

Fate of selected pharmaceuticals and their metabolites in soil aquifer treatment

Takashi Yonetani, Shinya Echigo and Sadahiko Itoh

ABSTRACT

Through a series of long-term column experiments, the fate of three common pharmaceuticals (carbamazepine (CBZ), diclofenac, and indomethacin) and their major phase I metabolites in soil aquifer treatment (SAT) were monitored. CBZ concentration increased by a factor of two (from 37 to ca. 70 ng/L) regardless of the treatment conditions, and its metabolites, 10,11-dihydro-10-hydroxycarbamazepine (approximately 500 ng/L after SAT) and CBZ-10,11-epoxide (12–42 ng/L after SAT) were not effectively removed after SAT. Our results indicated that some metabolites of pharmaceuticals are present at much higher concentration than the original forms in the SAT effluent, and that some metabolites are more persistent during SAT with a relatively short retention time (i.e., 30 days). The study indicated that more attention should be paid to the formation and fate of metabolites in the water quality management of SAT effluent.

Key words | metabolites, pharmaceuticals, soil aquifer treatment

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INTRODUCTION

In many parts of the world, water shortage is a serious problem. In addition to the uneven distribution of water resources and the high population concentration in large cities, extreme weather conditions resulting from global climate change have exacerbated the situation (Arnell 1999). Water reclamation has become an important method to mitigate this problem. Over the past several decades, wastewater reclamation has even become employed for potable use in arid areas of the world (e.g., Asano *et al.* 2007).

Soil aquifer treatment (SAT) is a common method for water reclamation (Quanrud *et al.* 1996; Dillon *et al.* 2006). Many studies have demonstrated its ability to decompose or remove organic compounds by biodegradation and/or adsorption (e.g., Quanrud *et al.* 2003).

Pharmaceuticals and personal care products (PPCPs) are a major safety concern in the reuse of wastewater effluent. The safety of PPCPs for humans at the high doses

intended for medical use and, in some cases, aquatic ecosystems (Anzai *et al.* 2007), have to be confirmed before they are employed. However, the effects of PPCPs themselves and their metabolites on human health and the natural environment through the long-term exposure in the form of mixtures are not yet fully understood. Many researchers have reported the decomposition of various PPCPs by SAT (e.g., Massmann *et al.* 2006; Maeng *et al.* 2011 and references therein), but information on the presence and fate of PPCP metabolites in SAT is still limited despite recent research efforts (e.g., Montgomery-Brown *et al.* 2003; Schulz *et al.* 2008; Li *et al.* 2013; Hübner *et al.* 2014).

In this study, we monitored the behaviors of three selected pharmaceuticals and their metabolites through a series of column experiments in order to better understand the fate of micropollutants in SAT under practical conditions. Carbamazepine (CBZ), diclofenac (DCF), and indomethacin (IDM) were selected as the target parent compounds. These compounds are commonly found at relatively high concentrations in the effluents from wastewater treatment plants (Nikolaou *et al.* (2007) and references therein; Narumiya *et al.* 2009).

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MATERIAL AND METHODS

Reagents

The target compounds and their metabolites monitored in this study are listed in Table 1 with their abbreviations, manufacturers, and purity. For their analysis by liquid chromatography with tandem mass spectrometry (LC-MS/MS), formic acid, methanol, and acetonitrile (LCMS grade, Wako, Japan) were used for the preparation of mobile phases. All the other chemicals used in this study were purchased from Wako (Japan), and of the highest grade available unless otherwise stated. They were used as received without further purification. All the aqueous solutions were prepared with ultrapure water produced with a Millipore Academic-A10 system.

Column experiments

To monitor the fate of the target compounds in SAT, three laboratory-scale acrylic columns (i.d. 15 cm; height 150 cm) and three pilot-scale rectangular columns (length 1.5 m; width 1.5 m; height 3.0 m) were used under aerobic conditions, with different packing materials (sand and weathered granite soil (WGS)), saturation conditions, and hydraulic retention times (HRTs). The conditions for the column experiments are summarized in Table 2. The HRT

of the unsaturated column is the sum of the HRTs in the saturated and unsaturated zones. The sand and WGS were collected in the Shiga area, Japan, and used without sieving (see Table 3 for soil properties). The temperature of the laboratory-scale reactors was maintained at 20 °C. The saturation conditions were controlled by adjusting the height of the exit ports.

The effluent collected from an anaerobic-anoxic-aerobic (A2O) process wastewater treatment plant in Kyoto City (Japan) after removing large particulate matter was used as the feed water for this study. Target compounds were not added to the feed water, as they were already present in the feed water. For the laboratory-scale experiments, the same feed water was used over any given week. We collected feed water once a week, stored it in a refrigerator, and fed the water to the columns directly by peristaltic pumps from the container in the refrigerator. The water temperature was increased to room temperature during transfer by placing a portion of the transfer line into a water bath. We did not account for the time lag between samplings of feed water and effluent water as the PPCP concentrations were stable (Yonetani *et al.* 2013). This was also true for the triplicated sampling of the three target PPCPs used in this study. For the pilot-scale columns, A2O effluent was directly and continuously fed from an actual wastewater treatment facility (i.e., the columns were stationed in the facility). We did not account for the HRT (i.e., time lag) because of the limited access to the facility. However, according

Table 1 | List of target parent compounds and metabolites studied in this work

Original drug	Metabolites	Abbreviation	Manufacturer	Purity
Carbamazepine		CBZ	Wako	>97%
	2-hydroxide	CBZ-2OH	Wako	98%
	3-hydroxide	CBZ-3OH	Wako	98%
	10-hydroxide	CBZ-10OH	Wako	98%
	epoxide	CBZ-Ep	Wako	96%
	hydroxide	CBZ-DiOH	Santa Cruz Biotechnology	>97%
Diclofenac*		DCF	Wako	>98%
	4'-hydroxide	DCF-4'OH	Wako	95.50%
	5-hydroxide	DCF-5OH	Wako	97%
Indomethacin		IDM	Wako	>98%
	desmethyl metabolite	DMI	Toronto Research Chemicals	98%
	deschlorobenzoyl metabolite	DBI	Wako	>98%

*Purchased in the form of sodium salt.

Table 2 | Basic properties of soil and sand used in this study

	WGS	Sand
pH	7.4	6.6
CEC ^a (meq/100 mg-dry)	15.6	2.39
TOC ^b (%)	0.0159	0.0094
Porosity	0.40	0.44

^aCation exchange capacity.^bTotal organic carbon.

to a report of the long-term monitoring of PPCPs preceding this study (Yonetani *et al.* 2013), the PPCP concentrations were stable, and it was assumed that there was no need to account for the HRT.

The basic water quality of the feed water and SAT effluents during long-term operation are summarized in Table 4. All the sand columns were under aerobic conditions, and removal of dissolved organic carbon (DOC) and UV absorbance at 254 nm (UV₂₅₄) were improved by increasing the HRT. The low dissolved oxygen (DO) and low nitrate of the effluents from the WGS columns indicates the presence of both aerobic and anaerobic zones in the WGS columns. The relatively high DO values in the effluents of the unsaturated sand columns indicates that oxygen supply was fast, and that most DO consumption occurs in the top layer of SAT columns. Lower DO values for WGS columns may be associated with higher biological activity due to smaller particle size (i.e., larger surface area).

Each column was operated for at least one year before sampling. Samples were collected three times for all the columns in December 2013 at approximately one-week intervals.

Table 3 | Summary of the conditions for the column experiments

Column code	Reactor type	Soil type	Height of soil (cm)	Height of saturated zone (cm)	Height of unsaturated zone (cm)	Loading rate (mm/day)	HRT (day)
SA3.5unsat	Laboratory scale, unsaturated	sand	70	50	20	80	3.5
SA7sat	Laboratory scale, saturated	sand	120	120	–	80	7
SA7unsat	Laboratory scale, unsaturated	sand	120	100	20	80	7
SA30unsat	Pilot scale, unsaturated	sand	237	220	17	30	30
WGS30sat	Pilot scale, saturated	WGS	250	250	–	30	30
WGS30unsat	Pilot scale, unsaturated	WGS	250	220	30	30	30

Analytical methods

The target compounds and their metabolites were analyzed by LC-MS/MS in multiple reaction monitoring mode. CBZ and its metabolites were measured in positive mode, and the others were measured in negative mode. Before analysis, all samples were filtered with a 0.3 µm glass-fiber membrane (GF-75, Advantec), and the influent and effluent samples were concentrated 100 and 200 times, respectively, using OASIS-HLB cartridges (see Yonetani *et al.* (2012) for details). Details of the LC-MS/MS analysis conditions are shown in Table 5 and Tables S1 and S2 (available with the online version of this paper). The recoveries of target PPCPs and their metabolites were determined for the feed water and SAT effluents, respectively, by a standard addition, and these values were used for the calculation of their aqueous phase concentration in the samples. The limits of detection (method detection limit) and quantification (method quantification limit) were determined based on signal-to-noise ratios of 3 and 10, respectively.

RESULTS AND DISCUSSION

Concentrations of target pharmaceuticals and their metabolites in the feed water

Table 6 summarizes the concentrations of the three pharmaceuticals and their metabolites in the A2O water. While the concentration of CBZ-10OH was much lower than that of CBZ (37 ng/L), the concentrations of CBZ-2OH, CBZ-3OH, and CBZ-Ep were comparable to that

Table 4 | Summary of basic water quality

Laboratory-scale	DOC (mg/L) ^a	UV ₂₅₄ (/cm) ^a	DO (mg/L) ^b	NO ₃ ⁻ (mg/L) ^a
A2O for laboratory-scale columns	3.9 ± 0.5	0.086 ± 0.016	7.6 ± 1.6	4.1 ± 0.7
SA3.5unsat	1.2 ± 0.2	0.031 ± 0.006	6.3 ± 1.4	4.7 ± 0.5
SA7sat	1.1 ± 0.1	0.030 ± 0.013	4.0 ± 2.0	4.7 ± 0.7
SA7unsat	1.1 ± 0.2	0.026 ± 0.006	6.1 ± 1.2	4.7 ± 0.4
Pilot-scale	DOC (mg/L) ^d	UV ₂₅₄ (/cm) ^d	DO (mg/L) ^d	NO ₃ ⁻ (mg/L) ^d
A2O for pilot-scale columns	3.7 ± 0.5	0.083 ± 0.019	3.5 ± 1.6	3.8 ± 1.0
SA30unsat	0.8 ± 0.2	0.022 ± 0.010	4.5 ± 1.9	4.1 ± 0.9
WGS30sat	1.0 ± 0.2	0.024 ± 0.011	0.3 ± 0.6	0.1 ± 0.2
WGS30unsat	0.8 ± 0.2	0.018 ± 0.009	0.4 ± 0.7	0.1 ± 0.1

^a*n* = 16–17, Apr 2013–Jan 2014.^b*n* = 49–53, Apr–Aug 2013, May–Feb 2015.^c*n* = 37–41, Jan 2013–Feb 2015.^d*n* = 29–31, Jan 2013–Feb 2015.**Table 5** | Summary of the conditions for LC-MS/MS analysis

	Model	Prominence 20A (Shimadzu)
LC	Column	Kinetex C-18 100A 2.1 × 50 mm 2.6 μm
	Column temperature	40 °C
	Injection volume	10 μL
	Mobile phase	0.1 formic acid/acetonitrile (ESI+) 0.1 formic acid/methanol (ESI-)
	Flow rate	0.4 mL/min
	Measuring time	22 min
MS/MS (Positive mode/Negative mode)	Model	4000 QTRAP (AB SCIEX)
	Ionization	ESI+ /ESI-
	Curtain gas	10 psi/25 psi
	Ion spray voltage	5,000 V/ - 4,000 V
	Turbo ion spray temp.	600 °C/550 °C
	Nebulizer gas pressure	60 psi/60 psi
	Turbo gas pressure	50 psi/40 psi
Collision gas	6/6	

of the original compound. Furthermore, the concentration of CBZ-DiOH was more than ten times higher than that of CBZ. CBZ-Ep is known to be as pharmacologically active as CBZ (Tomson *et al.* 1990), and the total activity of CBZ and its metabolites is expected to be at least twice as much as CBZ alone.

The ratios of DCF-4'OH and DCF-5OH concentrations to DCF concentration were 60% and 10%, respectively,

and were lower than those in human urine (Sawchuk *et al.* 1995). This may suggest faster decomposition of these compounds than the original compounds in wastewater treatment. The pharmacological activities of DCF-4'OH and DCF-5OH are lower than DCF (Wiesenberg-Boettcher *et al.* 1991), and thus the health risk associated with these metabolites is likely to be low. In a previous work conducted in Norway, these hydroxylated metabolites were dominant

Table 6 | Concentrations of the three target compounds and their metabolites in the A2O effluent ($n = 6$, three samples were those for laboratory-scale columns and the rest were those for pilot-scale reactors)

Compound	Concentration (ng/L)
CBZ	37 ± 8
CBZ-2OH	44 ± 10
CBZ-3OH	35 ± 8
CBZ-10OH	3 ± 3
CBZ-Ep	30 ± 6
CBZ-DiOH	529 ± 47
DCF	128 ± 5
DCF-4'OH	79 ± 4
DCF-5OH	13 ± 9
IDM	77 ± 8
DMI	7 ± 5
DBI	16 ± 3

(Langford & Thomas 2011), but the higher concentration of DCF (i.e., the parent compound) in the present study was consistent with another survey in Japan (Onoda *et al.* 2010).

DMI and DBI were present at lower levels (10% and 20%, respectively) than IDM. It is known that the antipyretic, analgesic, and anti-inflammatory activities of IDM are lost (Duggan *et al.* 1972) upon the transformation to DMI and DBI, thus the risks associated with their presence are unlikely to be significant.

Fate of the target pharmaceuticals and their metabolites in SAT

Figure 1 shows the concentrations of CBZ and its metabolites before and after SAT. The CBZ concentration increased approximately by a factor of ca. two during SAT (from 37 to 72 ng/L), indicating the formation of CBZ in SAT (i.e., the difference between A2O and SAT effluents was statistically significant ($p < 0.05$ by Mann–Whitney U test)). Similar results for the fate of CBZ in wastewater treatment have been previously reported (Kobayashi *et al.* 2006; Radjenovic *et al.* 2008; Sponberg & Witter 2008; Zhang *et al.* 2008). Deconjugation has been proposed as a possible mechanism for the increase of CBZ levels in wastewater treatment (Zhang *et al.* 2008), but has not been confirmed yet. Our observation is the first reported

indication of an increase of CBZ in SAT. It is noteworthy that the hydrolysis of A2O water at pH 3.0 and 80 °C for 30–60 min increased the CBZ level by 98%, while the hydrolysis reaction of each metabolite and the SAT effluent under the same reaction conditions did not result in CBZ increase. This result suggests the presence of an unknown CBZ precursor (e.g., conjugates) in A2O water.

Regardless of HRT, the CBZ concentrations were similar for the sand columns. That is, the backward (i.e., deconjugation) reaction rate occurs relatively rapidly, and the free CBZ formed is persistent in sand columns with HRT up to 30 days. The CBZ concentrations for the WGS columns were slightly lower (by 5–10 ng/L on average) than that of SA30unsat. This may be due to the strictly anaerobic conditions at the bottom of the WGS columns as was pointed out by Schmidt *et al.* (2004), but the effect was not statistically significant ($p > 0.05$ in the Mann–Whitney U test). Our results indicate that CBZ is produced, but the rate of decomposition, if any, is slow in SAT with relatively short HRTs (30 days or less).

CBZ-2OH concentrations decreased in SAT even with a short HRT (3.5 days), and further removal was observed by extending the HRT for the sand columns. For SA30unsat, the removal was more than 97%, and was statistically significantly different to SA7unsat and SA7sat ($p < 0.05$ by Mann–Whitney U test). For the WGS columns, the removal of CBZ-3OH tended to be better for WGS30unsat than that for WGS30sat, and this was in agreement with the trend observed for DOC removal. The faster oxygen supply in the unsaturated zone may have contributed to this improved removal. A similar trend was observed for CBZ-3OH, but the removal was slightly higher. Brezina *et al.* (2015) also observed faster removal by biodegradation of CBZ-3OH than CBZ-2OH in soil batch experiments. CBZ-10OH was minimized even with an HRT of just 3.5 days.

The CBZ-Ep concentration appeared to increase in SAT with HRTs of 3.5 and 7 days (140%, from 29 to 41 ng/L on average), but the difference was not statistically significant ($p > 0.05$ by Mann–Whitney U test). The increase of CBZ-Ep is possible as it is a primary transformation product of CBZ in soil (Li *et al.* 2013). While a decrease in CBZ-Ep was observed with an HRT of 30 days, the removal was lower than those of CBZ-3OH and CBZ-2OH (15–60%).

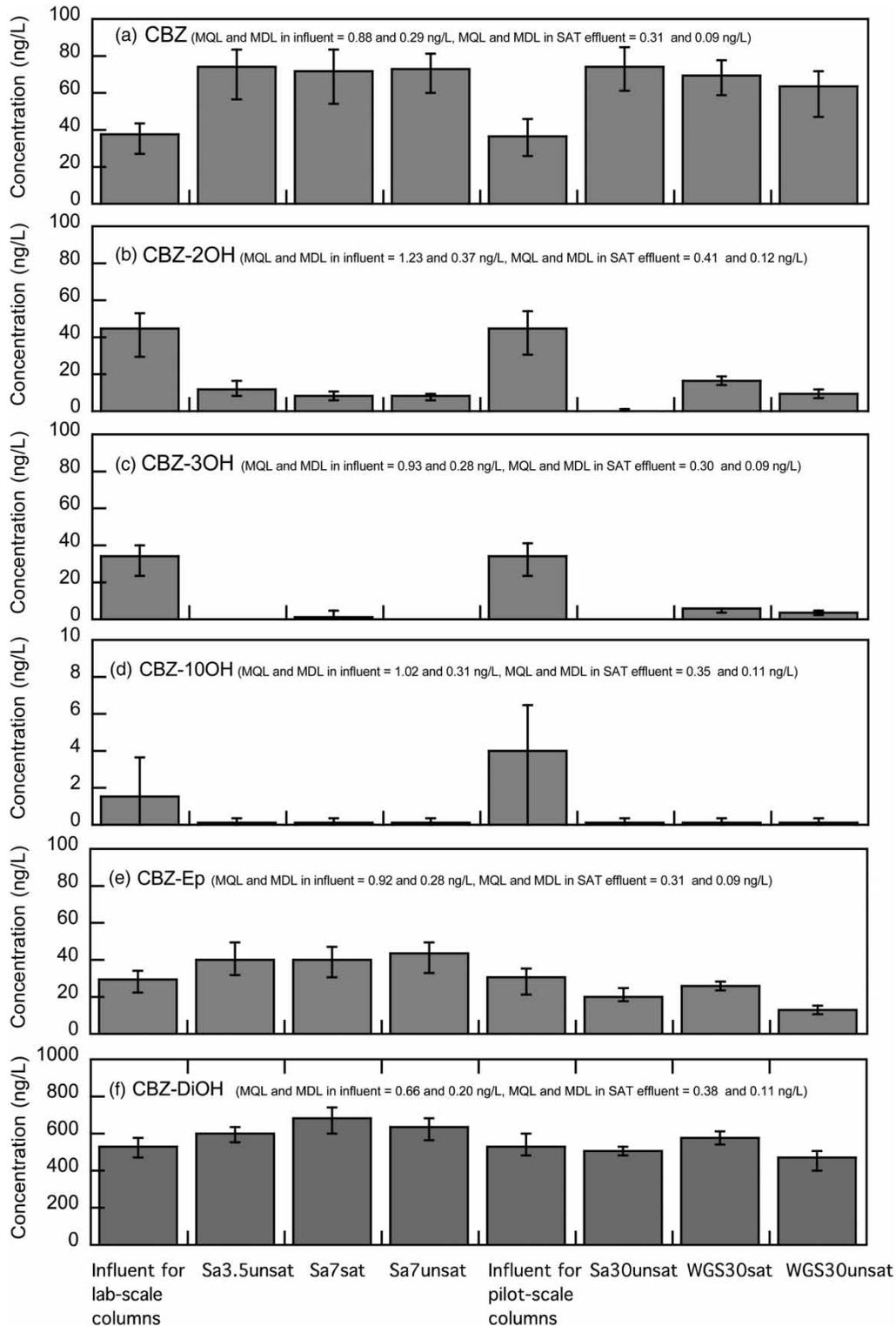


Figure 1 | Concentrations of CBZ and their metabolites before and after SAT. (The top and bottom ends of error bars show maximum and minimum concentrations, respectively. For a data set with three data points below the quantification limit (QL), max = QL, midpoint = QL/2, min = zero were assigned; for a data set with two data points below the QL, min = zero, midpoint = QL were assigned; for a data set with a data point below the QL, min was set to zero.)

No removal of CBZ-DiOH during SAT was observed, and CBZ-DiOH was the dominant (ca. 500 ng/L) CBZ related compound both before and after SAT. This observation is in agreement with the trend in other biological treatments (Zhang *et al.* 2008; Kaiser *et al.* 2014) and biodegradation in liquid culture with white-rot fungus (Golan-Rozen 2015).

The above results show that the majority of CBZ and its related compounds remain (and even increase) in SAT, while minor metabolites are degraded. To better control these persistent compounds, the combination of SAT with a chemical treatment (e.g., ozonation (Hübner *et al.* 2014)) should be further researched.

DCF and DCF-4'OH followed a similar trend (Figure 2). That is, they were efficiently removed by SAT, especially in the sand columns. The removal mechanisms for DCF involve both biodegradation and sorption (He *et al.* 2015). The presence of the anaerobic zone and the saturated conditions inhibited their removals. Conversely, the DCF-5OH concentration appeared to increase (or at least did not

decrease) in SAT under HRTs of 3.5 and 7 days. This may be another example of the accumulation of transformation products with the degradation of a parent compound. Grönning *et al.* (2007) reported that the major transformation product of DCF by the indigenous microflora in river sediments was DCF-5OH, and this pathway may have contributed to the apparently slower removal of DCF-5OH. With a longer HRT (i.e., 30 days), however, its concentration was lower than in the influent concentration. Similarly to DCF and DCF-4'OH, both biodegradation and sorption could be involved in the removal of this compound.

IDM and DMI were removed almost completely in SAT with both sand and WGS columns (Figure 3). For IDM, the major phase I metabolite as well as the parent compound was effectively removed even with a short HRT. The removal mechanism for IDM is not clear, but strong sorption around neutral pH is not expected as IDM molecules should be ionized (note that its pK_a is 4.5 (Syracuse Research Corporation 2014)) similarly to DCF. Much faster

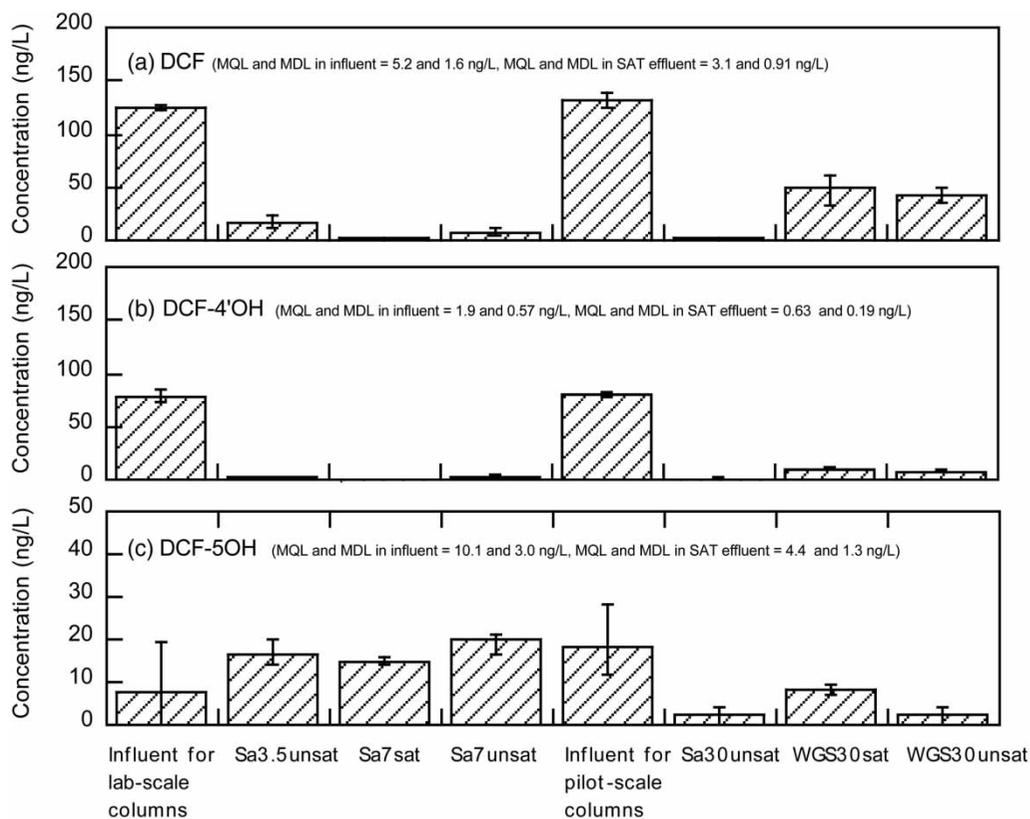


Figure 2 | Concentrations of DCF and their metabolites before and after SAT. (The top and bottom ends of error bars show maximum and minimum concentrations, respectively. For the handling of data points below the QL, see the caption in Figure 1.)

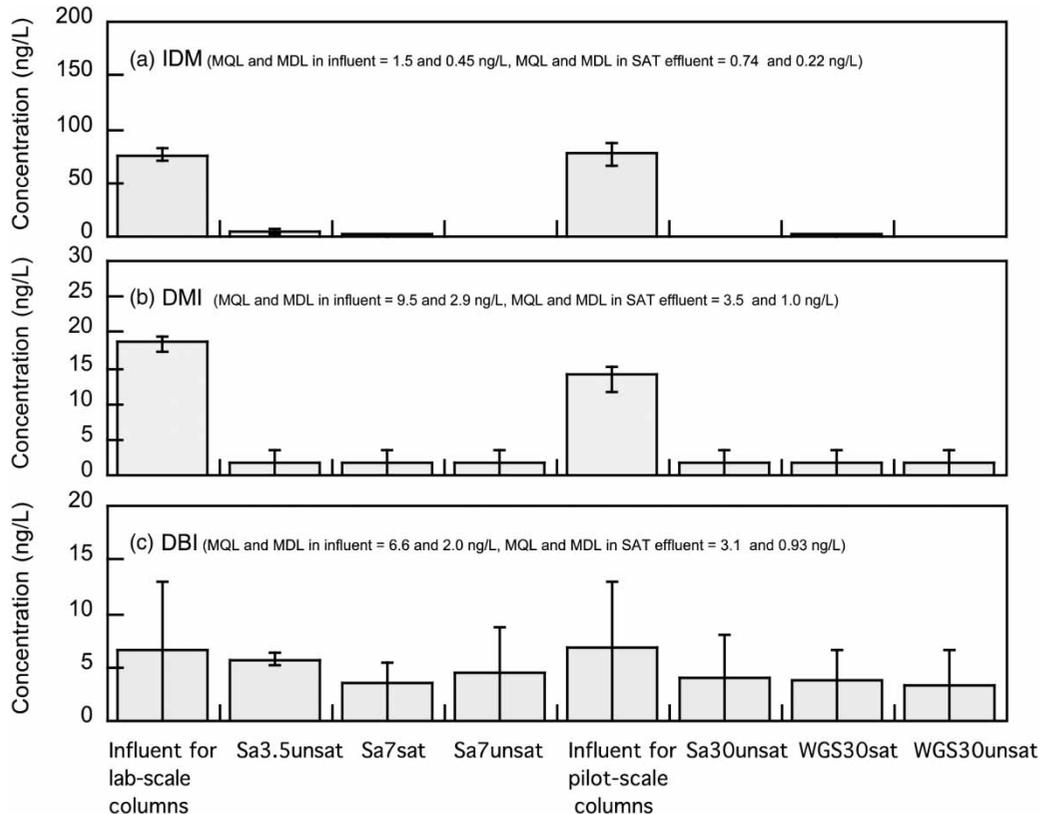


Figure 3 | Concentrations of IDM and their metabolites before and after SAT. (The top and bottom ends of error bars show maximum and minimum concentrations, respectively. For the handling of data points below the QL, see the caption in Figure 1.)

removal than DCF may indicate biodegradation. DBI stayed longer in SAT, and the removals with short HRTs were less than 50% (e.g., 16% for a HRT of 3.5 days).

CONCLUSIONS

Our results clearly showed that some metabolites are present in SAT effluent in a much higher concentration, and/or behave differently in SAT systems than their parent compounds. Thus, more attention should be paid to the formation and fate of metabolites in the water quality management of SAT effluents. The presence of an anaerobic zone in WGS columns had no positive impact on the removal of the target compounds and their metabolites. In fact for DCF, its metabolites, CBZ-2OH, and CBZ-3OH, the removals were even lower. Also, similar results were observed for both SA7sat and SA7unsat indicating that the

role of the unsaturated zone under the conditions tested in this study was minor. One possible reason for minor impact of the presence of the unsaturated zone may be the low DOC in the feed water (i.e., sufficient oxygen was provided even without the unsaturated zone for most cases).

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