

Canadian Environmental Protection Act

Priority Substances List
Assessment Report

Di-*n*-Octyl Phthalate



Government
of Canada

Gouvernement
du Canada

Environment
Canada

Environnement
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Santé
Canada



PRIORITY SUBSTANCES LIST
ASSESSMENT REPORT

DI-*n*-OCTYL PHTHALATE

Government of Canada
Environment Canada
Health Canada

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Synopsis

Di-*n*-octyl phthalate (*DnOP*), the straight chain dioctyl ester of phthalic acid, is not produced in Canada. Approximately one tonne, however, is used in Canada each year. Di-*n*-octyl phthalate has been detected occasionally in industrial liquid effluents and in sewage sludge in Canada, and less frequently in surface waters and sediments. No data have been identified on concentrations of *DnOP* in air, precipitation, soil, or biota in Canada. This substance is not persistent in air or surface water, but may persist and accumulate in sediment under anaerobic conditions.

The maximum concentration of *DnOP* reported for surface waters in Canada is approximately five times less than the chronic effects threshold estimated for the most sensitive aquatic species. Although no data were identified on the toxicity of *DnOP* to wildlife and benthic organisms, it is considered that, on the basis of its limited use, exposure of these organisms is unlikely to result in harmful effects.

Based on the limited use of *DnOP* in Canada and its rapid removal from the atmosphere by photo-oxidation, concentrations in the atmosphere are likely to be small. Consequently, *DnOP* is not expected to contribute significantly to formation of ground-level ozone, global warming, or depletion of stratospheric ozone.

The available information was considered inadequate to quantitatively estimate the exposure of the general population in Canada to *DnOP* or the associated potential health risk.

Based on these considerations, it has been concluded that di-*n*-octyl phthalate is not entering the environment in a quantity or concentration or under conditions that are having a harmful effect on the environment or that constitute a danger to the environment upon which human life depends. There are insufficient data to conclude whether *DnOP* is entering the environment in a quantity or concentration or under conditions that constitute a danger to human life or 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 of the Act may be placed on Schedule I of CEPA. Consideration can then be given to developing regulations, guidelines, or codes of practice to control any aspect of this substance's life cycle, from the research and development stage through manufacture, use, storage, transport, and ultimate disposal.

The assessment of whether di-*n*-octyl phthalate (DnOP) 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 DnOP is "toxic" to the environment under CEPA were identified from existing review documents, published reference texts, and on-line searches conducted between September 1991 and March 1993, of the following commercial databases: 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 DnOP is "toxic" to the environment obtained after April 1993, have not been included.

To identify toxicological data relevant to the assessment of whether DnOP is "toxic" to human health under CEPA, a background review was prepared under contract by the British Industrial Biological Research Association Toxicology International (BIBRA) in 1991. Information therein was identified on the basis of a literature search of BIBRA's data sources and the online bibliographic databases TOXLINE/TOXLIT, MEDLINE, BIOSIS, National Technical Information System (NTIS) (all, 1962 to 1991),

and the Hazardous Substances Data Bank (HSDB) on TOXNET. The following computerized databases were also searched for relevant data in November 1991: Hazardous Substances Data Bank (HSDB), Registry of Toxic Effects of Chemical Substances (RTECS), Integrated Risk Information System (IRIS), Chemical Carcinogenesis Research Information System (CCRIS), TOXLINE and TOXLIT (all, 1981 to 1991). Dr. A.B. DeAngelo of the U.S. Environmental Protection Agency (U.S. EPA) was also contacted in June 1992, in an attempt to identify additional data relevant to the assessment of the toxicity of DnOP.

To identify data relevant to the estimation of exposure of the general population to DnOP, the following computerized databases were searched in November 1991: Environmental Bibliography (1973 to 1991), Enviroline (1971 to 1991), POLLUTION ABSTRACTS (1970 to 1991), Environment Canada Departmental Library Catalogue (ELIAS) (1991), AQUAREF (1970 to 1991), Canadian Research Index (MICROLOG) (1979 to 1991), and Co-operative Documents Project (CODOC) (1991). Dr. G. Jenkins of the Ontario Ministry of the Environment, Mr. D. Spink of the Alberta Ministry of the Environment, and Mr. H. St.-Martin of Environment Quebec were also consulted in an attempt to identify data on concentrations in environmental media to which humans are exposed (i.e., drinking water). Data relevant to assessment of whether DnOP is "toxic" to human health obtained after August 1992 were not considered for inclusion.

Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether DnOP 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

L. Brownlee
C. Fortin
K. Lloyd
P. Paine
K. Taylor

Health Canada

P.K.L. Chan
M.E. Meek

In this report, a synopsis is presented concerning DnOP that will appear in the *Canada Gazette*. Section 2.0 is an extended summary of the technical information that is critical to the assessment. The assessment of whether DnOP is "toxic" is presented in Section 3.0. Supporting documentation that presents the technical information in greater detail has also been prepared.

As part of the review and approvals process established by Environment Canada, the environmental sections of this report were peer 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). 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 the unpublished supporting documentation are available upon request from:

Commercial Chemicals Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Boulevard
Hull, Quebec
K1A 0H3

Environmental Health Centre
Health Canada
Room 104
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

2.0 Summary of Information Critical to Assessment of "Toxic"

2.1 Identity, Properties, Production, and Uses

Di-*n*-octyl phthalate, a phthalic acid ester, has the CAS (Chemical Abstracts Service) Registry Number 117-84-0, the molecular formula C₂₄H₃₈O₄, and a molecular weight of 390.6. Synonyms include: DnOP and 1,2-benzenedicarboxylic acid, dioctyl ester. The structure of di-*n*-octyl phthalate is shown in Figure 1. Di-*n*-octyl phthalate is a clear, viscous liquid at ambient temperature, with a reported vapour pressure of 0.02 Pa at 25⁰C (Mabey *et al.*, 1982) and Henry's Law Constant of 1.7 Pa·m³/mol (Mabey *et al.*, 1982). Determination of the water solubility of phthalic acid esters is complicated since these compounds easily form colloidal dispersions in water (Klöpfer *et al.*, 1982) and are subject to the phenomenon referred to as "molecular folding" (Callahan *et al.*, 1979). Reported water solubilities ranged from 20 (DeFoe *et al.*, 1990) to 3000 µg/L (Wolfe *et al.*, 1980). The range of values for the octanol/water partition coefficient (log K_{ow}) reported in the literature is between 5 and 9.9 (CMA, 1984; DeFoe *et al.*, 1990; Mabey *et al.*, 1982; Veith *et al.*, 1984).

The most sensitive and selective analytical method for the determination of phthalic acid esters, including DnOP, in environmental media is gas chromatography with electron capture detection (Kohli *et al.*, 1989).

Two problems have plagued the chemical analysis and the reporting of concentrations of DnOP. The first, applicable to phthalic acid esters as a group, is due to the fact that this group of compounds frequently occurs as plasticizers in analytical equipment and as contaminants in laboratory air and solvents. Therefore, a great deal of care is needed to prevent contamination during collection, storage, and analysis of samples (Hites and Budde, 1991; Kohli *et al.*, 1989; Mathur, 1974; Mayer *et al.*, 1972; U.S. EPA, 1982). For instance, DnOP was specifically identified by Bauman *et al.* (1967) as a contaminant in lipid and soil samples collected in plastic-lined bags. Many studies conducted before 1980 reporting environmental concentrations have not

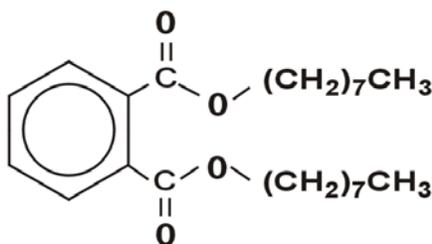


Figure 1 Structure of Di-*n*-octyl Phthalate

accounted for this problem (Pierce *et al.*, 1980). The second problem, specific to *DnOP*, is that the terminology is not consistent in the technical literature, with the substance sometimes being referred to as "dioctyl phthalate". This has led to confusion with the branched-chain isomer, bis(2-ethylhexyl) phthalate (DEHP), also sometimes referred to as "dioctyl phthalate" or "DOP". As a consequence, the frequency of occurrence of *DnOP* in the environment may have been overestimated, since reports of environmental concentrations of "dioctyl phthalate" could pertain to DEHP, which has been used in much higher quantities than *DnOP*.

Di-n-octyl phthalate is used as a plasticizer to impart flexibility to polymers, particularly polyvinyl chloride (PVC) used to make products such as gloves, flooring, and flexible sheets (Law, Sigurdson & Associates, 1993).

There are no Canadian producers of *DnOP* (Law, Sigurdson & Associates, 1993; SRI International, 1991). On the basis of confidential business information provided to Environment Canada, it is estimated that approximately one tonne of this substance is used annually in Canada (C. Fortin, 1993). *Di-n*-octyl phthalate is not commercially available in North America and is only made on special order (Law, Sigurdson & Associates, 1993; Camford Information Services Inc., 1992). Available data are insufficient, however, to estimate the amounts of *DnOP* imported in mixtures with other plasticizers or in plastic products.

2.2 Entry into the Environment

The occurrence of naturally produced phthalates in biological and geochemical samples has been suggested, but in most cases the possibility of contamination during sampling or analysis could not be ruled out (Mathur, 1974). However, it is unlikely that the amounts of phthalates produced naturally would be significant compared with those from anthropogenic sources (WHO, 1992).

Recent information specifically related to the release of *DnOP* to the Canadian environment is limited to that reported by the Ontario Ministry of the Environment under the Municipal/industrial Strategy for Abatement (MISA) program. Between February 1990 and January 1991, the mean concentration of *DnOP* in effluents being discharged into Lake Ontario from one organic chemical plant located in Whitby, Ontario was 2.3 µg/L (loading value of 0.001 kg/day) (OME, 1992). *Di-n*-octyl phthalate was detected in 9 of 15 Canadian municipal sludges sampled between 1980 and 1985, with concentrations ranging from traces to 115 mg/kg [dry weight (d.w.)]; the median concentration was 7 mg/kg (Webber and Lesage, 1989).

In the early 1980s, *DnOP* was reported at concentrations in the range of 1 to 10 µg/L in effluents of Canadian chemical plants discharging into the St. Lawrence River at Cornwall, Ontario, and into the St. Clair River at Sarnia, Ontario, (CCREM, 1987; Munro *et al.*, 1985).

Although unable to distinguish between *DnOP* and DEHP, Brownlee and Strachan (1977) reported 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. Similarly, "dioctyl phthalate" was 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

Processes affecting the distribution and transformation of DnOP in the environment include atmospheric photo-oxidation, partitioning to soil, sediment and biota, and aerobic degradation (Callahan *et al.*, 1979; Howard *et al.*, 1991; Kohli *et al.*, 1989; Pierce *et al.*, 1980; Sanborn *et al.*, 1975). No measured bioconcentration factors were identified for DnOP.

Howard *et al.* (1991), on the basis of scientific judgement, estimated a photo-oxidation half-life for DnOP in air of less than 1.9 days, and aerobic biodegradation half-lives for DnOP in soil and surface water ranging between 1 and 4 weeks, with an estimated hydrolysis half-life of 107 years at pH 7. From the results of an experiment conducted in a laboratory model ecosystem, Sanborn *et al.* (1975) reported a degradation half-life for DnOP of 5 days in the water column. Identified transformation products included mono-*n*-octyl phthalate and phthalic acid. Di-*n*-octyl phthalate, like many other dialkylphthalates, may form water soluble complexes with fulvic acids, found commonly in fresh water and soils. This may increase its mobilization and reactivity in soil and its solubility in water (Kohli *et al.*, 1989).

Callahan *et al.* (1979) reviewed the fate of DnOP in water and, by comparison with other phthalic acid esters, concluded that sorption onto particulate matter and biota, bioaccumulation, and aerobic biodegradation were probably the most important fate processes for this substance.

In a laboratory model ecosystem with an exposure period of 33 days, algae accumulated the highest concentration of DnOP (1.8 mg/kg), *Daphnia* the least (0.16 mg/kg), while fish (0.59 mg/kg), snail (0.85 mg/kg), and mosquito larvae (0.59 mg/kg) accumulated intermediate concentrations of DnOP (Sanborn *et al.*, 1975). Reliable bioconcentration factors could not be derived because the concentration of DnOP in the water continued to decrease throughout the study.

2.3.2 Concentrations

Very limited information is available concerning concentrations of DnOP in Canadian surface waters and sediments, and there are no reliable data on air, precipitation, soil, or biota.

Di-*n*-octyl phthalate was detected in one of 45 samples of raw surface water collected in Alberta between 1987 and 1992, at a concentration of 4 µg/L (detection limit, 1 µg/L) (Halina, 1993). Germain and Langlois (1988) reported a mean concentration of 9 ng/L DnOP (detection limit, 0.04 ng/L) in the St. Lawrence River

between Cornwall and Quebec city in 1987. The Niagara River Data Interpretation Group (1990) reported that mean concentrations in water samples collected during 1988 and 1989 at Fort Erie and Niagara-on-the-Lake were 2.9 and 5.2 ng/L (detection limit, 0.15 ng/L). Di-*n*-octyl phthalate was detected in 50 of 51 water samples from Fort Erie and in 38 of 44 water samples from Niagara-on-the-Lake. It was not detected in 22 samples of raw drinking water collected in 1992 from 11 municipalities in the Lac St-Jean and Charlevoix areas of Quebec (detection limit, 1.0 µg/L) (MENVIQ, 1993).

Information on concentrations of DnOP in surface waters in the NAQUADAT/ENVIRODAT database is limited to approximately 80 records for Alberta and two records for British Columbia dating from 1985 to 1988, with concentrations ranging from <1 to 7 µg/L (NAQUADAT, 1993). Concentrations of DnOP between 1 and 10 µg/L (actual values not specified) were reported in 4 out of 24 samples of intake water for industrial chemical plants located on the St. Clair River in 1979-80 (Munro *et al.*, 1985).

Rogers and Hall (1987) reported levels of DnOP of 94 ng/g and <15 ng/g dry weight in sediments 0.5 km and 1 km, respectively, downstream from a sewage outfall in the Fraser River estuary. Fallon and Horvath (1985) reported concentrations in sediment ranging from 90 to 260 ng/g for three samples collected in 1982 from the south end of Grosse Ile in the Detroit River. The concentration of DnOP in St. Clair River sediments near Sarnia, Ontario, was reported to be 15 µg/g (EC/OME, 1986).

Information has not been identified on concentrations of DnOP in food. Available data relevant to estimation of human exposure are restricted to the lack of detection (limit of detection, 1.0 µg/L) of DnOP in 232 of 246 drinking water supplies in Alberta (in the remaining 14, maximum: 11 µg DnOP/L; overall mean: below limit of detection) (Halina, 1993); 25 drinking water supplies in one area in the United States (Perwak *et al.*, 1981); the lack of detection in small numbers of fish in harbours of the Great Lakes (detection limit not specified) (DeVault, 1985); and reported levels of 0.081 and 0.11 µg/g wet-weight in 2 out of 10 samples of fish in British Columbia (Swain and Walton, 1989). However, the authors of the latter investigation concluded that their results were not reliable owing to possible sources of contamination in sampling and analysis.

2.4 Effects-related Information

2.4.1 Experimental Animals and In Vitro

In several studies, the acute toxicity of DnOP in laboratory animals has been low (Dogra *et al.*, 1987;1989; Fassett, 1963; NIOSH, 1987). The lowest oral LD₅₀ in rats and mice was 13 g/kg body weight (b.w.) (Dogra *et al.*, 1989; Fassett, 1963).

Administration of 1000 mg/[kg (b.w.)·day] of DnOP to various strains of male rats either in the diet or by stomach tube for up to three weeks produced liver enlargement accompanied in some cases by fat accumulation and cell damage (Lake *et al.*, 1984;

Mann *et al.*, 1985; Oishi and Hiraga, 1980). Increases in peroxisome numbers were not observed upon electron microscopic examination; however, a marginal increase in the peroxisomal marker enzyme (cyanide-insensitive palmitoyl CoA oxidase) was reported (Lake *et al.*, 1984; Mann *et al.*, 1985). Tissue damage in the thyroid and reduced serum thyroxine have also been observed following exposure of male Wistar albino rats to DnOP for 3, 10, or 21 days in their diet {2000 mg/[kg (b.w.)·day]} (Hinton *et al.*, 1986).

Information identified on subchronic toxicity is restricted to inadequately documented studies. In an incomplete report of a study in which male rats were exposed to two doses (and controls) of DnOP in the diet for 11 weeks (DeAngelo *et al.*, 1988) in a study for which additional documentation is not available (DeAngelo, 1992) exhibited marked liver damage (characterized by cellular enlargement and proliferation, vacuolization, chronic inflammation, and necrosis). These male Fischer 344 rats were exposed to dietary levels of 0.5 or 1% DnOP {300 or 600 mg/[kg (b.w.)·day]} {LOEL = 300 mg/[kg (b.w.)·day]}. Alterations in serum enzyme levels were consistent with the liver damage. In another study, small groups of mice were exposed to an unspecified concentration of DnOP in air for up to 16 weeks (Lawrence *et al.*, 1975). There were no overt signs of toxicity and lungs in these mice were normal upon microscopic examination. Other investigations were restricted to examining a limited range of effects following exposure by routes not similar to those by which humans are principally exposed in the general environment (for example, intraperitoneal injection of DnOP to an unspecified strain of rats - Khanna *et al.*, 1990).

Information is extremely limited on chronic toxicity or carcinogenicity of DnOP in experimental animals. Pieckacz (1971) gave an incomplete account of a limited investigation in which a single dose {175 mg/[kg (b.w.)·day]} of an unspecified isomer of dioctyl phthalate was administered to an unspecified species and strain of animal for 12 months. The reported effects were restricted to a decrease in body weight and increases in liver and kidney weights and activities of serum enzymes (Pieckacz, 1971). In another study for which additional documentation is not available, "numerous" liver nodules were reported in male rats administered 1% DnOP {600 mg/[kg (b.w.)·day]} in the diet for 65 weeks. The activity of a number of lysosomal enzymes was also increased in these rats (Carter *et al.*, 1989). A six-fold increase has also been reported in the numbers of gamma-glutamyltransferase-positive foci in the livers of rats administered a single dose of diethylnitrosamine and then exposed to 600 mg/kg (b.w.) DnOP for 10 weeks (DeAngelo *et al.*, 1986).

There has been no convincing evidence of the genotoxicity of DnOP based on the results of a small number of in vitro bioassays of mutagenicity or DNA repair in bacteria (Florin *et al.*, 1980; Kuarata, 1975; Seed, 1982; Yoshikawa *et al.*, 1983; Zeiger *et al.*, 1985).

Available data on the developmental toxicity of DnOP are limited to a study in which exposure-related developmental effects were not observed following oral exposure of pregnant mice to a single dose level [9780 mg/kg (b.w.)] (Hardin *et al.*, 1987); an incomplete account of a reduction in fetal weight in rats administered an unspecified

isomer of dioctyl phthalate [340 and 1700 mg/kg (b.w.)] during pregnancy (Pieckacz, 1971); and malformations in the offspring of rats exposed to an unspecified isomer of dioctyl phthalate [489 and 9780 mg/kg (b.w.)] by a nonphysiological route of administration [intraperitoneal (i.p.) injection] on selected days of pregnancy (Singh *et al.*, 1972).

There was no evidence of treatment-related testicular damage or any effect on the weight of the testes and accessory glands when 2800 mg/[kg (b.w.)·day] DnOP was administered to two different strains of rats (Sprague-Dawley or Wistar) either by stomach tube for 4 to 10 days or at 2% in the diet {approximately 1200 mg/[kg (b.w.)·day]} for up to 21 days (Foster *et al.*, 1980; Gray and Butterworth, 1980; Mann *et al.*, 1985; Oishi and Hiraga, 1980). The level of zinc, essential for the maintenance of normal testicular cell function, was depleted in the testes of Wistar rats (Oishi and Hiraga, 1980) but not in Sprague-Dawley rats (Foster *et al.*, 1980). There was atrophy of the seminiferous tubules following intraperitoneal administration to male rats of 100 mg/[kg (b.w.)·day], 5 days/week for 90 days, with damage increasing in severity in the higher dose groups (Khanna *et al.*, 1989).

In a relatively extensive study in which the reproductive toxicity of several phthalates was investigated (Heindel *et al.*, 1989; Morrissey *et al.*, 1989), DnOP had no effect on fertility or reproductive performance in Swiss albino CD-1 mice (20/sex/group) at doses up to 7500 mg/[kg (b.w.)·day] in the diet for 7 days before and then throughout a 98-day continuous breeding period. There were no significant differences in the fertility and reproductive performance of the parental generation compared to controls. Reproductive effects were also examined in the high-dose group of offspring (second generation, F₁) at maturity and mating. There was a decrease in the weight of the seminal vesicles in the absence of any changes in the weight of the testes, prostate, and epididymis, or effects on the sperm of the F₁. There were no significant differences in the fertility and reproductive performance of the parental generation compared to controls, though the liver weight in both sexes and the kidney weights in females were increased in the F₁. The authors suggested that the maximal tolerated dose might not have been reached because of the lack of observed body weight depression at the highest dose {5% or 7500 mg/[kg (b.w.)·day]}; however, it should be noted that increases in organ weights were observed at this dose. Effects (e.g., histopathological changes) other than those on reproductive indices were not examined.

Investigation of the immunological effects of DnOP revealed tissue damage upon histopathological examination of the thymus, spleen, adrenals, and lymph nodes of rats following i.p. injection of 600 mg/[kg (b.w.)·day] for 45 to 90 days; there were also slight histopathological changes in the spleen at the lower dose levels {100 and 300 mg/[kg (b.w.)·day]} (Dogra *et al.*, 1985). There was a dose-dependent modification of the immune response and host resistance to endotoxin sensitivity and parasitic challenge in male albino rats administered 2500, 5000, or 10 000 mg/[kg (b.w.)·day] DnOP orally for five days (Dogra *et al.*, 1987). Immune function was impaired in 3-month-old Swiss albino mice, based on increased susceptibility to the lethal effects

of viral or protozoal infection following oral administration of 650 or 2600 mg/[kg (b.w.)·day] of di-*n*-octyl phthalate for 5 days (Dogra *et al.*, 1989).

Data have not been identified on the neurological effects of *DnOP* in experimental animals.

2.4.2 Humans

Data on effects in humans are restricted to a case report of irritation of the eye and upper respiratory tract of workers exposed to phthalates (including dioctyl phthalate, isomer unspecified) (Zdražil and Picha, 1965); poorly documented studies on neurological and reproductive effects in small groups of workers exposed in the occupational environment to phthalates including dioctyl phthalate (isomer unspecified) (Milkov *et al.*, 1973; Gilioli *et al.*, 1978; Aldyreva *et al.*, 1975); and poorly documented clinical studies of skin irritation and sensitization in volunteers upon dermal contact with an unspecified isomer of dioctyl phthalate (Harris, 1953; Mallette and von Haam, 1952).

2.4.3 Ecotoxicology

The information identified concerning the toxicity of *DnOP* was limited to a few studies on aquatic organisms. In many studies, no adverse effects were found even at the highest concentrations of *DnOP* tested. In other studies, adverse effects on aquatic organisms were found only at nominal concentrations in the upper portion of the range of water solubility reported for the substance.

Impairment of reproduction was the most sensitive endpoint identified on the toxicity of *DnOP* in aquatic biota. McCarthy and Whitmore (1985) reported a 16-day lowest-observed-effect-level (LOEL) [75% reduction in number of young produced per adult: reported no-observed-effect-level (NOEL) = 320 µg/L] of 1 mg *DnOP*/L for *Daphnia magna*. The same authors also reported a 20-day LOEL of 10 mg *DnOP*/L for the fathead minnow based on reduced hatching rate (McCarthy and Whitmore, 1985).

No information was identified on the adverse effects of *DnOP* on micro-organisms, algae, benthic organisms, plants, amphibians, or reptiles.

3.0 Assessment of "Toxic" Under CEPA

3.1 CEPA 11(a) Environment

There are no Canadian producers of *DnOP*. Approximately one tonne of this substance is used annually in Canada. Di-*n*-octyl phthalate has been detected occasionally in industrial effluents and in sewage sludges in Canada and less frequently in surface waters and sediments. No data were identified on concentrations of *DnOP* in air, soil, or precipitation in Canada.

The lowest reported LOEL for dissolved *DnOP* on freshwater aquatic organisms was 1 mg/L (exposure for 16 days reduced the number of young per adult by 75% in *Daphnia magna*). This effect level was divided by a net factor of 30 (10 to account for differences in sensitivity between species and to extrapolate from laboratory to field conditions, and 3 because of the large reduction in reproduction associated with the LOEL), resulting in an estimated effects threshold of 33 µg/L. The highest concentration of *DnOP* reported for Canadian surface waters (7 µg/L) is about five times less than this estimated effects threshold.

No data were identified to serve as a basis for comparison of an estimated effects level with environmental levels in Canadian sediments, the only other medium in which *DnOP* has been detected. Similarly, no information pertaining to adverse effects of *DnOP* on plants, birds, or wild mammals has been identified in the literature. However, on the basis of its very limited use in Canada, exposure of these organisms to *DnOP* is unlikely to result in harmful effects.

Therefore, based on available data, *DnOP* is not considered to be entering the environment in a quantity or concentration or under conditions that are having a harmful effect on the environment.

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

There are no data available concerning the concentration of *DnOP* in the atmosphere in Canada. However, based on its limited use in Canada and its rapid removal from the atmosphere by photo-oxidation (half-life of less than 2 days), concentrations in the atmosphere are likely to be small. Consequently, *DnOP* is not expected to contribute significantly to formation of ground-level ozone, global warming, or depletion of stratospheric ozone.

Therefore, based on available data, *DnOP* 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

Available data are few and unreliable on concentrations of DnOP in environmental media to which humans are exposed in Canada and elsewhere. Consequently, the available information is inadequate for quantitative estimation of the exposure of the general population in Canada to DnOP.

Available data on the toxicity of DnOP are also limited. Reports on effects in humans are limited to a small number of poorly documented studies of small groups of workers exposed in the occupational environment to other phthalates and unspecified isomers of dioctyl phthalate.

Available data are inadequate to assess the carcinogenicity of DnOP in experimental animals owing to incomplete documentation and examination of a limited range of endpoints in identified studies (Carter *et al.*, 1989; DeAngelo *et al.*, 1986; DeAngelo, 1992; Pieckacz, 1971). There has been no convincing evidence of the genotoxicity of DnOP based on the results of a small number of investigations in *in vitro* bioassays of mutagenicity or DNA repair in bacteria or mutagenicity of a mixture of dialkyl phthalates in cultured mouse lymphoma cells.

Di-*n*-octyl phthalate has been classified, therefore, in Group V ("Inadequate Data for Evaluation") of the classification scheme developed for use in the derivation of the "Guidelines for Canadian Drinking Water Quality" (Health and Welfare Canada, 1989). For compounds classified in Group V, a Tolerable Daily Intake (TDI) is derived on the basis of division of a no- or lowest-observed-(adverse)-effect-level [NO(A)EL or LO(A)EL] in animal species by an uncertainty factor.

Identified information on the subchronic toxicity of DnOP is restricted to an incomplete report of a study in which male rats were exposed to two doses (and controls) of DnOP in their diet for 11 weeks (DeAngelo *et al.*, 1988) for which additional documentation is not available (DeAngelo, 1992); an inadequately documented study in which small groups of mice were exposed to an unspecified concentration of DnOP in air for up to 16 weeks (Lawrence *et al.*, 1975); and investigations of a limited range of effects following exposure by routes not similar to those by which humans are principally exposed in the general environment (intraperitoneal injection of DnOP to an unspecified strain of rats - Khanna *et al.*, 1990).

Though a well conducted and documented two generation reproduction study in mice has been identified (Heindel *et al.*, 1989; Morrissey *et al.*, 1989), it was considered to be inadequate to serve as a basis for the development of a TDI since effects (e.g., histopathological changes), other than those on reproductive indices, were not examined. Similarly, a 90-day study has also been identified on the immunological effects of DnOP in mice administered for 45 or 90 days by a route to which man is not exposed in the general environment (i.p.) (Oishi, 1990); however, endpoints relevant to assessment of general systemic toxicity were not examined.

Available data are considered inadequate, therefore, to develop a tolerable daily intake for *DnOP*. Consequently, it is not possible to evaluate whether current concentrations of *DnOP* present in the environment constitute a danger in Canada to human life or health.

Therefore, based on available data, there is insufficient information to conclude whether *DnOP* is entering the environment in a quantity or concentration or under conditions that constitute a danger to human life or health.

3.4 Conclusion

Based on these considerations, it has been concluded that *DnOP* is not entering the environment in a quantity or concentration or under conditions that are having a harmful effect on the environment or that constitute a danger to the environment upon which human life depends. There are insufficient data to determine whether *DnOP* is entering the environment in a quantity or concentration or under conditions that constitute a danger to human life or health.

4.0 Recommendations for Research and Evaluation

Acquisition of additional data in the following areas would permit a more complete evaluation of the effects of *DnOP* on human health and environmental organisms in Canada. At present, the priority for this work is considered to be low because *DnOP* is currently used in Canada in very small quantities.

1. Monitoring of *DnOP* in all environmental media (i.e., air, food, drinking water) to which Canadians are exposed and in surface water, air, sediment, and biota in the proximity of industrial sources.
2. Chronic toxicity tests on selected benthic organisms, algae, and rodents.
3. A carcinogenicity bioassay for *DnOP* in two species of experimental animals.
4. Additional data on developmental toxicity, reproductive toxicity, and neurotoxicity of *DnOP* in another species (e.g., rats).

Based on consideration of other priorities for assessment under the Act, it is recommended that the results of a subchronic study on *DnOP* being conducted under contract to Health Canada be assessed for the determination of whether *DnOP* is "toxic" as defined under the Act.

5.0 References

- Aldyreva, M.V., T.S. Klimova, A.S. Izyumova, and L.A. Timofievskaya, "Effect of Plasticizers on Reproductive Function", *Gigiene Truda I Professional'nye Zabolevaniya*, 12:25-29 (from an English translation of a Soviet study) (1975).
- Bauman, A.J., R.E. Cameron, G. Kritchevsky, and G. Rouser, "Detection of Phthalate Esters as Contaminants of Lipid Extracts from Soil Samples Stored in Standard Soil Bags", *Lipids*, 2: 85-86 (1967).
- 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).
- CCREM, *Canadian Water Quality Guidelines*, prepared by the Task Force on Water Quality Guidelines of the Canadian Council of Resource and Environment Ministers (1987).
- CMA, "Generation of Environmental Fate and Effects Data Base on 14 Phthalate Esters. Summary Report - Environmental Studies - Phase I", Chemicals Manufacturers Association, Phthalate Esters Program Panel, Washington, DC (1984).
- 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, U.S. Environmental Protection Agency, Washington, DC (1979).
- Camford Information Services Inc., "CPI Product Profiles - Dioctyl Phthalate", Camford Information Services Inc., Don Mills, Ont., 4 p. (1992).
- Carter, J.H., H.W. Carter, A.B. DeAngelo, and F.B. Daniel, "Sub-lethal Autolysis in Livers of Rats Exposed to Phthalates", *J. Cell Biology*, 109(4): 182a, Abstract No. 1003 (1989).
- DeAngelo, A.B., Personal communication, U.S. Environmental Protection Agency (1992).
- DeAngelo, A.B., C.T. Garrett, L.A. Manolukas, and T. Yario, "Di-n-octyl Phthalate (DOP), A Relatively Ineffective Straight Chain Isomer of the Environmental Contaminant Di(2-ethylhexyl) Phthalate (DEHP), Enhances the Development of Putative Preneoplastic Lesions in Rat Liver", *Toxicology*, 41:279-288 (1986).

- DeAngelo, A.B., J. Cicmanec, L.P. McMillan, and P.A. Wernsing, "Comparative Toxicity of Di(2-ethylhexyl) Phthalate (DEHP) and Di-n-octyl Phthalate (DOP)", *The Toxicologist*, 8(1): 38, Abstract No. 150 (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 Harbours and Tributary Mouths", *Arch. Environ. Contam. Toxicol.*, 14:587-594 (1985).
- Dogra, R.K.S., S. Khanna, S.L. Nagala, L.J. Shukla, S.N. Srivastava, M.C. Bhatnagar, P.K. Gupta, and R. Shanker, "Effect of Dioctyl Phthalate on Immune System of Rat", *Ind. J. Exper. Biology*, 23:315-319(1985).
- Dogra, R.K.S., S. Khanna, L. Shukia, S. Srivastava, S. Gupta, J.C. Katiyar, and R. Shanker, "Modification of the Immune Response in Rats by Di-octyl Phthalate", *Ind. Health*, 25:97-101(1987).
- Dogra, R.K.S, K. Chandra, S. Chandra, S. Khanna, S.N. Srivastava, L. Shukia, J.C. Katiyar, and R. Shanker, "Di-octyl Phthalate Induced Altered Host Resistance: Viral and Protozoal Models in Mice", *Ind. Health*, 27:83-87 (1989).
- 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).
- EC/OME, "St. Clair River Pollution Investigation (Sarnia Area)", Unpublished report prepared under the Canada/Ontario Agreement Respecting Great Lakes Water Quality, Environment Canada/Ontario Ministry of the Environment (1986).
- Fallon, M.E. and F.J. Horvath, "Preliminary Assessment of Contaminants in Soft Sediments of the Detroit River", *J. Great Lakes Res.*, 11:373-378 (1985).
- Fassett, D.W., "Esters", in: *Patty's Industrial Hygiene and Toxicology, Vol. 11, Toxicology, 2nd Edition*, Interscience Publishers, John Wiley & Sons, New York (1963).
- Florin, I., L. Rutberg, M. Curvall, and C.R. Enzell, "Screening of Tobacco Smoke Constituents for Mutagenicity Using the Ames Test", *Toxicology*, 15:219-232 (1980).
- Fortin, C., Personal communication, Phthalate Ester Task Group Leader, Commercial Chemicals Branch, Environment Canada (1993).
- Foster, P.M.D., L.V. Thomas., M.W. Cook, and S.D. Gangolli, "Study of the Testicular Effects and Changes in Zinc Excretion Produced by Some n-alkyl Phthalates in the Rat", *Toxicol. Appl. Pharmacol.*, 54:392-398 (1980).

- Germain, A. and C. Langlois, "Contamination des eaux et des sediments 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).
- Gilioli, R., C. Bulgheroni, T. Terrana, G. Filippini, N. Massetto, and R. Boeri, "A Neurological, Electromyographic and Electroneurographic Study in Subjects Working at the Production of Phthalate Plasticizers: Preliminary Results", *Medicina del Lavoro.*, 69:620-631 (in Italian, from an English abstract) (1978).
- Gray, T.J.B. and K.R. Butterworth, "Testicular Atrophy Produced by Phthalate Esters", *Arch. Toxicol. Suppl.*, 4:452-455 (1980).
- Halina, G.P., Letter from G.P. Halina, Environment Alberta to K. Taylor, Environment Canada, (April 27, 1993).
- Hardin, B.D., R.L. Schuler, J.R. Burg, G.M. Booth, K.P. Hazelden, K.M. MacKenzie, V.J. Piccirillo, and K.N. Smith, "Evaluation of 60 Chemicals in a Preliminary Developmental Toxicity Test, *Teratogen. Carcinogen. Mutagen.*, 7:29-48 (1987).
- Harris, D.K., "Health Problems in the Manufacture and Use of Plastics", *Br. J. Indust. Med.*, 10:255-268 (1953).
- Health and Welfare Canada, "Derivation of Maximum Acceptable Concentrations and Aesthetic Objectives for Chemicals in Drinking Water", in: *Guidelines for Canadian Drinking Water Quality - Supporting Documentation*, Environmental Health Directorate, Bureau of Chemical Hazards (1989).
- Heindel, J.J., D.K. Gulati, R.C. Mounce, S.R. Russell, and J.C. Lamb IV, "Reproductive Toxicity of Three Phthalic Acid Esters in a Continuous Breeding Protocol", *Fund. Appl. Toxicol.*, 12:508-518 (1989).
- 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., R.S. Boethling, W.F. Jarvis, W.M. Meylan, and E.M. Michalenko, *Handbook of Environmental Degradation Rates*, Lewis Publishers Inc., Chelsea, MI (1991).
- Khanna, S., R.K.S. Dogra, M.C. Bhatnagar, V. Sundaraman, L.J. Shukla, S.N. Srivastava, and R. Shanker, "Light and Electronmicroscopic Changes in Testis of Di-octyl Phthalate Treated Rats", *J. Environ. Biol.*, 10:355-362 (1989).

- Khanna, S., R.K.S. Dogra, M.C. Bhatnagar, L.J. Shukia, S.N. Srivastava, and R. Shanker, "Nephrotoxicity of Di-octyl Phthalate Treated Rats. Histological Evidence", *J. Environ. Biol.*, 11:27-34 (1990).
- Klöppler, 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).
- 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, pp. 243-281(1989).
- Kuarata, H., "Studies on the Mutagenic Effects of Phthalates", Report to Ministry of Health and Welfare (Japan), Scientific Research Food Hygiene Program (1975). [(cited in Omori, Y., "Recent Progress in Safety Evaluation Studies on Plasticizers and Plastics and their Controlled Use in Japan", *Environ. Health Perspect.*, 17: 203-209 (1976)].
- Lake, B.G., W.R. Pels Rijcken, T.J.B. Gray, J.R. Foster, and S.D. Gangolli, "Comparative Studies of the Hepatic Effects of Di- and Mono-*n*-octyl Phthalates, Di-(2-ethylhexyl) Phthalate and Clofibrate in the Rat", *Acta Pharmacol. Toxicol.*, 54:167-176 (1984).
- Law, Sigurdson & Associates, "Chemical Use Analysis: Di(*n*-octyl) Phthalate in Canada", Report prepared for Environment Canada, Chemicals Evaluation Division, Ottawa, Ont. (April, 1993).
- Lawrence, W.M., M. Malik, J.E. Turner, A.R. Singh, and J. Autian, "A Toxicological Investigation of Some Acute, Short-term and Chronic Effects of Administering Di-2-ethylhexylphthalate (DEHP) and Other Phthalate Esters", *Environ. Res.*, 9:1-11(1975).
- MENVIQ, Ministère de l'Environnement de Québec, Unpublished data (1993).
- Mabey, W.R., J.H. Smith, R.T. Podoll, H.L. Johnson, T. Mill, T.-W. Chou, J. Gates, I. Waight Partridge, H. Jaber, and D. Vandenberg, "Aquatic Fate Process Data for Organic Priority Pollutants", U.S. Environmental Protection Agency, EPA 440/4-81-014, NTIS PB87-169090, Washington, DC (1982).
- Malette, F.S. and E. von Haam, "Studies on the Toxicity and Skin Effects of Compounds Used in the Rubber and Plastics Industries. II. Plasticizers", *Arch. Ind. Hyg. Occup. Med.*, 6:231-236 (1952).
- Mann, A.H., S.C. Price, F.E. Mitchell, P. Grasso, R.H. Hinton, and J.W. Bridges, "Comparison of the Short-term Effects of Di(2-ethylhexyl) Phthalate, Di(*n*-hexyl) Phthalate and Di(*n*-octyl) Phthalate in Rats", *Toxicol. Appl. Pharmacol.*, 77:116-132(1985).

- Mathur, S.P., "Phthalate Esters in the Environment: Pollutants or Natural Products?", *J. Environ. Qual.*, 3:189-197 (1974).
- Mayer, F.L., Jr., D.L. Stalling, and J.L. Johnson, "Phthalate Esters as Environmental Contaminants", *Nature*, 238:411-413 (1972).
- McCarthy, J.F. and D.K. Whitmore, "Chronic Toxicity of Di-*n*-butyl and Di-*n*-octyl Phthalate to *Daphnia magna* and the Fathead Minnow", *Environ. Toxicol. Chem.*, 4:167-179 (1985).
- Milkov, L.E., M.V. Aldyreva, T.B. Popova, K.A. Lopukhova, Y.L. Makarenko, L.M. Malyar, and T.K. Shakova, "Health Status of Workers Exposed to Phthalate Plasticizers in the Manufacture of Artificial Leather and Films Based on PVC", *Environ. Health Perspect. Exp. Iss.*, 3:175-178 (1973).
- Morrissey, R.E., J.C. Lamb IV, R.W. Morris, R.E. Chapin, D.K. Gulati, and J.J. Heindel, "Results and Evaluations of 48 Continuous Breeding Reproduction Studies Conducted in Mice", *Fund. Appl. Toxicol.* 13:747-777 (1989).
- 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 (September, 1985).
- NAQUADAT (National Water Quality Data Bank), Surveys and Information Systems Branch, Ecosystem Sciences and Evaluation Directorate, Environment Canada (1993).
- NIOSH, *Registry of Toxic Effects of Chemical Substances. 1985-1986 Edition*, DHHS (NIOSH) Pub; No. 87-114, National Institute for Occupational Safety and Health, Cincinnati, OH (1987).
- Niagara River Data Interpretation Group, "Joint Evaluation of Upstream/downstream Niagara River Monitoring Data, 1988-1989", edited by K.W. Kuntz, Environmental Quality Branch, Ontario Region, Environment Canada, Burlington, Ont., 72 pp. (1990)
- OME, "MISA, Twelve-month Monitoring Data Report. Organic Chemical Manufacturing Sector (Oct. 1, 1989 to September 30, 1990)", Water Resources Branch, Ontario Ministry of the Environment (January, 1992).
- Oishi, S. and K. Hiraga, "Testicular Atrophy Induced by Phthalic Acid Esters: Effect on Testosterone and Zinc Concentrations", *Toxicol. Appl. Pharmacol.*, 53:35-41 (1980).
- Oishi, S., "Effects of Phthalic Acid Esters on Testicular Mitochondrial Functions in the Rat", *Arch. Toxicol.*, 64:143-147 (1990).

- Perwak, J., M. Goyer, M. Schimke, G. Eschenroeder, A. Fiksel, K. Scow, and D. Wallace, "An Exposure and Risk Assessment for Phthalate Esters", Prepared for U.S. Environmental Protection Agency, EPA-440/4-81-020, PB85-211936, Washington, DC (1981).
- Pieckacz, H., "The Influence on Rat Organism of Dibutyl Phthalate and Dioctyl Phthalate Administered Perorally for a Prolonged Period. III. The Influence on the Fertility and Foetal Development", *Rocz. Panstw. Zakl. Hig.*, 22(5):519-526 (in Polish, with English abstract) (1971).
- 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)
- 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)
- SRI International, "1991 Directory of Chemical Producers - Canada", SRI International, Menlo Park, CA, 149 pp. (1991)
- Sanborn, J.R., R.L. Metcalf, C.-C. Yu, and P.-Y. Lu, "Plasticizers in the Environment: The Fate of Di-*n*-octylphthalate (DOP) in Two Model Ecosystems and Uptake and Metabolism of DOP by Aquatic Organisms", *Arch. Environ. Con tam. Toxicol.*, 3:244-255 (1975).
- Seed, J.L., "Mutagenic Activity of Phthalate Esters in Bacterial Liquid Suspension Assays", *Environ. Health Perspect.*, 45: 111-114 (1982).
- Singh, A.R., W.H. Lawrence, and J. Autian, "Teratogenicity of Phthalate Esters in Rats", *J. Pharmac. Sci.*, 61:51-55 (1972).
- Swain, L.G. and D.G. Walton, "Fraser River Estuary Monitoring. Report on the 1988 Fish Monitoring Program", British Columbia Ministry of Environment, 147 pp. (1989)
- U.S. EPA, "Methods for Organic Chemical Analysis of Municipal and Industrial Wastewater", U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory, EPA 600/4-82-057, NTIS PB83-201798, Cincinnati, OH (July, 1982).
- Veith, G.D., D. DeFoe, and M. Knuth, "Structure-activity Relationships for Screening Organic Chemicals for Potential Ecotoxicity Effects", *Drug Metab. Rev.*, 15:1295-1303 (1984).

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

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

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

Yoshikawa, K., A. Tanaka, T. Yamaha, and H. Kurata, "Mutagenicity Study of Nine Monoalkyl Phthalates and a Dialkyl Phthalate Using *Salmonella typhimurium* and *Escherichia coli*", *Food and Chem. Toxicol.*, 21(2):221-223 (1983).

Zdražil J. and F. Picha, "Phthalic Acid Esters in the Atmosphere during the Processing of Polyvinyl Chloride", *Pracovni Lékarstvi.*, 17(6):257-260 (English abstract) (1965).

Zeiger, E., S. Haworth, K. Mortelmans, and W. Speck, "Mutagenicity Testing of Di(2-ethylhexyl) Phthalate and Related Chemicals in *Salmonella*", *Environ. Mutagen.*, 7:213-232 (1985).