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English only

Di(2-ethylhexyl)adipate in Drinking-water

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

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

Di(2-ethylhexyl)adipate in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, is an update of the background document published in the second edition of the GDWQ. The update was prepared by Mr J. Fawell, United Kingdom, to whom special thanks are due.

The work of the following working group coordinators was crucial in the development of this document and others in the third edition:

Mr J.K. Fawell, United Kingdom (*Organic and inorganic constituents*)
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Prof. Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
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The contribution of peer reviewers is greatly appreciated. The draft text was posted on the world wide web for comments from the public. The revised text and the comments were discussed at the Final Task Force Meeting for the third edition of the GDWQ, held on 31 March to 4 April 2003, at which time the present version was finalized. The input of those who provided comments and of participants in the meeting is gratefully reflected in the final text.

The WHO coordinators were as follows:

Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters, and formerly WHO European Centre for Environmental Health
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Ms C. Vickers provided a liaison with the International Chemical Safety Programme, WHO Headquarters.

Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

Acronyms and abbreviations used in the text

CAS	Chemical Abstracts Service
DEHA	di(2-ethylhexyl)adipate
DNA	deoxyribonucleic acid
IARC	International Agency for Research on Cancer
LD_{50}	median lethal dose
MEHA	mono(2-ethylhexyl)adipate
NOAEL	no-observed-adverse-effect level
PVC	polyvinyl chloride
TDI	tolerable daily intake
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	103-23-1
Molecular formula:	$C_{22}H_{42}O_4$

Di(2-ethylhexyl)adipate is also known as DEHA, bis(2-ethylhexyl)adipate and dioctyladipate.

1.2 Physicochemical properties (1–3)

Property	*Value*
Physical state	Light-coloured oily liquid
Melting point	-67.8 °C
Boiling point	417 °C at 101.3 kPa
Density	0.922 g/cm^3 at 25 °C
Vapour pressure	<0.00133 kPa at 20 °C
Water solubility	Insoluble (0.78 ± 0.16 mg/litre)
Log octanol–water partition coefficient	6.3

1.3 Major uses

DEHA is used mainly as a plasticizer for synthetic resins such as PVC, but significant amounts are also used as a lubricant and for hydraulic fluids (*1*).

1.4 Environmental fate

Model experiments with activated sewage sludge systems have demonstrated the essentially complete biodegradation, measured as carbon dioxide evolution, of relatively high concentrations of DEHA in 35 days (*3,4*). Because of its low water solubility, DEHA released into the environment would be expected to partition to solids (biota, sediment, soil). Under ideal equilibrium conditions, it would partition mainly to the atmosphere and to terrestrial soil, and less than 1% of environmental DEHA would be found in the aquatic environment (*3*).

2. ANALYTICAL METHODS

DEHA in tap water and surface water has been determined by gas chromatography with flame ionization detection or identification by mass spectrometry. In surface water, the detection limit is stated to be 0.2 µg/litre (*3*), although lower levels have been reported for both surface water (*5*) and drinking-water (*6*).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Water

DEHA was found at µg/litre levels in two out of five samples of finished water from a waste treatment plant in the USA (*6*). A survey of 23 major rivers and lakes in the USA showed that 7% of the samples contained DEHA at levels ranging from 0.25 to 1.0 µg/litre (*3*). Water samples from the Great Lakes contained a maximum level of 7.0 µg/litre (*5*). In Europe, DEHA has been identified as a trace-level contaminant of the Rhine (*7*). Finished drinking-water in five cities in the USA had levels of about 0.001–0.1 µg/litre (*6,8,9*).

3.2 Food

Food is the major source of exposure of the general population to DEHA because of its migration, particularly to fatty foods such as cheese and meat, from PVC films used for food packaging that have been plasticized with it. The estimated daily intake of DEHA through the diet in the United Kingdom is 16 mg (*10*); in the USA, it has been estimated to be as high as 20 mg (US Food and Drug Administration, personal communication, 1981).

3.3 Estimated total exposure and relative contribution of drinking-water

Air and drinking-water are insignificant sources of human exposure to DEHA compared with the intake via food.

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

DEHA appears to be readily absorbed when given orally to rats and mice. It is widely distributed in the body; the highest levels have been reported in adipose tissue, liver and kidney (*11,12*). Transplacental transport of DEHA has been noted (*12*).

DEHA is initially hydrolysed to mono(2-ethylhexyl)adipate (MEHA), adipic acid and 2-ethylhexanol, which are excreted as such or further oxidized to several different compounds before being eliminated in the expired air, urine or faeces of experimental animals. Major metabolites of DEHA are MEHA and its glucuronide (monkey), the glucuronide of 2-ethylhexanoic acid (mouse, rat) and adipic acid (mouse, rat). Single oral doses of DEHA seem to be completely excreted by rats, mice and monkeys in 48 h (*11,13*).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

The acute oral toxicity of DEHA is low. The oral LD_{50} has been estimated to be 45 g/kg of body weight in male rats, 25 g/kg of body weight in female rats, 15 g/kg of body weight in male mice and 25 g/kg of body weight in female mice (*14*).

5.2 Short-term exposure

Short-term (3–4 weeks) mouse and rat toxicity studies have demonstrated that high dietary levels of DEHA (≥6000 mg/kg) induce liver toxicity, including increased liver weights, histopathological liver changes and proliferation of liver peroxisomes, accompanied by increased activities of catalase and of enzymes involved in the oxidation of fatty acids as well as hypolipidaemia. DEHA-induced peroxisomal proliferation with accompanying biochemical events was found to be a dose-dependent phenomenon. A NOAEL of 100 mg/kg of body weight per day can be identified from these studies (*15–17*).

A 13-week toxicity study was conducted in F344 rats and $B6C3F_1$ mice at dietary concentrations of up to 25 000 mg of DEHA per kg. At 25 000 mg/kg, decreased weight gain was observed in both species and sexes. At 12 500 mg/kg, male and female rats as well as male mice showed slightly reduced body weight gain. At 6300 mg/kg, body weight gain was decreased in female mice and male rats. No compound-related increased mortality, histopathological changes or reduction in feed consumption were observed (*14*).

5.3 Long-term exposure

In a 103-week study in which DEHA was administered to F344 rats and $B6C3F_1$ mice at dietary levels of 12 000 or 25 000 mg/kg, no dose-related effect on longevity was seen. A dose-related depression of growth rate was observed in mice. Except in the liver, where tumours developed, no histopathological changes were observed in the mouse. Growth rate was depressed in rats fed 25 000 mg of DEHA per kg. No DEHA-related histopathological changes were seen in rats (*14*).

5.4 Reproductive and developmental toxicity

A fertility study was performed in which male and female Wistar rats were fed DEHA in the diet from 10 weeks before mating up to 36 days postpartum at levels of 300, 1800 or 12 000 mg/kg. At 12 000 mg/kg of diet, body weight gain was marginally reduced in females, and liver weights of both male and female parental animals were significantly increased. There were no effects on male or female fertility or on gestation length. At the highest dose level, total litter weights, body weight gain of pups and mean litter size were reduced. No effect on pup survival was found at any treatment level. No treatment-related macroscopic abnormalities were found in the pups (*18*).

In a teratogenicity study, pregnant Wistar rats were fed DEHA in the diet at levels of 300, 1800 or 12 000 mg/kg, corresponding to daily doses of 28, 170 or 1080 mg/kg of body weight, on days 1–22 of gestation. Administration of 12 000 mg/kg resulted in slight maternal toxicity, expressed as a small reduction in body weight gain. There were no effects at any dietary level on fetal weight, litter weight or number of intrauterine deaths. At the highest dose level, a small increase in pre-implantation loss as well as a minimal increase in post-implantation loss were noted. Incidences of major or minor external or visceral effects were low and were not increased by treatment with DEHA. However, two visceral variants (dilated and kinked ureter) were observed in increasing incidences in a dose-related manner at the two highest dose levels. Minor skeletal defects, indicating slightly poorer ossification, were also increased in a dose-related manner at the two highest dietary DEHA levels. No fetal effects were noted at 300 mg of DEHA per kg of diet. A NOAEL of 28 mg/kg of body weight can be identified from this study (*19*).

5.5 Mutagenicity and related end-points

DEHA shows no structural alerts for genotoxicity. It was negative in the *Salmonella* assay *in vitro* and in the mouse bone marrow assay for clastogenicity (*20,21*). Orally administered DEHA does not bind covalently to mouse liver DNA (*22*).

5.6 Carcinogenicity

In a 103-week carcinogenicity study, DEHA was administered to F344 rats and $B6C3F_1$ mice in the diet at levels of 12 000 or 25 000 mg/kg, equivalent to a daily intake of 600 or 1250 mg/kg of body weight in rats and 1715 or 3570 mg/kg of body weight in mice. No increased tumour incidences were noted in rats. An increased number of hepatocellular carcinomas was found in female mice at both doses. Hepatocellular adenomas and carcinomas combined occurred in high-dose mice of both sexes and in low-dose female mice at incidences that were dose-related and significantly higher than those in control mice. The association of liver tumours in male mice with the administration of DEHA was not considered to be conclusive because the increased number of liver tumours in males reflected only an increase in adenomas in the high-dose group and because the time to observation of tumours was not significantly different in dosed and control males (*14*).

As DEHA fails to elicit mutagenic or genotoxic responses in available test systems and does not form adducts with DNA, it may be an epigenetic carcinogen for which a dose threshold exists, probably related to its ability to induce peroxisomal proliferation. Liver tumours are likely to occur only at doses causing proliferation of peroxisomes; as there is a dose threshold for such proliferation, there is probably also a dose threshold for tumour development. The available information suggests that primates are less sensitive than rodents to chemically induced peroxisomal proliferation (*23*).

6. CONCLUSIONS

IARC has concluded that there is limited evidence that DEHA is carcinogenic in mice (*1*). It is not classifiable as to its carcinogenicity in humans (*24*). Although DEHA is carcinogenic in mice, its toxicity profile and lack of mutagenicity support the use of a TDI approach to setting a guideline value for DEHA in drinking-water.

A TDI of 280 µg/kg of body weight can be calculated by applying an uncertainty factor of 100 (for inter- and intraspecies variation) to the lowest observed NOAEL of 28 mg/kg of body weight in a fetotoxicity study in rats (*19*). This gives a health-based value of 80 µg/litre (rounded figure), based on an allocation of 1% of the TDI to drinking-water.

However, because DEHA occurs at concentrations well below those at which toxic effects are observed, it is not considered necessary to derive a health-based guideline value.

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