

Di(2-ethylhexyl)phthalate in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

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Preface

One of the primary goals of WHO and its member states is that “all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water.” A major WHO function to achieve such goals is the responsibility “to propose regulations, and to make recommendations with respect to international health matters”

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-Water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO Guidelines for drinking-water quality (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A “final task force” meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health

Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues, and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

Acknowledgements

The work of the following coordinators was crucial in the development of this background document for development of WHO *Guidelines for drinking-water quality*:

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The efforts of all who helped in the preparation and finalization of this document, including those who drafted and peer reviewed drafts, are gratefully acknowledged.

The convening of the experts meetings was made possible by the financial support afforded to WHO by the Danish International Development Agency (DANIDA), Norwegian Agency for Development Cooperation (NORAD), the United Kingdom Overseas Development Administration (ODA) and the Water Services Association in the United Kingdom, the Swedish International Development Authority (SIDA), and the following sponsoring countries: Belgium, Canada, France, Italy, Japan, Netherlands, United Kingdom of Great Britain and Northern Ireland and United States of America.

GENERAL DESCRIPTION

Identity

CAS no.: 117-81-7

Molecular formula: C₂₄H₃₈O₄

Di(2-ethylhexyl)phthalate (DEHP) is also known as 1,2-benzenedicarboxylic acid bis(2-ethylhexyl)ester, bis(2-ethylhexyl) phthalate, and dioctyl phthalate (DOP).

Physicochemical properties (1,2) [Conversion factor in air: 1 ppm = 1.59 mg/m³]

<i>Property</i>	<i>Value</i>
Physical state	Light-coloured, viscous liquid
Melting point	-46 °C (pour-point)
Boiling point	370 °C at 101.3 kPa
Density	0.98 g/cm ³ at 20 °C
Vapour pressure	0.056 × 10 ⁻⁷ kPa at 20 °C
Water solubility	23–340 µg/litre at 25 °C
Log octanol–water partition coefficient	4.88

Organoleptic properties

DEHP is odourless.

Major uses

DEHP is used primarily as a plasticizer in many flexible polyvinyl chloride products and in vinyl chloride co-polymer resins. It is also used as a replacement for polychlorinated biphenyls in dielectric fluids for small (low-voltage) electrical capacitors (1,2).

Environmental fate

DEHP is insoluble in water (23–340 µg/litre) (2,3). Because of the readiness with which it forms colloidal solutions, its "true" solubility in water is believed to be 25–50 µg/litre. DEHP has a very low volatilization rate. Photolysis in water is thought to be a very slow process (2). Hydrolysis half-lives of over 100 years at pH 8 and 30 °C have been found. DEHP biodegrades rapidly in water and sludges, especially under aerobic conditions; degradation of 40–90% in 10–35 days has been found. Biodegradation in sediment and water under anaerobic conditions is assumed to be very slow; however, the available information is contradictory (3).

ANALYTICAL METHODS

DEHP can be determined by gas chromatography with electron-capture detection; the method has a detection limit of 0.1 ng (4). The detection limit with flame ionization detection is 1 µg/litre. The identity of the compound can be confirmed by mass spectrometry with "single-ion" monitoring, especially when electron-capture detection is used (3,5).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

It should be noted that some reported occurrences of DEHP in certain matrices have been found to result from contamination of the latter by plasticizer extracted from plastic tubing or other equipment (1,2).

Air

DEHP has been detected in ocean air at levels ranging from 0.4 ng/m³ over the Gulf of Mexico to 2.9 ng/m³ over the North Atlantic (1,2). Ambient air above the Great Lakes contains an average of 2 ng/m³ (range 0.5–5 ng/m³) (6). In the North Pacific, the average concentration in air was 1.4 ng/m³ (range 0.3–2.7 ng/m³) (3).

In city air, concentrations of phthalates in atmospheric particulate matter range from 5 to 132 ng/m³ (7,8), but a concentration of 300 ng/m³ has been reported in the vicinity of a municipal incinerator (9). Where DEHP is used inside houses, the concentration increases with temperature but decreases with humidity; after 4 months, the concentration will be about 0.05 mg/m³ (5).

Water

In Japan, DEHP was detected in 71 out of 111 samples of rainwater; average concentrations were in the range 0.6–3.2 µg/litre, the highest average value being found in an industrial town (5). In the North Pacific, the average concentration in rainwater was 55 ng/litre (range 5.3–213 ng/litre) (3).

DEHP has been detected in water from several rivers at levels of up to 5 µg/litre (1,2,5). In the Netherlands, sediments of the Rhine and the Meuse contained 1–70 and 1–17 mg/kg, respectively (1). The average concentration in water from the Rhine in 1986 was 0.3 µg/litre (range 0.1–0.7 µg/litre) and in suspended particulate matter 20 mg/kg (range 10–36 mg/kg) (10). In surface water near industrial areas, levels of up to 300 µg/litre were found (1,2).

In contaminated groundwater in the Netherlands, 20–45 µg of DEHP per litre was reported (11). A groundwater sample from New York State contained 170 µg/litre (12).

DEHP was detected in tapwater in two cities in the USA at an average level of 1 µg/litre and in Japan at levels in the range of 1.2–1.8 µg/litre. In “finished” drinking-water in two cities in the USA, average concentrations were 0.05–11 µg/litre; in several major eastern cities in the USA, average levels were below 1 µg/litre. The highest concentrations in drinking-water (up to 30 µg/litre) were reported in older surveys (1975) (1,2).

Food

Levels of DEHP below 1 mg/kg were detected in fish in different parts of the USA; most fish contained less than 0.2 mg/kg. In a sampling of a wide variety of foods, the highest levels were found in milk (31.4 mg/litre, fat basis) and cheese (35 mg/kg, fat basis). In a study of the migration of DEHP from plastic packaging films, it was found in tempura (frying) powder (0.11–68 mg/kg), instant cream soup (0.04–3.1 mg/kg), fried potato cake (0.05–9.1 mg/kg), and orange juice (0.05 mg/kg) (1,2).

Analysis of bottled beverages with polyvinyl chloride seals plasticized with DEHP demonstrated that very little migration occurs; all the concentrations reported were less than 0.1 mg/kg, the vast majority being below 0.02 mg/kg. Draught beer samples contained similar levels of DEHP (<0.01–0.04 mg/kg) (13).

Estimated total exposure and relative contribution of drinking-water

Exposure among individuals may vary considerably because of the wide variety of products into which DEHP is incorporated. The estimated average daily adult dose from the consumption of commodities highly likely to be contaminated (such as milk, cheese, margarine) is about 200 µg (14). Levels in community drinking-water are generally thought to

be negligible, although there may be individual instances of high levels of contamination. Exposure from air is negligible compared with that associated with food (e.g. when the concentration in city air is 50 ng/m³, the daily exposure will be less than 1 µg). Patients undergoing kidney dialysis may be exposed to high levels of DEHP; it is estimated that each patient will receive up to 90 mg per treatment (15). Exposure also occurs during the transfusion of stored whole blood. Concentrations will be low in frozen plasma. The Netherlands standard for the migration of DEHP from blood containers is 10 mg of DEHP per 100 ml of ethanol (16).

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

In rats, DEHP is readily absorbed from the gastrointestinal tract after oral administration. It is hydrolysed to a large extent to mono(2-ethylhexyl)phthalate (MEHP) with release of 2-ethylhexanol (EH) before intestinal absorption (17). Absorption is lower in primates (including humans). In rats, over 90% was excreted in urine after dietary administration, whereas only 0.9% was excreted in urine by marmosets (2,18). In humans, 11–25% of an ingested dose was found in urine (2,19).

DEHP undergoes further modification after hydrolysis to the monoester. Several species (primates, including humans, and some rodent species) form glucuronide conjugates with the monoester, but rats appear unable to do so. In rats, the residual 2-ethylhexyl moiety is oxidized extensively (17). In mice and rats, urinary metabolites consist primarily of terminal oxidation products (diacids, ketoacids); in primates (monkeys, humans), they consist primarily of unoxidized or minimally oxidized products (MEHP, hydroxyacid) (18).

DEHP and its metabolites are extensively distributed throughout the body in rodents, the highest levels being found in the liver and adipose tissue. Little or no accumulation occurs in rats. Estimated half-lives for DEHP and its metabolites in rats are 3–5 days for fat and 1–2 days for other tissues (20).

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Acute exposure

DEHP has a low acute oral toxicity in animals; the oral LD₅₀ for mice and rats is over 20 g/kg of body weight (1).

Short-term exposure

Liver and testes appear to be the main target organs for DEHP toxicity. DEHP can cause functional hepatic damage, as reflected by morphological changes, alterations in energy-linked enzyme activity, and changes in lipid and carbohydrate metabolism. The most striking effect is proliferation of hepatic peroxisomes (21).

In short-term oral studies in rats with dosing periods ranging from 3 days to 9 months and dose levels ranging from 50 to 25 000 mg/kg of diet (2.5–2500 mg/kg of body weight per day), doses greater than 50 mg/kg of body weight per day caused a significant dose-related increase in liver weight, a decrease in serum triglyceride and cholesterol levels, and microscopic changes in the liver, namely periportal accumulation of fat and mild centrilobular loss of glycogen. An initial burst of DNA synthesis in the liver (indicative of liver hyperplasia) followed by a decrease in liver DNA content (indicative of liver hypertrophy) were observed. Changes to peroxisomes, mitochondria, and endoplasmic reticulum in the liver were seen. Significant increases in hepatic peroxisomal enzyme activities and in the number of peroxisomes in the liver were found (22–26). NOAELs for changes in liver weight were 25 mg/kg of body weight per day by gavage (23) and 500 mg/kg of diet (25 mg/kg of

body weight per day) (22). Morton (22) found significantly decreased serum triglyceride levels at 50, 100, and 500 mg/kg of diet, whereas Barber et al. (25) did not find this effect at 1000 and 100 mg/kg of diet.

NOAELs for peroxisomal proliferation (based on changes in peroxisome-related enzyme activities or ultramicroscopic changes) were 25 mg/kg of body weight per day (LOAEL 100 mg/kg of body weight per day) in a 14-day gavage study in Sprague-Dawley rats (23), 50 mg/kg of diet (2.5 mg/kg of body weight per day) in a 7-day study in Sprague-Dawley rats (22) (LOAEL 100 mg/kg of diet or 5 mg/kg of body weight per day), and 100 mg/kg of diet (10 mg/kg of body weight per day) in a 3-week study in F344 rats (LOAEL 1000 mg/kg of diet or 100 mg/kg of body weight per day) (25). Marked species differences in the occurrence of peroxisomal proliferation exist, the available information suggesting that primates, including humans, are less sensitive to this effect than rodents (26).

Changes in the kidneys and thyroid in Wistar rats have also been observed. The effects on the thyroid (increased activity accompanied by a decrease of plasma T₄) were observed at doses of 10 000 mg/kg of diet (1000 mg/kg of body weight per day) and higher (24).

Long-term exposure

In 2-year oral toxicity studies in rats, doses of 100–200 mg/kg of body weight and higher caused growth depression, liver and kidney enlargement, microscopic changes in the liver, and testicular atrophy. The NOAEL was 50–65 mg/kg of body weight (2,27,28). Increased activities of peroxisome-associated enzymes were found in another study even at the lowest dose level of 200 mg/kg of diet (10 mg/kg of body weight per day) (26).

Reproductive toxicity, embryotoxicity, and teratogenicity

Testicular effects, namely atrophy, tubular degeneration, and inhibition or cessation of spermatogenesis, were seen in mice, rats, guinea-pigs, and ferrets (29), supposedly caused by MEHP (2,30). In rats, testicular changes were seen at oral doses above 100 mg/kg of body weight per day (31).

In a reproduction study in mice, complete suppression of fertility in both sexes was seen at 0.3% DEHP in the diet (430 mg/kg of body weight per day). At 0.1% in the diet (140 mg/kg of body weight per day), significantly reduced fertility indices, again in both sexes, were observed, but no effects on fertility were seen at 0.01% in the diet (15 mg/kg of body weight per day) (26).

In mice, fetal mortality, fetal resorption, decreased fetal weight, neural tube effects, and skeletal disorders (exencephaly, spina bifida, open eyelid, exophthalmia, major vessel malformations, club-foot, and delayed ossification) were seen in teratogenicity studies. The NOAEL for these effects was 0.025% in the diet (35 mg/kg of body weight per day) (32). The LOAELs were 0.05 mg/kg of body weight per day (33) and 0.05% in diet (70 mg/kg of body weight per day) (32). MEHP was more active than DEHP, which may, therefore, act as a result of conversion into MEHP. However, it was also hypothesized that 2-ethylhexanoic acid, the oxidation product of 2-ethylhexanol, was the proximate teratogen, as indicated in studies with rats (26).

Rats were less susceptible than mice to DEHP-related adverse effects on fetal development. At oral doses above 200 mg/kg of body weight per day, decreased fetal weights and an increased number of resorptions were observed (34,35). Teratogenic effects were not observed in F344 rats at dose levels of 0.5–2.0% in the diet (250–1000 mg/kg of body weight per day). Embryofetal toxicity was seen at levels of 1.0% in the diet and higher (=500 mg/kg of body weight per day) (32).

Mutagenicity and related end-points

DEHP showed negative results in most short-term mutagenicity studies *in vitro* and *in vivo* (i.e. it did not induce gene mutations in bacterial systems, eukaryotic systems, or mammalian systems *in vitro*, or chromosomal aberrations or sister chromatid exchange in mammalian cells *in vitro*, or chromosomal aberrations in somatic or germ cells *in vivo*). No evidence was found for a covalent interaction of DEHP with DNA, the induction of single-strand breaks in DNA, or unscheduled DNA repair. However, DEHP induced aneuploidy in eukaryotic cells *in vitro* and cell transformations in mammalian cells *in vivo* and *in vitro* (20,36).

In general, MEHP and EH did not induce gene mutations in bacteria or mammalian cells *in vitro*. Contradictory results were reported for MEHP with respect to the induction of chromosomal aberrations and sister chromatid exchange in mammalian cells *in vitro*, but EH showed negative results in these test systems. In mammalian cells *in vivo*, MEHP and EH did not induce chromosomal aberrations (36).

Carcinogenicity

In a 2-year oral study in mice, increased incidences of hepatocellular carcinomas were seen in males and females at 3000 and 6000 mg/kg of diet. Rats given 6000 or 12 000 mg of DEHP per kg of diet for 2 years showed increased incidences of hepatocellular carcinomas and hepatic neoplastic nodules (2,37).

It has been suggested that the increased incidences of liver tumours in mice and rats in chronic bioassays are caused by the prolonged proliferation of hepatocellular peroxisomes and the enhanced production of the peroxisomal metabolic by-product, hydrogen peroxide. Primates, including humans, are far less sensitive to peroxisomal proliferation than mice and rats (38).

In *in vivo* studies with B6C3F₁ mice, DEHP had no tumour-initiating activity in the liver but, in the same strain, showed promoting activity, also in the liver, as indicated by an increase in focal hepatocellular proliferative lesions, including hyperplastic foci and neoplasms. In rats, *in vivo* studies showed neither tumour-initiating or promoting activity, nor sequential syncarcinogenic activity in the liver (26).

EFFECTS ON HUMANS

Two male volunteers dosed with 10 g of DEHP experienced mild gastric disturbances and moderate catharsis; a 5-g dose had no effect (1,2).

Dialysis patients receiving approximately 150 mg of DEHP intravenously per week were examined for liver changes. At 1 month, no morphological changes were observed by liver biopsy but, at 1 year, peroxisomes were reported to be "significantly higher in number" (20).

A high incidence of polyneuropathy was reported in studies on industrial workers exposed to different phthalic acid esters, including DEHP (39), but this was not confirmed in another study (40). In a small cohort study, eight deaths were observed among 221 workers exposed to DEHP for periods of 3 months to 24 years. One carcinoma of the pancreas and one bladder papilloma were reported. The study was considered to be inadequate to provide proof of a causal association (1,2).

Occupational exposure to 0.01–0.016 mg of DEHP per m³ over 10B34 years did not cause an increase in the frequency of chromosomal aberrations in blood leukocytes (1,2).

GUIDELINE VALUE

IARC has concluded that DEHP is possibly carcinogenic to humans (Group 2B) (41). Induction of liver tumours in rodents by DEHP was observed at high dietary dose levels. A relationship between the occurrence of hepatocellular carcinoma and prolonged induction of peroxisomal proliferation in the liver was suggested, although the mechanism of action is still unknown. On the basis of toxicity data in experimental animals, the induction of peroxisomal proliferation in the liver seems to be the most sensitive effect of DEHP, and the rat appears to be the most sensitive species. The available literature suggests that humans are less sensitive to chemically induced peroxisomal proliferation than rodents.

In 1988, JECFA evaluated DEHP and recommended that human exposure to this compound in food be reduced to the lowest level attainable. The Committee considered that this might be achieved by using alternative plasticizers or alternatives to plastic material containing DEHP (26).

In view of the absence of evidence for genotoxicity and the suggested relationship between the occurrence of hepatocellular carcinomas and prolonged proliferation of liver peroxisomes, a TDI was derived using the lowest observed NOAEL of 2.5 mg/kg of body weight per day based on peroxisomal proliferation in the liver in rats (22). Although the mechanism for hepatocellular tumour induction is not fully resolved, using a NOAEL derived from the species by far the most sensitive with respect to the particularly sensitive end-point of peroxisomal proliferation justifies the use of an uncertainty factor of 100 (for inter- and intraspecies variation). Consequently, the TDI is 25 µg/kg of body weight. This yields a guideline value of 8 µg/litre (rounded figure), allocating 1% of the TDI to drinking-water.

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