Canadian Environmental Protection Act

Priority Substances List
Assessment Report

Bis(2-ethylhexyl) Phthalate

Government of Canada / Gouvernement du Canada
Environment Canada / Environnement Canada
Health Canada / Santé Canada

Canada

CANADA'S GREEN PLAN

Canadian Environmental Protection Act

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

BIS (2-ETHYLHEXYL) PHTHALATE

Government of Canada
Environment Canada
Health Canada

Also available in French under the title:
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Synopsis

Bis(2-ethylhexyl) phthalate [also known as di(2-ethylhexyl) phthalate or DEHP], a branched-chain dioctyl ester of phthalic acid, is the most important phthalate plasticizer used in Canada. In 1991, production of bis(2-ethylhexyl) phthalate in Canada totalled approximately 5 kilotonnes (kt) and an additional 5 kt were imported. Bis(2-ethylhexyl) phthalate is also imported into the country in plasticized polyvinyl chloride (PVC) and in plastic products. Although quantitative data are very limited, bis(2-ethylhexyl) phthalate is released into the Canadian environment as a result of its manufacture and its industrial uses. Relatively small amounts of the substance are also released from plastic goods. Bis(2-ethylhexyl) phthalate is rapidly removed from the atmosphere by photo-oxidation and has a half-life of several hours. Bis(2-ethylhexyl) phthalate is not expected to be persistent under aerobic conditions, having a half-life in surface water of a few weeks or less. Under anaerobic conditions bis(2-ethylhexyl) phthalate is more persistent, with a half-life of one year or more.

Data are very limited on the concentrations of bis(2-ethylhexyl) phthalate in the atmosphere, surface water, industrial effluents, and sewage sludges in Canada. Moreover, no data were identified for sites near known Canadian production facilities. No toxicological data were identified for sediment-dwelling biota in Canada. Recent information that is available concerning concentrations of bis(2-ethylhexyl) phthalate in biota is insufficient for estimating the exposure of terrestrial wildlife to this substance.

Bis(2-ethylhexyl) phthalate is estimated to be present at relatively low concentrations in the atmosphere and has a short half-life in that medium. As such, it is not expected to contribute significantly to the formation of ground-level ozone, global warming, or to the depletion of stratospheric ozone.

Based on limited available data on concentrations of bis(2-ethylhexyl) phthalate in food, indoor air, ambient air, drinking water, soil, and children's products, the total average daily intakes of bis(2-ethylhexyl) phthalate have been estimated for various age groups in the general population. The estimated average daily intakes of bis(2-ethylhexyl) phthalate for some age groups of the general population in Canada may slightly exceed the tolerable daily intake developed on the basis of studies in laboratory animals. The tolerable daily intake is the intake to which it is believed that a person can be exposed over a lifetime without deleterious effect.

Based on these considerations, there is insufficient information to conclude whether bis(2-ethylhexyl) phthalate is entering or may enter the environment in a quantity or concentration or under conditions that are having a harmful effect on the environment. It has been concluded, however, that bis(2-ethylhexyl) phthalate is not entering the environment in a quantity or concentration or under conditions that constitute a danger to the environment on which human life depends. It has also been concluded that bis(2-ethylhexyl) phthalate may enter the environment in a quantity or concentration or under conditions that may constitute a danger in Canada to human health.

1.0 Introduction

The Canadian Environmental Protection Act (CEPA) requires the Minister of the Environment and the Minister of Health to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents, and wastes that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" as defined under Section 11 of the Act, which states:

> "…a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions
>
> a) having or that may have an immediate or long-term harmful effect on the environment;
>
> b) constituting or that may constitute a danger to the environment on which human life depends; or
>
> c) constituting or that may constitute a danger in Canada to human life or health."

Substances that are assessed as "toxic" as defined under Section 11 may be placed on Schedule I of the Act. Consideration can then be given for possible development of regulations, guidelines, or codes of practice to control any aspect of these substances' life cycle, from the research and development stage through manufacture, use, storage, transport, and ultimate disposal.

The assessment of whether bis(2-ethylhexyl) phthalate is "toxic", as defined under CEPA, was based on the determination of whether it **enters** or is likely to enter the Canadian environment in a concentration or quantities or under conditions that could lead to **exposure** of humans or other biota at levels that could cause adverse **effects.**

Data relevant to the assessment of whether bis(2-ethylhexyl) phthalate is "toxic" to the environment under CEPA were identified from existing review documents, published reference texts and online searches conducted between September 1991, and March 1993, of the following commercial data bases: CAB Abstracts (1984 to 1993), CHEMICAL ABSTRACTS (1985 to 1991), Chemical Evaluation Search and Retrieval System (CESARS), Hazardous Substances Data Bank (HSDB), IRPTC-LEGAL and POLLUTION ABSTRACTS (1985 to 1991). Data relevant to the assessment of whether bis(2-ethylhexyl) phthalate is "toxic" to the environment obtained after April 1993, have not been included.

For assessment of data other than those considered to be critical for determination of "toxic" to human health under the Act, evaluations of the United States Agency for Toxic Substances and Disease Registry (ATSDR, 1989; 1991), the International Programme on Chemical Safety (IPCS, 1992), Woodward (1988), the United States Consumer Product Safety Commission (CPSC, 1985), the International Agency for

Research on Cancer (IARC 1982), the United States Environmental Protection Agency (U.S. EPA, 1980; 1981; 1991), and a background review prepared under contract by Meta Systems Inc. from February 1989 to June 1989, have been consulted where appropriate.

To identify toxicological data, literature searches were conducted on the following computerized data bases: HSDB (1989), Registry of Toxic Effects of Chemical Substances (RTECS) (1989), Integrated Risk Information System (IRIS) (1989), Chemical Carcinogenesis Research Information System (CCRIS) (1992), CA Search (1982 to 1989), Medline (1988 to 1989), and TOXLINE (1981 to 1992). In addition, searches of the three most recent monthly editions of the Current Contents were conducted in December, 1992. Additional information identified by BIBRA Toxicology International based on preliminary review of an early draft of the sections of the supporting documentation related to assessment of effects on human health and searches of in-house sources and the online bibliographic data bases TOXLINE/TOXLIT, Medline, BIOSIS, and NTIS (1992) were also incorporated. To identify data relevant to the estimation of exposure of the general population to bis(2-ethylhexyl) phthalate, the following data bases were searched: Environmental Bibliography (1973 to 1992), Enviroline (1971 to 1992), Food Science and Technology Abstracts (1969 to 1992), POLLUTION ABSTRACTS (1970 to 1992), Environment Canada Departmental Library Catalogue (ELIAS) (1992), AQUAREF (1970 to 1992), Micromedia, Canadian Research Index (MICROLOG) (1979 to 1992), Co-operative Documents Project Databases, University of Guelph (CODOC/ODOC) (1992), and Canadian Institute for Scientific and Technical Information (CISTIMON) (1992). Relevant unpublished reports were provided by the Chemical Manufacturers Association (CMA, 1984; Rodricks and Turnbull, 1984) and Consumer and Corporate Affairs Canada (CCAC, 1992). Data relevant to assessment of whether bis(2-ethylhexyl) phthalate is "toxic" to human health obtained after the completion of these sections of this report (i.e., December, 1992) were not considered for inclusion.

Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether bis(2-ethylhexyl) phthalate is "toxic" under CEPA have been critically evaluated by the following Environment Canada staff (entry, and environmental exposure and effects) and Health Canada staff (human exposure and effects on human health):

Environment Canada	Health Canada
L. Brownlee	P.K.L. Chan
C. Fortin	M.E. Meek
K. Lloyd	F. Wandelmalier
P. Paine	
K. Taylor	

In this report, a synopsis that will appear in the *Canada Gazette* is presented. Section 2.0 is an extended summary of the technical information that is critical to the

assessment. The assessment of whether bis(2-ethylhexyl) phthalate is "toxic" is presented in section 3.0. Supporting documentation in which the technical information is presented in greater detail has also been prepared.

As part of the review and approvals process established by Environment Canada for its contributions to Priority Substances List assessments, the environmental sections of this report were reviewed by: Dr. Foster Mayer (U.S. EPA, Gulf Breeze, FL), Dr. W.J. Adams (ABC Laboratories, Columbia, MO), and Dr. V. Zitko (Fisheries and Oceans Canada, St. Andrews, NB). Following external peer review by staff of BIBRA Toxicology International, Dr. R. Cattley (Chemical Industry Institute of Toxicology; supporting documentation only), Dr. A. DeAngelo (U.S. EPA, Health Effects Laboratory), and Dr. R. Okita (Washington State University), sections related to the effects on human health were approved by the Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazards of Health Canada. The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

Copies of this Assessment Report and of the unpublished supporting documentation are available upon request from:

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2.0 Summary of Information Critical to Assessment of "Toxic"

2.1 Identity, Properties, Production, and Uses

Bis(2-ethylhexyl) phthalate, a phthalic acid ester, has the CAS (Chemical Abstracts Service) Registry Number 117-81-7, the molecular formula $C_{24}H_{38}O_4$, and a molecular weight of 390.6. Synonyms include: DEHP; 1,2-benzenedicarboxylic acid, bis(2-ethylhexyl) ester; phthalic acid, bis(2-ethylhexyl) ester; and di(2-ethylhexyl) phthalate. The structure of bis(2-ethylhexyl) phthalate is shown in Figure 1. Bis(2-ethylhexyl) phthalate is a colourless, oily liquid (Montgomery and Welkom, 1990), with reported vapour pressures ranging between 8.3 x 10^{-6} Pa (Montgomery and Welkom, 1990) and 8.6 x 10^{-4} Pa @ 25^0C (Howard *et al.*, 1985), Henry's Law Constant of 3.0 x 10^{-2} Pa.m^3/mol (Volskay and Grady, 1988), log octanol-water partition coefficient (log K_{ow}) of 5.11 (Geyer *et al.*, 1984) to 9.61 (U.S. EPA, 1982a), and solubility in water of 270 to 400 µg/L @ 25^0C (DeFoe *et al.*, 1990; Volskay and Grady, 1988). The determination of the solubility in water and octanol/water partition coefficient of phthalic acid esters is complicated since these compounds easily form colloidal dispersions in water (Klopfer *et al.*, 1982) and are subject to "molecular folding" (Callahan *et al.*, 1979). Bis(2-ethylhexyl) phthalate absorbs infrared radiation, including wavelengths in the 7 to 13 µm region (Sadtler Research Laboratories, 1982), which is characteristic of trace gases that contribute to warming of the troposphere.

In environmental media, gas chromatography with electron capture detection is the most sensitive and selective analytical method for the determination of phthalic acid esters, including bis(2-ethylhexyl) phthalate (Kohli *et al.*, 1989).

Two problems are associated with the chemical analysis and the reporting of environmental concentrations of bis(2-ethylhexyl) phthalate. The first problem, which

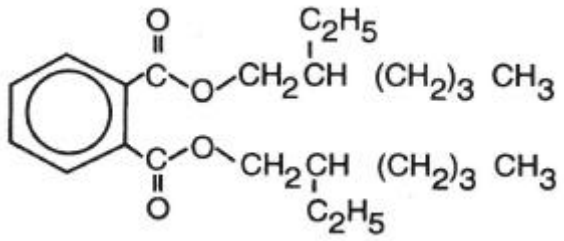

Figure 1 Structure of Bis(2-ethylhexyl) Phthalate

applies to phthalates as a group, is that these chemicals frequently occur as contaminants in laboratory air and solvents, and as plasticizers in analytical equipment. This may cause contamination of environmental samples and result in overestimation of the concentration of phthalates in these samples. For example, Ishida *et al.* (1980) determined bis(2-ethylhexyl) phthalate in laboratory solvents at concentrations as high as 1.96 mg/kg (in benzene) and in solid reagents at concentrations of up to 4.12 mg/kg (in carboxymethylcellulose), while the heavy-walled tubing they analyzed contained 67.2% of bis(2-ethylhexyl) phthalate. Therefore, a great deal of care is needed to prevent contamination during the collection, storage and analysis of samples (Hites and Budde, 1991; Kohli *et al.*, 1989; Mathur, 1974; U.S. EPA, 1982b). In many studies reporting environmental concentrations conducted before 1980, potential contamination was not adequately taken into account (Pierce *et al.*, 1980), and the accuracy of such studies is questionable. The second problem, specific to bis(2-ethylhexyl) phthalate, is that in the technical literature it is sometimes referred to as "dioctyl phthalate" which has led to confusion with the straight-chain isomer, di-*n*-octyl phthalate (D*n*OP), also sometimes referred to as "dioctyl phthalate" or "DOP".

Bis(2-ethylhexyl) phthalate accounts for well over 50% of the total use of phthalate plasticizers, with a worldwide production of about 1000 kilotonnes (kt) of bis(2-ethylhexyl) phthalate per year (IPCS, 1992).

At present, there are two operating bis(2-ethylhexyl) phthalate production facilities in Canada. Production of bis(2-ethylhexyl) phthalate totalled 5 kilotonnes in 1991, compared to 14.8 kilotonnes in 1984. Approximately 5 kilotonnes of bis(2-ethylhexyl) phthalate were imported into Canada in 1991 (virtually all from the United States), less than the maximum annual importation into Canada of about 7.5 kilotonnes in 1990 (CIS, Inc., 1992). Bis(2-ethylhexyl) phthalate is also imported into Canada already mixed with polyvinyl chloride (PVC). In 1991, 14.4 kilotonnes of plasticized PVC were imported into Canada. Assuming that this material contained a minimum of 10% bis(2-ethylhexyl) phthalate by weight, then at least an additional 1.4 kilotonnes of bis(2-ethylhexyl) phthalate would have entered Canada via this route in 1991. Available information does not permit an estimation of the amount of bis(2-ethylhexyl) phthalate imported in finished plastic products. Sales of bis(2-ethylhexyl) phthalate for export amounted to less than 2 tonnes in both 1990 and 1991 (CIS, Inc., 1992).

In 1991, about 35% of the total Canadian supply of bis(2-ethylhexyl) phthalate was used as a plasticizer in PVC films and sheets, 6% in PVC flooring, 3.5% in plasticized PVC exports, about 51% in other vinyl products (such as coated fibres, etc.), 2.6% in nitrile-butadiene rubber, and 1.8% in miscellaneous applications (CIS, Inc., 1992). The amount of bis(2-ethylhexyl) phthalate used in PVC resins is variable, depending on the type of product. Industrial hoses may contain 10 to 15% bis(2-ethylhexyl) phthalate by weight, while some types of flexible PVC films may contain more than 40% bis(2-ethylhexyl) phthalate (CIS, Inc., 1992).

2.2 Entry into the Environment

Very limited data were identified concerning the release of bis(2-ethylhexy1) phthalate to the Canadian environment.

The occurrence of phthalates from natural sources in biological and geochemical samples has been suggested, but has not been confirmed, at least in part because of possible contamination during sampling or analysis (Mathur, 1974). However, it is unlikely that the amounts of phthalates present naturally would be significant compared with those arising from anthropogenic sources (IPCS, 1992).

Worldwide, the release of phthalates directly to the atmosphere is believed to be the most important mode of entry to the environment. The sources of such releases include emissions during the manufacture and use of these substances and through the incomplete combustion of plastic material (IPCS, 1992). In the United States, it was estimated that in 1989, manufacturing facilities released approximately 500 tonnes of bis(2-ethylhexyl) phthalate to the environment, 97% of which was released to the atmosphere (TRI89, 1991). Recent data on releases of phthalates in Canada have not been identified. Leah (1977) estimated that 2 to 4.5% of the total Canadian supply of phthalates is lost to the environment during production and processing, with about 95% of this loss resulting from processing. Peakall (1975) estimated that articles containing phthalate-plasticized material may lose about 1%/yr of their phthalate content when in contact with liquids and 0.1%/yr when in contact with air. In Canada, Eisenreich *et al.* (1981) predicted that atmospheric deposition is a significant source of phthalates in the Great Lakes, with a calculated total deposition of 48 tonnes/year (t/yr) to the five Great Lakes, with values for each ranging from 3.7 t/yr in Lake Ontario to 16 t/yr in Lake Superior.

Bis(2-ethylhexyl) phthalate has been detected at concentrations of up to 40 µg/L in effluents from a Canadian textile mill in a 1985/86 survey (detection frequency = 19/19; detection limit 1 µg/L) (Environment Canada, 1989). Bis(2-ethylhexyl) phthalate has also been detected in effluents from Canadian chemical plants at concentrations within the range of 1 to 100 µg/L (Munro *et al.*, 1985; OME, 1992a;b). Loadings in liquid effluents from the organic chemical industry in Ontario totalled about 1.6 kg of bis(2-ethylhexyl) phthalate per day (12-month average) (OME, 1992a) while those from the inorganic chemical industry totalled about 0.6 kg of bis(2-ethylhexyl) phthalate per day (12-month average) (OME, 1992b).

Concentrations of bis(2-ethylhexyl) phthalate of up to 59 µg/L have been reported in municipal wastewater from Vancouver, British Columbia, in 1982 (Rogers *et al.*, 1986). Bis(2-ethylhexyl) phthalate was detected in 14 out of 15 Canadian municipal sludges sampled between 1980 and 1985, with concentrations ranging from 3 to 215 mg/kg dry weight (d.w.) and a median concentration of 80 mg/kg (Webber and Lesage, 1989).

Bis(2-ethylhexyl) phthalate was detected at concentrations often exceeding 10 µg/L (actual concentration not reported) in samples of wastewater collected from 1982 to 1984 at Canadian coal mines, coal preparation plants, and coal storage transfer terminals. Concentrations in sediments from these facilities were within the range of 5 to 30 mg/kg (d.w.) (actual concentration not reported) (Atwater *et al.*, 1990).

Phthalates may be leached from hazardous waste landfills. Although no Canadian data were identified, the concentration of bis(2-ethylhexyl) phthalate in one United States municipal landfill leachate was 0.20 mg/kg (Ghassemi *et al.*, 1984).

Spills are potential sources of bis(2-ethylhexyl) phthalate entry into the environment. Two spills of "dioctyl phthalate" were reported on Environment Canada's National Analysis of Trends in Emergencies System (NATES) data base: a discharge of 5 tonnes from a tank truck at Cornwall, Ontario in 1984, and a discharge of 5.6 tonnes at an industrial plant at Brantford, Ontario in 1986 (NATES, 1992).

Although it was not possible to distinguish between di-*n*-octyl phthalate and bis(2-ethylhexyl) phthalate, there are reports that "dioctyl phthalate" was present at a concentration of 15 µg/L in the effluent of a kraft pulp and paper mill at Red Rock, Ontario, on Lake Superior (Brownlee and Strachan, 1977). "Dioctyl phthalate" was also detected but not quantified in extracts of municipal incinerator fly ash from Ontario (Eiceman *et al.*, 1979).

2.3 Exposure-related Information

2.3.1 *Fate*

The most important processes affecting the distribution and transformation of bis(2-ethylhexyl) phthalate in the environment include atmospheric photo-oxidation; partitioning to soil, sediment, and biota; and aerobic degradation (Al-Omran and Preston, 1987; Howard, 1989; Howard *et al.*, 1991; Sullivan *et al.*, 1982; Wolfe *et al.*, 1980a; Zurmühl *et al.*, 1991).

More than 50% of the bis(2-ethylhexyl) phthalate in the atmosphere occurs in the vapour phase, rather than in association with suspended particulate matter (Cautreels and Van Cauwenberghe, 1978; Giam *et al.*, 1980). Howard *et al.* (1991) reported an estimated photo-oxidation half-life of gaseous bis(2-ethylhexyl) phthalate of 2.9 to 29 hours. Bis(2-ethylhexyl) phthalate adsorbed to atmospheric particulate matter would probably have a longer half-life (U.S. EPA, 1987). Washout by precipitation and dry deposition are believed to play significant roles in the removal of bis(2-ethylhexyl) phthalate from the atmosphere (Eisenreich *et al*, 1981). On the basis of experimental data on photolysis of dimethyl phthalate, Howard *et al.* (1991) estimated the photolysis half-life of bis(2-ethylhexyl) phthalate in the atmosphere to be longer than 144 days.

Bis(2-ethylhexyl) phthalate is considered to be less biodegradable than other phthalic acid esters with shorter alkyl chains (IPCS, 1992). Aerobic biodegradation half-lives of bis(2-ethylhexyl) phthalate in water ranging from 5 days to 1 month have

been reported in the literature (Howard *et al.,* 1991; Saeger and Tucker, 1976; Schouten *et al.,* 1979; Tabak *et al.,* 1981). Under anaerobic conditions, bis(2-ethylhexyl) phthalate persists longer. Howard *et al.* (1991) estimated a half-life for bis(2-ethylhexyl) phthalate in water ranging between 42 and 389 days under anaerobic conditions on the basis of results presented by other authors. They also estimated the photolysis half-life of bis(2-ethylhexyl) phthalate in water to be 144 days or longer based on reported values of aqueous photolysis for dimethyl phthalate. Volatilization of bis(2-ethylhexyl) phthalate from water is considered to be very slow, with an estimated evaporative half-life of about 15 years from a pond 1-m deep (Branson, 1978). However, Klöpfer *et al.* (1982) determined an evaporative half-life for bis(2-ethylhexyl) phthalate of about 140 days in a 21-cm deep vessel. Chemical hydrolysis of bis(2-ethylhexyl) phthalate in water is extremely slow, with an estimated half-life of over 100 years (Wams, 1987; Wolfe *et al.,* 1980b).

Bis(2-ethylhexyl) phthalate has a strong tendency to partition to sediments from the water column (Al-Omran and Preston, 1987; Sullivan *et al.,* 1982; Wolfe *et al.,* 1980a), although some may be subsequently desorbed from the sediments back into the water column (Atwater *et al.,* 1990). Biodegradation (ring cleavage) of bis(2-ethylhexyl) phthalate occurred to a greater degree in aerobic (13.8% degradation) than in anaerobic sediments (9.9% degradation) after 28 days under laboratory conditions (Johnson *et al.,* 1984).

Bis(2-ethylhexyl) phthalate also has a strong tendency to adsorb to soil, and as such would not be expected to evaporate from soil or leach into groundwater (Howard, 1989; Zurmühl *et al.,* 1991). Bis(2-ethylhexyl) phthalate, however, may form a complex with water-soluble fulvic acid which may increase its mobilization and reactivity in soil (Khan, 1980). Bis(2-ethylhexyl) phthalate is biodegraded to mono(2-ethylhexyl) phthalate and phthalic acid in soil, and these products are then either mineralized or converted into soil-bound residues (Schmitzer *et al.,* 1988). The half-life of bis(2-ethylhexyl) phthalate in soil has been estimated to range from 5 to 23 days, based on aerobic biodegradation rates (Howard *et al.,* 1991). However, Kirchmann *et al.* (1991) reported that between 20 and 50% of added bis(2-ethylhexyl) phthalate remained in soil after 80 days with initial concentrations of 5 and 250 mg/kg, respectively. Degradation occurred much more quickly during the first 10 days at the lower concentration.

Bioconcentration factors for bis(2-ethylhexyl) phthalate for various aquatic algae and invertebrates ranged from 6.9 for the oyster, *Crassostrea virginica* (24-h exposure period) (Wofford *et al.,* 1981) to 5400 for the alga, *Chlorella fusca* (24-h exposure) (Geyer *et al.,* 1984). Bioconcentration factors for fish ranged from 8.9 for rainbow trout, *Oncorhynchus mykiss,* (4-d exposure) (Tarr *et al.,* 1990) to 1380 for the fathead minnow *(Pimephales promelas)* (28-d exposure) (Mayer and Sanders, 1973). In general, bioconcentration factors appeared to be higher for algae and aquatic invertebrates than for fish. Fish appear to metabolize bis(2-ethylhexyl) phthalate quite readily (Callahan *et al.,* 1979; Johnson *et al.,* 1977; Wofford *et al.,* 1981). For example, Mayer (1976) reported that the fathead minnow *(Pimephales promelas)* metabolized bis(2-ethylhexyl)

phthalate with a biological half-life averaging 12.2 days. Bis(2-ethylhexyl) phthalate is metabolized in fish by enzymatic hydrolysis to mono-2-ethylhexyl phthalate, phthalic acid, and glucuronides of these compounds (Stalling *et al.,* 1973). The gill is the dominant site of bis(2-ethylhexyl) phthalate metabolism in rainbow trout, reducing the systemic availability of bis(2-ethylhexyl) phthalate by >95%, therefore, limiting the accumulation of this substance (Barron *et al.,* 1989). On the basis of this metabolic activity, it is considered that biomagnification of bis(2-ethylhexyl) phthalate through the aquatic food chain is not likely to occur (ATSDR, 1991). Data on biomagnification, however, have not been identified in the literature.

In vegetation, uptake of bis(2-ethylhexyl) phthalate through plant roots is very low, resulting in negligible bioconcentration (Schmitzer *et al.,* 1988). No information was identified on the bioaccumulation of bis(2-ethylhexyl) phthalate in wild mammals.

2.3.2 *Concentrations*

Data on the concentrations of bis(2-ethylhexyl) phthalate in the Canadian environment were identified for surface water, sediment, soil, and biota. However, most of these data were collected before 1980 and adequate care may not have been taken to prevent laboratory contamination of samples. The reliability of such information, therefore, is questionable. With the exception of food, available data are limited on concentrations of bis(2-ethylhexyl) phthalate in media to which the general population in Canada is exposed.

There are no recent data available on measured concentrations of bis(2-ethylhexyl) phthalate in the atmosphere in Canada. Based on atmospheric concentrations of bis(2-ethylhexyl) phthalate at a number of oceanic and inland areas as reported by Giam *et al.* (1978; 1980), Eisenreich *et al.* (1981) estimated that atmospheric concentrations of bis(2-ethylhexyl) phthalate in the Great Lakes area ranged from 0.5 to 5 ng/m^3, and that concentrations of bis(2-ethylhexyl) phthalate in rain water in this area ranged from 4 to 10 ng/L. In an early study, several phthalic acid esters were identified in samples of air collected near a municipal incinerator in Hamilton, Ontario (Thomas, 1973). The concentration of bis(2-ethylhexyl) phthalate (number of samples not reported) was 300 ng/m^3 (detection limit = 10 ng/m^3). Weschler (1981) reported about 20 ng/m^3 of bis(2-ethylhexyl) phthalate in the Arctic aerosol at Barrow, Alaska, in 1979.

Only one report of concentrations of bis(2-ethylhexyl) phthalate in indoor air was identified, in which measurements were taken in nine homes in Montreal (Otson and Benoit, 1985). The maximum concentration of bis(2-ethylhexyl) phthalate in indoor air sampled for three consecutive periods of 20 days each during the summer/fall (August to October) and winter (January to March) of 1983 and 1984, respectively, was 3.10 µg/m^3 (nominal quantitation limit, 0.50 µg/m^3). No other information on measured concentrations (e.g., mean values) was presented in the published account of this study. Data have not been identified on concentrations in indoor air in other countries.

Information on concentrations of bis(2-ethylhexyl) phthalate in surface waters in the NAQUADAT/ENVIRODAT data base is limited to approximately 80 records for

Alberta and two records for British Columbia dating from 1985 to 1988. Reported concentrations of bis(2-ethylhexyl) phthalate ranged from <1 to 14 µg/L (NAQUADAT, 1993). The Alberta Ministry of the Environment reported that bis(2-ethylhexyl) phthalate was detected in 5 of 45 samples analyzed during monitoring of raw surface water from 16 municipalities between 1987 and 1992. The average concentration was below the detection limit (1 µg/L), while the maximum concentration was 8 µg/L (Halina, 1993). Under the Municipal and Industrial Strategy for Abatement (MISA) program in Ontario, bis(2-ethylhexyl) phthalate was detected in the intake water of two organic chemical manufacturing plants at average concentrations of 6.1 and 7.1 µg/L (both plants located on the St. Clair River) (OME, 1992a). For water samples collected in 1988 and 1989 using large-volume sampling methods designed to lower the detection limit, the Niagara River Data Interpretation Group (1990) reported a mean concentration of 28.63 ng/L at Fort Erie [51 samples all contained bis(2-ethylhexyl) phthalate concentrations above the detection limit of 0.16 ng/L; maximum 265.88 ng/L). A mean concentration of 38.48 ng/L was reported at Niagara-on-the-Lake [40 out of 44 samples contained bis(2-ethylhexyl) phthalate concentrations above the detection limit; maximum 136.18 ng/L]. In 1987, Germain and Langlois (1988), also using large-volume sampling techniques, reported a mean concentration of 78 ng/L bis(2-ethylhexyl) phthalate in the St. Lawrence River in the Montreal area. Bis(2-ethylhexyl) phthalate was not detected in 22 samples of raw drinking water supplies from 11 municipalities in the Lac St-Jean and Charlevoix areas of Quebec (detection limit, 1 µg/L) (MENVIQ, 1993). In an older study, concentrations of bis(2-ethylhexyl) phthalate as high as 300 µg/ L (from Black Bay in the Ontario section of Lake Superior, sampling date not stated) were reported by Mayer *et al.* (1972). In 1979, maximum concentrations of bis(2-ethylhexyl) phthalate in the range of 10 to 100 µg/L were reported for chemical plant intake water from the St. Clair River (Munro *et al.*, 1985).

In a survey of drinking water from selected surface (18) and groundwater (10) supplies sampled in Alberta between 1985 and 1986 (n = 329), the average concentrations of bis(2-ethylhexyl) phthalate were 3.0 µg/L (trace to 35.0 µg/L) and 2.0 µg/L (trace to 9.0 µg/) for surface and groundwater, respectively (Spink, 1986). In a more recent survey of a total of 1237 samples in Alberta taken in 1987 to 1992, the mean concentrations were similar to those reported earlier (Halina, 1993). In a survey of an unspecified number of samples of municipal drinking water supplies of seven cities in the Niagara and Lake Ontario regions conducted in October and November, 1984, concentrations of bis(2-ethylhexyl) phthalate were at or below the detection limit of 1.0 µg/L (OME, 1984).

Single sediment samples collected in 1983 from the estuary of the Fraser River, British Columbia, 0.5 km below a sewage outfall, contained 0.844 mg of bis(2-ethylhexyl) phthalate/kg (d.w.). The concentration in sediment 1.0 km below the outfall was 0.404 mg of bis(2-ethylhexyl) phthalate /kg (d.w.) (Rogers and Hall, 1987).

In the only study identified where concentrations of bis(2-ethylhexyl) phthalate in soil in Canada were reported, levels varied from less than 0.1 to 11 µg bis(2-ethylhexyl)

phthalate/kg dry weight (n =30) in samples from Port Credit and Oakville/Burlington, Ontario (Golder Associates, 1987).

Williams (1973) reported a concentration of 0.104 µg/g in eel from an unspecified Canadian lake or river. Swain (1978) reported mean concentrations of bis(2-ethylhexyl) phthalate as high as 1.3 µg/g wet weight (whole fish) in siscowet trout *(Salvelinus namaycush siscowet)* and 0.7 µg/g in whitefish *(Coregonus clupeaformis)* from the vicinity of Isle Royale, Lake Superior, and 0.3 µg/g in lake trout *(Salvelinus namaycush)* from Lake Superior exclusive of the Isle Royale area. A maximum concentration of 2.2 µg of bis(2-ethylhexyl) phthalate/g was reported for skinless fillets of whitefish from Lake Superior (Glass *et al.,* 1977). Mayer *et al.* (1972) reported concentrations of bis(2-ethylhexyl) phthalate of up to 0.8 µg/g in walleye *(Stizostedion vitreum)* from Black Bay, Lake Superior. Concentrations of bis(2-ethylhexyl) phthalate in commercial fish lipid extracts of up to 7.24 µg/g wet weight (w.w.) were measured in muscle of herring *(Clupea harengus harengus)* from the Bay of Fundy (Burns *et al.,* 1981). Concentrations of bis(2-ethylhexyl) phthalate in whole fish from harbours and tributary mouths of various United States Great Lakes ranged from <0.04 to 32 µg of bis(2-ethylhexyl) phthalate/g (w.w.) in 1980 and 1981 (DeVault, 1985). Zitko (1972) reported bis(2-ethylhexyl) phthalate in the blubber of the common seal, *Phoca vitulina,* from Atlantic Canada at a concentration of 10.6 µg/g lipid. No other data concerning the concentration of bis(2-ethylhexyl) phthalate in Canadian wild birds and mammals were found in the literature.

In a market basket survey of 98 different food types obtained in Halifax in 1986 (NHW, 1992), bis(2-ethylhexyl) phthalate was detected in:

- dairy products (range, 0.01 µg/g in skim milk to 3.4 µg/g in butter);
- meat, poultry, and fish (range, 0.1 µg/g in freshwater fish, ground beef, and canned fish to 2.6 µg/g in poultry); cereal products (range, 0.02 µg/g in wheat and bran cereal to 1.5 µg/g in whole wheat bread);
- danishes and donuts (3.4 µg/g);
- coleslaw (0.14 µg/g);
- fresh tomatoes (0.09 µg/g);
- cucumbers and pickles (0.17 µg/g);
- canned citrus fruit (0.05 µg/g); bottled grape juice (0.04 µg/g);
- plums and prunes (0.07 µg/g);

- margarine (1.24 µg/g);
- chocolate bars (0.51 µg/g);
- muffins (1.0 µg/g); and
- canned meat soup (0.1 µg/g).

The detection limits, which were not specified for individual foodstuffs, varied depending on the reagent blank values, interferences arising from coextracted food components, and the fat content of the food (range, 0.01 to 0.5µg/g).

Bis(2-ethylhexyl) phthalate is present widely as a plasticizer in consumer products, including those used by children. In a preliminary survey of twenty-four samples of children's products in Canada (ten pacifiers, four teethers, three nipples, and seven flexible toys), three of the 24 samples examined contained between 20 and 23% bis(2-ethylhexyl) phthalate on a weight/weight (w/w) basis (CCAC, 1992). Of the remaining 21, the bis(2-ethylhexyl) phthalate content in four ranged between 0.1 and 0.4% w/w, while that in the others was below 0.05% (detection limit = 0.05% for a 5-gram sample).

2.4 Toxicokinetics

Following ingestion by mammals, bis(2-ethylhexyl) phthalate is initially hydrolyzed by a nonspecific lipase in the gastrointestinal tract to produce mono(2-ethylhexyl) phthalate (which is readily absorbed) and 2-ethylhexanol. Bis(2-ethylhexyl) phthalate appears to be more efficiently absorbed from the gastrointestinal tract of rats than from that of primates (Rhodes *et al.,* 1986). Although data available on absorption following ingestion in humans are limited, absorption of bis(2-ethylhexyl) phthalate following inhalation appears to be considerably less than that from the gastrointestinal tract (Pegg, 1982; cited in U.S. EPA, 1987). Bis(2-ethylhexyl) phthalate is relatively poorly absorbed through the skin (El Sisi *et al.,* 1985). Once absorbed, bis(2-ethylhexyl) phthalate and mono(2-ethylhexyl) phthalate are widely distributed in the body with no apparent accumulation. Available data indicate that there are considerable species differences in the tissue distribution of bis(2-ethylhexyl) phthalate and its metabolites after oral exposure, with bioavailability of bis(2-ethylhexyl) phthalate in primates being considerably less than that in the rat (Eriksson and Darnerud, 1985; Pollack *et al.,* 1985a; Rhodes *et al.,* 1986).

Bis(2-ethylhexyl) phthalate is converted by oxidative metabolism involving lipolytic cleavage to form mono(2-ethylhexyl) phthalate and 2-ethylhexanol and rapid oxidation of mono(2-ethylhexyl) phthalate to more polar derivatives via ?- and ?-1-oxidation of the aliphatic side-chain. It is believed that this step is followed by a dehydrogenase-dependent oxidation to the ketone or carboxylic acid, with subsequent a- and ß-oxidation of the acids (Albro *et al.,* 1973). An analysis of the excreta from cynomolgus monkeys administered a single oral dose of 100 mg/kg (b.w.) of

^{14}C-bis(2-ethylhexyl) phthalate by gavage in corn oil indicated that they had a lower capacity than F344 rats to metabolize bis(2-ethylhexyl) phthalate by ß-oxidation (Short *et al.,* 1987). Furthermore, the metabolites identified represented about 30% and 19% of the administered dose for rats and monkeys, respectively.

Available data also indicate that some rodents do not conjugate metabolites of bis(2-ethylhexyl) phthalate whereas in primates, they are excreted as glucuronide derivatives. In African green monkeys administered 50 mL (0.5 µmol/mL or 195 µg/mL) of ^{14}C-bis (2-ethylhexyl) phthalate intravenously, 80% of the urinary metabolites were glucuronide conjugates (Albro *et al.,* 1981). This was similar to results reported in humans (Schmid and Schlatter, 1985), but not in rats. Urinary metabolites of bis(2-ethylhexyl) phthalate in rats were largely unconjugated and consisted primarily of derivatives more highly oxidized than those in monkeys or humans (Gibson *et al.,* 1976; Teirlynck and Belpaire, 1985).

2.5 Effects-related Information

2.5.1 *Experimental Animals and* In Vitro

The acute toxicity of bis(2-ethylhexyl) phthalate has been low in extensive studies in a variety of species and strains of experimental animals. Oral LD_{50}s have generally exceeded 25 000 mg/kg (b.w.) in mice and rats (Woodward, 1988), 33 900 mg/kg (b.w.) in rabbits (Shaffer *et al.,* 1945), and 26 000 mg/kg (b.w.) in guinea pigs (Krauskopf, 1973).

There have been numerous investigations of the short-term toxicity of bis(2-ethylhexyl) phthalate following oral administration, most of which have been designed to investigate hepatic toxicity in rats and several of which have been limited to administration of single-dose levels. In general, short-term oral administration of bis(2-ethylhexyl) phthalate to rats has resulted in decreases in the rates of body weight gain at concentrations greater than 625 mg/[kg (b.w.)·d] (NTP, 1982). Increases in liver weight and transient mitotic bursts have been observed at doses greater than 50 mg/[kg (b.w.)·d] in rats (Morton, 1979; Lake *et al.,* 1991; Mitchell *et al.,* 1985). Alterations in the activity of hepatic enzymes consistent with peroxisome proliferation or increases in peroxisome numbers have been observed at doses greater than 25 to 100 mg/[kg (b.w.)·d] in rats (Morton, 1979; Lake *et al.,* 1991; Dostal *et al,* 1987; Barber *et al.,* 1987). Alterations in serum triglycerides have been reported at doses as low as 2.5 mg/[kg (b.w.)·d] (Morton, 1979), though the significance of this observation is unclear, in view of the lack of confirmation or conflicting results in other studies (CMA, 1984). Effects on the kidneys, including increases in organ weight and changes in renal enzymes, have also been observed following exposure to higher doses of bis(2-ethylhexyl) phthalate {1000 to 2000 mg/[kg (b.w.)·d]; Dostal *et al.,* 1987; Reubsaet *et al.,* 1990}. In general, male rats have been more sensitive to the effects of bis(2-ethylhexyl) phthalate than females (Mitchell *et al.,* 1985).

In short-term studies, there have been marked differences in liver toxicity among species. Whereas in rats, increased peroxisomal enzyme activities were observed after exposure to 100 and 250 mg/[kg (b.w.)·d] of bis(2-ethylhexyl) phthalate for 14 days, effects were considerably less severe in hamsters exposed to doses as high as 1000 mg/[kg (b.w.)·d] of bis(2-ethylhexyl) phthalate (Lake *et al.,* 1984). In parallel morphological investigations, there was a greater increase in hepatic peroxisome numbers in rats than in hamsters. Liver enlargement was observed in both species; the increases were significant at 100 mg/[kg (b.w.)·d] and above in the rats but only at 1000 mg/[kg (b.w.)·d] in the hamsters. The lowest-observed-effect-levels (LOELs) based on these parameters of liver toxicity are considered to be 100 mg/[kg (b.w.)·d] and 1000 mg/[kg (b.w.)·d] for rats and hamsters, respectively. In another study (Short *et al.,* 1987), there was metabolic, biochemical, and morphological evidence of peroxisomal proliferation in male F344 rats that consumed diets containing 1000 ppm {105 mg/[kg (b.w.)·d]} or higher for 21 days with an accompanying increase in liver weight at 6000 ppm {667 mg/[kg (b.w.)·d)} and above. In contrast, peroxisomal proliferation was not observed in cynomolgus monkeys that received up to 500 mg/[kg (b.w.)·d] of bis(2-ethylhexyl) phthalate by gavage for the same period. Further, oral and intraperitoneal administration of doses of bis(2-ethylhexyl) phthalate up to 1950 mg/[kg (b.w.)·d] for 14 days to the marmoset monkey did not induce morphological or biochemical changes in the liver comparable to those observed in Wistar rats administered a similar dose, owing to less efficient absorption based on the profile for excretion and concentrations of radioactivity in tissues following administration of a radio-labelled dose (Rhodes *et al.,* 1986).

Although effects on the liver have generally not been as well examined in subchronic studies, they have been similar to those reported in short-term studies, including reductions in body weight gain at doses of 400 mg/[kg b.w.)·d] or greater in rats (Shaffer *et al.,* 1945) and 100 mg/[kg b.w.)d] in mice (NTP, 1982). Hepatomegaly and adverse effects on the testes have also been observed at doses greater than 143 mg/[kg (b.w.)·d], respectively, in rats (Gray *et al.,* 1977). Clinical signs and mortality have been observed only at higher doses in rats though at doses of 370 mg/[kg (b.w.)·d] and above in mice (NTP, 1982). In a study conducted by Price *et al.* (1988), alterations were reported in the thyroid of an unspecified number of rats exposed to 1000 mg/[kg (b.w.)·d] of bis(2-ethylhexyl) phthalate for three months. Marked lesions in the kidney of DDY/SCL mice fed diets containing concentrations equivalent to 500 or 5000 mg/[kg (b.w.)·d], respectively, for one to three months have also been reported (Ota *et al.,* 1974).

Gray *et al.* (1977) administered 0, 0.2, 1.0, or 2.0% of bis(2-ethylhexyl) phthalate in the diet {equivalent to 0, 143, 737, or 1440 and 0, 154, 797, 1414 mg/[kg b.w.)·d] for males and females, respectively} to groups of 15 Sprague-Dawley rats for 17 weeks. At 2% bis(2-ethylhexyl) phthalate in the diet in both sexes, there were consistent increases in the relative weights of the stomach, small intestine, caecum, kidney, heart and brain, fur loss, and reduction in the rate of weight gain from Day 2 onwards in both sexes. This reduction in body weight gain was also noted in males at 1.0% from Day 6 onwards but was not noted in females until Day 83. Hemoglobin concentrations, packed cell volumes,

and erythrocyte counts were reduced in males at 1% bis(2-ethylhexyl) phthalate at Week 2. By Week 17, 2/15 animals administered 1% and 10/15 receiving 2% had severe testicular damage; damage was only slight (4/15) in animals administered 0.2% in the diet. Hepatomegaly was noted in all exposed animals.

In available studies of the chronic toxicity of bis(2-ethylhexyl) phthalate, most of which were conducted in rats and several of which were designed to investigate sensitive endpoints in the liver, increases in peroxisome proliferation and alterations in related hepatic enzymes have been observed at doses of 12 to 15 mg/[kg (b.w.)·d] and greater (Ganning *et al.*, 1987; 1991). Adverse effects on the kidney, such as nephritis, have been observed in male Wistar rats at doses as low as 30 mg/[kg (b.w.)·d], although the validity of these results could not be assessed on the basis of only an English abstract available at the date of completion of this assessment (Nagasaki *et al.*, 1974). After one year of exposure, a significant decrease in kidney creatinine clearance and an increase in the severity of renal cyst formation were also observed in rats (strain unspecified) in a study in which only one dose level was administered {0.92 mg/[kg (b.w.)·d]}. Similar effects [considered to be accelerated development of spontaneous nephropathy (IPCS, 1992)], however, have not been confirmed elsewhere at such low doses (Crocker *et al.*, 1988).

The potential carcinogenicity of bis(2-ethylhexyl) phthalate was examined extensively in a study sponsored by the National Toxicology Program (NTP, 1982; Kluwe *et al.*, 1982). In this study, groups of 50 F344 rats of each sex received 0, 6000, or 12 000 ppm of bis(2-ethylhexyl) phthalate while groups of 50 B6C3F_1 mice of each sex received 0, 3000, or 6000 ppm in their diet for 103 weeks. Equivalent doses were 0, 322, and 674 mg/[kg (b.w.)·d] for male rats; 0, 394, and 744 mg/[kg (b.w.)·d] for female rats; 0, 672, 1325 mg/[kg (b.w.)·d] for male mice; and 0, 799, and 1821 mg/[kg (b.w.)·d] for female mice. In rats, there was a dose-related decrease in mean body weight gain in both males and females receiving the high dose. Daily mean food consumption was reduced slightly in this dose group. No other clinical signs of toxicity or dose-related trends in mortality were observed. The incidences of neoplastic nodules of the liver were increased in exposed animals [males: control- 2/50 (4%), low- 5/49 (10%), high- 7/49 (14%); females: 0/50 (0%), 4/49 (8%), 5/50 (10%)]. The combined incidences of neoplastic nodules and hepatocellular carcinomas were greater than those in the control groups [males: 3/50 (6%), 6/49 (12%), 12/49 (24%), $p = 0.010$; females: 0/50 (0%), 6/49 (12%), 13/50 (16%), $p = 0.003$]. There were no other dose-related increases in tumour incidence. Degeneration of the seminiferous tubules was observed in males in the high-dose group [1/49 (2%), 2/44 (5%), 43/48 (90%)]. Hypertrophy of cells in the anterior pituitary was increased in male rats in the high-dose group [1/46 (2%), 0/43 (0%), 22/49 (45%)].

In mice, there was a dose-related decrease in mean body weight gain in females. No other clinical signs of toxicity or dose-related trends in mortality were observed. The incidences of hepatocellular carcinomas in male and female mice administered bis(2-ethylhexyl) phthalate were significantly greater than those in the control groups [males: 9/50 (18%), 14/48 (29%), 19/50 (38%), $p = 0.022$; females: 0/50 (0%),

7/50(14%), p = 0.006**;** 17/50 (34%), p <0.001]. The combined incidences of hepatocellular carcinomas and adenomas were also elevated in males in the low- (25/48, 52%) and high-dose (29/50, 58%) groups and in females in the low- (12/50, 24%) and high-dose (18/50, 36%) groups. The combined incidences in male and female controls were 14/50 (28%) and 1/50 (2%), respectively. Degeneration of the seminiferous tubules was observed in males in the high-dose group [1/49 (2%), 2/48 (4%), 7/49 (14%)].

On the basis of the above-mentioned non-neoplastic effects, the LOELs for rats and mice were considered to be 322 and 672 mg/[kg (b.w.)·d], respectively. In addition, under the conditions of this bioassay, the NTP concluded that "bis(2-ethylhexyl) phthalate was carcinogenic for F344 rats and B6C3F_1 mice, causing increased incidences of female rats and male and female mice with hepatocellular carcinomas, and induced an increased incidence of male rats with either hepatocellular carcinomas or neoplastic nodules".

Northup *et al.* (1982) noted that "the maximum tolerated dose (MTD) was exceeded in both species because body weight gain was depressed by more than 10% in the exposed groups". In addition, the significance of the bis(2-ethylhexyl) phthalate- induced increases in liver tumours was also questioned because of variations in incidences of liver tumours in controls (in the same strains) in bioassays conducted simultaneously in the same rooms as the NTP study, and because some data on food consumption, clinical pathology, clinical signs, intestinal micro-organisms, and nutritional status were lacking. The authors (Kluwe *et al.*, 1983) responded that in the NTP study, survival was not adversely affected, and statistical analyses failed to demonstrate any correlation between the occurrence of non-neoplastic lesions and the development of hepatocellular tumours in rats and mice of both sexes. On the basis of clinical evaluations conducted throughout the study, morbidity or signs of debilitation were not detected. Further, there was relatively little variation in the incidence of liver tumours among the National Toxicological Program historical controls.

In a study designed to elucidate the mechanism of bis(2-ethylhexyl) phthalate hepatocarcinogenesis under the conditions of the NTP bioassay (Cattley *et al.*, 1987; Popp *et al.*, 1987), groups of 20 female F344 rats were fed a diet containing 0, 0.03, 0.1, or 1.2% bis(2-ethylhexyl) phthalate {equivalent to 0, 15, 50, or 600 mg/[kg (b.w.)·d]} for 2 years (extent of histopathological examination was not specified). In animals in the two highest dose groups, the activity of cyanide-insensitive palmitoyl CoA oxidase was increased while in hepatocytes, DNA replication, an indication of cell proliferation, was not affected. The number of foci was not elevated in the bis(2-ethylhexyl) phthalate-exposed animals compared to controls, even though there was a statistically significant increase in liver tumours (combined hepatocellular carcinoma and neoplastic nodule) in the high dose group (1/18, 1/19, 6/20). Therefore, 50 mg/[kg (b.w.)·d] was considered to be a LOEL based on the increase in enzyme activity; the no-observed-effect-level (NOEL) for this effect was 15 mg/[kg (b.w.)·d)].

In a more limited study conducted by Rao *et al.* (1990), small groups (n = 14) of male F-344 rats consumed a diet containing 2% bis(2-ethylhexyl) phthalate *ad libitum* for

108 weeks { 1200 mg/[kg (b.w.)·d]}. A group of 10 rats served as controls. A complete necropsy was performed on the liver and representative sections from the liver, lungs, kidneys, and pancreas were processed for light microscopy. The body weights of bis(2-ethylhexyl) phthalate-exposed rats were significantly less than those in the control group. The livers of animals fed bis(2-ethylhexyl) phthalate were dark brown, markedly enlarged, and relative weights were 100% greater than those in controls. At necropsy, livers were quantitatively analyzed for total tumour incidence and the number of lesions per liver after slicing through the entire organ at 1 - to 2-mm intervals. Neoplastic nodules and/or hepatocellular carcinomas were observed in 11 of 14 exposed rats. When evaluated according to the size, nodules ranging from 1 to 3, 3 to 5, and greater than 5 mm in diameter were observed in 57, 16, and 36% of the rats, respectively. The number of nodules per liver ranged from 0 to 4. Only 1/10 control rats had a liver tumour (diameter 15 mm).

Increased incidences of tumours were not observed in chronic bioassays in Sherman or Wistar rats receiving diets containing up to 0.4% or 0.5% bis(2-ethylhexyl) phthalate (Carpenter *et al.,* 1953*;* Harris *et al,* 1956*).* However, owing to the limitations of these early investigations (e.g., small numbers of animals used and high mortality due to disease), these results add little additional information relevant to assessment of the weight of evidence of the carcinogenicity of bis(2-ethylhexyl) phthalate. There were no effects on median survival time or tumour incidences as compared with control groups in hamsters following intraperitoneal administration and inhalation of bis(2-ethylhexyl) phthalate (Schmezer *et al.,* 1988).

Two hypotheses have been proposed to explain the mechanism(s) by which bis(2-ethylhexyl) phthalate induces liver tumours in rodents. One relates to its action, similar to that of some other nongenotoxic chemical carcinogens, to alter the number and function of peroxisomes in rodent liver cells. On the basis of this hypothesis, it is assumed that the hepatocarcinogenesis of bis(2-ethylhexyl) phthalate is not related to a direct initiating effect of bis(2-ethylhexyl) phthalate or its metabolites, but to biologically active products, mainly hydrogen peroxide, of proliferated peroxisomes (Rao and Reddy, 1987). Alternatively, the carcinogenesis of bis(2-ethylhexyl) phthalate may be related to the induction of hyperplasia. Based on this hypothesis, carcinogenesis is the result of the initiation of increased cell division and DNA synthesis by exposure to bis(2-ethylhexyl) phthalate (Busser and Lutz, 1987; Smith-Oliver and Butterworth, 1987; Marsman *et al.,* 1988). It is proposed that the increase in liver cell division that results from exposure to bis(2-ethylhexyl) phthalate increases susceptibility to the action of genotoxic compounds. Alterations of DNA in rapidly dividing cells become permanent as cells divide faster than DNA repair enzymes can correct the damage (Smith-Oliver and Butterworth, 1987; Hsia, 1990). Though not entirely consistent, available data suggest that bis(2-ethylhexyl) phthalate may act as a co-carcinogen or a promoter in rodents. It is impossible to separate the effects of the two processes or to determine if one is more related to hepatocarcinogenesis than the other; indeed tumour formation could be a function of both mechanisms. It is unlikely, therefore, that bis(2-ethylhexyl) phthalate induces hepatic tumour formation at dose levels that do not produce either significant peroxisome proliferation or cell replication.

The genotoxicity of bis(2-ethylhexyl) phthalate has been extensively examined in *in vitro* and *in vivo* assays, the protocols and results of which have been summarized in several reviews (ATSDR, 1989; 1991; Butterworth, 1987). The overwhelming weight of evidence indicates that bis(2-ethylhexyl) phthalate and its primary metabolites [mono(2-ethylhexyl) phthalate and 2-ethylhexanol] are not genotoxic in most microbial and mammalian assay systems.

In numerous studies conducted primarily in rats, effects on the testes, including decreased organ weights, histological changes in the seminiferous tubules, inhibition of the respiratory functions of Sertoli cell mitochondria and testicular enzyme activities, reduction in sperm counts, and a reduction in testicular zinc, have been observed following oral exposure to bis(2-ethylhexyl) phthalate. Available data also indicate that sensitivity to bis(2-ethylhexyl) phthalate-induced testicular atrophy varies with age (Gray and Butterworth, 1980) and that hamsters and marmosets are considerably less sensitive to the testicular effects of bis(2-ethylhexyl) phthalate than rats (Gray *et al.*, 1982), presumably because of postulated differences in metabolism. The lowest dose at which such effects have been observed is that reported by Gray *et al.* (1977) in which "slight damage" to the testes was observed following ingestion of 0.2% bis(2-ethylhexyl) phthalate by Sprague-Dawley rats in their diet { 143 mg/[kg (b.w.)·d] } for 17 weeks. A slightly lower {100 mg/[kg (b.w.)·d]} dose was considered the NOEL for effects on the testes in a study conducted by Dostal *et al.* (1988) in which smaller groups of rats of the same strain were exposed to bis(2-ethylhexyl) phthalate in the diet for up to 12 weeks. The lowest-observed-adverse-effect-level (LOAEL) for reduced fertility in mice in a study conducted by Reel *et al.* (1982) was similar to that in the study of Gray *et al.* (1977), namely 130 mg/[kg (b.w.)d]; the NOEL in this study was 0.1% in the diet {13 mg/[kg (b.w.)d]}. It should be noted, however, that the administered doses in the Reel *et al.* (1982) study were quite widely spaced.

In the well documented study by Reel *et al.* (1982; Lamb *et al.*, 1987), groups of CD-1 mice were administered 0, 0.01, 0.1, or 0.3% bis(2-ethylhexyl) phthalate in the diet {equivalent to approximately 0, 13, 130, and 390 mg/[kg (b.w.)·d]} during a 7-day pre-mating period and a 98-day cohabitation period. Fertility was completely suppressed in the high dose group and significantly reduced in the intermediate dose group. In the animals receiving 0.1% {130 mg/[kg (b.w.)]} and above, the breeding pairs produced fewer litters and had fewer male and female live pups per litter than did the controls. Based on histological examination, the concentration of sperm and the percentage of motile sperm in males in the high-dose group were significantly reduced. Further, testicular and epididymal weights were reduced and there was extensive destruction of the seminiferous tubules. In the females in the high-dose group, the weights of the ovaries, oviducts, uterus, and vagina were also significantly decreased. The NOEL in this study , therefore, is considered to be 0.01% {13 mg/[kg (b.w.)·d]; LOAEL = 130 mg/[kg (b.w.)·d]}.

In identified studies of developmental toxicity, bis(2-ethylhexyl) phthalate has been fetotoxic both in the presence and absence of maternal toxicity. [Teratogenic effects in the absence of maternal toxicity based on examination of body weight changes

only, were reported in one study by Shiota and Mima (1985)]. The lowest reported effect levels in these studies were those of Wolkowski-Tyl *et al* (1984a), Hamano *et al* (1977), and Shiota *et al* (1980). The LO(A)EL in mice in the investigation by Wolkowski-Tyl *et al* (1984a) and Tyl *et al* (1988), in both mothers and offspring, was 91 mg/[kg((b.w.)·d], at which maternal toxicity (treatment-related rough fur coat and lethargy) and increased numbers of malformed fetuses were observed. The NOEL for both mothers and offspring was 44 mg/[kg (b.w.)·d]. The LOAEL in mice in the study of Hamano *et al* (1977) in both mothers and offspring was 130 mg/[kg (b.w.)·d], at which there were significant decreases in the weights of the spleen and increases in the weights of the kidney and livers of the mothers and increases in embryo resorptions and decreases in the numbers of live fetuses; the NOEL in this study was 13 mg/[kg (b.w.)·d], though it should be noted that the administered doses were widely spaced. Shiota *et al.* (1980; Shiota and Nishimura, 1982) reported increases in the numbers of resorptions in the absence of maternal toxicity at 0.1% bis(2-ethylhexyl) phthalate {190 mg/[kg (b.w.)·d]}; the NOAEL in this study for offspring was 0.05% {70 mg/[kg (b.w.)·d]}.

In two well documented studies, bis(2-ethylhexyl) phthalate was fetotoxic and teratogenic at maternally toxic doses in CD-1 mice and fetotoxic at maternally toxic doses in F344 rats (Tyl *et al.,* 1988; Wolkowsky-Tyl *et al.,* 1984a;b). In CD-1 mice, there was a significant dose-response trend toward reduced maternal body weight on days 12, 16, and 17 of gestation in groups receiving 0.1% or 0.15% bis(2-ethylhexyl) phthalate (equivalent to approximately 191 or 292 mg/[kg (b.w.)·d] based on data on food consumption). There was a dose-related increase in maternal liver weight in these two highest dose groups when compared with controls. Treatment-related clinical signs in the mothers were limited to rough coat and lethargy at 0.05 to 0.15%. The number and percentage of resorptions and fetal deaths were increased, and number of live fetuses was decreased at 0.10% and 0.15%. Malformed fetuses per litter were increased in a dose-dependent manner at 0.05 to 0.15% {91 to 292 mg/[kg (b.w.)·d]}. There was a dose-related decrease in the body weights of the fetuses and the differences were statistically significant at 0.15% when compared with controls. The major malformations in CD-1 mice included external, visceral, and skeletal defects. The NOEL in this study was 0.025% {44 mg/[kg (b.w.)·d]} where there was no significant maternal or developmental toxicity and the LO(A)EL was 0.05% {91 mg/[kg (b.w.)·d]}. In F344 rats fed diets containing 0, 0.5%, 1.0%, 1.5%, or 2.0% bis(2-ethylhexyl) phthalate {equivalent to doses of approximately 0, 357, 666, 856, or 1055 mg/[kg (b.w.)·d] based on data on food consumption} on days 0 to 20 of gestation, the maternal body weight and maternal gestational weight gain were significantly reduced at the three highest doses. Maternal absolute and relative liver weights were significantly increased in all exposed groups. The incidences of piloerection and rough fur coat were increased in a dose-related manner but "predominantly" at 1.0 to 2.0% bis(2-ethylhexyl) phthalate. Significantly reduced body weights of fetuses were observed at the three highest doses. At the highest dose, there were increased numbers of resorptions and a decreased number of live fetuses, although no significant increase in malformations was observed. Therefore, 0.5% in the diet {357 mg/[kg (b.w.)·d]} was considered to be a NOEL for the offspring and a LOEL for the mothers.

In the study reported by Hamano *et al.* (1977), JCL:ICR mice were administered 0.01, 0.1, or 1.0% in food {equivalent to 13, 130, or 1300 mg/[kg ((b.w.)·d]} throughout 18 days of gestation. There were no significant differences in maternal body weights, the mortality of maternal mice, the rate of spontaneous abortions, or the rate of premature births between the control and exposed groups. There were 15 pregnant mice in the high-dose group and one in the mid-dose group that failed to carry live fetuses due to full mortality of the implanted embryos. A statistically significant decrease in spleen weight, and increases in the weights of the liver and kidneys of the mothers, was observed at 0.1% and above. Significant increases in embryo resorptions were observed in mice administered the two highest concentrations and there was a decrease in the weight of male fetuses at 0.1%. Although external anomalies (spina bifida, exencephaly, tail malformation, and non-closing eyelid) were observed in offspring of mothers receiving 0.1% in the diet, increases in incidence were not significant. There were significant increases in the frequency of skeletal anomalies and delayed ossification in the mid-dose group. Therefore, the NOEL in this study was considered to be 0.01% in the diet {13 mg/[kg (b.w.)·d] } for both mothers and fetuses.

The potential of bis(2-ethylhexyl) phthalate to induce developmental toxicity appears to vary considerably depending on the route of administration, with the compound being more potent following oral versus intraperitoneal (i.p.) administration to ICR-JCL mice (Shiota and Mima, 1985). Groups of pregnant mice were administered 250, 500, 1000, or 2000 mg/kg (b.w.) by gastric intubation or 500, 1000, 2000,4000, or 8000 mg/kg (b.w.) by i.p. injection on days 7, 8, or 9 of gestation. There were increases in resorptions and malformations in mice exposed orally to the two highest dose levels (maternal toxicity based on examination only of body weight gain was detected at the highest dose), with anencephaly and exencephaly being the most predominant abnormalities. Fetal weights were also suppressed at the two highest doses. No teratogenic effects were observed in animals exposed by intraperitoneal injection. This variation in toxicity might be a function of the metabolism to mono(2-ethylhexyl) phthalate in the gastrointestinal tract.

With the exception of a report on peroxisome proliferation in the neurons of the cerebral cortex of rats exposed by lactation to bis(2-ethylhexyl) phthalate (Dabholkar, 1988), data have not been identified on the neurotoxicity and immunotoxicity of bis(2-ethylhexyl) phthalate. Hinton *et al.* (1986) reported that the level of thyroxine decreased in Wistar rats (n = 4) fed 2% {2000 mg/[kg (b.w.)·d] } bis(2-ethylhexyl) phthalate in the diet for 21 days. There was microscopic evidence of marked changes in thyroid ultrastructure following exposure to bis(2-ethylhexyl) phthalate.

2.5.2 *Humans*

Information on the carcinogenicity, reproductive, or developmental effects in human populations exposed in the occupational or general environments to bis(2-ethylhexyl) phthalate has not been identified. Data on the effects of chronic exposure on the blood, nervous system, and pulmonary function in small studies in occupationally exposed populations are limited and inconclusive (Thiess *et al.,* 1978a;b

in IPCS, 1992; Nielsen *et al.*, 1985). In a study conducted by Thiess and Flieg (1978, in IPCS, 1992), there was no difference in the prevalence of chromosomal abnormalities in the peripheral lymphocytes of a small group of workers (n = 10) occupationally exposed for 10 to 34 years to 0.0006 to 0.01 ppm of bis(2-ethylhexyl) phthalate (9.6 to 160 µg of bis(2-ethylhexyl) phthalate/m^3), compared to that in 20 age-matched control workers.

2.5.3 *Ecotoxicology*

The effects-related information for bis(2-ethylhexyl) phthalate includes acute and chronic data for a number of species of various trophic levels from bacteria and algae through to fish and amphibians in the aquatic environment. No information was identified on effects of bis (2-ethylhexyl) phthalate on mammalian wildlife.

Volskay and Grady (1988) reported a 30-minute IC_{50} for inhibition of respiration of > 400 g/L for activated sludge micro-organisms.

A 140-h EC_{50} of >100 µg of bis(2-ethylhexyl) phthalate/L was reported for the alga *Selenastrum capricornutum* based on numbers of cells (CMA, 1990).

For aquatic organisms, the lowest identified acutely toxic concentration was for the cladoceran, *Daphnia pulex,* with a 48-h LC_{50} of 133 µg/L (nominal concentration) (Passino and Smith, 1987). No other studies were identified in which acute toxicity values for aquatic organisms were less than the highest reported solubility in water for bis(2-ethylhexyl) phthalate (400 µg/L). The lowest reported effect level for chronic toxicity was for *Daphnia magna*, with a 21-day LOEL (survival reduced by 25%) of 160 µg of bis(2-ethylhexyl) phthalate/L and a 21-day NOEL of 77 µg/L (Springborn Bionomics, 1984). This study was carried out under flow-through conditions, with concentrations of bis(2-ethylhexyl) phthalate measured weekly.

The CMA (1990) reported 96-h LC_{50} values of >320 µg/L and 670 µg/L for the rainbow trout *(Oncorhynchus mykiss)* and the fathead minnow *(Pimephales promelas),* respectively. DeFoe *et al.* (1990) reported a 96-h LC_{50} of >327 µg/L for the fathead minnow. Following a 90-day exposure to 502 µg/L [the highest bis(2-ethylhexyl) phthalate concentration tested], no significant adverse effects on hatchability, growth, or survival of rainbow trout were detected.

No toxicological data were identified for sediment-dwelling biota in Canada.

After a 230-day exposure to feed containing 0.5 or 1.0 g/l00 g of feed, domestic chickens stopped laying eggs and had enlarged livers and kidneys, and abnormal ovaries (Ishida *et al.*, 1982). However, as this occurred at both exposure levels studied, a LOEL and NOEL could not be determined.

3.0 Assessment of "Toxic" under *CEPA*

3.1 CEPA 11(a) Environment

Bis(2-ethylhexyl) phthalate is the most important phthalate plasticizer used in Canada. In 1991, domestic production totalled 5 kt, and an additional 5 kt were imported. Bis(2-ethylhexyl) phthalate is also imported into the country in plasticized polyvinyl chloride (PVC) and in plastic products. Data on releases of bis(2-ethylhexyl) phthalate to water were limited to a few measurements of industrial effluents, and no data were identified on its release to the atmosphere. However, limited information from international sources indicates that releases from manufacturing facilities are mostly to the atmosphere. No recent data were identified on the concentrations of bis(2-ethylhexyl) phthalate in the atmosphere in Canada. Very limited recent data were identified concerning the concentrations of bis(2-ethylhexyl) phthalate in Canadian surface water, industrial effluents, and sewage sludges. Moreover, no data were identified for sites near known production facilities in Canada. The reliability of data relating to the concentration of bis(2-ethylhexyl) phthalate in sediments and biota in Canada is questionable because of possible contamination during sampling or analysis. These data are therefore not considered adequate for assessment purposes.

Although bis(2-ethylhexyl) phthalate does not persist in aerobic environments because of degradation processes such as photo-oxidation and biotransformation, it can persist and accumulate under anaerobic conditions such as in buried sediments. The information reviewed for this assessment indicates that bis(2-ethylhexyl) phthalate has the potential for bioaccumulation in aquatic invertebrates, although biomagnification through the aquatic food chain is not likely to occur.

For dissolved bis(2-ethylhexyl) phthalate, the lowest reported chronic effect level on freshwater aquatic organisms was 160 µg/L (21-day LOEL, survival) for *Daphnia magna.* This effect level was divided by a factor of 20 (10 to account for differences in sensitivity between species and to extrapolate from laboratory to field conditions, and 2 because of the sizeable reduction in survival associated with the LOEL), resulting in an estimated effects threshold of 8 µg/L. Limited data indicate that mean concentrations in Canadian surface waters are generally below this threshold. However, no data were identified for sites near production facilities in Canada. Therefore, it is considered that there are insufficient reliable data available to determine whether bis(2-ethylhexyl) phthalate is harmful to aquatic organisms in Canada.

No toxicological data were identified for sediment-dwelling biota in Canada.

No adequate information was identified concerning concentrations of bis(2-ethylhexyl) phthalate in biota or in environmental media to estimate the exposure of terrestrial plants or wildlife to the substance.

Therefore, on the basis of available data, it is not possible to determine whether bis(2-ethylhexyl) phthalate is entering or may enter the environment in a quantity or concentration or under conditions that are having or may have a harmful effect on the environment.

3.2 CEPA 11(b) Environment on Which Human Life Depends

Although bis(2-ethylhexyl) phthalate absorbs infrared radiation of wavelengths ranging from 7 µm and 13 µm, it is removed rapidly from the atmosphere by photo-oxidation (half-life ranging from 2.9 to 29 hours) and will not persist in the troposphere. As such, bis(2-ethylhexyl) phthalate is not expected to contribute significantly to the formation of ground-level ozone, global warming, or depletion of stratospheric ozone.

Therefore, on the basis of available data, bis(2-ethylhexyl) phthalate is not considered to be entering the environment in a quantity or concentration or under conditions that constitute a danger to the environment upon which human life depends.

3.3 CEPA 11(c) Human Life or Health

3.3.1 *Population Exposure*

Estimated intakes of bis(2-ethylhexyl) phthalate by the general population are presented in Table 1. Based on the limited available data on concentrations of bis(2-ethylhexyl) phthalate in environmental media to which the general population in Canada is exposed and reference values for body weights, the volume of air breathed and quantities of food, water, and soil ingested (EHD, 1992), the major pathway of exposure to bis(2-ethylhexyl) phthalate for the general population is from ingestion of food. Estimated intakes from indoor air based on a range of values (mean not reported) in a small number of homes and drinking water are considerably less than that from food. Intake in ambient air (although the reported values on which this estimate is based were not well documented) and soil, based on an observed range (mean not reported) are estimated to be relatively small. Total daily intakes for various age groups in the general population from these media are estimated to range from 5.8 to 19.0 µg/[kg (b.w.)·d].

For infants and toddlers, the total intake may be higher as a result of exposure from children's products that contain bis(2-ethylhexyl) phthalate, although estimates of exposure from this source are considered to be highly uncertain due to such factors as variations in bis(2-ethylhexyl) phthalate levels, mouthing behaviour, and lack of reliable data on leaching rates. Based on the concentrations of bis(2-ethylhexyl) phthalate in children's products reported by Consumer and Corporate Affairs Canada (CCAC, 1992), the assumptions that exposure may be for ten hours per day for two years and three hours per day for an additional year, and the estimated average leaching rate of 30 µg/h

Table 1 Estimated Daily Intake of Bis(2-ethylhexyl) Phthalate for the General Population in Canada

Substrate/ Medium[a]	Estimated Intake {µg/[kg(b.w.)·d]}				
	Age				
	0 to 0.5 yr[b]	0.5 to 4 yr[c]	5 to 11 yr[d]	12 to 19 yr[e]	20 to 70 yr[f]
Ambient Air: Great Lakes Region Indoor Air Drinking Water Food Soil	0.000 03 to 0.000 3 0.86 0.13 to 0.38 7.88 0.000 064	0.000 03 to 0.000 3 0.99 0.06 to 0.18 17.81 0.000 042	0.000 04 to 0.000 4 1.15 0.03 to 0.10 12.85 0.000 014	0.000 03 to 0.000 3 0.95 0.02 to 0.07 7.18 0.000 004	0.000 03 to 0.000 3 0.85 0.02 to 0.06 4.91 0.000 003
Total Estimated Intake	8.87 to 9.12	18.86 to 18.98	14.03 to 14.10	8.15 to 8.20	5.78 to 5.82
Children's Products	<0.025 to 11.51	<0.008 9 to 4.07			

a Mean concentrations in ambient air based on a limited (i.e., not well documented) study over the Great Lakes Region were 0.5 to 5.0 ng/m^3 (Eisenreich *et al*, 1981); the rather high concentrations in ambient air near an incinerator reported in an early study by Thomas (1973) were not incorporated into the estimation of total daily intake since they are not likely to be representative for the general population under current conditions and have not been confirmed elsewhere. The maximum concentration in indoor air was 3.10 µg/m^3 based on a very small number (n = 9) of homes in Montreal; mean values were not specified (Otson and Benoit, 1985). It is assumed that people generally spend 4 hours outdoors and 20 hours indoors (EHD, 1992). Mean concentrations in drinking water were 1.0 µg/L (detection limit) in a regional study in Ontario (OME, 1984) and 2.0 to 3.0 µg/L across Alberta (Spink, 1986). Intake of bis(2-ethylhexyl) phthalate was estimated based on the concentrations in the various food types of a market basket survey (NHW, 1992) muliplied by the age-specific intakes of various food stuffs from the Nutrition Canada survey (EHD, 1992). Bis(2-ethylhexyl) phthalate content in the soil in urban areas of Port Credit, Oakville, and Burlington, Ontario, ranged from <0.1 to 11 ng/g (Golder Associates, 1987). Average concentrations of bis(2-ethylhexyl) phthalate in children's products ranged from <0.05 to 23.01% w/w for a number of samples each of pacifiers, teethers, nipples, and flexible toys (CCAC, 1992). It is assumed that the leaching rate of bis(2-ethylhexyl) phthalate is 30 µg/h and that oral exposure may be for 10 h/day for 2 years and 3 h/day for an additional one year (Rodricks and Tumbull, 1984).

b Weighs 6 kg, breathes 2 m^3 air, drinks 0.75 L water, and ingests 35 mg soil/day (EHD, 1992).

c Weighs 13 kg, breathes 5 m^3 air, drinks 0.8 L water, and ingests 50 mg soil/day (EHD, 1992).

d Weighs 27 kg, breathes 12 m^3 air, drinks 0.9 L water, and ingests 35 mg soil/day (EHD, 1992).

e Weighs 57kg, breathes 21 m^3 air, drinks 1.3 L water, and ingests 20 mg soil/day (EHD, 1992).

f Weighs 70kg, breathes 23 m^3 air, drinks 1.5 L water, and ingests 20 mg soil/day (EHD, 1992).

(Rodricks and Turnbull, 1984), the estimated intakes for children in the Canadian population aged 0 to 0.5 years and 0.5 to 4 years are <0.03 to 11.5 µg/[kg(b.w.)·d] and <0.009 to 4.1 µg/[kg (b.w.)·d], respectively. The total daily estimated intakes for infants (0 to 0.5 yr) and children between 0.5 to 4 years of age including that from such products are, therefore, 8.9 to 20.6 µg/[kg (b.w.)·d] and 18.9 to 23.1 µg/[kg (b.w.)·d], respectively.

3.3.2 *Effects*

Carcinogenicity is potentially the most sensitive endpoint for assessment of "toxic" under CEPA. The weight of evidence for the carcinogenicity of bis(2-ethylhexyl) phthalate has been assessed, therefore, on the basis of the classification scheme developed for this purpose (EHD, 1992).

The potential carcinogenicity of bis(2-ethylhexyl) phthalate has not been examined in epidemiological studies in human populations. However, in the most extensive bioassays in experimental animals conducted to date, bis(2-ethylhexyl) phthalate has been carcinogenic in both rats and mice, increasing the incidence of benign and malignant hepatic tumours (NTP, 1982; Rao *et al.,* 1990), but only at doses [>300 mg/kg (b.w.)] greater than those at which alterations in the number and function of hepatic peroxisomes have been observed. Indeed, in short- and long-term studies, alterations in activity of hepatic enzymes consistent with peroxisome proliferation have been observed at doses as low as 12 to 15 mg/[kg (13.w.)·d] in rats (Ganning *et al.,* 1987; 1991).

Based on the weight of evidence in extensive investigations both *in vitro* and *in vivo* in experimental animals, bis(2-ethylhexyl) phthalate is not considered to be genotoxic. The weight of evidence also indicates that the metabolites of bis(2-ethylhexyl) phthalate, mono(2-ethylhexyl) phthalate, and 2-ethylhexanol, are not genotoxic.

It has been hypothesized that the hepatocarcinogenicity of bis(2-ethylhexyl) phthalate in rodents may be a result of biologically active products of proliferated peroxisomes, an effect to which humans are less sensitive than rodents (CPSC, 1985; Rhodes *et al.,* 1986; Short *et al.,* 1987). Based on available data on the effects of peroxisome proliferators, including bis(2-ethylhexyl) phthalate, it has recently been concluded that rats and mice are very responsive, hamsters less responsive, and guinea pigs, marmosets, and cynomolgus monkeys "non-responsive" (IPCS, 1992). It should be noted, however, that no study has been identified in which the livers of guinea pigs have been adequately examined for peroxisome proliferation following exposure to bis(2-ethylhexyl) phthalate. For primates, identified data are limited to groups of two male cynomolgus monkeys exposed to five doses of bis(2-ethylhexyl) phthalate and groups of five males and five female marmosets exposed to a single dose of bis(2-ethylhexyl) phthalate (Short *et al,* 1987; Rhodes *et al,* 1986).

The variations in sensitivity of various species to peroxisome proliferation (and hence, carcinogenicity) by bis(2-ethylhexyl) phthalate may be attributable in part, to differences in absorption and metabolism, though limited available data in humans preclude prediction of sensitivity for humans on this basis. Available data indicate that bis(2-ethylhexyl) phthalate is more extensively absorbed and metabolized (primarily by oxidation) in rodents than in primates. Also, some rodents do not conjugate metabolites of bis(2-ethylhexyl) phthalate whereas in primates, they are excreted as glucuronide derivatives.

On the basis of limited additional data on other peroxisome proliferators, it seems likely that hepatic tumours in rodents exposed to high doses of bis(2-ethylhexyl) phthalate can be ascribed to mechanisms of toxicity and/or metabolism to which humans are much less sensitive. Increases in cancer risk have not been observed in follow-ups of clinical trials of patients receiving hypolipidemic drugs (clofibrate or gemfibrozil) identified as hepatic peroxisome proliferators in rodents. It should be noted, however, that the power of these studies to detect increases in cancer was relatively poor (Oliver *et al.*, 1984; Frick *et al.*, 1987). Although the group sizes were large (1788 deaths and 4081 patients, respectively), the periods of administration of the drugs (approximately 5 years in both studies) and follow-up (13.2 and 5 years, respectively) were short in relation to latency periods required for the development of most cancers induced by exposure to chemical substances. In an *in vitro* study, mono(2-ethylhexyl) phthalate [a metabolite of bis(2-ethylhexyl) phthalate] stimulated peroxisome proliferation in cultured hepatocytes from the rat, but not in humans (Butterworth *et al.*, 1989; Elcombe and Mitchell, 1986).

It should be noted, however, that Ganning *et al.* (1987) reported an increase in peroxisomes in the liver after one year but not after one month in an unspecified number of hemodialysis patients, claimed not to be receiving any drugs known to affect peroxisomes. Although the authors considered this increase to be due possibly to bis(2-ethylhexyl) phthalate from plastic tubing, they also acknowledged the potential effects of renal insufficiency and a continuous suburemic state to effects on the structure and function of various organelles.

Based on these considerations, bis(2-ethylhexyl) phthalate has been classified in Group IV (unlikely to be carcinogenic to humans) of the classification scheme for carcinogenicity developed for the assessment of "toxic" under Paragraph 11(c) of CEPA (EHD, 1992). It should be noted, however, that the available data base concerning effects of bis(2-ethylhexyl) phthalate in primates and humans is not extensive and on this basis, classification in Group III (possibly carcinogenic to humans) might also be appropriate.

For compounds classified in Group IV on the basis of the above-mentioned classification scheme, a tolerable daily intake (TDI) is derived on the basis of a No- or Lowest-Observed-(Adverse)-Effect-Level [NO(A)EL or LO(A)EL] in humans or animal species divided by an uncertainty factor. For bis(2-ethylhexyl) phthalate, by far the majority of studies have been conducted by the oral route of exposure and on the basis of

limited available data on concentrations in various media (Section 2.3.2), this is believed to be the most important route of exposure to bis(2-ethylhexyl) phthalate for the general population.

In the very limited available epidemiological studies, health effects attributable to bis(2-ethylhexyl) phthalate have not been observed consistently; these data are, therefore, insufficient to serve as a basis for establishment of an effect level for derivation of a TDI.

With the exception of changes associated with peroxisome proliferation in the liver of rodents {to which humans are considered to be less sensitive; LOEL =12 mg/[kg (b.w.)·d] or greater}, the lowest doses at which adverse effects have been consistently observed are approximately 90 to 100 mg/[kg(b.w.)·d] of bis(2-ethylhexyl) phthalate in adequately conducted and documented studies. Although (adverse) effects on serum lipids and the kidney have been reported at lower doses {lowest LOEL = 2.5 mg/[kg (b.w.)·d] and 0.92 mg/[kg (b.w.)·d], respectively}, available data are not consistent. At 100 mg/[kg (b.w.)·d]* a decrease in body weight gain (greater than 10%) was observed in female mice in the subchronic NTP bioassay (NTP, 1982). However, there were no other indications of adverse effects and no non-neoplastic effects were observed in the same strain of mice exposed to much higher concentrations of bis(2-ethylhexyl) phthalate {6000 ppm in the diet; 1821 mg/[kg (b.w.)·] } for two years (NTP, 1982). Therefore, the most sensitive endpoints for development of a TDI are, reproductive and developmental effects. The lowest reported LOAEL for reduced fertility in mice was 130 mg/[kg (b.w.)·d] {NOEL = 13 mg/[kg (b.w.)·d]; widely spaced doses} (Reel *et al.,* 1982). In developmental studies, the LO(A)EL in mice in the investigation by Wolkowski-Tyl *et al.* (1984a) in both mothers and offspring was 91 mg/[kg (b.w.)·d], at which maternal toxicity and increased numbers of resorptions and dead fetuses were observed {NOEL for both mothers and offspring was 44 mg/[kg (b.w.)·d] }. In another study in mice (Hamano *et al.,* 1977), the LOAEL in both mothers and offspring was 130 mg/[kg (b.w.)·d] {the NOEL in this study was 13 mg/[kg (b.w.)·d], though it should be noted that the administered doses were widely spaced}.

Therefore, on the basis of these data, a TDI has been derived as follows:

$$\text{TDI} = \frac{44\text{mg/[kg(b.w.)·d]}}{1000}$$

$$= 0.044 \text{ mg/[kg (b.w.)·d]}$$
$$\{44 \text{ µg/[kg (b.w.)·d]}\}$$

* This dose has been calculated based on standard conversion factors; however, based on conversions developed from the chronic NTP bioassay, intake may have exceeded this value.

where:

- 44 mg/[kg (b.w.)·d] is the NOEL for effects other than those related to hepatic peroxisome proliferation* [i.e., adverse developmental effects observed at the next highest dose in the investigation by Wolkowski-Tyl *et al.* (1984a); lower NOELs in other developmental studies are a function predominantly of wider spacing of the administered doses].

- 1000 is the uncertainty factor [x 10 for interspecies variation, x 10 for intraspecies variation and x 10 for potential teratogenicity - teratogenic effects observed at higher doses in the critical study and evidence of teratogenicity in the absence of maternal toxicity (though limited examination of the latter) in the study of Shiota and Mima (1985)]. Available data indicate that bis(2-ethylhexyl) phthalate is less extensively absorbed and metabolized by oxidation and excreted in conjugated forms to a greater extent in primates than in rodents; humans might, therefore, be less sensitive than rodents to effects of bis(2-ethylhexyl) phthalate, on this basis. However, available information was considered insufficient to take these aspects into account in the development of the uncertainty factor.

Based on very limited data, the estimated total average daily intakes of bis(2-ethylhexyl) phthalate for various age groups in the general population in Canada range from 5.8 to 19.0 g/[kg (b.w.)·d]. Based on estimated additional intake from children's products, the total average intakes for infants (0 to 0.5 yr) and children between 0.5 to 4 years of age are estimated to range from 8.9 to 23.1 µg/[kg (b.w.)·d] (one sixth to one half of the TDI). Estimated intakes for the greatest proportion of the lifespan (i.e., adults) are close to the lower end of the above reported range. However, intake from food (the principal medium of exposure) for all age groups is likely to be underestimated since it is based on assumed values of zero for concentrations in those foodstuffs in which bis(2-ethylhexyl) phthalate was not detected. Estimated intakes based on assumed values of the highest detection limit in those foods in which bis(2-ethylhexyl) phthalate was not detected would be about twofold greater. Average daily intakes of bis(2-ethylhexyl) phthalate for some age groups of the general population in Canada may, therefore, approach or slightly exceed the TDI.

Therefore, on the basis of available data, it has been concluded that bis(2-ethylhexyl) phthalate may enter the environment in a quantity or concentration or under conditions that may constitute a danger in Canada to human health.

* This TDI is similar to a value which would be derived on the basis of peroxisome proliferation and/or tumourgenesis in the rat liver.

3.4 Conclusion

On the basis of available data, there is insufficient information to conclude whether bis(2-ethylhexyl) phthalate is entering or may enter the environment in a quantity or concentration or under conditions that are having a harmful effect on the environment. It has been concluded, however, that bis(2-ethylhexyl) phthalate is not entering the environment in a quantity or concentration or under conditions that constitute a danger to the environment on which human life depends. It has also been concluded that bis(2-ethylhexyl) phthalate may enter the environment in a quantity or concentration or under conditions that may constitute a danger in Canada to human health.

4.0 Recommendations for Research and Evaluation

Several data gaps were identified that limited the assessment of the environmental and human health effects of bis(2-ethylhexyl) phthalate. It is recommended, therefore, that the following studies be conducted on a high priority basis:

1. monitoring of current concentrations of bis(2-ethylhexyl) phthalate in areas where it is either manufactured or used industrially, since the data concerning concentrations of bis(2-ethylhexyl) phthalate in indoor and ambient air, drinking water, surface water, sediments, soil, and biota are limited and sometimes conflicting;

2. a determination of current quantities of bis(2-ethylhexyl) phthalate released to the atmosphere;

3. toxicity tests with benthic organisms representative of the Canadian environment to determine the effects of sediment-bound bis (2-ethylhexyl) phthalate;

4. acquisition of additional information on the possible teratogenicity of bis(2-ethylhexyl) phthalate in experimental animals in studies in which maternal toxicity is well examined;

5. studies of the neurotoxicity and immunotoxicity of bis(2-ethylhexyl) phthalate in experimental animals;

6. studies of cardiotoxicity following subchronic exposure;

7 epidemiological studies of developmental, reproductive, and carcinogenic effects in populations occupationally exposed to bis(2-ethylhexyl) phthalate;

8. additional investigation of the effects of bis(2-ethylhexyl) phthalate on peroxisome proliferation in dialysis patients;

9. examination of cancer incidence and mortality, and reproductive and developmental effects in extended follow-ups of populations exposed to hypolipidemic drugs that are identified peroxisome-proliferators in rodents; and

10. in view of the small difference between the estimated total daily intake and Tolerable Daily Intake of bis(2-ethylhexyl) phthalate, concentrations of bis(2-ethylhexyl) phthalate in indoor air, ambient air, children's products, and food, and the amount of this compound produced and used in Canada should continue to be monitored.

5.0 References

ATSDR (Agency for Toxic Substances and Disease Registry), "Toxicological Profile for Di-(2-Ethylhexyl)Phthalate", United States Public Health Service, 119 pp. (1989).

ATSDR (Agency for Toxic Substances and Disease Registry), "Toxicological Profile for Di(2-ethylhexyl) Phthalate", draft for public comment, Agency for Toxic Substances and Disease Registry, United States Dept. of Health & Human Services, 131 pp. (1991).

Al-Omran, L.A. and M.R. Preston, "The Interactions of Phthalate Esters with Suspended Particulate Material in Fresh and Marine Waters", *Environ. Pollut., 46:*177-186 (1987).

Albro, P., R. Thomas, and L. Fishbein, "Metabolism of Diethylhexyl Phthalate by Rats: Isolation and Characterization of the Urinary Metabolites", *J. Chromatog, 76:*321-330 (1973).

Albro, P.W., J.R., Hass, C.C. Peck, D.G. Odam, J.T. Corbett, F.J. Bailey, H.E. Blatt, and B.B. Barrett, "Identification of the Metabolites of DEHP in Urine from the African Green Monkey", *Drug Metab. Dispos., 9:*223-225 (1981).

Atwater, J.W., S.E. Jasper, P.D. Parkinson, and D.S. Mavinic, "Organic Contaminants in Canadian Coal Wastewaters and Associated Sediments", *Water Pollut. Res. J. Can., 25:*187-200 (1990).

Barber, E.D., B.D. Astill, E.J. Moran, B.F. Schneider, T.J.B. Gray, and B.G. Gray, "Peroxisome Induction Studies on Seven Phthalate Esters", *Toxicol. Ind. Health, 3:*7-22 (1987).

Barron, M.G., I.R. Schultz, and W.L. Hayton, "Presystemic Branchial Metabolism Limits Di-2-ethylhexyl Phthalate Accumulation in Fish", *Toxicol. Appl. Pharmacol., 98:*49-57 (1989).

Branson, D.R., "Predicting the Fate of Chemicals in the Aquatic Environment from Laboratory Data", in: *Estimating the Hazard of Chemical Substances to Aquatic Life,* J. Cairns, Jr., K.L. Dickson, and A.W. Maki (eds.) ASTM STP 657, American Society for Testing and Materials, pp. 55-70 (1978).

Brownlee, B. and W.M.J. Strachan, "Distribution of Some Organic Compounds in the Receiving Waters of a Kraft Pulp and Paper Mill", *J. Fish. Res. Board Can., 34:*830-837 (1977).

Burns, B.G., C.J. Musial, and J.F. Uthe, "Novel Cleanup Method for Quantitative Gas Chromatographic Determination of Trace Amounts of Di-2-ethylhexyl Phthalate in Fish Lipid", *J. Assoc. Off Anal. Chem., 64:*282-286 (1981).

Busser, M.T. and W.K. Lutz, "Stimulation of DNA Synthesis in Rat and Mouse Liver by Various Tumour Promoters", *Carcinogenesis, 8*:1433-1437 (1987).

Butterworth, B.E., "Genetic Toxicology of Di(2-ethylhexyl)Phthalate", in: *Banbury Report 25: Nongeniotoxic Mechanisms in Carcinogenesis*, pp.257-276 (1987).

Butterworth, B.E., T. Smith-Oliver, L. Earle, D.J. Loury, R.D. White, D.J. Doolittle, P.K. Working, R.C. Cattley, R. Jirtle, G. Michalopoulos, and S. Strom, "Use of Primary Cultures of Human Hepatocytes in Toxicology Studies", *Cancer Res., 49*:1075-1084(1989).

CCAC (Consumer and Corporate Affairs Canada), "A Survey of Bis[2-ethylhexyl] Phthalate in Children's Products", Project No.: 91-0358, Scientific and Laboratory Services Division, Product Safety Branch, Ottawa, Ont. (1992, Unpublished).

CIS (Camford Information Services, Inc.) "CPI Product Profiles - Dioctyl Phthalate", Camford Information Services Inc., Don Mills, Ont., 4 p. (1992).

CMA (Chemical Manufacturers Association), "A 21-day Dose Relationship Study of Di-2-ethylhexyl Phthalate in Rats", prepared by the British Industrial Biological Research Association, July, Report No. 0512/1/84 (1984).

CMA (Chemical Manufacturers Association), "Comments of the Phthalate Esters Panel of the Chemical Manufacturers Association on EPA's Proposed Ambient Water Quality Criteria for DEHP", Docket OW-FRL-3762-9, Chemical Manufacturers Association, (August, 1990).

CPSC (United States Consumer Product Safety Commission), "Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Di-(2-ethylhexyl)Phthalate (DEHP)", Washington, DC 20 pp. (1985).

Callahan, M.A., M.W. Slimak, N.W. Gabel, I.P. May, C.F. Fowler, J.R. Freed, P. Jennings, R.L. Durfee, F.C. Whitmore, B. Maestri, W.R. Mabey, B.R. Holt, and C. Gould, *Water-related Environmental Fate of 129 Priority Pollutants* Volume II. Halogenated Aliphatic Hydrocarbons, Halogenated Ethers, Monocyclic Aromatics, Phthalate Esters, Polycyclic Aromatic Hydrocarbons, Nitrosamines, Miscellaneous Compounds, EPA-440/4-79-029b, United States Environmental Protection Agency, Washington, DC (1979).

Carpenter, C.P., C.J. Weil, and H.F. Smyth, "Chronic Oral Toxicity of DEHP for Rats, Guinea Pigs and Dogs", *Am. Med. Assoc. Arch. Ind. Hyg., 8:*219-226 (1953).

Cattley, R C., J . G. Conway, and J.A. Popp, "Association of Persistent Peroxisome Proliferation and Oxidative Injury with Hepatocarcinogenicity in Female F344 Rats Fed Di(2-ethylhexyl)Phthalate for 2 Years", *Cancer Lett., 38:*15-22 (1987).

Cautreels, W. and K. Van Cauwenberghe, "Experiments on the Distribution of Organic Pollutants Between Airborne Particulate Matter and the Corresponding Gas Phase", *Atmospheric Environment, 12*:1133-1141(1978).

Crocker, J.F.S., S.H. Safe, and P. Acott, "Effects of Chronic Phthalate Exposure on the Kidney", *J. Toxicol. Environ. Health, 23:*433444 (1988).

Dabholkar, A.S., "Peroxisomes in the Rat Brain and the Effects of Di-(2-ethylhexyl)Phthalate During Postnatal Development", *Acta Anat, 131***:**218-221(1988).

DeFoe, D.L., G.W. Holcombe, D.E. Hammermeister, and K.E. Biesinger, "Solubility and Toxicity of Eight Phthalate Esters to Four Aquatic Organisms", *Environ. Toxicol. Chem., 9*:623-636 (1990).

DeVault, D.S., "Contaminants in Fish from Great Lakes Harbors and Tributary Mouths", *Arch. Environ. Contam. Toxicol., 14:*587-594 (1985).

Dostal, L.A., W.L. Jenkins, and B.A. Schwetz, "Hepatic Peroxisome Proliferation and Hypolipidemic Effects of DEHP in Neonatal and Adult Rats", *Toxicol. Appl. Pharmacol., 87*:81-90 (1987).

Dostal, L.A., R.E. Chapin, S.A. Stefanski, M.W. Harris, and B.A. Schwetz, "Testicular Toxicity and Reduced Sertoli Cell Numbers in Neonatal Rats by Di(2-ethylhexyl)Phthalate and the Recovery of Fertility as Adults", *Toxicol. Appl. Pharmacol, 95***:**104-121(1988).

EHD (Environmental Health Directorate), "Approach to the Assessment of "Toxic" Under Paragraph 11(c) of CEPA", Bureau of Chemical Hazards, (1992, Unpublished).

Eiceman, G.A., R.E. Clement, and F.W. Karasek, "Analysis of Fly Ash from Municipal Incinerators for Trace Organic Compounds", *Anal. Chem., 51*:2343-2350 (1979).

Eisenreich, S.J., B.B. Looney, and J.D. Thornton, "Airborne Organic Contaminants in the Great Lakes Ecosystem", *Environ. Sci. Technol., 15:*30-38 (1981).

El Sisi, A.E., D.E. Carter, and I.G. Sipes, "Dermal Absorption and Tissue Distribution of Phthalate Esters", *Toxicologist, 5:*246 (1985).

Elcombe, C.R. and A.M. Mitchell, "Peroxisome Proliferation due to Di(2-ethylhexyl) Phthalate (DEHP): Species Differences and Possible Mechanisms", *Environ. Health Perspect., 70*:211-219 (1986).

Environment Canada, "Environmental Assessment of the Canadian Textile Industry", Industrial Programs Branch, Report EPS 5/TX/l (1989).

Eriksson, P. and P.O. Darnerud, "Distribution and Retention of Some Chlorinated Hydrocarbons and a Phthalate in the Mouse Brain During the Pre-weaning Period", *Toxicology, 37*:189-203 (1985).

Frick, M.H., O. Elo, K. Haapa, O.P. Heinonen, P. Heinsalmi, P. Helo, J.K. Huttunen, P. Kaitaniemi, P. Koskinen, V. Manninen, H. Maenpaa, M. Malkonen, M. Manttari, S. Norola, A. Pasternack, J. Pikkarainen, M. Romo, T. Sjoblom, and E.A. Nikkila, "Helsinki Heart Study: Primary-prevention Trial with Gemfibrozil in Middle-aged Men with Dyslipidemia, Safety of treatment, Changes in Risk Factors and Incidence of Coronary Heart Disease", *New Engl. J. Med., 317*:1237-1245 (1987).

Ganning, A.E., U. Brunk, C. Edlund, A. Elhammer, and G. Dallner, "Effects of Prolonged Administration of Phthalate Ester on the Liver", Environ. Health Perspect., *73:*251-258 (1987).

Ganning, A.E., M.J. Olsson, U. Brunk, and G. Dallner, "Effects of Prolonged Treatment with Phthalate Ester on Rat Liver", *Pharmacol. Toxicol, 68:*392-401(1991).

Germain, A. and C. Langlois, "Contamination des eaux et des sédiments en suspension du fleuve Saint-Laurent par les pesticides organochlorés, les biphényles polychlorés et d'autres contaminants organiques prioritaires", *Water Pollut. Res. J. Canada, 23:*602-614 (1988).

Geyer, H., G. Politzki, and D. Freitag, "Prediction of Ecotoxicological Behaviour of Chemicals: Relationship Between N-octanol/Water Partition Coefficient and Bioaccumulation of Organic Chemicals by Alga, *Chlorella", Chemosphere, 13*:269-284 (1984).

Ghassemi, M., S. Quinlivan, and J. Bachmaier, "Characteristics of Leachates from Hazardous Waste Landfills", *J. Environ. Sci. Health, Al*9:579-620 (1984).

Giam, C.S., E. Atlas, H.S. Chan, and G.S. Neff, "Phthalate Esters, PCB and DDT Residues in the Gulf of Mexico Atmosphere", *Atmospheric Environment, 14:*65-69 (1980).

Giam, C.S., H.S. Chan, G.S. Neff, and E.L. Atlas, "Phthalate Ester Plasticizers: A New Class of Marine Pollutant", *Science, 199*:419-421(1978).

Gibson, T.P., W.A. Briggs, and B.J. Boone, "Delivery of Di-2-ethylhexyl Phthalate to Patients During the Hemodialysis", *J. Lab. Clin. Med., 87:*519-524 (1976.)

Glass, G.E., W.M.J. Strachan, W.A. Wiliford, F.A.I. Armstrong, K.L.E. Kaiser, and A. Lutz, "Organic Contaminants", in: *The Waters of Lake Huron and Lake Superior, Volume III (Part B), Lake Superior,* report to the International Joint Commission by the Upper Lakes Reference Group, EPA-600/J-77-042, pp. 417-429, 499-502 (1977).

Golder Associates, "Testing of Specific Organic Compounds in Soils in Background Urban Areas: Port Credit and Oakville/Burlington", Ontario, Working Paper to Shell Canada Ltd. and Texaco Ltd. by Golder Associates (August, 1987).

Gray, T.J. and K.R. Butterworth, "Testicular Atrophy Produced by Phthalate Esters", *Arch. Toxicol (Suppl), 4*: 452-4554 (1980).

Gray, T.J.B., K.R. Butterworth, I.F. Gaunt, P. Grasso, and S.D. Gangolli, "Short-term Toxicity Study of Di(2-ethylhexyl)Phthalate in Rats", *Fd. Cosmet. Toxicol., 15*:389-399 (1977).

Gray, T.J., I.R. Rowland, P.M. Foster, and S.D. Gangolli, "Species Differences in the Testicular Toxicity of Phthalate Esters", *Toxicol. Lett., 11:*141-147 (1982).

Halina, G.P., Letter from G.P. Halina, Environment Alberta to K. Taylor, Environment Canada (April 27, 1993).

Hamano, Y., A. Kuwano, K. Inoue, Y. Oda, H. Yamamoto, B. Mitsuda, and N. Kunita, "Studies on Toxicity of Phthalic Acid Esters, 1st Report - Teratogenic Effects in Mice Administered Orally", *Osaka-furitsu Koshu Esei kenkyusho Kenkyu Hokoka Shokukhim Eisei Hen., 8:*29-33 (1977).

Harris, R.S., H.C. Hodge, E.A. Maynard, and H.J. Blanchat, "Chronic Oral Toxicity of 2-ethylhexyl Phthalate in Rats and Dogs", *Arch. Ind. Health, 3:*259-264 (1956).

Hinton, R.H., F.E. Mitchell, A. Mann, D. Chescoe, S.C. Price, A. Nunn, P. Grasso, and J.W. Bridges, "Effects of Phthalic Acid Esters on the Liver and Thyroid", *Environ. Health Perspect, 70:*195-210 (1986).

Hites, R.A. and W.L. Budde, "EPA's Analytical Methods for Water: the Next Generation", *Environ. Sci. Technol, 25:*998-1006 (1991).

Howard, P.H., *Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Volume 1. Large Production and Priority Pollutants,* Lewis Publishers Inc., Chelsea, MI (1989).

Howard, P.H., S. Banerjee, and K.H. Robillard, "Measurement of Water Solubilities, Ooctanol/water Partition Coefficients and Vapor Pressures of Commercial Phthalate Esters", *Environ. Toxicol. Chem., 4:*653-661 (1985).

Howard, P.H., R.S. Boethling, W.F. Jarvis, W.M. Meylan, and E.M. Michalenko, *Handbook of Environmental Degradation Rates,* Lewis Publishers Inc., Chelsea, MI (1991).

Hsia, M.T.S., "The Relationship Between Carcinogenesis and Peroxisome Proliferation in Rodent Liver After Exposure to the Plasticizer (DEHP) and (DEHA)", Contract

report prepared by The MITRE Corporation for United States Food and Drug Administration, MTR-90W00034 (1990).

IARC (International Agency for Research on Cancer), "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Some Industrial Chemicals and Dyestuffs", Vol.29, Lyon, France, pp.269-294 (1982).

IPCS (International Programme on Chemical Safety), "Diethylhexyl Phthalate", Environmental Health Criteria 131, World Health Organization, Geneva, Switzerland, 141 pp. (1992).

Ishida, M., K. Suyama, and S. Adachi, "Background Contamination by Phthalates Commonly Encountered in the Chromatographic Analysis of Lipid Samples", *J. Chromatog, 189:*421-424(1980).

Ishida, M., K. Suyama, S. Adachi, and T. Hoshino, "Distribution of Orally Administered Di-ethylhexyl Phthalate in Laying Hens", *Poult. Sci., 61:*262-267 (1982).

Johnson, B.T., M.A. Heitkamp, and J.R. Jones, "Environmental and Chemical Factors Influencing the Biodegradation of Phthalic Acid Esters in Freshwater Sediments", *Environ. Pollut. (Ser. B), 8:*101-118 (1984).

Johnson, B.T., D.L. Stalling, J.W. Hogan, and R.A. Schoettger, "Dynamics of Phthalate Acid Esters in Aquatic Organisms", in: *Fate of Pollutants in the Air and Water Environment,* I.H. Suffet (ed.), Part 2, *Adv. Environ. Sci. Technol, 8*:283-300. Wiley Interscience, New York, NY (1977).

Khan, S.U., "Role of Humic Substances in Predicting Fate and Transport of Pollutants in the Environment", in: *Dynamics, Exposure and Hazard Assessment of Toxic Chemicals,* Symposium, Miami Beach, FL, Sept. 11-13, 1978, R. Haque (ed.), Ann Arbor, Science Publishers, Inc., Ann Arbor, MI, pp.215-230 (1980).

Kirchmann, H., H. Åström, and G. Jönsäll, "Organic Pollutants in Sewage Sludge. 1.Effect of Toluene, Naphthalene, 2-methylnaphthalene, 4-n-nonylphenol and Di-2-ethylhexyl Phthalate on Soil Biological Processes and their Decomposition in Soil", *Swedish J. Agric. Res., 21*:107-113 (1991).

Klöpfer, W., G. Kaufmann, G. Rippen, and H.-J. Poremski, "A Laboratory Method for Testing the Volatility from Aqueous Solution: First Results and Comparison with Theory", *Ecotoxicol Environ. Safety, 6:*545-559 (1982).

Kluwe, K.M., J.K. Haseman, J.F., Douglas, and J.E. Huff, "The Carcinogenicity of Dietary DEHP in Fischer 344 Rats and B6C3F_1 Mice", *J. Toxicol. Environ. Health, 10*:797-815 (1982).

Kluwe, W.M., J.K. Haseman, and J.E. Huff, "The Carcinogenicity of Di(2-ethylhexyl)Phthalate (DEHP) in Perspective", *J. Toxicol Environ. Health, 12:*159-169 (1983).

Kohli, J., J.F. Ryan, and B.K. Afghan, "Phthalate Esters in the Aquatic Environment", in: *Analysis of Trace Organics in the Aquatic Environment*, B.K. Chau and A.S.Y. Chau (eds.), CRC Press, Inc, Boca Raton, FL, P.243-281(1989).

Krauskopf, L.G., "Studies on the Toxicity of Phthalates Via Ingestation", *Environ. Health Perspect, 3:*61-72 (1973).

Lake, B.G., P.O. Brantom, S.D. Gangolli, K.R. Butterworth, and P. Grasso, "Studies on the Effects of Orally Administered Di-(2-ethylhexyl) Phthalate in the Ferret", *Toxicology, 6:*341-356(1976).

Lake, B.G., W.M. Cook, N.R. Worrell, M.E. Cunninghame, J.G., Evans, R.J. Price, P.J. Young, and F.M.B. Carpanini, "Dose-response Relationships for Induction of Hepatic Peroxisome Proliferation and Testicular Atrophy by Phthalate Esters in the Rat", *Hum. Exp. Toxicol, 10:*67 (abstract, 1991).

Lake, B.G., T.J.B. Gray, J.R. Foster, C.R. Stubberfield, and S.D. Gangolli, "Comparative Studies on Di(2-ethylhexyl) Phthalate Induced Hepatic Peroxisome Proliferation in the Rat and Hamster", *Toxicol. Appl Pharmacol, 72:*46-60(1984).

Lamb, J.C. IV, R.E. Chapin, J. Teague, A.D. Lawton, and J.R. Reel, "Reproductive Effects of Four Phthalic Acid Esters in the Mouse", *Toxicol Appl Pharmacol, 88:*255-269 (1987).

Leah, T.D., "Environmental Contaminants Inventory Study No.4. The Production, Use and Distribution of Phthalic Acid Esters in Canada", Inland Waters Directorate, Report Series 47, Fisheries and Environment Canada, 67 pp. (1977).

MENVIQ, Quebec Ministry of the Environment (Unpublished data, 1993).

Marsman, D.S., R.C. Cattley, J.G. Conway, and J.A. Popp, "Relationship of Hepatic Peroxisome Proliferation and Replicative DNA Synthesis to the Hepatocarcinogenicity of the Peroxisome Proliferators Di(2-ethylhexyl) Phthalate and [4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic acid (Wy-14,643) in Rats", *Cancer Res., 48*:6739-6744 (1988).

Mathur, S.P., "Phthalate Esters in the Environment: Pollutants or Natural Products?", *J. Environ. Qual., 3:*189-197 (1974).

Mayer, F.L., "Residue Dynamics of Di-2-ethylhexyl Phthalate in Fathead Minnows *(Pimephales promelas)", J. Fish. Res. Board Can., 33:*2610-2613 (1976).

Mayer, F.L., Jr. and H.O. Sanders, "Toxicology of Phthalic Acid Esters in Aquatic Organisms", *Environ. Health Perspect., 3:*153-157 (1973).

Mayer, F.L., Jr., D.L. Stalling, and J.L. Johnson, "Phthalate Esters as Environmental Contaminants", *Nature, 238:*411-413 (1972).

Mitchell, F.E., S.G. Price, R.H. Hinton, P. Grasso, and J.W. Bridges, "Time and Dose-response Study of the Effects on Rats of the Plasticizer Di(2-ethylhexyl) Phthalate", *Toxicol Appl. Pharmacol, 81:*371-392 (1985).

Montgomery, J.H. and L.M. Welkom, *Groundwater Chemicals Desk Reference,* Lewis Publishers Inc., Chelsea, MI (1990).

Morton, S.J., "The Hepatic Effects of Dietary Di-2-ethyl-hexyl Phthalate", Ph.D. Dissertation, The Johns Hopkins University. UMI Dissertation Information Service, Ann Arbor, MI, 120 pp. (1979).

Munro, J.R., M.G. Foster, T. Pawson, A. Stelzig, T. Tseng, and L. King, "St. Clair River Point Source Survey 1979 - 1980", Ontario Ministry of the Environment and Environment Canada (1985).

NAQUADAT (National Water Quality Data Bank), Surveys and Information Systems Branch, Ecosystem Sciences and Evaluation Directorate, Environment Canada (1993).

NATES (National Analysis of Trends in Emergencies System), data base, Environmental Emergencies Branch, Environment Canada (1992).

NHW (National Health and Welfare), "Market Basket Survey of Foods from Halifax", Food Research Division, Food Directorate, Health Protection Branch, Ottawa (unpublished results, 1992).

NTP (National Toxicology Program), "Carcinogenesis Bioassay of Di(2-ethylhexyl) Phthalate (CAS No.117-81-7) in F344 Rats and B6C3F_1 Mice (Feed study)", NTP-80-37, NIH Publication No.82-1773, Research Triangle Park, NC, 127 pp. (1982).

Nagasaki, H., S. Tomii, T. Mega, K. Hirao, Y. Shinohara, and N. Ito, "Chronic Toxicity of Dioctyl Phthalate (DOP) in Male Rats and Mice", *J. Nara Med. Ass., 25:*649-654 (1974).

Niagara River Data Interpretation Group, "Joint Evaluation of Upstream/Downstream Niagara River Monitoring Data, 1988-1989", prepared by Data Interpretation Group, River Monitoring Committee, A joint publication of Environment Canada, United States Environmental Protection Agency, Ontario Ministry of the Environment, and New York State Department of Environmental Conservation (1990).

Nielsen, J., B. Akesson, and S. Skerfving, "Phthalate Ester Exposure-air Levels and Health of Workers Processing Polyvinylchloride", *Am. Ind. Hyg. Assoc. J., 46:*643-647 (1985).

Northup, S., L. Martis, R. Ulbricht, J. Garber, J. Miripol, and T. Schmitz, "Comment on the Carcinogenic Potential of Di(2-ethylhexyl) Phthalate", *J. Toxicol Environ. Health., 10:*493-518 (1982).

OME (Ontario Ministry of the Environment), "Drinking Water Survey of Selected Municipalities in the Niagara Area and Lake Ontario" (1984).

OME (Ontario Ministry of the Environment), "Municipal-Industrial Strategy for Abatement (MISA). Twelve Month Monitoring Data Report", Organic Chemical Manufacturing Sector (Oct. 1, 1989 to September 30, 1990), Water Resources Branch (1992a).

OME (Ontario Ministry of the Environment), "Municipal-Industrial Strategy for Abatement (MISA). Draft. Twelve Month Monitoring Data Report – Inorganic Chemical Sector", Periods covered: December 1, 1989 to November 30, 1990, February 1992b).

Oliver, M.F., J.A. Heady, J.N., Morris, and J. Cooper, "WHO Cooperative Trial on Primary Prevention of Ischaemic Heart Disease with Clofibrate to Lower Serum Cholesterol: Final Mortality Follow-up", *The Lancet, 8403:*600-604 (1984).

Ota, H., H. Onda, H. Kodama, and N. Yamada, "Biological Effects of Phthalate Esters; Histopathological Investigation by Experiments on Mice", *Nippon Eiseigaku Zasshi., 25:*519-524 (1974).

Otson, R. and F.M. Benoit, "Surveys of Selected Organics in Residential Air", in: *Indoor Air Quality in Cold Climates,* Walkinshaw, D.S. (ed.), An Air Pollution Control Association Speciality Conference, pp.224-236 (1985).

Passino, D.R.M. and S.B. Smith, "Acute Bioassays and Hazard Evaluation of Representative Contaminants Detected in Great Lakes Fish", *Environ. Toxicol Chem., 6*:901-907 (1987).

Peakall, D.B., "Phthalate Esters: Occurrence and Biological Effects", *Residue Rev., 54:* 1-41(1975).

Pegg, D.G., "Disposition of Di-2-ethylhexyl Phthalate Following Inhalation and Peroral Exposure in Rats", OTS 8(d) submission, Microfiche No.0206189 (unpublished, 1982).

Pierce, R.C., S.P. Mathur, D.T. Williams, and M.J. Boddington, "Phthalate Esters in the Aquatic Environment", National Research Council of Canada, Associate

Committee on Scientific Criteria for Environmental Quality, NRCC No.17583, Ottawa, Ont. (1980).

Pollack, G.M., R.C. Li, J.C. Ermer, and D.D. Shen, "Effects of Route of Administration and Repetitive Dosing on the Disposition Kinetics of DEHP and its Mono-de-esterified Metabolite in Rats", *Toxicol Appl. Pharmacol, 79*:246-256 (1985a).

Popp, J.A., L.K. Garvey, and R.C. Cattley, *"In vivo* Studies on the Mechanism of Di(2-ethylhexyl)Phthalate Carcinogensis", *Toxicol. Ind. Health., 3:* 151 - 163 (1987).

Price, S.C., D. Chescoe, P. Grasso, M. Wright, and R.H. Hinton, "Alterations in the Thyroids of Rats Treated for Long Periods with Di-(2-ethylhexyl)Phthalate or with Hypolipidaemic Agents", *Toxicology Lett., 40:*37-46 (1988).

Rao, M.S. and J.K. Reddy, "Peroxisome Proliferation and Hepatocarcinogenesis", *Carcinogenesis, 8:*637-645 (1987).

Rao, M.S., A.V. Yeldandi, and V. Subbarao, "Quantitative Analysis of Hepatocelular Lesions Induced by Di(2-ethylhexyl) Phthalate in F-344 Rats", *J. Toxicol. Environ. Health, 30:*85-89 (1990).

Reel, J.R., A.D. Lawton, and J.C. Lamb, "Diethylhexyl Phthalate (DEHP): Reproduction and Fertility Assessment in CD-l Mice when Administered in the Feed", Report 1SS RTI-31U-2344, RTI-72, NTP-84-079, PB84-181734, p.221 (1982).

Reubsaet, F.A.G., J.H. Veerkamp, H.A.A.M. Dirven, M.L.P. Bruckwilder, T. Hashimoto, J.M.F. Trijbels, and L.A.H. Monnens, "The Effect of Di(ethylhexyl)Phthalate on Fatty acid Oxidation and Carnitine Palmitoyltransferase in Various Rat Tissues", *Biochim. Biophys. Acta., 1047*:264-270 (1990).

Rhodes, C., T.C. Orton, I.S. Pratt, P.L. Batten, H. Bratt, and S.J. Jackson, "Comparative Pharmacokinetics and Subacute Toxicity of DEHP in Rats and Marmosets: Extrapolation of Effects in Rodents to Man", *Environ. Health Perspect., 65*:299-308 (1986).

Rodricks, J.V. and D. Turnbull, "Assessment of Possible Carcinogenic Risk Resulting from Exposure to Di(2-ethylhexyl)Phthalate (DEHP) in Children's Products", prepared for the Phthalate Esters Panel, Chemical Manufacturers Association, Washington, DC, 122 pp. (1984).

Rogers, I.H., I.K. Birtwell, and G.M. Kruzynski, "Organic Extractables in Municipal Wastewater, Vancouver, British Columbia", *Water Pollut Res. J. Canada, 21*:187-204 (1986).

Rogers, I.H. and K. J. Hall, "Chlorophenols and Chlorinated Hydrocarbons in Starry Flounder *(Platichthys stellatus)* and Contaminants in Estuarine Sediments Near a Large Municipal Outfall", *Water Pollut. Res. J. Canada, 22:*197-210(1987).

Sadtler Research Laboratories, "Infrared Spectra of Priority Pollutants and Toxic Chemicals", Sadtler Research Laboratories, Philadelphia, PA (1982).

Saeger, V.W. and E.S. Tucker, "Biodegradation of Phthalic Acid Esters in River Water and Activated Sludge", *Appl Environ. Microbiol, 31:*29-34 (1976).

Schmezer, P., B.L. Pool, R.G. Klein, D. Komitowski, and D. Schmahl, "Various Short-term Assays and Two Long-term Studies with the Plasticizer Di(2-ethylhexyl) Phthalate in the Syrian Golden Hamster", *Carcinogenesis, 9:*3743 (1988).

Schmid, P. and C. Schlatter, "Excretion and Metabolism of DEHP in Man *Xenobiotica, 15:*251-256 (1985).

Schmitzer, J.L., I. Scheunert, and F. Korte, "Fate of Bis(2-ethylhexyl) [^{14}C]Phthalate in Laboratory and Outdoor Soil-plant Systems", *J. Agric. Food Chem., 36:*210-215 (1988).

Schouten, M.J., J.W. Copius Peereboom, and U.A.Th. Brinkman, "Liquid Chromatographic Analysis of Phthalate Esters in Dutch River Water", *Int. J. Environ. Anal Chem.,* 7:13-23 (1979).

Shaffer, C.B., C.P. Carpenter, and H.F. Smyth, "Acute and Subacute Toxicity of DEHP with Note Upon its Metabolism", *J. Indust. Hyg. Toxicol, 27:*130-135 (1945).

Shiota, K., M.J. Chou, and H. Nishimura, "Embryotoxic Effects of DEHP and Di-n-butyl Phthalate (DBP) in Mice", *Environ. Res., 22:*245-253 (1980).

Shiota, K. and H. Nishimura, "Teratogenicity of Di(2-ethylhexyl)Phthalate (DEHP) and Di-n-butyl Phthalate (DBP) in Mice", *Environ. Health Perspect., 45:*65-70 (1982).

Shiota, K. and S. Mima, "Assessment of the Teratogenicity of DEHP and MEHP in Mice", *Arch. Toxicol, 56:*263-266 (1985).

Short, R.D., E.C. Robinson, A.W. Lington, and A.E. Chin, "Metabolic and Peroxisome Proliferation Studies with Di(2-ethylhexyl)Phthalate in Rats and Monkeys", *Toxicol. Ind. Health., 3:*185-194(1987).

Smith-Oliver, T. and B.E. Butterworth, "Correlation of the Carcinogenic Potential of Di(2-ethylhexyl)Phthalate (DEHP) with Induced Hyperplasia Rather than with Genotoxic Activity", *Mutation Res., 188*:21-28 (1987).

Spink, D., Alberta Environment (unpublished data, 1986).

Springborn Bionomics, "Chronic Toxicity of Fourteen Phthalate Esters to *Daphnia magna"*, toxicity test report submitted to Chemical Manufacturers Association, Washington, DC, Report No. BW-84-5-1567 (1984).

Stalling, D.L., J.W. Hogan, and J.L. Johnson, "Phthalate Ester Residues - Their Metabolism and Analysis in Fish", *Environ. Health Perspect., 3:*159-173 (1973).

Sullivan, K.F., E.L. Atlas, and C.S. Giam, "Adsorption of Phthalic Acid Esters from Seawater", *Environ. Sci. Technol, 16*:428-432 (1982).

Swain, W.R., "Chlorinated Organic Residues in Fish, Water, and Precipitation from the Vicinity of Isle Royale, Lake Superior", *J. Great Lakes Res., 4:*398-407 (1978).

TRI89, "Toxic Chemicals Release Inventory", National Library of Medicine, National Toxicology Information Program, Bethesda, MD (1991).

Tabak, H.H., S.A. Quave, C.I. Mashni, and E.F. Barth, "Biodegradability Studies with Organic Priority Pollutant Compounds", *J. Water Pollut. Contr. Fed., 53:*1503-1518 (1981).

Tarr, B.D., M.G. Barron, and W.L. Hayton, "Effect of Body Size on the Uptake and Bioconcentration of Di-2-ethylhexyl Phthalate in Rainbow Trout", *Environ. Toxicol Chem., 9*:989-995 (1990).

Teirlynck, O.A. and F. Belpaire, "Disposition of Orally Administered DEHP and MEHP in the Rat", *Arch. Toxicol., 57:*226-230 (1985).

Thiess, A.M. and I. Flieg, "Chromosomal Studies in Workers Exposed to Di-2-ethylhexyl Phthalate (DOP)", *Zentralbl Arbeitsmed., 28:*351-355 (1978) (in German, in IPCS, 1992).

Thiess, A.M., A. Korte, and H. Flieg, "Mortality Study in Workers Exposed to Di-2-ethylhexyl Phthalate (DOP)", in: *Possibilities and Limits of Biological Monitoring - Problems in Occupational Medicine of the Industrial Occupational Health Services",* proceedings of a conference, Frankfurt, May 1978, Stuttgart, A.W. Gertner, pp. 155-164 (1978a)(in German, in IPCS, 1992).

Thiess, A.M., A. Korte, and H. Flieg, "Morbidity Study in Workers Exposed to Di-2-ethylhexyl Phthalate (DEHP)", in: *Possibilities and Limits of Biological Monitoring - Problems in Occupational Medicine of the Industrial Occupational Health Services",* proceedings of a conference, Frankfurt, May 1978, Stuttgart, A.W. Gertner, pp. 137-154 (1978b) (in German, in IPCS, 1992).

Thomas, G.H., "Quantitative Determination and Confirmation of Identity of Trace Amounts of Dialkyl Phthalates in Environmental Samples", *Environ. Health Perspect., 3*:23-28 (1973).

Tyl, R.W., C.J. Price, M.C. Marr, and C.A. Kimmel, "Developmental Toxicity Evaluation of Dietary Di(2-ethylhexyl)Phthalate in Fischer 344 Rats and CD-1 Mice", *Fund. Appl. Toxicol., 10:*395-412 (1988).

U.S. EPA (United States Environmental Protection Agency), "Ambient Water Quality Criteria for Phthalate Esters", Office of Water Regulations and Standards, Washington, DC, EPA 440/5-80-067 (1981).

U.S. EPA (United States Environmental Protection Agency), "An Exposure and Risk Assessment for Phthalate Esters", Office of Water Regulations and Standards, Washington, DC, PB85-211936, 175 pp. (1981).

U.S. EPA (United States Environmental Protection Agency), "Aquatic Fate Process Data for Organic Priority Pollutants", EPA-440/4-81-014, NTIS PB87-169090, Washington, DC (1982a).

U.S. EPA (United States Environmental Protection Agency), "Methods for Organic Chemical Analysis of Municipal and Industrial Wastewater", Environmental Monitoring and Support Laboratory, Cincinnati, OH, EPA 600/4-82-057, NTIS PB83-201798 (July, 1982) (1982b).

U.S. EPA (United States Environmental Protection Agency), "Health Effects Assessment for Selected Phthalic Acid Esters", EPA-600/8-88-053, NTIS PB88-178934, Washington, DC (1987).

U.S. EPA (United States Environmental Protection Agency), "Drinking Water Criteria Document for Phthalic Acid Esters (PAES)", Final Report. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, 321 pp. (1991).

Volskay, V.T., Jr. and C.P.L. Grady Jr., "Toxicity of Selected RCRA Compounds to Activated Sludge Microorganisms", *J. Water Pollut. Contr. Fed., 60:*1850-1856 (1988).

Wams, T.J., "Diethylhexylphthalate as an Environmental Contaminant - a Review", *Sci. Total Environ., 66*:1-16(1987).

Webber, M.D. and S. Lesage, "Organic Contaminants in Canadian Municipal Sludges", *Waste Manage. Res., 7:*63-82 (1989).

Weschler, C., "Identification of Selected Organics in the Arctic Aerosol", *Atmospheric Environment, 15:*1365-1369 (1981).

Williams, D.T., "Dibutyl- and Di-(2-ethylhexyl)Phthalate in Fish", *J. Agric. Food Chem., 21*:1128-1129(1973).

Wofford, H.W., C.D. Wilsey, G.S. Neff, C.S. Giam, and J.M. Neff, "Bioaccumulation and Metabolism of Phthalate Esters by Oysters, Brown Shrimp, and Sheepshead Minnows", *Ecotoxicol Environ. Safety, 5*:202-210(1981).

Wolfe, N.L., L.A. Burns, and W.C. Steen, "Use of Linear Free Energy Relationships and An Evaluative Model to Assess the Fate and Transport of Phthalate Esters in the Aquatic Environment", *Chemosphere, 9*:393402 (1980a).

Wolfe, N.L., W.C. Steen, and L.A. Burns, "Phthalate Ester Hydrolysis: Linear Free Energy Relationships", *Chemosphere, 9*:403-408 (1980b).

Wolkowski-Tyl, R., C. Jones-Price, M.C. Marr, and C.A. Kinmel, "Teratologic Evaluation of Diethylhexyl Phthalate in CD-1 Mice", Final Report, National Center for Toxicological Research, Jefferson, AR, PB85-105674 (1984a).

Wolkowski-Tyl, R., C. Jones-Price, and M.C. Marr, "Teratologic Evaluation of Diethylhexyl Phthalate (CAS No. 117-81-7) in Fischer 344 Rats", Report: ISS RTI-60, FDA/NCTR-84/135, PB85-105658 (1984b).

Woodward, K.N., *Phthalate Esters Toxicity and Metabolism,* CRC Press Inc., Boca Raton, FL, Vol I & II (1988).

Zitko, V., "Determination of Phthalates in Biological Samples", *Int. J. Environ. Anal. Chem., 2*:241-252 (1972).

Zurmühl, T., W. Durner, and R. Herrmann, "Transport of Phthalate-Esters in Undisturbed and Unsaturated Soil Columns", *J. Contaminant Hydrol, 8*:111-133 (1991).