Research Article

Occurrence of pharmaceutically active compounds, parabens, and their main metabolites in soils amended with sludge and compost

Juan Luis Santos ⓘD **, Julia Martín, Irene Aparicio, Esteban Alonso**

Departamento de Química Analítica, Escuela Politécnica Superior, Universidad de Sevilla, Seville E 41011, Spain.

Correspondence to: Prof. Juan Luis Santos, Departamento de Química Analítica, Escuela Politécnica Superior, Universidad de Sevilla, C/ Virgen de África, 7. Seville E 41011, Spain. E-mail: jlsantos@us.es

Abstract

The presence of pharmaceuticals and personal care products (PPCPs) in the environment has aroused considerable interest in the last few years. However, the occurrence and fate of parent compounds and their metabolites and/or transformation products in soils have been scarcely evaluated to date. In this work, the dissipation kinetics of PPCPs, which are most frequently detected in the environment, and their main metabolites, is evaluated in soil amended with digested and composted sludge. The studied compounds were monitored for 60 days after digested or compost application to the soil. Several kinetic models were used to evaluate the dissipation kinetics of the processes. Parabens and their metabolites were the compounds with the fastest dissipation rates, while the antiepileptic carbamazepine and its metabolites were the poorest degraded compounds studied. Most of the compounds showed a single first-order dissipation kinetics. The application of biphasic kinetic models can improve the knowledge about the dissipation behavior of some of them. For instance, whereas compounds such as carbamazepine showed a high persistence showing a lag phase in its dissipation, resulting in an approximately constant concentration for the first days of batch experiments, others, such as sulfamethoxazole and diclofenac, followed a dissipation kinetics in two phases: a fast dissipation attributed to the amount of compound associated to the soil-water solution and a slow dissipation that could be due to the amount of the compound adsorbed onto the soil particle. For most of the compounds, the dissipation was faster in sludge-amended soil than in soil without organic amendment. This fact could be due to the influence of microbial activity and organic matter on their dissipation.

INTRODUCTION

Currently, one of the main destinations of sewage sludge is its valorization as organic amendment in agricultural soils. Such practice allows the improvement of biological activity and physical properties of the soil[1]. More than 50% of the approximately 15 million tons of sludge generated in the European Union in 2021[2] were applied to soils[3]. This practice is the main sludge disposal option in countries such as Cyprus, Denmark, France, Ireland, and Spain, and, to a lesser extent, in countries such as Finland or Sweden[4]. However, sewage sludge tends to concentrate persistent organic pollutants present in wastewater, which could be accumulated into soils by sludge amendment. As a result, inorganic and organic contaminants such as metals[5,6], plasticizers[7], surfactants, and other industrial pollutants[8,9], and pharmaceuticals and personal care products (PPCPs)[10] have been reported in soils at concentrations in the range from a few nanograms to milligrams per kilogram. Among them, PPCPs have arisen considerable interest not only because they are continuously being discharged into the environment but also because they have been designed to cause effects in living organisms.

Moreover, in the case of pharmaceutically active compounds, they have been designed to be nonbioaccumulative and easily removed after their administration[11]. As a result, these compounds can be accumulated in sewage sludge and on sludge-amended soils. They can be present not only as parent compounds but also as their metabolites that, in some cases, can be discharged into the environment at higher concentrations than their parent compounds[10]. However, although the presence of these compounds has been previously reported in soils[2,12,13], studies about their occurrence and distribution in the terrestrial environment are scarce[10,11,14,15]. The therapeutic groups of pharmaceutically active compounds most frequently detected, and the ones at the highest concentrations, are antibiotics, anti-inflammatories, and antiepileptics[2,14], whereas methylparaben (MeP) and propylparaben (PrP) are the most frequently detected personal care products. Only a few studies have evaluated the presence of metabolites of pharmaceutically active compounds and parabens in soils[14,16,17]. Among them, the most studied metabolites are N⁴-acetylsulfamethoxazole (Ac-SMZ), acetylsulfapiridine[16], carboxy-ibuprofen (CBX-IBU), 4-hydroxy-diclofenac (4-OH-DIC), and 10,11-dihydro-10-hydroxycarbamazepine (10-OH-CBZ). However, these studies were mainly focused on the evaluation of sorption-desorption processes[10,11,18-21].

The behavior and degradation of PPCPs and their metabolites in the soil depend not only on the physicochemical characteristics of the compound but also on the characteristics of the soil[10,22,23]. For example, Kodešová *et al.* reported that soil texture, organic matter content, and biological activity are key factors affecting the half-life of pharmaceutically active compounds[22]. Biel-Maeso *et al.* described a faster degradation of some pharmaceuticals such as ibuprofen, diclofenac, or gemfibrozil under aerobic conditions and pointed out the importance of microbial activity in their degradation process[18]. In 2021, Malvar *et al.* studied the distribution of PPCPs and their main metabolites, most frequently detected in the environment, in different types of Mediterranean soils. Their results revealed the influence of soil characteristics on the removal of the studied compounds and the high persistence of carbamazepine (CBZ) and its metabolites among the evaluated compounds[10]. However, although these studies have revealed the occurrence of some PPCPs in soil, only a few of them have addressed their dissipation kinetics in soil and, in most cases, a single first-order (SFO) kinetic model has been applied[10,11,15,18,22]. However, although SFO enables a first approximation to the kinetics of the process, the use of other kinetic models allows evaluation of other

issues related to the heterogeneous nature of the soil, such as biphasic kinetics, or lag period, in which the compounds follow slow degradation for the first period followed by a fast kinetics. To the best of our knowledge, until now, only two studies have assessed different dissipation kinetic models of pharmaceuticals in soil using different models, and in these studies, only the kinetics of sulfamethoxazole[24] and metformin[25] were evaluated.

This work aimed to evaluate the influence of sludge or compost amendment on the dissipation of PPCPs in amended soils and to evaluate the kinetics of the process. The study was carried out using Mediterranean soil amended with anaerobically-digested and dehydrated sludge or with composted sludge. The studied compounds were selected considering their high consumption, frequency of detection and concentrations measured in environmental samples, their ecotoxicity effects and persistence. Moreover, the metabolites with the highest excretion rate were selected for each parent compound. According to these criteria, the selected compounds were the anti-inflammatories ibuprofen (IBU) and diclofenac (DIC) and their metabolites 1-hydroxyibuprofen (1-OH-IBU), 2-hydroxyibuprofen (2-OH-IBU), CBX-IBU and 4-OH-DIC; the antiepileptic carbamazepine (CBZ) and its metabolites 3-hydroxycarbamazepine (3-OH-CBZ), 10-OH-CBZ, and carbamazepine-10,11-epoxide (EP-CBZ); the antibiotic sulfamethoxazole (SMX) and its metabolite AcSMX; the parabens MeP and PrP and their metabolites methyl protocatechuate (OH-MeP), 3,4-dihydroxybenzoic acid (3,4-DHB), and 4-hydroxybenzoic acid (4-HB).

METHODS

Soil, sludge, and compost collection

The studies were carried out with Cambisol-type Mediterranean soil. It was selected from the results of a previous study in which the degradation rates of the target compounds in alluvial, *terra rosa*, and Cambisol soils were evaluated[10]. The poorest degradation rates were obtained in Cambisol soil, and because of that, it was selected for the present study. Cambisol type is a sandy loam soil (65.6%-18.4%-16.0%, sand-silt clay) widely extended in several European countries such as France, Germany, Greek, Italy, and Spain. Its physicochemical properties are shown in Supplementary Table 1. Five kilograms of soil were collected from the surface (approximately from 0 to 20 cm) of agricultural land sited in Seville (south of Spain).

Anaerobically-digested and dehydrated sludge was collected from a wastewater treatment plant sited in Seville City. Two kilograms of sludge were collected in an amber glass bottle after the centrifugation process.

Compost was collected from a composting plant sited in Seville, where anaerobically-digested and dehydrated sludge produced in Seville City is composted. The composting process consists of a natural process using dynamic batteries thermally controlled in which aeration is facilitated by turning. Two kilograms of compost were obtained by mixing several aliquots collected from different points of the compost pile, approximately 30 to 50 cm in depth.

All samples were homogenized, sieved (particle size < 2 mm), and stored (-18 ºC) until batch experiments were carried out.

Batch experiments

Two batch experiments were carried out by amending the soil with (i) anaerobically digested and dehydrated sludge and (ii) composted sludge. Although target compounds have been measured in digested and in composted sludge[26], both types of sludge were spiked with the compounds to ensure their presence in the amended soil. Sludge (or compost) was mixed with soil in a 1:99 proportion, according to the reported agricultural application rate in Andalucía Region (south of Spain) from 2020 to 2022 (rate from

0.01% to 0.61% (w/w) (Consejería de Agricultura, Pesca, Agua y Desarrollo Rural from the Andalucía government)[27].

Batch experiments were carried out according to OECD guideline 307[28] as described by Malvar *et al.*[10]. Sludge and compost were spiked at 50 mg·kg^{-1} of each compound to achieve an initial concentration of 500 µg·kg^{-1} in the sludge-amended soil. For this purpose, 50 mL of a standard solution containing the target compounds at 100 mg·L^{-1} was added to 100 g of sludge (or compost). The mixture was shaken for 2 h in a rotator shaker (LLG-uniLOOPMIX2) at 40 rpm. After that, they were stored at 4 °C for 24 h. Then, the spiked soils were frozen, lyophilized (Cryodos-50 lyophilizer, Telstar, Terrasa, Spain), and sieved with a 2 mm mesh side. Fifteen grams of the sludge or compost were added to 1,485 g of the soil. The mixture was homogenized and distributed into five glass reactors (300 g of the mixture in each reactor). Then, deionized water was added to achieve a 20% v/w of soil humidity. Two reactors containing non-spiked sludge or compost were used as blanks. Batch experiments were done in a climatic chamber (Selecta, Barcelona, Spain) under the following climatic conditions: 33% of relative humidity, 20% of soil humidity, and an irradiation level of 1,091 W·m^{-2}. The loss of humidity was corrected by adding the proper amount of deionized water.

Target compounds in each reactor were monitored for 60 days with the following sampling frequency: four weekly samples were collected during the first four weeks, three weekly samples were collected during the 5th and 6th weeks, and two weekly samples were collected during the 7th and 8th weeks. The last sample was collected on the 60th day. On each sampling day, 2 g of sample was collected from each reactor. Collected samples were frozen, lyophilized, and stored at -18 °C until analysis.

Target compound analysis
Analysis of the target compounds was carried out according to a previously developed and validated analytical method[29]. The analytical method was based on selective pressurized liquid extraction and determination by liquid chromatography-tandem mass spectrometry. A brief description of the method can be found in the supplementary material. More details about the analytical method can be found in Malvar *et al.* and Supplementary Table 2[29].

Data analysis
Dissipation kinetic models
The evaluation of the dissipation kinetics was carried out following the FOCUS guidance document on estimating persistence and degradation kinetics from environmental fate studies on pesticides[30], and previously reported studies[24,31]. Several kinetic models were used to evaluate the kinetics of the dissipation processes and to estimate the endpoints for the studied compounds (DT50 and DT90, corresponding to the dissipation of the 50% and 90%, respectively, of the initial concentrations). Six kinetic models were used: a single first-order (SFO) kinetic model; three biphasic kinetic models: a bi-exponential model (BEM), a first-order two-compartment (FOTC) model, and a first-order double-exponential decay (FODED) model; and two models suitable to describe the dissipation pattern with a lag phase: a modified hockey-stick model (MHSM), and a logistic model (LM).

Single first-order kinetic model
This model assumes that the number of molecules in the soil is small in relation to the number of active sites in the soil. In this case, the dissipation of a compound is proportional to the remaining concentration. The equation for this model is:

$$C = C_0 e^{-k_1 t} \tag{1}$$

where t corresponds to time (days), k_1 is the first-order rate constant (day^{-1}), C_0 corresponds to the initial concentration ($\mu g \cdot kg^{-1}$), and C corresponds to the concentration at time t (day) ($\mu g \cdot kg^{-1}$).

Bi-exponential model

Bi-exponential model (BEM) considers that the degradation occurs in two compartments[24]. The first compartment corresponds to the soil-water phase, where the contaminants are available for microorganisms. In this compartment, a fast dissipation is expected. The second compartment corresponds to a phase where the contaminants are adsorbed to soil particles and the dissipation is controlled by sorption-desorption processes. In this model, the dissipation rate can be represented by the sum of first- and second-order differential equations (2):

$$\frac{dC}{dt} = -(k_1 C + k_2 C^2) \tag{2}$$

This equation can be integrated as follow:

$$e^{-k_1 t} = \frac{C(k_1 + k_2 C_0)}{C_0(k_1 + k_2 C)} \tag{3}$$

As a result:

$$C = \frac{k_1 C_0}{(k_1 + k_2 C_0) e^{k_1 t} - k_2 C_0} \tag{4}$$

where k_1 is the first-order rate constant (day^{-1}), k_2 is the second-order rate constant (kg·μg^{-1}·day^{-1}), t is time, and C_0 and C are the concentrations ($\mu g \cdot kg^{-1}$) at the beginning of the experiment and at time *t*, respectively. The equation is reduced to a single first-order equation when k_2 = 0.

First-order double-exponential decay model

As in BEM model, First-order double-exponential decay (FODED) model considers the dissipation of the compound into two compartments, a solution phase, and a sorbed phase, where the compounds are adsorbed onto soil particles. However, FODED model considers first-order kinetics for both processes. For this model, the equation is (5):

$$C = C_{sol} e^{-k_1 t} + C_{sorb} e^{-k_2 t} \tag{5}$$

where t is time (day); C_{sol} and C_{sorb} are the concentrations of the compounds initially distributed into the solution phase and adsorbed onto soil particles, respectively; k_1 (day^{-1}) and k_2 (day^{-1}) are the dissipation rate constants for each compartment. Usually, k_1 is higher than k_2, indicating a higher degradation rate of the compound in the solution compartment than adsorbed onto soil. Moreover, when k_1 is equal to k_2, or one of the concentrations (C_{sol} or C_{sorb}) is zero, the model is mathematically transformed into SFO model.

First-order two-compartment model
This model considers the dissipation of the compounds in a complex system as a heterogeneous soil. This dissipation takes place in a two-compartment system[32]. In one compartment, fast degradation occurs because of physical, photochemical and other processes. In the other compartment, the degradation is slow and mainly due to microbial, chemical or enzymatic processes[24,25,31]. First-order two-compartment (FOTC) model includes a component of transference between the two compartments not considered in BEM and FODED models. The equations can be written as follows:

$$\frac{dC_1}{dt} = -(k_1 + k_r)C_1 \qquad (6)$$

$$\frac{dC_2}{dt} = k_r C_1 - k_2 C_2 \qquad (7)$$

where t is the time, k_r (day^{-1}) is the transfer rate constant of the compound between both compartments; k_1 (day^{-1}) and k_2 (day^{-1}) are the rate constants for the fast and slow degradation compartments, respectively; and C_1 and C_2, are the concentrations in each compartment. The total concentration at time t is the sum of C_1 and C_2. Therefore:

$$C = C_0 e^{-(k_1+k_r)t} + C_0 \frac{k_r}{k_1+k_r-k_2}(e^{-k_2 t} - e^{-(k_1+k_r)t}) \qquad (8)$$

Modified hockey-stick model
The concentrations of organic compounds could be virtually constant (or with a very poor dissipation rate) for a period of time, followed by a dissipation process governed by SFO or biphasic kinetics[30]. The initial phase is referred to as the lag phase and could be caused by several facts such as a slow adaptation of degrading microorganisms, the inhibition of the degrading microflora at high concentrations of contaminants, or a high persistence of the compound, among others. Modified hockey-stick model (MHSM) considers a constant concentration of the compound (or a very slow decrease) up to the breakpoint (time = t_b) followed by a SFO kinetic model. This model can be described by the equation (9):

$$C = C_0 e^{-k(t-t_b)} \qquad (9)$$

where k (day^{-1}) is the rate constant, t_b is the time of lag phase, and C and C_0 are the concentrations at time *t* and the initial concentration (µg·kg^{-1}), respectively.

Logistic model

Logistic model (LM) considers that the degradation rate constant increases after the application of sludge or compost to a maximum value. Once the kinetic constant has reached its maximum value, the kinetic approach is first order[30]. The equation is as follows:

$$C = C_0 \left(\frac{a_{max}}{a_{max} - a_0 + a_0 e^{rt}} \right)^{\frac{a_{max}}{r}} \qquad (10)$$

where a_0 is the kinetic constant at the beginning of the batch experiment, a_{max} is the maximum value of the kinetic constant, r is the microbial growth rate, t is time, and C and C_0 are the concentrations at time *t* and at *t* = 0. For this model, the higher the r or a_0 value, the lower the lag phase of the compound.

Evaluation of data fitting to the kinetic models

For each compound, the parameters implied in each of the studied models (C_0, k_1 in the case of SFO; C_0, k_1, and k_2 for BEM; k_1, k_2, C_{sorb}, and C_{sol} for FODED; C_0, k_1, k_2, and k_r for FOTC; C_0, k, and t_b for MHSM, and C_0, a_{max}, a_0, and r for the case of LM) were optimized using Microsoft Excel-Solver tool. The values of the model parameters providing the best fit to the experimental data were optimized by minimizing the mean of the square error, that is, the sum of the square of the residuals (SSR) divided by the number of experimental data.

Following the FOCUS guidance document[30], the fit of each model to the experimental data was first evaluated through visual assessment. For this evaluation, the experimental mean concentrations and the calculated curves were represented *vs.* time. In addition, experimental concentrations were plotted *vs.* the concentrations obtained by the models. The goodness fit of the model was evaluated considering the coefficient of determination (R^2) and the slope (close to 1) of the linear curve.

DT50 and DT90 determination

For each applied model, DT50 and DT90 values were determined. In the case of the SFO model, DT50 and DT90 were determined by applying the following equations[30]:

$$DT50 = \frac{ln2}{k_1} \qquad (11)$$

$$DT50 = \frac{ln10}{k_1} \qquad (12)$$

There is no analytical equation for the estimation of DT50 and DT90 values in biphasic models. Consequently, these values should be determined using an interactive procedure that was carried out using the Goal Seek function from Excel.

RESULTS

Concentration of target compounds in spiked sludge and compost applied to the soil

Batch experiments were carried out using spiked anaerobically-digested and dehydrated sludge and compost. Previously to the spiking procedure, soil, sludge, and compost samples were analyzed [Supplementary Table 3]. None of the studied compounds was detected in soil. The parent compounds MeP, CBZ, and DIC were measured at concentrations up to 29.0, 0.83, and 1.09 $\mu g \cdot kg^{-1}$, respectively, in digested sludge. In the case of compost, DIC was not detected, while MeP and CBZ were measured at concentrations up to 13.9 and 1.95 $\mu g \cdot kg^{-1}$. Considering the studied metabolites, six of them were measured in digested sludge at mean concentrations from 1.86 to 114 $\mu g \cdot kg^{-1}$, while in the case of compost, only the metabolites of parabens were measured (mean concentrations up to 52.2 $\mu g \cdot kg^{-1}$). These concentrations were similar to those reported by other authors in sludge from the same stabilization technologies[26,33-35]. Considering these initial concentrations, sludge and compost were accordingly spiked previously to their application to the soil to obtain a final concentration of 500 $\mu g \cdot kg^{-1}$ in amended soils. The mixtures were analyzed in quintuplicate. Results are shown in Table 1.

Mean concentrations were in the ranges 123-764 $\mu g \cdot kg^{-1}$ and 44.5-575 $\mu g \cdot kg^{-1}$ in sludge-amended soil (SAS) and compost-amended soil (CAS), respectively. These concentrations correspond to a percentage of the spiked concentration from 24.6% to 153% in the case of SAS, and from 8.4% to 115% for CAS. For most of the target compounds, these percentages were in the range between 41% and 153% in the case of SAS, and from 56% to 115% for CAS. The concentrations of the metabolites of parabens and 4-OH-DIC in amended soils were even lower, from 9% to 39% of the spike concentration. This fact could be explained not only by their low adsorption on the solid, as was reported previously[20], but also by their high degradation in the soil[2,10]. However, the concentrations measured for all target compounds at the beginning of batch experiments were high enough to evaluate their degradation in sludge-amended soils.

Degradation of PPCPs and their metabolites in sludge-amended soil

Dissipation of SMZ and AcSMZ

The concentrations of SMZ and AcSMZ obtained in batch experiments are shown in Supplementary Figures 1 and 2, respectively. Optimized parameters of the kinetic models applied to the degradation of the studied compounds in SAS and CAS are shown in Supplementary Tables 4 and 5, respectively. The concentrations of both compounds decreased quickly during the first 7 days of the batch experiment to concentrations lower than 50% of the initial concentrations. Considering the dissipation kinetics of these compounds [Figure 1], all models applied were transformed to a SFO model. In the case of BEM model, because of the low k_2 values; in the case of FODED model, because $k_1 = k_2$ or low value of k_2; in the case of FOTC model, $k_1 = k_2$; in the case of MHSM model because of low t_b value and; in the case of LM model $a_{max} = a_0$. This kinetic behavior, previously described for SMZ[36], could be due to the high mobility of SMZ and AcSMZ in sludge, compost, and soil[20].

Determination coefficients were calculated to evaluate the fit of the experimental concentrations to SFO model. They were in the range from 0.941 to 0.966 (slope from 0.88 to 1.0) for SMZ and from 0.964 to 0.996 for AcSMZ (slopes from 0.95 to 1.0). The SFO constants determined in SAS were in the range of 0.169 to 0.174 d^{-1} for SMZ and 0199 to 0.290 d^{-1} for AcSMZ. The SFO constants determined in CAS were slightly lower in the case of SMZ (from 0.121 to 0.159 d^{-1}) and higher in the case of AcSMZ (0.305 d^{-1}). These values were similar to those previously reported for SMZ. For example, Kodešová *et al.* evaluated the dissipation of SMZ and other pharmaceutical compounds in thirteen different soil conditions, obtaining kinetic constants for this compound in the range between 0.0045 and 0.149 d^{-1}[22]. Furthermore, the application of FODED model to the dissipation of SMZ in CAS revealed that the compound could follow a biphasic kinetics with two compartments: in the first one, it follows a fast dissipation kinetics with a kinetic constant of 0.159 d^{-1},

Table 1. Concentrations and relative standard deviations (RSD) of the target compounds in spiked sludge-amended soil and compost-amended soil (*n* = 5)

	Spiked sludge-amended soil			Spiked compost-amended soil		
	Range (µg·kg⁻¹)	Mean (µg·kg⁻¹)	RSD (%)	Range (µg·kg-1)	Mean (µg·kg⁻¹)	RSD (%)
MeP	190-233	204	9.0	297-376	297	25
OH-MeP	264-305	282	6.3	133-386	281	34
PrP	278-337	304	7.9	266-515	352	27
3,4-DHB[1]	114-135	123	6.6	89.1-123	107	44
4-HB[1]	513-533	524	1.6	24.7-55.5	44.6	16
CBZ	379-449	422	6.8	342-728	575	25
3-OH-CBZ	423-495	464	6.3	358-732	565	24
10-OH-CBZ	381-484	438	8.9	315-647	516	24
EP-CBZ	291-347	325	9.2	274-473	374	26
DIC	250-275	260	3.9	221-419	311	24
4-OH-DIC	209-296	244	13	122-356	194	14
IBU	250-292	270	5.6	199-356	308	21
1-OH-IBU	373-453	424	7.6	294-640	537	26
2-OH-IBU	303-364	341	6.8	248-523	443	25
CBX-IBU	318-376	356	6.6	267-540	462	24
SMZ	523-876	764	21	436-584	529	15
AcSMZ	373-452	416	7.3	310-637	496	24

AcSMZ: acetylsulfamethoxazole; CBX-IBU: carboxy-ibuprofen; CBZ: carbamazepine; DIC: diclofenac; EP-CBZ: carbamazepine-10,11-epoxide; IBU: ibuprofen; MeP: methylparaben; OH-MeP: methyl protocatechuate; PrP: propylparaben; SMZ: sulfamethoxazole; 1-OH-IBU: 1-hydroxyibuprofen; 2-OH-IBU: 2-hydroxyibuprofen; 3,4-DHB: 3,4-dihydroxybenzoic acid; 3-OH-CBZ: 3-hydroxycarbamazepine; 4-HB: 4-hydroxybenzoic acid; 4-OH-DIC: 4-hydroxy-diclofenac; 10-OH-CBZ: 10-hydroxycarbamazepine.
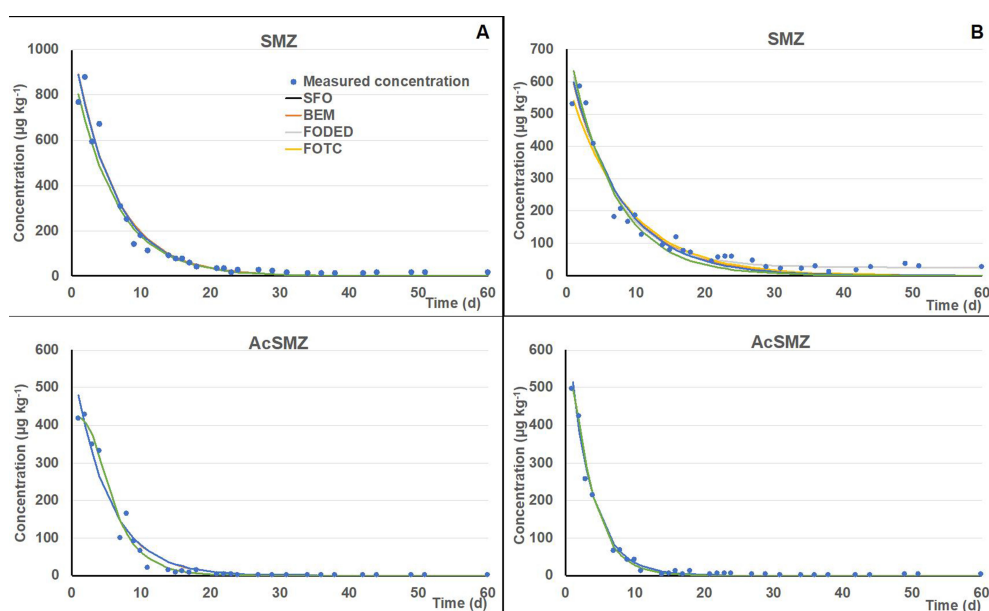

Figure 1. Mean concentrations of SMZ and AcSMZ as a function of time in (A) sludge-amended soil and (B) compost-amended soil with curves from kinetic models. AcSMZ: Acetylsulfamethoxazole; BEM: bi-exponential model; FODED: first-order double-exponential decay; FOTC: first-order two-compartment; SFO: a single first-order; SMZ: sulfamethoxazole.

while in the second one, where it can be potentially adsorbed onto the soil, could follow a slow dissipation kinetics with a kinetic constant of 0.001 d^{-1}. These results were similar to those observed by Srinivasan *et al.* (2014), who evaluated the dissipation of SMZ in topsoil and subsoil[24]. In this study, FODED and FOTC models were the best models for fitting the SMO dissipation. Moreover, this fact could explain the concentration of approximately 20 μg·kg^{-1} measured in SAS after 60 days of batch experiment.

To our knowledge, no data about the kinetic model of AcSMZ in soil has been reported yet. However, previous studies have reported that it suffers a quick dissipation in soil, higher than its parent compound SMZ[23,37,38]. This fact could be explained not only by its higher availability in soil, but also by its transformation by deacetylation into SMZ[37].

Endpoint values obtained for SMZ in SAS were slightly lower than those obtained in CAS. Moreover, these values were lower than in spiked soil without organic amended (SS) [Supplementary Table 6]. The opposite effect was observed for AcSMZ. Its DT50 and DT90 values decreased from SAS (from 3.48 to 5.62 days and from 11.2 to 16.1 days, respectively) to CAS (2.27-3.43 days and 7.55-8.18 days, respectively) and SS (1.20-1.31 days and 3.98-4.34 days, respectively). The behavior of SMZ could be due to the importance of biological processes in its dissipation, and the higher microbial biomass in SAS than in CAS or SS. The behavior of AcSMZ could be explained by greater sorption onto sludge than onto compost and soil, as previously reported[20], decreasing its bioavailability[36].

Degradation of DIC and 4-OH-DIC
The concentrations of DIC were reduced during the first 15 days of batch experiments from the initial concentrations (260 and 310 μg·kg^{-1} in SAS and CAS, respectively) to 60.0 and 19.9 μg·kg^{-1}, respectively. In the following 45 days, the concentrations measured in SAS remained approximately constant (mean concentration: 40.1 μg·kg^{-1}), while in CAS were reduced below 10 μg·kg^{-1} [Supplementary Figures 3 and 4]. The concentrations of 4-OH-DIC were reduced in the first 10 days from 244 μg·kg^{-1} to lower than 3.10 μg·kg^{-1} in SAS, and from 153 μg·kg^{-1} to lower than 5.48 μg·kg^{-1} in CAS.

Considering the dissipation kinetics of DIC [Figure 2], a similar behavior was observed in SAS and CAS. In both cases, BEM, MHSM and LM models were transformed to SFO model (kinetic constants of these models were 0.081 d^{-1} in SAS, and from 0.160 to 0.167 d^{-1} in CAS), while in the case of the FODED and FOTC models, the kinetics showed two components: a first component followed a SFO kinetics (kinetic constant of 0.132 and 0.178 d^{-1}, for SAS and CAS) and a second component corresponding to a constant concentration of 30.3 and 5.84 μg·kg^{-1}, respectively. These results could be explained by the distribution of DIC between the solution and the solid phase. In the solution phase, the concentration of DIC follows a SFO model. In the soil phase, its concentration remains constant, which can be explained by its adsorption onto soil particles making its degradation more difficult. This fact is consistent with the measured concentrations and the adsorption behavior of DIC in soil and sludge[39,40]. For example, Silva *et al.* showed the influence of pH on the adsorption of DIC onto soil[40]. They reported an increase in the ionic form of DIC at higher pH values which could explain its higher availability and, as a result, its higher microbial degradation in CAS (compost pH: 6.33) than in SAS (sludge pH: 5.85). In another study, Yan *et al.* reported a high correlation between the adsorption of DIC and the organic matter content of sludge[39]. This fact can explain the lower desorption and availability of DIC in sludge [OM: 48.5%, wt (by weight)] than in compost (OM: 27.3%, wt) [Supplementary Table 1].

All kinetic models applied were well fitting to the dissipation of 4-OH-DIC. Determination coefficients were higher than 0.922 and slopes were higher than 0.91. FOTC, MHSM, and LM models revealed that
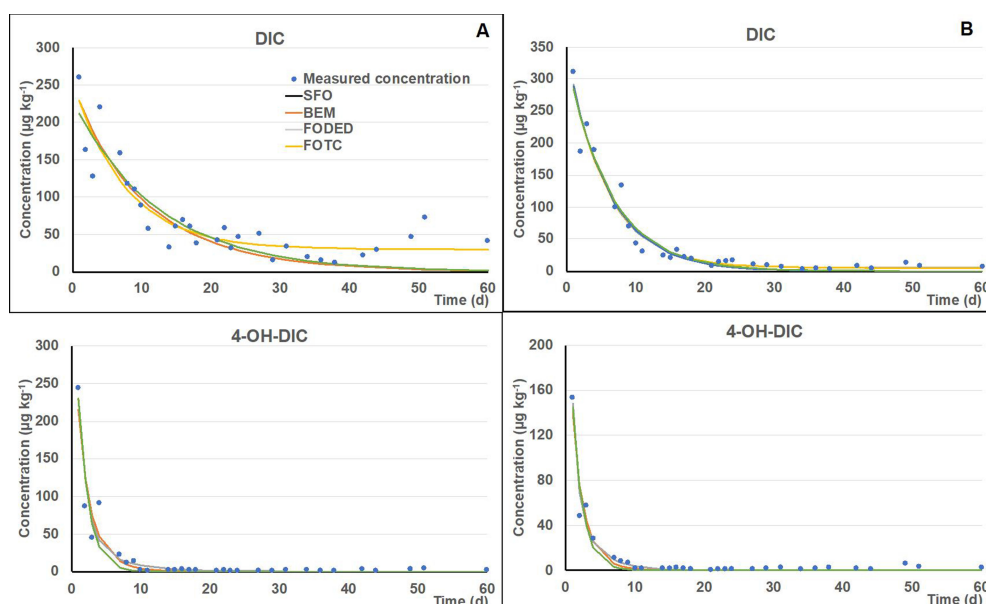
Figure 2. Mean concentrations of DIC and 4-OH-DIC as a function of time in (A) sludge-amended soil and (B) compost-amended soil and curves of the applied kinetic models. BEM: Bi-exponential model; DIC: Diclofenac; FODED: first-order double-exponential decay; FOTC: first-order two-compartment; SFO: a single first-order; 4-OH-DIC: 4-hydroxy-diclofenac.

dissipation corresponded to SFO model with kinetic constants of 0.646 and 0.653 d^{-1} in SAS and CAS, respectively. BEM and FODED models showed a biphasic kinetics in both matrices [Figure 2].

Regarding the endpoints, DT50 values of DIC were in the ranges 6.29-8.56 days, 3.98-4.33 days, and 5.89-6.66 days for SAS, CAS and SS, respectively. These results are in concordance with those previously reported. For example, Biell-Maeso *et al.* reported DT50 values of 3 and 4 days in two studied soils[18]. DT90 values were in the ranges from 25.6 to higher than 100 days in SAS, from 13.8 to 14.4 days in CAS, and from 22.1 to 25.1 days in SS. The highest DT90 value was obtained for SAS, which could be explained by the high retention of DIC in sludge resulting in the remaining amount in SAS (30.3 $\mu g \cdot kg^{-1}$). In the case of CAS, the measured concentrations and FODED and FOTC models showed the presence of DIC 60 days after batch experiments. These concentrations were lower than 10% of the initial concentrations. As a result, DT90 values were achieved before 15 days of batch experiments (25 days in the case of SS) [Supplementary Table 6].

Dissipation of CBZ and its metabolites
CBZ and its metabolites showed similar behavior in SAS and CAS [Supplementary Figures 5 and 6]. Concentrations of CBZ and EP-CBZ were approximately constant in SAS during the first 27 and 23 days, respectively, of the batch experiments and during 27 days (both compounds) in CAS. After that, a fast decrease in the concentrations occurred, whereas the concentrations of the hydroxylated metabolites (3-OH-CBZ and 10-OH-CBZ) decreased since the beginning of the batch experiments.

No good fit to kinetic models was observed for the dissipation of CBZ and EP-CBZ [Figure 3], neither in SAS nor in CAS. Determination coefficients were in the ranges 0.530-0.538 and 0.676-718 for CBZ and EP-CBZ, respectively, in SAS and up to 0.685 and 0.648, respectively, in CAS for most of the models applied. This was in concordance with the poor fit to the SFO model reported by Al-Rajab *et al.*[41]. LM model was the best fitting one to the measured concentrations: determination coefficients were 0.683 and 0.853 for
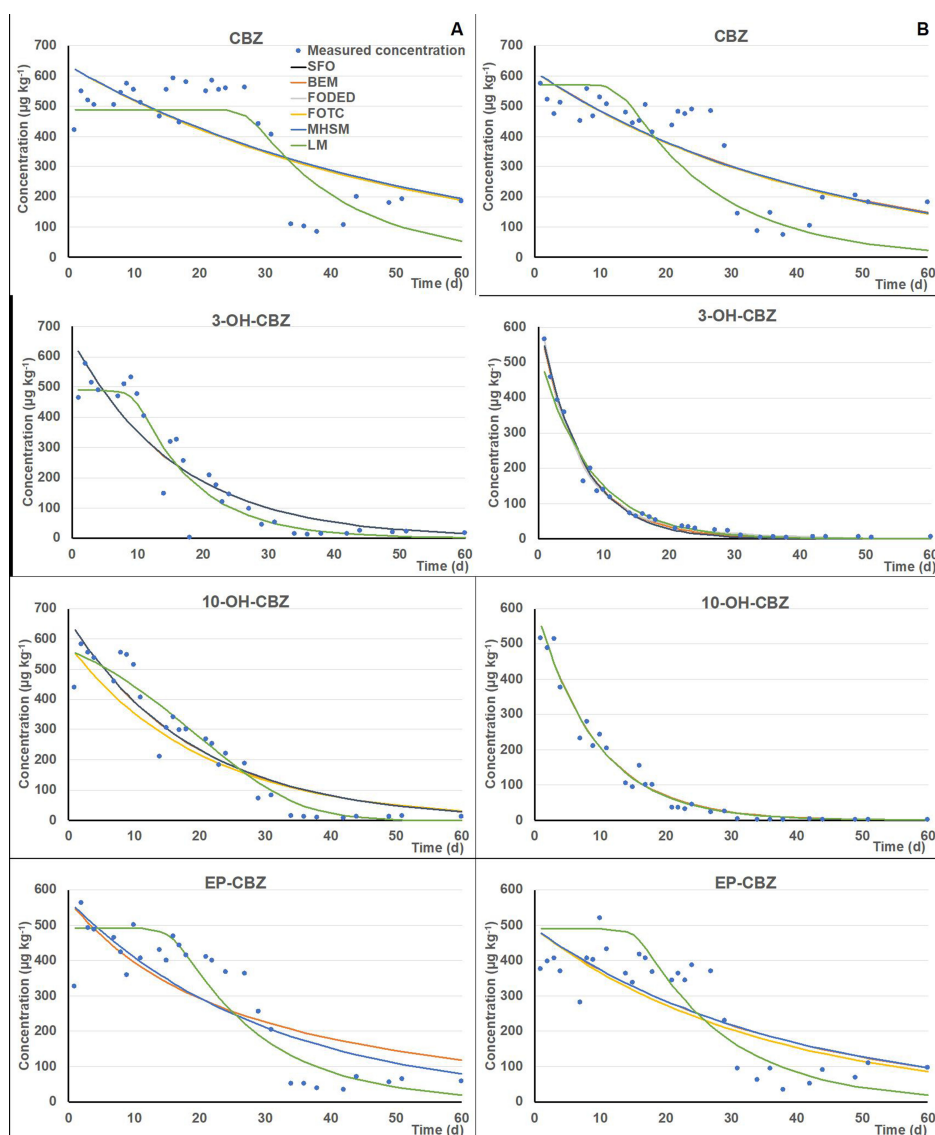
Figure 3. Mean concentrations of CBZ and its metabolites as a function of time in (A) sludge-amended soil and (B) compost-amended soil and curves from the applied kinetic models. BEM: Bi-exponential model; CBZ: carbamazepine; EP-CBZ: carbamazepine-10,11-epoxide; FODED: first-order double-exponential decay; FOTC: first-order two-compartment; LM: logistic model; MHSM: modified hockey-stick model; SFO: a single first-order; 3-OH-CBZ: 3-hydroxycarbamazepine; 10-OH-CBZ: 10-hydroxycarbamazepine.

CBZ and EP-CBZ, respectively, (slopes 0.86 and 0.95) in SAS and 0.728 and 0.788 for CBZ and EP-CBZ, respectively, (slopes 1.0 and 1.1) for CAS. These results showed a lag phase for the dissipation of these compounds. In LM model, the rate constant increased from its initial value to a maximum value (0.067 d^{-1} for CBZ and 0.072 d^{-1} for EP-CBZ). Then, the diffusion behavior approached a first-order kinetics. The poor fit between measured concentrations and LM model could be explained by considering that, after the lag phase, the dissipation of CBZ and EP-CBZ occurs in two phases. In the first phase, a fast dissipation occurs, possibly in soil-water phase. In the second phase, the compound is poorly degraded, probably due to being adsorbed to soil particles. As a result, concentrations higher than 145 and 51.7 $\mu g \cdot kg^{-1}$ were measured for CBZ and EP-CBZ, respectively, in the last 25 days of batch experiments. These results are in concordance with the high persistence of CBZ previously noticed by other authors[15;42]. Despite the high persistence of these compounds in amended soil, the results obtained after the application of sludge and compost to the

soil revealed a higher degradation of both compounds in amended soil than in SS[10], in which no dissipation, especially in the case of CBZ, was measured.

The degradation of the hydroxylated metabolites was faster than that of CBZ and EP-CBZ. The analysis of kinetic models revealed a SFO kinetics for both compounds. All kinetic models were transformed to a SFO model. Only LM and FODED models showed different behavior. In the case of SAS, LM model gave the best fit with R^2: 0.919 for 3-OH-CBZ and 0.933 for 10-OH-CBZ. These results show a slow degradation in SAS during the first days of the batch experiments, followed by a first-order kinetics. A faster dissipation was obtained for all compounds in CAS and SAS than in SS, except for 3-OH-CBZ. Mean DT50 and DT90 values in SAS were 22 and 67 days, respectively; 15 and 44 days, respectively, in CAS, and 74 and 281 days, respectively, in SS.

Dissipation of IBU and its metabolites
The concentrations of IBU and its metabolites obtained from batch experiments are shown in Supplementary Figures 7 and 8. The metabolite CBX-IBU showed a higher dissipation with concentrations lower than 5.71 µg·kg^{-1} ten days after the beginning of the experiments. However, its concentration increased from days 38 to 60. The compounds IBU and 1-OH-IBU showed higher persistence in SAS than in CAS. For example, whereas in SAS, the concentration of IBU decreased from 270 to 123 µg·kg^{-1} during the first 30 days, in CAS, the concentration of IBU decreased from 307 to 31.9 µg·kg^{-1} in the first 20 days. The same pattern was observed for 1-OH-IBU. The metabolites 2-OH-IBU and CBX-IBU had similar behavior in both matrices.

A high dispersion of results was obtained for all compounds, especially in SAS [Figure 4]. Because of that, a poor goodness-of-fit was achieved for all kinetic models applied. Their determination coefficients were worst in SAS [from 0.535 to 0.826 for most of the models and compounds, except for CBX-IBU (from 0.290 to 0.469)] than in CAS (from 0.641 to 0.980). The best goodness-of-fit was provided by SFO model (from 0.722 to 0.980). For all studied compounds, except for 2-OH-IBU, the obtained dissipation was slower in SAS (kinetic constant values from 0.048 to 0.119 d^{-1}) than in CAS (0.143-0.229 d^{-1}) and SS (0.076 to 0.245 d^{-1}).

The lowest endpoint values were obtained for CBX-IBU (mean DT50 and DT90 values up to 7.6 and 23 days, respectively), followed by 1-OH-IBU (up to 11.1 and 34.1 days, respectively), IBU (14.8 and 52 days), and 2-OH-IBU (19.8 and 63 days). The fast dissipation of CBX-IBU could be explained by its lower retention in the organic-amended soil[20] and, consequently, its higher availability. In addition, the greater mobility of the metabolite 1-OH-IBU could explain its faster dissipation in comparison to that of IBU. However, the metabolite 2-OH-IBU, in spite of its physicochemical properties and adsorption behavior onto the sludge and soil are similar to those of 1-OH-IBU[20], showed the slowest dissipation. This fact is in concordance with previous studies which reported a high persistence of 2-OH-IBU[10,43]. The high persistence of this compound could be explained not only by its poor degradation but also by the potential transformation of IBU into 2-OH-IBU under aerobic conditions, as has been previously described[44,45]. This fact could also explain the high variability of the concentrations measured for this compound in batch experiments.

Dissipation of parabens and their metabolites
The concentrations of parabens and their metabolites in SAS and CAS are shown in Supplementary Figures 9 and 10, respectively. These concentrations quickly decreased during the first ten days of batch experiments. In SAS, the concentration of MeP decreased in 2 days from the initial concentration of 204
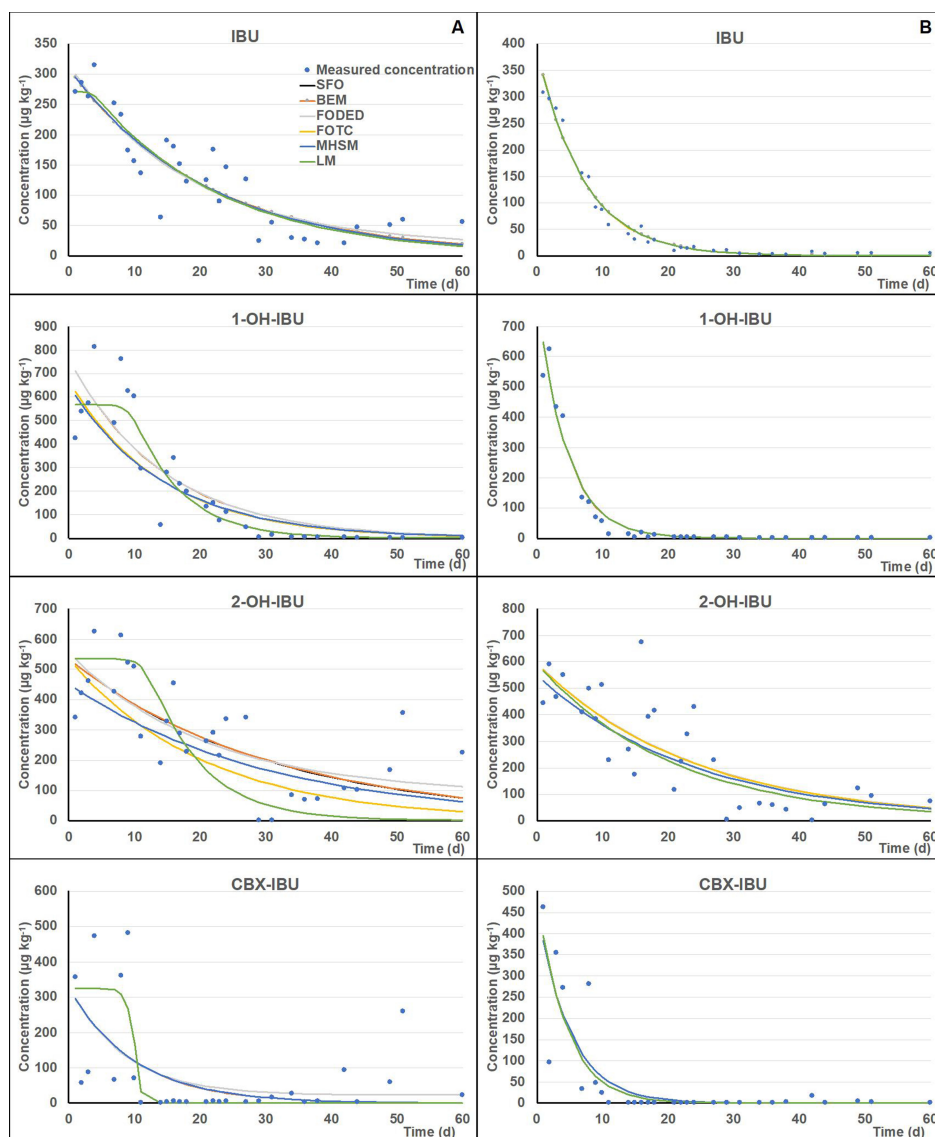
Figure 4. Mean concentrations of IBU and its metabolites as a function of time in (A) sludge-amended soil and (B) compost-amended soil and curves of the applied kinetic models. BEM: Bi-exponential model; CBX-IBU: carboxy-ibuprofen; FODED: first-order double-exponential decay; FOTC: first-order two-compartment; IBU: Ibuprofen; LM: logistic model; MHSM: modified hockey-stick model; SFO: a single first-order; 1-OH-IBU: 1-hydroxyibuprofen; 2-OH-IBU: 2-hydroxyibuprofen.

$\mu g \cdot kg^{-1}$ to 2.16 $\mu g \cdot kg^{-1}$, whereas the concentration of PrP decreased from 304 $\mu g \cdot kg^{-1}$ to 3.45 $\mu g \cdot kg^{-1}$ in 3 days. The same behavior was observed in CAS, where the concentrations strongly decreased, except for the metabolite 4-HB, after the first days of batch experiments. These results are in concordance with the low persistence previously reported for parabens[46,47]. For example, Arachchige *et al.* reported that more than 90% of parabens were dissipated after three days of the beginning of the experiment[46]. The dissipation of the studied compounds was lower in SS than in SAS and CAS, especially in the case of MeP, PrP, and OH-MeP[10].

The results showed a good fit of the kinetics of dissipation to a SFO model for most of the compounds and matrices [Supplementary Figures 5 and 6]. Only the metabolite 4,3-DHB showed a low determination coefficient and poor slope (0.65-0.68) in sludge-amended soil, which could be due to the wide dispersion of
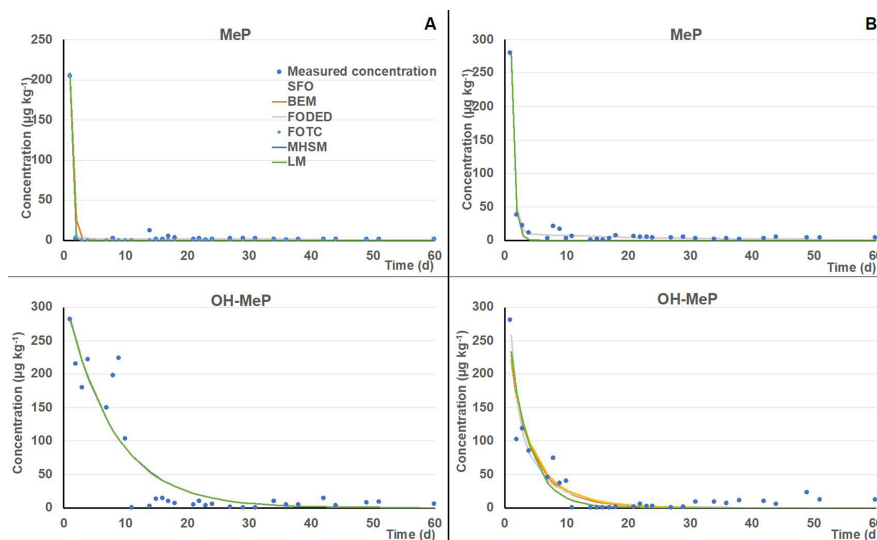
Figure 5. Mean concentrations of MeP and its metabolites measured as a function of time in (A) sludge-amended soil and (B) compost-amended soil and curves of the applied kinetic models. BEM: Bi-exponential model; FODED: first-order double-exponential decay; FOTC: first-order two-compartment; LM: logistic model; MeP: Methylparaben; MHSM: modified hockey-stick model; OH-MeP: methyl protocatechuate; SFO: a single first-order.
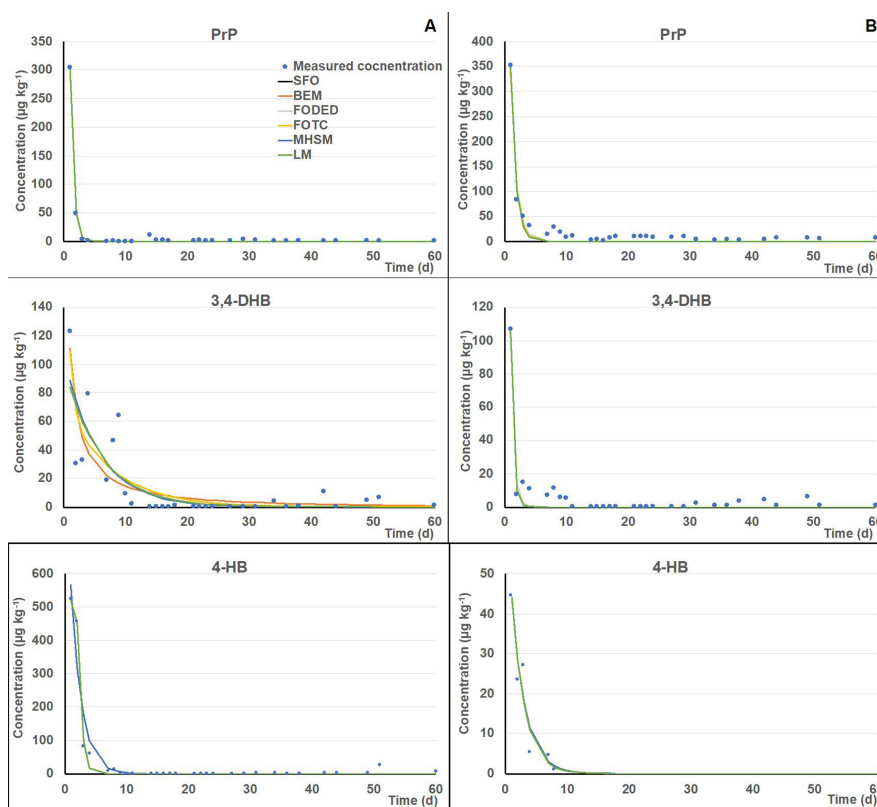

Figure 6. Mean concentrations of PrP and its metabolites as a function of time in (A) sludge-amended soil and (B) compost-amended soil and curves of the applied kinetic models BEM: Bi-exponential model; FODED: first-order double-exponential decay; FOTC: first-order two-compartment; MHSM: modified hockey-stick model; PrP: Propylparaben. SFO: a single first-order; 3,4-DHB: 3,4-dihydroxybenzoic acid; 4-HB: 4-hydroxybenzoic acid.

concentrations measured in these samples. For OH-MeP in CAS, the best fit was obtained from FODED and FOCT models [Supplementary Table 5], which could show a degradation kinetics in two compartments for this compound in this experiment.

In general, after sludge or compost application onto soil, the parent compounds MeP and PrP showed the fastest dissipation (DT50 and DT90 values up to 0.37 and 1.24 days, respectively, in SAS, and up to 0.56 and 2.10 days, respectively, in CAS), while the metabolite OH-MeP showed the lowest dissipation rate (DT90 up to 18.0 days in SAS and 7.60 days in CAS). The dissipation of the parent compounds was considerably faster in amended soil than in SS [Supplementary Tables 4 to 6]. No relevant difference was obtained between the endpoint values of the metabolites. These results could be explained by the potential transformation of parent compounds into their metabolites under aerobic conditions. The degradation of MeP and PrP in amended soil could result in the formation of their metabolites, compensating for the decrease of the concentration of metabolites by dissipation. This compensation is most significant in amended soils than in soils where the dissipation of parent compounds is slower.

CONCLUSIONS

The occurrence and dissipation kinetics of most recurrent PPCPs and their metabolites in the environment have been evaluated in soil amended with anaerobically-digested and dehydrated sludge or with compost. Obtained results were compared with those reported for the same compounds in soil without organic amendment. Batch experiments were carried out using spiked sludge and compost. The adsorption of the studied compounds in sludge and compost (from 8.4% to 153%) was enough to evaluate their occurrence in soil after organic amendment.

In general, parabens and their metabolites were the compounds with the fastest dissipation in all studied matrices, followed by the antibiotic SMZ and its metabolite, DIC and its metabolite 4-OH-DIC, IBU and its metabolites, and CBZ and its metabolites, in that order. Most of them were well fitting to a SFO dissipation kinetic model. The application of FODED model showed that some of the studied compounds, such as DIC or SMZ, could follow a dissipation kinetics in two phases: a fast dissipation that could be attributed to the amount of the compound associated with the aqueous compartment and a slow dissipation that could be due related to the amount of the compound strongly adsorbed onto soil particles. This fact could result in a high persistence of the compound, similar to the case of DIC which remains in the soil 60 days after batch experiments.

The compounds CBZ and EP-CBZ showed a high persistence, with a lag phase on their dissipation, resulting in a concentration approximately constant during the first days of batch experiments.

For most of the compounds, the dissipation kinetics was faster in SAS and CAS than in SS, which could show the influence of microbial activity and organic matter content in their dissipation.

The use of several kinetic models, including SFO and biphasic models, to evaluate the dissipation of PPCPs and their metabolites can clarify the dissipation behavior of some of the studied compounds. For example, while compounds such as parabens and their metabolites followed a SFO model associated with a high degradation 60 days after batch experiments, compounds such as SMZ or DIC were still present in CAS and SAS after that period of time. This fact could be due to their higher adsorption onto the organic matter of sludge and compost.

DECLARATIONS

Authors' contributions

Involved in conceptualization: Santos JL, Alonso E

Involved in methodology and verification of results/experiments, application of statistical models to analyze or synthesize study data: Santos JL, Martín J

Involved in presentation and visualization of data: Martín J

Involved in writing - Original Draft: Santos JL

Involved in writing - Review & Editing: Aparicio I

Involved in project administration and funding acquisition: Alonso E

Availability of data and materials

Data are available in the Supplementary Material.

Financial support and sponsorship

Conflicts of interest

All authors declared that there is no conflict of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

REFERENCES

1. Cherfouh R, Lucas Y, Derridj A, Merdy P. Metal speciation in sludges: a tool to evaluate risks of land application and to track heavy metal contamination in sewage network. *Environ Sci Pollut Res Int* 2022;29:70396-407. DOI PubMed

2. Mejías C, Martín J, Santos JL, Aparicio I, Alonso E. Occurrence of pharmaceuticals and their metabolites in sewage sludge and soil: a review on their distribution and environmental risk assessment. *Trends Environ Anal Chem* 2021;30:e00125. DOI

3. EurEau. Europe's water in figures. An overview of the European drinking water and waste water sectors. 2021 edition. Available from: https://www.eureau.org/resources/publications/eureau-publications/5824-europe-s-water-in-figures-2021/file. [Last accessed on 5 Jun 2023].

4. EurEau. Waste water treatment-sludge management. 2021, pp. 1-32. Available from: https://www.eureau.org/resources/briefing-notes/5629-briefing-note-on-sludge-management/file. [Last accessed on 5 Jun 2023].

5. Elango D, Devi KD, Jeyabalakrishnan HK, et al. Agronomic, breeding, and biotechnological interventions to mitigate heavy metal toxicity problems in agriculture. *J Agric Food Res* 2022;10:100374. DOI

6. Zhu Q, Liang Y, Zhang Q, et al. Biochar derived from hydrolysis of sewage sludge influences soil properties and heavy metals distributed in the soil. *J Hazard Mater* 2023;442:130053. DOI

7. Xing H, Yu X, Huang J, et al. Characteristics and health risks of phthalate ester contamination in soil and plants in coastal areas of south China. *Int J Environ Res Public Health* 2022;19:9516. DOI PubMed PMC

8. Abril C, Santos JL, Martín J, Aparicio I, Alonso E. Uptake and translocation of multiresidue industrial and household contaminants in radish grown under controlled conditions. *Chemosphere* 2021;268:128823. DOI PubMed

9. Jha G, Kankarla V, McLennon E, et al. Per- and polyfluoroalkyl substances (PFAS) in integrated crop-livestock systems: environmental exposure and human health risks. *Int J Environ Res Public Health* 2021;18:12550. DOI PubMed PMC

10. Malvar JL, Santos JL, Martín J, Aparicio I, Alonso E. Occurrence of the main metabolites of the most recurrent pharmaceuticals and

personal care products in mediterranean soils. *J Environ Manage* 2021;278:111584. DOI PubMed

11.   Carsella JS, Mutz J, Zuniga T, Kinney CA. Pharmaceuticals and personal care products as contaminants of emerging concern in sewage sludge and soils and the role of transformation products in their fate and environmental impact. In: Núñez-delgado A, Arias-est évez M, editors. Emerging Pollutants in Sewage Sludge and Soils. Cham: Springer International Publishing; 2023. pp. 243-65. Available from: https://link.springer.com/chapter/10.1007/698_2022_858. [Last accessed on 6 Jun 2023].

12.   Song L, Li L, Yang S, et al. Sulfamethoxazole, tetracycline and oxytetracycline and related antibiotic resistance genes in a large-scale landfill, China. *Sci Total Environ* 2016;551-552:9-15. DOI

13.   Marti R, Scott A, Tien YC, et al. Impact of manure fertilization on the abundance of antibiotic-resistant bacteria and frequency of detection of antibiotic resistance genes in soil and on vegetables at harvest. *Appl Environ Microbiol* 2013;79:5701-9. DOI PubMed PMC

14.   Santos JL, Martín J, Mejías C, Aparicio I, Alonso E. Pharmaceuticals and their metabolites in sewage sludge and soils: distribution and environmental risk assessment. In: Núñez-delgado A, Arias-estévez M, editors. Emerging Pollutants in Sewage Sludge and Soils. Cham: Springer International Publishing; 2023. pp. 19-36. DOI

15.   Menacherry SPM, Kočárek M, Kacerova T, Kotíková Z, Kačer P, Kodešová R. The impact of initial concentration of selected pharmaceuticals on their early stage of dissipation in soils. *J Soils Sediments* 2022;22:522-35. DOI

16.   García-Galán MJ, Díaz-Cruz S, Barceló D. Multiresidue trace analysis of sulfonamide antibiotics and their metabolites in soils and sewage sludge by pressurized liquid extraction followed by liquid chromatography-electrospray-quadrupole linear ion trap mass spectrometry. *J Chromatogr A* 2013;1275:32-40. DOI PubMed

17.   Rossini D, Ciofi L, Ancillotti C, et al. Innovative combination of QuEChERS extraction with on-line solid-phase extract purification and pre-concentration, followed by liquid chromatography-tandem mass spectrometry for the determination of non-steroidal anti-inflammatory drugs and their metabolites in sewage sludge. *Anal Chim Acta* 2016;935:269-81. DOI

18.   Biel-Maeso M, González-González C, Lara-Martín PA, Corada-Fernández C. Sorption and degradation of contaminants of emerging concern in soils under aerobic and anaerobic conditions. *Sci Total Environ* 2019;666:662-71. DOI PubMed

19.   Wojsławski J, Białk-Bielińska A, Stepnowski P, Dołżonek J. Leaching behavior of pharmaceuticals and their metabolites in the soil environment. *Chemosphere* 2019;231:269-75. DOI PubMed

20.   Martín J, Mejías C, Santos JL, Aparicio I, Alonso E. Pharmaceuticals and their main metabolites in treated sewage sludge and sludge-amended soil: availability and sorption behaviour. *Molecules* 2021;26:5910. DOI PubMed PMC

21.   Paz A, Tadmor G, Malchi T, et al. Fate of carbamazepine, its metabolites, and lamotrigine in soils irrigated with reclaimed wastewater: sorption, leaching and plant uptake. *Chemosphere* 2016;160:22-9. DOI

22.   Kodešová R, Kočárek M, Klement A, et al. An analysis of the dissipation of pharmaceuticals under thirteen different soil conditions. *Sci Total Environ* 2016;544:369-81. DOI

23.   Koba O, Golovko O, Kodešová R, Fér M, Grabic R. Antibiotics degradation in soil: a case of clindamycin, trimethoprim, sulfamethoxazole and their transformation products. *Environ Pollut* 2017;220:1251-63. DOI

24.   Srinivasan P, Sarmah AK, Rohan M. Deriving sulfamethoxazole dissipation endpoints in pasture soils using first order and biphasic kinetic models. *Sci Total Environ* 2014;488-489:146-56. DOI PubMed

25.   Briones RM, Sarmah AK. Modelling degradation kinetics of metformin and guanylurea in soil microcosms to derive degradation end-points. *Environ Pollut* 2019;245:735-45. DOI PubMed

26.   Malvar J, Luis Santos J, Martín J, Aparicio I, Alonso E. Occurrence of the main metabolites of pharmaceuticals and personal care products in sludge stabilization treatments. *Waste Manag* 2020;116:22-30. DOI PubMed

27.   Aplicación de lodos tratados de depuradora. Información sobre las aplicaciones realizadas de lodos tratados de depuradora en suelos agrarios hasta el 30/09/2022. Available from: https://www.juntadeandalucia.es/sites/default/files/inline-files/2022/10/Recintos_Confirmados_hasta_2022_09_30.ods. [Last accessed on 5 Jun 2023].

28.   OECD. Test No. 307: Aerobic and Anaerobic Transformation in Soil. OECD Guidelines for the testing of chemicals, section, vol. 3, OECD Publishing, Paris (2002). Available from: https://archive.epa.gov/scipoly/sap/meetings/web/pdf/307_aerobic_anaerobic_transformation.pdf. [Last accessed on 6 Jun 2023].

29.   Malvar JL, Santos JL, Martín J, Aparicio I, Alonso E. Simultaneous pressurized liquid extraction and clean-up for the determination of metabolites in complex environmental solid matrices. *Microchem J* 2020;152:104370. DOI

30.   FOCUS (2006). "Guidance document on estimating persistence and degradation kinetics from environmental fate studies on pesticides in EU registration." Report of the FOCUS Work Group on Degradation Kinetics, EC Documents Reference Sanco/10058/2005 Version 2.0, 434 pp. Available from: https://esdac.jrc.ec.europa.eu/public_path/projects_data/focus/dk/docs/finalreportFOCDegKinetics.pdf. [Last accessed on 5 Jun 2023].

31.   Sarmah AK, Close ME. Modelling the dissipation kinetics of six commonly used pesticides in two contrasting soils of New Zealand. *J Environ Sci Health B* 2009;44:507-17. DOI

32.   Hill BD, Schaalje GB. A two-compartment model for the dissipation of deltamethrin on soil. *J Agric Food Chem* 1985;33:1001-6. DOI

33.   Martín J, Santos JL, Aparicio I, Alonso E. Pharmaceutically active compounds in sludge stabilization treatments: anaerobic and aerobic digestion, wastewater stabilization ponds and composting. *Sci Total Environ* 2015;503-504:97-104. DOI PubMed

34.   Verlicchi P, Zambello E. Pharmaceuticals and personal care products in untreated and treated sewage sludge: occurrence and environmental risk in the case of application on soil - a critical review. *Sci Total Environ* 2015;538:750-67. DOI PubMed

35.   Ivanová L, Mackuľak T, Grabic R, et al. Pharmaceuticals and illicit drugs - A new threat to the application of sewage sludge in agriculture. *Sci Total Environ* 2018;634:606-15. DOI PubMed

36.   Zhang Y, Hu S, Zhang H, Shen G, Yuan Z, Zhang W. Degradation kinetics and mechanism of sulfadiazine and sulfamethoxazole in an agricultural soil system with manure application. *Sci Total Environ* 2017;607-608:1348-56. DOI

37.   Geng C, Bergheaud V, Garnier P, Zhu YG, Haudin CS. Impact of sludge treatments on the extractability and fate of acetyl sulfamethoxazole residues in amended soils. *Chemosphere* 2018;194:828-36. DOI PubMed

38.   Andriamalala A, Vieublé-Gonod L, Dumeny V, Cambier P. Fate of sulfamethoxazole, its main metabolite N-ac-sulfamethoxazole and ciprofloxacin in agricultural soils amended or not by organic waste products. *Chemosphere* 2018;191:607-15. DOI PubMed

39.   Yan J, Zhang X, Lin W, Yang C, Ren Y. Adsorption behavior of diclofenac-containing wastewater on three kinds of sewage sludge. *Water Sci Technol* 2019;80:717-26. DOI

40.   Silva S, Rodrigues JA, Coelho MR, et al. Occurrence of pharmaceutical active compounds in sewage sludge from two urban wastewater treatment plants and their potential behaviour in agricultural soils. *Environ Sci : Water Res Technol* 2021;7:969-82. DOI

41.   Al-Rajab AJ, Sabourin L, Lapen DR, Topp E. Dissipation of triclosan, triclocarban, carbamazepine and naproxen in agricultural soil following surface or sub-surface application of dewatered municipal biosolids. *Sci Total Environ* 2015;512-513:480-8. DOI PubMed

42.   Kodešová R, Chroňáková A, Grabicová K, et al. How microbial community composition, sorption and simultaneous application of six pharmaceuticals affect their dissipation in soils. *Sci Total Environ* 2020;746:141134. DOI

43.   Dolu T, Nas B. Full-scale anaerobic digestion of sewage sludges: fate evaluation of pharmaceuticals and main metabolites. *J Water Process Eng* 2023;51:103366. DOI

44.   Tiwari B, Sellamuthu B, Ouarda Y, Drogui P, Tyagi RD, Buelna G. Review on fate and mechanism of removal of pharmaceutical pollutants from wastewater using biological approach. *Bioresour Technol* 2017;224:1-12. DOI PubMed

45.   Weigel S, Berger U, Jensen E, Kallenborn R, Thoresen H, Hühnerfuss H. Determination of selected pharmaceuticals and caffeine in sewage and seawater from Tromsø/Norway with emphasis on ibuprofen and its metabolites. *Chemosphere* 2004;56:583-92. DOI PubMed

46.   Chamila Samarasinghe SV, Krishnan K, Aitken RJ, Naidu R, Megharaj M. Persistence of the parabens in soil and their potential toxicity to earthworms. *Environ Toxicol Pharmacol* 2021;83:103574. DOI PubMed

47.   Emmanouil C, Bekyrou M, Psomopoulos C, Kungolos A. An insight into ingredients of toxicological interest in personal care products and a small–scale sampling survey of the greek market: delineating a potential contamination source for water resources. *Water* 2019;11:2501. DOI