Groups of male mice were administered a range of doses for each of the esters, five days a week, and an apparent LD_{50} calculated for that week. This dosing schedule was continued until two criteria were met: (1) mice were injected for at least ten weeks, and (2) the apparent LD_{50} remained constant for three consecutive weeks. DEHP and DOP were included in the list of esters studied. The first week, the LD_{50} for DEHP was 38.35 ml/kg and 67.18 ml/kg for DOP. The second week, the LD_{50} was reduced to 6.40 ml/kg for DEHP and 25.51 ml/kg for DOP. By the end of the 12th week, the LD_{50} was reduced to 3.09 ml/kg for DEHP and to 1.37 ml/kg for DOP. A cumulative toxicity factor was calculated for each of the esters (acute LD_{50}/chronic LD_{50}) and for DEHP this value was 27.99 (indicating that the toxicity had increased by this factor). A similar calculation for DOP came to 21.74. The other esters had cumulative toxicity factors ranging from 2.05 to 4.01, indicating that cumulative toxicity was only minimal over the time period the animals were studied. The implication of the high cumulative toxicity factors for both DEHP and DOP is not clear and the reasons for these results, when compared to the other esters, are presently not explainable. It is possible to speculate that very high exposure doses prevent the body from eliminating the compound and metabolites to the same degree as occurs when repeatedly lower doses are administered. It is also not known if oral doses would have led to the same or similar results, since this type of administration was not done in the study by Lawrence, et al. (1975).

Earlier studies by Shaffer, et al. (1945) Carpenter, et al. (1953) and Harris, et al. (1956), demonstrated the low chronic toxicity of DEHP but they also noted that at the higher daily doses kidney and liver enlargement occurred. These investigators, however, could not find light microscopic evidence of injury to these organs using histopathological methods. The enlargement of an organ such as the liver may not necessarily indicate that a toxic event has occurred, as suggested by Golberg (1966).

In studies by Lake, et al. (1975), rats were orally dosed with DEHP in corn oil at a concentration of 2,000 mg/kg/day for periods of 4, 7, 14, and 21 days. Control animals received 0.5 ml/100 g body weight of the vehicle. The investigators noted relative liver weight increased progressively during the treatment to 215 percent of the controls at the end of 21 days. Liver homogenates were prepared for each time period and the following biochemical activities and/or levels determined (for each of the time periods): succinate dehydrogenase, aniline 4-hydroxylase, biphenyl 4-hydroxylase, glucose-6-phosphatase, cytochrome P-450, protein contents, and alcohol dehydrogenase. Alcohol dehydrogenase activity and microsomal protein and cytochrome P-450 contents increased markedly initially but then decreased during the time of treatment. On the other hand, microsomal glucose-6-phosphatase, aniline 4-hydroxylase, and mitochondrial succinate dehydrogenase activity decreased significantly. Electron microscopy of liver tissue of treated animals demonstrated changes in hepatocytes. At the end of seven days, there was an increase in microbodies and there also appeared to be a dilation of the smooth endoplasmic reticulum and swelling of the mitochondria.

Lake, et al. (1975) studied the monoester and found that liver changes in treated rats closely resembled those produced by DEHP. They concluded that in general the toxic effects of DEHP are due to the metabolite, mono-2-ethylhexyl phthalate.

Daniel and Bratt (1974) fed dietary concentrations of 1,000 and 5,000 ppm of ^{14}C-DEHP to groups of female rats for 35 and 49 days, respectively. Two animals from each group were sacrificed at various intervals and the heart, brain, liver, and abdominal fat removed for radiochemical analysis. Remaining animals were returned to a normal diet and sacrificed at intervals during the subsequent two to three weeks and tissues prepared for analysis. At the 5,000 ppm level, liver weight relative to total body weight increased progressively during the first week to a value approximately 50 percent above the control and remained constant in the remaining time period. Electron microscopy of liver tissue revealed only a slight increase in the amount of smooth endoplasmic reticulum. Returning animals to a normal diet resulted in liver weight returning to normal. There was no apparent change in liver weight in those animals receiving the 1,000 ppm DEHP. Additional studies by these authors did not reveal the accumulation of DEHP in body organ tissues.

Nikonorow, et al. (1973) reported that a daily dose level of 0.35 percent (in feed) of DEHP caused a decrease in body weight of rats after 12 months. In other chronic studies on DEHP, livers of treated animals were significantly larger than livers from control animals not receiving DEHP.

Kevy, et al. (1978) studied the toxic effects of DEHP solubilized in monkey blood or blood products by storing the animal blood (or blood product) in PVC blood bags. These products were then transfused into the animals for time periods ranging from six months to one year. This dosing program attempted to mimic actual transfusion levels expected in selected patients requiring large-volume blood or blood products. The total concentration of DEHP received by the monkeys ranged from 6.6 mg/kg to 33 mg/kg. Liver damage was noted by several sensitive tests (hepato-splenic ratio using an isotopic technique and BSP kinetic compartmental analyses) as well as routine light microscopy of liver tissue. Even up to 32 months after the last transfusion, liver changes persisted. DEHP was also found in liver tissue in treated animals many months after the last transfusion. The work of Kevy and his associates has significance since DEHP can enter man through various PVC medical devices. Mild-to-moderate hepatic toxicity may occur depending upon the dose, the frequency of exposure, and the health status of the patient.

Biochemical studies on rat blood and liver at 21 days after i.p. injection of 5 ml/kg DEHP on days one, five and ten produced the following results: a decrease in the activity of succinic dehydrogenase and an increase in alkaline phosphatase activity in the liver; serum enzyme values were not altered. This study was conducted by Srivastava, et al. (1975) who pointed out that DEHP may also play a role in interfering with energy metabolism of the cell.

Though it is recognized that different routes and dosage forms will alter the pharmacokinetic disposition of compounds, DEHP from several different routes (oral, i.p., i.v.) can produce hepatotoxic responses depending upon the specific dose and the freauency of exposure.

Seth, et al. (1977) administered i.p. 5 ml/kg of DEHP (undiluted) to 10 male and 20 female rats on days 1, 5, and 10. On the 22nd day of the study, all animals were sacrificed and one testis or ovary was removed and retained for enzymatic studies. A control group of rats received an eaual volume of saline. Results of the study demonstrated that the scrotums in all animals were enlarged but no gross abnormality was discerned. Succinic dehydrogenase (SDH) and adenosine triphosphatase (ATPase) activities were significantly reduced, while that of β-glucuronidase was increased in both organs of the test animals. Histopathologic examination of the testes of the animals revealed degenerated tubules showing marked vacuolization of the cytoplasma of spermatogonial cells and eccentric nuclei. No apparent alterations (histopathologic) were noted in the ovaries of the DEHP treated rats.

Carter, et al. (1977) alluded to an unpublished study on DEHP in which rats were fed various dose levels of the ester for 90 days. At a daily level of 0.2 percent, DEHP produced testicular injury. When the level of DEHP was increased to 1.0 percent, testicular injury was noted in two weeks. The authors further state that DEHP and dibutyl phthalate have about the same potency in causing testicular atrophy in rats. Even though mention was made that other esters of phthalic acid were studied, no data were presented. Thus, the reader may assume that these other esters did not have the same toxic properties to testes as either DEHP or the dibutyl ester. It seems possible that DEHP, like dibutyl phthalate, may affect zinc metabolism in the testes which, in turn, may be the causative factor in bringing about atrophy of the organ.

In a series of papers, Bell, et al. (1976, 1978) have demonstrated that feeding rats DEHP can have an effect upon lipid metabolism including inhibition of hepatic sterologenesis, inhibition of fatty acid oxidation by heart mitochondria, stimulation of fatty acid oxidation by hepatic mitochondria, and an ability to modify the pattern of circulating plasma lipoproteins. In several of the studies, rabbits and pigs were also used and led to the conclusion that the response of mammalian tissues to phthalate esters is variable depending upon the species. The toxic implications of alteration in lipid metabolism to man are presently obscure.

The toxic properties of DEHP are most likely related to the formation of the monoester (in the gut or liver) and/or to other metabolites produced in the body. Studies by Lake, et al. (1975) demonstrated that neither phthalic acid nor 2-ethylhexanol reproduced the toxic effect of DEHP, suggesting that the metabolites must play the major factor in producing a toxic response. It also appears that man, rats, baboons, and ferrets may handle DEHP as well as other esters in a similar manner (Lake, et al. 1977).

Synergism and/or Antagonism

There are no data available on the synergism or antagonism of phthalate esters.

Teratogenicity

Singh, et al. (1975) included eight phthalic acid esters in a rat teratogenic study. The esters included the following: dimethyl, dimethoxyethyl, diethyl, dibutyl, diisobutyl, butyl carbobutoxymethyl, dioctyl and di-2-ethylhexyl phthalates. For all the esters, except two, the dose administered i.p. to pregnant female rats was 1/10, 1/5, and 1/3 the acute LD_{50}. For these esters, the doses ranged from a low of 0.305 ml/kg for dibutyl phthalate to a high of 2.296 ml/kg for butyl carbobutoxymethyl phthalate. Di-2-ethyhexyl phthalate and dioctyl phthalate were given at doses of 5 and 10 ml/kg because of their very low acute toxicity. Control groups included: untreated rats, rats treated with 10 mg/kg of distilled water, rats treated with 10 ml/kg of normal saline and rats treated with 10 ml/kg and 5 ml/kg of cottonseed oil. All treatments took place on days 5, 10, and 15 of gestation. On the 20th day, all the rats were sacrificed and the uterine horns and ovaries were surgically exposed to permit counting and recording of the number of corpora lutea, resorption sites, and viable and dead fetuses. Additionally, both viable and nonviable fetuses were excised, weighed, and examined for gross malformation. From 1/3 to 1/2 of the fetuses, using those which showed no gross malformation when possible, were prepared as transparent specimens to permit visualization of skeletal deformities.

All of the esters produced gross or skeletal abnormalities which were dose related. The most common gross abnormalities in the treated animals were absence of tail anophthalmia, twisted hands and legs, and hematomas. Skeletal abnormalities included elongated and fused ribs (bilateral and unilateral), absence of tail bones, abnormal or incomplete skull bones, and incomplete or missing leg bones. Dead fetuses were found in the groups treated with dimethyl, dimethoxyethyl, and diisobutyl phthalates. The most embryotoxic agent in the series was dimethoxyethyl phthalate. Each of the esters also reduced the weight of the fetuses when compared to the controls.

Even at the high dose levels (5 and 10 ml/kg), di-2-ethylhexyl and dioctyl phthalates had the least adverse effects on embryo fetus development.

Since the study by Singh, et al. (1972) was carried out i.p., results should not be extrapolated to possible teratogenic effects if the compounds have been administered orally or by other routes.

In another study by Peters and Cook (1973), pregnant rats were administered i.p. 4 ml/kg DEHP on days three, six and nine of gestation. At this dose level, implantation was prevented in four of five rats. When the dose was reduced to 2 ml/kg, a similar response was noted in three of five rats. These authors also noted adverse effects on parturition in dams treated with DEHP such as excessive bleeding, incomplete expulsion of fetuses and maternal deaths. Teratogenic studies on dibutyl and dimethyl phthalates were also conducted by these authors, but the adverse effects were less than those observed for the DEHP-treated rats. It was interesting to note that adverse effects prior to gestation day six were primarily on implantation, while after this day the effect was primarily on parturition.

In another study by Singh, et al. (1975), rats were injected i.p. with labeled di-2-ethylhexyl phthalate and diethyl phthalate. The results demonstrated that these phthalates could pass through the placental barrier suggesting that the embryo-fetal toxicity and teratogenesis of the phthalic acid esters could be the result of the direct effect of the compound (or its metabolites) upon developing embryonic tissue.

Bower, et al. (1970), studied the effects of eight commercial phthalate esters in chick embryos. They found that dibutyoxyethyl phthalate, di-2-methoxyethyl phthalates, and octyl isodecyl phthalate produced damage to the central nervous system of the developing chick embryo when compared to control embryos receiving an oil and to an untreated group.

In a study reported by Nikonorow, et al. (1973), pregnant rats were administered orally 0.34 and 1.70 g/kg/day of DEHP during the gestation period. Another series of rats received orally 0.120 and 0.600 g/kg/day of dibutyl phthalate. Olive oil was used as a control and administered in a similar manner as the esters to a group of rats. There was a statistically significant reduction in fetus weight at both dose levels for DEHP but only at the higher dose level for the dibutyl phthalate. The number of resorptions were noted for DEHP at both dose levels but only at the higher dose level for dibutyl phthalate. No detectable differences were observed in the number of sternum ossification foci, development of the bones at the base of the skull, paws of the front and hind legs, and rib fusion in fetuses when compared to the control animals.

Since the quantity of phthalate esters ingested by humans on a daily basis is extremely small as compared to the doses used in the previous studies, it seems remote that teratogenic effects would be produced in humans. Further studies in which the esters are administered orally to pregnant females should, however, be carried out to verify this assumption.

Mutagenicity

Studies of the effect of phthalic acid esters on genetic changes in animals are not adequate to conclude if one or more of these compounds presents a threat to animals and man. One of the few studies published on this topic is by Singh, et al. (1974). These authors included DEHP and dimethoxyethyl phthalate (DMEP) in a study on the mutagenic and antifertility effects in mice. The experiment followed the general procedure used in conducting the dominant lethal assay for mutagens. A group of ten males were injected i.p. with each compound at three doses. For the DEHP, the doses were 1/3 (12.8 ml/kg), 1/2 (19.2 ml/kg), and 2/3 (25.6 ml/kg) of the LD_{50}. A similar dose pattern was used for the DMEP or 1/3 (1.19 ml/kg), 1/2 (1.78 ml/kg) and 2/3 (2.38 ml/kg) of the LD50.

Each group of male mice was injected with the doses shown above and, immediately following injection, each male was caged with two virgin adult female mice. Each week for 12 weeks, two new virgin females replaced the previous week's female mice.

Results of the study indicated that at the high dose of both esters a distinct reduction in the incidence of pregnancies occurred. Fewer effects were noted at the lower dose levels. DEHP appeared to have a more persistent effect over the time period studied than DMEP. Both esters produced some degree of dose and time-dependent antifertility and mutagenic effect. Early fetal deaths occurred indicating the potential mutagenic effects of these compounds. The increase in early fetal deaths was not large, however, it was above the values for the control animals.

Rubin, et al. (1979) included a number of phthalate esters in an Ames mutagenic assay. The esters included: dimethyl, diethyl, dibutyl, mono-2-ethylhexyl, di-2-ethylhexyl, and butyl benzyl phthalate as well as phthalate acid. Positive responses were found for the dimethyl and diethyl phthalates. The remaining compounds were found to be non-mutagenic under test conditions.

Studies by Turner, et al. (1974), showed the DEHP did not produce genetic damage in lymphocytes but did inhibit mitosis and growth. It is clear that more studies on the mutagenic effects must be conducted before a definite conclusion can be made concerning the risk of a population exposed to the phthalate esters. The antifertility effect appears to be much stronger and the question which still needs to be answered is what effects would lower doses have upon males repeatedly exposed to these esters. Epidemiological evidence on this subject is lacking, and thus human risks cannot accurately be portrayed.

Carcinogencity

A recent report by Rubin, et al. (1979), alluded to under Mutagenicity in which an _in vitro_ mutagenic assay was conducted on a group of phthalate esters (dimethyl, diethyl, dibutyl, mono-2-ethylhexyl, di-2-ethyhexyl, and butyl benzyl phthalates) and on phthalic acid showed that both dimethyl and diethyl phthalates produced a positive response suggesting but not proving that these compounds may have a cancer liability. The National Cancer Institute is currently conducting bioassays on butyl benzyl phthalate (feed), diethyl hexyl phthalate (feed), and diallyl phthalate (gavage). The results of these bioassays will be reviewed when they are published.

Other Biological Effects

Cellular Toxicity: In recent years, a number of _in vitro_ tests have become useful in assessing the toxicity of chemicals. Even though the results may not always be extrapolated to animals or humans, the proper _in vitro_ system can generate very useful data which can assist in determining the toxic consequences of a chemical. Tissue and organ culture methods are now widely used in toxicity testing methods.

Nematollahi, et al. (1977) synthesized and purified a number of phthalic acid esters and then included them in a toxicity screening program using two cell lines (chick embryo and L-cells). The esters, as solids or liquids, were placed on the surface of agar which overlaid the cells. A vital dye was also included in the cells. For the solids, 20 mg of the ester were placed on the surface while for the liquids, 35 mg of the ester were placed on a paper disk which was previously placed on the agar. After 24 hours of incubation, the cells were examined for cytotoxicity. Table 5 includes the results of the screening tests. In the same table are the results from a mouse toxicity test. Three mice were injected i.p. at a concentration level of 5 moles/kg in either cottonseed oil or castor oil, depending upon the solubility of the specific compound. As will be seen from the table, the lower molecular weight esters were cytotoxic and lethal to mice. Several of the highest molecular weight esters also demonstrated some signs of toxicity.

Jacobson, et al. (1974), found that solubilized DEHP in serum inhibited cell growth (normal diploid fibroblasts established from skin) in tissue culture experiments. A concentration of 0.18 mM, which is equivalent to that in 21-day-old whole blood stored at 4°C, inhibited cell growth by 50 percent. A 20 percent reduction in cell growth occurred when the DEHP concentration was reduced to 0.10 mM which is comparable to the concentration found in whole blood stored at 4°C for 14 days.

In another tissue culture study Jones, et al. (1975) reported the ID_{50} (concentration required to inhibit cell growth by 50 percent) on a number of phthalic acid esters. The ID_{50} values are shown in Table 6. As will be noted from the table, ID_{50} for DEHP came to 70 µM. In comparing this ID_{50} with the one reported by Jacobson, et al. (1974) (0.18 mM), it should be remembered that the Jacobson group reported the concentration they added to the culture medium, whereas Jones, et al. (1975), indicatmd the actual solubility in the medium. The 70 µM solubility concentration would be approximately 0.05 mM which is in line with the Jacobson value considering that slightly different techniques were employed. The most cytotoxic ester in the series was butyl glycolyl butyl phthalate.

TABLE 5

Results of the Toxicity Evaluation of Phthalate Esters on the Mammalian Cell Cultures and Mice*

Alkyl Group	Phthalates		
	Chick Embryo Cells	L-Cells	Mice
CH_3	+	+	+
C_2H_5	+	+	+
n-C_3H_7	+	+	+
iso-C_3H_7	+	+	+
n-C_4H_9	±	+	+
iso-C_4H_9	+	+	±
n-C_5H_{11}	-	±	-
iso-C_5H_{11}	+	+	+
Cyclo-C_5H_9	+	+	±
n-C_6H_{13}	-	-	-
Cyclo-C_6H_{11}	-	-	-
n-C_7H_{15}	-	-	-
Cyclo-C_7H_{13}	+	+	-
n-C_8H_{17}	-	-	-
Cyclo-C_8H_{15}	-	-	...
n-C_9H_{19}	-	-	-
n-$C_{10}H_{21}$	+	+	±
n-$C_{11}H_{23}$	-	-	-
n-$C_{12}H_{25}$	+	+	-

Note: In tissue culture test: + indicates cytotoxic; - indicates noncytotoxic; ± indicates questionable results.

In mouse test: + indicates 2 or 3 deaths; - indicates no deaths; ± indicates only one death.

*Source: Nematollahi, et al. 1967

TABLE 6

ID_{50} Values for a Series of Phthalate Esters Using WI-38 Cells*

Agent (Phthalate)	Molecular Weight	ID_{50} µM	Solubility (mole/l)
Di-n-butyl	278	135	0.008
Di-iso-butyl	278	85	Very low
Dimethoxyethyl	282	3,500	0.040
Butyl glycol butyl	336	12	Very low
Di-n-octyl	391	170	Very low
Di-2-ethylhexyl	391	70	Very low

*Source: Jones, et al. 1975

The ᴵD$_{50}$ do group of phthalate esters has been reported for mouse fibroblasts in cell culture (Autian, 1973). These values are included in Table 7. It is interesting to note that the most cytotoxic agent in the series was DEHP, an agent having a very low order of acute toxicity in animals and man. As can be seen from the table, the toxicity of these compounds, in general, increased as the molecular weight increased.

A report by Dillingham and Autian (1973), indicates that dimethyoxyethyl phthalate is much more toxic to mouse fibroblast cells undergoing significant rates of cell division than nonreplicating cells. This observation suggests that any tissue which undergoes periodic increases in protein turnover related to changes in cell division rate and metabolic activity (protein synthesis) may increase the susceptibility of these cells to the toxic effects of phthalic esters. Thus, it is possible that the teratogenic and embryotoxic effects of several of the esters reported in rats may be due to the fact that differentiating embryonic tissues have periodic major changes in cell division rates and metabolic activity in contrast to somatic cells which have a much lower rate of cell division and metabolism of the somatic tissue.

Kasuya (1974) cultured cerebella from newborn rats and tested three phthalate esters (dimethyl, diethyl and dibutyl phthalates). Various concentrations of each of the esters were dissolved in calf serum and then added to the cells. The overall toxicity to the cells was in the following order: DBP>DEP>DMP. As will be noted, the toxicity of the three esters increased with molecular weight similar to cell culture results reported by Dillingham and Autian (1973).

At a concentration of 4 μg/ml in tissue culture media, DEHP produced complete cessation of beating chick embryo heart cells maintained in tissue

TABLE 7

ID_{50} of a Group of Phthalic Acid Esters in Tissue Culture (Mouse Fibroblasts)*

Ester	Molecular Weight	Water Sol. (mole/l)	ID_{50}
Dimethyl	194	0.0263	0.007
Diethyl	222	0.0048	0.003
Dibutyl	278	0.008	0.0001
Dimethoxyethyl	282	0.0400	0.0084
Di-2-ethylhexyl	390	0.0004	0.00005

*Source: Autian, 1973

culture (Rubin and Jaeger, 1973). Up to 98 to 99 percent of the cells were found to be dead within a 24-hour period. This result, along with the other tissue culture reports, reinforces that DEHP is highly toxic at the cellular level.

Blood Components/Lungs/Heart: In the past there has been concern that DEHP, when extracted from medical devices such as blood bags and tubings, might have a deleterious effect upon blood components and also lead to the syndrome referred to as "shocked lungs." DEHP, solubilized with a surfactant and injected i.v. in rats, produced lung involvement and death. Stern, et al. (1977) have stressed the importance of the physical form of DEHP when injected i.v.: the naturally solubilized DEHP showing a "nontoxic" effect while DEHP solubilized with a surfactant produced a toxic effect.

Rubin (1975) reported that DEHP, solubilized with a surfactant and injected i.v. in rats, produced a biexponential disappearance of the DEHP from blood with half-lives of 3.5 and 35 minutes. A naturally solubilized DEHP, on the other hand, has a monoexponential disappearance with a half-life of 19 minutes. In humans, Rubin (1975) found that the half-life of naturally solubilized DEHP led to a monoexponential rate with a mean half-life of 28 minutes. Rats administered the surfactant solubilized DEHP showed death and lung involvement similar to the shocked lung syndrome (Rubin, 1975).

Hypotensive rats, in which DEHP is added to the animal's own blood and then transfused back into the rat, produced hemorrhagic lungs in each of the six rats used in the experiment (Rubin, 1976). Control rats, treated in a similar manner but not receiving any DEHP, did not demonstrate the toxic lungs.

Berman, et al. (1977) conducted studies in which rats were administered blood or blood components, previously in contact with PVC strips, to detect the effect DEHP (extracted from the plastic) would have on lung tissue. ACD-preserved rat blood was stored in glass vials alone or in the presence of sterile plastic strips. One set of plastic strips was also enriched with 34 percent DEHP. After storage for two weeks, 0.5 ml of blood were administered i.v. to groups of rats in the following forms: as whole blood, as whole blood minus platelets and buffy coat, as platelet-rich plasma, as platelet-poor plasma. Additional groups of rats received CPD-preserved rat or human blood after storage in glass alone or in glass containing PVC strips and/or PVC enriched with DEHP. Concentration of DEHP in whole blood in contact with PVC was 81.5 μg/ml and 90.2 μg/ml for the blood in contact with PVC enriched with DEHP.

Evans Blue was used as an indicator to detect the permeability of excised lung tissue. Animals given ACD-preserved blood which had contact with PVC demonstrated an increased permeability when compared to control animals. Administration of platelet-rich and platelet-poor plasma showed no significant increase in lung permeability. CPD-preserved blood in contact with the plastic strips showed an increased permeability which was greater than the CPD blood used as controls but not as great as the permeability shown by the ACD-preserved blood. Histopathologic examinations of lungs having received blood in contact with PVC and PVC enriched with DEHP showed variable degrees of septal thickening, perivascular edema and perivascular accumulation of mononuclear cells when compared to lungs of control rats. The authors suggest that blood-plastic contact during storage may adversely affect blood and also the effects may be in part due to accumulation of DEHP in red cells. It has also been found that PVC infusion containers, if agitated, will produce liquid particles of DEHP which, in turn, can be administered to humans (Needham and Luzzi, 1973). Depending upon the size-frequency of these particles and the concentration of DEHP released to the solution, possible toxic effects may result even though human experience has not yet indicated that adverse effects have occurred.

Vessman and Rietz (1978) have reported the presence of mono-2-ethylhexyl phthalate (hydrolysis product of DEHP) in blood plasma stored in PVC blood bags. Ten blood bags with plasma were removed from storage (-20.C) and the monoester was found to range from 4 to 56 µg/ml. Eight of the plasma samples were then transferred to glass bottles and stored at room temperature. After two weeks of storage the monoester contents had increased to values between 27 and 79 µg/ml. Fractionated protein albumin also contained the monoesters in amounts from less than 3 to 290 µg/g. The authors suggest that the conversion of DEHP in plasma is due to some enzymatic activity taking place in the product. They indicate that when measuring DEHP content of blood and blood products stored in PVC bags, attention should also be given to determining the monoester content, thereby gaining a true picture of phthalate content.

Sleeping Time: Sleeping time experiments were reported by Rubin and Jaeger (1973) who studied the effect of DEHP and butyl glycolyl butyl phthalate. These esters were also emulsified with acacia and injected at 250 mg/kg and 500 mg/kg dose levels. After 30 minutes, hexobarbital solution was administered i.p. A significant increase in sleeping time was produced by DEHP at both dose levels, while only the higher dose of butyl glycolyl butyl phthalate produced a longer sleeping time than the control animals. Rats were also employed by the authors in a similar sleeping time experiment with the results being similar but the magnitude less than with the mice. Rubin and Jaeger (1973) conducted additional experiments and concluded that the increase in hexobarbital sleeping time was not due to an increase in CNS sensitivity to hexobarbital nor an alteration in rate of hexobarbital metabolism by the liver, but to the effect of DEHP in the distribution of hexobarbital into various organs.

Swinyard, et al. (1976) also found an increase in hexobarbital sleeping time from DEHP. It was interesting to note that olive oil also produced an increased sleeping time similar to DEHP. These authors concluded that the effect of DEHP was nonspecific due to the physical characteristic of the ester which enlarged the lipophilic reservoir for hexobarbital rather than to a pharmacological property of the compound.

Daniel and Bratt (1974) noted that hexobarbital sleeping time (in rats) was increased when DEHP was used at a dose of 600 mg/kg of emulsified agent. When rats were given orally five successive daily doses of DEHP (500/kg) hexobarbital sleeping time was decreased.

From the information available, it is clear that DEHP prolongs the sleeping time of short-acting barbiturates. In the instance of acute studies, the cause of the prolongation of sleeping time may, in fact, be due to nonspecific factors, probably to the lipophilic reservoir mechanism advocated by Swinyard, et al. (1976). On the other hand, repeated pretreatments with DEHP may have an effect upon the liver and enzyme systems. Since liver involvement has been noted by several investigators in subacute toxicity studies in rats and monkeys, the DEHP may, in these cases, be producing a specific toxicological effect.

CRITERION FORMULATION

Existing Guidelines and Standards

The Threshold Limit Value (TLV) for dimethyl, dibutyl and di-2-ethylhexyl phthalate esters established by the American Conference of Governmental and Industrial Hygienists (ACGIH) is 5 mg/m^3.

The Food and Drug Administration (FDA) has approved the use of a number of phthalate esters in food packaging materials. Prior to 1959 (before enactment of the food additive amendment), FDA approved five esters. These are: diethyl phthalate, diisobutyl phthalate, ethyl phthalyl ethyl glycolate, diisooctyl phthalate and di-2-ethylhexyl phthalate. Since then, 19 additional phthalates used in packaging material for foods of high water content have also been approved. More specific uses and restrictions of phthalic esters are set forth by FDA in its regulations.

Current Levels of Exposure

Lack of sufficient data prevents an accurate assessment of levels of exposure of man and animals to phthalate esters. Is is now, however, well known that man is exposed to these esters through a number of routes such as industrial sites in which the esters are manufactured or used. Phthalate esters may also reach man through indirect means such as inhalation of the esters inside vehicles containing PVC products from foods and from water. Direct injection i.v. of specific phthalate esters can also occur when PVC blood bags and tubings are used to transfuse blood and blood products to man. The ubiquitous nature of the phthalate ester is apparent since tissues of deceased persons have revealed the presence of phthalic acid esters, even though the individuals were not apparently exposed to these esters.

Even though it is well established that workers in occupations in which phthalate esters are used are exposed to various levels of phthalate esters and thus can absorb these esters through inhalation or through dermal absorption, the lack of sufficent data precludes establishing what are the levels of exposure. Dermal absorption of the low molecular weight esters such as dimethyl phthalate (mosquito repellent) and diethyl phthalate (in cosmetic products) probably is also occurring but the quantity absorbed through the skin is not known.

A survey was conducted by the Bureau of Foods (FDA) in 1974 to determine if phthalate esters were entering the food supply through the processing, packaging, handling and transportation chain. In the study, ten basic and stable food products were analyzed for the presence of these esters. Conclusions reached in the report are presented here:

1. The frequency and levels of phthalate esters reported as well as the possible cumulative intake of phthalates in baked beans in cans or jars, canned whole kernel corn, margarine, cereals, eggs, bread, corn meal, meat, milk, and cheese do not pose a hazard to the consumer.

2. DEHP was the ester most frequently detected in the food commodities. Dibutyl phthalate, dicyclohexyl phthalate and butylphthalylbutyl glycolate were found in comparatively few samples. Diisoctyl and diisodecyl phthalates, although looked for, were not detected.

3. Phthalate ester contamination was found in a higher proportion of milk and cheese samples than in other foods. However, the findings are uncertain.

In the above survey, the highest levels of phthalate esters were present in margarine (13.7 and 56.3 ppm on fat basis). In cheese, the highest levels of esters were 22.8 and 24.9 ppm for DNBP and 35 ppm for DEHP but most cheese samples contained less than 5 ppm of phthalates.

In a published study by Tomita, et al. (1977), information is presented dealing with phthalate (DEHP and DNBP) residues in various commercial foodstuffs in Japan. They concluded that foods packaged in plastic films with printing are a greater source of contamination to the product with the esters than if the foods were in plastic bottles. They also noted that persons had significantly higher levels of the esters after meals from foods packaged in the film. Extremely high levels of the two esters (combined) were found in tempura powder stored for eight months (up to 454 ppm). The residue level of the esters from plastic films containing the plasticizers, as would be expected, migrated to fatty foods or fatty-like foods to a greater extent than to foods having low fat content. The authors included in their conclusion the following: "The daily intake of PAEs (phthalic acid esters) from present foodstuffs may not exceed the ADI of DNBP and DEHP but an effort to reduce the PAE levels in foodstuffs should be continuously made."

The Bureau of Foods (FDA) in another survey on fish from a number of locations in the U.S. noted that the highest level of DEHP (7.1 ppm) was present in shark (smooth, hound). In most other instances, the fish which were studied were free of the esters.

Patients receiving repeated transfusions with whole blood, packed cells, platelets and plasma stored in PVC may receive up to 70 mg of DEHP and, in some instances, the quantity even exceeds 500 mg. Hemodialysis patients may receive up to 150 mg of DEHP.

Special Groups at Risk

Two groups are at risk in regard to phthalic acid esters. These are workers in the industrial environment in which the phthalates are manufactured or used and patients receiving chronic transfusion of blood and blood products stored in PVC blood bags.

Basis and Derivation of Criterion

From the available information, the phthalic acid esters have not been found to be carcinogenic in animals or man. At high doses when injected i.p., the esters can act as teratogenic agents and possibly as mutagenic agents in rats. These esters also have an effect upon gonads in rats. Evidence is also at hand to show that the esters may bring about biochemical and pathological changes in the liver of rats when repeatedly administered orally or by i.p. When solubilized in blood components, DEHP has demonstrated liver involvement when these products have been repeatedly administered i.v. to monkeys. Inhalation studies in rats and man suggest that certain phthalates may be responsible for neurological disorders, but these results need further verification since other nonphthalate esters may also have been present leading to the problems.

Since a number of phthalate esters are in the environment or may be present in water, it was thought appropriate to review chronic toxicity data in which well established chronic toxicity data for these esters were reported to establish an acceptable daily intake (ADI). In Table 8 can be found a summary of the studies chosen for the purpose of determining an ADI. The table includes those phthalate esters for which at least one reasonable adequate chronic ingestion toxicity study was available. Only in the case of di-2-ethylhexyl phthalate was a choice between studies involved. The Carpenter, et al. (1953) study was chosen because it was considered the most representative.

The no-effect level from this study was supported by a majority of the other chronic studies. In calculating the ADI, an uncertainty factor of 100 was used based on the National Academy of Sciences (NAS, 1977) guidelines.

TABLE 8

Calculated Allowable Daily Intake in Water and Fish
for Various Phthalate Esters*

Ester	Species	Weeks	No Effect Dose[a] (mg/g/day)	ADI (mg/day)	F[b]	Water Quality Criterion (mg/l)	Reference
1. Dimethyl	Rat	104	1,000	700	36	313	Draize, et al. 1948
2. Diethyl	Rat	104	1,250	875	73	350	Food Research Lab Inc., 1955
3. Dibutyl	Rat	52	125	88	89	34	Smith, 1953
4. Di-2-ethyl-hexyl	Rat, Guinea Pig, Dog	104, 52, 52	60	42	130	15	Carpenter, et al. 1953
5. Ethylphthalyl ethyl glycolate	Rat	104	250	175	NE	--	Hodge, et al. 1953
6. Butylphthalyl butyl glycolate	Rat	104	1,000	700	NE	--	Solver, et al. 1950; Hazelton Labs., 1950

*Source: Shibko, 1974

[a]When only a concentration in the diet was available, it was assumed that a rat consumes 5% of its body weight per day, on the average.

[b]Bioconcentration factor

This safety factor is justified because all of the animal studies provide sufficient data on chronic (greater than one year) exposure.

For the sake of establishing water quality criteria, it is assumed that on the average a person ingests 2 liters of water and 6.5 grams of fish. The amount of water ingested is approximately 100 times greater than the amount of fish consumed. Since fish may biomagnify the esters to various degrees, a biomagnification factor (F) is used in the calculation. Bioconcentration factors for dimethyl, diethyl, dibutyl and di-2-ethylhexyl esters were derived by the U.S. EPA ecological laboratories, Duluth, Minnesota (see Ingestion from Food section).

Due to lack of data, bioconcentration factors could not be derived for dicyclohexyl, methyl phthalyl ethyl glycolate, ethyl phthalyl ethyl glycolate, and butyl phthalyl ethyl glycolate.

The equation for calculating an acceptable amount of ester in water based on ingestion of 2 liters of water and 6.5 g fish is:

$$(2\ 1)\ X + (0.0065 \times F)\ X = ADI$$

where 2 1 = 2 liters of drinking water consumed

0.0065 = amount of fish consumed daily in kg

F = bioconcentration factor

ADI = Allowable Daily intake (mg/day for 70 kg person)

X = Water quality criterion

For example, consider that the ADI for dimethyl phthalate is 700 mg/day and the bioconcentration factor is 36, the above equation can be solved as follows:

$$2(X) + (0.0065 \times 36)\ (X) = 700$$

$$2X + (0.23)X = 700$$

$$2.23X = 700$$

$$X = 313 \text{ (or} \sim 310 \text{ mg/l)}$$

Thus, the recommended water quality criterion is 313 mg/l for dimethyl phthalate.

Similar calculations were made for each of the esters and are presented below:

Diethyl Phthalate

$$2(X) + (0.0065 \times 73)(X) = 875$$

$$2X + 0.47X = 875$$

$$2.47X = 875$$

$$X = 354 \text{ mg/l (or} \sim 350 \text{ mg/l)}$$

Dibutyl Phthalate

$$2(X) + (0.0065 \times 89)(X) = 88$$

$$2X + 0.578X = 88$$

$$2.578X = 88$$

$$X = 34.1 \text{ mg/l (or} \sim 34 \text{ mg/l)}$$

Di-2-ethylhexyl Phthalate

$$2(X) + (0.0065 \times 130)(X) = 42$$

$$2X + 0.845X = 42$$

$$2.845X = 42$$

$$X = 14.8 \text{ mg/l (or} \sim 15 \text{ mg/l)}$$

Thus, the recommended water quality criteria for four phthalate esters are:

dimethyl = 313 mg/l

diethyl = 350 mg/l

dibutyl = 34 mg/l

di-2-ethylhexyl = 15 mg/l

(see Table 8).

It seems clear that exposure from the water route presents no real risk to the population in regard to the phthalate esters. Reported levels of phthalate esters in U.S. surface waters have only been in the ppb range, at approximately 1 to 2 µg/l (see Ingestion from Water section).

Other routes of exposure such as inhalation (industrial sites manufacturing the esters), dermal exposure, consumption of certain fatty or fatty-like foods and certain fish will be the major contributors to the body-load of phthalate esters. Phthalate ester residues in foods such as margarine, cheese and milk may, on some occasions, reach 50 ppm. Also a special group at risk will be patients to whom chronic transfusions of blood and blood products are administered.

Although it is recognized that routes of exposure other than water contribute more to the body burden of phthalate esters, this information will not be considered in forming ambient water quality criteria until additional analysis can be made. Therefore, the criteria presented assumed a risk estimate based only on ambient water exposure.

The need for more accurate determination of residue content of foods, fish, and water is still very apparent and, as more data become available, a reevaluation should be made as to the possible hazard to the population by the ingestion of phthalate esters.

In summary, based on the use of chronic toxicologic data and uncertainty factors of 100, the criteria levels for phthalate esters have been established. The percent contribution of drinking water and of ingesting contaminated fish is given in Table 9. Also given are the criteria levels recommended if exposure is assumed to be from fish and shellfish products alone.

TABLE 9

Summary of Criterion Formulation

Esters	Criterion Level mg/l	% Contribution of Drinking Water	% Contribution of Fish Products	Criteria of Exposure if from Fish Alone mg/l
Dimethyl	313	90	10	2,901
Diethyl	350	81	19	1,842
Dibutyl	34	78	22	154
Di-2-ethylhexyl	15	70	30	50

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