The impact of temperature on the transformation of illicit drug biomarkers in wastewater

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Abstract

In the emerging field of wastewater-based epidemiology (WBE), temperature – a well-known, key factor, influencing the transformation kinetics of organic chemicals, has thus far been ignored in predicting chemical consumption rates in urban catchments. This is problematic as WBE data are collected from and compare sewer catchments with highly varying wastewater temperatures.

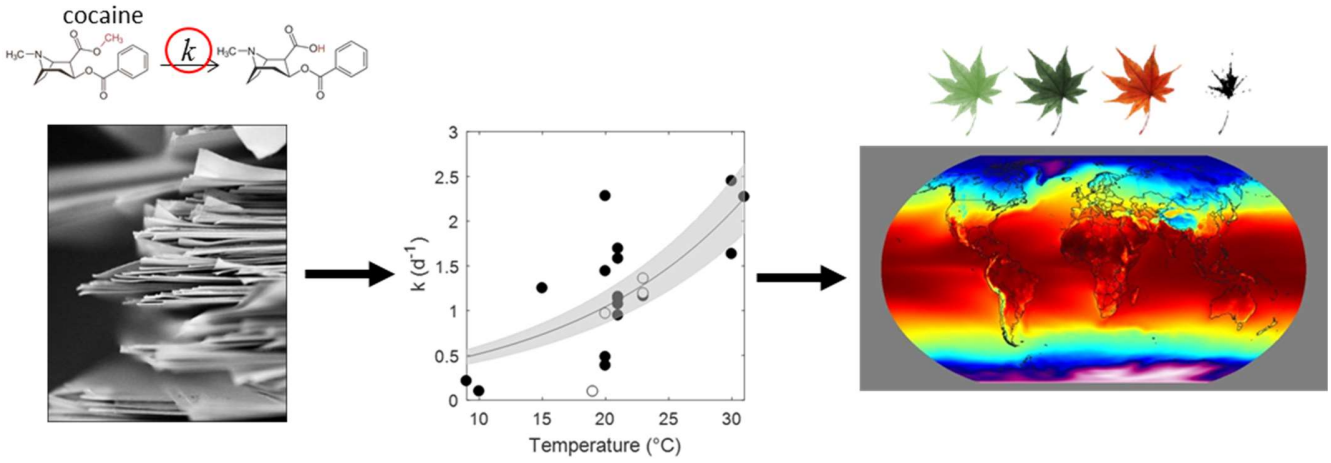
In this study, we assessed, for the first time, the influence of temperature on the transformation of biomarker transformation in wastewater and its ensuing implications on the back-calculation of chemical consumption rate in urban catchments using the example of selected illicit drugs. Literature data, obtained in laboratory-scale experiments, on the stability of drug biomarkers in untreated wastewater – occurring at trace levels – was systematically reviewed, and transformation rates obtained at different temperatures were collected. Robust correlations, using the Arrhenius equation, were inferred to describe the transformation of selected cocaine and morphine biomarkers in environmentally relevant temperature ranges (from 2–9°C to 30–31°C), with estimated Θ coefficients between 1.04 and 1.18. These empirically-derived relationships were used to assess the influence of temperature on the transformation of drug biomarkers during in-sewer transport and its effect on the back-calculation of drug consumption rate in synthetic urban catchment scenario simulations. As for quantifying the uncertainty of temperature effects, up to 4-fold increase in removal efficiency was estimated when wastewater temperature increased from 15 ºC to 25°C – a range representative, notably, to seasonal variations in continental urban catchments, e.g., Spain, where some of the highest drug consumption rates are observed in Europe. Findings from this study can help reducing the uncertainty intrinsic to wastewater-based epidemiology studies, and will be beneficial in comparing chemical consumption estimates from different catchments worldwide.

Keywords: Wastewater-based epidemiology, stability, temperature, biotransformation, Arrhenius equation, illicit drugs

Highlights:

- Assessing impacts of temperature on biomarker transformation and on WBE predictions.
- Broad literature review on transformation rates combined with temperature data
- Robust, Arrhenius-based correlation identified to account for temperature effects; described temperature-dependent transformation of biomarkers
- Findings facilitate significant reduction of uncertainties in WBE assessment. comparative estimation of drug consumption in WBE studies

Graphical abstract



1. Introduction

Wastewater-based epidemiology (WBE) is a growing research field to improve social behavior predictions in an epidemiological context. It is based on the analysis of substance residues (biomarkers) in wastewater and back-calculation of population consumption/exposure at catchment level. Substance use biomarkers, such as illicit drug abuse and exposure to pesticides, have been the main focus of WBE studies (Gracia-Lor et al., 2017). A number of uncertainties (e.g., chemical analysis, determination of catchment population) have been associated to the determination of community drug use (Castiglioni et al., 2013). Furthermore, neglecting in-sewer transformation can also be a significant source of bias since biomarker concentration levels at the excretion point can differ from the sampling point (Li et al., 2018). In-sewer stability of drugs is mainly associated to abiotic transformation (without the presence of biomass) and biotransformation in the presence of suspended and attached biomass.

In WBE studies, two main approaches have been used to translate measured concentration to consumption rate: (i) lumped correction factors that include e.g., excretion ratios and in-sewer transformation; (ii) in-sewer process kinetic models together with excretion ratios. The first approach is commonly used due to its simplicity, with the major drawback of lacking catchment specificity. Conversely, process models explicitly rely on first- or second-order equations (McCall et al., 2016; Plósz et al., 2013; Ramin et al., 2016) to describe transformation kinetics, therefore allowing to account for a number of influencing factors (e.g. redox conditions, in-sewer residence time, transformation pathways and biomarker concentrations) depending on the complexity level. A factor known to influence microbial activity—hence biomarker stability—is temperature. The impact of temperature on the transformation of organic micropollutants has been assessed in activated sludge (Li et al., 2005) and in anaerobic digestion (Carballa et al., 2007). As to illicit drug biomarkers, stability studies in untreated wastewater (Bisceglia and Lippa, 2014; Devault et al., 2017) have overall revealed enhanced transformation kinetics with

increasing temperature. While the effect of temperature on microbial growth kinetics is considered in models for conventional pollutants (e.g., activated sludge models), very few examples exist on quantifying the temperature dependence of kinetic model parameters for trace organic chemical transformation (Li et al., 2005; Wick et al., 2009).

In sewers, wastewater temperature exhibits seasonal and geographical variations and may further vary within the same catchment. During a recent Europe-wide sampling campaign (conducted simultaneously in 47 cities), the temperature of raw wastewater at sampling points was reported in the range between 7 ºC and 28ºC (Ort et al., 2014). Consequently, the impact of temperature on the stability of drug biomarkers in sewers may significantly vary from catchment to catchment, and the associated uncertainties propagating to the back-calculated consumption rate could be reduced in WBE approaches using more robust temperature models – the main focal area chosen for this study.

Considering existing limitations, the objectives of this study were: (i) to assess the effect of temperature on in-sewer drug biomarker stability, based on findings from published literature; (ii) Use empirical equations to describe temperature-dependent transformation kinetics of selected biomarkers in wastewater under aerobic conditions; (iii) to assess the influence of temperature on the in-sewer removal of drug biomarkers through synthetic urban catchment simulations.

2. Materials and methods

2.1. Literature review and data treatment

Published scientific literature was reviewed (last update: 31/03/2018) to select drug biomarker stability studies in untreated wastewater, i.e. without the influence of biofilm. Further screening for sound and rigorous literature evidences was performed using the following criteria: (i) stability studies were performed under aerobic conditions; (ii) biomarker transformation kinetics were explicitly reported or could be derived (calculated) based on presented results (e.g., concentration profiles in batch experiments); (iii) estimation of model parameters (see Eq. 1) was associated with good match between measured and predicted concentration profiles (R^2>0.7). Ten literature studies were eventually selected (Table 1), providing relevant information on stability of cocaine (COC), ecgonine-methyl-ester (EME), cocaethylene (CE), norcocaine (NorCOC) and 6-monoacetylmorphine (6-MAM).

The first-order transformation rate coefficient (k, d^{-1}) was used as indicator of biomarker stability in wastewater. Notably, k accounts for both abiotic and biotransformation kinetics, given that abiotic control experiments were absent in most of the selected studies. When k values were not explicitly reported, they were estimated by fitting experimental data with a first-order kinetic equation (Eq. 1):

$$C(t) = C_0 \, e^{-kt} \qquad \text{(Eq. 1)}$$

where C_0 and $C(t)$ are biomarker concentrations at time 0 and at time t, respectively.

In two cases (McCall et al., 2016; Ramin et al., 2016), abiotic and biotransformation kinetics were separately assessed and quantified by estimating the first-order rate coefficients (k_{abio}, d^{-1}) and pseudo-first-order rate coefficients (k_{bio}, L g^{-1} d^{-1}), respectively. The two kinetic indicators were combined to obtain k (Eq. 2):

$$k = k_{abio} + k_{bio} X_{TSS} \qquad \text{(Eq. 2)}$$

where X_{TSS} (g L^{-1}) denotes the concentration of total suspended solids (TSS) in the experiments. Data from concentration profiles were extracted, when necessary, using the software *PlotDigitizer* (name of manufacturer, Country)

For each biomarker, the Arrhenius equation (Eq. 3) was used to describe variations in transformation rates as a function of temperature:

$$k_T = k_{25}\,\theta^{(T-25)} \qquad \text{(Eq. 3)}$$

where T(°C) denotes the temperature, at which a specific k_T value was derived, k_{25} the transformation rate at 25°C and θ (-) the exponential Arrhenius coefficient. Parameters θ and k_{25} were estimated for each biomarker using particle swarm optimization in MATLAB 2016b. A temperature of 25°C was selected as reference to improve the identifiability of both estimated parameters, as previously suggested (Schwaab et al., 2007).

<Table 1>

2.2. Back-calculation procedure

To back-calculate drug concentration at the release point e.g. after toilet flush (unknown), drug concentration at the influent of wastewater treatment plant (known) is considered in a hypothetical catchment. In-sewer transformation was simulated using Eq. 1 and assuming an average residence time of 4.5 h, corresponding to the average residence time in a recent European monitoring campaign (Ort et al., 2014).

2.3. Parameter estimation and quantification of uncertainties

Bayesian inference, employing prior knowledge in terms of model parameters, is employed to estimate Θ parameter values using ???. Additionally, propagation of parameter uncertainty onto the back-calculation results is quantified. Monte Carlo simulations of in-sewer biomarker transformation were

performed using prior parameter sets sampled using Latin Hypercube Sampling (LHS, Reference). To evaluate the impact of temperature on the removal of the selected drugs, three temperature conditions were considered, being representative of low (T=5°C), medium (T=15°C) and high (T=25°C) temperature.

3. Results and discussion

3.1. *Temperature-dependent transformation*

Considerable data variability in k rate values found in literature was noticed for most all selected drugs (Fig. 1), even considering the same temperature (e.g., 6-MAM) as a result of factors such as, differences in stability test conditions used in literature. Nevertheless, overall increase of k with increasing temperature was observed, especially when considering the mean of multiple measurements for each unique temperature.

Additionally, for each biomarker, Fig. 1 presents plots of fitted Arrhenius equations (and associated 95% confidence intervals (CI), shaded areas). Interestingly, many of the calculated data points (not reported in the original study) and estimated ones (reported in the original study) fall out of the CI (almost 50% of all data points). A portion of data points were found to be inside the CI, namely McCall et al. (74%), Bisceglia and Lippa (67%), Mardal et al. (56%), Devault et al. (37%), Baker and Kasprzyk-Hordern (33%) and van Nuijs et al. (33%). Low transformation (hence below CI) in Senta et al. (2014) and Chen et al. (2013) could be due to limited oxygen availability in test setups, resulting in lower microbial activity (Table 1). Conversely, high transformation observed in Ramin et al. (2016) could have resulted from high oxygen levels (~ saturation) in test reactors, determining significant microbial growth during batch experiments. Beside oxygen levels, under- or over-estimation of k (d^{-1}) values can be a consequence of the limited applicability of first-order kinetics to describe biomarker biotransformation, e.g. due to significant microbial growth or inhibition of biomass. This could be the case for Thai et al. data points which are placed both above and below CI. Moreover, partitioning of drug biomarkers to solid phases (suspended particles, reactor walls) are additional processes that need to be accounted for when estimating k (d^{-1}) (Ramin et al., 2016).

~~Besides the previously discussed inherent data variability, this may have resulted from the limited applicability of first-order transformation kinetics e.g. due to significant microbial growth during batch experiments (Ramin et al., 2016).~~

Estimated parameter values k_T (d^{-1}) and Θ for the selected biomarkers are reported in Table 2. It can be noticed that the estimated relative error was low, below 50%, except for NorCOC (0.78%) and parameter collinearity was low expect for EME (-0.75). This seems to suggest good parameter identifiability, based on criteria (error < 50% and collinearity < 0.7) set by (Frutiger et al., 2016). Nevertheless, these thresholds are subjective and the consideration of 25°C as reference temperature allowed for the improvement of parameter identifiability (achieving lower correlation).

Estimated Θ coefficient values were between 1.04 and 1.18, in agreement with previously reported values. That is, for primary metabolic processes (relevant for biomass growth) in sewers, Arrhenius-based temperature corrections have been suggested, with Θ values of 1.07 and 1.05 for aerobic water phase and biofilm processes, respectively (Hvitved-Jacobsen et al., 2013). Henze et al. (2000) also suggested similar coefficients to describe temperature dependency of biological processes in the Activated sludge model No. 2 (ASM2). These coefficients are ranging from low (Θ = 1.04) for hydrolysis to high (Θ = 1.12) for nitrification. Similar Θ values were also estimated for 17-β estradiol (E2) transformation by activated sludge, ranging from 1.03 to 1.09 for different biomass concentrations (Li et al., 2005). Wick et al. (2009) considered temperature-dependent biotransformation for successful prediction of season-dependent pharmaceutical and illicit drugs removal in WWTPs. The correction factor, Θ, for organic micropollutants such as pharmaceuticals was estimated in the range of 1.03–1.09 (Joss et al., 2006). Overall, previous and current findings demonstrate that temperature can have considerable impact on transformation, the extent of which is compound-dependent.

187 *3.2. Influence of temperature on back-calculation of drug use*

188 As expected, higher temperature resulted in higher in-sewer removal, with 40% (6-MAM) to almost 4-
189 fold (EME) increase of removal efficiency from medium to high temperature. Consistently, 6-MAM and
190 EME have lowest and highest Θ values (Table 2).

191 These results indicate that accounting for in-sewer transformation is important especially at elevated
192 temperatures (above 15°C). Consequently, the temperature dependency of k should be accounted for
193 explicitly in steady-state and dynamic model simulations. From this stand point, the Arrhenius equation
194 can be included in existing modeling frameworks for removal of drug biomarkers in wastewater such as
195 WATS—ASM-X (Ramin et al., 2016). We note that, in this study, the estimation of in-sewer removal
196 was performed based on individual biomarkers, and the transformation of biomarkers into/from other
197 biomarkers was neglected. It is common practice to back-calculate the consumption of COC based on
198 the concentration of its metabolite benzoylecgonine (BE) and COC itself. It has been found that BE,
199 beside formation, also under go transformation (McCall et al., 2016; Ramin et al., 2016), although some
200 studies reported negligible in-sewer BE transformation (Bisceglia and Lippa, 2014; Thai et al., 2014).
201 Further discussion on back-calculation of illicit drug consumption interested readers are referred to
202 available literature (Castiglioni et al., 2013; Khan and Nicell, 2011).

203 It is evident that further research is crucial for obtaining new evidence on drug stability at different
204 temperatures, especially for new psychoactive substances. This is generally relevant for other types of
205 biomarkers beyond illicit drugs, which wastewater-based epidemiologists have gained increasing interest
206 in (Gracia-Lor et al., 2017). We encourage authors to report conditions at which stability tests were
207 performed, similarly to Table 1. This would allow for better comparison and consistency evaluation
208 among different studies.

209

4. Conclusions

This study presents, for the first time, a comprehensive correlation analysis for the temperature dependence of transformation kinetics (abiotic and biotic) of biomarkers and quantifies its uncertainty implications on WBE back-calculation results. Five illicit drug biomarkers (COC, EME, CE, NorCOC, 6-MAM) were used in untreated wastewater under aerobic conditions. Following conclusions are made:

- Although affected by the considerable variability of measured transformation kinetics, the Arrhenius equation could capture trends of increasing transformation rates with increasing temperature within the applicability domain (from 2–9°C to 30–31°C).
- Arrhenius-based equations were estimated for each biomarker and used for removal predictions during transport in ideal sewers. Up to almost 4-fold removal efficiency was observed when temperature was changed from 15 °C to 25°C.
- These findings have considerable implications for back-calculation of drug consumption based on the analysis of untreated wastewater influents, especially for multi-catchment studies covering wide geographical areas. Further research should extend the investigation of temperature effects to (i) a larger number biomarkers; (ii) anaerobic conditions; and (iii) sewer biofilms.

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Figures

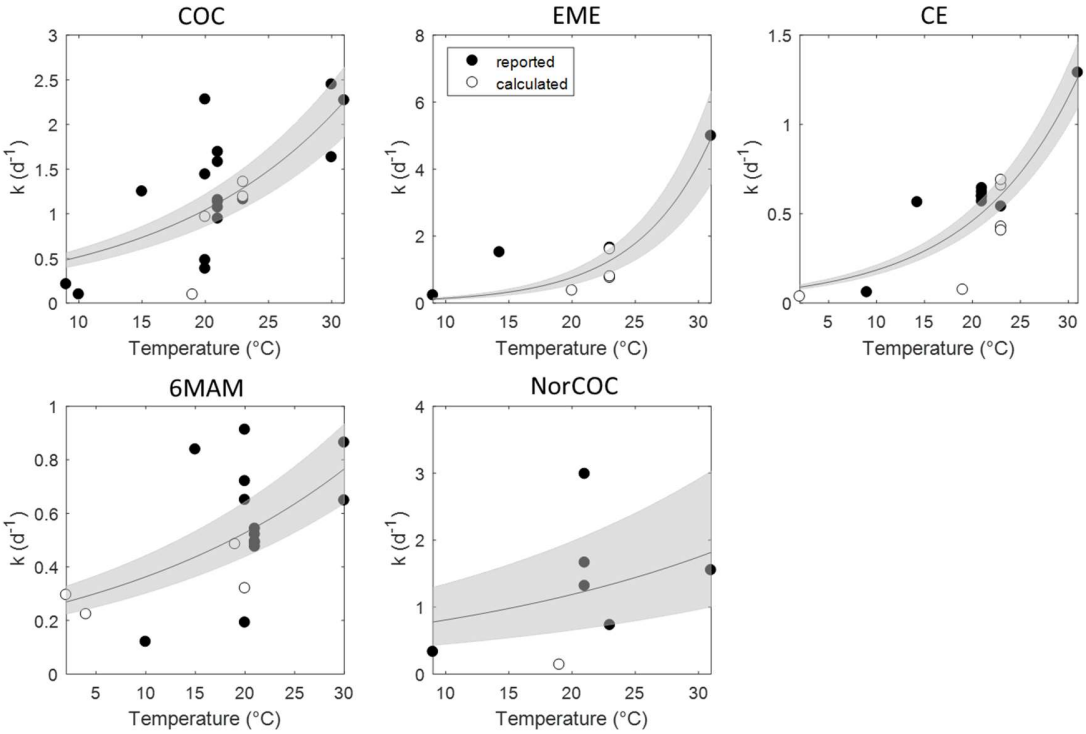

Figure 1. Arrhenius equation fits for degradation rates k (d^{-1}) as a function of temperature (ºC). These are based on the reported (full circles) and the estimated (empty circles) empirical values from literature. Lines are the best prediction and the shaded band is the 95% confidence interval of the prediction.

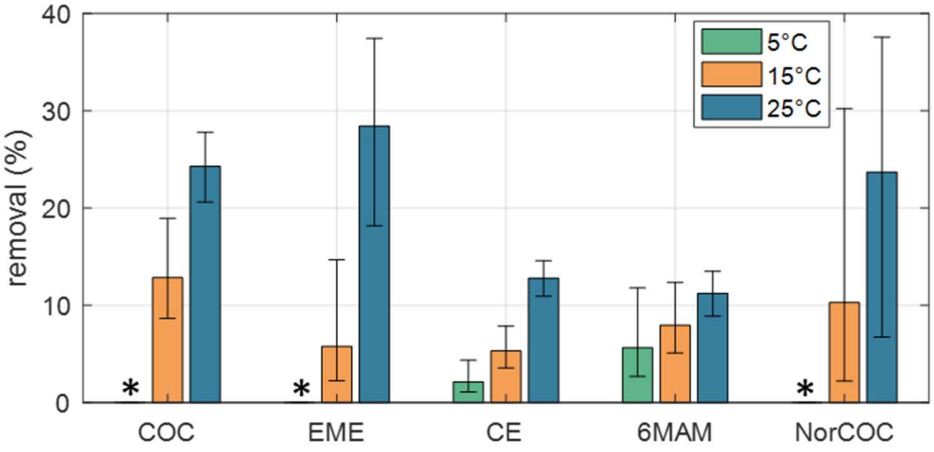

Figure 2. Estimated in-sewer removal (transformation) rates from excretion point to WWTP influent (in-sewer residence time = 4.5 h) for selected drug biomarkers, calculated using the identified Arrhenius regression equations. Error bars represent 95% confidence interval following Monte Carlo simulation. Asterisks (*) indicates that the temperature is out of applicability range.

325 **Table 1.** Overview of selected biomarker stability studies from published literature.

No.	Reference	Chemical	Data source for extraction of *k*	Temp. (ºC)	pH	DO (mg L^{-1})	Duration of experiment (h)	No. of samples taken	C_0 (µg L^{-1})	TSS (g L^{-1})
1	(Baker and Kasprzyk-Hordern, 2011)	COC, CE, 6MAM, NorCOC	Table	2, 19	7.4	-	72	4	1.0	-
2	(van Nuijs et al., 2012)	COC, EME, 6MAM	Graph	20	7.5	-	26	13	0.06–0.60	-
3	(Chen et al., 2013)	6MAM	Graph	4	7.4	-	336	6	>0.1	-
4	(Bisceglia and Lippa, 2014)	COC, EME, CE, NorCOC	Values reported	9, 23, 31	7.4	-	26	16	1.5–3.0	-
5	(Senta et al., 2014)	COC, 6MAM	Graph, values reported	20	7.5	-	72	7	0.2	-
6	(Thai et al., 2014)	COC, 6MAM	Values reported	20	7.5	-	12	9	10	-
7	(Mardal et al., 2016)	COC, EME, CE	Graph, Table	23	7-8	-	24	9	0.5-100	-
8	(Ramin et al., 2016)	COC, EME, CE, 6MAM	Values reported	14	8.6–8.8	10	48	9	10	0.32 ± 0.04
9	(McCall et al., 2016)	COC, CE, 6MAM, NorCOC	Values reported	21	8.0–8.9	5–8	24	11	2.0–3.0	0.14–0.29
10	(Devault et al., 2017)	COC, 6MAM	Values reported	20, 30	6.6, 7.6	-	24	7	1.0–3.0	-

[1]Used silanized amber glass bottles stored in the dark.
[2]Stability test performed in silanized glass flasks which were hand-shaken app. 10 times per hour.
[3]Bottles at 20ºC were placed under fume cupboard uncapped and gently stirred 3 times per day (distilled water was used to compensate for evaporation). Bottle at 4ºC was stored with cap on.
[4]Used Erlenmeyer flask equipped with foam stopper to allow air transfer. Reactor was shaken at 180 rpm in the dark.
[5]Glass bottles were capped with cotton plugs and placed in a thermostated cabinet.
[6]Used gravity sewer reactor with continuous mixing with magnetic stirrer (250 rpm) to enhance surface aeration.
[7]Urinary samples collected at a music festival was dilutted with wastewater and incubated in a temperature water bath
[8]Transformation study was performed in a covered jacketed reactor equipped with an agitator and oxygen diffuser.
[9]Transformaiton study was conducted in Erlenmeyer flask on a shaker table in the dark. Autoclaved wastewater was chosen to represent abiotic transformation.
[10]Glass bottles were placed in the dark and aerobic conditinos was maintained by shaking with a magnetic stir bar.

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Table 2. Estimated k_{T25} (d^{-1}) and θ and their correlation for the selected drugs. Parameters are estimated as the best fitted value together with 95% confidence interval. The predictions are valid in the reported temperature range.

	k_{T25} (d^{-1})	Θ	Correlation (k_{T25} and Θ)	Temperature range (°C)
COC	1.48 (1.23, 1.75)	1.07 (1.04, 1.11)	0.06	9–31
EME	1.78 (1.03, 2.54)	1.18 (1.09, 1.28)	-0.75	9–31
CE	0.73 (0.61, 0.85)	1.10 (1.06, 1.13)	0.07	2–31
6MAM	0.64 (0.49, 0.78)	1.04 (1.00, 1.07)	0.49	2–30
NorCOC	1.44 (0.32, 2.57)	1.04 (0.90, 1.18)	0.29	9–31