

Occurrence of chemicals with known or suspected endocrine disrupting activity in drinking water, groundwater and surface water, Austria 2017/2018

Zum Vorkommen von Chemikalien mit bekannter oder vermuteter endokriner disruptiver Wirkung in Trinkwasser, Grundwasser und Oberflächenwasser, Österreich 2017/2018

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Summary

Endocrine disrupting chemicals (EDCs) can cause adverse effects in individuals and their offspring. In 2017 and 2018, we performed a survey on representative samples of Austrian drinking water ($n = 20$), groundwater ($n = 22$), and surface water ($n = 12$), the latter including bathing water ($n = 5$) and rivers ($n = 7$). We analyzed 54 samples for 28 parameters, including estrogens, polybrominated diphenylethers (PBDEs), phthalates, perfluoroalkyl substances, alkylphenols, bisphenol A and triclosan, correlating to 1512 measurements. In 39 of the 54 samples (72.2%), at least one endocrine disrupting or potentially disrupting chemical was found at or above the limit of quantification. None of the samples yielded estrogens or triclosan in detectable levels. Bisphenol A (BPA) was detected in 4 (20.0%) samples of drinking water, in 1 (4.5%) groundwater sample, and in 1 (20%) bathing water sample, with a maximum concentration of 0.021 $\mu\text{g/l}$ found in one drinking water. Two drinking water samples yielded BPA in concentrations above the limit value of 0.01 $\mu\text{g/l}$, recently proposed by the European Commission for drinking water. Therefore, the ultimate public health goal must be to further reduce and restrict the production of EDCs and therewith decrease and eventually eliminate the contamination of drinking water resources.

Keywords: Chemicals, endocrine disruptors, hormone, bisphenol A, water, toxicology, risk assessment

Zusammenfassung

Endokriner Disruptoren (EDCs) können in Individuen und deren Nachkommenschaft adverse Effekte erzeugen. In den Jahren 2017 und 2018 untersuchten wir stichprobenartig österreichisches Trinkwasser ($n = 20$), Grundwasser ($n = 22$) und Oberflächenwasser ($n = 12$), letzteres einschließlich Badegewässer ($n = 5$) und Flüsse ($n = 7$). Wir analysierten die 54 Proben auf 28 Parameter (1512 Einzelmessungen), einschließlich Östrogene, polybromierte Diphenylether (PBDEs), Phthalate, Perfluoralkylsubstanzen, Alkylphenole, Bisphenol A (BPA) und Triclosan. In 39 der 54 Proben (72,2 %) wurde mindestens ein endokriner oder potenziell endokriner Disruptor gefunden. Keine der Proben wies Östrogene oder Triclosan in nachweisbaren Mengen auf. BPA wurde in vier (20,0 %) Trinkwasserproben, in einer (4,5 %) Grundwasserprobe und in einer (20 %) Badewasserprobe nachgewiesen, wobei die maximale Konzentration von 0,021 $\mu\text{g/l}$ in einer Trinkwasserprobe gefunden wurde. Zwei Trinkwasserproben enthielten BPA-Konzentrationen über dem von der Europäischen Kommission kürzlich für Trinkwasser vorgeschlagenen Grenzwert von 0,01 $\mu\text{g/l}$. Daher hat das oberste Ziel der öffentlichen Gesundheit zu sein, die Produktion von EDCs weiter zu reduzieren und einzuschränken und damit die Kontamination von Trinkwasserressourcen zu verringern und schlussendlich zu eliminieren.

Schlagnworte: Chemikalien, Endokrine Disruptoren, Hormone, Bisphenol A, Wasser, Toxikologie, Risikobewertung

1. Introduction

By WHO definition, an endocrine disruptor is “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations” (Bergman et al., 2013). A large number of substances from a wide range of chemical classes have been implicated and suspected as possible endocrine disrupting chemicals (EDCs). These include industrial chemicals, pesticides, heavy metals, pharmaceuticals, and different types of natural hormones and substances produced by plants and animals. The endocrine system is a critical component of body functions and consists of the glands that secrete hormones into the bloodstream, that then act as chemical messengers to trigger an effect in some other part of the body. This includes, for instance, the pituitary, thyroid and adrenal glands, and the male and female reproductive systems, all of which release hormones into the blood. Collectively, these glands and their hormones regulate or are engaged in processes such as reproduction, growth, development, aspects of behavior that include responses to stress and physiological functions such as blood pressure and heart rate (Street et al., 2018).

Endocrine disrupting chemicals are thought to cause adverse effects by a number of possible pathways (Kabir et al., 2015; Wang and Tian, 2015). EDCs may mimic the sex hormones and promote similar responses to them, or vice versa may block the activities of the sex hormones, estrogens or androgens. The “key-lock” mechanism is often used to describe the way in which hormones interact with receptors to trigger an effect; EDCs may act by sending the body a different message by altering or blocking the hormone (key) or the intended receptor (lock) (Schug et al., 2016). EDCs may also disturb the signaling system before the hormone reaches the receptor by altering essential protein production in the body, producing abnormal hormone levels or several other complex pathways. The effects may only be obvious at the tissue or hormonal levels in individuals exposed to specific EDCs, or may be more significant and lead to changes at the population level (Manning, 2005).

The evidence for occurrence of endocrine disruption includes results both from field observations and from laboratory studies that have shown that the growth, reproduction and development of many species, including mammals, birds, fish, frogs and invertebrates may be affected by the presence of EDCs in the environment. For instance, adverse effects con-

cerning developmental abnormalities and feminization of alligators in Florida followed an organochlorine pesticide spill, and waste water treatment plants and paper mill discharges caused feminization of fish in the US (Manning, 2005). The increased incidence of certain endocrine-related human diseases has also focused attention on the risks posed by exposure to chemicals that have the potential to cause effects at very low levels (Damstra et al., 2002). There are thousands of potential EDCs that can enter the aquatic environment as sewage effluent or other ways of pollution, but there is still little data available concerning the presence of these compounds in drinking water. Many of these compounds are quite stable and resistant to water treatment methods, and there is concern that they may pass through into drinking water in relatively large concentrations (Kabir et al., 2015; Fürhacker, 2017; Forner-Piquer et al., 2018; Fucic et al., 2018). It was the aim of our study to survey drinking water, groundwater and surface water in Austria for contamination with possible endocrine active/endocrine disrupting substances.

As to the parameters chosen for testing in this study, Directive 2013/39/EU of the European Parliament and the Council amending Directives 2000/60/EC (water framework directive - WFD) and 2008/105/EC (Directive on environmental quality standards) lays down a strategy against the pollution of water. That strategy involves the identification of priority substances amongst those that pose a significant risk to, or via, the aquatic environment at European Union level. Problems surrounding EDCs are their continuous release into the environment through industrial, domestic and hospital effluents and inefficient removal by wastewater treatment plants (WWTPs). For this reason, the WFD established a priority list of 33 new and 8 previously regulated chemical pollutants, some of which have been shown to exhibit endocrine disrupting potential (e.g., octyl-, nonylphenol, di-(2-ethylhexyl) phthalate). Additionally, 15 compounds were also placed onto a “watch list” of potential priority substances, containing estrogen compounds (estradiol, ethinylestradiol). The parameters of our study were selected on the basis of this priority list.

2. Materials and methods

2.1 Samples

Twenty-two groundwater sites and twenty nearby drinking water sites all over Austria were selected for sampling. The

choice of sites was based on risk-assessment according to the presence of substances previously detected by AGES and the federal environment agency (Ages and Umweltbundesamt, 2015) indicating contamination by humans. Moreover, five lakes used for bathing (bathing water) and seven rivers, five of them transboundary sampling sites, were arbitrarily selected. Figure 1 shows the location of the 54 sample sites. Drinking water, groundwater and surface water were sampled by the accredited sampling personnel from August 2017 until February 2018, within the framework of the Austrian ordinance on the monitoring of the quality of water (“Gewässerzustandsüberwachungsverordnung”, “GZÜV”), Federal Law Gazette No 479/2006, following the requirements of ISO 5667-4 (Guidance on sampling from lakes, natural and man-made), ISO 5667-5 (Guidance on sampling of drinking water from treatment works and piped distribution systems), ISO 5667-6 (Guidance on sampling of rivers and streams), and ISO 5667-11 (Guidance on sampling of groundwater). Samples (one 1-litre glass bottle, and two 1-litre aluminium bottles each) were transported cooled at 4°C, and tested within 72 hours. Samples were quantitatively analyzed on estrone (E1), 17β-estradiol (E2), estriol (E3), 17α-ethinylestradiol (EE2), bisphenol A/S (BPA/BPS), triclosan (TCS), nonylphenol-mono-ethoxylate (NP1EO), nonylphenol-diethoxylate (NP2EO), octylphenol (OP) and its ethoxylates (OP1EO, OP2EO), perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), benzylbutylphthalate,

di-(2-ethylhexyl)phthalate, di-isononylphthalate, di-n-butylphthalate, dimethylphthalate, di-n-octyl-nonylphthalate, diethylphthalate, diisodecylphthalate, and polybrominated diphenylethers BDE 28, 47, 99, 100, 153, 154.

2.2 Analytical methods

2.2.1 Detection of estrogens, alkylphenols/ethoxylates, PFOA/PFOS, and triclosan

For liquid chromatography—high resolution mass spectrometry (LC–HRMS), samples were filtered using 0.45 μm syringe filters. For the 20 mL online-enrichment of the endocrine disruptors, two 10 mL vials were filled and spiked with labelled surrogates shown in Table 1. Ethoxylates were measured through 5 ml enrichment with a separate method. Table 1 displays the limit of quantification (LOQ) and the limit of detection (LOD) for these methods.

The chromatographic system consisted of a Thermo QExactive mass spectrometer, coupled to an Ultimate 3000 UHPLC system equipped with an EQUAN On-Line SPE (Thermo Fisher Scientific, San Jose CA, USA). An Acclaim Polar Advantage II (Thermo Fisher Scientific, San Jose CA, USA) and a Waters Xselect HSS T3, respectively, were used as analytical columns, and an OASIS HLB (Waters Corporation, Milford MA, USA) for pre-concentration. Two different types of scans were conducted: A high resolution full-MS-scan which triggers an MS² if relevant

Table 1. Selected analytes with corresponding internal standards
Tabelle 1. Ausgewählte Analyten mit den jeweiligen internen Standards

Analyte	Internal Standards	LOQ [ng/l]	LOD [ng/l]
Estrone (E1)	Estrone-D4	0.13	0.035
Estradiol (E2)	Estradiol-D4	0.11	0.030
Estriol (E3)	Ethinylestradiol-D7	0.44	0.118
Ethinylestradiol (EE ₂)	Ethinylestradiol-D7	0.084	0.023
Bisphenol A (BPA)	Bisphenol A-D16	6.5	1.8
Bisphenol S (BPS)	Bisphenol A-D16	6.2	1.7
Triclosan (TCS)	Triclosan-D3	3.3	0.9
Perfluorooctanoic acid (PFOA)	Perfluorooctanoic acid- ¹³ C8	1.95	0.5
Perfluorooctanesulfonic acid (PFOS)	Perfluorooctanesulfonic acid- ¹³ C8	2.8	0.77
Nonylphenol-mono-ethoxylate (NP1EO)	Atrazin-D5	8.9	2.5
Nonylphenol-di-ethoxylate (NP2EO)	Atrazin-D5	6.9	1.9
4-tert-octylphenol (4-tert.-OP)	4-tert-octylphenol-D2	3.7	1.0
Octylphenol-mono-ethoxylate (OP1EO)	Atrazin-D5	8.20	1.7
Octylphenol-di-ethoxylate (OP2EO)	Atrazin-D5	6.2	1.3

masses are identified (full MS / ddMS²), as well as parallel-reaction monitoring (PRM). All analytes were detected in negative mode, except for the ethoxylates. Used conditions of the chromatographic system for the endocrine disruptors in negative mode utilized an Thermo QExactive LC-HRMS-apparatus, a Acclaim Polar Advantage II-column (150 × 2.1 mm, 3 μm), negative electrospray ionization (ESI negative), 20 mL injection volume, a mobile phase A of H₂O + 1 mM NH₄F, and a mobile phase B of acetonitrile/MeOH 50:50.

Used conditions of the chromatographic system for the ethoxylates in positive mode utilized a Thermo QExactive LC-HRMS-apparatus, an Xselect HSS T3 (150 mm × 2.1 mm ID 3.5 μm)-column, positive electrospray ionization (ESI positive), 5 mL injection volume, a mobile phase A of H₂O + 1 mM NH₄F + 0.1 % formic acid, and a mobile phase B of MeOH + 1 mM NH₄F + 0.1 % formic acid.

2.2.2. Detection of phthalates

Eight individual substances of the phthalate group (dimethylphthalate, diethylphthalate, di-n-butylphthalate, benzylbutylphthalate, di-(2-ethylhexyl)phthalate, di-n-octylphthalate, di-iso-nonylphthalate, di-iso-decylphthalate) were

Table 2. Phthalates: limits of detection (LOD) and of quantification (LOQ)

Tabelle 2. Phthalate: Nachweisgrenzen (LOD) und Bestimmungsgrenzen (LOQ)

Parameter	LOQ [μg/l]	LOD [μg/l]
Dimethylphthalate	0.010	0.0050
Diethylphthalate	0.020	0.010
Di-n-butylphthalate	0.050	0.025
Benzylbutylphthalate	0.010	0.0050
Di-(2-ethylhexyl)phthalate	0.20	0.10
Di-n-octylphthalate	0.010	0.0050
Di-iso-nonylphthalate	0.20	0.10
Di-iso-decylphthalate	0.20	0.10

analyzed by GC/MS according to DIN EN ISO 18856. The glassware was thoroughly pre-cleaned. After adding the deuterated surrogate standards and sodium chloride, the enrichment of the phthalates was carried out from the aqueous phase by means of liquid-liquid extraction with n-hexane. With every preparation, series blank values and recovery rates were quantified. A Thermo Trace GC/ISQ MS apparatus with a column DB-5MS 60 meter/0.25 mm/0.25 μm was operated in electron impact ionization mode. The re-

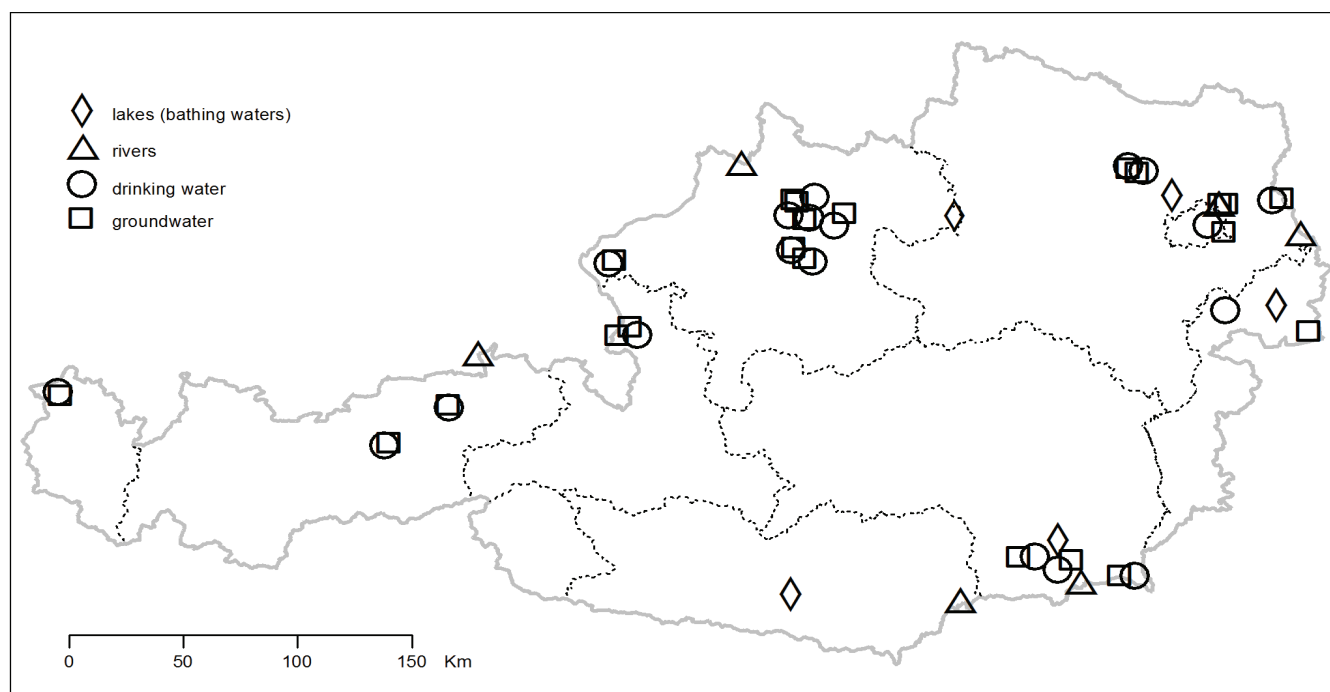


Figure 1. Location of the 54 sample sites distinguished by matrix
Abbildung 1. Lage der 54 Probenorte, nach Matrix unterschieden

Table 3. Polybrominated diphenylethers (PBDEs): limits of quantification (LOQ)

Tabelle 3. Polybromierte Diphenylether (PBDE): Bestimmungsgrenzen (LOQ)

Parameter	LOQ	LOQ
	Period 1 [$\mu\text{g/l}$]	Period 2 [$\mu\text{g/l}$]
BDE 28 (2,4,4'-Tribromodiphenylether)	0.0000072	0.0000083
BDE 47 (2,2',4,4'-Tetrabromodiphenylether)	0.00023	0.00025
BDE 99 (2,2',4,4',5-Pentabromodiphenylether)	0.00020	0.00014
BDE 100 (2,2',4,4',6-Pentabromodiphenylether)	0.000040	0.000029
BDE 153 (2,2',4,4',5,5'-Hexabromodiphenylether)	0.000012	0.0000093
BDE 154 (2,2',4,4',5,6'-Hexabromodiphenylether)	0.000016	0.000016

sults were blank-corrected and the quantification was done by the external standard method with recovery correction through adding deuterated surrogate standards. The limits of detection and of quantification for the individual substances are summarized in Table 2.

2.2.3 Detection of polybrominated diphenylethers (PDBEs)

Six congeners (BDE 28, BDE 47, BDE 99, BDE 100, BDE 153 and BDE 154) of polybrominated diphenylethers have been selected based on the list of priority substances in the field of water policy (EC, 2013) and were analyzed according to EPA method 1614. ^{13}C -labelled surrogate standards were added to the samples prior to continuous liquid-liquid extraction with toluene. Subsequently, the samples were subjected to a multi-stage column-chromatographic clean-up, using the fully automated sample preparation system Miura GO-2HT (MIURA Co Ltd., Matsuyama City, Ehime, Japan). Following the addition of an injection standard, the measurement was done by GC/HRMS. A Thermo Trace GC Ultra/Finnigan MAT 95 XP MS apparatus with a DB-5 60 meter/0.25 mm/0.25 μm column was used. The HRMS was operated in MID mode with a mass resolution of 8000. Identification and quantification was done by isotope dilution method with recovery correction referred to the added ^{13}C surrogate standards. For PBDE, the limits of quantification are mainly influenced by blanks. Therefore, blank control samples have

been analyzed regularly. The relatively long time period in which the samples were determined, led to two different limits of quantification due to shifts in the blank levels. For period 1 (October to December 2017), 10 blank control samples, and for period 2 (January to March 2018), 13 blank control samples were analyzed. In Table 3, the calculated LOQ values for the two time periods are listed.

2.2.4 Limits of detection and quantitation

The limits of detection and limits of quantitation were determined as described in DIN 32645:2008-11 (Chemical analysis - Decision limit, detection limit and determination limit under repeatability conditions - Terms, methods, evaluation).

3. Results

In 39 of the 54 samples, at least one endocrine disrupting or potentially disrupting chemical was found at or above the limit of quantification (LOQ). None yielded estrogens or triclosan in detectable levels. PBDEs were detected in 3 drinking water samples, and in 4 groundwater samples. Phthalates were detected in 2 (10%) drinking water samples, in 11 groundwater samples, in 3 bathing water samples and in 4 river samples. Perfluoroalkyl substances were detected in 5 drinking water samples, in 8 groundwater samples, in 2 river samples and in 2 bathing water tested. Presence of 4-nonylphenol monoethoxylate (NP1EO) could be shown in 2 groundwater samples and in 1 river sample. Bisphenol A was detected in 4 samples of drinking water, in 1 groundwater sample, and in 1 bathing water sample.

Tables 4, 5, 6 and 7 depict the specific situations in the different water compartments (drinking water, groundwater, bathing water, and river) regarding the measured parameters; measurements that revealed concentrations at or above the individual LOQs are qualitatively denominated as "positive". In drinking water specimens, 539 out of 560 (96.3%) measurements revealed no analytes at or above the respective LOQ, 576 out of 616 (93.5%) measurements none in groundwater, and 322 out of 336 (95.8%) measurements showed no analytes in surface water specimens.

The specimens from water sources positive for at least one analyzed parameter, and the values found at or above the specific limits of quantification are summarized in Table 8. Of the 1,512 measurements, 75 (5.0 %) revealed an endocrine disrupting or potentially disrupting chemical at or above the limit of quantification. Nine out of 120 (7.5%)

Table 4. Drinking water: distribution of positive (pos) results among individual samples (Param. = test parameter; E1 = Estrone, E2 = Estradiol, E3 = Estriol, EE2 = Ethinylestradiol, PFOA = Perfluorooctanoic acid, PFOS = Perfluorooctanesulfonic acid, OP = 4-tert-octylphenol, BPA = Bisphenol A, BPS = Bisphenol S, TCS = Triclosan, OP1EO = Octylphenol-mono-ethoxylate, OP2EO = Octylphenol-di-ethoxylate, NP1EO = Nonylphenol-mono-ethoxylate, NP2EO = Nonylphenol-di-ethoxylate, BDE 100 = 2,2',4,4',6-Pentabromodiphenylether, BDE 153 = 2,2',4,4',5,5'-Hexabromodiphenylether, BDE 154 = 2,2',4,4',5,6'-Hexabromodiphenylether, BDE 28 = 2,4,4'-Tribromodiphenylether, BDE 47 = 2,2',4,4'-Tetrabromodiphenylether, BDE 99 = 2,2',4,4',5-Pentabromodiphenylether, BBP = Benzylbutylphthalate, DEHP = Di-(2-ethylhexyl)phthalate, DEDP = Di-iso-decylphthalate, DINP = Di-iso-nonylphthalate, DBP = Di-n-butylphthalate, DOP = Di-n-octylphthalate, DEP = Diethylphthalate, DMP = Dimethylphthalate)

Tabelle 4. Trinkwasser: Verteilung der positiven (pos) Ergebnisse bei einzelnen Proben (Param. = Testparameter; E1 = Estron, E2 = Estradiol, E3 = Estriol, EE2 = Ethinylestradiol, PFOA = Perfluorooctansäure, PFOS = Perfluorooctansulfonsäure Säure, OP = 4-tert-Octylphenol, BPA = Bisphenol A, BPS = Bisphenol S, TCS = Triclosan, OP1EO = Octylphenolmonoethoxylat, OP2EO = Octylphenol-diethoxylat, NP1EO = Nonylphenolmonoethoxylat, NP2EO = Nonylphenol-diethoxylat, BDE 100 = 2,2', 4,4', 6-Pentabromdiphenylether, BDE 153 = 2,2', 4,4', 5,5' - Hexabromdiphenylether, BDE 154 = 2,2', 4,4', 5,6'-Hexabromdiphenylether, BDE 28 = 2,4,4'-Tribromdiphenylether, BDE 47 = 2,2', 4,4'-Tetrabromdiphenylether, BDE 99 = 2,2', 4,4', 5-Pentabromdiphenyläther, BBP = Benzylbutylphthalat, DEHP = Di-(2-ethylhexyl) phthalat, DEDP = Diisodecylphthalat, DINP = Diisononylphthalat, DBP = Di-n-Butylphthalat, DOP = Di-n-Octylphthalat, DEP = Diethylphthalat, DMP = Dimethylphthalat)

Sample/ Param.	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	XVI	XVII	XVIII	XIX	XX	Sum
E1																					
E2																					
E3																					
EE2																					
PFOA				pos		pos			pos												3
PFOS									pos							pos	pos				3
OP																					
BPA	pos						pos	pos								pos					4
BPS																					
TCS																					
OP1EO																					
OP2EO																					
NP1EO																					
NP2EO																					
BDE 100																		pos		pos	2
BDE 153											pos										1
BDE 154											pos										1
BDE 28																				pos	1
BDE 47																		pos	pos		2
BDE 99																		pos	pos		2
BBP																					
DEHP																					
DEDP																					
DINP																					
DBP						pos															1
DOP																					
DEP															pos						1
DMP																					

Table 5. Groundwater: distribution of positive (pos) results among individual samples (abbreviations as used in Table 4)
Tabelle 5. Grundwasser: Verteilung der positiven (pos) Ergebnisse bei einzelnen Proben (Abkürzungen wie in Tabelle 4 verwendet)

Sample/ Param.	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	XVI	XVII	XVIII	XIX	XX	XXI	XXII	Sum	
E1																								
E2																								
E3																								
EE2																								
PFOA					pos							pos		pos		pos	pos		pos			pos		7
PFOS			pos		pos									pos		pos								4
OP																								
BPA	pos																							1
BPS																								
TCS																								
OP1EO																								
OP2EO																								
NP1EO				pos	pos																			2
NP2EO																								
BDE 100												pos	pos					pos						3
BDE 153																								
BDE 154																					pos			1
BDE 28																								
BDE 47												pos	pos					pos						3
BDE 99												pos	pos					pos						3
BBP				pos																				1
DEHP	pos				pos																			2
DEDP																								
DINP																								
DBP												pos	pos		pos				pos			pos		5
DOP																								
DEP								pos			pos	pos										pos		4
DMP				pos	pos	pos		pos																4

measurements in drinking water, and 10 out of 132 (7.6%) measurements in groundwater revealed PBDEs, with a maximum concentration of 0.00062 µg/l for BDE 47 in groundwater. Two out of 160 (1.3%) measurements in drinking water, 16 out of 176 (9.1%) measurements in groundwater, 3 out of 40 measurements in bathing water, and 5 out of 56 measurements in river revealed phthalates, with a maximum concentration of 0.37 µg/l found for di-(2-ethylhexyl)phthalate in groundwater. Six out of 40 measurements in drinking water, 11 out of 44 measurements in groundwater, 2 out of 14 measurements in river, and 2 out of 10 measurements in bathing water revealed perfluoroalkyl substances, with a maximum concentration

of 0.0433 µg/l found for perfluorooctanesulfonic acid in drinking water. Presence of 4-nonylphenol monoethoxy-late (NP1EO) could be shown in 2 out of 22 measurements in groundwater samples and in 1 out of 7 measurements in river samples, with a maximum concentration of 0.0234 µg/l found in groundwater. Four out of 20 measurements in drinking water, 1 out of 22 measurements in groundwater, and 1 out of 5 measurements in bathing water revealed bisphenol A, with a maximum concentration of 0.021 µg/l found in drinking water.

Table 8 lists the individual limits of quantification (LOQs) and puts them into comparison to analytes and their number found at or above these LOQs.

Table 6. Bathing water: distribution of positive (pos) results among individual samples (abbreviations as used in Table 4)
 Tabelle 6. Badegewässer: Verteilung der positiven (pos) Ergebnisse bei einzelnen Proben (Abkürzungen wie in Tabelle 4 verwendet)

Sample/ Param.	I	II	III	IV	V	VI	Sum
E1							
E2							
E3							
EE2							
PFOA		pos	pos				2
PFOS							
OP							
BPA						pos	1
BPS							
TCS							
OP1EO							
OP2EO							
NP1EO							
NP2EO							
BDE 100							
BDE 153							
BDE 154							
BDE 28							
BDE 47							
BDE 99							
BBP							
DEHP					pos		1
DEDP							
DINP							
DBP							
DOP							
DEP				pos		pos	2
DMP							

4. Discussion

The WHO/United Nations Environment Programme (UNEP) report from 2012 (WHO, 2013) dealing with endocrine disrupting chemicals challenged many well established principles in toxicology and risk assessment. The dose-response principle (“The dose makes the poison”), with linear dose-response and threshold, was questioned by the statement that the affinity of an endocrine disruptor to a hormone receptor is not equivalent to its potency; that endocrine disruptors produce non-linear dose response curves both in vitro and in vivo, by a variety of mecha-

nisms. The general dogma championed by the WHO so far—that a health-based value like the acceptable daily intake (ADI) is valid for all life-stages because based on lifetime-exposure results—was challenged. Assertions were made such as sensitivity to endocrine disruption is highest during tissue development, and developmental effects will occur at lower doses than are required for effects in adults. The opinion on EDCs peaked in the postulation that, when interpreting the results of studies on EDCs or when designing studies to clarify the effects of EDCs and quantifying the risks to human and wildlife health, it must be taken into consideration that endocrine disruption represents a special form of toxicity (WHO, 2013). Since the release of this report, debates have continued between researchers who support its conclusions and those who oppose them. Borgert et al. (2013), as typical examples of opposition to the conclusions of the report, argue that potency differences, laws of mass action, and the basic design and physiological functions of the endocrine system require and ensure the presence of thresholds. Supporters of the report such as Gore et al. (2015) counter that receptor down-regulation, when hormones are present in high concentrations, bind to their receptors, and decrease receptor number, leads to non-monotonic dose response resulting in fewer available receptors and a natural shift in the receptor-mediated response. Vice versa, minuscule concentrations may cause an effect.

In Table 8, the concentrations found above the specific limits of quantification are listed against (proposed) limit values of regulatory bodies or tolerable levels derived from health-based assessments (ATSDR, 2017; EC, 2018; ECHA, 2016; EFSA, 2005, 2011; EPA, 2017; US CPSC, 2010; WHO, 2003, 2017a,b).

In all cases, the limits of quantification were below the current health-based guidance values (or drinking water thresholds derived from these). However, there might be one exception, even though arguable, regarding octylphenol (OP) where special sensitivity of males cannot be excluded. In a low-dose study, Blake et al. (2004) found that the lowest-observed-adverse-effect-level (LOAEL) for sperm tail abnormalities was 20 ng/kg bw/day in male rats exposed to OP in drinking water. With a total safety factor of 300 for OP, a tolerable daily intake (TDI) for men was calculated at 0.067 ng/kg bw/d (Jonsson, 2006). Taking the WHO allocation concept into consideration—60 kg body weight, 2 liters water/day for an adult (WHO, 2017b)—the drinking water parametric value would be 0.0004 µg/l. The LOQ of our study was 0.0037 µg/l.

Table 7: Rivers: distribution of positive (pos) results among individual samples (abbreviations as used in Table 4)

Tabelle 7. Flüsse: Verteilung der positiven (pos) Ergebnisse bei einzelnen Proben (Abkürzungen wie in Tabelle 4 verwendet)

Sample/ Param.	I	II	III	IV	V	VI	VII	Sum
E1								
E2								
E3								
EE2								
PFOA							pos	1
PFOS					pos			1
OP								
BPA								
BPS								
TCS								
OP1EO								
OP2EO								
NP1EO						pos		1
NP2EO								
BDE 100								
BDE 153								
BDE 154								
BDE 28								
BDE 47								
BDE 99								
BBP								
DEHP								
DEDP								
DINP								
DBP								
DOP								
DEP	pos	pos				pos	pos	4
DMP	pos							1

In contrast to that, Baser et al. (2004) came to a TDI of 0.5 ng/kg bw/d, considering the same LOAEL. This would result in a drinking water value of 0.003 µg/l, a value at the level of our LOQ.

Although not exceeding the currently valid limit value, bisphenol A was found in concentrations higher than the recently envisaged maximum level: Its concentrations up to 0.021 µg/l in drinking water were above the limit value of 0.01µg/l for drinking water and groundwater proposed by the European Commission (based on the precautionary principle) (EC, 2018a; EC, 2018b)

Estrogens

The realization that hormones can reach the environment, even after treatment of sewage water, strengthened the search for the presence of pharmaceuticals and endocrine disrupting chemicals in water sources, such as sewage water effluent, surface water and groundwater (Kuch and Ballschmiter, 2001). These substances were associated with changes in microbial ecology, toxicological effects in aquatic species, and a negative effect on human health (Shore and Shemesh, 2016). Estrogen hormones are crucial for human biology and physiology. They help regulate reproduction, cardiovascular function, bone strength, cognitive behavior, successful pregnancy and gastrointestinal systems. Nevertheless, Adeel et al. (2017) illustrate in their review that they can have serious adverse effects if allowed to accumulate in the environment and to enter the human food chain. If consumed at levels above safe thresholds, they can increase the risk of cancer and induce cardiovascular diseases in humans. Supra-optimal levels of estrogens have been linked with increased incidence of breast cancer in females and prostate cancer in men, although cause-and-effect is debatable. Estrogens preferentially bind with receptor cells in breast tissues leading to cell proliferation that can ultimately form tumors (Adeel et al., 2017).

Loos et al. (2018) describe a proposal of the Joint research Centre (JRC) of the European Commission regarding the estrogens 17-alpha-ethinylestradiol (EE2), 17-beta-estradiol (E2), and estrone (E1), their Predicted no-effect concentration (PNECs), and criteria that substances can be taken out of the watch list. None of the three estrogens could be detected above the LOQ. In the case of E1 and E2 the LOQ (0.00013 and 0.00011 µg/l, respectively) was below the specific PNEC (0.0036 and 0.0004 µg/l, respectively). Even the JRC proposal was fulfilled laying down criteria that substances can be taken out of the watch list when ½ LOQ is below or equal to the PNEC. With EE2, a slightly different situation occurred because the PNEC (0.000035 µg/l) is below the LOQ (0.000084 µg/l) in our study, and therefore, no conclusion could be drawn whether the goal is reached or not. In Canada, mean influent concentrations of 17β-estradiol were 15.6 ng/l (range 2.4–26 ng/l), and of estrone 49 ng/l (range 19–78 ng/l); in final effluents, these were reduced to mean concentrations of 1.8 ng/l (range 0.2–14.7 ng/l) and 17 ng/l (range 1–96 ng/l), indicating a wide extent of variability of removal in different sewage treatment plants (Falconer, 2006). An Australian study showed the advantages of tertiary sewage

Table 8. Analytes found in concentrations above the limit of quantification (EQS = EU Environmental quality standards; PFOA = Perfluorooctanoic acid; PFOS = Perfluorooctanesulfonic acid; BPA = Bisphenol A; NP1EO = 4-nonylphenol monoethoxylate; BDE = Brominated diphenylether; PBDEs = Polybrominated diphenyl ethers) compared to limit values (* Default assumption for adults taking into consideration the WHO allocation concept; EQS = environmental quality standards; PV = parametric value according to the EU drinking water directive; GV = WHO guideline value; DWEL = US EPA drinking water equivalent level).

Tabelle 8. Analyte in Konzentrationen über der Bestimmungsgrenze (EQS = EU-Umweltqualitätsnormen; PFOA = Perfluorooctansäure; PFOS = Perfluorooctansulfonsäure; BPA = Bisphenol A; NP1EO = 4-Nonylphenolmonoethoxylat; BDE = bromierter Diphenylether; PBDE = Polybromierte Diphenylether) im Vergleich zu Grenzwerten (* Standard-Annahme für Erwachsene unter Berücksichtigung des WHO-Zuteilungskonzepts; EQS = Umweltqualitätsnormen; PV = Parameterwert gemäß EU-Trinkwasserrichtlinie; GV = WHO-Richtwert; DWEL = US EPA Trinkwasser-Äquivalenzniveau).

Source	Parameter	Number of samples/sources above LOQ/total number	Range/values	PV/GV/DWEL drinking water	Reference
			µg/l	µg/l	
drinking water	PFOA	3 out of 20	0.0042–0.0107	4	WHO, 2017a
bathing water		2 out of 5	0.0040–0.0050		
groundwater		7 out of 22	0.0026–0.0137		
river		1 out of 7	0.0032		
drinking water	PFOS	3 out of 20	0.0029–0.0433	0.4	WHO, 2017a
groundwater		4 out of 22	0.0036–0.0373		
river		1 out of 7	0.0052		
drinking water	BPA	4 out of 20	0.0075, 0.0089, 0.0131, 0.0209	0.01	EC, 2018b
groundwater		1 out of 22	0.0089		
bathing water		1 out of 5	0.0145	0.1	WHO, 2017a
drinking water	BDE28	1 out of 20	0.0000088	0.018*	ATSDR, 2017
drinking water	BDE 47	2 out of 20	0.00046–0.00049	1.03*	EFSA, 2011
groundwater		3 out of 22	0.00043–0.00062		
drinking water	BDE 99	2 out of 20	0.00015–0.00021	0.025*	EFSA, 2011
groundwater		3 out of 22	0.00014–0.00025		
groundwater	BDE 100	3 out of 22	0.000035–0.000056	12*	EPA, 2017
drinking water		2 out of 20	0.000048–0.000049		
drinking water	BDE 153	1 out of 20	0.00003	0.058*	EFSA, 2011
drinking water	BDE 154	1 out of 20	0.000029	1.2*	EPA, 2017
ground water		1 out of 22	0.000021		
bathing water	Di-(2-ethylhexyl)phthalate	1 out of 5	0.21	8	WHO, 2017b
groundwater		2 out of 22	0.32–0.37		
drinking water	Di-n-butylphthalate	1 out of 20	0.11	40.2*	ECHA, 2016
groundwater		5 out of 22	0.051–0.19		
drinking water	Diethylphthalate	1 out of 20	0.29	3000*	WHO, 2003
bathing water		2 out of 5	0.021–0.052		
river		4 out of 7	0.021–0.036		
groundwater		4 out of 22	0.022–0.094		
groundwater	Benzylbutylphthalate	1 out of 22	0.01	3000*	EFSA, 2005
groundwater	Dimethylphthalate	4 out of 22	0.012–0.024	toxicity less than other phthalates	US CPSC, 2010
river		1 out of 7	0.013		

treatment reducing 17β -estradiol levels of up to 19 ng/l by only traditional clarification and to < 7 ng/l by additional use of ozone or UV (Falconer, 2006). In the Paris region, all river samples showed both natural and synthetic estrogens at concentrations of 1.0 to 3.2 ng/l, with 35 to 50% of the estrogenic activity in the form of ethinylestradiol (Cargouët et al., 2003). In German rivers, the steroid hormones were found at 0.2 to 5 ng/l in surface waters and in drinking water at concentrations of 0.1 to 2 ng/l (Kuch and Ballschmiter, 2001). Our findings did not result in any detection of those hormones in Austria, with LODs ranging from 0.023 ng/l (ethinylestradiol) to 0.118 ng/l (estriole).

Brominated flame retardants

Brominated flame retardants (BFRs) are widely used in polymers and textiles and applied in construction materials, furniture, and electronic equipment. BFRs with the highest production volume are the polybrominated diphenyl ethers (PBDEs). Because of their persistence and low biodegradation profile, several of the PBDE congeners accumulate in biota and are widely found in the aquatic food chain (Weijs et al., 2015). Their levels in the environment and in humans have increased during the last decades, in contrast, for example, to compounds such as polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDT) (Usenko et al., 2016). PBDEs exhibit a great variety of biological effects, depending on the bromine substitution pattern. They are potential endocrine disruptors, based on shared toxicity with the structurally related PCBs, polychlorinated dibenzofurans (PCDFs), and polychlorinated dibenzodioxins (PCDDs) (Vos et al., 2003). Regarding polybrominated diphenyl ethers (PBDEs) in surface waters, no single value and also not the sum of measured parameter values reached by far the permissible maximum concentration of 0.14 µg/l referred to by Brielmann et al. (2018). They were not even found above the LOQ in rivers or bathing waters. In our measurements of PFAs, the permissible maximum concentration of PFOS in surface waters in Austria (Brielmann et al., 2018), 36 µg/l, was not reached, being several orders of magnitude below. These values also came significantly below the proposed values (in a future amendment of the EU Drinking Water Directive) of 0.1 µg/l for the single substance and of 0.5 µg/l for the sum of PFAS (Briemann et al., 2018), in analogy to the EU pesticides regulation. Lütjohann et al. (2006) found the levels of BFRs of up to more than 130 ng/l in the German surface waters, with a mean of about 30 ng/l.

Christale et al. (2013) investigated PBDEs along a river affected by urban and industrial pressures in the UK and detected BDE 209 in most of the sampled sites in concentrations ranging from 17 to 295 ng/l depending on the location. In our study, PBDEs were detected in 3 (15%) drinking water samples, and in 4 (18.2%) groundwater samples, but not in surface water, with a maximum concentration of 0.62 ng/l for BDE 47 in groundwater.

Phthalates

Phthalates are found in a large number of articles. What is common to this group is that the objects are wholly or partly made of soft PVC. Ortho-phthalates comprise a large group of substances presenting both different and similar toxicological effects. Impairment of reproduction, especially in humans, is an effect which has been linked to a number of low molecular weight phthalates. These have been reported for diethylhexyl phthalate (DEHP), the most widely studied phthalate in the low molecular weight phthalate group, but also for dibutyl phthalate (DBP), benzyl butylphthalate (BBP), and diisobutyl phthalate (DIBP) (Kay et al., 2013). One feature these four phthalates have in common is that they produce an antiandrogenic pattern of effects and should, therefore, also be assessed together (Kay et al., 2013). Also, the high molecular weight phthalate diisononyl phthalate (DINP) is suspected of possibly being toxic for reproduction based on an antiandrogenic pattern of effects; however, DINP is not classified as toxic for reproduction (Kay et al., 2013). Diisodecyl phthalate (DIDP), another very common high molecular weight phthalate, is suspected of being toxic for reproduction, but probably via a different type of mechanism. Therefore, DIDP does not contribute to the antiandrogenic effects (KEMI, 2015). Peijnenburg and Struijs (2006) found phthalates in Dutch fresh water in concentrations of up to 2.35 µg/l and of up to 4.96 µg/l in surface water. In water samples from the Irish Shannon river basin, DEHP was found to occur at levels of 0.77–92.84 µg/l (Jones et al., 2017). We found phthalates in 2 (10%) drinking water samples, in 11 (50%) groundwater samples, in 3 (60 %) bathing water samples, and in 4 (57.1%) river samples. The highest value was with di-(2-ethylhexyl)phthalate (0.37 µg/l, groundwater).

Per- and polyfluoroalkyl substances (PFAS)

Per- and polyfluoroalkyl substances (PFAS) are a group of man-made chemicals that include perfluorooctanoic acid

(PFOA), and perfluorooctane sulfonic acid (PFOS). PFAS have been manufactured and used in a variety of industries around the globe. PFAS often can be found—amongst other—in drinking water, typically localized and associated with specific facilities (e.g., manufacturer, landfill, wastewater treatment, firefighter training facility) (Banzhaf et al., 2017).

It is known from animal studies that short chain PFAS are almost completely absorbed orally and by inhalation, but that skin absorption may be negligible. Both short- and long-chain perfluoroalkyl acids (PFAAs) are considered metabolically inert. The strong C-F bonds exclude any normal degradation pathway. Any functional derivative (precursor) will ultimately be transformed through several steps to the acids (Health Canada, 2016). In animal experiments, the acute toxicity of short-chain PFAS is low. After repeated exposure, large doses of short-chain PFAS may damage the liver and kidneys. In general, PFAS are more toxic to males than females having a higher elimination rate (Health Canada, 2016). In various animal and in vitro studies, PFAS have shown effects on thyroid hormones and decreased their levels. The toxicokinetics and toxicity in humans for short-chain PFAS are mainly investigated for perfluorohexane sulfonic acid (PFHxS), a substance that has rather similar properties as PFOS. There are studies showing associations between PFHxS and effects on lipid metabolism, fertility, thyroid hormones, asthma, and children's behavior (Kjølholt et al., 2015).

In their recent comprehensive paper on worldwide occurrence and levels of newly-identified perfluoroalkyl and polyfluoroalkyl substances in drinking water, Kaboré et al. (2018) screened, in total, 29 target and 104 suspect-target PFASs in drinking water samples ($n = 97$) from Canada and other countries (Burkina Faso, Chile, Ivory Coast, France, Japan, Mexico, Norway, and the USA) in 2015–2016. Out of the 29 PFASs quantitatively analyzed, perfluorocarboxylates (PFCAs: C4/14), perfluoroalkane sulfonates (PFSAs: C4, C6, C8), and perfluoroalkyl acid precursors (e.g., 5:3 fluorotelomer carboxylate (5:3 FTCA)) were recurrently detected in drinking water samples in concentrations up to 39 ng/l. Tap water samples from Canada showed noteworthy differences depending on their source; for instance, the sum of the 29 PFAS was significantly greater in samples from the Great Lakes/St. Lawrence river ecosystem than those produced from other sources (14 versus 5.3 ng/l). We found perfluoroalkyl substances, perfluorooctanoic acid and perfluorooctanesulfonic acid, in 5 (25%) drinking water samples, in 8 (36.4%) groundwater samples, in

2 (28.6%) river samples, and in 2 (40%) bathing water samples, with a maximum concentration of 0.0433 $\mu\text{g/l}$ found for perfluorooctanesulfonic acid in drinking water.

Alkylphenols

Alkylphenols are ultimate breakdown products of alkylphenol polyethoxylate (APEs) that are used in cleaning and industrial processes. The most commonly used APEs in the market are the nonylphenol ethoxylates (NPEs) and octylphenol ethoxylates (OPEs). As a result of their widespread use and their lipophilic nature, these compounds are ubiquitous in the environment and currently of concern because of their toxicity and estrogenic properties (Kovarova et al., 2013). Alkylphenol ethoxylates, including their degradation products alkylphenols octylphenol (OP) and nonylphenol (NP), have long been known to be estrogenic (Dodds and Lawson, 1938). OP and NP have been found to be estrogenic in several in vitro and in vivo systems, where OP is the most potent of the alkylphenols. Critical effects due to OP exposure are changes in sperm morphology in rats and increased length of gestation in pigs. The critical effect of NP exposure is increased kidney weight (Jonsson, 2006). Our sole findings of substances of that group regarded 4-nonylphenol-monoethoxylate (NP1EO) in one river and in two groundwater samples, with a maximum value of 23.4 ng/l (groundwater).

Bisphenol A

Bisphenol A (BPA) is an estrogen mimic used in the manufacture of plastics, lacquers, and packaging materials. Although initially considered to be a weak environmental estrogen, more recent studies have demonstrated that BPA may be similar in potency to estradiol in stimulating some cellular responses. Moreover, emerging evidence suggests that BPA may influence multiple endocrine-related pathways (Rubin, 2011). BPA has been shown to play a role in the pathogenesis of several endocrine disorders, including female and male infertility, precocious puberty, hormone dependent tumors, such as breast and prostate cancer, and several metabolic disorders, including polycystic ovary syndrome (PCOS) (Konieczna et al., 2015).

Staniszewska et al. (2015) reported concentrations of bisphenol A (BPA), 4-tert-octylphenol (OP) and 4-nonylphenol (NP) in surface and near-bottom water of the Gulf of Gdansk, as well as in flowing rivers in samples taken in the period 2011–2012; BPA in concentrations ranging

from < 5.0 to 277.9 ng/l; OP from < 1.0 to 834.5 ng/l, and NP from < 4.0 to 228.6 ng/l. The authors argue these values to be similar to those in other regions of Europe. Lv et al. (2016) detected OP and NP with concentrations ranging from below LOD to 0.49 ng/l and below LOD to 3.27 ng/l in two drinking water works, which take the source water from Taihu Lake in Jiangsu province (China). In these drinking water facilities, bisphenol A was found in concentrations ranging from below LOD up to 17.73 ng/l by Lv et al. (2016).

Besides, the already mentioned values of < 5.0 to 277.9 ng/l (Konieczna et al., 2015), in a German study, bisphenol A was found in surface waters at concentrations of 0.5 to 16 ng/l, and in drinking water at concentrations of 0.3 to 2 ng/l (Kuch and Ballschmiter, 2001).

We detected BPA in 4 (20%) drinking water samples, in 1 (4.5%) groundwater sample, and in 1 (20%) bathing water sample, with a maximum value of 20.9 ng/l (drinking water). Recent restrictions on the use of bisphenol A (BPA), in varnishes and coatings intended to come into contact with food, have been imposed by Regulation No 2018/213 at the European level (EC, 2018c). By amending Regulation (EU) No 10/2011, this latest regulation tightens or introduces new measures on the uses of BPA as a monomer in the production of plastic materials, such as polycarbonate plastic, and in epoxy resins used in varnishes and coatings. Under REACH, in addition to identifying BPA as a substance of very high concern (SVHC) (ECHA, 2017), a new restriction for BPA present in thermal paper will apply from 2020 (EC, 2016). Stricter threshold values have also been introduced for toys and in the workplace (EC, 2017a), whilst exemptions will need to be requested in the future on its use in medical devices (EC, 2017b). The European Commission, moreover, announced plans to undertake a new strategy in the future to minimize exposure to endocrine disruptors, including from food packaging (EC, 2018b).

Triclosan

Triclosan has been used worldwide as a broad-spectrum antibacterial agent for over 40 years. Increasingly, reports indicate frequent detection and broad exposure to triclosan in the natural environment and the human body. Laboratory studies in various species provide strong evidence for its disrupting effects on the endocrine system, especially affecting reproductive hormones. Multiple modes of action have been suggested, including disrupting hormone

metabolism, displacing hormones from hormone receptors and disrupting steroidogenic enzyme activity (Wang and Tian, 2015). Although epidemiological studies on its effects in humans are mostly negative and conflicting, the evidence suggests that triclosan is an EDC (Wang and Tian, 2015).

In the United States (1999–2012), triclosan was detected, most frequently in untreated waters (92% detection frequency; mean \pm standard error, 11 270 \pm 2925 ng/l; n = 237), but concentrations were significantly reduced in effluent waters (83% detection frequency; 775 \pm 311 ng/l; n = 192, α = 0.05) (Perez et al., 2013). Triclosan concentration in effluent-impacted environmental waters (62% detection frequency; 130 \pm 17 ng/l; n = 228) was not significantly reduced from effluent waters but was significantly greater than triclosan in environmental waters not classified as effluent impacted (11% detection frequency; 13 \pm 3 ng/l; n = 1195). In finished drinking water, triclosan was largely undetected (1% detection frequency; 4 \pm 2 ng/l; n = 453), suggesting that for the United States, drinking water is not an appreciable source of triclosan exposure. In post treatment water, average triclosan concentrations were below part-per-billion levels (Perez et al., 2013). In our samples, triclosan was not found above an LOQ of 3.31 ng/l.

EDCs in thyroid-signaling pathway

There is growing evidence that EDCs can disrupt thyroid homeostasis, even though the most important knowledge on this topic derives from animal studies, while clinical studies are still few and controversial (Gore et al., 2015). All the substance groups investigated are suspected of having anti-thyroid effects in some way, with specific attention to fetal and early childhood exposure, potentially affecting various brain processes such as neurogenesis, neural differentiation and migration, as well as neural connectivity, leading to morphological brain abnormalities (e.g., cortical thinning) consistent with neurodevelopmental impairment. Ghassabian and Trasande (2018) describe the following in a review: a) Experimental studies have shown that PBDEs, at environmentally relevant doses, bind to receptors, inhibit binding of triiodothyronine (T3) to thyroid hormone receptors (TRs) and suppress T3 actions; b) In vivo, bisphenol A can impair thyroid hormone action by antagonizing T3-induced TR activation (TR α 1 and TR β 1) and by suppressing its transcriptional activity in a dose-dependent manner; c) Triclosan affects thyroid hormone-dependent

metamorphosis in animals; d) Urinary phthalates are cross-sectionally associated with lower free thyroxine (fT₄) and higher thyroid stimulating hormone (TSH); e) PFASs interfere with binding of thyroid hormone to transthyretin and upregulate deiodinase in the thyroid gland. Thyroid disruption is of particular interest because several EDCs interfere with thyroid function in a sex-specific manner, which might explain the sexual dimorphism in the brain effect of EDCs (de Cock et al., 2014).

Exposure to EDCs and neurobehavioral development

US children's centers are exploring associations between brain development and environmental toxicants such as, amongst others: phthalates, bisphenol A, and polybrominated diphenyl ethers (US EPA, 2017). Prenatal exposure has shown a relationship between gestational levels of BPA or phthalates to adverse cognitive and behavioral outcomes, demonstrating links to attention deficit hyperactivity disorder, reduced intelligence quotient, lessened self-regulatory capacities, anxiety, depression, lower memory function and structural changes to the brain (Palanza et al., 2016; US EPA, 2017).

5. Conclusions

In 39 (72.2%) of the 54 samples tested in the Austrian survey presented, at least one endocrine disrupting or potentially disrupting chemical was found at or above the limit of quantification (LOQ). Regarding measurements, 539 (96.3%) out of 560 measurements in drinking water, 576 (93.5%) out of 616 measurements in groundwater, and 322 (95.8%) out of 336 measurements in surface water revealed no analytes at or above the respective LOQs. None yielded estrogens or triclosan in detectable levels. With one possible exception, no values were found above currently tolerable maximum levels (regulatory or health-based guidance values and drinking water thresholds derived from them). The sole exception regards the bisphenol A concentrations (0.013 and 0.021 µg/l) measured in drinking water, taking into account a proposed value of 0.01 µg/l in drinking water and groundwater (EC, 2018b). However, it has to be mentioned that the proposed values are set on the basis of the precautionary principle, taking the still debated sensitivities in the low-dose range into consideration. In contrast to that, using the WHO allocation system, the current tolerable daily intake (TDI) is 4 µg/kg bw/d, result-

ing in 24 µg/l drinking water for an adult or 5.3 µg/l for an infant (WHO, 2017a). In that case, there would be a safety margin of approximately three powers of ten between the values measured and the TDI, and the respective calculated maximum drinking water value. Compared to a preceding survey ARCEM (2003), where endocrine disruptors in Austrian waters were surveyed, it can be stated that a) the analytical sensitivity has been improved significantly in the meantime; the LOQs in the ARCEM project were much higher than in our study; b) for all parameters investigated, top values found in 2003 were substantially higher than those of our 2017/2018 survey; c) in the ARCEM project, at least some samples exceeded limit values, currently in effect or proposed and taken as basis for our assessment, both in groundwater and in surface water. These findings of the survey presented here underline the considerable improvement in environmental protection achieved during the past 15 years in Austria. However, although below the current maximum values for drinking water, a substantial number of drinking and groundwater samples yielded PFOA and PFOS, with the maximum levels detected somewhat lower for surface water than for groundwater and drinking water. This reflects in general the situation in North America and other European countries. Although measures are in place to restrict the production, use or major exposure risks to PFOS, the ubiquitous use of PFAAs within the built-up environment still causes their transfer to bio solids (Clarke and Smith, 2011). The use of bio solids as fertilizers may thus represent a source of soil and water contamination with PFOS (Clarke and Smith, 2011).

In this context, the ongoing activity of the European Food Safety Authority (EFSA) panel on contaminants in the food chain (CONTAM) regarding PFAS is worthy of notice, which may lead to a reduction of health based guidance values for PFOA and PFOS, and may induce a review of 'safe' or 'recommended' levels for brownfields (potentially contaminated sites) (re)development (Rose, 2017). Other substances found above the LOQ, although in minuscule amounts compared to the limit value, were the PBDEs, whereby a somewhat better situation was found with surface water than with drinking and groundwater, although—as mentioned before—at very low levels. PBDEs are ubiquitously present in the environment and likewise in biota and in food and feed (EFSA, 2011). Another group detected above the LOQ were the phthalates, with diethyl phthalate being the most abundant of our analytes, whereby the situation, not regarding the maximum level but the percentage of contamination, seems to

be somewhat better with drinking water than with groundwater or surface water. In addition to being in consumer products, phthalates are pervasive in the environment and have been found in food, drinking water, household dust, and indoor air (CPSC, 2010). Albeit ranging still well below the LOQ, we found di-(2-ethylhexyl)phthalate (DEHP) as a group member with the lowest margin of safety as against the guideline value. DEHP is used primarily as a plasticizer. In another study investigating surface water, groundwater and drinking water, concentrations of a few micrograms per liter of DEHP were found, that is, more than ten times the concentrations present in our samples (WHO, 2017b). In polluted surface water and groundwater, concentrations of more than a hundred micrograms per liter have been reported (WHO, 2017b).

The possible detrimental effects of endocrine disruptors on development, reproduction, growth, metabolism and obesity, constitute a serious public health issue. Concerning the mechanisms of action of EDCs, many questions remain unanswered. Moreover, nonlinear/non-monotonic action (as opposed to toxic dose-effect), cocktails consisting of EDCs with possible additive or synergistic or antagonistic effects, latency, window of exposure and the possibility of transgenerational effects are under intense scientific discussion.

Exposure to EDCs is ubiquitous and can occur during potentially sensitive periods of development that are important in the etiology of childhood neurodevelopmental disorders and obesity (Ghassabian and Trasande, 2018). The available research suggests that prenatal exposure to some EDCs are related to adverse neuro-behavioral outcomes in children, while prenatal exposure to other EDCs is related to reduced fetal growth and excess childhood adiposity (US EPA, 2017). The EU has put legislation in place which may lead to EDCs being removed from the market, because of regulating EDCs on the basis of their hazards, not of their risks (EC, 2009; EC, 2012).

The ultimate public health goal must be to further reduce and restrict the production of EDCs and therewith decrease and, eventually, eliminate the contamination of water resources by EDCs with technical and regulatory measures.

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References

- Adeel, M., Song, X., Wang, Y., Francis, D. and Y. Yang (2017): Environmental impact of estrogens on human, animal and plant life: A critical review. *Environment International* 99, 107–119.
- AGES and Umweltbundesamt (2015): Monitoringprogramm von Pharmazeutika und Abwasserindikatoren in Grund- und Trinkwasser. Forschungsprojekt – Endbericht, Vienna, 2015, ISBN 978-3-902611-97-0. https://www.bmgf.gv.at/home/Gesundheit/VerbraucherInnenengesundheit/Lebensmittel/Trinkwasser/Monitoringprogramm_von_Pharmazeutika_und_Abwasserindikatorenin_Grund_und_Trinkwasser. Accessed 12 July 2018.
- ARCEM (Austrian Research Cooperation on Endocrine Modulators) (2003): Hormonwirksame Stoffe in Österreichs Gewässern – Ein Risiko? Forschungsbericht. Umweltbundesamt GmbH, Vienna. <http://www.umweltbundesamt.at/fileadmin/site/publikationen/DP102.pdf>. Accessed on 12 July 2018.
- ATSDR (Substances and Disease Registry) and EPA (Environmental Protection Agency) (2018): Agency for Toxic Substances and Disease Registry. Minimal Risk Levels (MRLs) 2018. https://www.atsdr.cdc.gov/mrls/pdfs/atsdr_mrls.pdf. Accessed on 12 July 2018.
- Banzhaf, S., Filipovic, M., Lewis, J., Sparrenbom, C.J. and R. Barthel (2017): A review of contamination of surface-, ground-, and drinking water in Sweden by perfluoroalkyl and polyfluoroalkyl substances (PFASs). *Ambio* 46, 335–346.
- Baser, M. (2004): Risk assessment on butylphenol, octylphenol and nonylphenol, and estimated human exposure of alkylphenols from Swedish fish. *Ekotoxikologiska avdelningen Nr 109*. Graduate project in ecotoxicology from the Department of Environmental Toxicology, Evolutionary Centre, Uppsala University. http://www.uu.se/digitalAssets/177/177024_3jonsson-beatrice-report.pdf. Accessed on 12 July 2018.
- Bergman, A., Heindel J.J., Jobling, S., Kidd, K.A. and R.T. Zoeller (Eds.) (2013): State of the Science of Endocrine Disrupting Chemicals – 2012. An Assessment of the State of the Science of Endocrine Disruptors Pre-

- pared by a Group of Experts for the United Nations Environment Programme and World Health Organization, United Nations Environment Programme and the World Health Organization, Geneva, Switzerland, ISBN: 978-92-807-3274-0 (UNEP) and 978 92 4 150503 1 (WHO).
- Blake, C.A., Boockfor, F.R., Nair-Menon, J.U., Millette, C.F., Raychoudhury, S.S. and G.L. McCoy (2004): Effects of 4-tert-octylphenol given in drinking water for 4 months on the male reproductive system of Fischer 344 rats. *Reproductive Toxicology* 18, 43–51.
- Borgert, C.J., Baker, S.P. and J.C. Matthews (2013): Potency matters: Thresholds govern endocrine activity. *Regulatory Toxicology and Pharmacology* 67, 83–88.
- Brielmann, H., Wemhöner, U., Clara, M., Scharf, S., Grath, J., Zieritz, I., Kulcsar, S., Schuhmann, A. and R. Philippitsch (2018): Spurenstoffe im Grundwasser – Untersuchungen zum Vorkommen von Quecksilber und 30 ausgewählten organischen Substanzen anthropogener Herkunft. Bundesministerium für Nachhaltigkeit und Tourismus, Wien. https://www.bmnt.gv.at/wasser/wasserqualitaet/grundwasser/spurenstoffe_gw_2018.html. Accessed on 11 September 2018.
- Cargouët, M., Perdiz, D., Mouatassim-Souali, A., Tamisier-Karolak, S. and Y. Levi (2003): Assessment of river contamination by estrogenic compounds in Paris area (France). *Science of the Total Environment* 324, 55–66.
- Christale, J., Katsoyiannis, A., Sweetman, A.J., Jones, K.C. and S. Lacorte (2013): Occurrence and risk assessment of organophosphorus and brominated flame retardants in the River Aire (UK) *Environmental Pollution* 179, 194–200.
- Clarke, B.O. and S.R. Smith (2011): Review of ‘emerging’ organic contaminants in biosolids and assessment of international research priorities for the agricultural use of biosolids. *Environment International* 37, 226–247.
- CPSC (U.S. Consumer Product Safety Commission, Division of Health Sciences) (2010): Overview of Dialkyl Ortho-Phthalates. <http://www.cpsc.gov/about/cpsia/phthalover.pdf>. Accessed on 12 July 2018.
- Damstra, T., Barlow, S., Bergman, A., Kavlock, R. and G. Van Der Kraak (2002): Global Assessment of the State-of-the-Science of Endocrine Disruptors. WHO publication no. WHO/PCS/EDC/02.2. World Health Organization, Geneva, Switzerland.
- de Cock, M., de Boer, M.R., Lamoree, M., Legler, J. and M. van de Bor (2014): Prenatal exposure to endocrine disrupting chemicals in relation to thyroid hormone levels in infants – a Dutch prospective cohort study. *Environmental Health* 13, 106.
- Dodds, E.C. and W. Lawson (1938): Molecular structure in relation to oestrogenic activity. Compounds without a phenanthrene nucleus. *Proceedings of the Royal Society of London* 125, 222–232.
- EC (European Commission) (2009): EC, 2009. Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. *Official Journal L* 309/1, 24.11.2009.
- EC (European Commission) (2012): Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products. *Official Journal L* 167/1, 27.6.2012.
- EC (European Commission) (2017a): Commission Directive (EU) 2017/898 amending, for the purpose of adopting specific limit values for chemicals used in toys, Appendix C to Annex II to Directive 2009/48/EC of the European Parliament and of the Council on the safety of toys, as regards bisphenol A. *Official Journal L* 138/128, 25.5.2017.
- EC (European Commission) (2013): Directive 2013/39/EU of the European parliament and of the council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy. *Official Journal L* 226/1, 24.8.2013.
- EC (European Commission) (2016): Commission Regulation (EU) 2016/2235 amending Annex XVII to Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards bisphenol A. *Official Journal L* 337/3, 13.12.2016EC, 2017b.
- EC (European Commission) (2017a): Commission Directive (EU) 2017/164 establishing a fourth list of indicative occupational exposure limit values pursuant to Council Directive 98/24/EC, and amending Commission Directives 91/322/EEC, 2000/39/EC and 2009/161/EU. *Official Journal L* 27/115, 1.2.2017.
- EC (European Commission) (2017b): Regulation (EU) 2017/745 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. *Official Journal L* 117/1, 5.5.2017.
- EC (European Commission) (2018a): European Commission. Q & A BPA. February 2018. <https://ec.europa>.

- eu/food/sites/food/files/safety/docs/cs_fcm_qa_bisphenol_a.pdf. Accessed on 12 July 2018.
- EC (European Commission) (2018b): European Commission. ANNEXES to the Proposal for a Directive of the European Parliament and of the Council on the quality of water intended for human consumption (recast). COM (2017) 753 final. Brussels, 1.2.2018.
- EC (European Commission) (2018c): Commission Regulation (EU) 2018/213 on the use of bisphenol A in varnishes and coatings intended to come into contact with food and amending Regulation (EU) No 10/2011 as regards the use of that substance in plastic food contact materials. Official Journal L 41/6, 14.2.2018.
- ECHA (European Chemicals Agency) (2017): Agreement of the Member State Committee on the Identification of 4,4'-Isopropylidenediphenol (Bisphenol A) as a Substance of Very High Concern According to Articles 57 and 59 of Regulation (EC) 1907/2006. Adopted on 14 December 2017. <https://echa.europa.eu/identification-of-svhc/-/substance-rev/18101/term>. Accessed on 12 July 2018.
- ECHA (European Chemicals Agency) and EFSA (European Food Safety Authority) with support from the JRC (Joint Research Centre) (2018): Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. Pre-publication version. Drafted by EFSA and ECHA staff, with support from JRC. EFSA Journal 16, 5311.
- EFSA (European Food Safety Authority) (2005): Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to Butylbenzylphthalate (BBP) for use in food contact materials. EFSA Journal 241, 1–14.
- EFSA (European Food Safety Authority) (2011): Scientific Opinion on Polybrominated Diphenyl Ethers (PBDEs) in Food. EFSA Panel on Contaminants in the Food Chain (CONTAM). EFSA Journal 9, 2156.
- Falconer, I.R. (2006): Are Endocrine Disrupting Compounds a Health Risk in Drinking Water? *International Journal of Environmental Research and Public Health* 3, 180–184.
- Forner-Piquer, I. (2018): Endocrine disruptors in the diet of male *Sparus aurata*: Modulation of the endocannabinoid system at the hepatic and ventral level by Di-isononyl phthalate and Bisphenol A. *Environment International* 119, 65–65.
- Fucic, A., Galea, K.S., Duca, R.C., El Yamani, M., Frery, N., Godderis, L., Halldorsson, T.I., Iavicoli, I., Ndaw, S., Ribeiro, E., Viegas, S. and H. Moshhammer (2018): Potential Health Risk of Endocrine Disruptors in Construction Sector and Plastics Industry: A New Paradigm in Occupational Health. *International Journal of Environmental Research and Public Health* 15, E1229.
- Fürhacker, M. (2017): Endokrine Disruptoren – eine komplexe Herausforderung. *Österreichische Wasser- und Abfallwirtschaft* 69, 317–326.
- Ghassabian, A. and L. Trasande (2018): Disruption in Thyroid Signaling Pathway: A Mechanism for the Effect of Endocrine-Disrupting Chemicals on Child Neurodevelopment. *Frontiers in Endocrinology* 9, 204.
- Gore, A.C., Chappell, V.A., Fenton, S.E., Flaws, J.A., Nadal, A., Prins, G.S., Toppari, J. and R.T. Zoeller (2015): EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocrine Reviews* 36, E1–E150.
- Health Canada (2016): Perfluorooctane Sulfonate (PFOS) in Drinking Water. Document for Public Consultation Prepared by the Federal-Provincial-Territorial Committee on Drinking Water. <http://healthycanadians.gc.ca/health-system-systeme-sante/consultations/perfluorooctane-sulfonate/alt/perfluorooctane-sulfonate-eng.pdf>. Accessed on 12 July 2018.
- Jones, L., Allen, C., Regan, F., Staines, A. and J. Lawler (2017): Phthalates in the Environment: An Irish Perspective. http://doras.dcu.ie/21968/3/Euroanalysis_2017_pdf.pdf. Accessed on 12 July 2018.
- Jonsson, B. (2006): Risk assessment on butylphenol, octylphenol and nonylphenol, and estimated human exposure of alkylphenols from Swedish fish. *Ekotoxikologiska Avdelningen Nr 109*, Uppsala University, http://www.uu.se/digitalAssets/177/177024_3jonsson-beatrice-report.pdf. Accessed on 12 July 2018.
- Kabir, E.R., Rahman, M.S. and I. Rahman (2015): A review on endocrine disruptors and their possible impacts on human health. *Environmental Toxicology and Pharmacology* 40, 241–258.
- Kaboré, H.A., Vo Duy, S., Munoz, G., Méité, L., Desrosiers, M., Liu, J., Sory, T.K. and S. Sauvé (2018): Worldwide drinking water occurrence and levels of newly-identified perfluoroalkyl and polyfluoroalkyl substances. *Science of the Total Environment* 616–617, 1089–1100.
- Kay, V.R., Chambers, C. and W.G. Foster (2013): Reproductive and developmental effects of phthalate diesters in females. *Critical Reviews in Toxicology* 43, 200–219.

- KEMI (Swedish Chemicals Agency) (2015): Phthalates which are toxic for reproduction and endocrine-disrupting – proposals for a phase-out in Sweden. Report from a government assignment. Swedish Chemicals Agency. Print: Arkitektkopia, Stockholm. ISSN 0284-1185. <https://www.kemi.se/global/rapporter/2015/report-4-15-phatalates.pdf>. Accessed on 12 July 2018
- Kjølholt, J., Jensen, A.A. and A.M. Warming (2015): Short-chain Polyfluoroalkyl Substances (PFAS). A literature review of information on human health effects and environmental fate and effect aspects of short-chain PFAS. Environmental project No. 1707, The Danish Environmental Protection Agency, Copenhagen, Denmark, ISBN no. 978-87-93352-15-5.
- Konieczna A, Rutkowska, A. and D. Rachoń (2015): Health Risk of Exposure to Bisphenol A (BPA). *Roczniki Państwowego Zakładu Higieny* 66, 5–11.
- Kovarova, J., Blahova, J., Divisova, L. and Z. Svobodova (2013): Alkylphenol ethoxylates and alkylphenols– update information on occurrence, fate and toxicity in aquatic environment. *Polish Journal of Veterinary Sciences* 16, 763–772.
- Kuch, H.M. and K. Ballschmiter (2001): Determination of endocrine-disrupting phenolic compounds and estrogens in surface and drinking water by HRGC-(NCI)-MS in the picogram per liter range. *Environmental Science & Technology* 35, 3201–3206.
- Loos, R., Marinov D., Sanseverino, I., Napierska, D. and T. Lettieri (2018): Review of the 1st Watch List under the Water Framework Directive and recommendations for the 2nd Watch List, EUR 29173 EN, Publications Office of the European Union, Luxembourg, ISBN 978-92-79-81839-4.
- Lütjohann, J., Vogt, M., Wunsch, H., Kuballa, J. and E. Jantzen (2006): Occurrence of Brominated Flame Retardants in Wildlife and the Environment. Electronic poster from GALAB Laboratories GmbH, Geesthacht; Germany. https://www.galab.de/de/umwelt/pdf/Poster_BFR.pdf. Accessed on 12 July 2018.
- Lv, X, Xiao, S., Zhang, G., Jiang, P. and F. Tang (2016): Occurrence and removal of phenolic endocrine disrupting chemicals in the water treatment processes. *Scientific Reports* 6, 22860.
- Manning, T. (2005): Endocrine-disrupting Chemicals: A review of the State of the Science. *Australasian Journal of Ecotoxicology* 11, 1–52.
- Palanza, P., Nagel, S.C., Parmigiani, S. and F.S. Vom Saal (2016): Perinatal exposure to endocrine disruptors: Sex, timing and behavioral endpoints. *Current Opinion in Behavioral Sciences* 7, 69–75.
- Peijnenburg, W.J. and J. Struijs (2006): Occurrence of phthalate esters in the environment of the Netherlands. *Ecotoxicology and Environmental Safety* 63, 204–215.
- Perez, A.L., De Saylor, M.A., Slocombe, A.J., Lew, M.G., Unice, K.M. and E.P. Donovan (2013): Triclosan occurrence in freshwater systems in the United States (1999–2012): A meta-analysis. *Environmental Toxicology and Chemistry* 32, 1479–1487.
- Rose, M. (2017): Per- and Polyfluorinated alkyl substances - EFSA activities. Presentation at Current Issues in Contaminated Land Risk Assessment – 2017. Royal Society of Chemistry, Burlington House, London. <http://www.rsc.org/events/download/Document/ac7b2a7e-40d9-4cd9-ac3e-c1db45892d83>. Accessed on 12 July 2018.
- Rubin, B.S. (2011): Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. *The Journal of Steroid Biochemistry and Molecular Biology* 127, 27–34.
- Schug, T.T., Johnson, A.F., Birnbaum, L.S., Colborn, T., Guillette, L.J., Crews, D.P., Collins, T., Soto, A.M., Vom Saal, F.S., McLachlan, J.A., Sonnenschein, C. and J.J. Heindel (2016): Minireview: Endocrine Disruptors: Past Lessons and Future Directions. *Molecular Endocrinology* 30, 833–847.
- Shore, L.S. and M. Shemesh (2016): Estrogen as an Environmental Pollutant. *Bulletin of Environmental Contamination and Toxicology* 97, 447–448.
- Staniszewska, M., Koniecko, I., Falkowska, L. and E. Krzemyk (2015): Occurrence and distribution of bisphenol A and alkylphenols in the water of the Gulf of Gdansk (Southern Baltic). *Marine Pollution Bulletin* 91, 372–379.
- Street, M.E., Angelini, S., Bernasconi, S., Burgio, E., Cassio, A., Catellani, C., Cirillo, F., Deodati, A., Fabbrizi, E., Fanos, V., Gargano, G., Grossi, E., Lughetti, L., Lazzeroni, P., Mantovani, A., Migliore, L., Palanza, P., Panzica, G., Papini, A.M., Parmigiani, S., Predieri, B., Sartori, C., Tridenti, G. and S. Amarri (2018): Current Knowledge on Endocrine Disrupting Chemicals (EDCs) from Animal Biology to Humans, from Pregnancy to Adulthood: Highlights from a National Italian Meeting. *International Journal of Molecular Sciences* 19, E1647.
- Usenko, C.Y., Abel, E.L., Hopkins, A., Martinez, G., Tijerina, J., Kudela, M., Norris, N., Joudeh, L. and E.D. Bruce (2016): Evaluation of Common Use Brominated

- Flame Retardant (BFR) Toxicity Using a Zebrafish Embryo Model. *Toxics* 4, E21.
- US EPA (Environmental Protection Agency) (2017): NIEHS/EPA Children's Environmental Health and Disease Prevention Research Centers Impact Report: Protecting children's health where they live, learn, and play. EPA Publication No. EPA/600/R-17/407. https://www.epa.gov/sites/production/files/2017-.10/documents/niehs_epa_childrens_centers_impact_report_2017_0.pdf?pdf=chidrens-center-report. Accessed on 12 July 2018.
- Vos, J.G., Becher, G., van den Berg, M., de Boer, J. and P.E.G. Leonards (2003): Brominated flame retardants and endocrine disruption. *Pure and Applied Chemistry* 75, 2039–2046.
- Wang, C.F. and Y. Tian, (2015): Reproductive endocrine-disrupting effects of triclosan: Population exposure, present evidence and potential mechanisms. *Environmental Pollution* 206, 195–201.
- Weijjs, L., Dirtu, A.C., Govindan, M. and A. Covaci (2015): Bioaccumulation and Biotransformation of Brominated Flame Retardants. *Comprehensive Analytical Chemistry* 67, 433–491.
- WHO (World Health Organization) (2017a): Regional Office for Europe. Drinking Water Parameter Cooperation Project. Support to the revision of Annex I Council Directive 98/83/EC on the Quality of Water Intended for Human Consumption (Drinking Water Directive). Recommendations. Bonn, 11 September 2017. http://ec.europa.eu/environment/water/water-drink/pdf/WHO_parameter_report.pdf. Accessed on 12 July 2018.
- WHO (World Health Organization) (2017b): Guidelines for Drinking-Water Quality: Fourth Edition Incorporating the First Addendum. World Health Organization, Geneva, Switzerland. <https://www.ncbi.nlm.nih.gov/books/NBK442376/>. Accessed on 12 July 2018.