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Occurrence and concentrations of pharmaceutical compounds in groundwater used for public drinking-water supply in California

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ABSTRACT

Pharmaceutical compounds were detected at low concentrations in 2.3% of 1231 samples of groundwater (median depth to top of screened interval in wells = 61 m) used for public drinking-water supply in California. Samples were collected statewide for the California State Water Resources Control Board's Groundwater Ambient Monitoring and Assessment (GAMA) Program. Of 14 pharmaceutical compounds analyzed, 7 were detected at concentrations greater than or equal to method detection limits: acetaminophen (used as an analgesic, detection frequency 0.32%, maximum concentration 1.89 μg/L), caffeine (stimulant, 0.24%, 0.29 μg/L), carbamazepine (mood stabilizer, 1.5%, 0.42 μg/L), codeine (opioid analgesic, 0.16%, 0.214 μg/L), *p*-xanthine (caffeine metabolite, 0.08%, 0.12 μg/L), sulfamethoxazole (antibiotic, 0.41%, 0.17 μg/L), and trimethoprim (antibiotic, 0.08%, 0.018 μg/L). Detection frequencies of pesticides (33%), volatile organic compounds not including trihalomethanes (23%), and trihalomethanes (28%) in the same 1231 samples were significantly higher. Median detected concentration of pharmaceutical compounds was similar to those of volatile organic compounds, and higher than that of pesticides.

Pharmaceutical compounds were detected in 3.3% of the 855 samples containing modern groundwater (tritium activity > 0.2 TU). Pharmaceutical detections were significantly positively correlated with detections of urban-use herbicides and insecticides, detections of volatile organic compounds, and percentage of urban land use around wells. Groundwater from the Los Angeles metropolitan area had higher detection frequencies of pharmaceuticals and other anthropogenic compounds than groundwater from other areas of the state with similar proportions of urban land use. The higher detection frequencies may reflect that groundwater flow systems in Los Angeles area basins are dominated by engineered recharge and intensive groundwater pumping.

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1. Introduction

Pharmaceutical compounds and other anthropogenic organic compounds are used for many beneficial purposes in modern society, but commonly constitute contaminants when they are encountered in the environment (Halling-Sørensen et al., 2002). Pharmaceutical compounds may enter the environment by many pathways, including discharge of treated wastewater, seepage from landfills, septic systems, and sewer lines, and runoff from animal wastes and land application of manure fertilizers (Glassmeyer et al., 2005; Wu et al., 2009; Ternes, 1998). Concentrations of individual pharmaceutical compounds in wastewater treatment effluents generally are less than 1 μg/L, although concentrations as high as several mg/L have been measured in effluent from treatment plants receiving waste from pharmaceutical manufacturing facilities (Phillips et al., 2010; Larsson et al., 2007). Although physical and biological processes occurring in aquatic environments may cause attenuation of many pharmaceutical compounds, trace concentrations of human and veterinary pharmaceutical compounds and metabolites have been detected in surface water, groundwater, and drinking water (Ternes, 1998; Sacher et al., 2001; Kolpin et al., 2002; Benotti et al., 2009; Bruce et al., 2010).

Groundwater withdrawals provide approximately 33% of public water supplies and 98% of domestic water supplies in the U.S. (Kenny et al., 2009). National reconnaissance studies of the occurrence of pharmaceutical compounds in groundwater (Barnes et al., 2008a) and untreated drinking-water sources, including groundwater (Focazio et al., 2008), targeted sites thought to be susceptible to contamination from human wastewater and/or animal wastes. These studies demonstrated that pharmaceutical compounds are indeed present in groundwater at detectable concentrations and set the stage for subsequent research: systematic investigation of the distribution of pharmaceutical compounds in groundwater resources. Studies documenting detections of pharmaceutical compounds have received considerable public attention, and public perception of water safety (based in part on these studies) is likely to affect use of groundwater resources (Benotti and Snyder, 2009). Therefore, it is important to

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have an accurate assessment of the degree to which pharmaceutical compounds are present in groundwater.

The objective of this study is to systematically evaluate the distribution of pharmaceuticals in untreated groundwater used for public drinking-water supplies in California. The study is part of the California State Water Resources Control Board's Groundwater Ambient Monitoring and Assessment (GAMA) Program Priority Basin Project (Belitz et al., 2003). The study is unique for the large number of sites sampled (1231 for pharmaceuticals), statistically representative sampling design, comprehensive suite of other water-quality and ancillary data collected on the same samples, and wide range of hydrologic settings included.

2. Experimental design

2.1. Site selection and sampling

The GAMA Priority Basin Project is a comprehensive assessment of groundwater quality in aquifers used for public drinking-water supply in the State of California (Belitz et al., 2003). The Supplemental

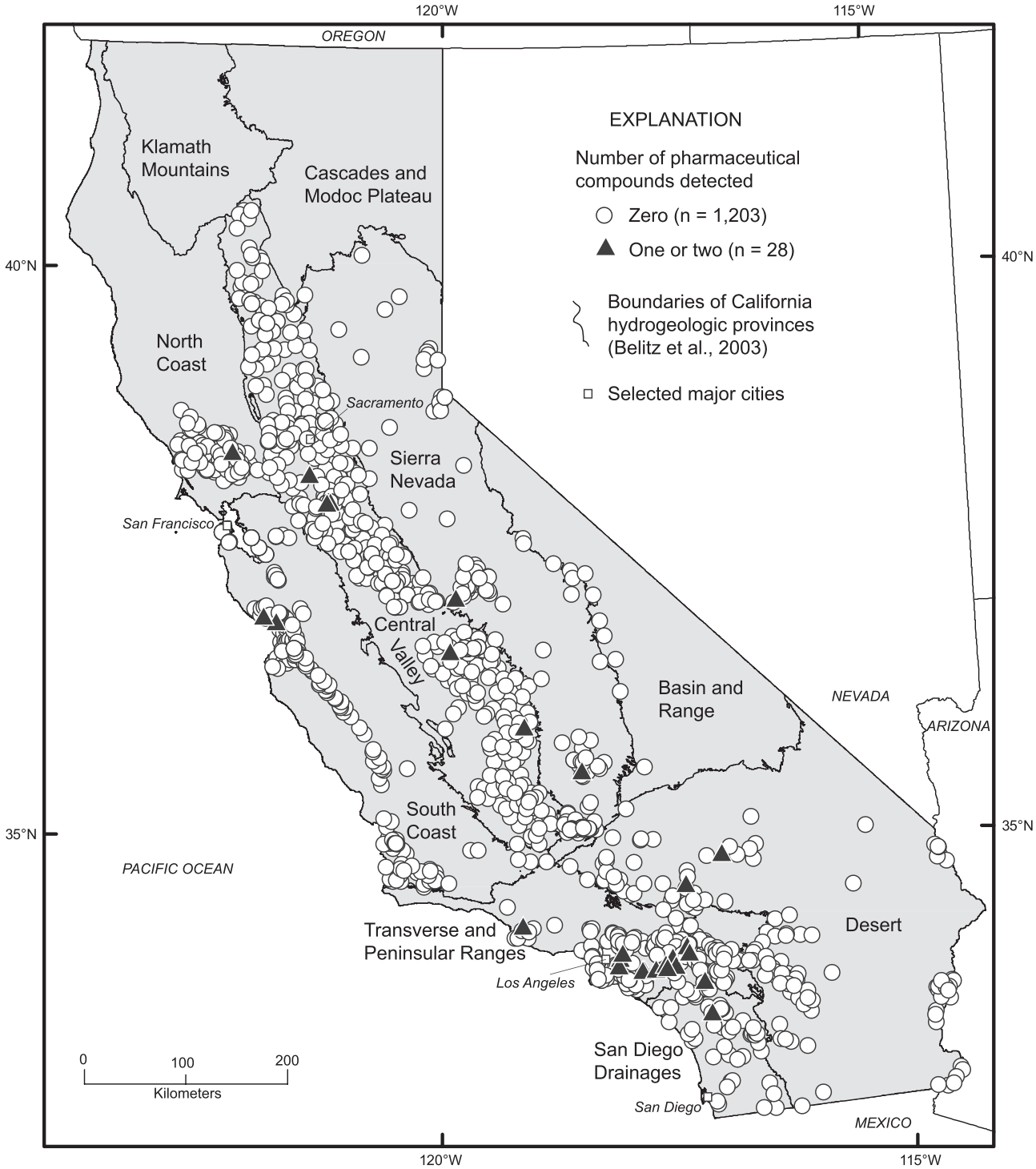

Fig. 1. Map of 1231 groundwater sites sampled for 14 pharmaceutical compounds for the California Groundwater Ambient Monitoring and Assessment (GAMA) Program Priority Basin Project, 2004–2010.

Material contains a detailed description of the project; a summary is presented here. Groundwater samples for this study were collected from 1231 sites in California between May 2004 and March 2010 and analyzed for a broad suite of water quality constituents, including pharmaceutical compounds (Fig. 1). The sites were located in 28 study units that represent a reasonably complete sampling of the range of hydrogeologic conditions and land-use patterns encountered in California. The study units were defined to include the 116 groundwater basins in the state that account for 95% of the groundwater use for public drinking-water supply occurring in groundwater basins (Belitz et al., 2003). Most of the basins are alluvial basins. Study units included basins in areas ranging from the heavily urbanized Los Angeles and San Francisco Bay regions, to dominantly agricultural regions of the Central Valley between Redding and Bakersfield, to relatively undeveloped mountainous and desert regions in the eastern and southeastern parts of the state. Most agricultural areas in California are extensively irrigated with surface water or groundwater, and groundwater recharge may be dominated by percolation of irrigation water (for example, Faunt, 2009). Engineered recharge using stormwater, treated wastewater, or imported surface water is used in many basins, most notably in the Los Angeles region where engineered recharge accounts for up to 75% of the groundwater pumped from the coastal aquifer system (Belitz et al., 2004; Reichard et al., 2003). Several study units also incorporated areas outside of groundwater basins that utilize fractured bedrock aquifers.

Detailed descriptions of site selection criteria and sample collection procedures can be found in USGS Data-Series Reports for the study units (listed in the Supplemental Material). The Data-Series Reports also contain all of the water-quality data for samples collected in each study unit. Briefly, each study unit was divided into equal-area grid cells, and within each cell, one well was randomly selected to represent the cell (Scott, 1990). This spatially-distributed, randomized well selection strategy yielded a network of wells that are statistically representative on an areal basis of the part of the aquifer system used for public drinking-water supply. Wells were selected primarily from the population of approximately 16,000 active public drinking-water supply wells in the database maintained by the California Department of Public Health (CDPH). The database lists wells used for municipal supply and wells used for community supply, such as for schools, campgrounds, and home-owners associations. In cells that had no accessible CDPH wells, irrigation, domestic, industrial, or monitoring wells with screened intervals at depths similar to the screened intervals of CDPH wells in the study unit were sampled. In some study units, additional, non-grid, wells were sampled to investigate particular water-quality issues of importance in the study unit. Most of these wells also were CDPH wells. The 1231 wells sampled for pharmaceuticals included 1000 grid wells and 231 non-grid wells. The median well depth was 134 m (interquartile range = 75 m to 198 m) and the median depth to the top of the screened interval in the wells was 61 m (interquartile range = 34 m to 101 m).

All wells were sampled by the USGS using consistent protocols (Koterba et al., 1995; U.S. Geological Survey, 2007). To minimize potential contamination during sample collection, use of products containing the targeted analytes, including caffeinated beverages, tobacco, and common non-prescription medications, was discouraged among field personnel. Groundwater to be analyzed for pharmaceuticals was filtered through a 0.3-μm nominal pore size baked glass–fiber filter during sample collection. Samples were collected in precleaned and baked, amber glass, 1-L bottles, and shipped on ice via overnight package service to the USGS National Water Quality Laboratory (NWQL) in Denver, Colorado for analysis.

2.2. Analytical method for pharmaceutical compounds

The analytical method included fourteen human prescription and non-prescription pharmaceutical compounds and selected metabolites (Table 1). These 14 compounds were selected because they are in commonly used prescription or non-prescription products, have physical properties that suggest potential for persistence in the environment, and perform acceptably in the chosen analytical procedure (Kolpin et al., 2002). Briefly, pharmaceutical compounds were extracted from water samples using solid-phase extraction cartridges, and separated and measured by high-performance liquid chromatography with mass spectrometry detection. Cahill et al. (2004) and Furlong et al. (2008) give detailed descriptions of the analytical procedures and method performance characteristics.

During the period that samples were analyzed for this study (May 2004 through March 2010), method detection limits (MDL) were established using several different methods. Initial MDLs were calculated using the 99-percent confidence interval for 7 replicate analyses of reagent water spiked with low levels of the compounds made during an analytical run (U.S. Environmental Protection Agency, 1997; Cahill et al., 2004; Furlong et al., 2008). These MDLs were used through September 2007. Subsequently, MDLs were evaluated annually using two methods: the 99-percent confidence interval for 16–24 analyses of low-level spiked reagent-water samples made over 8–12 month periods (Childress et al., 1999), and the 99th percentile of the laboratory set blanks analyzed during the same 8–12 month period (http://bqs.usgs.gov/ltmdl/background.shtml). These annually determined MDLs were generally higher than the initial MDLs. In order to compare data from samples analyzed in different years, all data were censored using the highest of the MDLs determined for each compound (Table 1). Detections reported by the NWQL with concentrations less than the selected MDL are reported as <MDL in this study and are not considered detections when calculating detection frequencies.

Our use of the MDL as the criteria for defining whether a result reported by the laboratory is considered a detection of the pharmaceutical compound in the groundwater sample (concentration ≥ MDL) or a nondetection (concentration < MDL) is different than the reporting convention used by some other studies. For the pharmaceutical method and other analytical methods for organic compounds that use mass spectrometric detection, laboratories may report results with concentrations less than MDLs if the detections met the chromatographic retention time and mass-spectral pattern criteria for confirmation of compound identity. Many other USGS studies count results with concentrations less than the MDL as detections when calculating detection frequencies (for example, Kolpin et al., 2002; Barnes et al., 2008a; Focazio et al., 2008). By counting results with concentrations less than MDLs that otherwise met analytical criteria for valid detections as detections, these studies minimize the probability of "false negative" results — results that would be reported as nondetections when the compound is actually present. Such an approach is valid and may be highly appropriate for research studies whose objective is to survey what compounds may be present in the environment.

However, given the recent spate of media coverage focused on occurrence of pharmaceuticals in drinking water and public sensitivity, we felt it was important to use the MDL as the criteria for defining detections in this study so that our results would conform to the meaning of detection as defined for regulatory purposes. The MDL is the concentration above which there is more than 99 percent probability that the measured concentration in the sample is greater than concentrations measured in blanks, i.e., that the result represents a detection of the compound present in the environmental sample (U.S. Environmental Protection Agency, 1997). Results with concentrations less than the MDL have increased probability of being "false-positive" detections of the compound in the environmental sample. Of the 550 individual detections of pharmaceutical compounds in groundwater samples, 484 had concentrations below MDLs.

2.3. Quality assurance and quality control

Evaluation of quality control data is described in detail in the Supplementary Material, and summarized briefly here. Laboratory set

Table 1
Summary of data for pharmaceutical compounds analyzed in 1231 groundwater samples collected for the California Groundwater Ambient Monitoring and Assessment (GAMA) Program Priority Basin Project, May 2004 through March 2010.

Compound	CASRN [a]	Method detection limit (μg/L) [b]	Detection frequency [c]	Median detected concentration (μg/L)	Maximum concentration (μg/L)	Typical use
Acetaminophen	103-90-2	0.06	0.32%	0.18	1.89	Prescription and non-prescription analgesic and antipyretic
Albuterol	18559-94-9	0.04	nd	nd	nd	Prescription antiasthmatic
Caffeine	58-08-2	0.10	0.24%	0.17	0.29	Non-prescription stimulant (coffee, colas, tea, etc.)
Carbamazepine	298-46-4	0.03	1.46%	0.04	0.42	Prescription mood stabilizer and anticonvulsant
Codeine	76-57-3	0.023	0.16%	0.123	0.214	Prescription analgesic and antitussive
Cotinine	486-56-6	0.019	nd	nd	nd	Metabolite of nicotine (tobacco products)
Dehydronifedipine	67035-22-7	0.04	nd	nd	nd	Metabolite of prescription antianginal and antihypertensive
Diltiazem	42399-41-7	0.04	nd	nd	nd	Prescription antihypertensive and antiarrhythmic
Diphenhydramine	147-25-0	0.02	nd	nd	nd	Non-prescription antihistimine
p-Xanthine	611-59-6	0.06	0.08%	0.12	0.12	Metabolite of caffeine
Sulfamethoxazole	723-46-6	0.08	0.41%	0.16	0.17	Prescription antibiotic
Thiabendazole	148-79-8	0.03	nd	nd	nd	Prescription and veterinary antihelminthic and agricultural antifungal
Trimethoprim	723-70-5	0.017	0.08%	0.018	0.018	Prescription antibiotic
Warfarin	81-81-2	0.05	nd	nd	nd	Prescription anticoagulant

[a] Chemical Abstracts Service Registry Number.
[b] Method detection limit (MDL) is the maximum of the up to 5 MDLs used for each compound during the period samples were analyzed. All concentrations reported in units of microgram per liter (μg/L).
[c] A total of 1231 groundwater samples were analyzed. Only detections with concentrations greater than or equal to the MDL were considered detections for calculation of detection frequencies. Compounds not detected reported as "nd".

blanks (LSB) were used to evaluate potential contamination with pharmaceutical compounds during laboratory processing and analysis of groundwater samples. One laboratory blank was processed and analyzed with each set of 10–16 environmental samples. During the period samples were analyzed for this study (May 2004 through March 2010), 691 LSBs were analyzed. The detection frequencies for the 14 compounds ranged from less than 1% for codeine and warfarin to 27% for diphenhydramine. Most of the detections in the LSBs had concentrations less than the MDLs used in this study; however, the concentrations were similar to those observed in the unscreened set of groundwater samples. The detection frequencies and concentrations observed in the LSBs analyzed during this study generally were much higher than those observed during the periods samples were analyzed for the studies by Kolpin et al. (2002), Focazio et al. (2008), and Barnes et al. (2008a,b).

Detections in LSBs were not randomly distributed during the period samples were analyzed for this study. Samples analyzed during periods with particularly high detection frequencies in the LSBs were subject to additional quality control screening which resulted in censoring of some detections of acetaminophen, diphenhydramine, and thiabendazole with concentrations greater than their respective MDLs.

Field blanks (FB) were collected at 136 sites between May 2004 and March 2010, and source-solution blanks (SSB) were collected at 77 of those sites. FBs were collected using the same protocols used for collection of groundwater samples; SSBs were collected at the field site by pouring blank water directly into the sample bottle. FBs assess potential contamination during sample collection, field processing, shipping, and laboratory processing and analysis; SSBs assess potential contamination during shipping and laboratory processing and analysis. The maximum detection frequency for the 13 compounds detected in FBs and the 3 compounds detected in SSBs was 7.4% and 3.9% (both diphenhydramine). The reason the FBs and SSBs were cleaner than the LSBs is unknown. No additional quality-control censoring of data was required on the basis of FB detections because all periods with high detection frequencies in FBs corresponded to periods with high detection frequencies in LSBs.

2.4. Statistical tests

Non-parametric statistical methods were used for this study. These methods are robust techniques that can be used with datasets containing many nondetections, are generally not affected by outliers, and do not require that the data follow any particular distribution (Helsel and Hirsch, 2002). The significance level (p) used for hypothesis testing was compared to a threshold value (α) of 5% ($\alpha = 0.05$) to evaluate whether the relation was statistically significant ($p < \alpha$). The Wilcoxon rank-sum test was used to test for differences between the median values of a parameter in two sets of samples. Contingency tables were used to test for differences between detection frequencies in two sets of samples (Helsel and Hirsch, 2002).

3. Results and discussion

3.1. Detections

Of the 1231 groundwater samples analyzed, 28 (2.3%) had detections ≥MDL of any of the pharmaceutical compounds tested (data are tabulated in the Supplementary Material). In the same set of 1231 groundwater samples, pesticides and pesticide degradates were detected in 33% of the samples at concentrations greater than or equal to the highest MDL used during the period samples were analyzed. VOCs (solvents, fumigants, gasoline oxygenates, and refrigerants) were detected in 23% of the samples, and THMs in 28% (Fig. 2). The prevalence of these 14 pharmaceuticals in aquifers used for public drinking water supply in California is significantly lower than that of pesticides, VOCs, or trihalomethanes (contingency table tests, $p < 0.001$).

The detection frequencies of pharmaceutical compounds in groundwater in this study were lower than the detection frequencies observed in the national reconnaissance studies of groundwater (Barnes et al., 2008a), and groundwater used for drinking-water supplies (Focazio et al., 2008). The national reconnaissance studies used the same laboratory (NWQL) and analytical methods for pharmaceutical compounds as used in this study, and for these comparisons, the detection frequencies in the national reconnaissance studies were calculated relative to the same MDLs as used in this study. Of the 25 groundwater samples analyzed by Focazio et al. (2008), 4 samples had detections of at least one pharmaceutical compound at concentrations greater than or equal to the MDLs used in this study. Of the 47 groundwater samples analyzed by Barnes et al. (2008a), 4 samples had detections of at least one pharmaceutical compound at concentrations greater than or equal to the MDLs used in this study. Note that carbamazepine – the compound with the highest detection frequency in this study and in Focazio et al. (2008) –

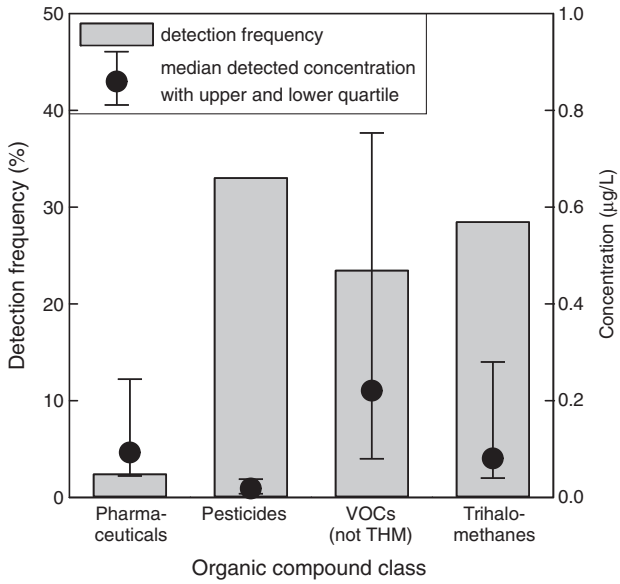

Fig. 2. Detection frequencies and median detected concentrations for pharmaceutical compounds, pesticides and pesticide degradates, volatile organic compounds (solvents, fumigants, gasoline oxygenates, and refrigerants), and trihalomethanes in 1231 groundwater samples collected for the California Groundwater Ambient Monitoring and Assessment (GAMA) Program Priority Basin Project, May 2004 through March 2010.

and diphenhydramine were not analyzed by Barnes et al. (2008b). The detection frequency in this study, 2.3%, is significantly lower than the detection frequencies in the other two studies (contingency table tests, $p<0.001$ and $p=0.012$, respectively).

Differences in strategies used to selected sites for sampling may explain the lower detection frequencies of pharmaceutical compounds in this study compared to the national reconnaissance studies. The national reconnaissance studies targeted sites thought to be susceptible to contamination from human wastewater and/or animal wastes; whereas, the sites sampled in this study were spatially distributed over the areal extent of aquifer systems used for public drinking-water supply and did not specifically target or avoid areas with higher (or lower) susceptibility to wastewater contamination.

Of the 14 pharmaceutical compounds analyzed, 7 were detected above their MDLs in at least one groundwater sample (Table 1): acetaminophen, caffeine, carbamazepine, codeine, *p*-xanthine, sulfamethoxazole, and trimethoprim. Of the 28 groundwater samples with detections, 22 had a detection of only one pharmaceutical compound. Carbamazepine and sulfamethoxazole were the most commonly co-occurring compounds in the six samples having detection of more than one compound.

3.2. Concentrations

Concentrations of pharmaceutical compounds generally were in the sub µg/L range: 33 of the 34 detections had concentrations less than 0.5 µg/L. Median detected concentrations of pharmaceutical compounds were similar to the median detected concentrations of VOCs and THMs in the same set of 1231 samples, and higher than the median detected concentrations of pesticides (Fig. 2). The GAMA Priority Basin Project (e.g., Landon et al., 2009; Bennett et al., 2010) and other studies (Toccalino et al., 2004; 2010) put concentrations of anthropogenic organic compounds in water samples in context through comparison with regulatory and non-regulatory human-health-based benchmarks for concentrations in treated drinking water. However, none of the compounds targeted in this study has human-health-based benchmarks.

One method for putting the concentrations of pharmaceutical compounds in water into context is to compare them to therapeutic doses of the compounds (e.g., Richardson and Bowron, 1985; Webb et al., 2003; Kostich and Lazorchak, 2008). As an example, we compare the cumulative masses of the compounds that would be consumed over a lifetime of drinking water containing the highest concentrations measured in this study to typical daily doses of the compounds [typical daily prescribed doses for acetaminophen, carbamazepine, codeine, sulfamethoxazole, and trimethoprim (U.S. National Library of Medicine, 2010), and the amount of caffeine in two cups of coffee for caffeine and *p*-xanthine]. The cumulative masses of the 7 compounds that would be ingested over 70 years of drinking water ranged from 0.5% to 18% of the mass that would be ingested in one typical daily therapeutic dose. In reality, most concentrations were lower than the maxima and drinking-water treatment may reduce the concentrations of some pharmaceutical compounds (Benotti et al., 2009), thus these may be maximum estimates of potential exposure.

Bruce et al. (2010) developed screening levels for 15 pharmaceutical compounds based on animal toxicity data and adverse effects on human health at therapeutic doses, and found that the equivalent concentrations in drinking water corresponding to those screening levels were factors of 10^2 to 10^7 higher than the maximum concentrations detected in drinking water. The equivalent concentrations in drinking water corresponding to the screening levels for the three compounds detected in this study, carbamazepine, sulfamethoxazole, and trimethoprim, were factors of 30, 10^5 and 4×10^5, respectively, higher than the maximum concentrations detected in this study. Bruce et al. (2010) concluded that exposure to the 15 compounds in drinking water is unlikely to have adverse effects on human health; however, the potential effects of exposure to other pharmaceutical compounds or to mixtures, and the potential effects on sensitive populations remain unknown. Other studies have similarly concluded that there is no well-established body of evidence linking exposure to the low concentrations of pharmaceutical compounds found in drinking water to short-term or long-term deleterious effects on human health (Khetan and Collins, 2007).

Evidence is emerging that chronic exposure to low concentrations of some pharmaceutical compounds may have deleterious effects on aquatic ecosystems. Although most of the biota examined have been surface water species and thus unlikely to be exposed to groundwater, comparison between concentrations observed to affect aquatic ecosystems and concentrations detected in groundwater may help put the magnitude of the measured concentrations in context. The lowest concentration at which chronic effects have been observed generally are in the range of 10 µg/L to 300 µg/L (Crane et al., 2006; Carlsson et al., 2006; Fent et al., 2006), concentrations that are factors of 10 to 10^4 higher than the maximum concentrations reported in this study. However, as more data are gathered on additional compounds, effects at even lower concentrations are being observed, such as alteration of aquifer bacteria growth and community composition by exposure to sulfamethoxazole at concentrations as low as 1.4 µg/L (Underwood et al., 2011) and changes in behavior of marine amphipods by exposure to fluoxetine (an antidepressant) at concentrations as low as 0.1 µg/L (Guler and Ford, 2010). Synthetic estrogens, a pharmaceutical class not analyzed in this study, can have dramatic and alarming effects on fish at concentrations less than 0.01 µg/L (Kidd et al., 2007). In addition, data indicate that some pharmaceutical compounds have additive effects, thus mixtures must also be considered (Pomati et al., 2006, 2008).

3.3. Behavior of individual pharmaceutical compounds

The 14 compounds investigated in this study – half of which were detected and half of which were not – have a number of properties that may explain which compounds were detected in groundwater and which were not. Carbamazepine was the most frequently detected

compound, with a detection frequency of 1.5%. This pharmaceutical is widely used because of its multiple therapeutic applications (Table 1). The maximum concentration detected, 0.42 μg/L, was similar to maximum concentrations detected in groundwater in other studies (Drewes et al., 2003; Sacher et al., 2001; Focazio et al., 2008; Godfrey et al., 2007; Rabiet et al., 2006).

As noted previously, carbamazepine is among the most frequently detected pharmaceutical compounds in groundwater both in the United States and in other countries. The greater detection frequency of carbamazepine compared to other compounds with much higher use (e.g., acetaminophen and caffeine) reflects the recalcitrant nature of the molecule. Laboratory experiments and field studies indicate that carbamazepine is not noticeably degraded and suffers little or no sorption in water-sediment systems (Löffler et al., 2005; Drewes et al., 2003; Snyder et al., 2004; Heberer et al., 2004), and that it is highly resistance to biodegradation (Clara et al., 2004; Suarez et al., 2010; Wu et al., 2010). It is resistant to hydrolysis (Lam et al., 2004) and its' molecular structure suggests that it exists as a neutral molecule at environmental pHs, resulting in limited interaction with the generally negatively-charged mineral surfaces in aquifer materials. These properties indicate that carbamazepine should be highly persistent in groundwater.

Acetaminophen, caffeine, and sulfamethoxazole were the next most frequently detected pharmaceutical compounds in this study. Acetaminophen and caffeine are relatively frequently detected in surface water (e.g., Kolpin et al., 2002), have much higher use than carbamazepine, but have chemical properties that make them less persistent in groundwater. In studies examining the differential levels of caffeine and acetaminophen in wastewater and in nearby groundwater, both are strongly attenuated by passage through aquifer materials (Löffler et al., 2005; Drewes et al., 2003; Snyder et al., 2004; Godfrey et al., 2007), likely because both biodegrade relatively rapidly (Benotti and Brownawell, 2009; Yu et al., 2006; Bradley et al., 2007). Sulfamethoxazole generally is minimally attenuated by passage through aquifer materials (Godfrey et al., 2007; Snyder et al., 2004; Sacher et al., 2001; Barber et al., 2009), and is nearly as resistant to biodegradation as carbamazepine (Benotti and Brownawell, 2009; Snyder et al., 2004; Suarez et al., 2010).

Seven compounds were not detected in groundwater samples in this study: albuterol, cotinine; dehydronifedipine, diltiazem, diphenhydramine, thiabendazole, and warfarin, and three were detected in less than 0.2% of samples: codeine, *p*-xanthine, and trimethoprim. The absence of these ten compounds likely reflects a combination of physical properties and source patterns. Albuterol, codeine, dehydronifedipine, diltiazem, and warfarin are rarely present in surface water at concentrations greater than the MDLs used in this study (Kolpin et al., 2002; Focazio et al., 2008), suggesting that they may be highly biodegradable and therefore unlikely to occur in groundwater. Cotinine, codeine, *p*-xanthine, trimethoprim, and warfarin undergo significant attenuation between wastewater sources and adjacent groundwater as the water passes through aquifer materials (Godfrey et al., 2007).

Albuterol, diltiazem, and nifedipine (the parent compound of dehydronifedipine) were all first approved by the USFDA in 1981 (U.S. Food and Drug Administration, 2010). The other 11 compounds were either approved for use before 1950 or are found in non-prescription substances that have been in use for centuries (i.e., tobacco, caffeinated beverages). Most of the wells in this study are long-screened public-supply wells tapping groundwater with a range of ages, and are relatively deep (median depth = 119 m, median depth to top of screen = 52 m for wells containing tritium ≥0.2 TU). The depths of these wells suggest that the fraction of very young groundwater (recharged since 1981) is likely to be small. Thus, it is unlikely that compounds not in use until 1981 would exist in samples from these wells at detectable levels.

Diphenhydramine and thiabendazole have not been commonly measured in previous studies. There is therefore little information on the potential for biodegradability of either compound. In laboratory microcosm experiments examining degradation of pharmaceutical compounds in soils amended with biosolids, diphenhydramine was as resistant to degradation as carbamazepine (Wu et al., 2010). This finding suggests that a process other than biogradation may be responsible for diphenhydramine not being detected in groundwater.

3.4. Relations to water quality, well depth, and land use

The previous section described findings in regards to the specific pharmaceutical compounds that were found in a small number of the 1231 groundwater sites tested. Equally important findings arise from an examination of the relations between the occurrence of pharmaceutical compounds and other water-quality constituents and potential explanatory factors, such as well depth and land use.

Occurrence of pharmaceutical compounds was found to be strongly correlated with the presence of modern water and with occurrence of other anthropogenic compounds. Groundwater samples with tritium activities greater than 0.2 TU contain at least some modern water (water recharged since 1952). [Natural background tritium levels in precipitation were approximately 5 TU prior to 1952 when atmospheric nuclear bomb testing began (Craig and Lal, 1961); groundwater recharged in 1950 with an initial tritium activity of 5 TU would have a tritium activity of less than 0.2 TU when the wells were sampled in 2004–2010.] Most of the wells had long screened intervals and thus the groundwater samples were mixtures of water of a wide range of ages. All 28 groundwater samples with detections of pharmaceutical compounds had tritium activities greater than 0.2 TU, indicating presence of at least some modern groundwater.

Total pesticide, total VOC (except THMs), and total THM concentrations in the 28 groundwater samples with detections of pharmaceutical compounds were significantly greater than median concentrations in the 839 samples containing at least some modern water and no detections of pharmaceutical compounds (Fig. 3a; Wilcoxon rank-sum test $p<0.001$). Also, both sets of samples containing at least some modern water had significantly greater median concentrations of pesticides, VOCs, and THMS than the 360 samples containing no modern water (Fig. 3a; Wilcoxon rank-sum test $p<0.001$). These correlations demonstrate that the well sites that produced samples with detectable levels of pharmaceuticals are also affected by other anthropogenic activities.

Of the 28 samples with detections of pharmaceutical compounds, 86% also contained pesticides at concentrations greater than the highest MDL used during the period of study, 71% also contained VOCs other than THMs (primarily solvents), and 61% also contained THMs. The types of pesticides detected in the samples with detections of pharmaceutical compounds suggest urban, rather than agricultural, sources. Among the 23 samples with detections of pesticides and pharmaceutical compounds, 74% had detections of prometon, 3,4-dichloraniline (degradate of diuron), or tebuthiuron, herbicides used in urban settings (rights-of-way and landscaping) in California (Kegley et al., 2005), and 30% had detections of fipronil (or its degradates), an insecticide used for structural pest control and in pest control products for pets. The detection frequencies of these three urban-use herbicides and of fipronil, 24% and 0.3%, respectively, were significantly lower in the 353 samples with detections of pesticides and not pharmaceuticals (contingency table tests, $p<0.001$).

If pharmaceutical compounds in the groundwater samples primarily were associated with recharge of treated wastewater, then one might expect that the occurrence of pharmaceuticals would be most strongly linked to occurrence of THMs, because THMs generally are formed during the disinfection step of wastewater treatment. However, in these data, the occurrence of pharmaceuticals is more strongly associated with occurrence of pesticides (contingency table test, $p=0.035$). This may reflect the physical properties of the compounds. None of the 14 pharmaceutical compounds tested are

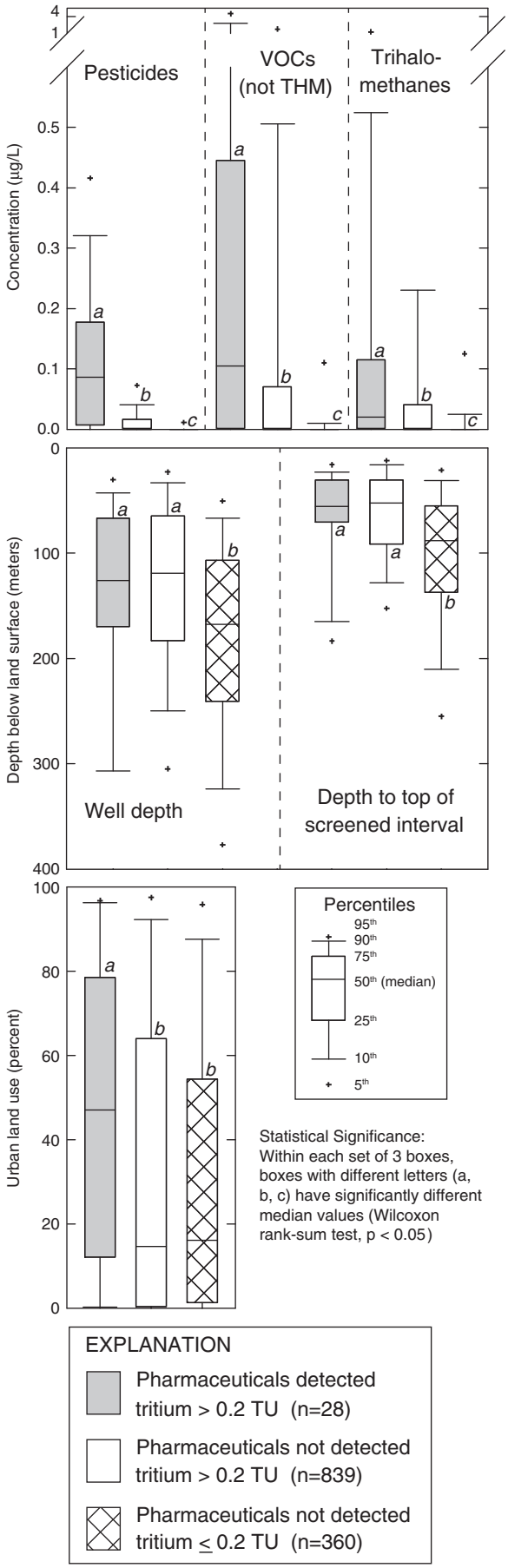

Fig. 3. Box plots of A) concentrations of pesticides, VOCs (other than THMs), and trihalomethanes and B) depth to top of screened interval in well, well depth, and percentage of urban land use within 500 m of the well site for 1231 groundwater samples also analyzed for pharmaceutical compounds and tritium activity for the California Groundwater Ambient Monitoring and Assessment (GAMA) Program Priority Basin Project, May 2004 through March 2010. Samples divided into three categories on the basis of presence or absence of detections of pharmaceutical compounds and tritium activity greater than or less than 0.2 TU.

volatile, and the chemical structures of the pharmaceutical compounds are more similar to pesticides than to THMs and many other VOCs, thus, the transport of pharmaceutical compounds in aquifer systems may more closely resemble that of pesticides.

Occurrence of pharmaceutical compounds in groundwater was not correlated with well depth or with depth to the top of the screened interval in the well. The median depth and depth to top of screen for wells with detections of pharmaceutical compounds (126 m and 55 m, respectively), were not significantly different than the medians for wells with evidence for modern water and no detections of pharmaceutical compounds (119 m and 53 m, respectively) (Fig. 3b). Barnes et al. (2008a) found that groundwater samples from shallower wells had significantly greater numbers of different wastewater indicator compounds (including pharmaceuticals) detected, compared to deeper wells. This differential finding may arise from the contrast in well selection strategies and well depths. Barnes et al. (2008a) targeted wells in areas with suspected sources of wastewater at the surface, and the wells were relatively shallow (median depth 19 m). Under those conditions, occurrence of pharmaceutical compounds may decrease with depth because increased travel distance from the surface source likely results in greater attenuation. Well selection for this study was not targeted to areas with suspected surface sources, thus, no correlation between well depth and occurrence was expected.

Occurrence of pharmaceutical compounds in groundwater was also found to be correlated with land use. Previous studies have demonstrated that land use in a 500-meter buffer around a well site is a useful predictor of occurrence of VOCs in groundwater (Johnson and Belitz, 2009). Land use classes from the nationwide USGS National Land Cover Dataset (Nakagaki et al., 2007) were consolidated into 3 groups: urban, agricultural, and undeveloped land uses. The percentage of urban land use around well sites with detections of pharmaceutical compounds and evidence for presence of modern water was significantly greater than the percentages of urban land use around well sites with no detections of pharmaceutical compounds and evidence for presence (Wilcoxon rank sum test $p = 0.035$) or absence (Wilcoxon rank sum test $p = 0.017$) of modern water (Fig. 3c). Occurrence of pharmaceutical compounds was not significantly correlated with agricultural land use.

Half of the groundwater samples with detections of pharmaceutical compounds are from the Los Angeles metropolitan area. This primarily reflects the fact that the Los Angeles area is the largest urbanized area in the state. The median percentage of urban land use at sites with samples containing some modern groundwater in the Los Angeles area was 79%, while that of sites with samples containing some modern groundwater in the rest of the study (7%) was significantly lower (Wilcoxon rank-sum test $p < 0.001$).

The higher amount of urbanization in the Los Angeles area, however, does not account entirely for the greater detection frequency of pharmaceutical compounds. Wells in the Los Angeles area showed higher detection frequencies of pharmaceuticals than wells in other parts of the state, even when the data were normalized for the degree of urban land use. Over nearly the entire range of urban land-use percentages, the Los Angeles area groundwater from wells containing some modern groundwater has greater detection frequencies of pharmaceuticals, pesticides, VOCs, and THMs than groundwater containing some modern groundwater from other areas of the state (Fig. 4abc). The greater detection frequency also is not due to

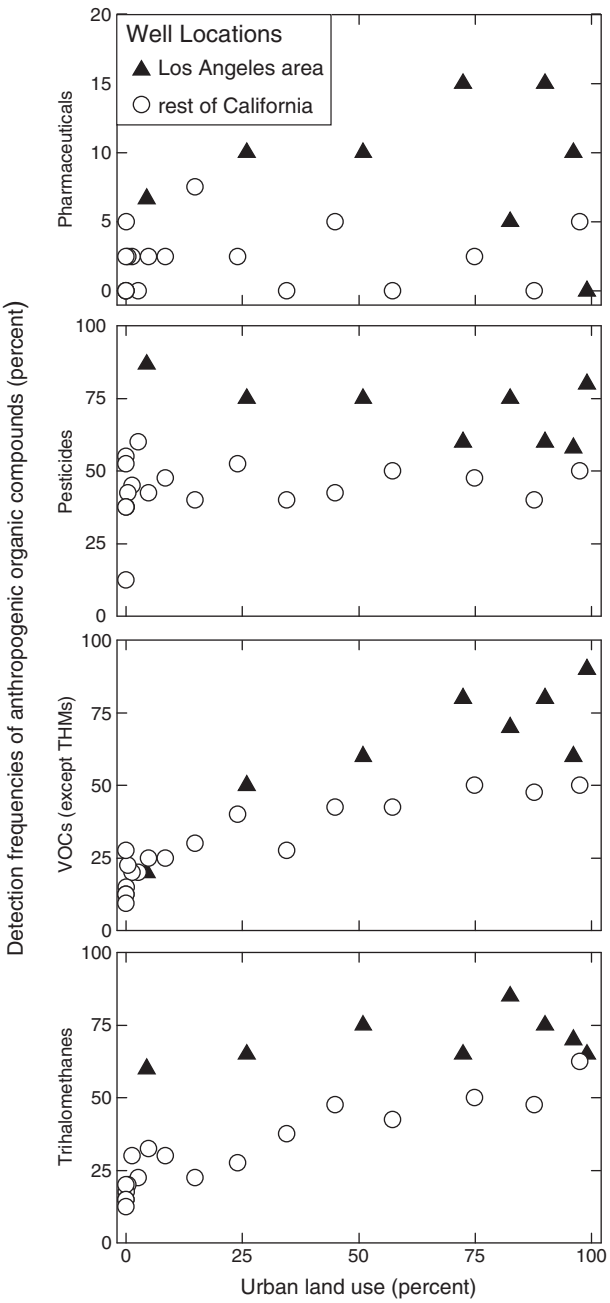

Fig. 4. Graphs showing average percentages of urban land use within 500 m of well sites and detection frequencies of pharmaceutical compounds, pesticides and pesticide degradates, VOCs (except THMs), and trihalomethanes for groups of samples from the Los Angeles area (study units S2, S3, and S4) and other areas of California. Samples from the Los Angeles area (n = 155) and from other areas of California (n = 712) with tritium activity >0.2 TU each were ordered by percentage of urban land use, and then divided into groups of 20 (Los Angeles) or 40 (other areas) for calculations of average land use and detection frequencies of classes of organic compounds.

wells being shallower than they are in other urbanized areas in the state: among all wells with greater than 50% urban land use and containing some modern water, wells in the Los Angeles area have significantly greater depths to the tops of the screened intervals (91 m) than do wells in the rest of the state (53 m) (Wilcoxon rank-sum test $p<0.001$).

The greater detection frequencies of pharmaceuticals and other anthropogenic organic compounds in Los Angeles area groundwater may be related to the highly engineered nature of the groundwater flow systems in many of the Los Angeles area groundwater basins. These flow systems are driven by engineered recharge, the use of treated wastewater and storm water for recharge, and significant amounts of groundwater pumping (Belitz et al., 2004; Dawson et al., 2000; Shelton et al., 2000). Infiltration basins for recharge of storm water and river baseflow (primarily treated wastewater) have been in use since the 1920s in some areas and this artificially-recharged groundwater has been drawn laterally across the basins by intensive groundwater pumping down-gradient from the recharge facilities. Artificial recharge accounts for up to 75% of the groundwater pumped from the coastal aquifer system (Belitz et al., 2004; Reichard et al., 2003). This flow system may serve to transport anthropogenic organic constituents from the surface into the aquifer system much more efficiently than in other urbanized areas of the state that do not use artificial recharge as intensively.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.scitotenv.2011.05.053.

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