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THE LEADER IN ENVIRONMENTAL TESTING

Ultra Trace Pharmaceuticals and Personal Care Products by LC/MS/MS and GC/MS

The Impact of Sample Salinity on the Analysis of Pharmaceuticals and Personal Care Products (PPCPs)

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Introduction

- Drinking water for the future
- Ongoing studies and regulations
- Common emerging PPCP contaminants
- Analytical challenges of water with high salinity
- Water bodies in the Puget Sound region
- Salinity and PPCP analyses performed
- Results
- Discussion
- Conclusion

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PPCPs
Often in the News

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Kids and parenting

Calif. weighs chemical ban in baby bottles

Bill would restrict bisphenol A in products designed for children under 3

AP Associated Press
updated 7:37 a.m. PT, Mon., Aug. 11, 2008

SACRAMENTO, Calif. – Responding to growing consumer anxiety, California lawmakers are considering enacting what could be the first statewide restrictions on a chemical found in plastic baby bottles and infant formula cans.

The bill would require that all products or food containers designed for children 3 years and younger contain only trace amounts of the chemical, bisphenol A.

There is little dispute that bisphenol A can disrupt the hormonal system, but scientists

Kids and parenting videos

A very special summer camp
Aug. 7: At Camp Great Rock, kids with epilepsy can enjoy summer fun and have life-changing experiences. NBC's Tiki Barber reports.

Too much unmarried sex on TV, says group
A not-so-Happy Meal?
Study looks at kids, fast food
Tighter laws take toll on Chinese adoption rates

EPA is seeking more information on the practices of the health care industry to inform future potential regulatory actions, and identify best management and proper disposal practices. This is one of several actions the agency is taking to strengthen its understanding of disposal practices and potential risks from pharmaceuticals in water.

"The agency's work to increase industry stewardship and scientific understanding of pharmaceuticals in water continues," said Benjamin

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Potential for ecological and human health impacts is driving public health concern and pre- regulatory assessments

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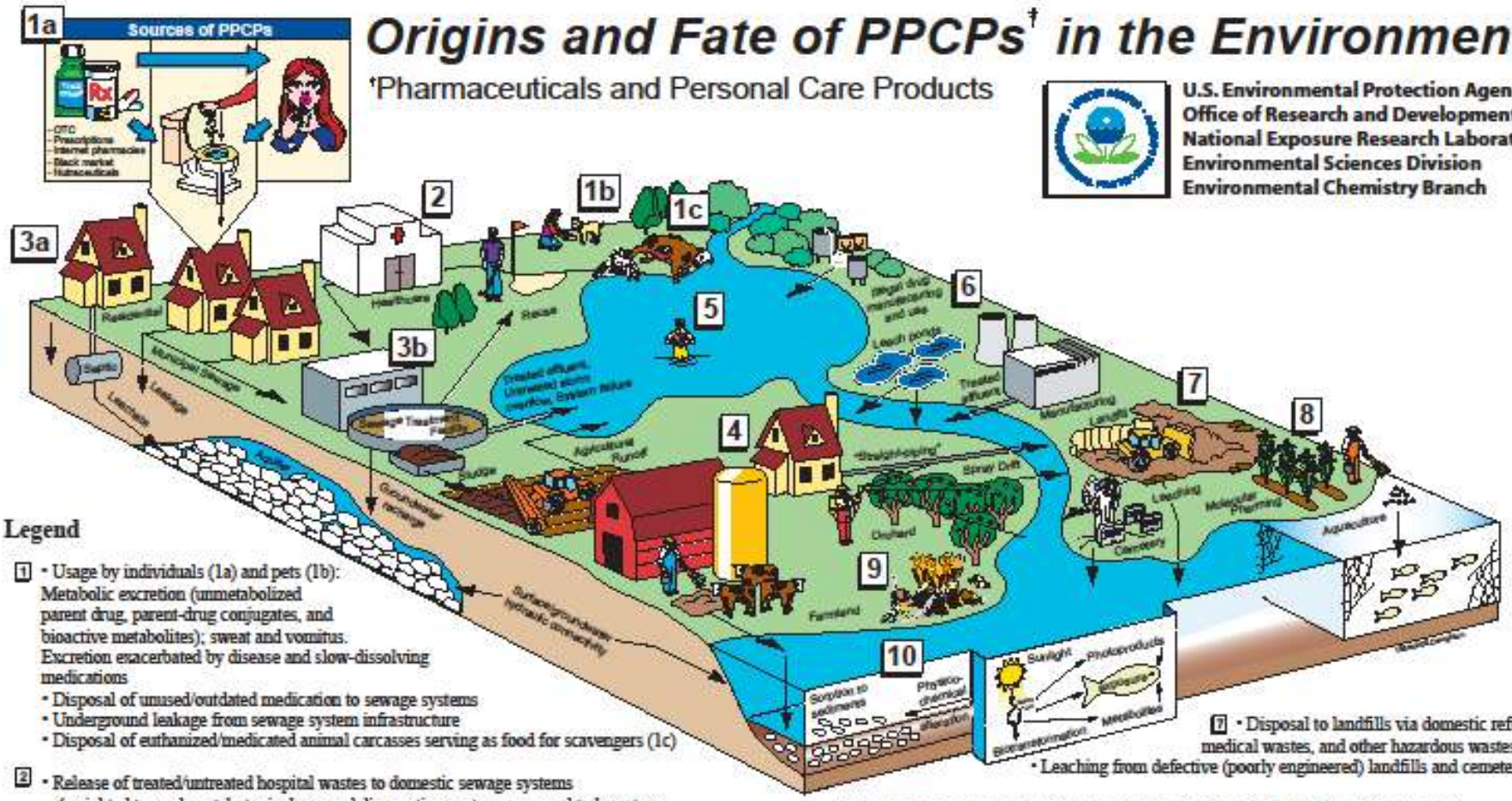
Drinking Water for the Future

- Water sources used for drinking water are shrinking and we are looking for new sources
- Desalination by reverse osmosis and other water reuse programs are quickly becoming the wave of the future
  - ~ Turning water high in salt into fresh water

Origins and Fate of PPCPs† in the Environment

†Pharmaceuticals and Personal Care Products

U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory
Environmental Sciences Division
Environmental Chemistry Branch



Legend

1 • Usage by individuals (1a) and pets (1b): Metabolic excretion (unmetabolized parent drug, parent-drug conjugates, and bioactive metabolites); sweat and vomitus. Excretion exacerbated by disease and slow-dissolving medications
- Disposal of unused/outdated medication to sewage systems
- Underground leakage from sewage system infrastructure
- Disposal of euthanized/medicated animal carcasses serving as food for scavengers (1c)

2 • Release of treated/untreated hospital wastes to domestic sewage systems (weighted toward acutely toxic drugs and diagnostic agents, as opposed to long-term medications); also disposal by pharmacies, physicians, humanitarian drug surplus

3 • Release to private septic/leach fields (3a)
- Treated effluent from domestic sewage treatment plants discharged to surface waters, re-injected into aquifers (recharge), recycled/reused (irrigation or domestic uses) (3b)
- Overflow of untreated sewage from storm events and system failures directly to surface waters (3b)

4 • Transfer of sewage solids ("biosolids") to land (e.g., soil amendment/fertilization)
- "Straight-piping" from homes (untreated sewage discharged directly to surface waters)
- Release from agriculture: spray drift from tree crops (e.g., antibiotics)
- Dung from medicated domestic animals (e.g., feed) - CAFOs (confined animal feeding operations)

5 • Direct release to open waters via washing/bathing/swimming

6 • Discharge of regulated/controlled industrial manufacturing waste streams
- Disposal/release from clandestine drug labs and illicit drug usage

7 • Disposal to landfills via domestic refuse, medical wastes, and other hazardous wastes
- Leaching from defective (poorly engineered) landfills and cemeteries

8 • Release to open waters from aquaculture (medicated feed and resulting excreta)
- Future potential for release from molecular pharming (production of therapeutics in crops)

9 • Release of drugs that serve double duty as pest control agents: examples: 4-aminopyridine, experimental multiple sclerosis drug → used as avicide; warfarin, anticoagulant → rat poison; azacholesterol, antilipidemics → avian/rodent reproductive inhibitors; certain antibiotics → used for orchard pathogens; acetaminophen, analgesic → brown tree snake control; caffeine, stimulant → *coqui* frog control

10 Ultimate environmental transport/fate:
- most PPCPs eventually transported from terrestrial domain to aqueous domain
- phototransformation (both direct and indirect reactions via UV light)
- physicochemical alteration, degradation, and ultimate mineralization
- volatilization (mainly certain anesthetics, fragrances)
- some uptake by plants
- respirable particulates containing sorbed drugs (e.g., medicated-feed dusts)

Christian G. Daughton, U.S. EPA-Las Vegas

March 2006
(original February 2001)

http://epa.gov/nerlesd1/chemistry/pharma/images/drawing.pdf
from: http://epa.gov/nerlesd1/chemistry/pharma/

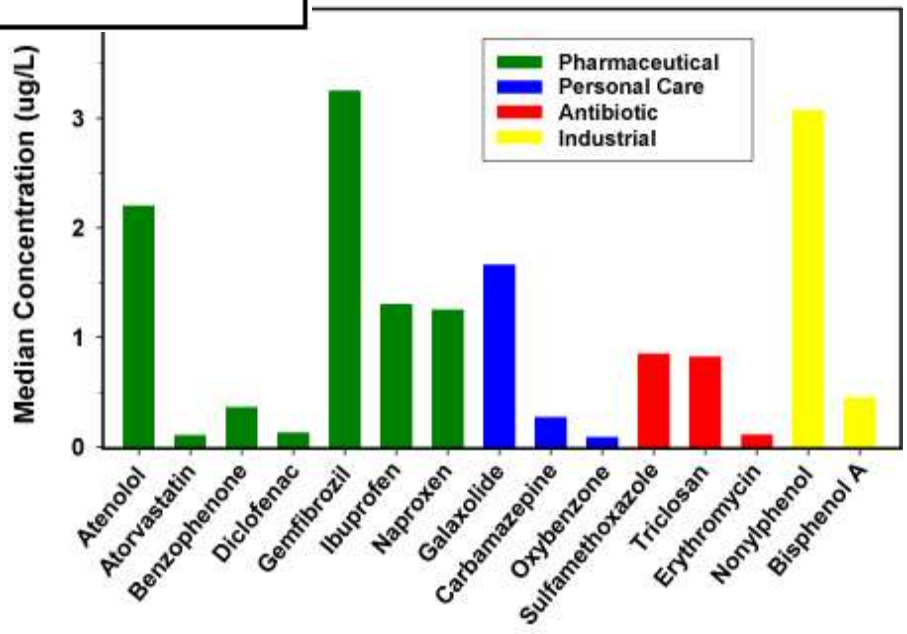
Ongoing Studies ….

FREQUENCY OF DETECTION OF PPCPS IN STREAMS

Percentage of streams in which contaminant was found	Category of contaminant	Representative substances found (median concentration, in ppb)
89%	Steroids	Cholesterol (0.83), coprostanol (fecal steroid) (0.88)
81%	Nonprescription drugs	Acetaminophen (0.11), caffeine (0.081), ibuprofen (0.2), cotinine (nicotine metabolite) (0.05)
74%	Insect repellent	DEET (0.06)
68%	Disinfectants	Phenol (0.04), triclosan (0.14)
48%	Antibiotics	Erythromycin metabolite (0.1), ciprofloxin (0.02), sulfamethoxazole (0.15)
37%	Reproductive hormones	17-alpha-ethynyl estradiol (0.073) (birth control), estrone (0.027)
32%	Other prescription drugs	Codeine (0.012), dehydronifedipine (antianginal) (0.012), diltiazem (0.021) (antihypertensive), fluoxetine (0.012) (antidepressant)
27%	Fragrances	Acetophenone (0.15)

SOURCE: Frequency of Detection of PPCPs in Streams. (2002). "Pharmaceuticals, Hormones and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance." *Environmental Science and Technology* 36, no. 6:202-1211

- Seminal 'streams' study by USGS- 2002
- California coastal estuary study



Regulatory Framework for PPCPs

- Regulations established under RCRA for handling and disposal of pharmaceuticals by manufacturers and healthcare industry.
- Regulations for classical acute affects for some regulated compounds under RCRA
- Regulations non-existent or under development for most PPCP compounds from non-point sources
- Recharge and Reuse permits increasingly reference PPCPs and other emerging contaminants
- EPA coordinating > 100 active studies on presence, fate, treatment and impact of PPCPs
- EPA Methods 1694 and 1698 for PPCPs published in early 2008 (1699 for low-level pesticides)
- Other Federal, State and local agencies also sponsoring studies
- Some PPCPs may be added to CCL and UCMR3 by 2011

Common Emerging PPCP Contaminants

Antibiotics
- Azithromycin
- Lincomycin
- Sulfamethoxazole
- Trimethoprim
- Tyolsin

Anti-inflammatories
- Ibuprofen
- Naproxen

Analgesic and Antipyretic
- Acetaminophen

Antibacterials
- Triclocarban
- Triclosan

Fibrates
- Gemfiborzil

Stimulants
- Caffeine

Aniticonvulsants
- Carbamazepine

Antidepressants
- Cotinine
- Fluoxetine

Benzothiazepines
- Diltiazem

Contrast Media
- Iopromide Isomers

Plastics Manufacturing
- Bisphenol A

Surfactants
- Octylphenol
- Nonylphenol
- Nonylphenol Monoethoxylate
- Nonylphenol Diethoxylate

Steroids and Hormones
- 17a-Estradiol
- 17a-Ethynyl Estradiol
- 17b-Estradiol
- Equilenin
- Estriol
- Estrone
- Progesterone
- Testosterone

Analytical Challenges of Water with High Salinity

- Standard analytical methods were developed for soils, sediments, fish, drinking water and fresh water
- Sea water presents a particular problem with standard analytical methods because of the abundance of both organic and inorganic interferences
- Organic interferences include bacteria, organisms as well as other organic material
- Inorganic interferences include salts, metals, silica, etc.

Water Bodies Low in Salinity in the Puget Sound region

Carbon River

Puyallup River

Water Bodies High in Salinity in the Puget Sound region

Gig Harbor

Commencement Bay

Outer Commencement Bay

Analytical Plan

- Performed the following General Chemistry analyses for pre-treatment processes:
  - pH by EPA Method 150.1
  - Specific Conductance by SM 2510B
  - Salinity by SM 2520B
- Use results from the General Chemistry analyses to determine the extraction process for PPCP analyses:
  - 1694 Pharmaceuticals and Personal Care Products by LC/MS/MS
  - 1694 Antibacterials by LC/MS/MS
  - Modified 1698 Steroids and Hormones by LC/MS/MS
  - ASTM D7065 Alkylphenols and Bisphenol A by GC/MS

General Chemistry Results

Sample ID	Salinity g/L	pH	EC uS/cm
55 g/L NaCl in DI Water (Control)	58.1	6.4	82800
Carbon River	0.06	7.47	124
Puyallup River	0.05	7.44	96
Gig Harbor	26.5	7.86	41600
Commencement Bay	23.8	7.75	37600
Outer Commencement Bay	30.3	7.69	46800

PPCP Analytical Results

Analyte	Lower Calibration Limit	MB	Carbon River	Puyallup River	Gig Harbor	Commencement Bay	Outer Commencement Bay
Acetaminophen	10	ND	ND	ND	**5.09**	ND	**1.10**
Cotinine	2	ND	**7.64**	**4.05**	**3.36**	ND	**1.12**
Caffeine	10	ND	ND	ND	**114.85**	**5.83**	**19.60**
Lincomycin	2	ND	ND	ND	ND	ND	ND
Trimethoprim	2	ND	**67.21**	**3.09**	**2.99**	**2.21**	**0.54**
Sulfamethoxazole	5	ND	**328.15**	**6.93**	**11.24**	**7.92**	**2.50**
Diltiazem	1	**2.76**	**13.08**	**3.44**	**3.80**	**3.59**	**3.08**
Carbamazepine	2	ND	**61.57**	**1.53**	**1.96**	**1.26**	**0.70**
Naproxen	10	ND	**3.52**	ND	**21.71**	**3.72**	**2.77**
Ibuprofen	5	ND	**3.39**	ND	**19.47**	**2.18**	**1.41**
Azithromycin	2	**5.10**	**34.50**	ND	**15.48**	ND	**15.06**
Iopromide	10	ND	ND	ND	ND	ND	ND
Tylosin	2	ND	ND	ND	ND	ND	ND
Fluoxetine	5	**2.49**	**10.17**	ND	ND	ND	**3.05**
Gemfibrozil	5	**1.31**	**232.04**	**5.58**	**12.86**	**5.27**	**4.12**
Triclocarban	10	ND	**28.23**	ND	ND	ND	ND
Triclosan	10	**5.75**	**11.09**	ND	ND	ND	**4.57**

PPCP Labeled Extraction Recoveries

Analyte	Control Limit	MB	Carbon River	Puyallup River	Gig Harbor	Commencement Bay	Outer Commencement Bay
13C2,14N-Acetaminophen	25-150	46.6%	114.0%	130.3%	99.0%	192.6%	113.8%
Cotinine-d3	1-10	1.6%	1.9%	2.8%	2.6%	7.9%	7.6%
13C3-Caffeine	25-150	101.5%	107.9%	149.9%	119.3%	150.4%	138.9%
13C3-Trimethoprim	25-150	100.6%	77.9%	134.2%	155.2%	188.5%	159.2%
13C6-Sulfamethoxazole	25-150	74.1%	20.3%	71.4%	27.6%	14.5%	13.6%
Carbamazepine-d10	25-150	85.5%	70.2%	85.0%	81.1%	128.7%	115.4%
13C-Naproxen-d3	25-150	111.4%	79.5%	85.8%	85.4%	127.4%	116.1%
13C3-Ibuprofen	25-150	98.2%	77.2%	73.0%	65.2%	88.4%	93.0%
Iopromide-d3	25-150	53.8%	25.3%	33.9%	46.8%	38.2%	52.6%
Fluoxetine-d5	25-150	48.2%	124.5%	135.6%	169.8%	129.4%	107.8%
Gemfibrozil-d6	25-150	76.2%	52.7%	65.7%	63.8%	49.9%	58.0%
13C6-Triclocarban	25-150	53.3%	30.7%	49.4%	53.3%	34.0%	47.1%
13C12-Triclosan	25-150	74.0%	49.1%	58.8%	61.5%	44.6%	50.4%

PPCP Avg. Matrix Spike Recoveries

Analyte	Control Limit	LCS	Carbon River MS/SD	Puyallup River MS/SD	Gig Harbor MS/SD	Commencement Bay MS/SD	Outer Commencement Bay MS/SD
Acetaminophen	50-150	77.4%	78.2%	83.2%	87.3%	82.9%	78.0%
Cotinine	60-140	118.6%	118.1%	94.2%	102.8%	109.6%	89.1%
Caffeine	60-140	88.0%	95.9%	94.1%	93.6%	89.6%	84.9%
Lincomycin	5-120	39.9%	70.7%	54.9%	83.1%	86.3%	87.6%
Trimethoprim	60-140	79.0%	111.7%	90.8%	98.2%	93.3%	92.0%
Sulfamethoxazole	60-140	88.8%	89.7%	112.4%	104.8%	89.2%	86.9%
Diltiazem	60-160	155.5%	112.6%	127.1%	154.1%	162.3%	151.4%
Carbamazepine	60-140	88.6%	119.1%	109.5%	103.6%	104.1%	95.7%
Naproxen	60-140	86.5%	96.4%	88.7%	90.8%	89.8%	85.8%
Ibuprofen	60-140	84.2%	86.0%	89.9%	96.1%	89.5%	85.8%
Azithromycin	60-140	102.0%	83.1%	61.0%	134.3%	96.0%	126.9%
Iopromide	60-140	105.3%	133.7%	98.7%	119.8%	117.8%	105.9%
Tylosin	15-150	19.2%	33.0%	34.8%	36.0%	28.2%	34.9%
Fluoxetine	60-140	89.3%	117.6%	110.2%	110.5%	107.6%	103.4%
Gemfibrozil	60-140	87.7%	99.9%	95.4%	97.0%	93.5%	88.0%
Triclocarban	60-140	87.0%	110.3%	90.2%	88.5%	92.4%	90.7%
Triclosan	60-140	87.2%	100.0%	95.8%	94.4%	90.6%	95.6%

Steroid and Hormone Analytical Results

Analyte	RL (ng/L)	MB (ng/L)	Carbon River (ng/L)	Puyallup River (ng/L)	Gig Harbor (ng/L)	Commencement Bay (ng/L)	Outer Commencement Bay (ng/L)
Estriol	10	ND	ND	ND	ND	ND	ND
Equilenin	1	0.98	ND	ND	ND	ND	ND
17B-Estradiol	1	ND	ND	ND	ND	ND	ND
17a-Estradiol	1	**2.41**	**1.54**	**1.53**	**1.75**	**1.58**	**1.76**
17a-Ethynylestradiol	5	ND	ND	ND	ND	ND	ND
Estrone	1	ND	ND	ND	ND	ND	ND
Testosterone	4	ND	ND	ND	ND	ND	ND
Progesterone	1	ND	ND	ND	ND	ND	ND

Steroid and Hormone Labeled Extraction Recoveries

Analyte	Control Limit	MB	Carbon River	Puyallup River	Gig Harbor	Commencement Bay	Outer Commencement Bay
17B-Estradiol-d4	25-150	88.2%	135.0%	107.8%	108.0%	117.8%	107.0%
17a-Ethynylestradiol-d4	25-150	80.2%	149.7%	140.0%	120.6%	132.7%	107.8%
Testosterone-d3	25-150	79.6%	53.2%	44.3%	44.5%	31.2%	53.2%
Progesterone-d9	25-150	62.7%	76.6%	67.7%	63.3%	47.5%	61.0%

Steroid and Hormone Avg. Matrix Spike Recoveries

Analyte	Control Limit	LCS	Carbon River MS/SD	Puyallup River MS/SD	Gig Harbor MS/SD	Commencement Bay MS/SD	Outer Commencement Bay MS/SD
Estriol	60-140	88.7%	58.3%	54.5%	73.8%	72.9%	63.2%
Equilenin	60-140	98.2%	101.5%	92.0%	102.6%	102.7%	97.6%
17B-Estradiol	60-140	91.3%	103.2%	99.9%	97.8%	104.3%	100.5%
17a-Estradiol	60-140	90.5%	100.4%	101.8%	96.9%	104.0%	96.4%
17a-Ethynylestradiol	60-140	97.8%	106.9%	106.8%	102.6%	111.9%	109.3%
Estrone	60-140	99.6%	83.7%	82.9%	84.2%	84.9%	93.6%
Testosterone	60-140	101.2%	113.2%	118.4%	117.9%	125.3%	125.2%
Progesterone	60-140	106.7%	116.9%	106.8%	104.3%	118.1%	105.4%

Alkylphenols and Bisphenol A Analytical Results and Surrogate Recoveries

Analyte	RL (ug/L)	MDL (ug/L)	MB (ug/L)	Carbon River (ug/L)	Puyallup River (ug/L)	Gig Harbor (ug/L)	Commencement Bay (ug/L)	Outer Commencement Bay (ug/L)
Bisphenol A	1	0.32	ND	ND	ND	ND	ND	ND
Octylphenol	1	0.32	ND	ND	ND	ND	ND	ND
NP Totals	5	1.6	ND	ND	ND	ND	ND	ND
NP1E0 Totals	10	3.2	ND	ND	ND	ND	ND	ND
NP2EO Totals	20	1.95	ND	ND	ND	ND	ND	ND
4-NP	1	0.26	ND	ND	ND	ND	ND	ND

Analyte	Control Limit %Rec.	MB %Rec.	Carbon River %Rec.	Puyallup River %Rec.	Gig Harbor %Rec.	Commencement Bay %Rec.	Outer Commencement Bay %Rec.
n-NP1EO (Surr)	40-140	66.5%	66.8%	70.7%	69.8%	68.4%	63.0%

Alkylphenols and Bisphenol A Average Matrix Spike and Surrogate Recoveries

Analyte	LCS	Carbon River MS/SD	Puyallup River MS/SD	Gig Harbor MS/SD	Commencement Bay MS/SD	Outer Commencement Bay MS/SD
BISPHENOL A	99.6%	109.0%	99.9%	96.7%	99.8%	86.9%
Octylphenol	103.7%	104.2%	96.9%	99.2%	102.1%	89.9%
NP Totals	99.7%	101.8%	95.2%	100.3%	99.1%	89.0%
NP1E0 Totals	98.3%	108.2%	99.7%	101.6%	100.6%	87.7%
NP2EO Totals	82.2%	89.2%	79.5%	80.0%	84.8%	72.1%
4-NP	99.4%	101.0%	92.3%	91.1%	96.3%	83.0%

Discussion of Results

- The data shows the fresh water rivers (which were low in salinity) have detections for some Pharmaceuticals and Personal Care Products ranging from the low to high ng/L levels
  - ~ Caffeine, Carbamazepine, Gemfibrozil, Trimethoprim and Sulfamethoxazole are among the highest detected analytes
- Some labeled extraction standards are outside the control limits
  - ~ Associated natives in the MS/SD aliquots are in control

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Conclusion

- It is possible to analyze historically difficult matrices for PPCP analyses by both LC/MS/MS and GC/MS
- There may be some matrix induced interferences, however using Isotope Dilution all concentrations are corrected to give accurate quantitation
- There are PPCP compounds that are found in our waterways at detectable amounts
- If we were to use the fresh water from this analysis to make drinking water we would be introducing persistent contaminants to the drinking water process

Why TestAmerica?

PPCP compounds and other endocrine disrupting compounds can be analyzed in the easy matrices as well as the tough ones

- Method 1694: Pharmaceuticals and Personal Care Products by LC/MS/MS
- Method 1698: Steroids and Hormones by LC/MS/MS
- Alkylphenols and Bispenol A by GC/MS
- Method 1613B: Polychlorinated Dioxins and Furans by HRMS
- Method 1668A: Congener Polychlorinated Biphenyls by HRMS
- Method 1614: Polybrominated Diphenyl Ethers by HRMS
- PFOA/PFOS by LC/MS/MS
- Nitrosamines by Ion Trap

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