This study demonstrates a relative exposure to estrogenic activity and other trace contaminants in drinking water compared with food, beverage, and air exposure. Drinking water for nearly 28 million people in 17 US cities plus 40 food and beverage items was screened for 51 trace contaminants, including suspected endocrine disrupting chemicals (EDCs), pharmaceuticals, personal care products, pesticides, phytoestrogens, and total in vitro estrogenic activity. Only three drinking water samples exhibited measurable estrogenic activity (0.19–0.77 ng/L as estradiol equivalents), whereas 34 of the 40 food and beverage items had measurable estrogenic activity (median estradiol equivalents, 0.55–4,200 ng/L). On an adult, per-serving basis, food and beverage intake of estrogenic activity was 4–21,000 times greater than in municipal drinking water. Of the literature studies available, air exposure for six suspected EDCs analyzed in this study resulted in at least 30–36,000 times the exposure from drinking water.

Estrogenic activity of US drinking waters: A relative exposure comparison

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Expanding population, limited access to freshwater, and continued growth in the manufacturing, pharmaceutical, and chemical industries increase the potential for exposure to a plethora of compounds through air, food, and water. Advances in analytical technology enable the scientific community to observe and quantify chemical contaminants in air and water at miniscule levels (parts per trillion and lower). Such technological advances have allowed researchers to detect trace levels of organic contaminants around the world in matrixes ranging from food to air to dust to water, yet the consequences of exposure to mixtures of these pollutants at low levels from multiple sources is still not fully understood.

The scientific community has been concerned about endocrine disrupting chemicals (EDCs) and pharmaceuticals potentially entering drinking water supplies since at least 1965 when Harvard University researchers discovered that natural and synthetic estrogens are not completely eliminated by wastewater treatment (Stumm-Zollinger & Fair, 1965). As early as 1972, the US Environmental Protection Agency (USEPA) discovered pharmaceuticals in wastewater effluent (Garrison et al, 1975). After these pioneering efforts, only sparse attention was paid to hormones and pharmaceuticals in the environ-

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ment until reproductive effects in fish were shown to be directly influenced by estrogens in wastewater outfalls (Snyder et al, 2001; Desbrow et al, 1998). Since this causality was demonstrated, there has been a proliferation of research and subsequent publications regarding estrogens and pharmaceuticals in water (Snyder et al, 2008). Despite the advances in conventional water treatment technology to cope with acute issues such as nutrients and pathogen control, many synthetic and natural organic compounds have still been detected down to parts per billion and lower in wastewater and, to a lesser extent, in drinking water (Benotti et al, 2009; Ye et al, 2007; Rodriguez-Mozaz et al, 2004; Roefer et al, 2000). Although adverse health effects in humans from exposure to trace EDCs and pharmaceuticals via municipal drinking water are unlikely (Snyder et al, 2008; Schwab et al, 2005; Webb et al, 2003; Schulman et al, 2002), some scientists have voiced concerns regarding the potential for mixture toxicity and subtle latent health effects (Daughton & Ruhoy, 2008; Daughton & Ternes, 1999). Advanced water treatment processes such as ozonation and reverse osmosis have shown great promise in reducing the concentrations of xenobiotic contaminants (Snyder et al, 2006a, 2006b; Yoon et al, 2006; Westerhoff et al, 2005), but evidence also suggests that no single water treatment process will be capable of reducing all trace organic contaminants to below increasingly sensitive analytical detection limits (Benotti et al, 2008; Snyder et al, 2007; Vanderford & Snyder, 2006).

As evidenced by a recent flurry of activity in the Associated Press and in the US Congress (Donn et al, 2008a–c; US Senate, 2008), much concern remains over trace detection of pharmaceuticals and EDCs in drinking water and their potential implications to public health. Many of these concerns have been catalyzed by reports demonstrating effects to reproductive physiology in aquatic species exposed to wastewater effluents (Snyder et al, 2004; Routledge et al, 1998; Jobling & Sumpter, 1993). Without question, humans are continuously exposed to both natural and anthropogenic chemicals through environmental media such as water, air, and food (Rudel & Perovich, 2009; Reemtsma et al, 2008; Zota et al, 2008; Lu et al, 2007; Maragou et al, 2006; Sidhu et al, 2005; Fromme et al, 2004; Guenther et al, 2002).

Although the effects of human exposure from trace levels of EDCs and pharmaceuticals are unknown, phytoestrogens have been well-studied for their estrogenic activity and effects on human health (Grace et al, 2004; den Tonkelaar et al, 2001; Lu et al, 2001; Shu et al, 2001; Murkies et al, 2000; Ingram et al, 1997; Wu et al, 1996). Phytoestrogens are a class of naturally occurring, estrogen-mimicking compounds in fruits, vegetables, and legumes that have generally shown beneficial health effects, including cancer prevention (Lu et al, 2001; Shu et al, 2001; Murkies et al, 2000; Ingram et al, 1997; Wu et al, 1996), although this has not been uniformly demonstrated (Grace et al, 2004; den Tonkelaar et al, 2001; Messina & Loprinzi, 2001).

TABLE 1 Estrogenic activity for drinking water, food, and beverage items

	Per Volume EEq—*ng/L*					
Food/Beverage Item	**Median**	**Minimum**	**Maximum**	**Occurence Frequency (Total Samples)**	**Serving Size *mL***	**Per Serving EEq *ng****
Source water	0.72	0.25	4.8	6 (18)		NA
Raw water	1.2	0.21	2.1	2 (17)		NA
Drinking water	0.20	0.19	0.77	3 (31)	240	0.18
Bottled water	< 0.16	< 0.16	< 0.16	0 (5)	240	< 0.16
Apple juice	0.74	0.73	0.79	3 (4)	240	0.19
Beer	6.0	0.80	140	5 (5)	360	50
Coffee†	3.0	2.6	4.1	4 (4)	240	1.0
Green tea	3.0	1.5	4.4	4 (4)	240	1.1
Infant formula	0.79	0.73	0.85	2 (2)	30	0.03
Milk	0.55	0.48	0.81	3 (3)	240	0.19
Soy infant formula	1,700	1,500	1,900	2 (2)	30	57
Soy milk	4,000	1,900	4,200	3 (3)	240	1,000
Soy sauce	220	28	510	4 (4)	15	7.7
Vegetable juice	2.6	2.1	3.3	4 (4)	240	0.79

EEq—estradiol equivalents, NA—not available

*Per serving amount based on maximum reported concentrations
†Purchased prebrewed; matrix too complex to obtain individual analyte data

The study presented in this article explores the comparative human exposure to natural and anthropogenic chemicals through drinking water, air, and food. To determine the relative source contributions for selected discrete chemicals and for net estrogenic activity (as measured by an in vitro bioassay), drinking water from 31 sampling sites across the United States was examined and this exposure was compared with a basket study of 10 common food and beverage items. Many of the foods selected for this study were expected to contain phytoestrogens and were included as a source of dietary estrogenic activity with potential health benefits to demonstrate that measurements of in vitro estrogenic activity are not necessarily indicative of risk. For a subset of the anthropogenic compounds, air concentration data were used to compare the daily air exposure with US drinking water exposure for these chemicals as well.

MATERIALS AND METHODS

Selection of compounds. A suite of organic chemicals was selected for evaluation based on representation of broad classes of pharmaceuticals, toxicity, occurrence, and chemical structure. The selection process and full list of analytes monitored have been described in detail previously (Benotti et al, 2009; Snyder, 2008). Briefly, data are reported for three human steroid hormones (testosterone, progesterone, and estrone), nine known or suspected EDCs (i.e., butylhydroxyanisole [BHA], butylhydroxytoluene [BHT], octylphenol, nonylphenol, benzophenone, tris [chloroisopropyl] phosphate [TCPP or Fyrol PCF], galaxolide, butyl benzyl phthalate, and diethylhexyl phthalate) and 10 phytoestrogens (genistein, daidzein, formononetin, biochanin A, apigenin, naringenin, coumestrol, chrysin, matairesinol, and glycitein). Though many additional compounds (51 in total) were analyzed for this data set, each compound chosen for reporting was required to be present in at least one food sample. For example, 17β-estradiol (E2) was detected in one raw water sample at 17 ng/L but was not detected above the reporting limit for any of the food and beverage samples analyzed; therefore, it is not included in the data tables for this article.

In addition to discrete compound evaluation, in vitro estrogenic activity was measured using the estrogen screen (E-screen) assay (MCF-7 breast cancer cell line) as published previously (Snyder et al, 2008; Drewes et al, 2005). Measured values from the E-screen assay are presented as estradiol equivalents (EEq), which represent the cell proliferation rate for a given sample extract relative to that of a 17β-estradiol standard. To evaluate the relative influence of the phytoestrogens on the estrogenic activity of each of the food and beverage items, response of the E-screen assay was measured for each of the phytoestrogens used for analysis in this study. Phytoestrogen standards were supplied to the laboratory in methanol, dimethyl sulfoxide, or acetonitrile, and data were fitted using a statistical computing software package[1] and a dose–response curve fitting library (R Development Core Team, 2006; Ritz & Streibig, 2005).

Water treatment plants (WTPs). Seventeen US WTPs were selected, based on geographic and treatment diversity (Benotti et al, 2009). Each site was sampled on at least one occasion; data from each plant are presented as mean, minimum, and maximum values to represent the range of concentrations measured. For the purposes of this article, the term "sites" refers to sampling location, not the actual number of samples collected; "source water" defines a sample taken from the body of water (e.g., lake, reservoir, river) before treatment; "raw water" refers to the influent to the plant; and "drinking water" refers to water treated to meet or exceed all federal and state standards and consists of finished water leaving the plants as well as distribution system samples. Detailed information about each of the treatment processes and a breakdown of the number of sample locations for each WTP has been published previously (Benotti et al, 2009).

Sample collection, preservation, extraction, and analysis. Foods and beverages were purchased from local vendors within Clark County, Nev. Food and beverage types were specifically chosen because of their probable estrogenic activity (i.e., phytoestrogen or steroid content) and consisted of: bottled water, apple juice, beer, coffee, green tea, dairy-based infant formula, milk, soy-based infant formula, soy milk, soy sauce, and vegetable juice. A minimum of two brands was evaluated for each type of food or beverage item. Perishable items were stored at 4°C until extraction, and all samples were extracted within one month of purchase and before the expiration date. Food and beverage items were kept in their original containers and were purchased prepared (ready for consumption) with the exception of green tea, which was prepared according to the manufacturer's directions. Extraction

FIGURE 1 Relative phytoestrogen composition of combined food and beverage items

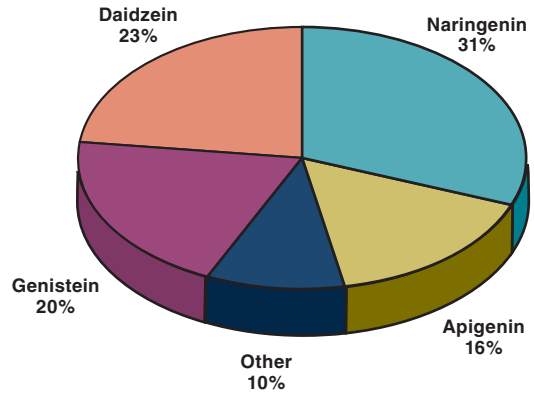


TABLE 2 Concentrations of steroids, phytoestrogens, and EDCs in nondairy, nonsoy beverage items—*ng/L*

	Bottled Water *n* = 5				Apple Juice *n* = 4				Vegetable Juice *n* = 4				Green Tea *n* = 4				Beer *n* = 5			
Analyte	**Median**	**Minimum**	**Maximum**	**ND**	**Median**	**Minimum**	**Maximum**	**ND**	**Median**	**Minimum**	**Maximum**	**ND**	**Median**	**Minimum**	**Maximum**	**ND**	**Median**	**Minimum**	**Maximum**	**ND**
Steroids																				
Estrone	< 0.2	< 0.2	< 0.2	0	< 100	< 100	< 100	0	< 25	< 25	< 25	0	< 25	< 25	< 25	0	940	940	940	1
Progesterone	< 0.5	< 0.5	< 0.5	0	< 100	< 100	< 100	0	< 5	< 5	< 5	0	< 5	< 5	< 5	0	< 100	< 100	< 100	0
Testosterone	< 0.5	< 0.5	< 0.5	0	< 100	< 100	< 100	0	15	15	15	1	< 5	< 5	< 5	0	< 100	< 100	< 100	0
Phytoestrogens																				
Apigenin	< 1	< 1	< 1	0	420	260	940	3	340	210	630	3	4,300	2,700	6,800	4	4,500	3,000	5,300	5
Biochanin A	< 1	< 1	< 1	0	< 210	< 210	< 210	0	< 210	< 210	< 210	0	24	24	24	1	< 150	< 150	< 150	0
Chrysin	< 1	< 1	< 1	0	410	260	580	3	< 210	< 210	< 210	0	49	41	56	2	< 150	< 150	< 150	0
Coumestrol	< 1	< 1	< 1	0	< 210	< 210	< 210	0	< 210	< 210	< 210	0	520	520	520	1	< 150	< 150	< 150	0
Daidzein	< 1	< 1	< 1	0	< 210	< 210	< 210	0	< 210	< 210	< 210	0	51	51	51	1	270	180	360	2
Formononetin	< 1	< 1	< 1	0	< 210	< 210	< 210	0	< 210	< 210	< 210	0	320	250	390	2	< 150	< 150	< 150	0
Genistein	< 1	< 1	< 1	0	< 210	< 210	< 210	0	< 210	< 210	< 210	0	77	24	130	2	420	300	540	2
Glycitein	< 1	< 1	< 1	0	< 210	< 210	< 210	0	< 210	< 210	< 210	0	130	53	920	4	< 150	< 150	< 150	0
Matairesinol	< 5	< 5	< 5	0	< 1,100	< 1,100	< 1,100	0	< 1,100	< 1,100	< 1,100	0	4,200	1,000	6,900	4	< 750	< 750	< 750	0
Naringenin	< 1	< 1	< 1	0	5,000	450	8,800	4	840,000	540,000	910,000	4	9,800	4,100	17,000	4	985	400	1,700	5
EDCs/suspected EDCs																				
Benzophenone	26	25	27	2	< 260	< 260	< 260	0	< 125	< 125	< 125	0	< 53	< 53	< 53	0	< 375	< 375	< 375	0
BHA	< 25	< 25	< 25	0	< 125	< 125	< 125	0	< 125	< 125	< 125	0	110	110	110	1	< 375	< 375	< 375	0
BHT	< 25	< 25	< 25	0	820	820	820	1	< 125	< 125	< 125	0	< 53	< 53	< 53	0	3,500	3,500	3,500	1
Butylbenzyl phthalate	< 50	< 50	< 50	0	350	350	350	1	< 250	< 250	< 250	0	< 105	< 105	< 105	0	< 750	< 750	< 750	0
Galaxolide	< 25	< 25	< 25	0	< 125	< 125	< 125	0	< 125	< 125	< 125	0	< 53	< 53	< 53	0	< 375	< 375	< 375	0
Nonylphenol	< 80	< 80	< 80	0	21,000	10,000	26,000	4	1,300	1,300	1,300	1	830	650	1,600	4	1,900	1,500	2,400	5
Octylphenol	< 25	< 25	< 25	0	< 125	< 125	< 125	0	< 125	< 125	< 125	0	< 53	< 53	< 53	0	< 375	< 375	< 375	0
TCPP (Fyrol PCF)	< 50	< 50	< 50	0	730	510	950	2	< 540	< 540	< 540	0	< 105	< 105	< 105	0	< 750	< 750	< 750	0

BHA—butylhydroxyanisol, BHT—butylhydroxytoluene, EDC—endocrine disrupting chemicals, *n*—number of products sampled, ND—number detected, TCPP—tris (chloroisopropyl) phosphate

TABLE 3 Concentrations of steroids, phytoestrogens, and EDCs in dairy and/or soy beverage/food items—*ng/L*

	Milk *n* = 3				Soy Milk *n* = 3				Infant Formula *n* = 2				Soy Infant Formula *n* = 2				Soy Sauce *n* = 4			
Analyte	**Median**	**Minimum**	**Maximum**	**ND**	**Median**	**Minimum**	**Maximum**	**ND**	**Median**	**Minimum**	**Maximum**	**ND**	**Median**	**Minimum**	**Maximum**	**ND**	**Median**	**Minimum**	**Maximum**	**ND**
Steroids																				
Estrone	< 125	< 125	< 125	0	< 125	< 125	< 125	0	< 20	< 20	< 20	0	< 100	< 100	< 100	0	< 1,000	< 1,000	< 1,000	0
Progesterone	3,100	2,700	3,700	3	< 25	< 25	< 25	0	150	120	170	2	< 30	< 30	< 30	0	< 1,000	< 1,000	< 1,000	0
Testosterone	30	26	33	2	< 25	< 25	< 25	0	< 20	< 20	< 20	0	< 30	< 30	< 30	0	< 1,000	< 1,000	< 1,000	0
Phytoestrogens																				
Apigenin	68	30	70	3	5,100	2,300	7,900	2	42	34	50	2	3,250	2,000	4,500	2	1,200	2,000	2,100	2
Biochanin A	< 21	< 21	< 21	0	< 2,100	< 2,100	0	0	< 20	< 20	< 20	0	455	170	740	2	< 0.33	< 0.33	< 0.33	0
Chrysin	< 21	< 21	< 21	0	< 2,100	< 2,100	< 2,100	0	< 20	< 20	< 20	0	38	23	53	2	< 330	< 330	< 330	0
Coumestrol	180	100	190	3	< 2,100	< 2,100	< 2,100	0	37	35	38	2	985	570	1,400	2	470	390	540	2
Daidzein	24	24	24	1	2.1×10^6	1.1×10^6	2.7×10^6	3	2,500	2,300	2,600	2	700,000	450,000	950,000	2	3.3×106	450,000	7.7×106	4
Formononetin	< 21	< 21	< 21	0	4,000	4,000	4,000	1	27	24	29	2	2300	1400	3100	2	920	810	6,800	3
Genistein	35	21	35	3	2.2×10^6	1.1×10^6	3.3×10^6	3	2,600	1,500	3,700	2	860,000	610,000	1.1×106	2	1.2×106	3400	2.2×106	4
Glycitein	< 21	< 21	< 21	0	110,000	71,000	240,000	3	260	230	280	2	110,000	96,000	130,000	2	840,000	200,000	1.3×106	4
Matairesinol	< 110	< 110	< 110	0	< 11,000	< 11,000	< 11,000	0	1,100	1,100	1,100	1	710	210	1,200	2	< 170	< 170	< 170	0
Naringenin	41	32	77	3	68,000	47,000	140,000	3	330	74	590	2	41,000	34,000	47,000	2	20,000	1,200	43,000	3
EDCs/suspected EDCs																				
Benzophenone	< 750	< 750	< 750	0	890	890	890	1	< 5,000	< 5,000	< 5,000	0	< 5,000	< 5,000	< 5,000	0	7,000	1,900	12,000	2
BHA	< 750	< 750	< 750	0	3,900	3,900	3,900	1	< 5,000	< 5,000	< 5,000	0	< 5,000	< 5,000	< 5,000	0	< 1,750	< 1,750	< 1,750	0
BHT	< 750	< 750	< 750	0	15,000	15,000	17,000	3	< 5,000	< 5,000	< 5,000	0	< 5,000	< 5,000	< 5,000	0	4,700	3,300	20,000	4
Butylbenzyl phthalate	< 1,250	< 1,250	< 1,250	0	< 1,250	< 1,250	< 1,250	0	< 10,000	< 10,000	< 10,000	0	< 10,000	< 10,000	< 10,000	0	< 3,500	< 3,500	< 3,500	0
Galaxolide	< 750	< 750	< 750	0	< 625	< 625	< 625	0	< 5,000	< 5,000	< 5,000	0	< 5,000	< 5,000	< 5,000	0	2,000	2,000	2,000	1
Nonylphenol	< 1,250	< 1,250	< 1,250	0	3,300	1,800	4,500	3	< 10,000	< 10,000	< 10,000	0	11,000	11,000	11,000	1	16,000	11,000	20,000	2
Octylphenol	< 750	< 750	< 750	0	690	690	690	1	< 5,000	< 5,000	< 5,000	0	< 5,000	< 5,000	< 5,000	0	< 1,750	< 1,750	< 1,750	0
TCPP (Fyrol PCF)	< 1,250	< 1,250	< 1,250	0	< 1,250	< 1,250	< 1,250	0	< 10,000	< 10,000	< 10,000	0	< 10,000	< 10,000	< 10,000	0	5,900	5,900	5,900	1

BHA—butylhydroxyanisol, BHT—butylhydroxytoluene, EDC—endocrine disrupting chemicals, *n*—number of products sampled, ND—number detected, TCPP—tris (chloroisopropyl) phosphate

volumes were based on suggested serving sizes. Details of extraction, analytical procedures, and all associated quality assurance/quality control (QA/QC) measures can be obtained from the corresponding author (contact information can be found at the end of this article).

Methods used for ensuring water sample integrity have been previously reported (Trenholm et al, 2006; Vanderford & Snyder, 2006). Briefly, water samples were collected in 1-L precleaned, presilanized amber glass bottles. Sodium azide and ascorbic acid were added to bottles before sampling as a preservative and oxide quencher, respectively. After sampling, bottles were kept on ice during transportation to the laboratory and stored at 4°C until extraction. All samples were extracted within 14 days of collection. When necessary, samples were filtered before extraction with prewashed 90-mm glass-fiber filters. (A complete description of extraction methods, cleanup, analysis, QA/QC protocols, and method reporting limits [MRLs] for each matrix are available from the corresponding author.) All analytical methods for individual analytes and estrogenic activity were optimized for surface waters and drinking waters.

All analytes except for the phytoestrogens were analyzed by isotope dilution (additional information available from the corresponding author); phytoestrogens were analyzed by external calibration using surrogate standards, although the reported phytoestrogen concentrations are not adjusted for surrogate recovery. Thus the data reported for the phytoestrogens in some foods may represent an underestimation of the actual concentrations present in those matrixes because of matrix suppression (recovery data are available from the corresponding author).

RESULTS AND DISCUSSION

US drinking water. All compounds reported in this article were detected in the source and/or raw waters for each of the WTPs investigated. However, only eight compounds were detected in the finished drinking water (available from the corresponding author) (Benotti et al, 2009). Of the compounds found in drinking water, TCPP was present at 11 sites from four geographically diverse regions (71–240 ng/L, WTPs 1–4, 7, and 8) and nonylphenol was present at six sites from three geographically diverse regions (89–110 ng/L, WTPs 2–4, 10, and 11; some drinking water treatment plants had multiple testing sites). Other compounds detected in drinking water included progesterone (0.57 ng/L, WTP 9), daidzein (1.7 and 5.8 ng/L, WTPs 7 and 9), genestein (1.2, 1.4, and 2.9 ng/L, WTPs 7–9), glycitein (1.3 ng/L, WTP 7), BHT (26 ng/L, WTP 12), and galaxolide (28 and 33 ng/L, WTPs 7 and 8). Also, as shown in Table 1, reportable estrogenic activity (MRL = 0.16 ng/L as EEq for drinking water) was observed at only three drinking water sites (0.20 ng/L at one of two sampling locations for WTP 1, 0.19 ng/L at WTP 2, and 0.77 ng/L at WTP 9). There was no correlation observed between estrogenic activity and the presence or absence of other compounds as reported by Benotti et al (2009).

Analysis of food and beverage items. Results from the analysis of the eight food and beverage items are summarized in Table 1 for in vitro analysis and in Tables 2 and 3 for instrumental analysis for specific analytes. Because of the complexity of the matrix, individual analyte data are unavailable for coffee. Of all the compounds analyzed in each of the food and beverage items, the phytoestrogens made up the largest portion of the

TABLE 4 Previously published concentrations of select contaminants in foods

Analyte	Range	Matrix	Reference
BHT	0.5–100 mg/L	Oils, snack foods	Soubra et al, 2007
BHA	50–220 mg/L	Oils, snack foods	Soubra et al, 2007
Nonylphenol	9–40 µg/L	Milk, soy milk	Lu et al, 2007
	19 µg/L, 14 µg/L	Apples, butter	Guenther et al, 2002
Octylphenol	3 µg/L	Milk, < MRL in soy milk	Lu et al, 2007
Bisphenol-A	Up to 15 µg/L	Canned milk	Maragou et al, 2007
Bisphenol-A	0.3–2.6 µg/L	Milk, formula	Casajuana et al, 2004
Diethylhexyl phthalate	15–27 µg/L	Milk, formula	Casajuana et al, 2004
Butylbenzyl phthalate	1–3 µg/L	Milk, formula	Casajuana et al, 2004
Benzophenone	5–14 µg/L	Milk, soy milk, apple juice	Sagratini et al, 2008
Galaxolide	230 µg/L (mean)	Breast milk, new mothers	Reiner et al, 2007
17 β-Estradiol (free)	1–40 ng/L	Milk, butter	Wolford & Argoudelis, 1979; Qin et al, 2004
Estrone (free)	3–56 (540)	Milk (butter)	Wolford & Argoudelis, 1979; Qin et al, 2004
Progesterone	2–73 µg/L	Milk, cream	Ginther et al, 1976

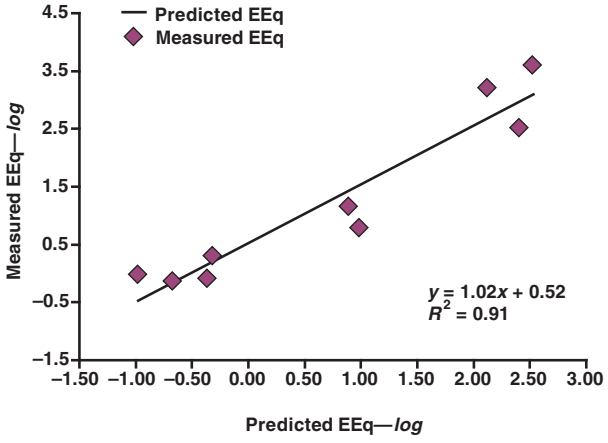
BHA—butylhydroxyanisol, BHT—butylhydroxytoluene, MRL—method reporting limit

detected compounds, up to milligram-per-litre concentrations, with the exception of apple juice. Soy products, as expected, had the highest levels of phytoestrogens relative to the other beverage items analyzed. A significant portion of the total phytoestrogens in foods and beverages was the result of only a few specific compounds (naringenin, genestein, daidzein, and apigenin) as shown in Figure 1. These findings are consistent with data reported in the literature (Antignac et al, 2009; Dip et al, 2008).

Bottled water had no reportable concentrations of any of the compounds analyzed for this study with the exception of benzophenone, which was present at concentrations just above the reporting limit. Nonylphenol was reported in all of the other items tested (650–26,000 ng/L), with the exception of the two dairy products—milk and dairy infant formula. Each of the four apple juice samples had the highest concentrations of nonylphenol among all of the food and beverage items analyzed (≤ 26,000 ng/L in two samples). Octylphenol was only detected in one soy milk sample (690 ng/L). In five of the nine food and beverage items, BHA or BHT was detected. This was expected because they are commonly used as food preservatives; however, neither BHA nor BHT was listed on the products' ingredient lists. The polycyclic fragrance galaxolide was detected in only one soy sauce, whereas the flame retardant TCPP was found in one soy sauce (5,900 ng/L) and two apple juice samples (510 and 950 ng/L). The steroid hormones testosterone and progesterone were both found in milk; testosterone at concentrations up to 30 ng/L and progesterone up to 3,100 ng/L. Estrone and E2 were not detected in milk, although they were likely present at levels below the matrix-specific MRLs for this study (Qin et al, 2004; Wolford & Argoudelis, 1979).

Comparison of food and beverage items with US drinking water exposure scenarios. In the 31 sample locations for US drinking water, only three phytoestrogens were detected (all < 6 ng/L), and the highest concentration of any of the remaining analytes was for TCPP at 510 ng/L, followed by nonylphenol at 210 ng/L. In contrast to these values, soy sauce had a maximum of 5,900 ng/L TCPP, whereas apple juice contained nonylphenol at concentrations up to 26,000 ng/L. Furthermore, progesterone was found in each of the dairy products (milk at a median concentration of 3,100 ng/L; infant formula at a median concentration of 145 ng/L) and testosterone was detected in milk at a median concentration of 30 ng/L. Of the 31 drinking water samples, only one had progesterone at 0.57 ng/L. E2 (the most potent of the natural estrogens) has been reported in human breast milk at concentrations as high as 18,500 ng/L (Choi et al, 2002) and bisphenol A as high as 1,900 ng/L (Ye et al, 2006). None of the drinking water samples contained E2 levels higher than the MRL, and only one sample contained bisphenol A at 25 ng/L. A survey of the peer-reviewed literature (Table 4) indicates that concentrations of the compounds reported here have been measured at even higher concentrations in other food and beverage matrixes, ranging from parts per billion to parts per million (Sagratini et al, 2008; Lu et al, 2007; Reiner et al, 2007; Soubra et al, 2007; Maragou et al, 2006; Casajuana & Lacorte, 2004). Thus the exposure to natural estrogens and other suspected EDCs from drinking water pales in comparison to exposure through other dietary routes.

FIGURE 2 Correlation between measured EEq and predicted EEq based on phytoestrogen concentration and recovery



EEq—estradiol equivalents

TABLE 5 EC_{50} and potency factors for phytoestrogens analyzed in this study

Analyte	EC_{50} *ng/L*	Standard Error*	Potency Factor
E2 control	0.0016	0.00011	1
Apigenin	420	28	3.8×10^{-6}
Biochanin A	51	7.0	3.1×10^{-5}
Catechin	54,000	2,400	3.0×10^{-8}
Chrysin	800	33	2.0×10^{-6}
Coumestrol	2.6	0.31	6.4×10^{-4}
Daidzein	59	6.3	2.7×10^{-5}
Enterolactone	1,500	180	1.1×10^{-6}
Equol	12	0.85	1.4×10^{-4}
Formononetin	210	4.0	7.7×10^{-6}
Genistein	13	1.6	1.3×10^{-4}
Glycitein	28,000	1,800	5.8×10^{-8}
Kaempferol	980	37	1.6×10^{-6}
Matairesinol	Cytotoxic, no estrogenic response		
Naringenin	160	6.6	1.0×10^{-5}
Quercitin	10,000	240	1.6×10^{-7}

EC_{50}—the concentration of each analyte required to induce 50% of the maximum assay response

*Standard errors generated from dose–response curve fit

Phytoestrogens and estrogenic activity of food and beverage items. To evaluate the relative influence of the phytoestrogens on the estrogenic activity of each of the food and beverage items, E-screen assay response was measured for each of the phytoestrogens in this study. The results of the individual analyses are summarized in Table 5 and, to the authors' knowledge, provide the first comprehensive responses of these phytoestrogens using the E-screen bioassay. The only phytoestrogen that failed to develop an estrogenic response was matairesinol, which exhibited cytotoxicity before estrogenicity. All of the phytoestrogens demonstrated between four and eight orders of magnitude lower estrogenic activity than the E2 reference standard.

A correlation was observed between the log-transformed measured EEq of the samples and the log-transformed predicted EEq (Figure 2; predicted EEq for a given sample was calculated as the sum of relative estrogenic activities of the phytoestrogens, steroids, and EDCs multiplied by the measured concentrations and associated recoveries as demonstrated by Stanford and Weinberg (2010; additional details are available from the corresponding author). The observed relationship between the predicted EEq and measured EEq for all samples had a slope of 1.02 and an intercept of 0.52 with a Pearson correlation coefficient of 0.91, indicating a positive correlation between estrogenic analytes and measured estrogenic activity, although there was a slight underestimation of the measured activity. Such an underestimation could be the result of other estrogenic contaminants not quantified in this study, possible additive and synergistic effects, or different interactive mechanisms between the chemical receptor and potential EDCs. However, most of the estrogenic activity of the samples was attributable to the phytoestrogens alone (additional information is available from the corresponding author). Thus, the presence of estrogenic activity in the food and beverage items is largely attributable to compounds with potential beneficial health effects (phytoestrogens) rather than to those indicative of risk from consumption.

Comparison of estrogenic activity and other exposure scenarios. With respect to estrogenic activity, and in direct contrast to the finished and distribution system samples, most of the food and beverage items analyzed showed higher EEqs and greater frequency of detection than drinking water (Table 1). Of the plant-based products, apple juice had the lowest estrogenic activity (0.73–0.79 ng/L) and the lowest sum of phytoestrogens detected (Tables 2 and 3). The three soy products contained the highest level of estrogenic activity (28–4,200 ng/L), likely from the relatively large number and elevated concentrations of phytoestrogens detected, as discussed previously (Table 3). When the food and beverage items are compared with drinking water, even if the average daily intake rate of 2 L of water per day is used, the consumption of that same drinking water would result in a 0.4-ng EEq exposure per day per person, resulting in drastically lower exposure than through other dietary consumption. Furthermore, the World Health Organization (WHO) has established an acceptable daily intake for E2 in food at 50 ng/kg body weight (FAO/WHO, 2000), which equates to 3,500 ng/d for a person weighing 70 kg. The exposure to estrogenic activity from the drinking water analyzed for this study represents only 0.01% of the WHO recommendation (based on equivalent response of E2 in the E-screen bioassay). Additionally, E2 was not detected in any of the finished or distribution system samples. Conversely, consuming one 240-mL serving of soy milk would equate to 29% of the WHO acceptable daily intake for E2 as expressed in units of EEq by the E-screen bioassay. An infant consuming breast milk could be exposed to as much as 8,000–19,000 ng/L of 17β-estradiol (Choi et al, 2002). Thus, exposure to

TABLE 6 Relative exposure scenarios for drinking water and air

Analyte	Drinking Water *ng/L*	Exposure (2 L/d) *µg*	Indoor-air Concentration *ng/m³*	Reference	Exposure (24 m³/d) *µg*	Maximum Ratio of Air-to-water Exposure
Estrogenic activity	0.77	0.0015	0.19	Kennedy et al, 2009	0.0046	3
BHT	26	0.05	74,000	Chein et al, 2007	1,800	36,000
Butylbenzyl phthalate	< 50	< 0.10	575	Fromme et al, 2004; Rudel et al, 2003	14	> 140
Diethylhexyl phthalate	< 120	< 0.24	1,000	Fromme et al, 2004; Rudel et al, 2003	24	> 100
Galaxolide	33	0.07	300	Fromme et al, Rudel et al, 2003	7	100
Nonylphenol	110	0.22	420	Rudel et al, 2003	10	45
TCPP (Fyrol PCF)	510	1.0	1,260	Saito et al, 2004	30	30

BHT—butylhydroxytoluene, TCPP—tris (chloroisopropyl) phosphate

estrogenic activity through drinking water is orders of magnitude lower than exposure through other dietary routes, a finding reflected in data reported elsewhere (Leusch et al, 2009). Furthermore, the estrogenic activity of a food or beverage item is not an appropriate measure of relative risk.

If other scenarios such as airborne exposure are considered, another stark juxtaposition between the levels of suspected EDCs in drinking water and air becomes evident. A literature review was performed to evaluate potential airborne concentrations of the compounds analyzed in this study. All compounds reported in this article were used in the literature search terms, although air-specific data (i.e., not considering dust and particulate concentrations) could be found for only a limited subset. Several studies were identified in which measurable concentrations of BHT, butyl benzyl phthalate, diethylhexyl phthalate, galaxolide, nonylphenol, and TCPP were detected in indoor-air environments such as cars, homes, and schools (Chien, 2007; Saito et al, 2007; Fromme et al, 2004; Rudel et al, 2003). Table 6 illustrates the contrast between the concentration in air and drinking water of the analytes considered, in which maximum concentrations for each analyte in air and drinking water were used for comparison. To compare relative exposure, an average daily intake value of 2 L/d was used for water, whereas 24 m^3/d was used for air, both of which are values consistent with those used by the USEPA (1992). It was also assumed that a person would be exposed to the same air quality for 24 h/d. The airborne exposure to the detected contaminants ranged from 30 to 36,000 times that in drinking water, although estrogenic activity was only three times that of water. Thus, compared with air exposure, water consumption by humans may represent only a small fraction of pharmaceutical, personal care products, and EDC exposure.

CONCLUSIONS

Data from this study indicate that municipal drinking water represents only a small fraction of the integrated exposure to EDCs. Additionally, other EDCs, carcinogens, and particulates in air, known to be harmful to short-term and long-term human health (e.g., polycyclic aromatic hydrocarbons, polychlorinated biphenyl, vast arrays of pesticides, diesel particulates), were not analyzed in this study but constitute a major threat to human health (Ashmore & Dimitroulopoulou, 2009; Garcia-Jares et al, 2009; Zota et al, 2008; Sienra, 2006; Sidhu et al, 2005; Marklund et al, 2005). In sufficient concentration, some EDCs can affect the reproductive health of certain aquatic species (Kidd et al, 2007). However, there is no clear evidence to support the occurrence of adverse human health effects from the compounds targeted in this investigation at the concentrations determined to occur in US drinking waters. Similarly, the presence of in vitro estrogenic activity in food and beverage products can be associated with the presence of beneficial compounds (e.g., phytoestrogens); thus, the use and interpretation of such bioassays should not be the sole indicator of risk. Furthermore, the technologies required to remove, degrade, or transform more resilient organic contaminants in drinking water are energy-intensive and still cannot completely remove many of the compounds to below the detection limits of current analytical capabilities.

Therefore, it is clear that a holistic risk assessment incorporating all possible routes of exposure and an examination of multiple health endpoints are required to protect public health adequately from known chemical insult. In addition, the perceived risk of emerging contaminants in drinking water must be carefully balanced with the known environmental and monetary costs of energy-intensive treatment processes and the known risks of dietary and airborne exposure to these and other contaminants.

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FOOTNOTES

[1]R-2.4.0, The R Project for Statistical Computing, Boston, Mass.

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