

Facts about phthalate toxicity in humans and their occurrence in alcoholic beverages

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Phthalates are esters of phthalic acid and aliphatic alcohol added to plastic to improve its softness, flexibility, and extensibility. They easily migrate from plastic products into the environment because of their physical and chemical properties. This review summarises their characteristics, distribution in the environment, monitoring, use, toxic effects on human health, regulatory limits in different matrices and products, and tolerable daily intake. The studies we have reviewed suggest that phthalates have a potential to affect reproduction and development in humans. Due to the inconsistent data, further studies are needed and, in the meantime, precautionary policies must be implemented. Here we draw attention to the methods of determining phthalate levels in alcoholic beverages and reported levels in plum spirits produced in Croatia. Legally produced and moderately consumed plum spirits do not seem to increase the risk of phthalate toxicity for human health. We conclude with recommendations for the effective monitoring of phthalate exposure in humans and for the implementation of alternative materials in alcohol production.

KEY WORDS: *alcoholic drinks; endocrine disruptors; maximum allowed concentration; tolerable daily intake*

Phthalates or phthalic acid esters are synthetic compounds that are mostly used as plasticisers to improve the softness, flexibility, and extensibility of a variety of plastic products. In plasticised polyvinyl chloride (PVC) products they make up to 40 % (w/w) (1). Phthalates can be added to numerous products for general use such as toys, personal care and household products, car cosmetics, various solvents, adhesives, glues, pesticides, food packaging, medical devices, electronics, tubing, and building materials (2, 3).

Because phthalates do not chemically bind to plastic they can be washed off, evaporate, and readily migrate to food, drinking water, and beverages, mostly from packaging materials. Other sources of contamination with phthalates include tubes, piping systems, and tanks used in wine and spirit production (3-9). Phthalates as industrial chemicals have become ubiquitous environmental pollutants due to their widespread use (2).

According to the United States Environmental Protection Agency (US EPA), the US alone produces or imports more than 213,000 t of phthalates a year (10). The European Union (EU) is trying to reduce the use of di(2-ethylhexyl) phthalate (DEHP) or replace it with alternative plasticisers (11). Table 1 shows the phthalates that are commonly used as plasticisers and solvents (12, 13).

Because of the potential hazard to human health and the environment, several international health and environment organisations have classified phthalates as priority pollutants. The EU has issued a list of chemicals with proven or potential endocrine system disrupting activity, such as dibutyl phthalate (DBP), benzylbutyl phthalate (BBP), and DEHP (14).

LITERATURE SEARCH AND SELECTION

According to PubMed, the first scientific article about the toxicity of ingested phthalate was published by Krauskopf in 1973 (15). To the best of our knowledge, in 1995 Leibowitz et al. (16) measured phthalate concentrations in alcoholic beverages for the first time. Until the 2000s less than 100 articles about phthalates were published annually, while more than 700 were published in 2016, indicating the growing interest in the phthalate issue.

Our literature search relied on the studies of the toxic effects of phthalates in humans, chemical properties, metabolism and characteristics of phthalates and occurrence of phthalates in alcoholic beverages reported in articles covered by the PubMed database. To filter them we used combinations of the following key words: phthalate exposure, metabolism, reproductive toxicity, developmental toxicity, respiratory toxicity, endocrine disruptors, carcinogenicity, alcoholic beverages, unrecorded alcohol,

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Table 1 Summary of the most common phthalates and their use (12, 13)

Name	Abbreviation	Uses	Products
Dimethyl phthalate	DMP	Primarily used as a solvent	Cosmetics, perfumes, creams, candles, shampoos
Diethyl phthalate	DEP	Primarily used as a solvent and fixative in fragrances	Cosmetics, perfumes, creams, candles, shampoos, pesticides,
Dibutyl phthalate	DBP	Primarily used as a solvent	Cosmetics, perfumes, creams, candles, shampoos, adhesives, paints
Benzylbutyl phthalate	BBP	Used as a plasticiser for PVC and as a solvent	Vinyl flooring, sealants, adhesives, glues, car care products, exterior paint, food conveyor belts, food wrapping material, wallpapers, shower curtains, modelling clay
Dibutyl phthalate	DBP	Used as a plasticiser for PVC and rubber. Also used as solvent and fixative in paints and cosmetics	Latex adhesives, sealants, car care products, cosmetics, inks and dyes, pesticides, food wrapping materials, home furnishing, paints, clothing, and pharmaceutical coatings
Di-n-octyl phthalate	DOP	Primarily used as a plasticisers for PVC	Floorings, bottle cap liners, conveyor belts, garden hoses, modelling clay
Di(2-ethylhexyl) phthalate	DEHP	Primarily used as a plasticiser for PVC	Toys, shoes, clothing, medical devices (plastic tubing and intravenous storage bags), furniture, automobile upholstery, electronics, plumbing, floor tiles, modelling clay
Diisononyl phthalate	DINP	Primarily used as a plasticiser for PVC	Teethers, balls, spoons, toys, gloves, drinking straws, rubber, adhesives, ink, sealant, paints and lacquers, food packaging, clothes, shoes, car and public transport interior, flooring
Diisodecyl phthalate	DIDP	Primarily used as a plasticiser for PVC	Electrical cords, leather for car interiors and PVC flooring

analytical methods, and tolerable daily intake. Furthermore, we limited this review to studies published in English in peer reviewed journals since 2000.

PHTHALATE PROPERTIES, EXPOSURE, AND METABOLISM

Phthalates used as plasticisers have been released in the environment for the last 50 years. Fortunately, they are prone to bio, photo, and anaerobic degradation, which means that they do not survive long in the environment (10, 17). Those having short alkyl groups, such as methyl and butyl group [e.g. dimethyl phthalate (DMP) and DBP], are water-soluble, while those with long alkyl or aromatic moieties in the side chains (e.g. BBP and DEHP) are less water-soluble. Because of the long chain lipophilicity, the highest levels of phthalates are found in fatty foods, such as fish, meat, dairy products, and vegetable oils (6). There are two types of phthalate contamination: contamination with phthalate residues, which are undesired in products (for example, phthalates in beverages and food), and contamination with phthalates intentionally added to products (for example, phthalates in soft PVC products).

For humans, the main route of exposure is ingestion, followed by inhalation, dermal, and intravenous exposure (2). General population is mainly exposed through food products contaminated with DEHP from plastic containers or wrappers. Exposure from drinking water and ambient air makes a minor contribution to the total daily intake. Phthalates also readily cross the placental barrier (2, 18–20). While low-molecular-weight and more volatile phthalates [diethyl phthalate (DEP), DBP, and BBP] present in consumer products as solvents and fixatives are absorbed primarily through skin or inhalation, phthalates used as plasticisers, like DEHP, are mainly ingested (2). An important source of DEP is unrecorded alcohol (homemade and illegally produced alcohol) present on market for human consumption. DEP is used to denature ethyl alcohol (21).

Most studies cover human exposure to DEHP as the most abundant phthalate in consumer products (22). If we exclude occupational and medical exposure, estimated adult DEHP intake ranges from 2 to 20 $\mu\text{g kg}^{-1}$ body weight per day, mostly from food (23). Some suggest that adult exposure to DEHP might be much greater than previously reported and that child exposure is two times higher than that of the adults because of the lower body mass and hand-mouth activities (24).

Phase 1 biotransformation products (metabolites) of phthalates in humans are monoesters, which can further be metabolised to oxidative products. In the phase 2 biotransformation, monoesters and oxidative metabolites can conjugate with glucuronide, and free and conjugated forms are eliminated from the body through urine and faeces (22, 25). Because of rapid metabolism phthalates do not accumulate significantly in tissues (26). Oxidative

metabolites of, e. g., DEHP are not detected in the environment (river water) or in plastic bags, but have been determined in human urine, which makes them suitable biomarkers for monitoring human exposure to phthalates and for evaluating toxicological risk to human reproduction (27).

PHTHALATE TOXICITY

Human exposure to phthalates is associated with endocrine disruption, delays in fertility, impairment in foetal development, increased risk of allergies, asthma, and cancer. The current tolerable daily intake (TDI) values for DEHP, DBP, and BBP established by the EU Scientific Committee for Toxicity, Ecotoxicity and the Environment (CSTEE) are based on studies of reproductive toxicity, since reproductive effects seem to have greater relevance for humans than the proliferation of peroxisome in rat liver causing cancer (28–31). One should be aware that phthalate levels determined in the general population are far below the threshold levels at which the first effects were observed in animals (24, 32). However, due to the shared sources and routes of human exposure to different chemical classes (e.g. polychlorinated biphenyls, polybrominated diphenyl ethers, currently used pesticides – organophosphates and pyrethroids, bisphenol A, and phthalates) it is challenging to identify which chemical or metabolite is responsible for certain health effect (33).

Reproductive and developmental toxicity

Phthalates that have a long alkyl side-chain in the *ortho* position have a potential for reproductive and developmental toxic effects in humans. These include DEHP>DBP>BBP (in the order of their toxic potential), as well as diisononyl phthalate (DiNP), di-*n*-hexyl phthalate (DnHP), and diisobutyl phthalate (DiBP) (26, 34). Matsumoto et al. (35) observed an association between higher DEHP serum levels and shorter duration of pregnancy. This and other reproductive effects such as cryptorchidism and decreased semen quality could be owed to the ability of phthalate monoesters to cross the placental barrier and enter the umbilical cord blood of the foetus (36).

Several studies (20, 32, 37-40) have indicated that changes in male reproductive parameters, such as DNA sperm damage, decreased reproductive hormone levels, and anogenital distance (AGD, a biomarker of prenatal androgen exposure in male newborns) could be related with environmental exposure to phthalates. Exposure levels in these studies were in the range reported for the general population (20, 24, 39, 40). More recent studies with ambiguous results call for further research of the effects of adult exposure to phthalates at ambient levels on male reproductive endpoints (41-43).

In turn, animal studies of phthalate effects on female reproductive endpoints (serum oestradiol levels, ovary

weight) suggest that exposure to levels higher than ambient ones is necessary to induce relevant changes (44). Although increased DEHP, DBP, BBP, and di-*n*-octyl phthalate (DOP) levels were detected in the blood of women with endometriosis (45, 46), the problems in immune system functioning could also trigger the development of endometriosis (35).

Numerous studies point to phthalates as hormone disruptors (47, 48), which means that they interfere with the endocrine system responsible for growth and development and can ultimately lead to the feminisation of males, known as the “phthalate syndrome” (49), and reduced typical male behaviour in boys (50, 51). The other syndrome related to phthalate exposure is the testicular dysgenesis syndrome (TDS), which may involve lower sperm count, higher incidence of prostate cancer, cryptorchidism, and hypospadias (51). Exposure to phthalates *in utero* may affect testis formation and hormone production and cause problems in the reproductive function later in life (47, 52). Phthalates cross the placental barrier from mother's to foetus's blood and are excreted in breast milk (18, 53, 54). Their metabolites were determined in infants' urine (52). A Danish-Finish cohort study showed that increased concentrations of DBP metabolites in breast milk inversely correlated with free serum testosterone levels in 3-month-old male infants (55). Adibi et al. (56) studied intrauterine exposure to phthalates and concluded that urinary levels of phthalate metabolites inversely correlated with trophoblast differentiation gene expression, which is essential for human placental development. No correlation was found with the expression of genes characteristic for steroidogenesis.

Sathyarayana et al. (57) observed higher urine phthalate metabolite levels [monoethyl phthalate (MEP), monomethyl phthalate (MMP), and monoisobutyl phthalate (MiBP)] in infants and correlated them with the use of baby cosmetics (infant powder, lotions, and shampoo). They suggested that phthalate exposure could be minimised by reducing the use of childcare products.

Because of these reprotoxic effects, especially on developing organisms such as children, European Parliament and the European Commission have set the maximum allowed concentrations (MAC) of phthalates in children's toys, items for relaxation, food and pacifiers (14).

Regarding endocrine disruption, Stalhnut et al. (58) observed that low testosterone levels in adult men exposed to phthalates were associated with obesity and insulin resistance. Phthalates may affect thyroid signalling, metabolic homeostasis, and immune functions (59, 60). Higher levels of the DEHP metabolite mono-(2-ethylhexyl) phthalate (MEHP) in urine are associated with lower thyroid hormone and thyroid stimulating hormone levels (60). Urinary DBP metabolite monobutyl phthalate (MBP) in Taiwanese pregnant women inversely correlated with thyroxin levels (61). Children who ate food containing

DEHP had lower levels of thyroid stimulating hormone in serum (62).

The thyroid hormone is important for the development of the reproductive system. Its deficiency during foetal or postnatal development could lead to brain damage and neurological disorders.

Respiratory toxicity

Exposure to phthalates during childhood (as well as in the foetal and neonatal period) is often associated with impaired lung function, risk of bronchial obstruction, asthma and allergies in children, and asthma in adults (59, 63). The lungs of newborn rats exposed to DEHP exhibited histological changes similar to those observed in the lungs of children with bronchopulmonary dysplasia, a chronic lung disease typical of preterm infants (64). Wheezing, rhinitis, and asthma in children could be associated with higher concentrations of BBP and DEHP in house dust (65-67).

DNA damage and carcinogenesis

Hauser et al. (40, 68) reported that DEHP and DEP levels correlated with sperm DNA damage in exposed humans. Lopez-Carrillo et al. (47) suggested a possible connection between exposure to DEP through cosmetics and personal care products with an increased risk of breast cancer, which could be related to DEP demethylating the oestrogen receptor complex. The International Agency for Research on Cancer (IARC) has concluded that DEHP cannot be classified as human carcinogen because DEHP induces liver tumours in rodents by a mechanism activating PPAR α that is not relevant in humans (69, 70). However, as there were no available data for DEHP carcinogenicity in humans but there is sufficient evidence of DEHP carcinogenicity in experimental animals, it has been classified as *possibly carcinogenic to humans (Group 2B)* (71).

PHTHALATE MIGRATION AND REGULATIONS

Research suggests that phthalates migrate to tap and bottled water (7, 9, 72, 73) and soft and alcoholic drinks (5, 7, 8, 16, 74–80). Migration from plastic packaging to soft drinks is 5-40 times higher than migration to mineral water (7). One of the reasons may be the difference in pH: less than 3 in soft drinks and more than 5 in all mineral waters.

The MACs of the most common phthalate DEHP in drinking water set by the World Health Organisation (WHO) and US EPA are 8 $\mu\text{g L}^{-1}$ and 6 $\mu\text{g L}^{-1}$, respectively (10, 81). Croatia has not set any such limits for drinking water or for phthalate levels in the packaging material, soft drinks, and alcoholic beverages, but the EU has. One of the key acts is

the European Regulation (EC) No. 1907/2006 (REACH) and its amendments (until February 2017) (14). It stipulates that DEHP, BBP, DBP, and DIBP should not be used in any of the matrices, toys and childcare products in particular, from 21 February 2015 on (the so called “sunset date”) due to the evident strong toxic effects on reproduction (category 1B). More specifically, toys and childcare products containing phthalates in a concentration greater than 0.1 % of the plasticised material weight shall not be marketed. Other phthalates, namely DINP, diisodecyl phthalate (DIDP), and DOP have only been banned in toys and childcare products that children can put in the mouth (14).

The tolerable daily intake (TDI) set by the European Food Safety Authority (EFSA) is 50 $\mu\text{g kg}^{-1}$ bw for DEHP (30), 10 $\mu\text{g kg}^{-1}$ bw for DBP (29), 150 $\mu\text{g kg}^{-1}$ bw for DINP and DIDP (82, 83), and 500 $\mu\text{g kg}^{-1}$ bw for BBP (31).

With its Regulation No. 10/2011 EC of 14 January 2011 (84), the EU has set the so-called specific migration limits (SML) in plastics likely to come into contact with food and beverages. SML is the MAC of a given substance released from a material or article into food or food simulants. For DBP it is 0.3 mg kg^{-1} food, for DEHP 1.5 mg kg^{-1} food, and for BBP 30.0 mg kg^{-1} food. DIBP is not allowed in food contact materials. This regulation indirectly limits the maximum concentrations of these undesirable substances in alcoholic beverages.

In some EU countries, producers of spirits are not required to monitor phthalates in alcoholic beverages, but in some MACs are prescribed. For example, Slovakian Regulations on the General Code for Groceries and Contaminants in Food define the MAC for phthalates as a sum of DEHP and DBP, which is 0.7 mg kg^{-1} in the root vegetables and potatoes and 2 mg kg^{-1} in fruits, leaved vegetables, flour, and alcoholic beverages (85).

ANALYSIS OF PHTHALATES IN ALCOHOLIC BEVERAGES

Phthalates released from contact materials into alcoholic beverages call for some form of monitoring. Table 2 summarises the measurements made so far with different analytical methods. The most frequent phthalates detected in alcoholic beverages are DEHP and DBP, followed by BBP and DEP.

The most common method for the identification and quantification of low concentrations of phthalates in alcoholic drinks is gas chromatography coupled with mass spectrometry (GC-MS) (5, 8, 21, 74, 76–80). Prior to chromatographic analysis, phthalates are extracted from samples using organic solvents (5, 8, 21, 86), solid-phase extraction, or microextraction (76, 77, 79, 80). The most common method for calibration in such complex matrices as alcoholic beverages is the standard addition method, but it takes a lot of time because it requires a calibration curve for each sample (87). The internal standard method usually

involves an isotope-labelled standard, which allows greater precision and accuracy of the method, because isotope-labelled standards have the same physical and chemical properties as their unlabelled analogues present in the sample. To quantify phthalates in wines and spirits Carrillo et al. (76) and Chatonnet et al. (8) used deuterium-labelled phthalate standards and thereby increased the accuracy and sensitivity of the method and avoided the matrix effect compared to the standard addition method.

Alternatives to GC-MS include gas chromatography with flame ionisation detection (GC-FID) as described for DEP (88) or ultraviolet-visible (UV-VIS) and nuclear magnetic resonance spectroscopy (NMR) (89, 90).

Due to the widespread presence of phthalates in laboratory environments (air, glassware, and reagents) special care has to be taken to minimise sample contamination, as described by Fankhauser-Noti and Grob (91).

PHTHALATE OCCURENCE IN ALCOHOLIC BEVERAGES

According to the WHO Global Status Report on Alcohol and Health (92), spirits (which include all distilled beverages) constitute 15.4 % of all alcoholic beverages consumed in Croatia. In addition, Croatia is a great exporter of fruit-based spirits; in 2015, it exported as much as 485,000 L (93). Considering these quantities and the fact that phthalates migrate more readily to beverages containing ethanol than water or non-alcoholic beverages, we might wonder how serious the related exposure may be.

Phthalates can contaminate fruit as early as it is being picked and stored into plastic bags for transport to production facilities. Jurica et al. (5) detected DEP, DBP, and DIBP in plums at the entry point of production. The next point of contamination can be plastic and rubber components of the pumps and other equipment, especially the one in contact with the distillate, whose acidity favours phthalate (mainly BBP and DEHP) extraction (8, 94). Chatonnet et al. (8) reported major contamination by DBP and DIBP in epoxy coatings for storage and fermentation tanks. DIBP was detected in some synthetic corks used for wine and spirit bottling, even though they are not allowed as contact material. Last but not least, alcoholic beverages are often contaminated with phthalates from packaging. Leibowitz et al. (16) reported 200 and 204 $\mu\text{g L}^{-1}$ of DBP in samples of vodka in plastic packaging exported to Japan and in samples from the United States, respectively.

In contrast, Carrillo et al. (76) suggested that the culprit of phthalate migration to wine is not the plastic cork or packaging, but the technological process, as they found no significant difference in phthalate concentrations between wines plugged with a plastic or normal cork and those stored in plastic or glass. Similarly, Jurica et al. (5) reported no significant difference between plum spirit samples stored

Table 2. Phthalate concentrations in alcoholic beverages and analytical techniques to determine them

Technique of analysis	Matrix, Number of samples	Value	DMP	DEP	DIBP	DBP	BBP	DEHP	Comment	Ref.
LLE GC-MS	Vodka, N=50	Range ($\mu\text{g L}^{-1}$) / Detection frequency (%)	ND	NA	NA	<LOQ-204 / 36	ND	62-492 / 94	DOP: Range 75-131 $\mu\text{g L}^{-1}$ Detection frequency: 8 %	16
HS-SPME GC-MS	Wine, N=10	Median ($\mu\text{g L}^{-1}$) / Detection frequency (%)	<LOQ- 0.61 / 30	<LOQ- 4.22 / 60	NA	0.30-5.37 / 100	4.29 / 10	<LOQ-7.40 / 60	No significant differences regarding the type of stopper	76
SPE GC-MS	Wine, N=26 (glass bottle)	Median ($\mu\text{g L}^{-1}$) / Range ($\mu\text{g L}^{-1}$) / Detection frequency (%)	ND	ND	99 (47-260) / 100	53 (<LOQ-244) / 90	40 (<LOQ- 269) / 40	76 (<LOQ-242) / 100		
	Wine, N=10 (polyethylene coupled film brick)	Median ($\mu\text{g L}^{-1}$) / Range ($\mu\text{g L}^{-1}$) / Detection frequency (%)	ND	ND	76 (<LOQ- 173) / 100	115 (<LOQ-240) / 85	LOQ (<LOQ- 252) / 69	78 (25-276) / 96	No influence of the packaging material on phthalate content	77
	Wine, N=18 (from winemakers producer)	Median ($\mu\text{g L}^{-1}$) / Range ($\mu\text{g L}^{-1}$) / Detection frequency (%)	ND	ND	119 (<LOQ- 254) / 89	<LOQ (<LOQ-125) / 56	<LOQ (<LOQ- 237) / 22	57 (<LOQ-133) / 72		
	Wine, N=8 (from experimental pilot plant)	Median ($\mu\text{g L}^{-1}$) / Range ($\mu\text{g L}^{-1}$) / Detection frequency (%)	ND	ND	81 (62-197) / 100	<LOQ / 0	<LOQ / 0	57 (<LOQ-61) / 100		
SPE	White wine, N=3	Range ($\mu\text{g L}^{-1}$) / Detection frequency (%)	NA	NA	NA	10-21.3 / 100	0.4-7.0 / 100	9.2-16.0 / 100	BcEP was not present at detectable levels	79
GC-MS	Red wine, N=4	Range ($\mu\text{g L}^{-1}$) / Detection frequency (%)	NA	NA	NA	7.3-23.0 / 100	<LOQ-5.2 / 50	2.4-15.8 / 100		
Ultrasound- vortex- assisted dispersive LLME GC-MS	Wine N=11	Range ($\mu\text{g L}^{-1}$) / Detection frequency (%)	ND	ND	NA	(<LOQ-312) / 91	(<LOQ- 136) / 45	(LOQ-26.6) / 73	DMP, DEP and BcEP were not present at detectable levels	78

LLE GC-MS	Market-ready French wines, N=100	Mean±SD (µg kg ⁻¹)	NA	NA	ND	273±591	8±24	134±350	DIMP, DCHP, DINP, DIDP, DIPP, and DAP were not present at detectable levels
		Median (µg kg ⁻¹) / Range (µg kg ⁻¹) / Detection frequency (%)	NA	NA	NA	58.7 (<4-2212) / 59	0 (4-122) / 15	0 (<4-1132) / 15	
LLE GC-MS	Wine spirits from the southwest of France, N=30	Mean±SD (µg kg ⁻¹)	NA	NA	103±46	314±323	26±37	513±326	BOP was not present at detectable levels
		Median (µg kg ⁻¹) / Range (µg kg ⁻¹) / Detection frequency (%)	NA	NA	0 (<10-170) / 25	104 (<4-1083) / 90	0 (<4-96) / 40	353 (<4-1522) / 90	
LLE GC-MS	Brandy, N=1;	Mean (µg L ⁻¹) / Detection frequency (%)	NA	5.0 / 100	NA	65 / 100	NA	NA	BOP was not present at detectable levels
	Red wine, N=2	Mean (µg L ⁻¹) / Detection frequency (%)	NA	NA	ND	21 / 100	ND	NA	
LLE GC-MS	White wine, N=1;	Mean (µg L ⁻¹) / Detection frequency (%)	NA	4.2 / 100	NA	NA	NA	NA	BOP was not present at detectable levels
	Sangria, N=1	Mean (µg L ⁻¹) / Detection frequency (%)	NA	NA	NA	30 / 100	NA	NA	
LLE GC-MS/MS	Beer, N=3	Mean (µg L ⁻¹) / Detection frequency (%)	NA	0.7 / 67	ND	5.2 / 100	NA	NA	DOP was not present at detectable levels
	Chinese spirit, N=6	Range (µg kg ⁻¹) / Detection frequency (%)	14-166 / 83	4 / 17	4-695 / 100	5-1946 / 100	NA	156-1955 / 50	
LLE GC-MS	Plum spirit, N=20	Mean±SD	ND	16.7±15.3	38.3±13.9	414.5±355.9	78.9±39.7	423.8±524.6	No influence of the packaging material on phthalate content
		Median (µg L ⁻¹) / Range (µg L ⁻¹) / Detection frequency (%)	NA	7.8 (4.2-50.0) / 100	38.8 (20.1-65.7) / 100	405.6 (25.2-822.0) / 100	79.0 (10.5-122.0)	282.0 (16.0-1638.0)	

LLE – liquid-liquid extraction; HS-SPME – headspace solid phase microextraction; SPE – solid phase extraction; LLME – liquid-liquid microextraction; GC-MS – gas chromatography-mass spectrometry; GC-MS/MS – gas chromatography-tandem mass spectrometry; D – not detected; NA – not analysed; LOQ – limit of quantification; DMP – dimethyl phthalate; DEP – diethyl phthalate; DIBP – diisobutyl phthalate; DBP – dibutyl phthalate; BBP – benzylbutyl phthalate; DEHP – di(2-ethylhexyl) phthalate; DEHP – di(2-ethylhexyl) phthalate; DOP – di-n-octyl phthalate; BcEP – butyl cyclohexyl phthalate; DIMP – diisomethyl phthalate; DIPP – diisopropyl phthalate; DINP – diisononyl phthalate; DCHP – dicyclohexyl phthalate; DAP – diallyl phthalate; BOP – butyloctyl phthalate

in glass or plastic containers, even though phthalate concentrations were slightly lower in the spirit samples stored in glass.

Regardless of the way of entry/contamination, however, the end result is the same. Alcoholic beverages may contain high concentrations of phthalates. Jurica et al. (5) analysed phthalates in 20 glass-bottled plum spirit samples from five Central and Eastern European countries. DMP and DOP were below the limit of detection, but mean DEP, DIBP, DBP, BBP, and DEHP concentrations were 16.7, 38.3, 414.5, 78.9, and 423.8 $\mu\text{g L}^{-1}$, respectively. In other words, the two most common phthalates, DBP and DEHP, had the highest concentrations. Phthalate concentrations in wine reported by Carrillo et al. (76) ranged from 2.7 to 15 $\mu\text{g L}^{-1}$, and the most common phthalate was DBP, which was also detected in fruit brandy samples from Germany but not from Croatia (95).

In Eastern European countries, unregistered (illegal) alcoholic beverages may have high concentrations of DEP, which is used for the denaturation of ethanol. Even though these alcoholic beverages are banned, they find their way to the market. The authors of a study (21) reporting DEP concentrations as high as 608 mg L^{-1} and 210 mg L^{-1} in a Lithuanian sample suggested that the alcohol was declared as a perfume but was used for human consumption to avoid taxes. High concentrations of DEP in illegal vodka (850-1284 mg L^{-1}) (88) and a variety of illegal alcoholic beverages (275-1269 mg L^{-1}) from Russia (95) have also been attributed to the use of DEP as a denaturing agent.

Data about the presence of phthalates in alcoholic beverages and natural spirits in Croatia are sparse and MACs have not yet been regulated. However, their presence may present a problem for the exports to the EU countries where these limits exist.

RECOMMENDATIONS FOR EFFECTIVE CONTROL OF PHTHALATE EXPOSURE

As the quantity and frequency of human exposure to phthalates is often unknown, research should focus on the sources and routes and try to answer at which level the phthalates are dangerous for human health. It is certainly necessary to biomonitor phthalates by determining their metabolites in body fluids, primarily in the urine. Their MACs should be regulated in food, drinking water, and alcoholic beverages. To avoid economic losses in markets with defined MACs, the producers of alcoholic beverages should introduce phthalate monitoring through internal quality management and product safety systems.

In addition, exposure could further be reduced by finding and introducing alternative, phthalate-free materials and plasticisers into the production of consumer products or parts used in food and beverage processing and storage, especially in view of the recent EU legislation that bans certain types of phthalates.

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Činjenice o toksičnosti ftalata u ljudi i njihovoj pojavnosti u alkoholnim pićima

Ftalati su esteri ftalne kiseline i alifatskih alkohola koji poboljšavaju mekoću i savitljivost plastičnih proizvoda. Zbog svojih fizičkih i kemijskih svojstava ftalati brzo i lako migriraju iz plastičnih proizvoda u okoliš. U ovome preglednom radu ukratko su opisana svojstva i raspodjela ftalata u okolišu, monitoring, uporaba i toksični učinci na ljudsko zdravlje te zakonski okvir vezan uz maksimalno dopuštene koncentracije ftalata u različitim matricama i proizvodima, kao i dopušteni dnevni unos u ljudski organizam. Rezultati istraživanja upućuju na reproduktivne i razvojne toksične učinke ftalata na ljude. Zbog nedosljednih podataka potrebna su daljnja istraživanja i mjere opreza. Naglasak je na metodama određivanja koncentracije ftalata u alkoholnim pićima s osvrtom na njihovu pojavnost i koncentracije u šljivovici proizvedenoj u Hrvatskoj. Ftalati prisutni u legalno proizvedenim alkoholnim pićima prilikom umjerene konzumacije nisu dodatni rizik za ljudsko zdravlje. Uključena je i tematika vezana za dietil ftalat prisutan u alkoholnim pićima koja se ilegalno pojavljuju na tržištu. U zaključku su navedene preporuke za učinkovitiji monitoring putova izloženosti ljudi ftalata te preporuke da se koristi alternativni materijal prilikom tehnološkog procesa proizvodnje alkohola.

KLJUČNE RIJEČI: *alkohol; hormonski poremećaji; maksimalno dopuštena koncentracija; tolerirani dnevni unos; zakonska regulativa*