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Corresponding Author: Dr Knut Breivik, PhD

Corresponding Author's Institution: Norwegian Institute for Air Research (NILU)

First Author: Barbara Żukowska

Order of Authors: Barbara Żukowska; Knut Breivik, PhD; Frank Wania, PhD

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Evaluating the Environmental Fate of Pharmaceuticals Using a Level III Model Based on Poly-Parameter Linear Free Energy Relationships

Barbara Żukowska [a], Knut Breivik [b*], Frank Wania [c]

[a] Department of Analytical Chemistry, Chemical Faculty, Gdańsk University of Technology, 11/12 G. Narutowicza St., 80–952 Gdańsk, Poland

[b] NILU - Norwegian Institute for Air Research, P.O. Box 100, NO-2027 Kjeller, Norway

[c] Department of Physical and Environmental Sciences, University of Toronto at Scarborough, 1265 Military Trail, Scarborough, Ontario, Canada M1C 1A4

[*] Corresponding author.
Tel.: +47 63898000; fax: +47 63898050; e-mail address: knut.breivik@nilu.no

Abstract

We recently proposed how to expand the applicability of multimedia models towards polar organic chemicals by expressing environmental phase partitioning with the help of poly-parameter linear free energy relationships (PP-LFERs). Here we elaborate on this approach by applying it to eleven pharmaceutical substances. A PP-LFER-based version of a Level III fugacity model calculates overall persistence, concentrations and intermedia fluxes of polar and non-polar organic chemicals between air, water, soil and sediments at steady-state. Illustrative modeling results for the pharmaceuticals within a defined coastal region are presented and discussed. The model results are highly sensitive to the degradation rate in water and the equilibrium partitioning between organic carbon and water, suggesting that an accurate description of this particular partitioning equilibrium is essential in order to obtain reliable predictions of environmental fate. The PP-LFER based modeling approach furthermore illustrates that the greatest mobility in aqueous phases tend to be experienced by pharmaceuticals that combines a small molecular size with strong H-acceptor properties.

Key words

Pharmaceuticals, environment, Level III model, poly-parameter linear free energy relationships

1. Introduction

Substantial amounts of medically active substances (pharmaceuticals) are used worldwide to prevent or treat illnesses in humans and animals (e.g. Boxall et al. 2003). Although there is limited knowledge about environmental release pathways, pharmaceuticals used by humans may be discharged to the aquatic environment from sewage systems, whereas veterinary pharmaceuticals may have a more direct mode of entry to the environment. For example, soils may receive veterinary pharmaceuticals through field application of manure from treated animals, and aquatic environments may receive direct releases of such substances from growth promoters used in fish farming (Boxall et al. 2003). Pharmaceuticals need to be sufficiently stable in order to reach their target organ and it has been reported that certain pharmaceuticals may have an environmental persistence exceeding one year (Zuccato et al. 2000). There is a growing concern of potential harmful effects on the environment, following their widespread detection in various environmental compartments, such as soil, surface water and groundwater (e.g. Heberer et al. 1997; Ternes, 1998; Halling-Sørensen et al. 1998; Buser et al. 1999; Zuccato et al. 2000; Kolpin et al. 2002; Boxall et al. 2003).

Although there has been a significantly increased interest in the environmental occurrence and fate of pharmaceuticals over the last decade, important knowledge gaps remain (Dietrich et al. 2002). Among other issues, there is an urgent need to further develop models aimed at improving the understanding of pharmaceutical behavior in the environment. The key objectives of this study are (a) to present a modified multimedia fate modeling approach that may be utilized to predict pharmaceutical behavior in the environment, and (b) to present illustrative modeling results for selected pharmaceuticals, exemplified for a drainage basin in Norway. For this purpose we used a modified version (Breivik and Wania, 2003) of the original Level III Model by Mackay and Paterson (1991). The objectives of this study mirror those of the first paper presenting the Level III Model (Mackay and Paterson, 1991), namely to establish a general environmental behavior profile for selected pharmaceuticals, which may be used in a first assessment of the likely fate of such substances in a defined region. The actual estimations should therefore be considered more illustrative, rather than definitive, providing an estimate of the order of magnitude of the concentrations that can be expected from defined emission rates (Mackay and Paterson, 1991). It is our hope that these preliminary model results may serve as a tool in support of future monitoring activities and in

identifying key processes and knowledge gaps with respect to the environmental fate of such compounds.

2 Methods

2.1 Model description

Fugacity-based multimedia environmental fate models (Mackay, 2001) have become widely used tools to understand and predict the fate of chemicals in the environment (e.g. Cowan et al. 1995). A few studies have used such models to assess the fate of pharmaceuticals. For example, Di Guardo et al. (2001) proposed a general strategy how various generic and site-specific models of different complexity may be utilized to evaluate the environmental fate of pharmaceuticals (cyclophosamide, diazepam, ivermectin), whereas Khan and Ongerth (2004) recently used a fugacity-based mass balance model to study the fate of a large number of pharmaceuticals subject to sewage treatment.

In this study we used a modified version of the original Level III model by Mackay and Paterson (1991). The original Level III model is a generic fugacity-based non-equilibrium, steady-state multimedia mass balance model and includes four bulk environmental compartments; air, water, soil and sediment (Mackay and Paterson, 1991). Equilibrium is assumed to apply within each bulk compartment, but not between them. The model includes expressions for inter- and intramedia transport by diffusion and advection as well as degradation in all environmental media. Key input data to the model are parameters describing the characteristics of the environment, physical-chemical properties, and half-lives of the chemical in addition to emission rates (Mackay and Paterson, 1991). The model calculates concentrations in the four environmental media, rates of intermedia transport, advective flow and degradation rates, as well as an overall persistence value.

Common to the original Level III model and similar modeling tools are that they tend to rely on single-parameter linear free energy relationships (SP-LFERs) to predict equilibrium phase partitioning of chemicals in the environment. This SP-LFER-based approach has been criticized because no single parameter is able to provide an accurate description of the various molecular interactions that determine environmental phase partitioning processes (Goss and Schwarzenbach, 2001). Although SP-LFERs have been shown to work reasonably well for well-studied organic pollutants, many emerging contaminants, including most pharmaceuticals, have quite different partitioning characteristics from the ones for which the original SP-LFERs were derived. In response, Breivik and Wania (2003) modified the well-

known Level III model by Mackay and Paterson (1991) by implementing poly-parametric linear free energy relationships (PP-LFERs) to quantify equilibrium phase partitioning. They suggested that by utilizing this approach, multimedia fate models are better suited to address the fate of more polar organic chemicals. In particular, the PP-LFER based modeling approach is expected to provide more accurate descriptions of environmental phase partitioning and thus environmental fate (Breivik and Wania, 2003).

In the modified Level III model, the partitioning properties of chemicals are characterized by five linear free energy relationships (PP-LFERs), rather than SP-LFERs based on vapor pressure, water solubility, and the octanol-water partition coefficient (Breivik and Wania, 2003). For this purpose, the so-called solvation parameter model by Abraham (1993a) is applied;

$$\log SP = c + rR_2 + s\pi_2^H + a\sum\alpha_2^H + b\sum\beta_2^H + vV_x \qquad \text{[Eq.1]}$$

In Equation 1, SP represents the phase partition property. The equation includes various product terms that represent the contribution of individual intermolecular interactions to the overall partitioning. Specifically, the solute descriptors (R_2, π_2^H, $\sum\alpha_2^H$, $\sum\beta_2^H$ and V_x) represent the properties of the chemical and the system constants represent the media (c, r, s, a, b, v) as defined by the complementary interactions with the solute descriptors. The individual chemical solute descriptors needed as model input are: R_2: excess molar refraction ($cm^3/10$); π_2^H: dipolarity/polarizability; $\sum\alpha_2^H$: overall hydrogen-bond acidity; $\sum\beta_2^H$: overall hydrogen-bond basicity, and V_x: McGowan's characteristic volume or "cavity term" (cm^3 mol^{-1} 100^{-1}).

Regression equations based on the solvation parameter model exist for several environmentally relevant partition coefficients. Of key importance in this regard are the equations describing partitioning between water and air (Abraham et al. 1994a) as well as partitioning between organic carbon and water (Poole and Poole, 1999). No suitable regression currently exists for air-particle partitioning. As an interim solution, we previously assumed that the organic matter of atmospheric particles have the same partitioning properties as octanol (Breivik and Wania, 2003), making it possible to rely on the regression for the octanol-water partition coefficient (log K_{OW}) presented by Abraham et al. (1994b). From these three regressions, the following PP-LFERs for the fugacity capacities (in mol m^{-3} Pa^{-1}) of water, particulate organic carbon (POC) and octanol have been derived (Breivik and Wania, 2003):

$$\log Z_W = -0.99 + 0.58R_2 + 2.55\pi_2^H + 3.81\Sigma\alpha_2^H + 4.84\Sigma\beta_2^H - 0.87V_x - \log(RT) \quad \text{[Eq. 2]}$$

$$\log Z_{POC} = -0.78 + 1.32R_2 + 2.55\pi_2^H + 3.50\Sigma\alpha_2^H + 4.84\Sigma\beta_2^H - 2.27\Sigma\beta_2^0 + 1.22V_x - \log(RT) \quad \text{[Eq. 3]}$$

$$\log Z_O = -0.90 + 1.14R_2 + 1.50\pi_2^H + 3.84\Sigma\alpha_2^H + 1.38\Sigma\beta_2^H + 2.94V_x - \log(RT) \quad \text{[Eq. 4]}$$

In Equations 2-4, R is the universal gas constant (8.314 Pa m^3 mol^{-1} K^{-1}) and T is the environmental temperature (in K). Concentrations in various media are deduced by multiplying the polyparametric Z-value expressions (mol Pa^{-1} m^{-3}) with the calculated fugacities (Pa) of the corresponding media. It is important to note that the equation for Z_{poc} (Eq. 3) includes two overall hydrogen-bond basicity terms. The second term ($\Sigma\beta_2^0$) has been denoted "solute special overall hydrogen-bond basicity" and was introduced for certain groups of chemicals for which the hydrogen-bond basicity was found to change with the partitioning system being studied (Abraham, 1993b; 1996). The groups of chemicals for which $\Sigma\beta_2^0$ applies include certain sulfoxides, anilines, pyridines and some heterocyclic compounds (Abraham, 1996). For other chemicals, $\Sigma\beta_2^0$ is assumed to be equal to $\Sigma\beta_2^H$. For such chemicals, Equation 3 may be written as:

$$\log Z_{POC} = -0.78 + 1.32R_2 + 2.55\pi_2^H + 3.50\Sigma\alpha_2^H + 2.57\Sigma\beta_2^H + 1.22V_x - \log(RT) \quad \text{[Eq. 5]}$$

2.2 Model parameterization

Environmental parameters

The model was parameterized to reflect the environmental conditions of the Inner Oslofjord drainage basin, which is a densely populated region surrounding the capital of Norway. The drainage basin covers an area of about 1380 km^2, 14 % of which is taken up by the fairly enclosed water body of the Inner Oslofjord. Environmental properties and dimensions that were used in the model calculations are shown in Table 1. The site-specific input data were mainly derived from a dynamic multimedia fate model of the Inner Oslofjord (Breivik et al. 2004). Additional generic environmental input parameters, such as selected mass transfer coefficients, were adopted from the original Level III Model, as listed in Mackay (2001).

Physical-chemical properties

The pharmaceuticals to be studied were selected according to data availability and potential environmental relevance. The modified Level III model requires information on molecular mass, half-lives in individual environmental media, as well as solute descriptors of individual chemicals. Solute descriptors tend to be readily available for pharmaceuticals because of their use in evaluating transport properties of biological importance (e.g. Abraham and Chadha, 1996; Abraham et al. 2002; Abraham 2004). In contrast, data on vapor pressure, air-water partition coefficient or octanol-air partition coefficient, needed as input for SP-LFER-based modeling approaches, may often be difficult to obtain for pharmaceuticals, because these properties are of limited interest to the medicinal chemist and difficult to measure for these rather involatile substances. Solute descriptors, calculated using the method by Platts et al. (2000), were taken from Zhao et al. (2002). Data on half-lives in individual environmental media were estimated using the EPIWIN software (http://www.syrres.com/esc/).

The model is not capable of addressing substances that dissociate significantly at environmental pHs. This calls for a delineation of the boundaries of model applicability with respect to the degree of dissociation that may be tolerated. The relationship between pH, pK_A and degree of dissociation is given be the buffer equation:

$$pH = pK_A + \log[A^-/HA] \qquad \text{[Eq. 6]}$$

Here, we assumed that the model should not be used if more than 10% of a substance is dissociated ($A^-/HA>0.1$). For a soil pH of 4, this eliminates substances with a pK_A of less than 5. Similarly, for a typical seawater pH of 8, this excludes chemicals with a pK_A of less than 9. We emphasize that what may constitute an acceptable threshold is subjective and strongly depends on the desired degree of confidence in model outputs. The list of eleven selected pharmaceuticals, their molecular structure and their usage are presented in the Table 2. We chose pharmaceuticals, which are widely used, such as those producing effects on circulatory systems (e.g. antihypertensive, antiarrythmic) and hormones regulating functions of internal organs by stimulating and inhibiting biochemical processes (e.g. androgens, contraceptives) (Dębska et al. 2004). Data on molecular mass, solute descriptors, pK_A and environmental half-lives of selected pharmaceuticals are listed in Table 3.

Emissions

The actual emissions of selected pharmaceuticals in the Oslofjord drainage basin are not known. However, detailed statistics of the consumption of individual pharmaceuticals in various regions of Norway are available (Øydvin et al. 2000), and can provide an upper

boundary with respect to potential emissions. An accurate estimate of environmental release rates from consumption statistics of individual pharmaceuticals would require a detailed knowledge of metabolism and excretion rates, studies on the mode of emissions into the environment, and the fate of these compounds in sewage treatment systems within this region. Such detailed knowledge is currently lacking, but would be needed if predictions were to be compared directly with observed concentrations. For the purpose of direct comparability at this evaluative stage, we applied a similar emission rate and mode of release for all pharmaceuticals. Based on reported data for five of the selected pharmaceuticals (sotalol, atenolol, labetalol, verapamil and atropine), the average consumption rate within the drainage basin was estimated to range from ~0.03 kg $year^{-1}$ (atropine) to ~236 kg $year^{-1}$ (labetalol). For these calculations, we assume that only a limited fraction is released into the environment (~10%). This translates into an assumed emission rate of ~0.005 mol/h. For illustrative purposes, we furthermore assumed that 20 % (0.001 mol/h) enters the soil and 80 % (0.004 mol/h) enters the water compartment. Finally, we assumed that there is no inflow of pharmaceuticals from outside the model region.

3 Results and Discussion

Environmental distribution

In the Level III model, the environmental distribution is strongly affected by the mode by which a chemical is released (Mackay and Paterson, 1991). In this evaluative scenario, 80% of the total emissions are released to water and the remainder is released to soils. Results of the predicted environmental distribution (in % at steady-state) are shown in Table 4. The model calculations show that all studied pharmaceuticals tend to mostly remain in the water and soil compartments. The percentage in the water compartment at steady-state of three of the investigated pharmaceuticals (atenolol > sotalol > nadolol) is predicted to exceed 80%. Because the estimated degradation rate constants for these substances are the same in water and soil, this must be due to transfer from soil to water. These are therefore the pharmaceuticals that should be most susceptible to leaching and run-off. They are predicted to have the lowest partitioning coefficient between water and organic carbon (log K_{OC} < 2.2, see Table 3) among the 11 substances. All other pharmaceuticals with higher K_{OC}-values (2.5-4.7) are predicted to be present in soils in excess of 20%, with less than 80% in the water compartment. As there is again no difference in the estimated degradation rate constants and no transport pathway from water to soil (other than through the atmosphere), this must be due

to transfer of chemical to the sediments. Overall, the water compartment is suggested to be the key environmental reservoir of pharmaceuticals, containing more than 50% of the amount at steady-state. In general, bulk water concentrations on the order of $1 \cdot 10^{-9}$ mol·m^{-3} (verapamil) down to $2 \cdot 10^{-10}$ mol·m^{-3} are predicted (Table 4). Still, bulk water concentrations are suggested to be lower than bulk soil and bulk sediment concentrations.

Only a few of the selected pharmaceuticals are predicted to achieve a significant percentage (> 2.5%) in the sediment compartments (verapamil > progesterone > ethinylestradiol). These are pharmaceuticals that tend to combine a sufficiently long half-life in sediment (Table 3) and elevated sorption to organic carbon (log K_{OC} > 3.8). In contrast to the other pharmaceuticals, these three compounds are also predicted to achieve higher bulk concentrations in sediments than the soil compartment (Table 4).

Finally, it should be emphasized that the atmosphere is, as expected, of no significance in controlling the environmental distribution of the selected chemicals. Significant emissions into air seem unlikely, and very low air-water partition coefficients (log K_{AW} < -8 for all pharmaceuticals, see Table 3) exclude the possibility of significant evaporation from water.

Mechanisms affecting phase partitioning

Unlike the SP-LFER based approach to phase partitioning, the PP-LFER based approach facilitates mechanistic insights into the various interactions that influence the environmental distribution of pharmaceuticals. Partitioning into the gas phase can be neglected, and the partitioning in the remaining compartments of the environment is thus controlled by the distribution between organic carbon and water. The original equation derived for this partitioning equilibrium is given by (Poole and Poole, 1999):

$$\log K_{OC} = 0.21 + 0.74R_2 - 0.31\Sigma\alpha_2^H - 2.27\Sigma\beta_2^0 + 2.09V_x \qquad \text{[Eq. 7]}$$

It should be noted that the π_2^H term was not significant and was therefore omitted from this equation. This indicates that the propensity for dipolar-type interactions is equal in both phases and therefore cancels. The various product terms (i.e. the contribution of a specific intermolecular interaction) that contribute to the overall partitioning processes are plotted for individual pharmaceuticals in Figure 1. Positive numbers indicate that the product term favors OC (at the expense of water), while negative numbers highlight an interaction processes in favor of water (at the expense of OC). From Figure 1 it becomes clear that it is the hydrogen-bond basicity term that is the predominant interaction process that leads to

affinity for the water phase, and that it is the so-called cavity term that is the most significant product term favoring OC. It is therefore evident that the pharmaceuticals that end up in the water compartment in higher amounts (e.g. atenolol, sotalol, nadolol), tend to be characterized both by elevated hydrogen-bond basicity as well as limited solute size. On the other hand, pharmaceuticals that are found in higher amounts in soils and to some extent sediments tend to have product terms reflecting comparatively elevated solute size but limited hydrogen-bond basicity (e.g. verapamil).

Key processes controlling environmental fate

The concerted action of partitioning, transport and transformation controls the fate of organic chemicals in the model environment. Figure 2 presents a schematic representation of the main processes for two different pharmaceuticals. Relatively few processes are of significance in controlling the overall fate of these pharmaceuticals. Figure 2 thus provides useful guidance on which processes needs to be determined with greater accuracy if our understanding of the environmental fate of such pharmaceuticals is to be improved. Generally environmental degradation is the most important loss process. Overall, degradation accounts for between 93.5% (propranolol – Figure 2a) and 61.5% (verapamil - Figure 2b) of the total losses. Reflecting the media distribution discussed above, degradation in the water compartment contributes most to the total amount degraded. The results thus suggest that accurate quantitative information on environmental half-lives in water (and to some extent soil and sediments) are essential if reliable predictions of environmental fate are to be obtained (see e.g. Boreen et al. 2003). Advection by seawater could also be a significant loss process in spite of the fairly long residence time of water in the Inner Oslofjord (~8 months) accounting for between 6.5% (propranolol) and 35.0% (verapamil). For advection to be of significance in this particular environment, a sufficient lifetime of the chemical in the aquatic compartment is required. Other loss processes (sediment burial, leaching to groundwater) turn out to be of limited importance in terms of overall environmental fate in this particular case (<1% with the exception of verapamil). However, we note that the potential for leaching of pharmaceuticals is an issue of general interest in terms of groundwater protection (e.g. Webb et al. 2003; Oppel et al. 2004).

Overall persistence

Environmental persistence is an important criterion when assessing chemical contaminants (e.g. Webster et al. 1998; OECD, 2004). Typically, persistence is evaluated in terms of individual half-lives in four environmental media (air, surface water, soil and sediment), or as an overall environmental persistence (or residence time) calculated by a multimedia fate model (Webster et al. 1998). The overall environmental persistence may be predicted as the total amount of chemical in the environment at steady state divided by the total loss rate. It should be emphasized that the overall persistence is usually a strong function of the mode of chemical entry to the environment in cases for which the half-lives are different between compartments. For our selected pharmaceuticals, the calculated overall persistence ranges from 20 days (sotalol, propranolol) up to 159 days (verapamil) (Table 4). The total loss rate is dominated by reactive losses, rather than advective losses for all investigated pharmaceuticals in this particular environment (slow water exchange rates). However, different environmental conditions could easily change the relative importance of these two key loss processes (e.g. within a river environment).

Discussion

The results presented here illustrate that the PP-LFER based Level III model may be a useful tool to assess the environmental fate of pharmaceuticals, as an integrated part of an environmental risk assessment process. This model can provide useful information on approximate concentrations in various environmental media from defined emission rates. The model is capable of identifying as well as quantifying the dominant media of accumulation and the intermedia transport characteristics. Partitioning processes of importance are those between OC and water, because they determine; (1) the potential for transport from water to sediment, (2) the potential for transport from soil to water, and (3) the potential for leaching to groundwater. The PP-LFER based approach further illustrates that the smaller the molecule and the higher its hydrogen basicity, the higher its environmental mobility is likely to be.

Although the present model predictions have not been evaluated (or "verified") against observations, the PP-LFER based expressions are generally found to provide more accurate descriptions of environmental phase partitioning as compared to the SP-LFER based approach (e.g. Poole and Poole, 1999; Goss and Schwarzenbach 2001; Breivik and Wania, 2003). It follows that the confidence in model outputs should not be less than the original

Level III model. The PP-LFER based approach is also favored by the fact that the LSER solute descriptors for many pharmaceuticals have already been established. A worthwhile effort would be to evaluate how well the LSER for K_{OC} by Poole and Poole (1999) indeed describes measured K_{OC}-values for pharmaceuticals. We suggest that it may be misguided to spend major efforts in determining experimentally the "classical" physical chemical properties for most pharmaceutical substances, such as those describing partitioning between air, water and octanol (K_{OW}, $K_{AW,}$ K_{OA}), and vapor pressure (p_L). Furthermore, it may also be a challenge to experimentally determine accurate partitioning processes related to air, caused by the negligible vapor pressures exhibited by many pharmaceuticals. Whereas the precise values of K_{AW}, K_{OA} and p_L appear to be of little relevance for the environmental fate of these substances, K_{OC} and potentially important surface sorption coefficients (Roth et al. 2002) are better estimated with PP-LFERs than by SP-LFERs based on K_{OW}. Although the use of PP-LFERs is generally thought to be superior to the use of SP-LFER, the numerical values of the solute descriptors for complex molecules may depend on the molecular conformation in a specific solvent. For example, a study by Bürgi and Baiker (1998) has shown that the molecular conformation of cinchonidine can depend on solvent polarity.

The model results presented here show that many pharmaceuticals are not really multimedia pollutants, but rather tend to stay in the medium of emission (water or soil) where their rate of degradation is a primary fate process. Therefore, water quality models, such as GREAT-ER (e.g. Schowanek and Webb, 2002), seems to be particularly suited to describe the environmental fate of pharmaceuticals. We suggest that if measured K_{OC} values for such models are not available, PP-LFER equations are likely to be preferable to estimation methods based on K_{OW}.

Another benefit of the PP-LFER based multimedia model is that it is also capable of addressing the classical non-polar organic contaminants for which the original Level III model was developed. Therefore, both polar and non-polar organic contaminants may thus be evaluated using the same modeling tool. As pointed out by Breivik and Wania (2003), obstacles to the full implementation of the PP-LFER based approach still exist. The lack of PP-LFERs for expressing partitioning to aerosols appears to be of no consequence when simulating pharmaceuticals, because of the negligible role the atmosphere plays in their overall fate. One particular issue that needs further investigation is how variable environmental conditions (e.g. temperature) may be accounted for. According to Abraham et

al. (1999), solute descriptors are regarded as insensitive to temperature changes, whereas the system constants are affected by temperature fluctuations.

Model availability

The model presented herein is available free of charge via the internet at http://www.utsc.utoronto.ca/~wania.

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Table 1. Environmental input parameters.

Environmental dimensions and properties				
	Air	Water	Soil	Sediment
Area (m^2)	$1.38 \cdot 10^9$	$1.93 \cdot 10^8$		
Depth (m)	1500	48.2	0.1	0.05
Fraction organic carbon (g g^{-1})		0.2 [A]	0.02 [A]	0.04 [B]
Density (kg m^{-3})	1.19	1000 [C] 2120 [D]	2372 [D]	2344 [D]
Advective flow (m^3 h^{-1})	$8.5 \cdot 10^{11}$	$1.7 \cdot 10^6$		
Temperature (˚C)	25	25	25	25

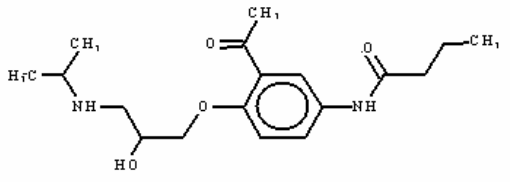
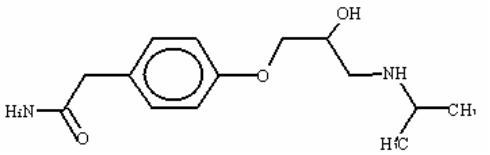
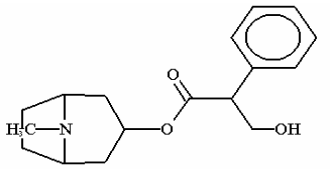
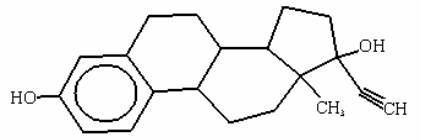
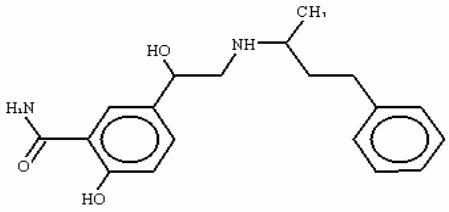
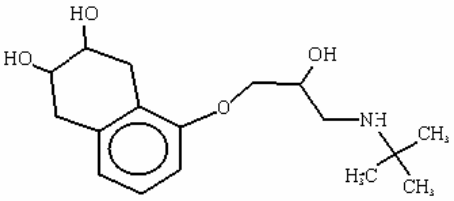
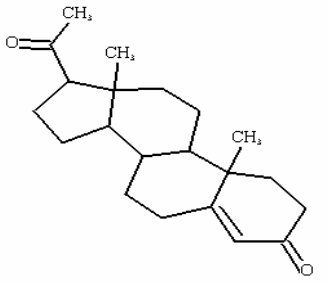
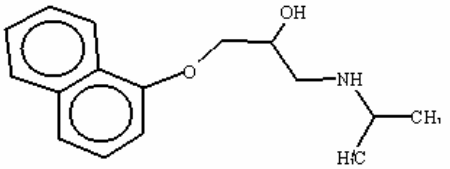
Volume fractions and scavenging ratio (-)			
Aerosols in air	$5 \cdot 10^{-12}$	Water in sediment	0.86
Air in soil	0.2	Particles in water	$2 \cdot 10^{-6}$
Water in soil	0.3	Scavenging ratio	68000

Mass transfer coefficients (m h^{-1})			
Air-water diffusion (air-side mtc)	5	Sediment-water diffusion mtc	$1 \cdot 10^{-4}$
Air-water diffusion (water-side mtc)	0.05	Sediment deposition rate	$4.6 \cdot 10^{-7}$
Soil-air diffusion (boundary-layer mtc)	5	Sediment re-suspension rate	$1.4 \cdot 10^{-7}$
Soil-air diffusion (air-phase mtc)	0.02	Sediment burial rate	$3.4 \cdot 10^{-7}$
Soil-air diffusion (water-phase mtc)	$1 \cdot 10^{-5}$	Soil water runoff	$7 \cdot 10^{-5}$
Dry deposition velocity	1.03	Soil solids runoff	$4 \cdot 10^{-10}$
Rain rate	$8.15 \cdot 10^{-5}$	Leaching to groundwater	$4 \cdot 10^{-6}$
Transfer rate to stratosphere	0		

Properties of atmospheric particles and phase densities			
Volume fraction OC on particles (-)	0.1	Density of mineral matter (kg m^{-3})	2400
Density of octanol (kg m^{-3})	820	Density of organic matter (kg m^{-3})	1000

[A] Solids in compartment, [B] The same value is assumed to apply for re-suspended sediment particles as for sediment solids, [C] pure water, [D] For bulk solids (*consisting only of mineral matter and organic carbon*) in these compartments, densities are calculated from the volume fraction of organic carbon as well as densities of mineral matter and organic carbon.

Table 2 Usage and chemical structure of modeled pharmaceuticals.

Name	Usage	Chemical structure
acebutolol	antihypertensive, antianginal, antiarrythmic	
atenolol	antihypertensive, antianginal, antiarrythmic	
atropine	anticholinergic, antispasmodic, antidote to organophosphous insecticides	
ethinylestradiol	oral contraceptive	
labetalol	antihypertensive	
nadolol	antihypertensive, antiarrythmic	
progesterone	to control habitual abortion, to suppress or synchronize estrus	
propranolol	antihypertensive, antianginal, antiarrythmic	

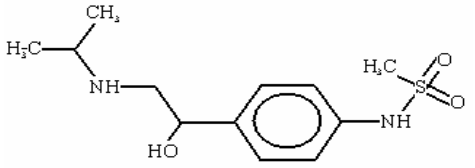
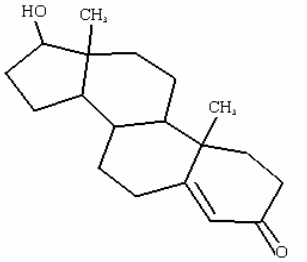
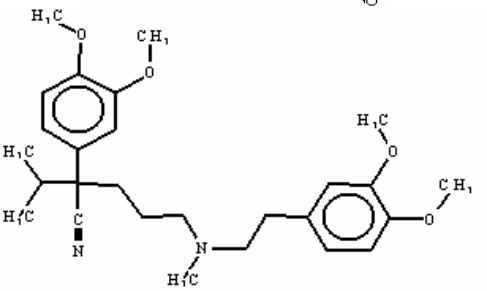
sotalol	antianginal, antiarrythmic, antihypertensive	
testosterone	androgen	
verapamil	antianginal, antiarrythmic	

Table 3 Molecular weight (g mol^{-1}), pKa, solute descriptors and environmental half-lives of selected pharmaceuticals.

			Solute descriptors [C]					Half lives (days) [D]				Calculated	
Chemical	MW [A]	pKa [B]	R_2	π_2^H	$\sum\alpha_2^H$	$\sum\beta_2^H$	V_x	Air	Water	Soil	Sediment	log K_{OC} [E]	log K_{AW} [F]
Acebutolol	336.4	9.2	1.6	2.4	0.58	1.97	2.76	0.09	38	38	150	2.51	-15.40
Atenolol	266.3	9.2	1.45	1.89	0.55	1.75	2.18	0.08	38	38	150	1.70	-13.34
Atropine	289.4	9.9	1.44	1.71	0.35	1.48	2.28	0.18	38	38	150	2.57	-10.72
Ethinylestradiol	296.4	10.6	2.12	2.5	0.97	1.16	2.39	0.09	60	60	240	3.84	-13.85
Labetalol	328.4	9	2.2	2.13	0.77	1.62	2.64	0.07	38	38	150	3.44	-14.20
Nadolol	309.4	9.5	1.61	1.63	0.7	1.88	2.49	0.06	38	38	150	2.12	-13.70
Progesterone	314.5	19.3	1.58	2.47	0	1.16	2.62	0.09	60	60	240	4.22	-9.56
Propranolol	259.4	9.4	1.85	1.36	0.1	1.29	2.15	0.03	15	15	60	3.11	-8.31
Sotalol	272.4	9.4	1.54	1.98	0.74	1.74	2.1	0.07	15	15	60	1.56	-14.37
Testosterone	288.4	16.2	1.61	2.32	0.35	1.13	2.38	0.09	38	38	150	3.70	-10.59
Verapamil	454.6	9	1.7	2.48	0	2.07	3.79	0.06	150	150	600	4.69	-13.04

[A] Budavari et al. (1989), [B] Jones et al. (2002), ACD/pKa DB vs. Experiment., Pallas 3.1.1.2, Hilal et al. (1996), EPIWIN software database (http://www.syrres.com/esc/), [C] Zhao et al. (2002), [D] Calculated using EPIWIN software (http://www.syrres.com/esc/), [E] Calculated phase equilibrium between organic carbon and water (log K_{OC}) from solute descriptors, according to Poole and Poole (1999). [F] Calculated phase equilibrium between air and water (log K_{AW}) from solute descriptors, according to Abraham et al. (1994a).

Table 4 Selected model results.

			Percentage in individual compartments of total amount				Bulk concentration in individual compartments [mol/m^3]			
Chemical	Overall persistence [days]	Total amount [mol]	Air	Water	Soil	Sediments	Air	Water	Soil	Sediments
Acebutolol	46	5.53	0	78.8	20.9	0.3	5.8E-30	4.7E-10	9.8E-09	1.6E-09
Atenolol	45	5.44	0	85.5	14.4	0.1	2.4E-28	5.0E-10	6.6E-09	6.6E-10
Atropine	46	5.54	0	78.5	21.2	0.3	7.9E-25	4.7E-10	9.9E-09	1.8E-09
Ethinylestradiol	70	8.41	0	72.8	24.5	2.7	1.2E-27	6.6E-10	1.7E-08	2.4E-08
Labetalol	47	5.6	0	76.1	22.9	1.0	3.9E-28	4.6E-10	1.1E-08	6.2E-09
Nadolol	46	5.5	0	81.4	18.4	0.2	7.2E-28	4.8E-10	8.5E-09	9.9E-10
Progesterone	72	8.64	0	70.3	24.0	5.7	5.5E-23	6.6E-10	1.7E-08	5.2E-08
Propranolol	20	2.44	0	78.6	21.0	0.4	3.5E-22	2.1E-10	4.3E-09	9.6E-10
Sotalol	20	2.41	0	83.8	16.1	0.1	6.8E-30	2.2E-10	3.3E-09	2.2E-10
Testosterone	47	5.63	0	75.5	22.9	1.6	1.6E-24	4.6E-10	1.1E-08	9.7E-09
Verapamil	159	19.09	0	53.8	27.1	19.1	1.1E-25	1.1E-09	4.4E-08	3.8E-07

Figure captions

Figure 1. Product terms (or specific intermolecular processes) affecting phase partitioning between organic carbon and water for selected pharmaceuticals (sorted by increasing log K_{OC} from top to bottom).

Figure 2. Model results for a) nadolol; b) verapamil (results are scaled according to total emissions).

Figure 1

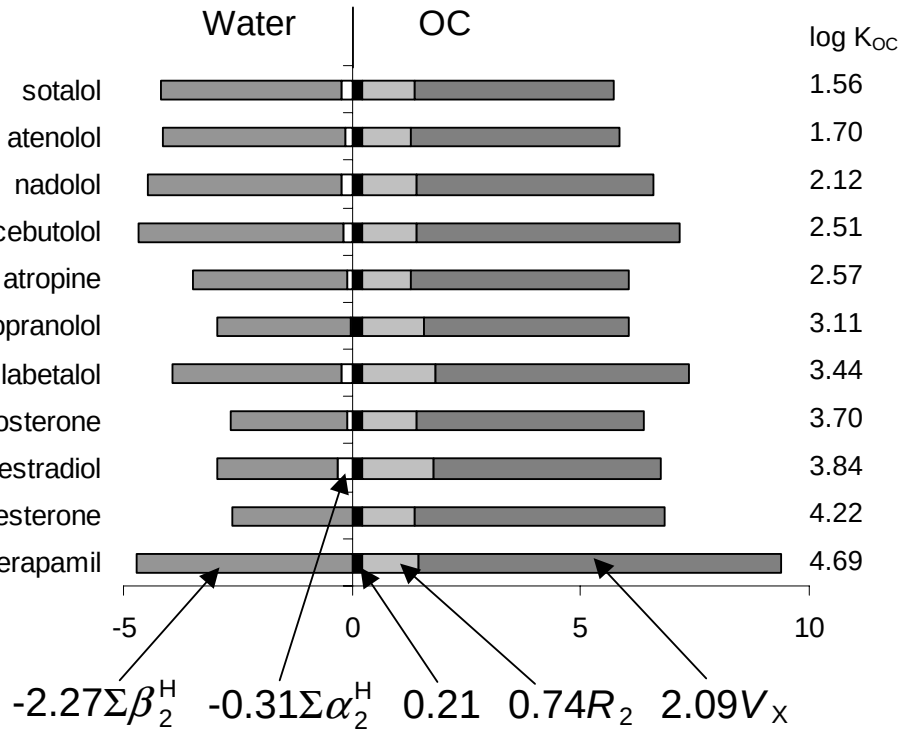
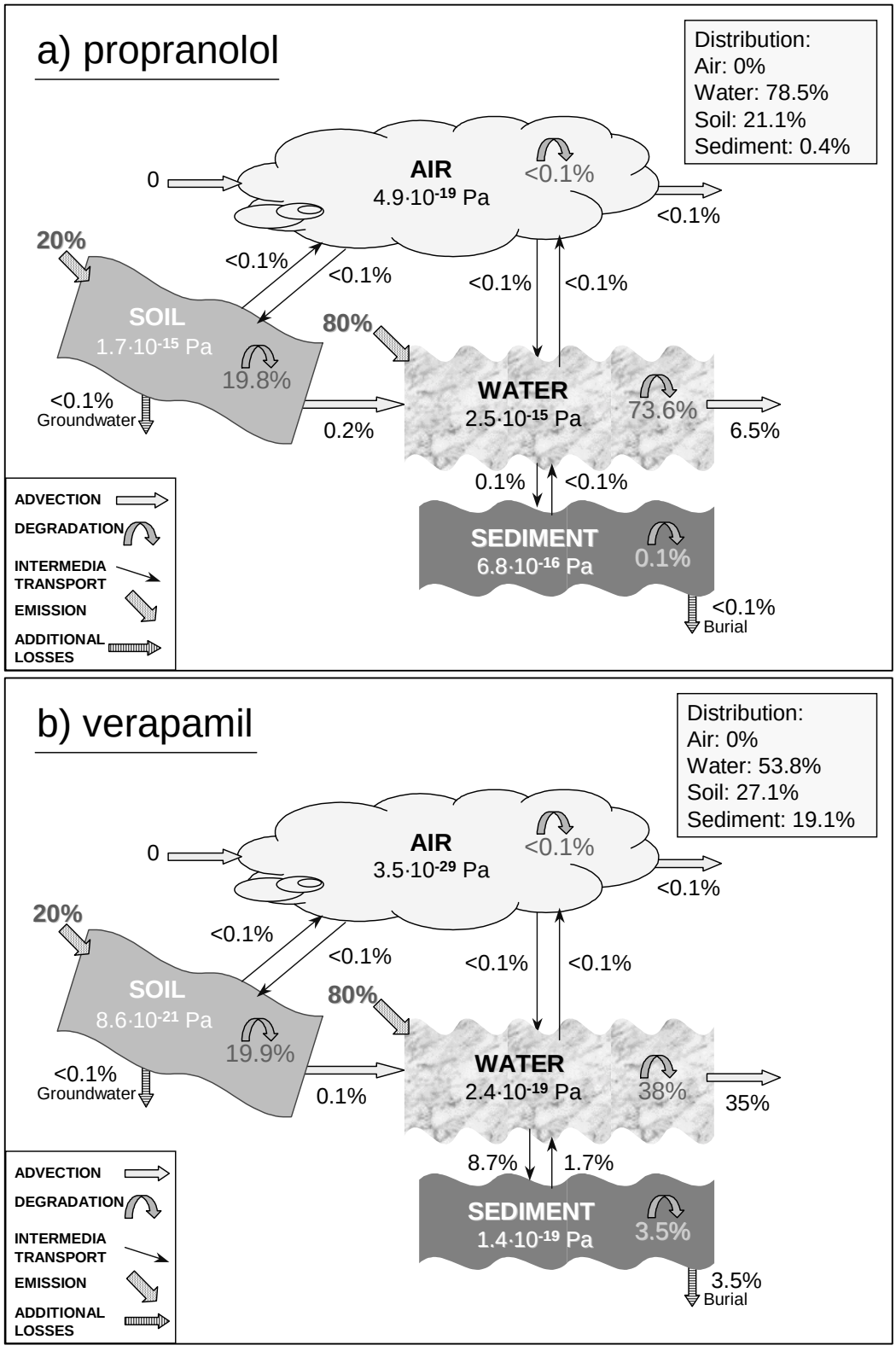


Figure 2



*** Responses to Reviewers' Comments**

Editor-in-Chief J.O. Nriagu,
Department of Environmental Health Sciences,
School of Public Health, University of Michigan, 109 S.
Observatory Street, Ann Arbor,
MI 48109-2029,
USA.

Kjeller, 2004-05-29.

Dear Prof. Nriagu,

Thank you for considering our manuscript (STOTEN-D-04-00554) for publication. Below you will find our detailed response to the specific concerns addressed by the reviewers.

Best wishes,
Knut Breivik.

Reviewers' comments:

Reviewer #1:

Manuscript illustrates the applicability of multi-media models for evaluating the environmental fate of pharmaceuticals using peviously derived linear free energy relationships (LFERs) based on the Abraham solvation parameter model. Many previous studies have shown that the Abraham model is able to correlate experimental for many different types of partitioning processes. Based on my experience with the Abraham model I would expect the model to accurately predict the partitioning behavior of pharmaceutical compounds, however, I would be very careful in applying the model to molecules that might have different molecular conformations in different solvent media. Pharmaceutical molecules are fairly complex, and there are a number of published papers (for example there is a published NMR and computational study in JACS in 1998 involving cinchonidine) that show molecular conformation can depend on solvent polarity. In the cinchonidine study, the molecule is reported to have three conformations (two closed conformations and an open conformation), with the open conformation being more stable in protic solvents. (The exact reference can be found using Scifinder Scholar - chemical search - cinchonidine - and then looking at the references that appear when one checks the properties box.) The numerical values of the solute descriptors in the Abraham model undoubtedly will depend on the molecular conformation.

Two sentences added on page 11 in response to this general concern.

The paper is well written, and easy to follow. The authors' proposed calculational methodology and conclusions reached are logical. It is difficult for me to assess how valuable the model will be, as there is no actual experimental data to compare the predictions against. (See page 10 - first and second paragraphs under Discussion section) Like all models proposed in the past, if the predictions and experimental data are found at some later date to be in agreement, then the authors' proposed model will be of enormous benefit. If, however, the predicted and experimental values differ signficantly, then someone else will come along with another proposed model.

No response required.

My recommendation is that the manuscript be accepted for publication. Although there are no experimental values to compare the predictions against, as the authors note several times in the manuscript, the Abraham solvation parameter model that they are using to estimate the input values needed in the environmental modelling is better at estimating partition coefficients than the single-parameter LFERs that others are currently using.

No response required.

Reviewer #4:

The authors use a methodology previously published to model pharmaceuticals. The adopted methodology is claimed to be superior to the previous one: SP-LFERs particularly in case of more polar organic compounds.
This reduces the novelty of the manuscript: it is a demonstration of a previous method, applied here to pharmaceuticals. Unfortunately, as common in this case of studies, the predicted behavior is not supported by actual measurements, so that the superiority of one method or another cannot be supported by real data.

No response required.

The authors should better describe the theoretical advantages of the proposed methodology compared to other approaches, both on a general point of view (SP- vs PP-LFER)

The theoretical advantages of PP-LFERs are extensively described in the literature we specifically refer to and build upon (e.g. papers by Abraham and coworkers, Goss and coworkers, Poole and Poole etc). We think it would be a waste of space to repeat these features in this paper, as a key objective of the paper is to expand on the applicability of the PP-LFER multimedia model concept as exemplified for pharmaceuticals. In addition, these advantages are extensively described in our first paper on PP-LFER based multimedia modelling, when this concept was first introduced (Breivik and Wania, 2003), see e.g. page 4, lines 4-6 in this manuscript.
No changes.

and on a specific point of view of the pollutants studied: pharmaceuticals. E.g. which values are predicted using other methods, and why the values obtained by the

proposed methods are more credible? Which role have the parameters introduced in the proposed equation? This part is addressed in the section "Mechanisms affecting phase partitioning": a further discussion comparing previous methods can be useful.

The theoretical and practical advantages for pharmaceuticals are already extensively described in the paper, for example:
Page 3, 2nd last line and further: pharmaceuticals tend to have different partitioning characteristics from the ones for which the original SP-LFERs were derived (e.g. more polar).
Page 6, lines 6-10: no need for experimental determination of the physical-chemical properties related to air partitioning for involatile pharmaceuticals (as is required for most other SP-LFER based environmental fate models).
Page 8, lines 18: it provides mechanistic insights into the environmental fate of pharmaceuticals.

The second point is now emphasised with an additional sentence on page 11, line 7-9.

To the latter point (comparing previous methods, i.e. PP-LFER vs SP-LFER), this was extensively discussed in our first paper (Breivik and Wania, 2003) and we feel it is redundant to repeat this analysis and discussion in this paper.

The comparison should involve the easiness to obtain the new requested parameters.

The availability of solute descriptors for pharmaceuticals is listed as exemplified with 3 key references on page 6, lines 4-6 to support the interested reader. It is furthermore mentioned (on page 6, line 10) that the solute descriptors may be calculated by the methods proposed by Platts et al (2000). No changes.

Revised version with changes highlighted (word editing tools)

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