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Endocrine-disrupting substances: I. Relative risks of PFAS in drinking water

Francisco Alberto Tomei Torres [a,*] and Susan J. Masten [b]

[a] Ibero-American Society of Environmental Health (SIBSA), Zabala 3555, Ciudad Autónoma de Buenos Aires (CABA), Rep. Argentina, CP 1427
[b] Department of Civil and Environmental Engineering, Michigan State University, East Lansing, MI 48823, USA
*Corresponding author. E-mail: fatomei@gmail.com

FAT, 0000-0002-5424-0355; SJM, 0000-0002-4983-4933

ABSTRACT

Concentrations of per and polyfluorinated alkyl substances (PFAS) in drinking water are significantly lower than *in vivo* levels of the native target hormone. These concentrations are orders of magnitude lower than the hormone in question, particularly when corrected for trans-activation. A pregnant woman can excrete about 7,000 μg/day of total estrogens. A low-dose oral contraceptive pill contains 20 μg estradiol. Soy-based baby formula contains phytoestrogens equivalent to a low-dose oral contraceptive pill. A woman on a low-dose oral hormone replacement therapy consumes about 0.5–2 mg/day of one or more estrogens. The levels of endocrine-disrupting substances (EDSs) exposure by oral, respiratory, or dermal routes have the potential to make removing PFAS from drinking water due to its estrogenic activity divert valuable resources. These levels become even less of a threat when their estrogenic potencies are compared with those of the target hormones present as contaminants in water and even more so when compared with levels commonly present in human tissues. The fact that PFAS constitute a tiny fraction compared to exposure to phytoestrogens makes the effort even more insignificant. If PFAS are to be removed from drinking water, it is not due to their estrogenic activity.

Key words: drinking water, endocrine-disrupting substances, estradiol, estrogen, PFAS, phytoestrogens

HIGHLIGHTS

- The levels of EDSs exposure by oral, respiratory, or dermal routes are significant.
- Exposure to estrogenic compounds is primarily through diet, not drinking water.
- PFAS in drinking water typically does not pose a threat due to estrogenic activity. PFAS in drinking water may pose a threat at contaminated sites, warranting remedial action.
- If PFAS is to be removed from drinking water, it is due to toxicity, not estrogenic activity.

INTRODUCTION

The Endocrine Society states that endocrine disruptors in environment, food, and consumer products can affect male and female reproduction, breast development and cancer, prostate cancer, neuroendocrinology, thyroid function, metabolism and obesity, and cardiovascular endocrinology (Diamanti-Kandarakis *et al.* 2009; Gore *et al.* 2015; Yilmaz *et al.* 2020). Endocrine-disrupting substances (EDSs) are suspected of increasing rates of low semen quality, genital malformations, adverse pregnancy outcomes, neurobehavioral disorders, endocrine-related cancers, early-onset of breast development in young girls, and increased prevalence of obesity and type 2 diabetes (e.g., see Bergman *et al.* 2013; Yang *et al.* 2015; Yilmaz *et al.* 2020).

Anthropogenic EDSs enter the environment from a variety of sources, including pharmaceuticals flushed down toilets, particles leached from plastic bottles, pesticides transported in runoff from agricultural areas and home lawns, sunscreens applied to the skin and excreted in urine, or antibacterial and antifungal agents in hygiene products (Jackson & Sutton 2008; Gore *et al.* 2015; La Merrill *et al.* 2020; Li *et al.* 2021; Wang *et al.* 2021). This review compares the estrogenic effects of per- and polyfluorinated alkyl substances (PFAS) in drinking water to that of natural estrogenic compounds in various substances. Table 1 provides a summary of EDSs and PFAS in various sources and typical concentrations or doses.

Table 1 | Concentrations of EDSs and PFAS in various sources

Source	Chemical	Concentration/Dose	Citation
Estrogens			
Oral contraceptive pills	Synthetic estrogen 17α-ethinyl estradiol	20–35 μg/day	Hatcher *et al.* (2013), Enna & Bylund (2007), Feisullin & Westhoff (2010)
Hormone replacement therapy	Estrogens	≥300 μg/day/dose	Fritz & Speroff (2011), Shen *et al.* (2016)
Human breast milk	Estrogens	0.5–2 μg/L milk or 0.5–2 μg/L for a nursing infant	Petrakis *et al.* (1987)
Milk and dairy products	Animal-derived estrogens	Estrone: 6.2–1,266 ng/L 17α-estradiol: 7.2–322 ng/L 17β-estradiol: 5.6–51 ng/L	Malekinejad & Rezabakhsh (2015)
Milk and dairy products	Animal-derived estrogens	Estrone: 130–260 ng/L 17β-estradiol: 28–62 ng/L	Farlow *et al.* (2012)
Drinking water	17α-ethinyl estradiol	<1 ng/L	Kumar *et al.* (2014)
Phytoestrogens			
Soy milk	Estradiol	4 μg/100 mL	Zava *et al.* (1998)
Various herbs		250 ng/g dried herb	Setchell *et al.* (1987), Adams (1995), Hatcher *et al.* (2013)
Consumer products			
Shampoos, lipsticks, soaps, and sunscreen	Benzophenone-3 (BP3)	Variable concentrations	Calafat *et al.* (2008), Krause *et al.* (2012), Ruszkiewicz *et al.* (2017)
Drinking water and food			
Drinking water	Benzophenone-3 (BP3)	n.d. – 72 ng/L levels	da Silva *et al.* (2015)
Foods	Per- and polyfluoroalkyl substances, PFAS	Average dietary intake in foods: ~20–75 ng/day	Ericson *et al.* (2008), Egeghy & Lorber (2011), Gebbink *et al.* (2015), Shan *et al.* (2016)
Fish and seafood (depends on type)	Sum of PFOS, PFOA, PFHpA (mean)	0.16–0.7 ng/g fresh weight	Ericson *et al.* (2008)
Pork, chicken, beef, mutton	Sum of 11 PFAS	3–28 ng/g wet weight	Shan *et al.* (2016)
Fruits and vegetables	Sum of 11 PFAS	1–7.5 ng/g wet weight	Shan *et al.* (2016)
Drinking water	PFOS	<1% of total exposure compared to food	Haug *et al.* (2011)
Drinking water	PFOA	~13% of total exposure compared to food	Haug *et al.* (2011)

Note: n.d., non-detect.

EDS concentrations have not been corrected for transactivity, which lowers the endocrine disruption activity by orders of magnitude as shown by Kjeldsen & Bonefeld-Jørgensen (2013).

Human beings, particularly women, already contain concentrations of natural estrogens in their tissues that are orders of magnitude (over a million times) higher than those found in drinking water. These natural estrogens show estrogenic potencies that are much higher than that of anthropogenic EDSs. Endocrine disruptors can be agonists or antagonists of endocrine function (Vestergren & Cousins 2009; Borgert *et al.* 2013; Borgert *et al.* 2018). Thus, concentrations of endocrine-disrupting micropollutants must be weighted for potency and agonist/antagonist properties to assess the risks from the endocrine-disrupting capabilities of the drinking waters.

Populations most at risk implicitly determine priorities for the regulation of EDSs. Women of childbearing age, children, and women being treated for menopause serve as examples to illustrate how the threat of endocrine disruption lies not with anthropogenic compounds but with natural estrogens.

Women undergo profound hormonal changes throughout their lives. Events of note are puberty, pregnancy, lactation, and menopause (Petrakis *et al.* 1987; Speroff & Darney 2011). No apparent correlation exists between breast fluid and serum estrogen levels.

1. Estrogen levels in breast fluid can be approximately 5–45 times higher than serum levels.
2. A pronounced increase in estrogen serum concentrations occurs during pregnancy.
3. Levels in breast fluids and blood sera drop significantly postpartum and during lactation.
4. At menopause, blood serum levels decrease, but levels in breast fluids remain high.
5. Babies receive increased concentrations when the lactating mother becomes pregnant or starts taking birth control pills.

Oral contraceptive pills are the primary anthropogenic endocrine disruptors in women. These pills have been the most popular mode of contraception among women of childbearing age (ages 15–49 years) for decades. About 25% of women in the United States took contraceptives at any given time during 2002–2017 (Mosher *et al.* 2004; Martinez *et al.* 2006; Jones *et al.* 2012; Daniels *et al.* 2014; Daniels & Abma 2018).

Women typically ingest 20–35 μg of synthetic estrogen 17α-ethinyl estradiol each time they take an oral contraceptive pill (Enna & Bylund 2007; Feisullin & Westhoff 2010; Hatcher *et al.* 2013). Oral contraceptives also contain progestin, too. Only 3 of about 100 pill formulations considered in the survey consisted of progestin alone. About 2% of women received only progestin (CDC 2002; Hatcher *et al.* 2013).

In later life, women on hormone replacement therapy take even higher amounts of estrogen. Premarin, a mixture of equine estrogens used to treat menopause (Fritz & Speroff 2011), is administered at doses of 300 μg and higher (Shen *et al.* 2016).

Children are at a significantly higher risk than adults for a particular level of exposure on a per-weight basis (Malekinejad & Rezabakhsh 2015; Lu *et al.* 2017). On a per-weight basis, a 4.5 kg baby who consumes 750 mL of human breast milk daily can receive over 10 times the dose an adult might receive. If the baby consumes 750 mL of cow's milk instead of human breast milk, the dose could double that which an adult might consume (Azzouz *et al.* 2011).

Milk and dairy products are the major sources of animal-derived estrogens in the human diet (Farlow *et al.* 2012; Malekinejad & Rezabakhsh 2015). They account for 60–70% of the estrogens consumed (Ganmaa *et al.* 2001). Soy milk contains about 4 μg of estradiol equivalents per 100 mL (Zava *et al.* 1998). If babies drink soy formula, as do 12% of babies receiving formula in the United States (Rossen *et al.* 2016), the adult-equivalent dose of estrogen increases to 30 μg, a dose typically found in low-dose oral contraceptives.

The level of estrogens in human breast milk is about 0.5 μg/L. However, the level in human breast milk increases to about 2 μg/L in pregnant lactating persons. As such, a nursing baby will receive 0.5–2 μg/day of estrogens from a lactating individual (Petrakis *et al.* 1987).

Ying *et al.* (2002) reviewed the occurrence and fate of hormone steroids in the environment. They measured 17α-ethinyl estradiol oral contraceptives at concentrations less than 100 ng/L in surface waters. These dosages must be contrasted with the presence of estradiol in sources of drinking water and EDSs that mimic estradiol. After drinking water treatment, concentrations are typically less than 1 ng/L (Kumar *et al.* 2014). A simple calculation would suggest that women using oral contraceptives with intended therapeutic effects experience far greater endocrine disruption by taking certain oral contraceptives than by drinking water. Similarly, Caldwell *et al.* (2010) estimated that a child's exposure to estrogens in drinking water is 730–480,000 times lower than exposure to milk.

Phytoestrogens

Phytoestrogens, another group of naturally occurring EDSs, can act as agonists and antagonists (up and down regulators) of estrogen receptors (Miksicek 1994; Kuiper *et al.* 1998a). Antagonists and agonists are associated with beneficial and detrimental health effects (Nie *et al.* 2017). Some phytoestrogens could constitute a cancer threat because, being estrogen agonists, they stimulate the synthesis of estrogens in human tissues. Other phytoestrogens, being estrogen antagonists, can prevent breast cancer in women and be used to treat breast cancer in women and men. The best example is 4-hydroxy tamoxifen, used to treat breast cancer (Jordan 2008). This estrogen antagonist shows over a hundred times more affinity for the estrogen receptor than estradiol (see Kuiper *et al.* 1998b).

Phytoestrogens are found in some foods in concentrations approaching potential use as oral contraceptives. For example, Zava *et al.* (1998) found that soy milk contains about 8 μg of estradiol equivalents per 200 mL. A low dose of an oral contraceptive pill contains 20 μg estradiol (Hatcher *et al.* 2013). They also found that dried herbs, including licorice, red clover, mandrake, bloodroot, and thyme, contain several micrograms per gram of dried herb. Other herbs, including yucca, turmeric, hops, verbena, yellow dock, and sheep sorrel, contained around 250 ng per g of dried herb. Studies ascribe fertility problems to sheep that consume the phytoestrogen coumestrol found in clover (Adams 1995) and cheetahs given soy-based foods (Setchell *et al.* 1987).

Consumer products as sources of EDS

There are numerous compounds in consumer products that have estrogenic activity. One example is benzophenone-3 (BP3), which is used in shampoos, lipsticks, soaps, and sunscreens as an ultraviolet (UV) light filter to prevent damage caused by excessive UV radiation to the skin, lips, and hair. BP3 is rapidly absorbed by the skin and transported into the bloodstream (Calafat *et al.* 2008; Krause *et al.* 2012).

BP3 is a known endocrine disruptor (Krause *et al.* 2012). The evidence suggests that the primary route of exposure to BP3 comes from the application of sunscreen products to the skin (Calafat *et al.* 2008). However, Ruszkiewicz *et al.* (2017) suggest that eating and drinking after applying sunscreen to one's hands and lips may result in gastrointestinal and pulmonary exposure.

A National Health and Nutrition Examination Survey (NHANES) study found that nearly 97% of humans show concentrations of BP3 in the urine of close to 23 μg/L. Concentrations were higher in women than men (Han *et al.* 2016) and higher in non-Hispanic whites than non-Hispanic blacks (Han *et al.* 2016). Han *et al.* (2016) also reported that the concentrations of BP3 in urine increased between 2005 and 2012 and that the highest income group was found to have higher levels of BP3 than other income groups. Calafat *et al.* (2008) state that the differences by sex and race/ethnicity probably reflect differences in the use of personal care products.

da Silva *et al.* (2015) found BP3 and other UV filtering chemicals from sunscreen products in concentrations in drinking water in the range of nanograms per liter. These substances are absorbed through the skin and excreted in the urine. Concentrations were highest during the summer but not detectable in winter. In this study, BP3 was not destroyed by water treatment that included chlorination (da Silva *et al.* 2015). Whereas the concentration of BP3 in surface waters is in the range of nanograms per liter, the concentration in human urine is in the range of micrograms per liter. Thus, exposure to UV filters in drinking water is a negligible fraction of the skin exposure levels.

Removal of BP3 and associated endocrine disruptors originating in sunscreen products from surface waters will not result in a measurable or meaningful decrease in health risks to human populations. The effort must be focused on sunscreen products themselves. In the United States, the FDA regulates sunscreens as over-the-counter drugs. The solution to any health risks posed by endocrine-disrupting UV filters in sunscreens is regulation to curtail their use, as was the case with triclosan (Halden 2014; Halden *et al.* 2017).

Human exposure to PFAS

The per- and polyfluoroalkyl substances, PFAS, are a group of chemicals that have been used extensively, are persistent in the environment, have been detected in human and animal blood worldwide, and are used in numerous consumer products. PFAS have been detected in water, air, fish, and soil across the globe. Under the Safe Drinking Water Act, US EPA may publish health advisories for contaminants not subject to national primary drinking water regulation. The US EPA set a health advisory of 0.07 parts per billion (70 parts per trillion; 70 ng/L) for the combination of perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) (US EPA 2016a).

Ericson *et al.* (2008) studied the intake of perfluorinated substances in foods from the market in Catalonia, Spain. They detected PFOS, PFOA, and perfluoroheptanoic acid (PFHpA) in the foodstuffs they examined. On average, the researchers estimated that the dietary intake of PFOS for a standard adult man (70 kg body weight) was 62.5 ng/day (assuming non-detection = 0) or 74.2 ng/day (assuming non-detection = half the limit of detection). They found that fish were the main contributors to PFOS intake, followed by dairy products and meats. The findings suggest a correlation between dietary intake and blood levels of PFOS, which is consistent with the work of Egeghy & Lorber (2011), Gebbink *et al.* (2015), and Shan *et al.* (2016). Numerous researchers (e.g., Fromme *et al.* 2009; Vestergren & Cousins 2009; Haug *et al.* 2011; Kjeldsen & Bonefeld-Jørgensen 2013; Behr *et al.* 2018; de Silva *et al.* 2021) concluded that diet (e.g., soy, yams, meat, and milk products) is the primary route of exposure to PFAS in most humans.

Hu *et al.* (2016) examined data obtained for two-thirds of the sources of drinking water facilities in the United States. The authors found that while the general population is exposed to levels below the health advisory issued by the US EPA, about 6.6 million people were exposed to levels above the health advisory. Of those 6.6 million, two-thirds were exposed to contaminated groundwater and a third to surface waters. These contaminated sites were primarily associated with airports and military facilities. A 2019 study by Hu *et al.* (2016, 2019) found that PFAS concentrations in tap water were a statistically

significant predictor of plasma concentrations and that the default relative source contribution of 20% for drinking water to human PFAS exposures is reasonable. However, it must be noted that these conclusions are based on 1989–1990 data.

Haug *et al.* (2011) found that PFOS in drinking water contributed less than 1%, and PFOA contributed about 13% of total exposure compared to food intake. Consistent with the work of Hu *et al.* (2016), Sunderland *et al.* (2019) and Vestergren & Cousins (2009) noted that exposure to PFAS through drinking water could be substantial if one is located near a contaminated site.

Other significant routes of exposure occur in the home and from personal care products. Haug *et al.* (2011) reported that the indoor environment accounted for up to 50% of the total intake for several women. In summary, based on the data presented herein, industrial estrogenic compounds contribute to about 0.0000025% of the daily intake of phytoestrogenic flavonoids in the diet (Safe 1995).

Per and polyfluoroalkyl compounds (PFAS) as endocrine disruptors

Perfluoroalkyl acids (PFAAs), in particular, have been associated in laboratory animals with hepatomegaly, hepatocellular adenomas, testicular and pancreatic tumors, reproductive and developmental deficits, neurotoxicity, immunotoxicity, and thyroid hormone alterations (see Kjeldsen & Bonefeld-Jørgensen (2013)). In a prospective cohort study, Braun *et al.* (2016) found that higher prenatal serum PFOA concentrations were associated with greater adiposity at 8 years and a more rapid increase in body mass index (BMI) at ages 2–8 years.

PFAS are associated with human immunotoxic and endocrine-disrupting effects (White *et al.* 2011). For example, Grandjean *et al.* (2012) studied serum vaccine antibody concentrations in children exposed to perfluorinated compounds. The researchers studied a fishing community in the Faroes, where the frequent intake of marine food is associated with increased exposure to perfluorochemicals (PFCs). Grandjean *et al.* (2012) found that elevated exposures to PFCs were associated with reduced humoral immune response to routine childhood immunizations (tetanus and diphtheria) in children aged 5 and 7 years. However, the responses did not fall below the clinically protective level of 0.1 IU/L.

Kjeldsen & Bonefeld-Jørgensen (2013) studied the mechanisms by which PFAAs can interfere with sex hormone function and cause an increased risk for health effects in humans. They studied the ability of seven PFAAs to affect estrogen receptor and androgen receptor transactivity (i.e., increased rate of gene expression) and aromatase activity. These PFAAs included perfluorohexanesulfonic acid (PFHxS), PFOS, PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDS), perfluoroundecanoic acid (PFUnA), and perfluorododecanoic acid (PFDoA). Of the seven, only three (PFHxS, PFOS, and PFOA) affected the agonistic estrogen receptor transactivity in a concentration-dependent manner (Kjeldsen & Bonefeld-Jørgensen 2013).

The estrogenic effects of PFHxS, PFOS, and PFOA were relatively weaker than the natural estrogen ligand (Kjeldsen & Bonefeld-Jørgensen 2013). This is substantiated by Behr *et al.* (2018), who found that none of the eight PFAS directly activated either the estrogen receptors α and β or the antigen receptor. In addition, none of the eight PFAS displayed endocrine properties *in vitro* at concentrations typical of human exposure. The potential health effects of these PFAAs because of their endocrine disruption properties are insignificant in the presence of 17β-estradiol. Estradiol's affinity for the estrogen receptor is 1 million to 10 million times stronger than that of the three PFAAs.

The National Center for Environmental Health/Agency for Toxic Substances and Disease Registry (ATSDR) recently declined to conduct an exposure investigation in a particular community because the contribution of the diet to blood serum levels in the citizens of concern could not be determined.

However, these fluorinated substances might threaten human health for reasons other than endocrine disruption (see Kjeldsen & Bonefeld-Jørgensen 2013). As endocrine disruptors, PFAS are part of a complex mixture of organic substances present in water. Their harmful effects might be enhanced or suppressed depending on the presence and properties of the other disruptors (e.g., whether these other disruptors are up agonist or antagonist regulators).

PFOA case study

The health outcomes associated with PFOA exposure do not correlate with its activity as an agonist of estradiol synthesis.

PFOA is an agonist of estradiol synthesis and an antagonist of testosterone synthesis in assays performed on zebra fish (Du *et al.* 2013). As such, we would expect that PFOA is likely associated with a higher incidence of breast cancer and much less so for testosterone cancer. Nevertheless, in the most extensively studied site contaminated with relatively high levels of PFOA, the estrogenic activity exhibited by PFOA did not result in any probable links with breast cancer (Barry *et al.* 2013).

On the other hand, the researchers did find a probable link between exposure to PFOA and testicular (and kidney) cancer, but not kidney disease (Barry *et al.* 2013). They also found probable links with ulcerative colitis (Steenland *et al.* 2013; Xu *et al.* 2020), thyroid disease (Winquist & Steenland 2014a; Ballesteros *et al.* 2017; Andersson *et al.* 2019), pregnancy-induced hypertension (including preeclampsia) (Darrow *et al.* 2013; Avanasi *et al.* 2016), and hypercholesterolemia (diagnosed high cholesterol) (Winquist & Steenland 2014b). A full report of the site appears on the C8 Science Panel website (C8 Science Panel 2017).

If PFOA represents a threat to public health, endocrine disruption is not likely the cause.

ASSAYS TO MEASURE ESTROGENIC ACTIVITY

If regulations about endocrine disruptors are promulgated, total estrogenic activity, as measured by bioassay, rather than individual concentrations of specific endocrine disruptors, should be used. Because drinking water contains a variety of endocrine disruptors, including agonists and antagonists, which are more likely than not naturally occurring, the concentration of specific endocrine disruptors is not a reliable measurement of endocrine disruption risk.

As previously noted, the human diet contains phytoestrogens at concentrations that usually exceed those of human-made endocrine disruptors by a wide margin (Safe 1995; Rietjens *et al.* 2017). We might also fail to detect a particular EDS that should be regulated but still find an estrogenic activity of undetermined origin (see Maggioni *et al.* 2013). Looking for specific manufactured endocrine disruptors can grossly underestimate the total estrogenic activity in the water. The use of bioassays presumably would reflect the net endocrine disruption potential of the water in question, irrespective of the source of individual components.

Endocrine disruptors show a diversity of chemical structures and estrogenic activities and potencies. For example, the leading human-made endocrine disruptors found in surface waters are natural (e.g., estradiol and related substances) and synthetic estrogens used in hormone therapies (e.g., oral contraceptives and hormone replacement therapies). Phytoestrogens, on the other hand, can be agonist or antagonist regulators of estrogenic activity. Because each of these substances shows differing estrogenic activities (i.e., some in similar concentrations show higher activity at equivalent concentrations), a weighted standard must be established. Several assays accomplish this task (Fang *et al.* 2000; Li *et al.* 2006; Bogers *et al.* 2007; Oh *et al.* 2007; Bergamasco *et al.* 2011; Nguyen *et al.* 2011; Sun *et al.* 2012; Brand *et al.* 2013; Kolkman *et al.* 2013; Resende *et al.* 2013; Real *et al.* 2015).

Bisphenol A (BPA), although estrogenic, is several orders of magnitude less potent than human 17β-estradiol. For example, Bergamasco *et al.* (2011) assessed the presence of estrone, 17β-estradiol, estriol, 17α-ethinylestradiol, and BPA in raw and treated waters. They searched for the selected EDSs using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and an *in vitro* bioluminescent yeast estrogen assay (BLYES). Of the 20 analyzed samples, 18 had at least one EDS detected by LC-MS/MS, and 16 rendered positive in BLYES. The estrogenic assay produced a positive response whenever the substances of interest were present. The only exception was BPA when present at low concentrations.

The highest values of estrogenic activity were detected in the most polluted sites. The maximum estrogenic activity observed was 8.7 ng equivalent of 17β-estradiol per liter in raw waters. Bergamasco *et al.* (2011) did not detect any estrogenic activity in treated waters, demonstrating that water treatment completely removed the estrogenic activity in the raw water. Similar results were obtained by Kennedy *et al.* (2013) who demonstrated that chlorination removed ~98% of the estrogenic activity. The researchers also found that the bioassay was more sensitive than chemical analysis, with a detection limit of 0.1 ng equivalent 17β-estradiol per liter.

On the other hand, estrogenic activity, along with estrogens, bisphenol-A, and phthalates, were detected in the treated drinking water in Pretoria and Cape Town, South Africa (Van Zijl *et al.* 2017). The potential causes proposed were ineffective

water treatment and leaching from plastic pipes in the distribution system. Nevertheless, the authors stated that the levels found were within acceptable human health risks.

Comparison of human exposures

The two primary sources of nutrition for infants, and thus for exposure to EDSs, are human milk and infant formula (Borgert *et al.* 2003). As previously noted, the human diet contains phytoestrogens at concentrations that usually exceed those of human-made endocrine disruptors (Safe 1995; Rietjens *et al.* 2017). Furthermore, the levels of exposure to EDSs in the human diet are usually higher than those in drinking water. This is particularly true when concentrations are corrected for relative endocrine disruption potency (see Stackelberg *et al.* (2004). A US Environmental Protection Agency (US EPA) fact sheet acknowledges the preeminent role that consumer products and food play as a primary route of exposure for PFOA and PFOS, with drinking water being an additional source in a small percentage of communities (US EPA 2016b).

Thus, removing EDSs from surface waters might not measurably reduce human exposure. Furthermore, EDSs in surface waters used as a source of drinking water do not constitute, in general, a public health risk, particularly after the water undergoes treatment (see Stackelberg *et al.* (2004). If EDSs in drinking water constitute a public health threat, FDA would have to issue an advisory on the use of soy-based infant formula, which contains concentrations of phytoestrogens approaching a low-dose oral contraceptive.

Because many endocrine disruptors occur naturally, the concentration of specific groups of endocrine disruptors is not a reliable measurement of endocrine disruption risk. The analysis of specific manufactured endocrine disruptors can grossly underestimate the total estrogenic activity in the water. If regulations about endocrine disruptors are to be promulgated, total estrogenic activity, as measured by bioassay should be the standard, rather than individual concentrations of specific endocrine disruptors.

Estrogenic activity of undetermined origin may be detected even in the absence of regulated EDSs (see Maggioni *et al.* (2013)). The use of bioassays would presumably reflect the net endocrine disruption potential of the water in question, irrespective of the source and nature of the individual components.

Thus, the need to remove anthropogenic EDSs in drinking water stems from the premise that they are found at concentrations that could threaten public health. The consensus in the peer-reviewed literature is that, with few exceptions, anthropogenic EDSs in drinking water typically pose a very low risk to human health (Rodriguez-Mozaz *et al.* 2004; Stackelberg *et al.* 2004; Falconer 2006; Rodriguez-Mozaz & Weinberg 2010; Leung *et al.* 2013). This is particularly true after the water undergoes treatment. Even where EDSs in surface water might represent a threat to public health, the levels of exposure from foods we eat, indoor air we breathe, and hygiene products we use (including sunscreens we apply to the skin) can significantly increase levels of human EDS exposure beyond those resulting from exposure to EDSs from drinking water. On the contrary, Genthe *et al.* (2013) report that the estradiol activity in the water from the Olifants River System in South Africa contains EDSs at concentrations above the 0.7 ng/L trigger value. They note that impoverished communities depend on this water and often drink it without treatment. This is an essential distinction between wealthy and impoverished nations. While our focus in this paper is on the wealthy nations, we are reminded that the threats that our neighbors in impoverished nations face are very different from those in wealthy nations. In addition, exposure to PFAS and other EDSs from drinking water at or near contaminated waste sites may be significant. As such, shifting to a different, uncontaminated water supply is the best practical solution, along with treating the contaminated source water.

SUMMARY

- This review has focused on estrogens and PFAS as disruptors of estrogenic activity. EDS sources include the following:
  - Endogenous estrogens produced by humans and other organisms
  - Environmental estrogens of endogenous origin
  - Natural estrogens, primarily of phytoestrogenic nature
  - Manufactured estrogens, which show a wide range of potencies, represent in general, an insignificantly small fraction of the total estrogen disruption activity to which humans are exposed.

- In general, current levels of PFAS in waters that serve as a source of drinking water do not constitute a public health risk due to their estrogenic activity. Except in cases where there is significant contamination due to industrial sources, exposure to PFAS and other EDSs via diet, house air, and skin is significantly greater than from drinking water.

If PFAS in drinking water constitute a risk to public health, the cause cannot be due to endocrine disruption *per se*. Thus, efforts to remove chemical contaminants from drinking water based on their estrogenic activity can be misguided. Their removal might not improve human health if no action is taken to lower exposure due to food, air, and consumer products.

DISCLAIMER

Francisco Alberto Tomei Torres, Ph.D. co-authored this publication in his personal capacity. The views expressed in this article are from the author and do not reflect the views of the Centers for Disease Control and Prevention (CDC), the Agency for Toxic Substances and Disease Registry (ATSDR), the Department of Health and Human Services (DHHS), or the U.S. government. The Ibero-American Society of Environmental Health welcomes the publication of the article where the author refers to himself as an active member of it.

DATA AVAILABILITY STATEMENT

All relevant data are included in the paper or its Supplementary Information.

CONFLICT OF INTEREST

The authors declare there is no conflict.

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