


Highly Sensitive Detection of Pharmaceuticals and Personal Care Products (PPCPs) in Water Using Agilent 6495 Triple Quadrupole Mass Spectrometer

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NEMC EMS
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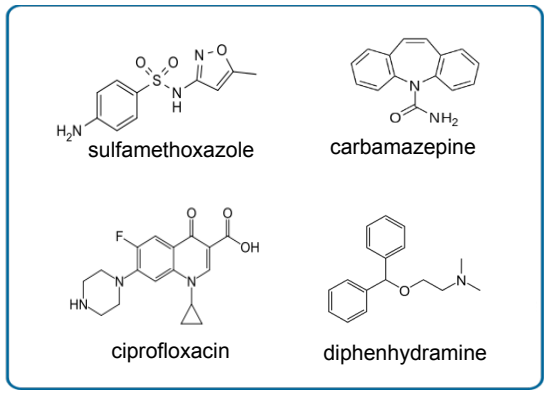
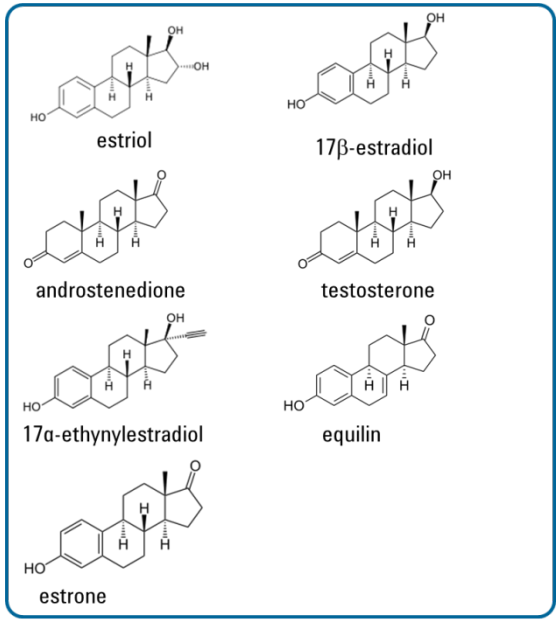
Pharmaceuticals & Personal Care Products

Chemical contaminants

Compounds Include

- Prescription and over-the counter therapeutic drugs
- Veterinary drugs
- Fragrances
- Cosmetics
- Sun-screen products
- Diagnostic agents
- Nutraceuticals (e.g., vitamins)

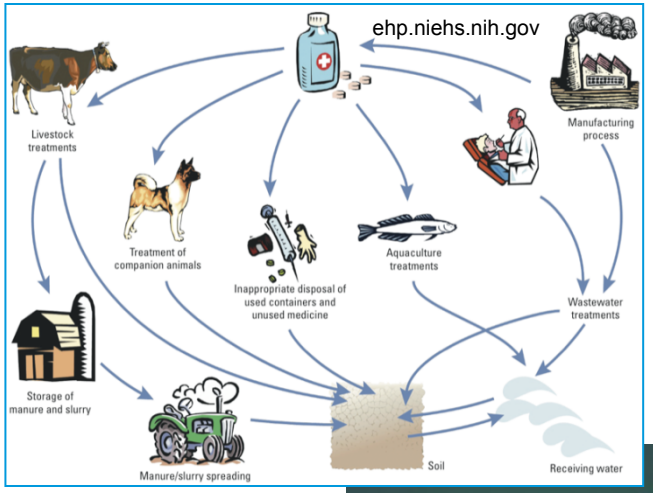


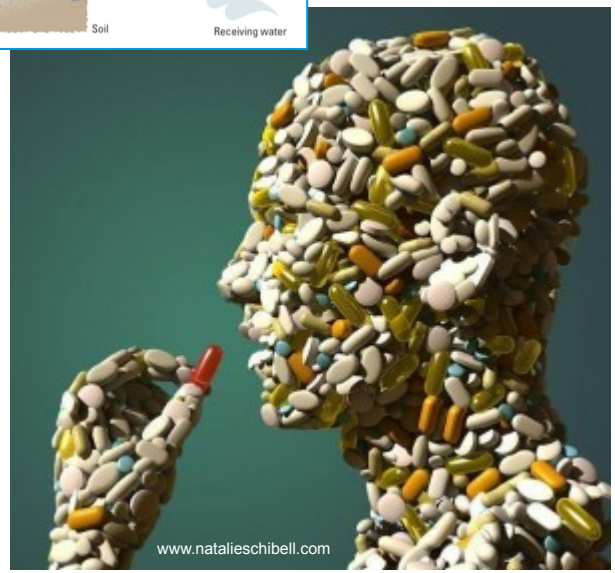


Pharmaceuticals & Personal Care Products Sources

Sources Include

- Human activity
- Residues from pharmaceutical manufacturing
- Residues from hospital WWT
- Illicit drugs
- Veterinary drug use, especially antibiotics and steroids





Pharmaceuticals & Personal Care Products Concerns

Appearance

- Contamination in environmental waters through waste treatment or run-off

Concerns

- Sewage systems are not fully or specifically equipped for PPCP removal.
- Removal varies based on the chemical and treatment facilities.
- Potential appearance in drinking water, especially with Direct Potable Reuse Initiatives

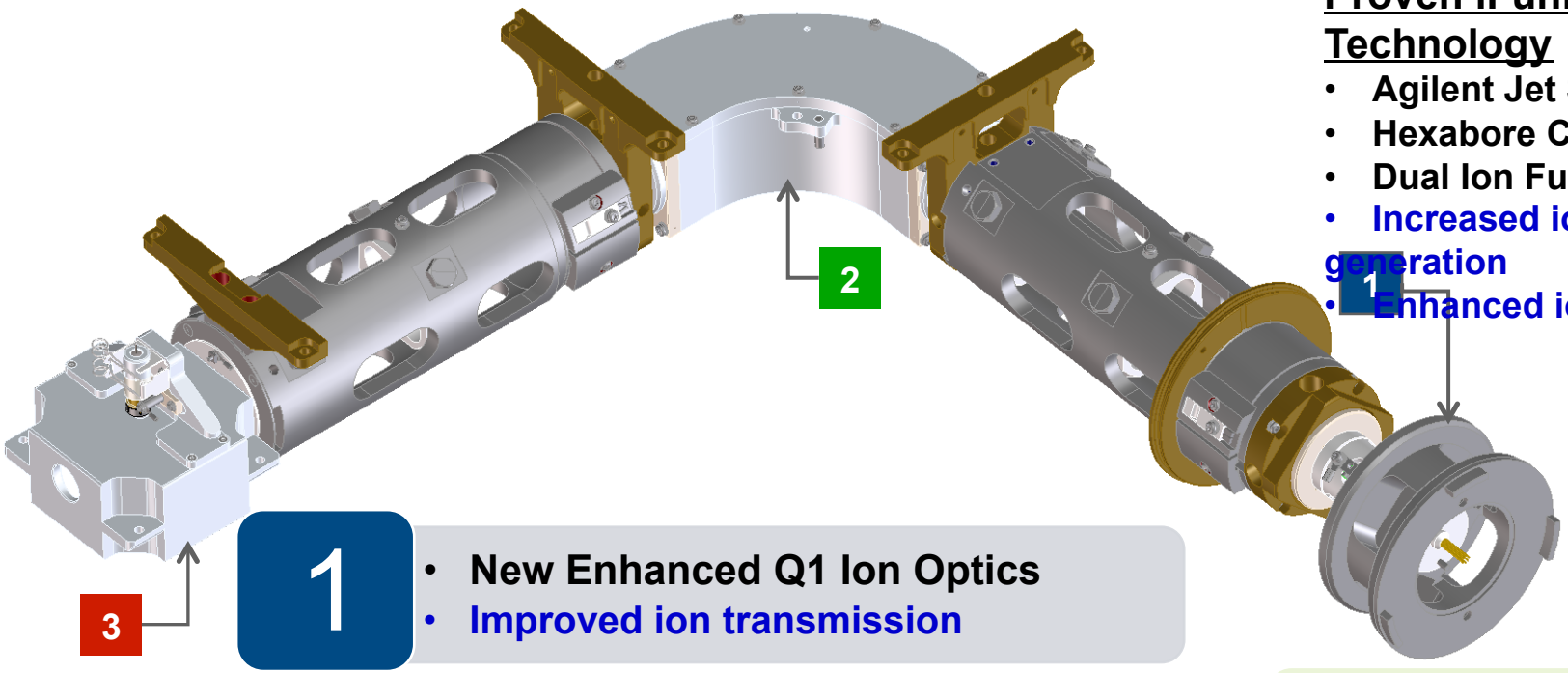
Risks

- Threat to aquatic organisms and to humans not fully known
- Resistance to antibiotics
- Natural and synthetic steroid disruption of aquatic endocrine systems
- Potential for synergistic affects due to mix of chemical contaminants present

The Drinking Water Advisor
(http://drinkingwateradvisor.com/)

1. Stuart et al 2011: Review of risk from potential emerging contaminants in UK groundwater (February 10, 2012)
2. Press Spin: Prozac-Contaminated Drinking Water May Be Link to Autism (June 7, 2012)
3. Pharmaceuticals in River Watersheds, China (April 9, 2015)

Model 6495 QQQ Technology
Continued Improvement



Proven iFunnel Technology

- Agilent Jet Stream
- Hexabore Capillary
- Dual Ion Funnel
- Increased ion generation
- Enhanced ion sampling

1

- New Enhanced Q1 Ion Optics
- Improved ion transmission

2

- New Tapered Hexapole Collision Cell
- Effective ion collection and transmission

3

- New Detector with High Energy Conversion Dynode
- Improved NEG ion detection with low noise

Quantitative Applications

- Enhanced peak area response
- Improved peak area %RSD
- More sensitive and precise
- Lower Limits of Detection (IDL)and Quantitation (LLOQ)

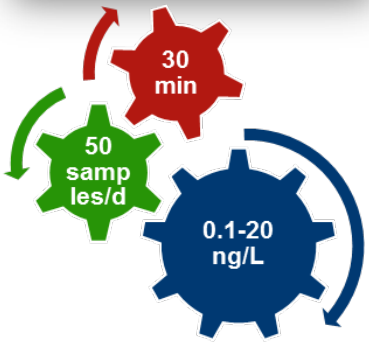
Analysis of Trace Organic Contaminants
Approaches to Sample Prep

Conventional SPE Method

0.5-1 L sample

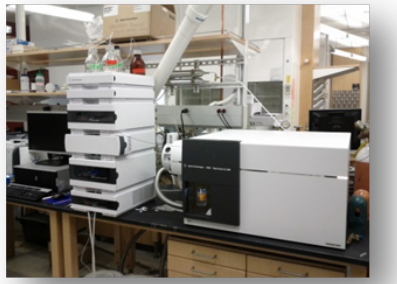
Online SPE Method

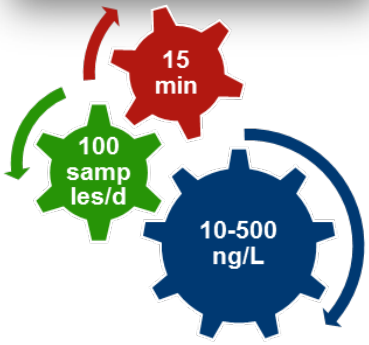
1.5 mL sample



Direct Injection Method

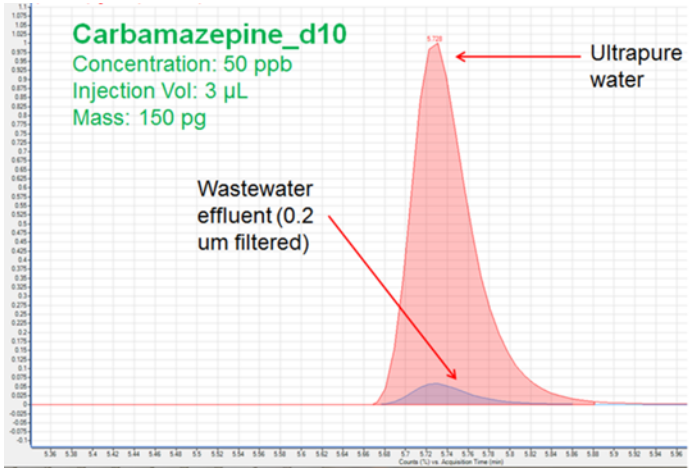
0.1 mL sample



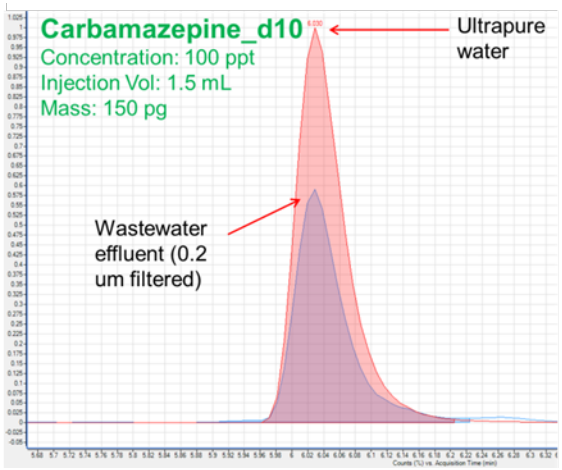


Dr. Shane Snyder, University of Arizona

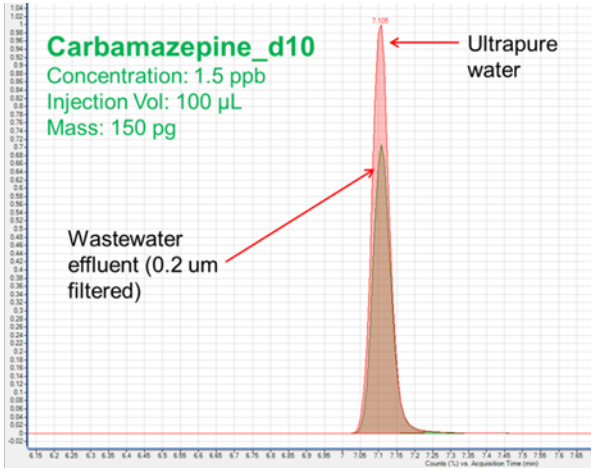
Analysis of Trace Organic Contaminants
Ion Suppression Comparison by Sample Prep Method



Conventional SPE
Concentration: 50 ppb



Online SPE
Concentration: 100 ppb



Direct Injection
Concentration 1.5 ppb

Dr. Shane Snyder, University of Arizona

Environmental Analysis of PPCPS IN Drinking and Surface water

Sensitivity, Precision, Accuracy and Linear Dynamic Range with Direct Injection

Experimental Overview
Positive and Negative Ion Mode Analysis

Objectives

- Precise and accurate quantitation of PPCP compounds from remote and urban source water, and Santa Clara tap water
- Positive ion Mode includes 118 targets with 316 MRM transitions
- Negative Ion Mode includes 22 compounds with 62 MRM transitions
- Direct injection of 40 µL water samples without solid phase extraction (SPE).

Chemical Targets
Positive Mode Ionization

Chemical Targets for Negative Mode Ionization					
10,11-dihydro-10-hydroxycarbamazepine	Clopidogrel carboxylic acid	Famotidine	Meprobamate	Norverapamil	Simvastatin
6-Acetylmorphine	Cocaethylene	Fentanyl	Metformin	Omeprazole	Sotalol
Acebutolol	Cocaine	Fluoxetine	Methadone	Oxazepam	Sulfamethazine
Acetaminophe	Codeine	Fluticasone propionate	Methamphetamine	Oxcarbazepine	Sumatriptan
Albuterol	Cotinine	Gabapentin	Methotrexate	Oxycodone	Tadalafil
Amitriptyline	DEET	Glyburide	Methylphenidate	Oxymorphone	Temazepam
Amitriptyline metabolite	Dehydroaripiprazole	Hydrocodone	Metoprolol	Oxymorphone glucuronide	Thiabendazole
Amphetamine	Desmethylcitalopram	Hydromorphone	Mevastatin	Paroxetine	Tramadol
Aripiprazole	Desmethylvenlafaxine	Hydroxybupropion	*m* -Hydroxybenzoylecgonine	Phenmetrazine	Trazadone
Atenolol	Dextromethorphan	Ketoprofen	Modafinil	Phentermine	Triamterene
Atorvastatin	Diltiazem	Lamotrigine	Monoethylglycinexylidide	Phenylpropanolamine	Trimethoprim
Atrazine	Diphenhydramine	Levorphanol	Montelukast	Pioglitazone	Tylosin
Benzoylecgonine	Disopyramide	Lidocaine	Morphine	Pregabalin	Valsartan
Buprenorphine	Donepezil	Loratadine	Nifedipine	Primidone	Venlafaxine
Bupropion	Duloxetine	Lorazepam	Nifedipine oxidized	Propranolol	Verapamil
Caffeine	Ecgonine methyl ester	MDA	Norfentanyl	Pseudoephedrine	Zolpidem
Carbamazepine	EDDP	MDEA	Norfluoxetine	Quetiapine	Zolpidem phenyl-4-carboxy
Carisoprodol	Erythromycin	MDMA	Normeperidine	Ritalinic acid	
Chlorpheniramine	Erythromycin-anhydro	Mefenamic acid	Norquetiapine	Sertraline	
Clenbuterol	Escitalopram	Meperidine	Norsertraline	Sildenafil	

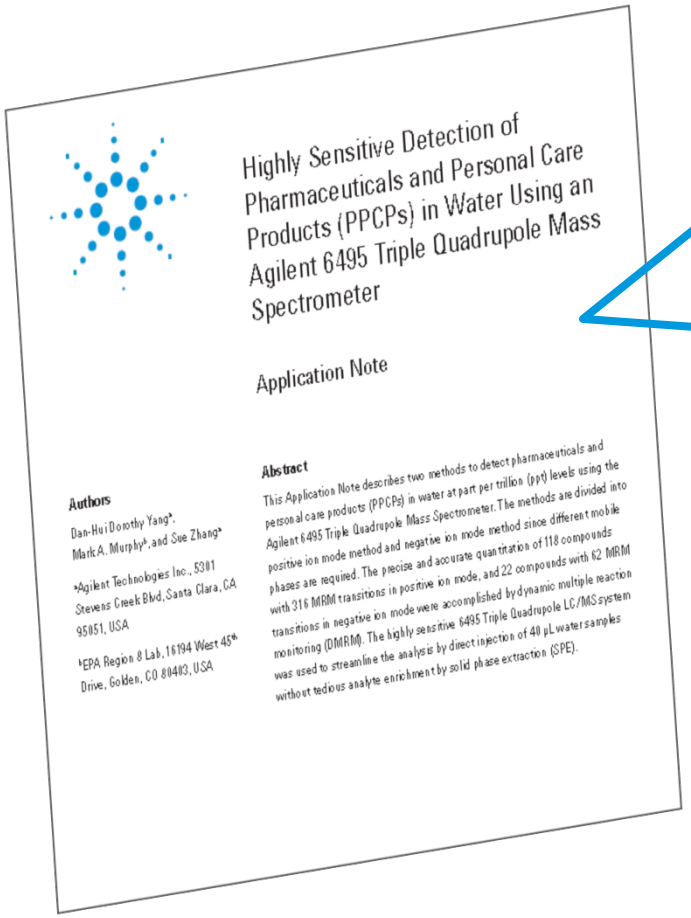
Agilent Publication 5991-5425EN

Chemical Targets
Negative Mode Ionization

Chemical Targets for Negative Mode Ionization	
Bezafibrate	Modafinil
Celecoxib	Naproxen
Chloramphenicol	n-Butylparaben
Diclofenac	Phenobarbital
Diclofenac 4-hydroxy	Phenytoin
Fenbufen	Pravastatin
Furosemide	Sulfamethoxazole
Gemfi brozil	Triclocarban
Hydrochlorothiazide	Triclosan
Ibuprofen	Warfarin
Methylparaben	(±)11-nor-9-carboxy-delta-THC

Agilent Publication 5991-5425EN

Key Applications - LC/MS/MS
Low Level Detection of PPCPs using Model 6495



Highly Sensitive Detection of Pharmaceuticals and Personal Care Products (PPCPs) in Water Using an Agilent 6495 Triple Quadrupole Mass Spectrometer

Application Note

Authors

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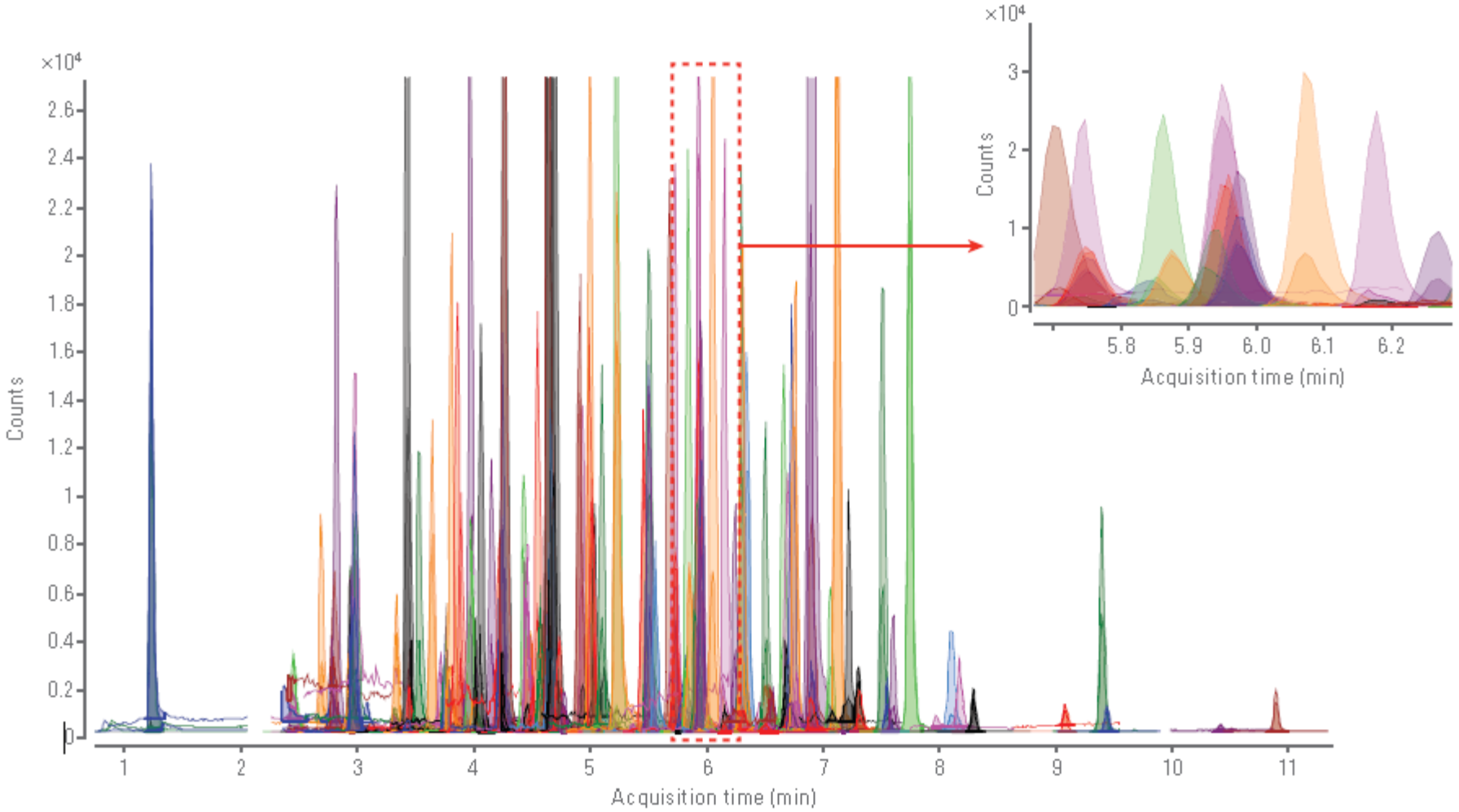
Abstract

This Application Note describes two methods to detect pharmaceuticals and personal care products (PPCPs) in water at part per trillion (ppt) levels using the Agilent 6495 Triple Quadrupole Mass Spectrometer. The methods are divided into positive ion mode method and negative ion mode method since different mobile phases are required. The precise and accurate quantitation of 118 compounds with 316 MRM transitions in positive ion mode, and 22 compounds with 62 MRM transitions in negative ion mode were accomplished by dynamic multiple reaction monitoring (DMRM). The highly sensitive 6495 Triple Quadrupole LC/MS system was used to streamline the analysis by direct injection of 40 µL water samples without tedious analyte enrichment by solid phase extraction (SPE).

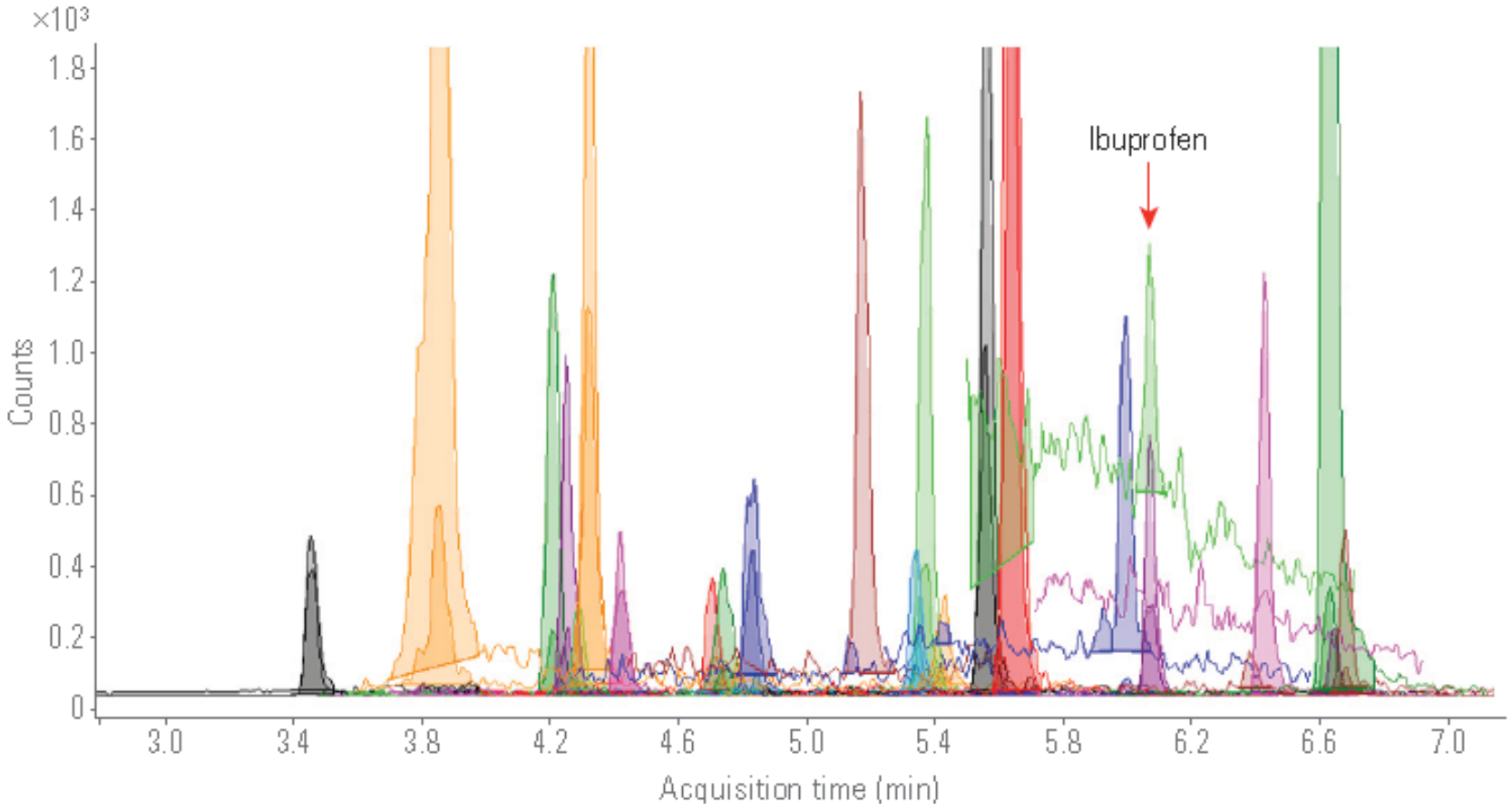
Key Points:

- Direct Injection of 40 µL water samples
- Optimized positive and negative ion mode
- Separation using Agilent ZORBAX Eclipse Plus Column
  (C18, 2.1 x 100 mm, 1.8 µm)
- Improved Negative Ion Mode
- Agilent Publication: 5991-5425EN

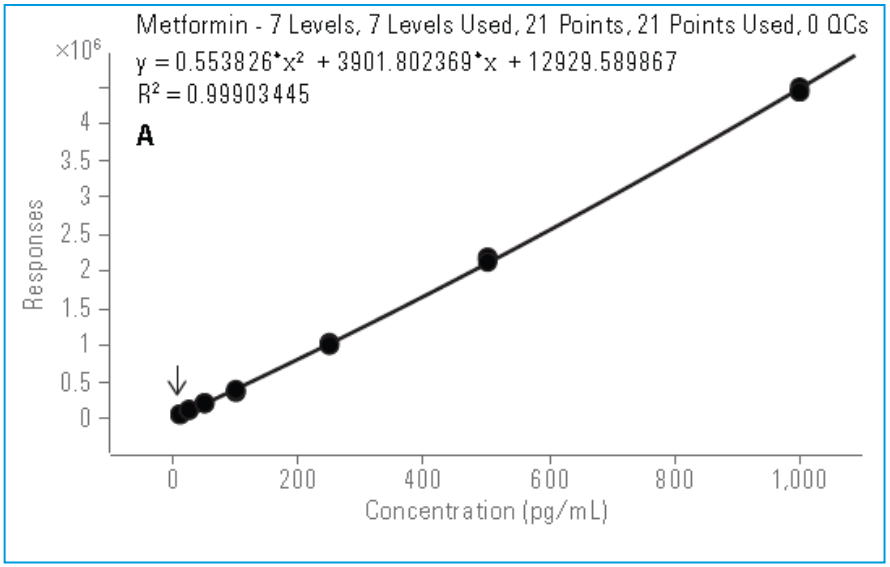
Chromatographic Performance
Positive Ion Mode

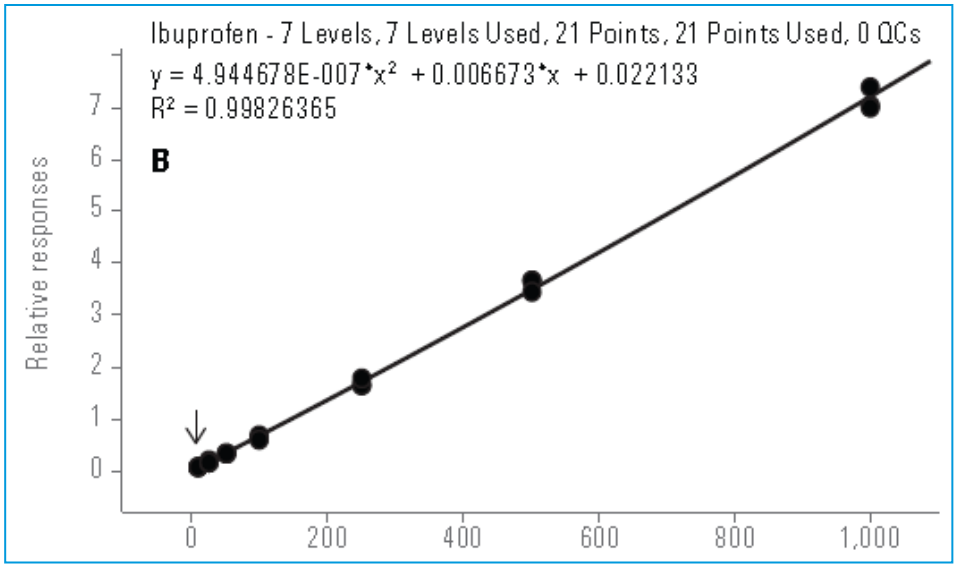


Chromatographic Performance
Negative Ion Mode



Select Calibration Curves
Positive and Negative Mode Ionization



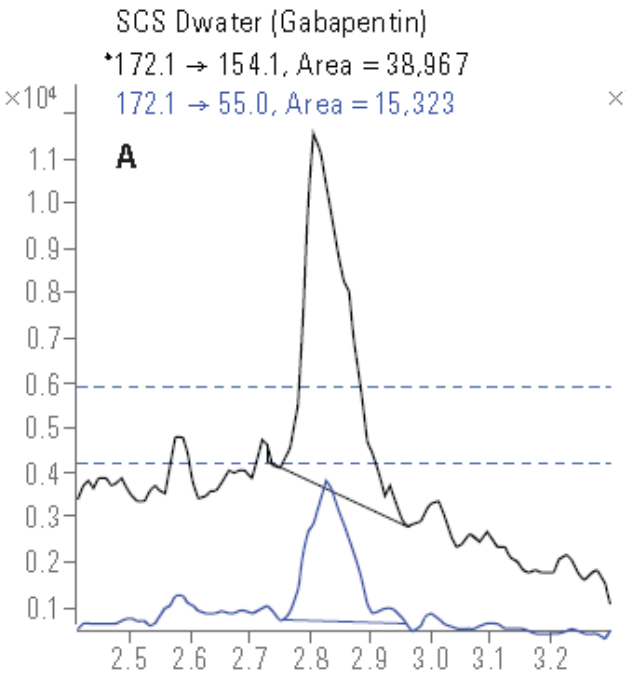


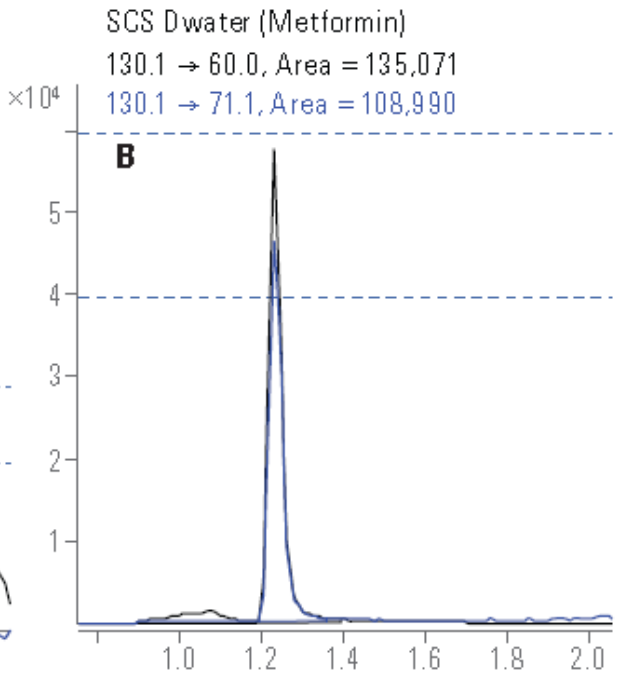
Metformin – Positive Ion Mode
R2 = 0.99903445

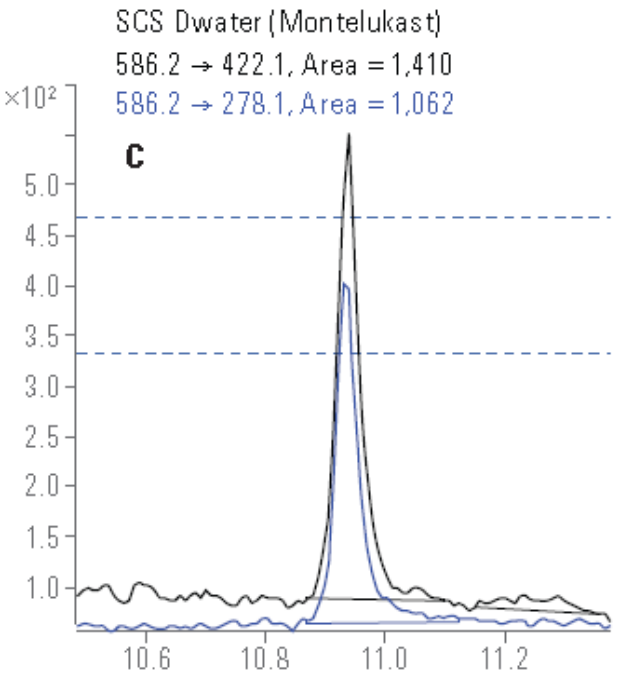
Ibuprofen – Negative Ion Mode
R2 = 0.99826365

PPCPs Identified Positive Ion Mode
Santa Clara Local Tap Water (>10ppt)

Name	Injection 1 (ppt)	Injection 2 (ppt)	Average (ppt)
Gabapentin	20.7	19.6	20.2
Metformin	31.2	30.1	30.6
Montelukast	12.7	12.3	12.5

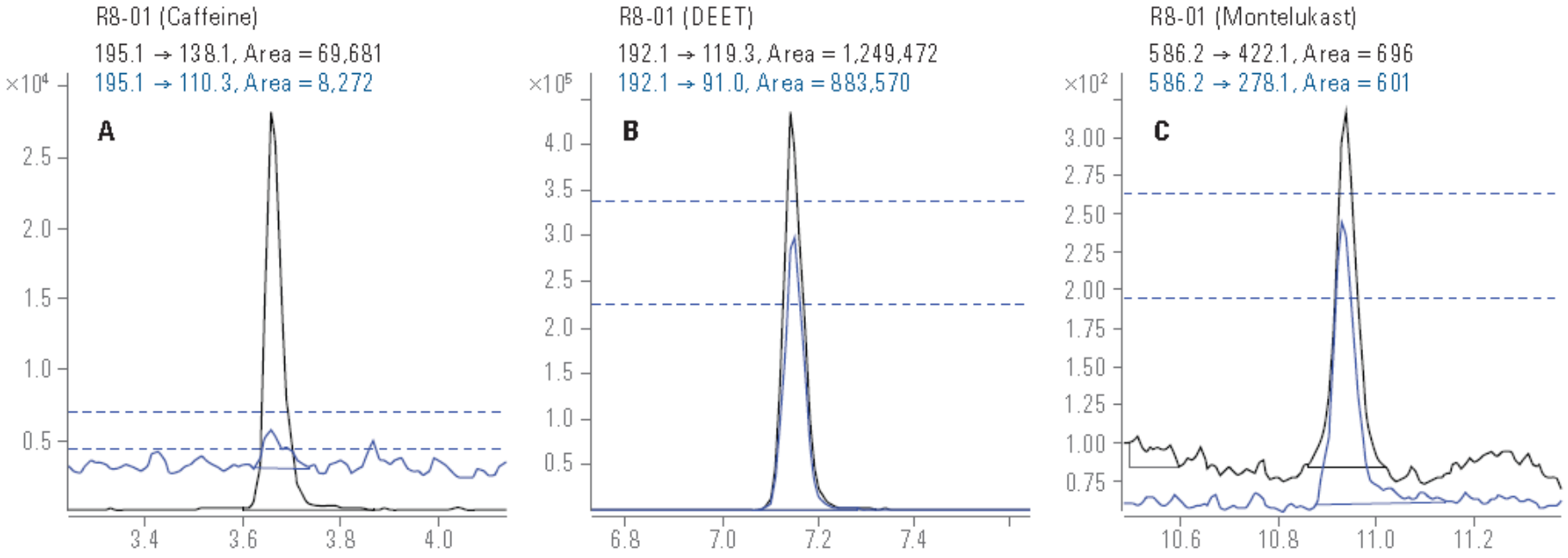






PPCPs Identified Positive Ion Mode
Remote Source Water (>10ppt)

Name	Injection 1 (ppt)	Injection 2 (ppt)	Average (ppt)
Montelukast	12.1	11.9	12.0
Caffeine	27.0	14.5	20.7
DEET	107.4	118.6	113.0



PPCPs Identified Positive Ion Mode

Urban Source Water (>10ppt)

Name	Injection 1 (ppt)	Injection 2 (ppt)	Average (ppt)
10,11-dihydro-10-hydroxycarbamazepine	903	861	882
Amitriptyline metabolite	30	30	30
Amitriptyline	29	29	29
Atenolol	2,599	2,212	2,405
Atorvastatin	40	37	39
Atrazine	43	41	42
Benzoylecgonine	221	206	214
Bupropion	169	154	162
Caffeine	1,473	1,241	1,357
Carbamazepine 10,11 epoxide	38	36	37
Carbamazepine	214	229	221
Carisoprodol	27	28	28
Clopidogrel carboxylic acid	223	204	214
Cocaine	37	35	36
Codeine	67	67	67
Cotinine	98	90	94
DEET	503	570	536
Desmethylcitalopram	107	88	97
Desmethylvenlafaxine	744	827	786
Dextromethorphan	31	42	36
Diltiazem	55	61	58
Diphenhydramine	205	205	205
Ecgonine methyl ester	39	39	39
EDDP	102	100	101
Erythromycin	44	44	44
Erythromycin-anhydro	38	31	34
Escitalopram	192	179	186
Fluoxetine	30	28	29
Gabapentin	>>1,000	>>1,000	>>1,000
Hydrocodone	28	24	26
Hydroxybupropion	260	253	257
Ketoprofen	17	15	16
Lamotrigine	868	1,013	940
Levorphanol	213	205	209
Lidocaine	360	325	343

Name	Injection 1 (ppt)	Injection 2 (ppt)	Average (ppt)
Loratadine	10	10	10
Lorazepam	137	143	140
Meprobamate	160	147	154
Metformin	3,956	3,956	3,956
Methadone	58	39	49
Methamphetamine	259	315	287
Metoprolol	295	334	315
Modafinil	16	14	15
Monoethylglycinexylidide	28	31	30
Montelukast	12	12	12
Norquetiapine	32	25	28
Norsertraline	32	24	28
Oxazepam	29	27	28
Oxcarbazepine	45	42	44
Oxycodone	95	83	89
Oxymorphone	17	14	15
Phentermine	117	117	117
Pregabalin	440	445	442
Primidone	77	58	68
Propranolol	70	71	70
Pseudoephedrine	211	236	223
Ritalinic acid	111	127	119
Sertraline	47	44	46
Sotalol	68	72	70
Sulfamethazine	10	13	11
Temazepam	89	83	86
Thiabendazole	37	43	40
Tramadol	708	727	717
Trazadone	35	30	33
Triamterene	100	111	106
Trimethoprim	277	321	299
Tylosin	13	10	11
Valsartan	475	517	496
Venlafaxine	446	384	415
Verapamil	11	10	11
Zolpidem phenyl-4-carboxylic acid	46	47	47

PPCPs Identified Negative Ion Mode
Urban Source Water (>10ppt)

Name	Injection 1 (ppt)	Injection 2 (ppt)	Average (ppt)
Celecoxib	45	41	43
Chloramphenicol	12	12	12
Diclofenac 4-hydroxy	41	45	43
Diclofenac	237	292	265
Furosemide	400	387	393
Gemfibrozil	309	337	323
Hydrochlorothiazide	503	487	495
Ibuprofen	140	139	139
Modafinil acid	118	114	116
Naproxen	354	347	350
Phenobarbital	55	53	54
Phenytoin	126	121	123
Pravastatin	57	52	54
Sulfamethoxazole	573	582	577
Triclocarban	40	39	39
Triclosan	242	268	255

PPCP Analysis in Environmental Waters
Conclusions

Project demonstrated

- Linear calibration
- Reproducible quantitation
- Low level LLOQs (ppt) achieved
- Viability of direct injection for the quantitative analysis of PPCP in water

Acknowledgements
Colleagues and Collaborators

Thank you to

- Mark Murphy, US EPA
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- Edgar Naegele, Agilent Technologies, Inc.

Thank you

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