Environmental Exposure Assessment of Ionisable Organic Compounds

Technical Report No. 123

EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS

Environmental Exposure Assessment of Ionisable Organic Compounds

Technical Report No. 123

Brussels, December 2013

ISSN-0773-8072-123 (print)

ISSN-2079-1526-123 (online)

ECETOC Technical Report No. 123

European Centre for Ecotoxicology and Toxicology of Chemicals
2 Avenue E. Van Nieuwenhuyse (Bte 8), B-1160 Brussels, Belgium.

Environmental Exposure Assessment of Ionisable Organic Compounds

CONTENTS

SUMMARY

This report seeks to improve the capability to estimate the bioavailability of ionisable organic compounds, and explores how this information could be used to derive more accurate environmental concentrations for use in assessing environmental risk. The report provides guidance on the analytical methods needed to measure key substance property data with respect to their applicability to ionisable compounds. Existing standard methods to determine acidity, partitioning and sorption were not always appropriate for ionisable compounds, while the methods for hydrolysis and biodegradation could be used for ionisable compounds without limitations. The report also reviews tools (computational methods) used to estimate those data. Some of the estimates based on quantitative structure activity relationships were more accurate when compared to a quality-assured database of 81 active pharmaceutical ingredients, compiled for the purpose.

Additionally, an investigation was made of the use of multimedia models to predict the environmental concentration of an ionisable organic compound. It is demonstrated how, at a low-tier (pre-screening) level, environmental behaviour can be assessed beginning with an evaluation of the 'chemical space' of the equilibrium partitioning of ionisable organic compounds at different acidities (pH values).

There remains a paucity of data directed at improving the mechanistic understanding of sorption, which is critical for improving the understanding of bioavailability and potential for bioconcentration and bioaccumulation. It would thus be prudent to focus future research needs on the development of improved mechanistic understanding. Comparable experiences and needs pertaining to the environmental fate and behaviour of ionisable organic compounds have been encountered by the agrochemicals industry, as summarised in an additional chapter of this report.

In summary, the Task Force recommends that the environmental risk assessment of ionisable organic compounds emphasise a need for projecting robust and reliable estimates and/or measurements of bioavailability. Specifically:

- Testing strategies, particularly those aimed at quantifying the octanol-water partition coefficient K_{OW}, distribution ratio D_{OW} and octanol-carbon partition coefficient K_{OC}, need to ensure that they account for the potential for ionisation during the test, and the implications of ionisation with respect to modelling $Clocal_{water}$ within the EU TGD framework are appropriately captured.
- With regard to analytical methods, the finalisation of OECD test guideline 122 for measuring the acid dissociation (pK_a), K_{OW} and D_{OW} is encouraged.
- The use of quantitative structure activity relationships to estimate K_{OW}, D_{OW}, and K_{OC} need to be checked for their applicability towards the chemical under investigation. Based on observations from data scrutinised within this report, greater confidence in estimation methods appears to be warranted for acids than for bases.
- It is recommended that users compare output from more than one estimation method, for instance between SPARC and ACD with respect to estimates of D_{OW}.
- There is a need for a wider debate regarding the relevance of regulatory triggers, such as K_{OW}, in screening ionisable organic chemicals for their potential to be persistent and bioaccumulative.
- Are there surrogates, other than octanol, that could be better used as a metric for bioaccumulation.

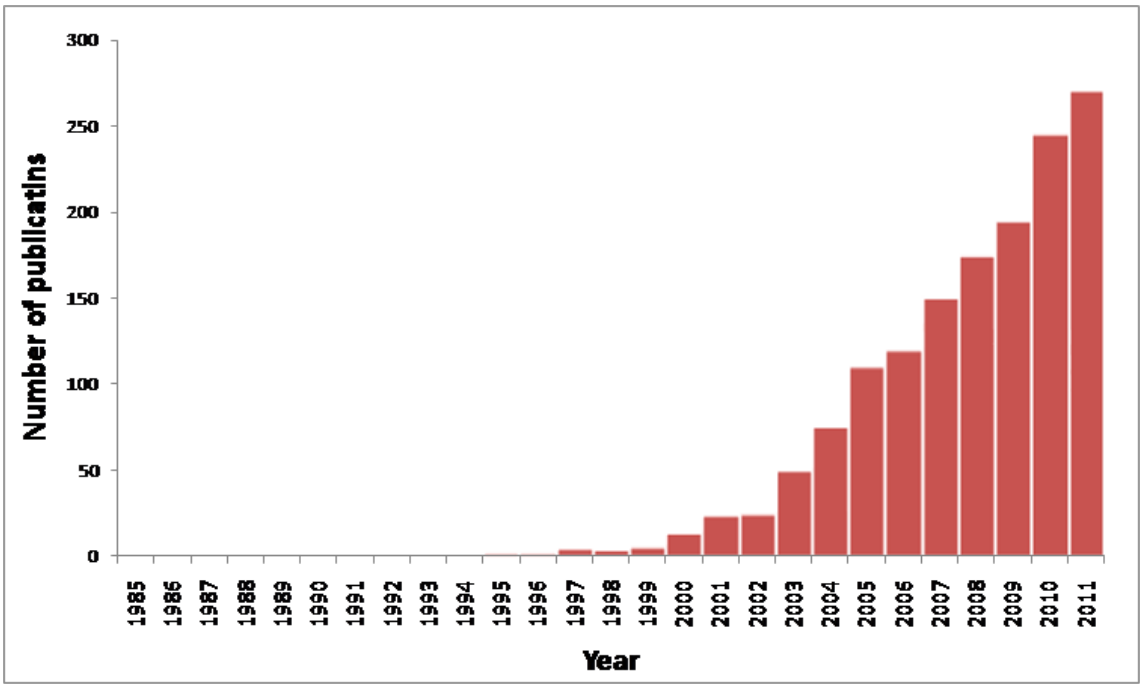
Given the recent interest in ionisable organic compounds, such as those used as APIs, it is of great importance to improve mechanistic understanding of their sorption to various environmental matrices. Research is thus needed to transition the current understanding, which is largely based on interactions associated with neutral organic compounds with organic carbon, to an improved framework for assessing the electronic interactions of a charged molecule with charged solid surfaces. In particular:

- Encourage updates to environmental risk assessment tools, such as SimpleBox and SimpleTreat, to better project concentrations of ionisable organic compounds.
- To complement knowledge gained towards an improved assessment of exposure, there is a need to encourage support to address the relevance of ecotoxicological testing strategies for ionisable organic compounds.

1. INTRODUCTION

The presence of active pharmaceutical ingredients (APIs) in the environment is not an area of new research. As far back as 1985, a review of the fate of pharmaceutical chemicals in the environment raised many of the issues that are still of concern today (Richardson and Bowron, 1985). It then took a decade, until field observations were made that sufficiently demonstrated an ecotoxicological effect on whole populations of fish following exposure to APIs (Harries et al, 1996, 1997), that research in this area began to grow. The trend is illustrated by results from a search of the literature on 'pharmaceuticals' and 'environment' for articles published in journals with an environmental focus (Figure 1).

Figure 1: Increase in number of environmental articles on APIs published from 1985 to 2011 [a]



[a] Results from the ISI Web of Science search engine using the terms 'pharmaceutical' and 'environment'.

Although it is not an exhaustive search, Figure 1 does demonstrate that there has been a significant growth of research in this area beginning in the late 1990's. For the first time pharmacologically active substances had been shown to have a significant, long lasting environmental effect. Perhaps the most seminal initial study was conducted on behalf of the US Geological Survey, involving a nation-wide reconnaissance of rivers and streams. The authors were able to detect APIs, hormones and other organic wastewater contaminants in 80% of the 139 locations investigated, causing widespread public debate (Kolpin et al, 2002).

A review of the removal of pharmaceuticals and personal care products (PPCPs) during wastewater treatment showed a large variation among removal efficiencies of the contaminants. The authors assumed that this was due to the different molecular structures of the APIs (even within the same class of compounds), but also to the large variability of a number of factors within the wastewater treatment process itself. In particular, treatment plant configuration, hydraulic residence time, sludge residence time, co-

contaminant presence, and temperature could all have an effect on compound removal to some extent (Onesios et al, 2009). Nevertheless, a further study on wastewater treatment of more than 100 micropollutants, including a number of APIs, indicated that secondary biological processes were significantly more effective at removing micropollutants than primary settling processes. For activated sludge processes, the authors reported > 50% removal for 70% of the micropollutants analysed. Membrane bioreactors and tertiary treatment were able to raise micropollutant removal rates still further (Choubert et al, 2011). Improved understanding of the fate of these APIs, the majority (up to 85%) of which are ionisable organic compounds (Manallack, 2009; Section 1.1), in wastewater treatment systems is thus an important component towards producing a more reliable environmental risk assessment (ERA) in each case.

The release of 'ionisable compounds' (where behaviour depends on pH, ionic strength, etc.), such as APIs, into the environment presents the risk assessor with particular problems. The Scientific Committee, therefore, agreed terms of reference and established a task force to examine the various parameters that might influence the environmental fate of ionisable (organic) compounds and provide guidance on how the ERA could be improved. Members of the Scientific Committee are stated at the end of the report.

1.1 Terms of Reference

The aim of the task force was to review the current understanding and available literature on partitioning property data of ionisable compounds at environmental relevant pHs, including estimation methods for these properties in case measured data are lacking, and that should lead to better predictions of the environmental concentration and bioavailability of ionisable compounds in aquatic environments. Members of the task force are given at the end of the report. The group adhered to the following terms of reference in compiling this report.

- Conduct a literature review to identify the availability of partitioning property data for ionisable compounds, specifically the acid dissociation constant pK_a, octanol-water partition coefficient K_{OW}, octanol-water distribution ratio D_{OW}, organic carbon-water partition coefficient K_{OC}, and adsorption desorption distribution coefficient K_d. Additionally, in the absence of good quality data, there will be a need to estimate these partitioning properties. Consequently, a review, summarising the various estimation methods available and their range of applicability, is required.
- Provide guidance on how to better estimate the predicted environmental concentration (PEC) of ionisable compounds in aquatic environments based on the relationship between pH, pK_a, and their partitioning properties.
- Make recommendations regarding what pH and soil properties are most useful for accurately predicting environmental concentrations, i.e. it may be possible to define a generic model environment for use in a predictive ERA. It may also be possible to advise the most appropriate testing conditions.
- Identify the key parameters needed to better predict the bioavailability of ionisable compounds.
- Determine how information obtained through improved estimates of PEC might be used to assess the aquatic risk of ionisable compounds. If possible, identify the key factors and relationships between bioavailability, and ecotoxicity that would improve the ERA of ionisable compounds.

1.2 Additional Considerations

It should be noted that the fundamental principles underlying an ERA of industrial chemicals have been primarily developed on the basis of an understanding of the environmental fate and behaviour of neutral compounds, which assumes generic exposure pathways and generic toxicological modes of action, such as non-polar narcotic, polar narcotic, and reactive. This is how ERA has been conducted in the EU for both 'new' and 'existing' substances (ECETOC, 2003a; Tarazona et al, 2009; Franco et al, 2010; Rayne and Forest, 2010). Consequently, the domain of applicability, with respect to the physical and chemical space defined for the tools, models, and regressions used to perform a traditional ERA, is thus likely to be limited, and not necessarily appropriate for chemical substances that are ionised at environmentally relevant pH. Indeed, Franco et al (2010) suggested that a significant fraction of industrial chemical substances that have been 'pre-registered' at the European Chemical Agency (ECHA) likely consist of ionisable organic chemicals. Nevertheless, it should be possible to apply the principles of a traditional ERA, whereby the 'risk characterisation' ratio (RCR), of the predicted environmental concentration (PEC) and the predicted no effect concentration (PNEC), being the < 1 is indicative of the absence of risk. Details on how to derive PECs and PNECs are given by the EC (1996, 2003) in its technical guidance document (TGD) and the books of van Leeuwen and Hermens (1995) and van Leeuwen and Vermeire (2007). Challenges arise, however, when estimating PECs and PNECs for chemicals that are ionised at environmentally relevant pH. The TGD, for instance, suggests that the water solubility of the ionised species can be orders of magnitude higher than the neutral form, and consequently recommends that input parameters, such as K_{OW}, Henry's Law constant, and the sorption coefficients for soil, sediment and suspended solids need to be corrected in order to account for the fraction that is in the ionised form (EC, 1996, 2003). Unfortunately, the correction does not consider electronic interactions that may occur between the ionised species and environmental surfaces; therefore, the guidance provided in the TGD may be inappropriate, resulting in a possible overestimate of the PEC to be derived.

In a survey of more than 900 APIs listed in the Australian Medicines Handbook, the majority of APIs were found to be ionisable (64.2%), with the remainder comprising compounds that had a high molecular weight (14.9%) or were neutral (12.4%), always ionised (4.7%), miscellaneous (2.4%) or inorganic salts (1.3%) (Manallack, 2009). When mixtures, salts, and high molecular weight chemicals were removed from the list, 85% of small molecular weight (< 1,000 Da) APIs were estimated to be ionisable (Manallack, 2009). Consequently, improved methods for ERA of APIs, which are predominantly ionisable organic compounds, is an area of particular interest. Indeed, under Article 8(3)(g) of Directive 2001/83/EC relating to medicinal products for human use, there is a specific requirement to indicate the potential risks posed by a medicinal product for the environment; the evaluation must be provided as part of the application for marketing authorisation (EU, 2001). Consequently, in 2006, the European Medicines Agency (EMEA) published a guideline for industry regarding the data requirements and steps needed to perform an ERA of medicinal products targeted for human use (EMEA, 2006). The guideline describes a two-phase process for ERA of the API being marketed, based directly on patient use. The first phase (Phase I) is a screening exercise, aimed at singling out those APIs whose usage (i.e. environmental exposure) is not likely to be of concern, and therefore do not require specific evaluation. Generally, APIs having a maximum daily dose of > 2 mg/d will require assessment in a second phase (Phase II). That is an in-depth ERA, requiring laboratory data on the environmental fate (degradation, partitioning) and effects (chronic toxicity) of the API. Within Phase II there are two tiers, A and B: Tier A focuses on the most likely point of environmental emission and

exposure, namely the fate and discharge of the API from a wastewater treatment plant with emphasis on the parent compound. Tier B addresses potential areas of concern highlighted from the results of Tier A, such as exposure of the terrestrial environment, high toxicity or bioaccumulation, and may include further analysis of the metabolites. Unfortunately, like the TGD, Tier A of the EMEA guideline does not appropriately describe how to estimate a PEC for ionising organic compounds such as most APIs.

Given that > 80% of all APIs are charged (Comer and Tam, 2007; Manallack, 2009) and the increased interest in ERA of ionisable organic compounds, it was decided to focus this report on chemicals used in the pharmaceutical industry. The scope was further restricted to those pharmaceuticals that are used for human health purposes and, therefore, are discharged down-the-drain into the environment (emission scenario). The task force believed that, by collecting and analysing a set of data on APIs used in human health only, the results might be of greater quantitative value. Nonetheless, many of the observations made in this report related to APIs for human use were expected to be generally applicable to all ionisable organic compounds that are more broadly used in commerce. While adopting this approach, the task force recommended that veterinary pharmaceuticals and ionisable organic agrochemicals (e.g. pesticides), which are discharged to the environment from diffuse sources, be addressed as a separate activity. As an incentive, the experience from the agrochemical industry has been captured in Chapter 5 of this report.

Additionally, based on the importance of the PEC estimate to trigger a Phase II assessment as part of the EMEA approach, the task force agreed to focus its efforts on investigating factors that might influence estimates of the PEC. These included various testing strategies aimed at quantifying the biodegradability of pharmaceuticals and their sorption behaviour. The combined understanding of biodegradation and sorption should help to understand removal by wastewater treatment plants. In the absence of empirical data, the applicability of QSARs was investigated in order to estimate various physical-chemical property data. Further, developments in multimedia fate modelling have led to improved prediction of the environmental fate and behaviour of ionisable organic compounds.

Finally, there is considerable interest in improving the understanding of bioaccumulation of ionisable organic compounds, with particular concerns being raised around the use of trigger values based on K_{OW} as a metric for bioconcentration testing. At the time of preparing this report, however, there was a paucity of data that would enable this question to be adequately addressed. Consequently, while this is an important issue that needs to be resolved, it was beyond the scope of this task force. Nevertheless, current regulatory requirements have resulted in a significant number of bioconcentration tests to be conducted, and the new data so obtained may provide future opportunities for better assessing the mechanisms influencing the bioconcentration and bioaccumulation of ionisable organic compounds. It is likely that, as an improved understanding of the controlling factors that influence bioconcentration emerges, there will also be opportunities to revisit the relevance of K_{OW} in this context.

2. MEASURED PARTITIONING PROPERTY DATA

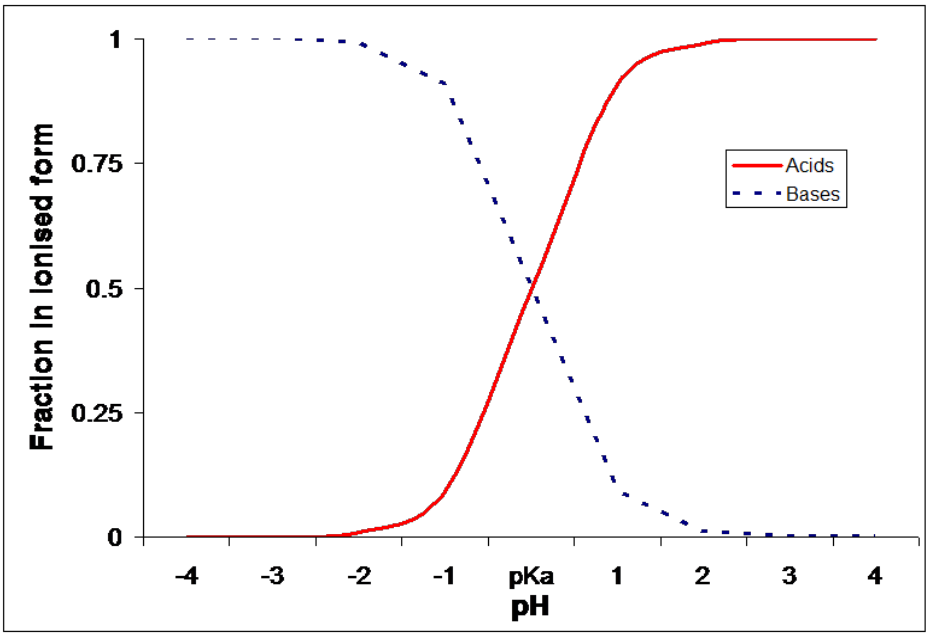
The practice of ERA of chemicals used in commerce is well established in a large number of jurisdictions. Guidance on how to perform an ERA, however, is primarily based on an understanding of the environmental fate and behaviour of neutral industrial chemicals, assuming generic modes of action and transport (Tarazona et al, 2009). There is a growing concern that the underlying assumptions used in a typical ERA do not accurately capture the environmental fate and behaviour of chemicals that ionise at environmentally relevant pH, are permanently charged, or are of unknown variable or biological composition. Estimates suggest that > 80% of APIs are ionisable organic compounds (Section 1.1); consequently their ERA must accurately reflect both the neutral and ionised species. For instance, at a given pH the fraction of an acid or base present as the anion (–ve) or cation (+ve) can be expressed as:

$$\alpha = \frac{1}{1+10^{A(pH-pK_a)}} \qquad \text{..... } \textit{(Eq. 1)}$$

Where A is +1 for acids and −1 for bases.

Figure 2 illustrates the speciation of a given acid or base relative to changes in pH. Strong organic acids with pK_a values less than environmentally relevant pH (5-9), will be largely present as the anion, and that strong organic bases with pK_a values greater than the environmental pH will be largely present as the cation. (The acidity constant pK_a is described in Section 2.1)

Figure 2: Fraction of acid or base in ionised form as function of pH [a]



[a] The Figure illustrates how the fraction of an acid or base changes with pH. For instance, the fraction of an acid or base is shown for contrasting scenarios where the pH is 4 units greater or lesser than the pK_a of the substance. When pH = pK_a, the acid and base forms are present at equal concentrations.

Equation 1 is used within the TGD as a correction factor for adjusting the partitioning properties of an ionisable organic compound. Thus the K_{OW} of a substance is adjusted by multiplying by α. For example, an organic base with a log K_{OW} of 4 and pK_a of 7 will have a corrected log K_{OW} value of 3.7 at pH 7. This simplistic approach acknowledges that the neutral and ionised forms of an ionisable organic compound will behave differently in the environment. This is an extremely important observation. Depending on the process considered, either the neutral or the ionic species may be the dominant factor influencing the environmental fate and behaviour of the chemical, even if the amount of that species is relatively small. Complicating this understanding, however, is the existence of ionisable organic compounds with more than one acid and/or base functional group with pK_a values at environmentally relevant pH, which can lead to the formation of zwitterions (ions carrying a +ve and –ve charge). For these substances, relatively small changes in pH can dramatically influence the species most strongly influencing environmental fate, thus creating significant challenges with respect to ERA.

A number of physical-chemical and fate properties used for ERA are potentially influenced by changes in pH. Table 1 lists the information typically required in the EU and USA.

Table 1: Initial information required by EMA and FDA

Property	**Requirement / reference**	
	EMEA (2006)	**FDA (1998)**
Physical-chemical		
Solubility in water	No (but often reported)	Yes
K_{OW}	Yes	Yes
pK_a	No	Yes
Vapour pressure or Henry's Law constant	No	Yes
Fate		
Hydrolysis	No (but often reported)	Yes
Stability	No	No
K_d, K_{OC}	Yes	Yes

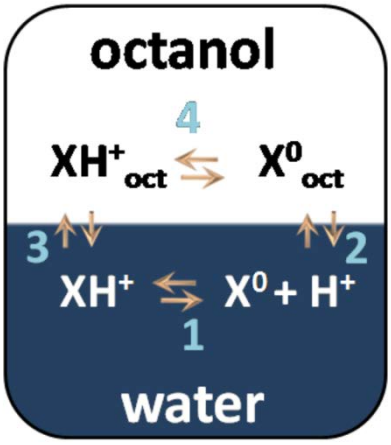
Most of the properties listed will reflect the neutral species, with minimal effort being made to determine the properties of the ionised species. One possible explanation for this is that the water solubility of the ionic form of an organic acid or base will typically be several orders of magnitude higher than the solubility of the neutral species. Given the limited and variable data regarding the solubility of organic salts, a general rule is often to assume that the ionised species will not be available for partitioning to air or organic material, and is thus entirely present in the dissolved phase. The total concentration in solution of the compound (non-dissociated and dissociated forms) is therefore strongly pH-dependent, and can be approximated by the fraction in neutral form, as defined by α (Equation 1).

Assumptions regarding the aqueous solubility of the ionised species will reflect how the air-water equilibrium partitioning, or Henry's Law constant, is defined. In this instance, it is generally assumed that the ionised species is non-volatile and will not be present in the gas phase. The air-water distribution ratio (D_{AW}) can therefore be simply given as the product of the fraction in non-dissociated form (α) and the air-water partition coefficient constant of the neutral compound (K_{AW}). Chemical equilibrium partitioning, however,

does not consider that some ionisable and surface active substances can be enriched at the air-water interface (boundary layer). Since the specific surface area of aerosols (cloud, mist and fog droplets) is usually large, the sorption capacity of the air can be high. This may have a significant impact on the fate of such compounds, and consequently for their long-range atmospheric transport and persistence (Rayne and Forest 2010; Franco et al 2011).

When determining the KOW for organic acids and bases, the assumptions used regarding the behaviour of the ionised species are somewhat more complicated. This is because, in addition to the neutral form of the acid or base, it is possible for ion pairs, formed with inorganic counter ions, as well as the ionic species itself to partition to the octanol compartment. Consequently, the DOW of an ionisable organic compound may have a significant high value, particularly if the molecule has a relatively large hydrophobic component. Figure 3 schematically illustrates what has been referred to as the four-equation partition model for a monoprotic base in an octanol-water system (Comer and Tam 2007).

Figure 3: Four-equation partition model for ionisation and partitioning of a weak base (X) a,b (adapted from Comer and Tam, 2007)



1. $X^0 + H^+ \leftrightarrows XH^+$

$$pK_a = \log \frac{[XH^+]}{[H^+][X^0]}$$

2. $X^0 \leftrightarrows X^0_{oct}$

$$K_{OW} = \frac{[X^0]_{oct}}{[X^0]_{aq}}$$

3. $XH^+ \leftrightarrows XH^+_{oct}$

$$K^1_{OW} = \frac{[XH^+]_{oct}}{[XH^+]_{aq}}$$

4. $X^0_{oct} + H^+ \leftrightarrows XH^+_{oct}$

$$pK_a^{oct} = \log \frac{[XH^+]_{oct}}{[H^+][X^0]_{oct}}$$

[a] Note that species XH^+ is expected to partition as an ion-pair with an anion from the aqueous phase

[b] K^1_{ow} represents the octanol-water partition coefficient of the charged species only.

Based on the information provided in Figure 3, D_{OW} can be defined as:

$$D_{OW} = \frac{[X^0]_{oct} + [XH^+]_{oct}}{[X^0]_{aq} + [XH^+]_{aq}} \quad \text{..... (Eq. 2)}$$

Or alternatively as:

$$D_{OW} = \frac{K_{OW} + K^1_{OW}[H^+]K_a}{1 + [H^+]K_a} \quad \text{..... (Eq. 3)}$$

The relationship described above and in Figure 3 also applies to a monoprotic acid. For multiprotic acids and bases, the equation is:

$$D_{OW} = \frac{K_{OW} + K_{OW}^{1}[H^{+}]\beta_1 + K_{OW}^{2}[H^{+}]^2\beta_2 + \cdots K_{OW}^{n}[H^{+}]^n\beta_n}{1 + [H^{+}]\beta_1 + [H^{+}]^2\beta_2 + \cdots [H^{+}]^n\beta_n}$$

…….. ***(Eq. 4)***

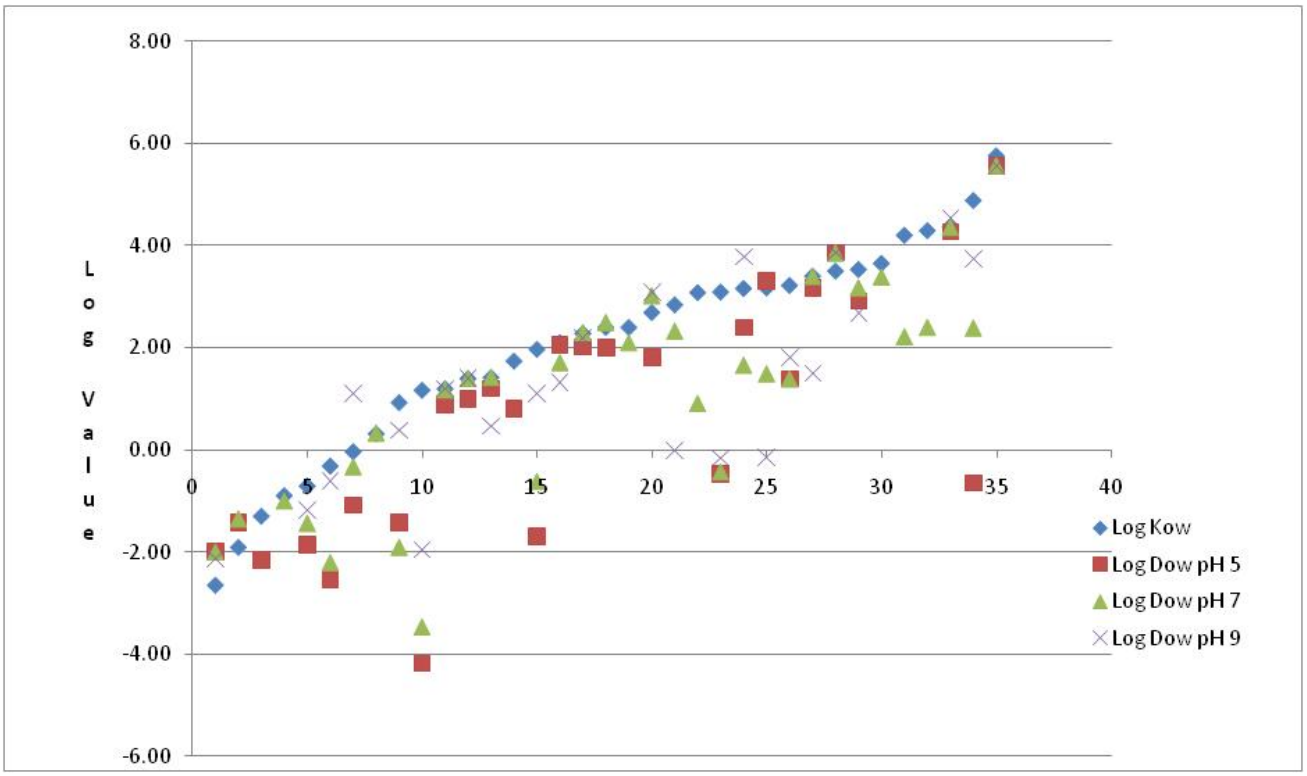
Where β represents the acid ionisation constants, Ka1, Ka2, etc.

In order to understand the behaviour of an ionisable organic compound it is thus necessary to obtain values for each of the ionisation constants and to measure D_{OW} with varying pH. For ERA, measurements of D_{OW} should be made within an environmentally relevant pH range, usually between 5 and 9.

A major challenge in utilising measurements of D_{OW} or K_{OW} for an ionisable organic compound relates to how this information is used to estimate the partitioning to natural organic phases. The estimate is normally based on single parameter relationships, such as those that relate the K_{OC} to K_{OW}, or those that attempt to estimate bioconcentration factors (BCFs) based on K_{OW}, since it is known that these natural organic phases will exhibit charged functionalities.

Figure 4 shows the extent of ionisation that may exist for certain compounds, noting the range between log K_{OW} and log D_{OW} values (at pH 5 - 9). As expected, log K_{OW} is a conservative estimate of the lipid partitioning; when the compound's potential to ionise is taken into account, the overall partitioning for all of its species (ionic + neutral) may be considerably less. For 35 compounds within of the API dataset (Section 3.1) where there were measured K_{OW} and D_{OW} data, 67% of the values were within 1 log unit, but for 17% they differed by 3 to 5 log units. The implication of the extent of ionisation and its role in partitioning into lipids, or sorption to the organic content of solids, is not necessarily related solely to this octanol-water partitioning. [It is noted that, for about 50% of substances, the DOW value is less than the existing KOW value of 3.0 or 3.5 that triggers BCF testing or PBT testing, respectively.]

Figure 4: Comparison of measured log KOW to log DOW values (at pHs 5, 7 and 9) for 35 compounds in the API dataset (Appendix F), presented by increasing log KOW value a



[a] The range of log K_{OW} and log D_{OW} values for each compound is smallest for neutral compounds where there is no ionisation (values essentially the same), and greatest for cationic compounds , up to a difference of 5 log units. The difference is most prominent for some compounds with pK_a > 9.0

It has been suggested to utilise equilibrium partitioning for specific classes of compounds, such as perfluorinated carboxylic and sulphonic acids, when the hydrophobic component dominates their sorption. For cationic and anionic chemicals, where the surface charge area of the molecule prevails, deviations from the equilibrium partitioning model could occur (Webster and Ellis, 2011). Thus, caution is warranted when attempting to make extrapolations between K_{OW} and K_{OC} or BCF, since octanol does not contain any charged functionality. Therefore, the extrapolation to natural organic phases may not always be applicable.

The next sections of this chapter summarise the available international standard test methods used to measure the acid dissociation, partitioning, sorption (physical-chemical), hydrolysis and biodegradation (fate) properties required to conduct an ERA, and comment on the applicability of the test method towards ionisable organic compounds. Where significant problems are identified, recommendations are provided on how the method could be modified to account for the ionised species. Details and references of the methods are provided in Appendix A to E.

2.1 Acid dissociation constant (K_a)

The extent to which an organic chemical partitions between environmental compartments is determined by the properties of the chemical and the properties of the compartment it is discharged to. A major influence on the partitioning of ionisable organic compounds is attributed to the acid-base interaction between chemical and aqueous or soil/sediment compartment (Harris and Hayes, 1990). The acid dissociation (acidity) constant (K_a) indicates which chemical species will be present at a particular pH. The neutral, anionic or cationic species often have vastly different properties with regard to water solubility, volatility, UV adsorption, adsorption to soil/sediment, bioconcentration, and toxicity (Babic et al, 2007; ECHA, 2008a).

Water solubility measurements for regulatory purposes are usually made in distilled water at pH 6 to 9, whereas the pH of aquatic toxicity test media is usually 7 to 8 and pH values in the environment normally range from 5 to 8. Consequently, the solubility of an ionisable substance may differ significantly between these systems, especially if the pK_a is between 5 and 9. This is because the extent of ionisation may vary according to pH or the level of counter ions in the test medium, and relatively small changes may significantly alter the equilibrium between dissociated and non-dissociated species. The dissociated and non-dissociated species may each have their own water solubility and partition coefficient, and therefore bioavailability and toxicity.

The K_a is also important in deciding which method or conditions should be used to determine the K_{OW} (Section 2.2) and K_{OC} (Section 2.3.1) (ECHA, 2008a).

2.1.1 Definition

An acid (HA) is a substance that dissociates in water, releasing a hydrogen ion (H^+) and a conjugate base (A^-). According to Arrhenius, the reaction of the acid-ionisation can be written as:

$$HA + H_2O \leftrightarrows A^- + H_3O^+ \qquad \text{..... } \textit{(Eq. 5)}$$

The value of the equilibrium constant for this dissociation reaction (K_a) is a quantitative measure of the strength of the acid in aqueous solution. In the equilibrium state, the K_a is defined as the quotient of the equilibrium concentrations of the dissociated ions and the free, undissociated acid (in mol/l):

$$K_a = \frac{[H^+][A^-]}{[HA]} \qquad \text{..... } \textit{(Eq. 6)}$$

Because the K_a value may span several orders of magnitude, it is usually expressed as a negative decadal logarithm, i.e. $pK_a = -\log 10\ K_a$. The larger the pK_a value, the smaller the extent of dissociation of the acid. Acids with a pK_a value of about −2 are considered to be strong acids, pK_a values of 12 indicate weak acids or strong bases. Strong acids with pK_a values of less than −2 are almost completely dissociated (> 99%) in aqueous solution at pH 0. The pK_a can be calculated:

$$pK_a = pH - \log\frac{[A^-]}{[HA]} \qquad \text{..... } \textit{(Eq. 7)}$$

The concentration of organic acids in the dissociated (A^-) and free (HA) forms are equal when pH = pK_a, and the ratio of A^- to HA increases by an order of magnitude for each unit of pH above pK_a. A comparison of the pK_a of an organic acid with the pH of the aqueous system of concern reveals the importance of acid dissociation of the organic compound in determining the environmental distribution.

Polyprotic acids are acids that can donate more than one proton to a base. The equilibrium constants for the successive dissociation reactions are referred to as K_{a1} for the first proton, K_{a2} for the second proton, etc. When the difference between successive pK_a values is ≥ 4, each species can be considered as an acid in its own right.

The acid-base behaviour of weakly basic organic compounds (B) is defined by the base dissociation constant, K_b, analogously:

$$B + H_2O \leftrightarrows BH^+ + OH^- \quad \text{..... } \textbf{\textit{(Eq. 8)}}$$

For convenience, it is preferable to address the behaviour of weak bases in terms of the K_a or pK_a values:

$$BH^+ + H_2O \leftrightarrows B + H_3O^+ \quad \text{..... } \textbf{\textit{(Eq. 9)}}$$

The K_a for the conjugate acid, BH^+, and K_b for the base, B, are related by the auto-dissociation constant of water K_w:

$$K_a = \frac{K_w}{K_b} \quad \text{..... } \textbf{\textit{(Eq. 10)}}$$

The acid strength can vary over about 50 orders of magnitude. In aqueous media however, the range of interest is restricted to acids with pK_a values of 0 to 14. At normal environmental pH (5 - 8), the range of acidities that are of concern is even more restricted, i.e. pK_a range of 3 to 10. If an organic species has a pK_a outside these limits, it is expected to be either completely (> 99%) dissociated (pK_a of organic acid < 3) or completely undissociated (pK_a of conjugate acid > 10) in an aqueous environment.

2.1.2 Ionisable groups

Functional groups that act as proton-donor or proton acceptor influence the capacity for a molecule to act as an acid or base. The most important functional groups with environmental relevance include aliphatic and aromatic carboxylic groups, aromatic hydroxyl groups (e.g. phenolic compounds), aliphatic and aromatic nitro amino groups, nitrogen atoms incorporated in aromatic compounds, and aliphatic or aromatic thiols. Table 2 lists examples of various ionisable functional groups.

Table 2: Important ionisable functional groups

Name	Formula [a]
Sulphonic acid	RSO_3H
Carboxylic acid	RCOOH
Sulphonamide	RSO_2NH_2
Thiol	RSH
Phenol	RPhOH
Amine salt	$R_3NH^+X^-$
Imide	RC(O)NHC(O)R'
Amide	RC(O)NHR'

[a] R or R', aliphatic; X^-, anion

The range in pK_a values for a given functional group may vary by many units because of the structural characteristics of the remainder of the molecule. Therefore, pK_a is influenced by the electronic and steric effects of substituents on the relatively stable acid-conjugate base or base-conjugate acid couple formed. This can include inductive effects, whereby the position of an electron-withdrawing substituent in relation to an acid or basic functional group can either stabilise the anion of an organic acid or destabilise the cation of an organic base. It can also include resonance and steric effects. It can therefore be difficult to establish general rules for quantifying the effects of structural entities on the pK_a of an acid or base function, although there are a number of linear free energy relationships (LFERs) that have been developed to estimate pK_a (Liao and Nicklaus, 2009).

2.1.3 Measurement

Acidity has long been recognised as an important property, and methods for measurement of pK_a are well established. The principal procedures involve experimental determination of the pH and the concentrations of the dissociated and undissociated forms of the chemical substance (Eq. 7). In principle, there are two ways to determine K_a: (i) titrating a known amount of substance with a standard acid or base, or (ii) determining the relative concentrations of the ionised and neutral forms and their pH dependence. Traditionally, titration, spectrophotometry and conductometry have been the most useful techniques due to their accuracy and reproducibility. The details are given in the OECD guideline 112 (OECD, 1981a) and the EPA OPPTS 830.7370 (US EPA, 1996). The three reference methods are summarised in Appendix A.

Acid dissociation constants in the range of pK_a 3 to 11 can generally be measured with a high degree of accuracy. However, the value of K_a is affected by several parameters, including: Molecular structure of the organic acid, increasing ionic strength of the aqueous medium (increasing ionic strength favours the ionic form of the conjugate acid/base pair), and temperature of the medium. However, the latter is of unimportant in the environmentally relevant temperature range.

The influence of the solution's ionic strength and the temperature is small compared to the influence of the molecular structure of the acid, i.e. K_a values generally change by less than one order of magnitude between

5 and 60°C (typically < 10%) (Harris and Hayes, 1990). If a significant temperature dependency is suspected, the pK_a determination should be conducted at different temperatures with intervals of 10°C (±0.1°C).

The strategy for measuring pK_a is determined by the solubility of a compound. The compound should be soluble and stable to ensure equilibrium is maintained.

Substances need to be submitted for pK_a measurement as free bases or inorganic acid salts in pure form, and must be of accurately known composition. In general, no reliable measurements can be made on organic acid salts. A suitable analytical method with sufficient sensitivity for the different species should be available. The analytical method used to determine the amounts of dissociated and non-dissociated forms present in solution should not affect the equilibrium, and should be capable of distinguishing between the chemical species involved.

2.1.4 Summary

Table 3 summarises the applicability of each of the methods reviewed above. They are further annotated in Appendix A. There is no particular recommendation.

Table 3: Overview of methods to determine pK_a according to OECD 112 and OPPTS 830.7370 (OECD, 1981a; US-EPA, 1996)

Principle	Applicability, remark
Titration (potentiometric)	
Known quantity of the substance is dissolved in distilled water (up to 0.01 mol/l or half-saturation concentration) and titrated against a standard acid or base solution. At least ten additions of titrant required and pH of the solution measured in order to complete a titration curve	Not suitable for poorly soluble substances Requires accurate knowledge of total quantities of the substance and of its concentration Typically, the compound is titrated towards the direction of its neutral form, resulting in a dramatic drop in solubility. Often several experiments are conducted to determine the concentration required for the compound to stay in solution. Data collected while precipitation is occurring produces incorrect results
Spectrophotometry	
Involves determination of the ratio of the undissociated molecule to the ionised species at a concentration of up to 0.01 mol/l. UV/visible absorbance spectrum of the non-ionised species is obtained by dissolving the substance in a non-absorbing buffer of known pH in which the substance does not dissociate. Extinction is measured at minimally 5 pH values and constant concentration; ionisation grades shall range from 10% to 90%	Only applicable for substances that have considerably different UV/Vis extinction coefficients in the ionised and unionised forms Suitable method for low solubility compounds
Conductometry	
Conductivity of a 0.1 molar solution of the substance in distilled water is measured. Additionally, measures of the conductivity of a range of dilutions are also made	Useful where the Onsager equation holds ($K_a = \alpha^2 C /(1-\alpha)$, where α is the degree of dissociation at concentration C The coefficient of variation using this guideline is ± 0.1 log unit, equivalent to 10% at pK 1 (ECETOC, 1998)

2.2 Partition coefficient (K_{OW}) and distribution ratio (D_{OW})

The n-octanol-water partition coefficient (commonly referred to as either K_{OW} or P_{OW}) is a widely used property for assessing the partitioning behaviour of chemicals in the environment. Over the last several decades, a number of single-parameter relationships based on K_{OW} have been developed to estimate the fate, behaviour and effects of chemicals in the environment, such as sorption to soils and sediment, bioavailability, bioconcentration, and ecotoxicity. Octanol is regarded as a model solvent that mimics lipid tissues in organisms and humans, and organic carbon in soils and sediments. Octanol has, therefore, been widely used as an appropriate surrogate for the partitioning of chemicals from aqueous media to organic matrices (Leo et al, 1971; Hansch and Leo, 1979). The generation of K_{OW} is integral to the ERA of chemical substances and therefore the reproducibility and accuracy of this value is of paramount importance. In this section, the standard methods for the measurement of K_{OW} are evaluated in terms of their applicability to the ERA of ionisable compounds and the most appropriate methods are recommended. A review of the key regulatory triggers associated with K_{OW}, together with an examination of the role of ionisation on bioconcentration potential is provided further below.

2.2.1 Definition

The K_{OW} is defined as the ratio of the equilibrium concentrations of a dissolved substance in a 2-phase system consisting of the largely immiscible solvents n-octanol and water, as the neutral form of the molecule (OECD, 1995a). As such, it is a measure of the hydrophobicity of the compound.

The property is moderately temperature-dependent and typically measured at 25°C.

$$K_{OW} = [X]_{n\text{-octanol}} / [X]_{water} \quad \text{..... } \textit{(Eq. 11)}$$

Where [X] indicates the concentration (mass/volume) in the specific solvent.

The octanol-water distribution ratio (D_{OW}) is a measure of K_{OW} that accounts for the pH dependency of an ionisable organic chemical, and is a measure of the distribution of dissociated and non-dissociated species in octanol and water as a function of pH. The extent to which an ionisable compound is dissociated across environmentally relevant pH ranges may have a marked effect on properties such as water solubility. It should be noted that the neutral form of the species is generally less water soluble and is thus more hydrophobic as compared to the ionised or charged form (Avdeef, 1996).

In general, D_{OW} can be correlated to K_{OW} and pK_a by the following relationships:

For acids: $$\log D_{OW} = \log K_{OW} - \log[1 + 10^{(pH - pK_a)}] \quad \text{..... } \textit{(Eq. 12)}$$

For bases: $$\log D_{OW} = \log K_{OW} -- \log[1 + 10^{(pK_a - pH)}] \quad \text{..... } \textit{(Eq. 13)}$$

Neutral and non-ionisable organic compounds will have a D_{OW} value that is equivalent to K_{OW}, since D_{OW} is a measure of the pH dependency of an ionisable organic compound. The available international standard methods are detailed and referenced in Appendix B.

2.2.2 Summary and recommendation

The different methods for determining K_{OW} are compared in Table 4 and detailed in Appendix B.

Table 4: Comparison of methods to determine K_{OW} for ionisable compounds

Method – Equipment/ Key condition	Measured endpoint	Reported value	Advantage	Disadvantage
OECD 107 – Shake flask				
Water and octanol solubility. Neutral compounds. Range −2 < log K_{OW} < 4	Concentration of test material in water and n-octanol.	log K_{OW}	Reliable. Can investigate low log K_{OW} values	Slow. Not suitable for ionisable compounds. Not suitable for high log K_{OW} (> 4) substances
OECD 107 – Shake flask at pH 5, 7 and 9				
Water and octanol solubility. Ionisable compounds. Range −2 < log K_{OW} < 4	Concentration of test material in water and n-octanol	log K_{OW} log D_{OW} at pH 5, 7 and 9	Reliable. Can investigate low log K_{OW} values. Suitable for ionisable compounds	Slow. Not suitable for high log K_{OW} (> 4) substances
OECD 117 – HPLC method				
Reverse phase HPLC. Reference substances. Neutral compounds. Range 0 < log K_{OW} < 6	Retention time on reverse phase column	log K_{OW}	Rapid. Small sample size. Several compounds at once	Variable retention times. Poor reproducibility
OECD 122 – pH-Metric method				
Soluble compounds. Range −2 < log K_{OW} < 7	Acid-base aqueous titration	pK_a, log D_{OW} across pH range, log K_{OW}	Rapid and convenient. log D_{OW} data for entire pH range. log K_{OW}	log K_{OW} and log D_{OW} are estimates based on pK_a titration. Insoluble or neutral compounds cannot be measured. Requires sophisticated analytical technology. Limited availability. OECD 122 has not been finalised
OECD 123 – Shake flask slow stirring method, option for pH 5, 7 and 9				
Water and octanol solubility. Hydrophobic substances. Range log K_{OW} > 4	Concentration of test material in water and n-octanol	log K_{OW}	Suitable for hydrophobic (log K_{OW} > 4) compounds	Slow
OECD 107 – EU A.8, option for pH 5, 7 and 9				
Insoluble and/or multi-protic substance. Surface active substance	Solubility in water and octanol. Turbidity measurements	log K_{OW} estimated	Practical alternative for water insoluble, surface active and multi-protic compounds	log K_{OW} is an estimated value. Correlation between solubility ratio and log K_{OW} is weak

The pH-metric (titration) method that is being finalised at OECD level (to be published as test guideline 122) has the potential to become the preferred method for measuring both D_{OW} and K_{OW} of ionisable compounds. It delivers the most comprehensive dataset of all the methods, including pK_a, K_{OW} and D_{OW} across a wide pH range, and is applicable across a wide range of log K_{OW} values (−2 - 7) (OECD, 2000a). However, it should be noted that K_{OW} and D_{OW} values are actually calculated from the measured (titrated) pK_a value and apparent shift in pK_a value when n-octanol is added. Nonetheless, the pH-metric procedure has been validated

against the traditional standard shake-flask method and many studies using it have been reported (Slater et al, 1994; Takács-Novák and Avdeef, 1996; Chamberlain et al, 1996; Avdeef, 2001). The published literature clearly indicates that this technique is a reliable, versatile, dynamic, and an accurate method for measuring K_{OW} (Avdeef, 2001; Kah and Brown, 2008). Other disadvantages are that, for example, the pK_a must be in the measureable pH range and that the method is not applicable to neutral or insoluble compounds.

The limited availability of this method offered by contract research organisations represents an additional obstacle. The pH titration method requires rather sophisticated and expensive analytical equipment and, as such, contract research organisations are unlikely to invest in this method unless demand reaches appreciable levels. Conceivably, the EMA (2010) recommendation that log D_{OW} should be determined as a function of pH covering an environmentally relevant pH-range, e.g. Draft Guideline OECD 122 (OECD, 2000a) will stimulate the required demand. The publication of the finalised OECD 122 (OECD, 2000a) guideline would also represent a step forward in promoting widespread acceptance of this method.

In contrast, the shake flask method (OECD 107) has traditionally been considered the 'Gold standard'. Whilst this method is undoubtedly slow, it does deliver reproducible and accurate measurements of K_{OW}. The method can be easily adapted to accommodate ionisable compounds by measuring D_{OW} at pH 5, 7 and 9. It is reliable and can be used for log K_{OW} values over a fairly wide range (−2 - 4). For hydrophobic compounds with predicted log K_{OW} > 4, the slow stirring method OECD 123 should be used. Until the pH-metric method becomes more widely available, the shake flask method at pH 5, 7 and 9 is likely to continue to be the default choice for the measurement of K_{OW} values for ionisable compounds.

2.2.3 Regulatory trigger values: Appropriateness, assumptions and gaps in science

The variation that exists for log K_{OW} trigger values for potential bioconcentration among regulatory guidelines suggests there is a level of uncertainty regarding what constitutes an appropriate value. In terms of ERA of chemicals, the TGD (EC, 2003) has been a common frame of reference for environmental risk assessors wanting to understand the relevance of log K_{OW} as an indicator of potential to bioconcentrate. Accordingly, the most important and widely accepted indication of bioaccumulation potential is a high value of log K_{OW} (EC, 2003). It is also maintained that for certain substances such as those that ionise in water, log K_{OW} values may not be suitable to calculate a BCF value. Therefore, the TGD explicitly acknowledged that the relationship between log K_{OW} and BCF for neutral organic compounds is predictive, whereas for ionisable substances the pH of the environment will influence the relevant quantities of neutral and dissociated species present. This has obvious implications on partitioning behaviour.

The distinction between neutral and ionised compounds in terms of their influence on bioconcentration potential is reiterated in the EU by the present REACH guidance and by other regulators (Table 5).

Table 5: Regulatory trigger values of log K_{OW} for bioconcentration potential

Property	Regulation [a]					
	REACH	**GHS/CLP**	**Fass**	**EMA ERA**	**FDA**	**VICH ERA**
log K_{OW} for PBT	> 4.5	> 4.0	≥ 4.0	> 4.5	-	> 4.0
log K_{OW} for BCF	> 4.5	> 4.0	≥ 4.0	> 3.0	≥ 3.5	> 4.0
Use of log D_{OW} for ionisable compounds	Yes	-	Yes	Yes	Yes	Yes?

[a] REACH, Registration, evaluation, authorisation and restriction of chemicals; GHS, Globally harmonised system; CLP, Classification, labelling and packaging of substances and mixtures; Fass, Farmacevtiska specialiteter i Sverige [Pharmaceutical specialties in Sweden], Environmental classification of pharmaceuticals; EMA, European Medicines Agency; FDA, Food and Drug Administration; VICH, International cooperation on harmonisation of technical requirements for registration of veterinary medicinal products

For REACH guidelines the relative extent to which an ionisable substance is likely to be dissociated in the environment (pH 5 - 9) can have a marked effect on its physical-chemical properties, especially the K_{OW} and water solubility, which in turn affect fate and behaviour (ECHA, 2008b). Moreover, the value for the dissociated molecule determined around a pH of 7 (sometimes referred to as D_{OW}) is considered more realistic for PBT and chemical safety assessment. However, REACH differs from its predecessor in that it considers the appropriate trigger for bioconcentration potential to be log K_{OW} ≥ 4.5, rather than 3.0. It seems likely that this latter value was adopted by the EMA ERA guidelines which, when finalised in 2006, required that a bioconcentration study be considered for pharmaceuticals exceeding a K_{OW} of 1,000 (EMEA, 2006). It is not evident whether the ionisable nature of most APIs was a consideration for these guidelines. However, more recently the EMA have recognised this property of APIs and clarified that for ionisable compounds log D_{OW} should be determined as a function of pH covering an environmentally relevant pH-range. Unlike REACH, the trigger value for BCF evaluation remains at log K_{OW} ≥ 3.0 (EMA, 2010). A different trigger value is considered by the Swedish Classification of Pharmaceuticals guidelines which, taking its cue from the CLP guidelines, states that bioconcentration potential may be indicated by log K_{OW} ≥ 4. The use of log D_{OW} at pH 7 as an indicator of bioconcentration for complex ionic molecules is explicitly accepted by these guidelines. In the USA, the FDA Environmental Assessment guidelines also acknowledge that for substances which dissociate in water, the K_{OW} may need to be evaluated at pH 5, 7 and 9. Once again, the trigger value differs from those in Europe, whereby a log K_{OW} ≥ 3.5 indicates that chronic toxicity testing may be required.

Overall, whilst there are differences between the regulatory log K_{OW} values (ranging 3.0 - 4.5) for bioconcentration potential, there is consensus that evaluation of the distribution coefficient (log D_{OW}) is appropriate for chemicals that dissociate in water at environmentally relevant pH 5 to 9. For pharmaceuticals with ionisable groups, it follows axiomatically that the charged state of these groups will vary according to the pK_a and environmental pH; this in turn may influence water solubility and partitioning behaviour. While there is significant support for this observation in the scientific literature (Avdeef, 1996; Kah and Brown, 2008; Rayne and Forest, 2010), the scientific basis for asserting log D_{OW} is more appropriate for predicting bioconcentration compared with the partitioning of the neutral form (log K_{OW}) remains largely untested.

2.3 Adsorption-desorption distribution (K_d) and organic carbon-water partition (K_{OC}) coefficients

The adsorption-desorption distribution coefficient (K_d) is an important parameter for understanding the mobility of a compound in the environment (partitioning) and its distribution between water, sludge, soil and sediment compartments (OECD, 2000b). The K_d value is used in various environmental models for estimating the extent of removal on sludge during wastewater treatment, of leaching through a soil column, and of runoff from agricultural land into adjacent waters, as examples (Wauchope et al, 2002). The distribution of a chemical between water and soil, sediment or sludge compartments is dependent upon the characteristics of the chemical as well as the matrix; it may be additionally influenced by external factors such as temperature and rainfall (OECD, 2000b; Wauchope et al, 2002). Characterisation of K_d in the laboratory and extrapolation to the field can be difficult, largely because of the complexity of adsorption mechanisms that may be relevant for a given chemical and matrix; the mechanisms may be known and unknown in nature (Boxall et al, 2004; ter Laak et al, 2006).

K_d is often normalised to the organic content of the matrix, in order to obtain the organic carbon-water partition coefficient, K_{OC} (Section 2.3.1); the latter is typically found in many of the current protocols today. While this approach was initially developed for hydrophobic compounds, it is not clear whether such normalisation is appropriate for ionisable substances (Chapter 4). Considerations of pH of the soil/sediment/sludge matrix may be more relevant endpoints for such normalisation, particularly when considering the potential effects of the pK_a of the chemical on its potential ionisation and subsequent sorption (Nicholls and Evans, 1991; Franco and Trapp, 2008).

For direct measurement of K_d values, a batch or slurry mixing experiment is usually used: a mass of soil m_s (g) is mixed with a volume V (ml) of water or another medium such as aqueous 0.1M $CaCl_2$ (to minimise disruption of the soil mineral balance). A mass m_p (g) of chemical is added to the slurry (or added to one phase before mixing) to give an initial concentration $Ci = m_p/V$ of chemical in the liquid phase. The slurry is then mixed gently in order to disturb the soil structure as little as possible for a period typically from 2 to 48 hours (24 h being a standard). Many studies have shown that the distribution of the chemical in the system approaches a pseudo-equilibrium within a few hours. The liquid phase is then analysed for the equilibrium concentration Ce of the chemical in aqueous solution. Ideally, the soil phase should also be analysed to confirm the mass balance, but this is usually more difficult and neglected.

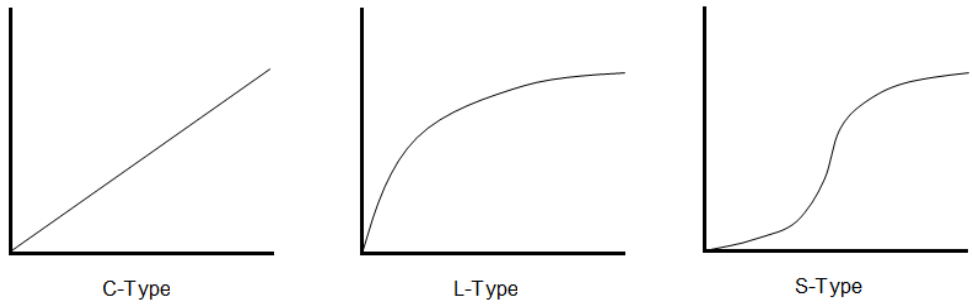
The soil sorption constant K_d is then calculated as follows: assuming that all chemical removed from the solution is adsorbed by the soil, the mass of this, historically symbolised by x, is calculated as $x = V(Ci-Ce)$. Then x/m_s (Cs) is the concentration of chemical in the solid phase (g/g) and K_d is defined by

$$K_d = Cs / Ce \qquad \text{..... } \textbf{\textit{(Eq. 14)}}$$

Thus, K_d (a partition coefficient) is a ratio of solid phase to solute concentrations. High values of K_d (of the order of 100 or more) indicate that, at any given time, the majority of the chemical is adsorbed to the soil surface and hence is less likely to move in soil, but it does not indicate the strength (reversibility) of that sorption. It should be noted that this is a macroscopic measurement and provides only indirect information on the type of surface interactions taking place. Often K_d values are determined over a range of

concentrations at a constant temperature. The resultant plot is termed an adsorption "isotherm", which can take a number of shapes as illustrated below (Figure 5).

Figure 5: Adsorption isotherm shapes



It has been hypothesised by Giles et al. (1960) that the shape of the isotherm obtained is indicative of the adsorption processes occurring. When considering the shape of the isotherm, it is important to note the concentration range over which the isotherm has been produced, as different shapes may be obtained over different concentration ranges.

The C-type isotherm is proposed to indicate that the affinity of the sorbate for the adsorbent remains constant and that the number of adsorption sites is unlimited.

L-type isotherms indicate that the proportion of sorbate adsorbed increases more slowly as the amount of material adsorbed increases and are the most common isotherms obtained for crop protection products.

A more complex situation is represented by the S-type isotherm. This was suggested by Giles et al. (1960) to arise as a result of previously sorbed molecules interacting with the surface to facilitate greater adsorption of subsequent molecules up to a point at which the effect declines. An alternative explanation was given by Sposito (1984) who suggested that other species in solution compete for the sorbate until these species are fully reacted leaving subsequent sorbate to adsorb unhindered. Further possibilities are that that the sorbate has a greater affinity for itself than the surface or that at low concentrations the sorbate is competing against other species in solution (including water) for adsorption sites.

In the next sections, the K_d, K_{OC} and isotherms are defined, and standard methods for the measurement of K_d (OECD 106, OPPTS 835.1110 and OECD 121) are evaluated in terms of their applicability to the ERA of ionisable compounds and recommendations given as to which method(s) are most appropriate.

2.3.1 Definition

K_d is defined as the ratio of the equilibrium concentrations of a substance adsorbed onto a solid sorbent to that dissolved in a liquid phase. The property is moderately temperature-dependent and typically measured between 20 and 25°C.

$K_d = C^{ads}_s (eq.) / C^{ads}_{aq}$ ..... ***(Eq. 15)***

Where: $C^{ads}_s (eq.)$ = content of substance adsorbed onto soil at adsorption equilibrium (µg/g)

$C^{ads}_{aq}(eq.)$= mass concentration of substance in aqueous phase at adsorption equilibrium (µg/cm^3)

K_{OC} definition

K_{OC} can be defined as the product of K_d and fraction of organic content (f_{OC}) of sorbent by the following equation:

$K_{OC}= K_d f_{OC}$ (cm^3/g) ..... ***(Eq. 16)***

Where: foc = (g/g)

Appendix C describes the test methods for measuring K_d or K_{OC}. The behaviour of a chemical in the test systems provides a means for assessing sorption/desorption within a standardised test. The value derived from the standardised test should thus be reproducible between different laboratories. In practice, variations in test conditions, such as the origin and amounts of organic and inorganic material used, can lead to variation of test results. Furthermore, standardised test conditions do not necessarily extrapolate well to real-world environments. Consequently, it is typical to find significant variability in K_{OC} values for a specific compound, which in some instances can extend over several orders of magnitude. Caution is thus warranted when interpreting data obtained for K_{OC} of ionisable organic compounds, particularly with respect to assessing exposure and bioavailability. This is because K_{OC} typically assesses the sorption/desorption behaviour of an organic chemical with the organic carbon content present in soil, sediment, and sludge, as seen in Eq. 16 above, but for ionisable organic compounds it may be that electronic interactions with inorganic material may be more important.

2.3.2 Freundlich isotherms

Assuming that quasi-equilibrium is achieved in a slurry experiment, the most commonly observed deviation from equation 1 is a gradual decrease in K_d with increasing apparent chemical equilibrium concentration, giving a non-linear isotherm with a negative curvature. This is usually fitted to a straight line via least-squares regression using a log-log transformation of the data; the result is referred to as the Freundlich isotherm.

$Cs = K_F (Ce)^{1/n}$ ..... ***(Eq. 17)***

Or $\log Cs = \log K_F + 1/n \log (Ce)$ ..... ***(Eq. 18)***

Where KF is Freundlich's constant, and 1/n is the exponent of non-linearity (explained below)

Non-linearity is observed, especially with chemicals which are not extremely hydrophobic and therefore not limited by solubility to extremely low concentrations. However, any sorption isotherm which covers a wide concentration range (say, more than two orders of magnitude), even if the whole range is at very low concentrations, will typically be non-linear, presumably because a range of sorption processes taking place.

The most important consequence of isotherm non-linearity of the Freundlich type with 1/n < 1 is that the mobility of chemicals at very high concentrations will be under-predicted *by* K_d or K_{OC} values measured at lower concentrations.

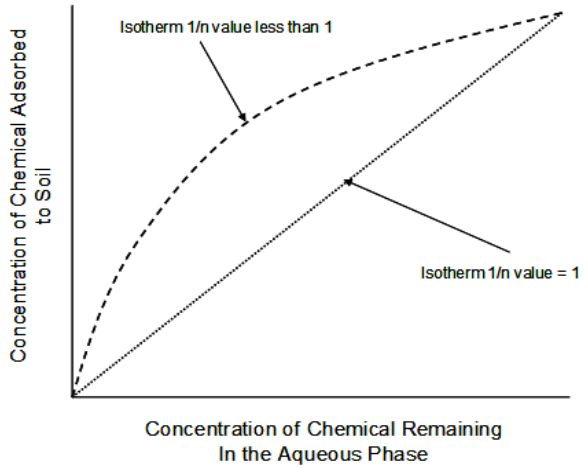
The interpretation of 1/n values and the usefulness of Freundlich regression

The 1/n value derived from the Freundlich equation serves to describe the linearity of adsorption or alternatively the degree of curvature of the isotherms described above across the concentration range tested.

Typically, 1/n values range from 1 downwards. A value of 1 signifies that the relative adsorption (adsorption partition) of the chemical was the same across the whole range tested (C-type isotherm), which is unusual (especially across the concentration range of two orders of magnitude often used in regulatory studies), but not unheard of.

More normally, 1/n values will range from 0.7 to 1.0. These values show that when the concentration of chemical under investigation increases, the relative adsorption decreases (L-type isotherm). This tends to be indicative of saturation of adsorption sites available to the chemical, resulting in relatively less adsorption. 1/n values of less than 0.7 describe highly curved isotherms. A simple visual representation of the typical isotherms (for 1/n ≤ 1) is shown below (Figure 6).

Figure 6: Typical isotherms for 1/n ≤ 1



1/n values of > 1 are indicative of S-type isotherms. These are relatively uncommon but are often observed at low concentration ranges for compounds containing a polar functional group. It has been hypothesised that, at low concentrations, such compounds are in competition with water for adsorption sites.

Care should be taken when extrapolating to obtain K_F values that are not within the concentration range tested. There is some evidence that especially at very low concentrations the proportion sorbed to the solid phase can increase significantly.

The reproducibility of the data used to generate the Freundlich adsorption coefficient can be judged to some degree by means of the coefficient of determination r^2. The closer to 1 the value is then the more reproducible the data used to calculate. Wherever possible, r^2 values should be greater than 0.9, showing a good degree of reproducibility, in turn giving confidence in the data. However, at either extremely small or high adsorption values, e.g. K_F values of greater than 50 or less than 0.5, the intrinsic variability of the experimental data will more often than not dictate that r^2 values less than this must be expected. For an indication of data reliability, the reader is advised to always look at the linear adsorption isotherm visually, rather than just use the r^2 value.

2.3.3 Summary and recommendation

The different methods for determining K_d/K_{OC} are compared in Table 6. Further details and references are given in Appendix C.

Table 6: Comparison of methods to determine K_d/K_{OC} for ionisable compounds

Method Title / key condition	Measured endpoint	Reported value	Advantage	Disadvantage
OECD 106 – Batch equilibrium for soil				
Solubility in 0.01M $CaCl_2$. Stability of test material during equilibrium phase. Use of ^{14}C-labelled test material	Concentration of test material in water and solid phase	K_d:K_{OC}; % sorption and desorption	Reliable and robust. Can investigate low K_d values. Mass balance analysis. Evaluated over concentration range	Lengthy and labour intensive
OPPTS 835.1110 – Batch equilibrium for sewage sludge				
Solubility in 0.01 M $CaCl_2$. Stability of test material during equilibrium phase. Use of ^{14}C-labelled test material	Concentration of test material in water and solid phase	K_d, K_{OC}; % sorption and desorption	Reliable and robust. Can investigate low K_d values. Mass balance analysis. Evaluated over concentration range	Lengthy and labour intensive
OECD 121 – HPLC for soil and sewage sludge				
Reverse phase HPLC. Reference substances. Neutral compounds. Range $0 < \log K_{OW} < 6$	Retention time (capacity factor) on reverse phase column	K_{OC} sorption	Fast method for estimating K_d. Does not require radiolabelled test material. May be helpful for volatile test materials	Variable retention times. Poor reproducibility

The preferred method for K_d/K_{OC} determination is the current gold standard, the OECD guideline 106 (OECD, 2000b). This recommendation concurs with the current EMA recommendation found in the EMA Questions and answers document (EMA, 2010). Determinations should be made with the appropriate matrix for the corresponding trigger (sludge K_{OC} for terrestrial; soil K_{OC} for groundwater/ water). Reading across matrices using K_{OC} should be avoided in determining whether a particular trigger has been exceeded.

2.3.4 Regulatory trigger values: Appropriateness, assumptions and gaps in science

EMA ERA Guidance (EMEA, 2006) currently uses a K_{OC} > 10,000 l/kg as a trigger for a Tier B terrestrial data package. The K_{OC} trigger value is based on a K_d of 3,700 l/kg sludge with an organic carbon content of 37% (EMEA, 2006). The questions and answers document (EMA, 2010) requires that a sludge K_{OC} value be determined using a batch equilibrium method and that HPLC method is not suitable for such a Tier B trigger assessment.

The trigger value implies that, when PEC surface water exceeds 0.01 µg/l and the K_{OC} for the test material exceeds 10,000, there is a potential risk for the terrestrial compartment. It is not clear whether the current trigger is protective of the terrestrial compartment for circumstances of a high volume compound with a K_{OC} value lower than 10,000. There is also a need to update the original terrestrial data set with new data generated since 1997 for both human and veterinary pharmaceuticals, and then reassess the appropriateness of the trigger. It would be helpful to broaden the number of classes of pharmaceutical active ingredients represented in the original data set beyond that of antibacterial, antimicrobial, anticoccidal, parasiticides and performance enhancers (Schmitt et al. 2010).

2.4 Hydrolysis

Hydrolysis information is critical before embarking on any kind of partitioning analysis. Hydrolysis is defined as a reaction of a test substance RX with water, with the net exchange of the group X with OH at the reaction centre. Where this occurs irreversibly, there will be a net disappearance of the substance RX with time, thus confounding any measurement of partitioning behaviour of the substance RX. An alternative form of hydrolysis can result in the incorporation of both the H and OH moieties into a single product.

There are a number of recognised methods for the measurement of hydrolysis at a fixed temperature. The available methods are effectively identical and are thus equally applicable. The principal protocols are given in the guidelines: OECD 111 – Hydrolysis as a function of pH, OPPTS 835.2120 – Hydrolysis and OPPTS 835.2130 – Hydrolysis as a function of pH and temperature.

The existing standard methods are recommended as being sufficiently appropriate for the characterisation of hydrolysis rates for ERA when needed. Details and references are provided in Appendix D.

2.5 Biodegradation

A chemicals' 'Persistence' is an important attribute in communicating the potential hazard (hazard identification) (ECHA, 2008c) of that chemical as well as in refining its PEC for ERA (EMEA, 2006). Both require data from biodegradation studies to either substantiate potential hazard identification, or to measure degradation kinetics that can be used to refine a PEC. Biodegradation tests may target specific

environmental compartments (sewage treatment, aquatic, terrestrial, benthic, and air) and generally fall into 3 tiers of testing, at screening ('ready'), intermediate ('inherent') and definitive ('simulation') level, that provide respective answers as to: i) whether a chemical will rapidly and completely biodegrade or not; ii) whether it has the potential to biodegrade; and iii) to what rate and extent does a chemical biodegrade. The three tiers typically progress in complexity and intend to simulate real conditions, specificity of endpoints, time to conduct the study and overall costs (Bowmer and Leopold, 2004; ECHA, 2008a). Overall, one will find a variety of standardised methods available as a result of this dual use of biodegradation data for hazard identification and risk assessment, the potential application of biodegradation testing across a variety of diverse regulatory frameworks (industrial chemicals, biocides/pesticides, fragrances, PCPs, pharmaceuticals), and the 3 levels or tiers of test methods employed. Standardised methods are available from OECD, as well as their equivalents found in OPPTS and MITI.

The next sections provide a high level overview of the OECD test guidelines typically used, whilst noting where certain test methods may be preferred for ionisable substances to what is currently recommended by the industry sector or regulatory framework. The authors acknowledge that, while this is a current topic of interest and debate, it is not the intention to capture all of the perspectives and nuances that may be associated with a given test, class of chemical or regulatory framework.

Standard methods for the measurement of biodegradation (ready: OECD 301; inherent: OECD 302; and simulation: OECD 303, OECD 314, OECD 308 and OECD 309) have been summarised in Appendix E and evaluated in terms of their applicability to ERA of ionisable compounds and support a recommendation as to which method(s) are most appropriate.

2.5.1 Definition(s) according to OECD

The OECD in their guidelines distinguish 6 forms of biodegradation, as follows (OECD, 1981b, 1991, 1992a, 1992b, 2001, 2002, 2004a, 2008).

1. Ultimate biodegradation (mineralisation): The level of degradation achieved when the test compound is totally utilised by micro-organisms resulting in the production of carbon dioxide, water, mineral salts and new microbial cellular constituents (biomass).
2. Primary biodegradation (biotransformation): The alteration in the chemical structure of a substance, brought about by biological action, resulting in the loss of a specific property of that substance.
3. Readily biodegradable: An arbitrary classification of chemicals which have passed certain specified screening tests for ultimate biodegradability; these tests are so stringent that it is assumed that such compounds will rapidly and completely biodegrade in aquatic environments under aerobic conditions.
4. Inherent biodegradable: A classification of chemicals for which there is unequivocal evidence of biodegradation (primary or ultimate) in any test of biodegradability.
5. Half-life ($t_{0.5}$): The time taken for 50% transformation of a test substance when the transformation can be described by first-order kinetics; it is independent of the initial concentration.
6. Disappearance time 50 (DT_{50}): The time within which the initial concentration of the test substance is reduced by 50 percent.

2.5.2 Summary and recommendation

Table 7 presents a summary of methods to determine biodegradation of chemicals. There are no specific limitations for ionisable compounds. Details and references are given in Appendix E.

Table 7: Comparison of methods to determine biodegradation for ionisable compounds (adapted from OECD 2002; EMEA, 2006; ECHA, 2008a)

Method name	Key condition	Measured endpoint	Value	Advantage	Disadvantage
Ready biodegradation OECD 301A-F	Stringent. Biomass ≤ 30 mg/l. Test material 20 - 100 mg/l	DOC, CO_2 evolution, O_2 uptake, DO	Pass or fail	Cost effective for classification of substances that is readily biodegradable	Many compounds typically fail. Only for classification purposes or to action to stop additional testing requirements
Inherent biodegradation OECD 302A-C	Biomass 100 - 2,000 mg/l; 20 -30 ml/l (50 - 400 DOC/l)	DOC, O_2 uptake, chemical specific endpoint	Pass or fail	Intermediate test that may gain sufficient data without progressing to simulation	Not necessarily conclusive
STP simulation: activated sludge OECD 303A or OPPTS 835.3240	Biomass 2,000 mg/l. Test material 5 - 50 mg/l	Chemical specific endpoint	Elimination rate (k_e)	More realistic conditions. Refined STP kinetics; site specific	Resource intensive to conduct. Continuous flow system
STP simulations: biofilms/trickling filter OECD 303B or OPPTS 35.3260	Biofilms in rotating tube bioreactor; test material 5 - 50 mg/l	Chemical specific endpoint	Elimination rate (k_e)	More realistic conditions specific for trickling filter treatment plants. Refined STP kinetics; site specific	Resource intensive to conduct. Continuous flow system
Simulation: STP, mixing zone, river die-away OECD 314A-E	Biomass 0 (pelagic) to 2,000 mg/l (activated sludge). Test material 1 - 1,000 mg/l	Chemical specific endpoint; CO_2 evolution	Elimination rate (k_e)	More realistic conditions. Batch test system; relatively easy to conduct and maintain	Requires ^{14}C-labeled test material
Simulation: water-sediment OECD 308	3:1 ratio of sediment to water; low and high organic sediments	Chemical specific endpoint; CO_2 evolution	Elimination rate (k_e) total system; mass balance; disposition; metabolites > 10%	For veterinary medicines, regulatory and US EPA, total system half used to revise PECs	Requires ^{14}C-labeled test material. Highly bound residues interfere with determination of elimination rate. Unable to report sediment half-life in most instances. Output is difficult to interpret. Not appropriate as a screening test
Simulation: river die-away OECD 309	Biomass 0 (pelagic) to 0.01 - 1 g/l (suspended solids). Test material 1 - 100 µg/l	Chemical specific endpoint; CO_2 evolution	Elimination rate (k_e)	More realistic conditions. Refined river water kinetics; adaptive for renewal-semi-continuous conditions	Multiple concentrations

The preferred strategy is to demonstrate that a test substance is 'readily biodegradable' and that no further fate testing is required. This strategy, however, is not particularly relevant for all commodity products, especially for products designed for their stability and shelf life, such as pharmaceuticals. In such instances, the next best approach is to determine the chemical specific kinetic data such that the PEC for that particular compartment (sludge, water, soil and sediment) may be revised for the observed biodegradation. This provides the necessary information to estimate PEC/PNEC ratio, or risk quotient for the ERA. In instances where further refinement is necessary, and only then, does one proceed to simulation testing targeted to that particular commodity item and the specific conditions of the release scenario.

2.5.3 Regulatory trigger values: Appropriateness, assumptions and gaps in science

Biodegradation testing is not necessarily 'triggered' by any one condition, but rather considered a base set of tests for ERA. Typically it is conducted in a tiered testing strategy, first to rule out any test substance that is 'readily biodegradable', then advance to more 'intermediate' and 'definitive' chemical specific tests as needed for the risk assessment. It is critical to match the design of a particular test method to the use of the product and its main route of discharge into the environment for the data to be relevant for the risk assessment. Type of product, continuous or intermittent use, continuous or intermittent discharge, the level of discharge for a particular substance and the target compartment are all essential factors when considering what test to conduct and under what conditions.

Activated sludge and biofilm biodegradation tests represent the two most commonly used wastewater treatment systems (activated sludge and trickling filter). The two may give different results for wastewater removal for a given chemical substance, therefore it is important to select the most appropriate test for a given application and/or based on what is generally defined as acceptable in a given regulatory framework.

The sediment biodegradation test does not have an available suite of tests for screening, intermediate testing and definitive simulation testing, especially for substances that are discharged into fresh water rivers from wastewater treatment plants. It does not appear that the OECD 308 can adequately represent all of the discharge scenarios and/or use of products. This may potentially lead to either over- or under-estimation of potential environmental risks. In these instances it is recommended that the parent total system half-life be used for classifying the potential hazard, since the sediment half-life cannot be readily determined in most cases where high non-extractible residues are observed. Further research and method development work is needed.

A number of other knowledge gaps in the science still exist today with some fundamental questions about: i) biodegradation at trace levels vs. the levels typically measured in laboratory biodegradation tests; ii) significance of acclimation, especially for continuous discharges at trace levels; and lastly iii) the potential impact of bound residues to their bioavailability and to their ultimate fate in the environment.

3. ESTIMATED PARTITIONING PROPERTY DATA

Chapter 2 provides an overview of various analytical methods to determine partitioning property data required for an ERA. Comments are provided for each of the methods regarding their applicability of each of the test protocols towards ionisable organic compounds. Specifically, it is demonstrated that a number of test methods developed for K_{OW} tend to be inappropriate for ionisable organic compounds. Given the relative importance of the use of K_{OW} within the risk assessment framework (i.e. as a trigger value for persistence and bioconcentration testing, and for assessing bioavailability), having methods that can reliably and reproducibly measure physical-chemical properties such as K_{OW} is of paramount importance.

Faced with the challenge of how to prioritise large datasets of chemicals, many of which will have limited measured physical-chemical property data, many regulatory bodies utilise a suite of physical-chemical property estimation methods, or quantitative structure activity relationships (QSARs) (Cronin et al, 2003; ECETOC, 2003a). In an earlier ECETOC task force report (ECETOC, 2003b), which reviewed a number of QSARs, it was suggested that the majority of QSARs used for physical-chemical property estimations generally provide reliable estimations. Issues surrounding ionisable organic compounds, however, were raised, particularly with respect to estimations of K_{OC} (ECETOC, 2003). Consequently, the ERA of ionisable organic compounds is likely to be complicated due to the pronounced influence of ionic interactions, which are poorly accounted for within standard tests or property estimation methods (ECETOC, 2003a). The importance for improving the need to address 'difficult' substances, such as ionisable organic compounds is highlighted in a recent study by Franco et al (2010), who analysed a subset of the 117 000 pre-registered substances published on the ECHA website. The subset of chemicals defined contained 1510 chemicals, 49% of which are described as being partly or totally ionisable organic compounds (27% as acids; 14% as bases; and 8% as zwitterions) (Franco et al, 2010). Consequently, analogous to the emphasis of chapter 2, there is a need to examine the use and applicability of well-established physical-chemical property estimation methods used within the regulatory framework for ionisable organic compounds.

3.1 Description of API dataset

It is estimated that about 3,000 different chemical substances are used as APIs, and that the environmental fate and behaviour for only a small subset of these chemicals have been investigated (Richardson and Ternes, 2011). Consequently, the environmental fate and effects of APIs is an area of emerging concern. Based on work by Manallack (2009), who demonstrated that the majority of APIs are ionisable organic compounds (Section 1.1), it seems reasonable to assume that improvements to adequately assess the environmental risks of APIs need to focus on ionisable APIs.

It is well understood that the fate of chemicals in the environment is controlled by a combination of factors. First, are the prevailing environmental conditions, such as temperature, flows, physical and chemical composition of environmental media, and pH; second are the properties of the chemical that influence partitioning and reactivity; and third are the patterns of use, how is the chemical emitted to the environment, and is the emission episodic or continuous. Addressing each of these factors are essential

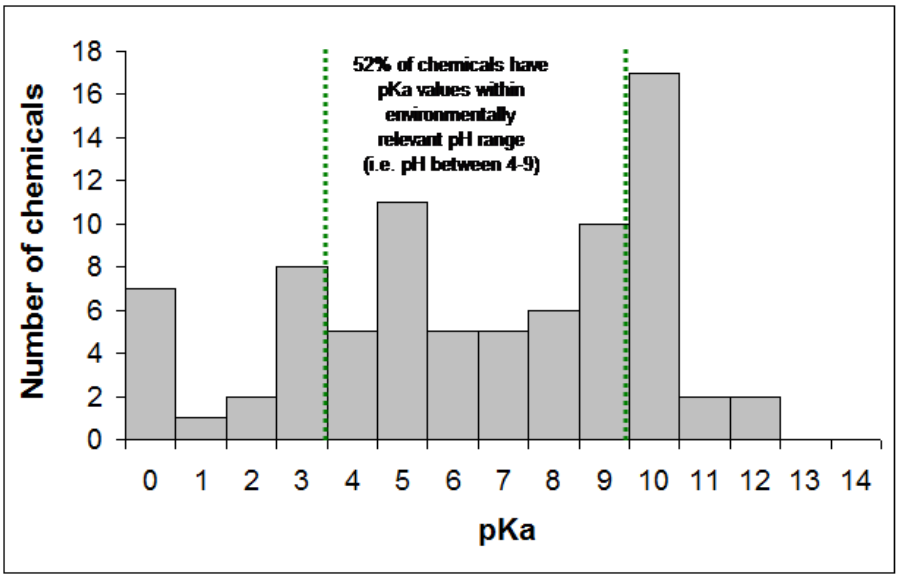
components to the ERA framework. For ionisable organic compounds, understanding and predicting how changes in the physical environment might influence the speciation and thus the fate and behaviour of the chemical is an area that is currently poorly understood (Boxall et al. 2012).

Over the last several decades there has been a great deal of effort that has gone towards assembling physical-chemical property data for a large number of neutral organic chemicals used in industrial applications or in general commerce. This information has been useful in helping define a variety of QSARs, which in turn are hoped to be useful in estimating environmental partitioning, reactivity, and uptake and effects on biota. In the case of pesticides, the application of QSARs has proved to be complicated by the large number of chemical classes, the frequent complexity of molecules, and the lack of experimental data needed to construct reliable QSARs. The current situation for APIs, with respect to the availability of reliable QSARs, is very similar to that of pesticides, except that it could be argued that the available data for APIs contains even greater variability than exists for pesticides. As discussed in Chapter 2, much of this variability can be attributed to analytical difficulties associated with measuring the various properties, or with the appropriateness of the test method. Additional analytical challenges are encountered when attempting to measure concentrations of APIs at very low concentrations.

In an effort to address the applicability of QSARs to estimate key property data, such as K_{OW} and K_{OC}, the Task Force assembled a database of chemicals used as APIs for which measured data have been made available. The database contains data for 81 APIs, including experimental data for pK_a, K_{OW}, D_{OW}, BCF, and K_{OC}. The data have been provided from companies represented on the Task Force, and have been produced following GLP guidelines. The data were thoroughly scrutinised and ranked according to the completeness of the property data typically required for an ERA. For instance, 26 chemicals have property data for pK_a, K_{OW}, and D_{OW} values measured at three different environmentally relevant pH; 17 chemicals have a similar dataset, except that there are only D_{OW} values measured at two environmentally relevant pH; whereas a further 26 chemicals have only one D_{OW} value. The completeness of the remaining APIs is more variable, and thus greater weight was placed towards those chemicals having the most complete set of property data.

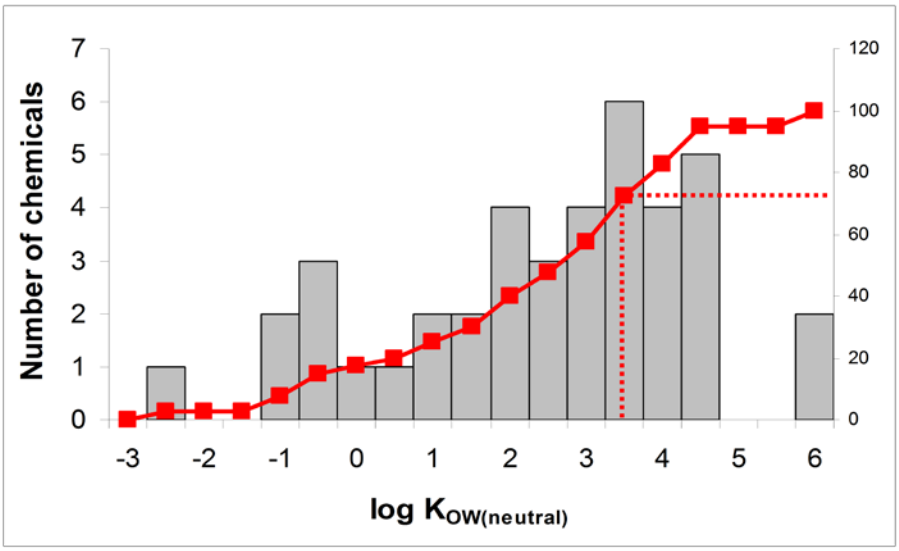
Figure 7 illustrates the distribution range of the first acid dissociation constants (pK_a) of the chemicals assembled within the API dataset. As can be seen 52% of the APIs have pK_a values within an environmentally relevant pH range (4 - 9). Approximately 44% of the APIs are polyprotic, with 20 chemicals having two pK_a values, and a further three have three pK_a values. The majority of APIs are ionisable organic compounds (88%), consisting mostly of bases (44%), acids (23%), and zwitterions (21%), whereas 5% are neutral organic compounds and 6% are always ionised.

Figure 7: Distribution of pK_a values reported for chemicals in the API dataset (Appendix F)



Given the importance of K_{OW} to the ERA framework, as illustrated by Table 5 which summarises the role of K_{OW} as a trigger value for BCF and PBT testing (Section 2.2.4), the task force devoted some energy towards examining the relevance of K_{OW} with respect to ionisable organic compounds. The distribution of log K_{OW} values represented in the assembled dataset is shown by the bar graph in Figure 8, based on measured data available for 40 chemicals among the API dataset. The line with dots shows the cumulative distribution, suggesting that approximately 25% of chemicals have a log K_{OW} value > 3.5, and would therefore possibly require BCF and/or PBT testing in the USA (Table 5 in Section 2.2.4). The relevance of this assumption is further explored in Chapter 4.

Figure 8: Distribution of log K_{OW} values measured for 40 chemicals in the API dataset (Appendix F) [a]



[a] As shown by the bar graphs. The line with dots shows the cumulative distribution.

In general, given the relative distribution inherent in the dataset, the assembled data are considered representative of the physical-chemical properties of APIs found in consumer use, and are thus useful in assessing the applicability of various QSARs for estimating the physical-chemical properties of APIs. Consequently, the data were used as a benchmark to assess QSAR performance and comments were made on their respective applicability. Ideally, the estimated values should correspond closely with measured values. Where there are significant discrepancies, however, the message that there remains a need to improve the estimation method in terms of accuracy and scope is reinforced.

3.2 Computational methods

The subject of estimating chemical properties from molecular structure and from related properties represents an area of active ongoing research. The ability to predict the behaviour of a chemical substance in a biological or environmental system largely depends on knowledge of the physical-chemical properties and reactivity of the chemical and closely related compounds. Chemical properties frequently used in an ERA include melting/boiling temperature, vapour pressure, various partition coefficients, water solubility, Henry's Law constant, sorption coefficient, bioconcentration factor, and diffusion properties. Reactivities, such as biodegradation, hydrolysis, photolysis, and oxidation/reduction are also critical determinants of environmental fate, and therefore typically used in risk assessment models, such as EUSES and the ECETOC targeted risk assessment. Unfortunately, measured values are often not available and where they are available, the reported data may be inconsistent or of doubtful validity. In these situations it may be appropriate and even essential to use estimation methods.

The relative importance for developing improved methods for estimating properties of ionisable organic compounds has been demonstrated in a number of recent studies that suggest that a significant number of chemicals used in commerce are partly or completely ionised in natural aquatic systems (Franco et al, 2010; Rayne and Forest, 2010; Boxall et al, 2012). Given that the majority of QSARs currently used within the regulatory framework have been typically developed on data based on neutral organic compounds, there is cause for concern regarding their use for ionisable organic compounds. In these instances, caution should be used in interpretation of estimated data. In this chapter, a review is presented of a number of commonly used property estimation methods, with an attempt to focus on methods defined as being applicable to ionisable organic compounds, such as SPARC and ACD, and methods that are more widely used, such as the EPI-Suite package of estimation programmes. Table 8 summarises the property data reviewed and the property estimation methods commonly used to estimate them. It is not a comprehensive list. For an in-depth review for methods used to estimate K_{OW}, please refer to Mannhold et al (2009), who review 30 state-of-the art methods, against 96,000 compounds. Liao and Nicklaus (2009), on the other hand, compare nine estimation methods for predicting pK_a values specifically for pharmaceutical substances. Doucette (2003) critically reviews a number of QSAR approaches for predicting soil-sediment sorption coefficients, or K_{OC}, and Pavan and Worth (2008) review estimation models for biodegradation. The references listed above provide a thorough summary of each of the methods, whereas the purpose of this chapter is to focus on those methods that are commonly used in the ERA of ionisable organic compounds, by industry and comment on their performance and applicability.

Table 8: Typical physical-chemical property data used in ERA of ionisable organic compounds and computer estimation programmes

Property data	Computer programme
K_{OW}	KOWWIN ACD/LogP SPARC ALogPS v. 2.1
pK_a	ACD/pK_a DB Pipeline PilotTM SPARC
Biodegradation	BIOWIN Catabol
K_{OC}	KOCWIN Various LFERs [a]

[a]Linear free energy relationships

3.2.1 log K_{ow}

The ratio of the concentration of a solute between water and octanol is a well-known property that is commonly used as a measure of hydrophobicity. The ratio is essentially independent of concentration, and is usually expressed in logarithmic terms (log K_{OW} or log P_{oct}), which are better suited for use as a free-energy based parameter in thermodynamic equations. There are a significant number of estimation methods that have been developed for log K_{OW}, and while no single review could possibly cover them all, the review by (Mannhold et al, 2009) provides a comprehensive summary of about 35 different methods. This report focuses primarily on the more commonly used methods, identified in Table 8 above, as KOWWIN, ACD/LogP, SPARC, and ALogPS v. 2.1.

KOWWIN

KOWWIN is an estimation method included in the suite of programs known as EPI (Estimation Programs Interface) Suite™. Other estimation methods included in EPISuite allow the user to estimate the properties for Henrys Law Constant, water solubility, vapour pressure, melting point, boiling point, etc., as well as estimates of a number of environmental fate endpoints (e.g. bioconcentration factor, atmospheric abiotic degradation etc.). It was developed and is maintained by the US Environmental Protection Agency (EPA) and the Syracuse Research Corporation (SRC). The current version of the program (version 4.1) is freely available for download at http://www.epa.gov/opptintr/exposure/pubs/episuite.htm. To estimate property and environmental fate endpoints a user simply inputs the chemical of interest to the interface as a SMILES code or by CAS, and all estimation programs can be run together. Alternatively, the user can run each of the estimation methods as stand-alone programs. Furthermore, a database is implemented containing one or more physical-chemical properties for more than 40,000 substances. These data may refine some of the model calculations.

The KOWWIN program estimates K_{OW} using an atom/fragment contribution approach. It was developed by Meylan and Howard (Meylan and Howard, 1995; Meylan et al, 1996; Meylan and Howard, 2000) using a training set of 2473 compounds, and a validation set of 10589 compounds representing molecules with simple to complex structures. From this 150 atom/fragments were defined and are used in combination with 250 correction factors, which account for steric interactions, H-bonding, and effects from polar substructures. The following general equation is used by KOWWIN for estimating log K_{OW}:

$$\log K_{OW} = \Sigma(f_i n_i) + \Sigma(c_j n_j) + 0.229 \quad \text{..... } \textit{(Eq. 19)}$$

Where f_i is the fragment coefficient, n_i the frequency of the fragment in the structure, c_j the correction factor coefficient, n_j the frequency of the factor in the structure, and 0.229 is the constant value generated by the multiple linear regression. KOWWIN also provides an alternative approach, whereby an experimental adjusted value can be used to better estimate the log K_{OW} of an unknown molecular structure based on the measured value of a molecule with a similar structure. Regarding calculations for charged molecules the most recent version of EpiSuite offers the possibility to draw the molecule including charges of single atoms.

ACD/logP

Like KOWWIN, the ACD/logP estimation method uses a fragment-based approach, whereby the contributions of separate atoms, structural fragments, and intramolecular interactions between different fragments are considered (Petrauskas and Kolovanov, 2000). The individual contributions have been quantified based on a database of about 18,400 structures having experimental log K_{OW} data, which resulted in over 1,200 different functional groups being defined with fragment contributions. The database for intramolecular interaction contributions contains increments for over 2400 different types of pair-wise group interactions. If a fragment or intramolecular interaction contribution for a molecule that is being estimated are not found, then the ACD/LogP program will calculate it through the use of a special secondary algorithm, and a larger uncertainty against the log K_{OW} estimate is defined. The value of log K_{OW} is thus calculated as:

$$\log K_{OW} = \Sigma f_j + (\Sigma Q_j) + \Sigma \text{aliph} - F_{ijk} + \Sigma \text{vinyl} - F_{ijk} + \Sigma \text{arom} - F_{ijk} \quad \text{..... } \textit{(Eq. 20)}$$

Where fi is the fragmental increments, Qj are the increments associated with superfragments, Fijk are increments of interactions between any two (ith and jth) groups separated by k-number of aliphatic, vinylic, or aromatic atoms.

The ACD/logP is part of a commercially available software package, licensed by Advanced Chemistry Development. More information is available at http://www.acdlabs.com/.

SPARC

SPARC (SPARC Performs Automated Reasoning in Chemistry) is a co-project founded by the Environmental Research Laboratory of the US-EPA and the Department of Chemistry of the University of Georgia. It uses existing knowledge to estimate different physical-chemical properties of substances as well as chemical reactivity parameters. On the basis of existing mathematical models SPARC is mainly working on theory and

mechanism of oriented substructure. Its computational approach is to analyse a substance's structure as well as its sub-structures relative to its different reactivities. Common theories in organic chemistry are applied to predict intermolecular interactions based on all available interaction forces e.g. dipole moment, induction, H-bonding etc. by use of the molecular sub-structure of the molecule. These sub-groups are functional groups with an intrinsic reactivity.

Within the current version 4.5 of SPARC estimations can be made regarding pK_a (also for solids and gases), log D, Henry's Law Constant as a function of pH, hydrolysis etc. as well as different properties like vapour pressure, boiling point, electron affinity, density, polarisability, Henry's Law Constant, solubility in water and other media, and distribution coefficients (e.g. log K_{OW}).

The fundamental approach used by SPARC is based on a blending of linear free energy relationships (LFERs), structure activity relationships, and perturbed molecular orbitals (PMO) to describe a variety of physical and reactivity parameters (Hilal et al., 2004). SPARC describes intermolecular interactions as a summation of all free energy changes :

$$\Delta G = \Delta G_{Dispersion} + \Delta G_{Induction} + \Delta G_{Dipole\text{-}dipole} + \Delta G_{H\text{-}Bond} + \Delta G_{other} \quad \text{.....} \quad \textbf{\textit{(Eq. 21)}}$$

Where the first four terms describe the change in the intermolecular free energy interactions accompanying the physical process of interest, in this instance the distribution of a chemical between octanol and water. Unlike the fragment-based approaches which calculate log K_{OW} based on the contributions of fragments contained within a molecule, SPARC calculates log K_{OW} by first calculating the activities of the chemical at infinite dilution in both octanol and water:

$$\log K_{OW} = \log \gamma^{\infty}_{octanol} - \log \gamma^{\infty}_{water} + \log R_m \quad \text{.....} \quad \textbf{\textit{(Eq. 22)}}$$

Where γ^{∞} are the activities at infinite dilution of the chemical in each phase, and R_m = -0.82, which is a coefficient that converts the mole fraction concentration to moles/l for water and octanol saturated with water. It is suggested that the water in the octanol phase makes the approach more realistic, as opposed to assuming a 'dry' octanol phase, since experimental methods will be using a saturated octanol phase in the test system. Although it is noted that the importance of including water in the octanol phase has a bigger influence on larger, hydrophobic molecules, as opposed to smaller molecules (Hilal et al. 2004).

The estimation method is freely available at http://archemcalc.com/sparc. The developers have also recently made available a commercial version that allows users to operate a stand-alone application, which may be appealing where proprietary chemicals are being assessed, or where batch runs are desirable.

Both SPARC and ACD/logP methods allow for the estimation of log D_{OW} values, whereby the influence of pH on ionisable organic compounds is accounted for in the calculations. The availability of this functionality has recently been utilised by Rayne and Forest (2010), who estimated the log D_{OW} values of 543 ionisable organic compounds listed on the Canadian Domestic Substances list. The study by Rayne and Forest (2010) demonstrated how the use of D_{OW} can significantly influence how chemicals might be screened for bioaccumulation potential and long-range atmospheric transport, as opposed to relying on log K_{OW} values, and they suggest that the use of log D_{OW} would be a more appropriate metric. This argument is echoed by Wells (2006) who also suggest that the use of log D_{OW} would lead to improvements in understanding the fate of ionisable organic compounds within waste water treatment systems. Consequently, the performance of

predictions of log D_{OW} is explored for both SPARC and ACD/LogP against measured data assembled in the dataset reported in Appendix F. The use of log D_{OW} within modelling tools is further assessed in Chapter 4, where the Task Force also speculate on its use within the regulatory framework as a potential trigger value for bioaccumulation potential and persistence testing.

ALogPS v. 2.1

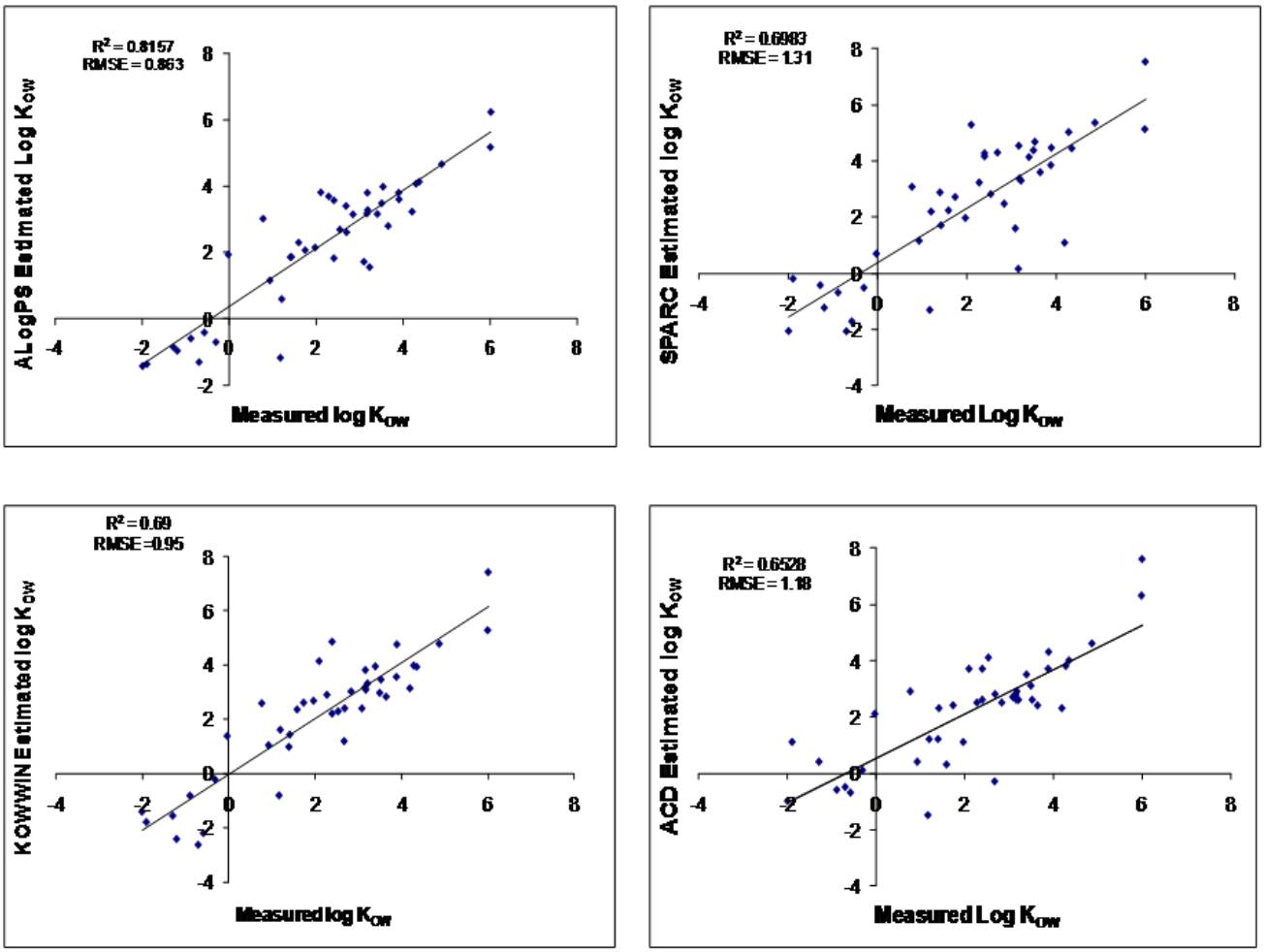
Using 75 descriptors, the ALogPS v. 2.1, freely available at http://www.vcclab.org/, uses a neural network method, based on 12908 molecules, with a RMSE of 0.35 (Tetko and Tanchuk, 2002; Tetko, 2002). The method used in ALogPS is based on E-state indices, which were developed to cover both topological and valence states of atoms, and have been used to develop QSARs for a number of physical-chemical and biological properties (Mannhold et al, 2009). The Task Force has included this method in their review based on results reported by Mannhold et al (2009), where the method is shown to perform relatively well on an extensive dataset. Indeed the results reported by Mannhold et al (2009) suggest that of the methods reviewed by the Task Force, the ACD/LogP performs best, followed by ALogPS and KOWWIN, both of which show similar performance, and then SPARC, which performed more poorly than the other three methods. Consequently, the four methods included in this review should thus reflect a range of relative performance with respect to estimating log K_{OW} the ratio of the concentration of a solute between water and octanol is a well-known property that is commonly used as a measure of hydrophobicity. The ratio is essentially independent of concentration, and is usually expressed in logarithmic terms (log K_{OW} or log P_{oct}), which are better suited for use as a free-energy based parameter in thermodynamic equations. There are a significant number of estimation methods that have been developed for log K_{OW}, and while no single review could possibly cover them all, the review by Mannhold et al (2009) provides a comprehensive summary of about 35 different methods. This report focuses primarily on the more commonly used methods, identified in Table 8, as KOWWIN, ACD/LogP, SPARC, and ALogPS v. 2.1.

Comparison of log K_{OW} estimation methods

Figure 9 summarises the comparison of the log K_{OW} estimated using the four different methods referred to in Table 8 against measured data reported in Appendix F. Results for SPARC and KOWWIN were shown to be comparable to one another, with ALogPS performing slightly better. ACD/LogP, which performed better than the other three methods in the review by Mannhold et al (2009), has a root-mean-square error (RMSE) of 1.18, which is comparable to previously reported observations.

Based on the results presented in Figure 9 for the class of chemicals investigated in this study, it is generally noted that ALogPS performs better than KOWWIN, ACD/LogP, and SPARC in estimating log K_{OW}. This is a curious observation, particularly given the near ubiquitous use of KOWWIN within regulatory agencies for screening chemicals for BCF and persistence testing. Careful interpretation of the data by the TF suggests that caution be used when relying on any single estimation program as a tool for estimating such trigger values, especially where molecules with complex molecular structures are being assessed.

Figure 9: Plots of log K_{OW} values estimated using different methods against measured values, for the chemicals in the dataset (Appendix F)



3.2.2 pK_a

Chapter 2 provides an overview of the underlying theory surrounding pK_a. Briefly, the acidity of organic compounds is widely recognised as an important property, particularly with respect to pharmaceuticals (Liao and Nicklaus, 2009; Lee and Crippen, 2009). Liao and Nicklaus (2009), suggest that along with the partition coefficient, solubility, and reaction rate, pK_a is a critical parameter used in drug formulation, since the degree of ionisation influences the solubility, dissolution rate, and gastrointestinal uptake into the bloodstream of an API. Consequently, large datasets of measured pK_a values for organic acids are available (for instance, Kortüm et al, 1960; Perrin, 1965; Serjeant and Dempsey, 1979; Dean, 1999; Lide, 1995). The majority of pK_a values are reported at 20 or 25°C, and at a given ionic strength, consequently, reported pK_a values may vary by about 0.3 pK_a units.

Estimation methods for pK_a have a relatively long history, with early approaches utilising empirical methods. For instance, Hammett (1940) introduced the use of a constant, which would account for the effect of substituents in either the meta- or para- position on the standard free energy change of dissociation of the carboxyl group. Consequently, linear free energy relationships (LFERs) that utilise Hammett Constants

represent an important group of pK_a estimation methods (Lee and Crippen, 2009). QSARs represent another group of estimation methods, whereby structural descriptors are defined as a tool for estimating pK_a, as are read-across methods that attempt to predict the pK_a of an unknown based on similarity in structure to a compound with a measured pK_a value (Lee and Crippen, 2009). More recently, quantum chemical methods have been developed, which attempt to predict pK_a from first principles (Liao and Nicklaus, 2009; Yu et al, 2011). The methods reviewed in this report each utilise an empirical approach.

ACD/pK_a DB

The ACD/pK_a DB uses a fragment-based approach for estimating pK_a values. The commercially available software consists of chemical structure fragments, and uses a proprietary algorithm to calculate predicted values for whole molecules based on its constituent fragments. pK_a values are derived using Hammett-type equations for more than 650 ionising centres (Manchester et al, 2010). The method is also extensively parameterised with more than 3,000 substituent constants and incorporates methods for estimating substituent effects for species outside the training set (Manchester et al, 2010). For instance, the commercial software has an option for adding proprietary experimental data, which can help improve the prediction accuracy for chemicals not adequately captured within the library. Additionally, an algorithm is implemented for estimating apparent pK_a values for multiprotic compounds, which can cause discrepancies between the predicted and measured values when the pK_a values of different ionising groups on the compound are within 1 to 2 log units (Manchester et al. 2010). More information regarding the ACD/pK_a DB can be found at www.acdlabs.com/physchem/.

Liao and Nicklaus (2009), Meloun and Bordovská (2007), and Manchester et al (2010) all observed that estimates of pK_a using the ACD/pK_a DB perform relatively well, especially when compared to other fragment-based approaches.

SPARC

As described above, the fundamental approach used by SPARC is based on a blending of linear free energy relationships (LFERs), structure activity relationships, and perturbed molecular orbitals (PMO) to describe a variety of physical and reactivity parameters (Hilal et al, 2004). As with the estimation of other properties, the molecular structure of a chemical input to SPARC, is classified into functional units defined as either a reaction centre or perturber (Hilal et al, 1996). The reaction centre (C) is the smallest subunit that has the potential to ionise and lose a proton to the solvent. The perturber (P) is the molecular structure appended to C. The perturber structure is assumed to be unchanged in the reaction. The pK_a value of an ionisable organic is expressed in terms of the contributions of both P and C:

$$pK_a = (pK_a)C + \delta P(pK_a)C \quad \text{..... } \textit{(Eq. 23)}$$

Where $(pK_a)C$ describes the ionisation behaviour of the reaction centre, and $\delta P(pK_a)C$ is the change in ionisation behaviour brought about by the perturber structure. SPARC computes reactivity perturbations that are then used to correct the ionisation behaviour of C in terms of potential mechanisms for interaction of P and C as:

$$\delta P(pK_a)C = \delta_{ele}(pK_a)C + \delta_{res}(pK_a)C + \delta_{solv}(pK_a)C + \delta_{H\text{-}Bond}(pK_a)C \quad \text{.....} \textit{(Eq. 24)}$$

Where $\delta_{res}(pK_a)C$, $\delta_{ele}(pK_a)C$, $\delta_{sol}(pK_a)C$, and $\delta_{H\text{-}Bond}(pK_a)C$ describe the differential resonance, electrostatic interaction, solvation, and hydrogen bonding of P with the protonated and unprotonated states of C respectively.

More information about SPARC for estimating pK_a and its use in estimating pK_a values for relatively large numbers of chemicals is given in Hilal et al (1994; 1995) and more recently by Meloun and Bordovská (2007).

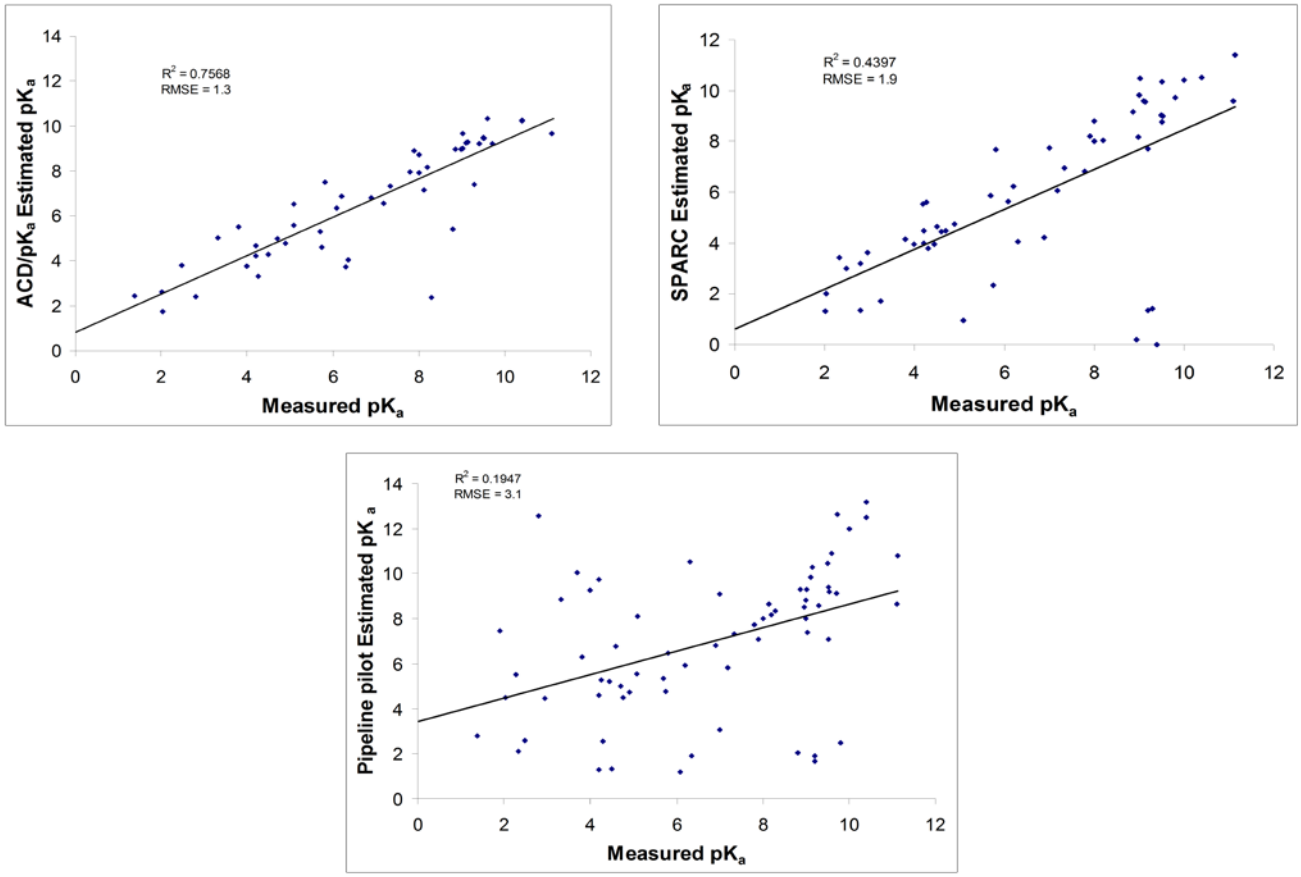
Pipeline PilotTM

A topological method is utilised in the Accelrys Pipeline PilotTM software package, in which ionising centres are captured using what is referred to as 'path fingerprints' (Manchester et al, 2010). The Pipeline PilotTM program consists of six models, trained on about 12000 chemicals, which are used to classify aliphatic and aromatic acids and bases, phenols, and heterocyclic amines. If a test compound cannot be classified into one of the six groups, then a generic model based on either all acids or all bases is used. The models correlate the presence of specific paths of up to six atoms from an ionising centre with the difference in pK_a of that centre relative to the mean for its respective category (Manchester et al, 2010). More information about Pipeline PilotTM can be found at http://accelrys.com/products/pipeline-pilot/.

Comparison of pK_a estimation methods

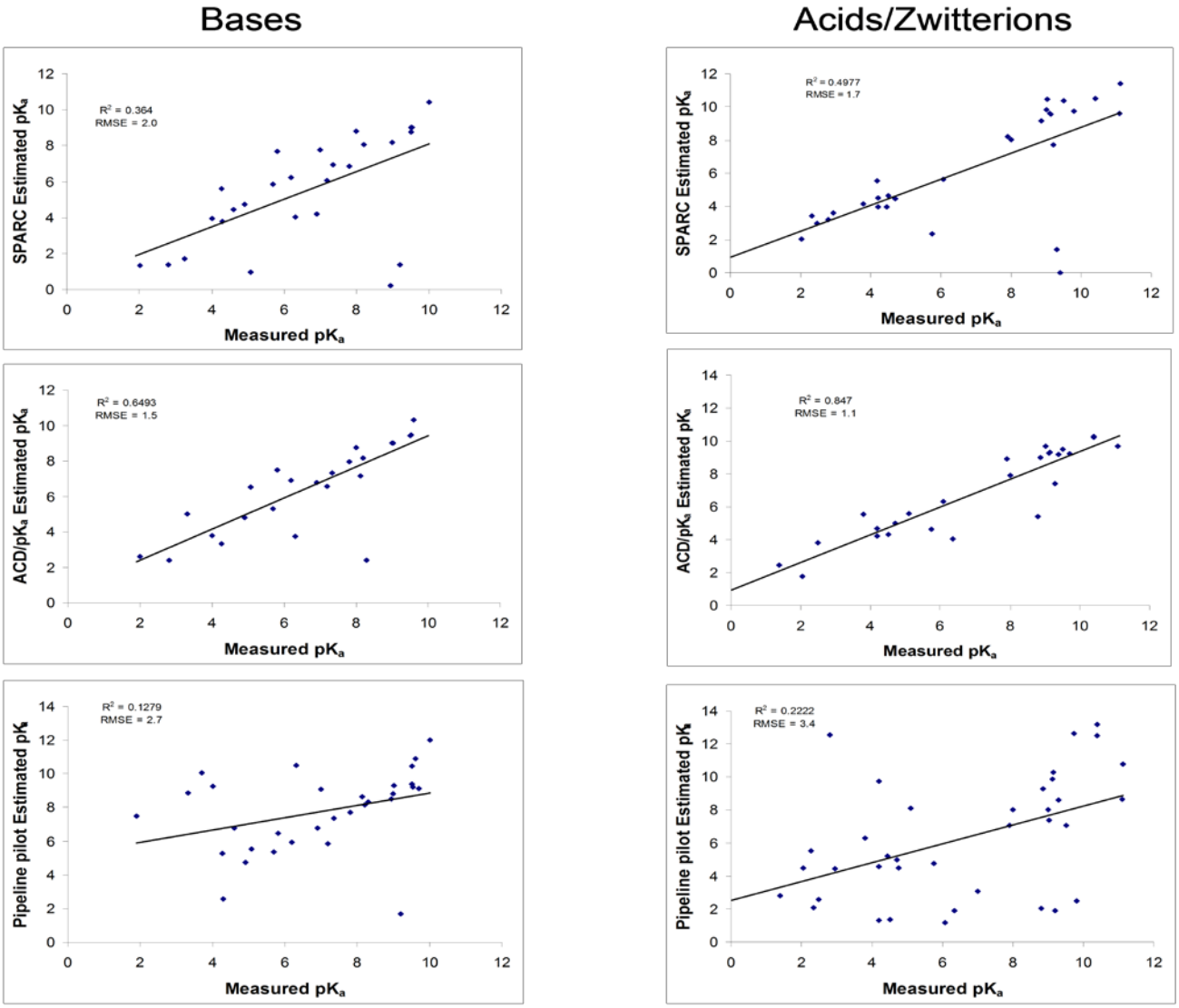
Figure 10 summarises the comparison of methods against measured values for data listed in Appendix F. Generally, the ACD/pK_a method performed relatively better than both SPARC and Pipeline Pilot, which is consistent with observations by Liao and Nicklaus (2009). The relationships shown in Figure 10, however, tend to be poorer than those reported by Liao and Nicklaus (2009). Two possible reasons are suggested for why the observed discrepancy may exist. First, the current comparison between measured data and estimation methods is not as thorough as that by Liao and Nicklaus (2009), in that no attempt was made to identify the individual protonation sites for each of the molecules included in the dataset. Rather, a simple comparison was made of the first dissociation constants between the measured data and the estimation programs. Closer examination of the data suggests that in some instances the measured data may not be as robust as the estimation method in defining the first dissociation constant, and it may be that the data are limited to reporting pK_a data within a physiologically relevant pH range (typically at pH of 7.4). Thus, there are some concerns regarding the accuracy of the measured data. Second, Liao and Nicklaus (2009) as well as Balogh et al (2009) observed that several of the estimation methods for pK_a performed significantly poorer when estimating pK_a values for chemicals with protonation sites in the pK_a range of 5.4 to 9.4, including ACD/pK_a, Pipeline Pilot, and SPARC. Nevertheless, Liao and Nicklaus ,(2009) observed that most of the estimation methods they assessed performed generally very well, and suggest that they are useful tools in drug development.

Figure 10: Plots of log pK_a values estimated using different methods against measured values, for the first dissociation of chemicals in the dataset (Appendix F)



When comparing the performance of the different methods for bases as opposed to acids and zwitterions, it is interesting to see that most methods tend to show poorer performance when predicting pK_a values of bases, but do relatively well when just predicting pK_a of acids and zwitterions. Figure 11 illustrates these different relationships. It is unclear what might be driving this observation, but even with the relatively small dataset, it is of interest to note that the observation is consistent with results reported by Yu et al (2011). It is further demonstrated that both ACD and SPARC are prone to error when encountering ortho- substitution of aromatics and intramolecular H-bonding accompanying ortho- substitution (Yu et al, 2011).

Figure 11: Plots of log pK_a values estimated using different methods against measured values, for the first dissociation of bases and acids/zwitterions



A number of recent studies, in addition to that of Liao and Nicklaus (2009), have provided additional assessments between various estimation methods (see for instance Meloun and Bordovská (2007); Balogh et al (2009); Manchester et al (2010); Yu et al (2011)). The ACD/pK_a method consistently performs better than the three other estimation methods. Thus, the predictions based on ACD/pK_a are likely to be more accurate than other methods, which is an important factor when utilising pK_a data in the estimation of log D_{OW}. As a way to increase the level of confidence, the TF also supports the recommendation of Yu et al (2011) who suggest a consensus modelling approach, which would combine output from ACD and SPARC, whereby similar predictions between the two methods would provide a lower level of uncertainty.

3.2.3 log D_{OW}

Whereas the K_{OW} of a substance is defined as the ratio of the concentration in octanol and water for the neutral species, for ionisable organic compounds, the distribution ratio is defined as:

D_{OW} = (concentration in octanol phase) / (Concentration in buffer phase) ..... ***(Eq. 25)***

Where the concentration in octanol is represented by the total concentration of an ionisable organic in octanol, which is assumed to be dominated by the non-dissociated form, and concentration in the buffer phase will be represented by the fraction in dissociated and non-dissociated forms, depending on the pH and pK_a of the substance.

The magnitude of D_{OW} may nevertheless be relatively large, regardless of changes in pH, particularly if the molecule contains a significant hydrophobic component, whereby the dissociated form may still behave similar to the neutral species. The type and amount of counter ions present in the test system can also significantly influence the partitioning behaviour (Csizmadia et al, 1997). Thus, estimating the octanol-water distribution ratio of an organic acid or base requires consideration of a variety of species in both phases.

In general terms, it has been observed that the partition coefficient of the neutral species is typically more than two orders of magnitude larger than the distribution ratio of the ionic species. Thus at pH < pK_a +2 for acids and pH > pK_a -2 for bases, the neutral species is the dominant species in determining D_{OW}. While this general rule has been shown to apply to monoprotic substances, complications arise when faced with polyprotic or zwitterions, where the problem of predicting log D_{OW} becomes more complicated (Csizmadia et al, 1997). Nevertheless, assuming that only the neutral form of the molecule will partition into the organic phase, it should be possible to estimate the log D_{OW} value of a substance from log K_{OW} and pK_a as:

$$\log D_{OW}(pH) = \log K_{OW} - \log(1 + 10^{(pH - pKa)\Delta i}) \quad \textit{(Eq. 26)}$$

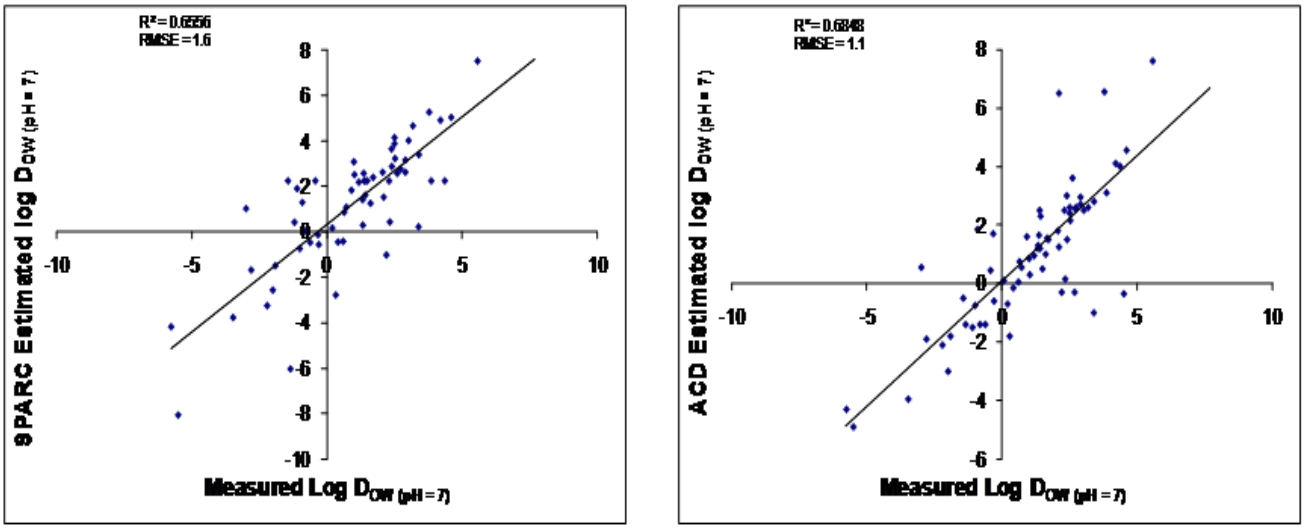
Where $\Delta i = 1$ for acids and -1 for bases.

If the molecule in question has several functional groups that can be ionised, resulting in more than one pK_a value, correction terms must be included in the above equation for each species (see for instance Csizmadia et al, 1997). Thus, log D_{OW} can be subject to error due to errors in both log K_{OW} and pK_a predictions (Livingstone, 2003; Kah and Brown, 2008). Of the log K_{OW} estimation methods assessed here, only ACD/logD and SPARC have the capacity to estimate log D_{OW}. ALogPS does have the capacity to estimate log D_{OW} based on self-learning properties of associative neural networks, but the method requires measured data of chemicals with similar structures to be input. The method utilised by ACD/logD and SPARC is based on the approach described by (Csizmadia et al. 1997).

In their comparison of different estimation methods to predict log D_{OW} of six acidic pesticides (Kah and Brown, 2008), observed that deviations in log D_{OW} predictions were strongly influenced by predictions of the pK_a and log K_{OW}. Nevertheless, it was suggested that predictions of log D_{OW} from SPARC performed better than values derived from other estimation packages, including ALogPS and KOWWIN (Kah and Brown, 2008). It should be noted, however, that the assessment by (Kah and Brown, 2008) is based on a relatively small dataset, limited to six acidic pesticides, and that their analysis may not extend to other classes of chemicals, such as APIs.

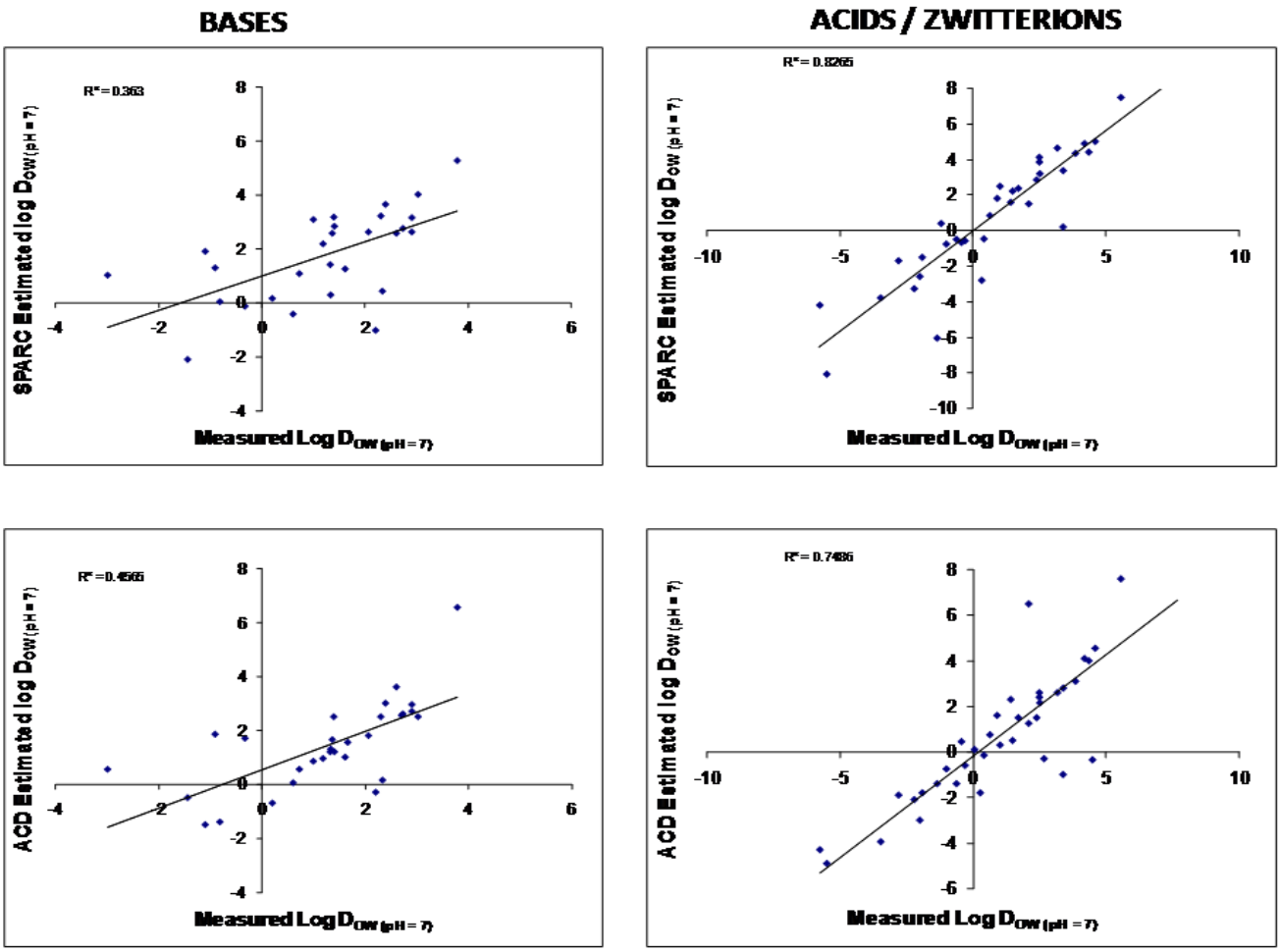
In an effort to investigate the relative performance of both ACD/logD and SPARC to estimate log D_{OW} values, the estimates were compared against measured data reported for chemicals in Appendix F. Figure 12 summarises the comparison between the different methods and measured data.

Figure 12: Comparison of estimated log D_{OW} at pH = 7 with measured data reported in Appendix F for both SPARC and ACD.



The data indicate that a good, linear and positive correlation between measured and calculated log D_{OW} values is given. Considering that calculations of log D_{OW} largely depend on the accuracy of pK_a and log K_{OW}, the bases were separated from the acids and zwitterions, as done in Figure 10, to assess any changes in relative performance. The results indicate a significant decrease in the predictive powers of log D_{OW} for bases using either SPARC or ACD, which is most likely related to poorer predictions of pK_a for bases, as shown in Figure 13 on the left. The graphs on the right side of Figure 13 illustrate that both SPARC and ACD perform better for acids/zwitterions than they do for bases. It is suggested that to further highlight the importance of having good estimates and/or measured data to assist in estimating log D_{OW}.

Figure 13: Comparison of predicted log D_{OW} against measured data reported in Appendix F, separated for bases and acids/zwitterions.



Based on the results in Figures 12 and 13, the TF recommends that estimates of log D_{OW} for APIs be based on a combination of approaches, i.e. using both ACD and SPARC, and that caution be used particularly when using estimated values for bases as opposed to acids/zwitterions. This is because estimates of log D_{OW} using either SPARC or ACD/logP are based on estimates of pK_a and log K_{OW}, and therefore errors in those estimates will be translated in the calculation of log D_{OW}. Since estimates of pK_a values for bases tend to be less reliable then for acids/zwitterions, the propagation of this error with respect to D_{OW} estimates is inevitable.

3.2.4 log K_{OC}

Fate, transport, and risk assessment models all contain terms for sorption to organic carbon in soils, sediment, and sludge. Sorption to solids is often the key process that controls the removal of organic compounds in municipal waste treatment plants, affecting both the efficiency of the treatment system and the management of wastewater solids. In many instances, a linear relationship between the concentration of chemical sorbed to solids and the concentration in water can exist, which leads to the equilibrium sorption coefficient, K_d. There are a number of variables that can influence the magnitude of the sorption coefficient, all of which are dependent on a variety of intermolecular interactions that can occur between

the solute and the solid and aqueous phase, including quantity of organic matter and type, clay mineral content and type, clay to organic matter ratio, particle size distribution and surface area of the sorbent, pH, ionic strength, suspended particulates or colloidal material, temperature, dissolved organic matter concentration, solute and solid concentrations, and phase separation techniques. Consequently, there are instances when a nonlinear sorption isotherm can be observed, whereby a Freundlich model is used to describe the relationship between the sorbed and aqueous phase concentration.

The sorption coefficient for a given organic chemical can vary dramatically between different types of soils or sediments, depending on the properties of the sorbent. Nevertheless, it has been demonstrated that the sorption coefficient for a large number of organic chemicals, particularly neutral hydrophobic organic compounds, is directly proportional to the quantity of organic matter associated with the solid. Thus a normalised organic carbon to water partition coefficient (K_{OC}), described as the ratio between the sorption coefficient K_d, and the organic carbon content of the sorbent, in units of mass of organic carbon (OC) per mass of soil (g OC/g soil) is commonly used to assess the extent to which an organic chemical is sorbed (Hamaker and Thompson, 1972).

$$K_{OC} = K_d/OC \quad \text{.....} \quad \textit{(Eq. 27)}$$

Given the importance surrounding the role of organic carbon in relation to sorption the vast majority of methods that have been developed to estimate K_{OC} are based on chemical descriptors used to define hydrophobicity, in particular K_{OW} and aqueous solubility (S) (Doucette, 2003). Estimation methods based on K_{OW} or S tend to be based on regression analysis. Doucette (2003) summarises a large number of different methods that have been developed to estimate K_{OC}, including both regression-based as well as structural-based models. Doucette (2003) suggests that the use of K_{OC} for predicting sorption of nonpolar organic compounds onto soils and sediments is an appropriate approach, and that even for polar or ionisable organic compounds, or in instances where the organic carbon content of the sorbent is relatively low (< 0.1%), K_{OC} can still be used to provide a conservative estimate of sorption. However, as noted by Doucette (2003), the use of K_{OC} for estimating sorption of organic acids and bases assumes that the neutral form, or hydrophobic component, of the chemical dominates the interactions with the sorbent at the pH of the solution.

Used within a regulatory context, it should be noted that recommendations given in the EU TGD (EC, 2003) suggest that the basic parameters used in the exposure assessment, such as K_{OW} and K_d, are only applicable to the neutral form of a chemical, and that a correction needs to be made in order to assess the undissociated fraction of the compound at a given pH. However, in the absence of measured data the TGD does provide a number of QSARs for specific groups of substances for estimating K_{OC}, but also recommends assessing worst case scenarios by using high K_{OC} values, for instance in the case of cationic substances where it is suggested that strong sorption is known to occur. The TGD also notes that estimating K_{OC} based on corrected K_{OW} values for acids and bases as input to SimpleTreat may lead to an overestimation of the aquatic exposure concentration, since SimpleTreat predicts a low elimination on the basis of K_{OW}, whereas sorption to sludge may be a significant elimination mechanism (EC, 2003).

Table 9 provides a summary of a number of regression-based QSARs that have been proposed for various groups of chemical classes taken from the EU TGD (EC, 2003). Caution is recommended when applying these regressions for ionisable organic compounds.

Table 9: Summary of regression-based QSARs described in EU TGD (EC, 2003)

Chemical class	Regression ($\log K_{OC} = a \times \log K_{OW} + c$)		Statistics [a]		
	a	c	n	r^2	Standard error
Phenols, anilines, benzo-nitriles, nitrobenzenes	0.63	0.9	54	0.75	0.40
Acetanilides, carbamates, esters, phenylureas, phosphates, triazines, triazoles, uracils	0.47	1.09	216	0.68	0.43
Alcohols, organic acids	0.47	0.5	36	0.72	0.39
Acetanilides	0.40	1.12	21	0.51	0.34
Alcohols	0.39	0.5	13	0.77	0.40
Amides	0.33	1.25	28	0.46	0.49
Anilines	0.62	0.85	20	0.82	0.34
Carbamates	0.37	1.14	43	0.58	0.41
Dinitroanilines	0.38	1.92	20	0.83	0.24
Esters	0.49	1.05	25	0.76	0.46
Nitrobenzenes	0.77	0.55	10	0.70	0.58
Organic acids	0.60	0.32	23	0.75	0.34
Phenols, benzonitriles	0.57	1.08	24	0.75	0.37
Phenylureas	0.49	1.05	52	0.62	0.34
Phosphates	0.49	1.17	41	0.73	0.45
Triazines	0.30	1.50	16	0.32	0.38
Triazoles	0.47	1.41	15	0.66	0.48

[a] n, number of samples; r^2, coefficient of determination (end of Section 2.3.2)

Many of the QSARs described are largely based on polar and ionisable pesticides and industrial chemicals, but may have limited applicability to chemical groups typically associated with pharmaceutical active ingredients. Whereas two regressions listed are applicable for organic acids, there is limited information regarding how to estimate the partitioning of organic bases, amphoters, or other electrolytes. Since it is anticipated that the charged species of an organic base has the potential for significant electronic interactions with negatively charged surfaces in the environment, the lack of a defined relationship likely leads to greater uncertainty regarding the reliance of the PEC calculated for organic bases.

Franco and Trapp (2008) attempted to address the lack of consideration given to organic bases within the EU TGD by investigating the sorption of 164 electrolytes, composed of 65 bases, 93 acids, and six amphoters. Franco and Trapp (2008) expanded the linear regressions summarised in Table 9 to include consideration of the pK_a of the acid, base, or amphoter. Table 10 summarises the suggested regressions for the prediction of K_{OC}.

Table 10: Summary of regressions described by Franco and Trapp (2008)

Chemical class	Equation [a]	pH_{opt}
Organic acids	$\log K_{OC} = \log (\phi_n \cdot 100.54 (\log P_n + 1.11) + \phi_{ion} \cdot 100.11 (\log P_n + 1.54)$	5.8
Organic bases	$\log K_{OC} = \log (\phi_n \cdot 100.37 (\log P_n + 1.70) + \phi_{ion} \cdot 10pK_a \text{^} 0.65 (f \text{^} 0.14))$	4.5
Amphoters	$\log K_{OC} = \log (\phi_n \cdot 100.50 (\log P_n + 1.13) + \phi_{neg} \cdot 100.11 (\log P_n + 1.54 + \phi_{pos} \cdot 10pK_a \text{^} 0.65(f \text{^} 0.14)$	5

[a] Where: ϕ_n and ϕ_{ion} refer to the fractions of a chemical in its neutral and ionised state, ϕ_{neg} and ϕ_{pos} refer to the negative and positive charge fractions of an amphoter, P_n refers to the octanol-water partition coefficient of the neutral species, f is $K_{OW}/(K_{OW} + 1)$, and pH_{opt} is the pH to input for the calculation of the neutral and ionic fraction.

In each of the equations shown in Table 10, the first term quantifies the hydrophobic absorption of the neutral fraction, and the second term quantifies the contribution associated with the ionic fraction. This approach of separating the sorption behaviour of the ionising species from the neutral species is believed to provide a more robust estimate of sorption, as opposed to simply combining both fractions as is the case with the regressions shown in Table 9.

In addition to the linear regression models captured in Tables 9 and 10, other methods including non-linear relationships (Wen et al, 2012), molecular connectivity indices (Sabljic 1987; Schuurmann et al, 2006), and those based on linear solvation energy relationship (LSER) models (Nguyen et al, 2005; Kipka and di Toro, 2011a,b) have also been proposed. Consequently there are a variety of approaches available for estimating K_{OC}, many of which are not formally identified as being applicable for use within an ERA under the EU TGD. Models that appear to be more applicable to ionisable organic compounds, such as the LSERs, non-linear regressions, or those based on molecular structure, tend to be somewhat more complex in nature and may therefore lack the transparency that the linear regression-based approaches defined in Table 9 provide. Thus, from a regulatory perspective, methods that tend to be simple and transparent would be preferable, but unfortunately these methods do not appear to perform well for ionisable organic compounds, typically overestimating the PEC. A confounding problem related to the use of linear regression-based methods pertains to how K_{OW} is defined, i.e. whether it is measured or estimated, and whether the value reflects the neutral or ionised species, and what the pH of the reference system is in relation to the pK_a of the substance. Given the importance of K_{OC} in estimating removal of organic chemicals by sorption processes, particularly in a waste water treatment system, there appears to be a need to re-examine how K_{OC} is estimated within a regulatory context, particularly for ionisable organic compounds. This issue is explored in greater detail in Chapter 4.

3.2.5 Biodegradation

Biodegradation refers to the transformation of a chemical by enzymatic reactions in micro-organisms. In soil and sediment, biodegradation is often the most important factor in the removal of the chemical from the environment. Depending on the ambient conditions, different modes and rates of biodegradation may predominate and may make a chemical readily biodegradable at one site, but not at another, largely due to different degradation capacities of the surrounding environment. In general, microbial transformation is the main mechanism by which an organic chemical can be completely mineralised. In Chapter 2 a review of various OECD biodegradation test systems are summarised, and their applicability to ionisable organic compounds is discussed. This Section briefly reviews some of the more common estimation methods used for biodegradation.

Like other estimation methods, approaches to estimate biodegradation can be categorised according to the development method. The most common approaches are chemical class-specific regression models, expert systems (including probabilistic models) and hybrid approaches. A recent review by (Pavan and Worth, 2008) provides a more thorough review of the various estimation methods. Complementing the biodegradation review is the summary of biodegradation removal of pharmaceuticals in waste water treatment systems by (Onesios et al, 2009), which provides an indication of some of the challenges associated with estimating removal by biodegradation of the APIs that are highlighted in this report.

BIOWIN

The biodegradation probability program (BIOWIN) represents one of the most widely used estimation method for the biodegradation of general chemicals (Pavan and Worth, 2008). The program was developed by the Syracuse Research Corporation on behalf of the US EPA, and is freely available for download at http://www.epa.gov/oppt/exposure/docs/episuitedl.htm. There are currently seven different modules included in the BIOWIN program that include both linear and non-linear regression models based on 36 pre-selected fragments and molecular weight. Table 11 summarises each of the different models.

Table 11: Summary of BIOWIN models [a]

Number	Description
1.	Linear probability model based on the BIODEG database. Gives quantitative prediction of the probability that a chemical biodegrades 'fast'
2.	Non-linear probability model based on the BIODEG database. Gives quantitative prediction of the probability that a chemical biodegrades 'fast'
3.	Ultimate biodegradation model based on expert survey. Semi-quantitative prediction based on the following subjective scoring of persistence: 5 = hours; 4 = days; 3 = weeks; 2 = months; 1 = recalcitrant
4.	Primary biodegradation model based on expert survey. Semi-quantitative prediction based on the following subjective scoring of persistence: 5 = hours; 4 = days; 3 = weeks; 2 = months; 1 = recalcitrant
5.	Linear probability model based on the Japanese MITI database. Gives quantitative prediction of the probability that a chemical is readily biodegradable or non-readily biodegradable, i.e. whether it passes or fails the MITI test
6.	Non-linear probability model based on the Japanese MITI database. Gives quantitative prediction of the probability that a chemical is readily biodegradable or non-readily biodegradable, i.e. whether it passes or fails the MITI test
7.	Linear probability model to predict anaerobic biodegradation, based on the conditions of the 'serum bottle' test

[a] Adapted from Pavan and Worth, 2008

The BIOWIN model is used as a tool within the EU TGD to assess persistence when no data are available for a particular substance, or the available data are difficult to interpret (EC, 2003). The EU TGD recommends the use of the BIOWIN2 model output < 0.5 or BIOWIN6 model output < 0.5 and BIOWIN3 output ≥ months (< 2.2) should reliably indicate a substance that will not readily biodegrade, and therefore has the potential to be persistent in the aquatic environment EC, 2003). In general the recommendations present in the EU TGD reflect the performance of the BIOWIN models, in that they typically perform well when predicting non-readily biodegradable substances better than predicting readily biodegradable substances.

A shortcoming of the BIOWIN models is that they utilise a fragment approach, and therefore poorly account for the influence of neighbouring substituents and substituent position (ref BIOWIN programme). Two examples for which known problems exist are chlorinated phenols and napthoic acids. Other problems with the approach are related to the summation of fragments, no matter what their type or number, which can work well when the molecule in question is small but leads to errors when the frequency of the fragment in the molecule is relatively large. Additionally, not all fragments of significance for biodegradation are included, and it is acknowledged that BIOWIN lacks fragment coefficients for phosphonate; imidazole ring; pyrimidine ring; ethoxylate ether; cycloaliphatics; quaternary nitrogen (except BIOWIN7 which does have this fragment); and others. If a chemical contains a unique or unusual substructure not included in the model's fragment library, these features will not be considered in the prediction process. About 20% of the APIs included in Appendix F include either an imidazole or pyrimidine ring, and in some instances both. Nevertheless, based on the output from the BIOWIN programme, the majority of substances listed in Appendix F would be classified as non-readily biodegradable, with only 5 chemicals being identified as readily degradable (phenyephrine; piperazine; pregabalin; zanamiver; mupirocin). The criteria for predicting readily degradable is if the BIOWIN3 result is ‘weeks' or faster and the BIOWIN5 probability is ≥ 0.5. This observation is in general agreement with empirical data that attempt to measure the removal efficiency of APIs in waste water treatment systems, where it is widely acknowledged that the dominant removal mechanism is via sorption to suspended organic matter that is subsequently removed by coagulation (Oulton et al., 2010).

OASIS

The most recent version v5.11.1 offers the user two main fields of applicability namely biodegradation and bioaccumulation, both of high relevance regarding the hazard assessment of chemical substances. However, further detail regarding the relevance of the bioaccumulation model for ionisable organic compounds requires further investigation, as this represents an area of emerging research.

The biodegradation models are separated into two sub-groups: CATALOGIC models which apply metabolic pathways and kinetic information on transformation and the so called pioneer models of CATABOL which are not accounting for such techniques. (Table 12).

Table 12: OASIS biodegradation models

	OECD test guideline
CATALOGIC	
Abiotic 28 days – MITI	301C
BOD Kinetic	301F
Soil BioPath	-
BOD 28 days – MITI	301C
CATABOL	
BOD 28 days – MITI	301C
BOD 28 days – READY Sturm	301B

A mechanistic approach is used in CATALOG for modelling metabolism. This includes a library of known enzymatic reactions. Each enzymatic reaction is defined as a specific biotransformation. Within each of these specific processes a chemical functional group or a sub-structural fragment of a molecule is modified by the specific enzyme. As a result, the respective metabolic derivative is formed. Subsequently, metabolic pathways are predicted by applying a recursive method that identifies the individual biotransformation paths which are possible for the target chemical. Then every metabolite again is treated as a new target chemical to create the metabolite tree which consists of different metabolic pathways of a different probability each. This recursive application of the biotransformation rules allows a reproducible generation of a metabolic tree.

While the metabolic tree is easily reproduced, there are limited data sets that establish its relevance to what's actually observed in the environment. Recent work by Ericson (2012) using the University of Minnesota Biocatalysis Database and Profiling System (Gao et al, 2010) noted that many of the predictions shown for pharmaceuticals do not match up with what's seen in the OECD 308 water-sediment biotransformation test; or requiring extensive filtering through the predictions to find the observed transformation product. It is thought that the rules in the prediction system may have not used pharmaceuticals in their training sets and/or have not accounted for some of the unique chemistries used in pharmaceuticals to provide desired pharmacokinetics, distribution and/or elimination.

Consistent with the output from the BIOWIN models, the majority of substances listed in Appendix F would be classified as non-readily degradable based on output from the BOD 28 days MITI (301C) model. Seven substances, however, have a projected biodegradation of > 60% after 28 days, those being albuterol, carvedilol, fluorouracil, naratriptam, salmeterol, phenylephrine, and pregabaline, where the latter two were also identified as readily degradable by BIOWIN.

4. MULTIMEDIA MODELS TO DERIVE PEC USED FOR ERA OF IONISABLE ORGANICS

The main objective of an ERA is to provide an estimate regarding the potential for a chemical substance to cause an adverse effect following its release to the environment. The level of risk is measured by calculating the ratio of the PEC of a chemical to the PNEC. The emphasis of this report has focused on evaluating the parameters that will influence the PEC for ionisable organic compounds. The previous chapters highlighted potential concerns pertaining to tests and property estimation methods in relation to their applicability to ionisable organic compounds.

The PEC of a chemical substance is determined based on information about the emission rate of the chemical into the system in relation to a variety of removal processes, such as by sorption, volatilisation, and degradation, i.e. the PEC is based on calculating a mass balance for the model system, whereby the mass of the chemical in the system will be equivalent to the difference of the mass entering the system and the mass leaving the system. Whereas the emissions of a chemical into a system depend on how the chemical is used, the removal processes that influence the environmental fate of a chemical are largely influenced by how the physical-chemical properties of the chemical behave in the environment into which it has been emitted. Different regulatory jurisdictions utilise a variety of models to calculate PECs. In the EU, for instance, the TGD describes a set of methods and hypotheses that are to be used for the risk assessment of new and existing substances. The European Union System for the Evaluation of Substances (EUSES) represents a model framework within which several models may be used to derive information on the fate of chemicals, based on principles defined in the TGD. The modelling approach has been developed to represent a reasonable ‘worst-case' risk assessment.

In a review of different modelling approaches used in the risk assessment of ‘down-the-drain' chemicals, Keller (2006) effectively summarises how EUSES is utilised within a regulatory framework. EUSES includes three main modules that are used for projecting the PEC of a chemical substance, these include:

1. Substance identification and chemical specific physical-chemical properties, specifically: Molecular weight, $K_{OW,}$ Water solubility, Boiling point and Melting point
2. Release estimation, which is dependent on the use pattern and production volume of the chemical.
3. Environmental distribution as defined based on output from various multimedia fugacity-based environmental fate models, such as SimpleTreat and SimpleBox.

Keller (2006) suggests that EUSES is an effective tool for ERA of chemicals in a generic environment, in that it can help decision-makers prioritise the environmental media in which the greatest potential for risk is most likely to occur. Chemicals with a ‘down-the-drain' emission profile, however, are likely to result in the greatest risk to the aquatic environment, and therefore site-specific water quality models, such as GREAT-ER, may provide a more accurate projection of the PEC (Keller, 2006).

The main disadvantage of using a site-specific water quality model is that it does not typically include a multimedia component, and therefore may lead to an overestimation of the PEC in that it will not directly account for losses due to sorption. Whereas a multimedia fate model, such as the modules included within EUSES, have the capacity to account for sorption, they may not adequately project the behaviour of ionisable

organic compounds, since they have been largely parameterised based on the fate and behaviour of neutral organic compounds.

Recently the European Medicines Agency has defined an approach to calculate PECs for APIs used for human use (EMEA, 2006). Similar to the EU TGD, the approach defined for the risk assessment of APIs also uses a 'worst-case' scenario assessment, based on a tiered-approach. Table 13 summarises the phased approach defined for APIs.

Table 13: Phased approach in ERA of APIs used for human use (EMEA, 2006).

Stage in regulatory evaluation	Stage in risk assessment	Objective	Method	Test / data requirement
Phase I	Pre-screening	Estimation of exposure	Action limit	Consumption data, log K_{OW}
Phase II tier A	Screening	Initial prediction of risk	Risk assessment	Base set aquatic toxicology and fate
Phase II tier B	Extended	Substance and compartment-specific refinement and risk assessment	Risk assessment	Extended data set on emission, fate, and effects

The Phase I estimate of the PEC starts with a 'worst-case' scenario for the aquatic environment, based on the dose, a default market penetration of 0.01 (1%) of the API, and amount of water per inhabitant per day and typical dilution factor: Specific market penetration supported by published epidemiology studies may be used at this point, if that information is available.

PEC = [(Dose of API)(fraction of market penetration)] / [(water per inhabitant per day)(dilution factor)] ..... ***(Eq. 28)***

In the Phase I pre-screening assessment, removal processes are not considered. Where the PEC value < 0.01 µg/l it is assumed that the environmental risks associated with the use of the API are likely to be negligible, and no additional testing is required. Where the PEC value > 0.01 µg/l a Phase II environmental fate and effect analysis should be performed. It is only during a Phase II risk assessment, however, where information regarding the removal of the API from a waste water treatment system, based on its physical-chemical properties, is considered along with more specific marketing information to better define the PEC. During this phase of the risk assessment output from the SimpleTreat model may be used to obtain the fraction of the API removed prior to being discharged to surface waters. Given the reliance of PEC estimates within the risk assessment framework on multimedia fate models, the issue regarding the applicability of models, such as SimpleTreat and SimpleBox, for ionisable organic compounds thus needs to be addressed.

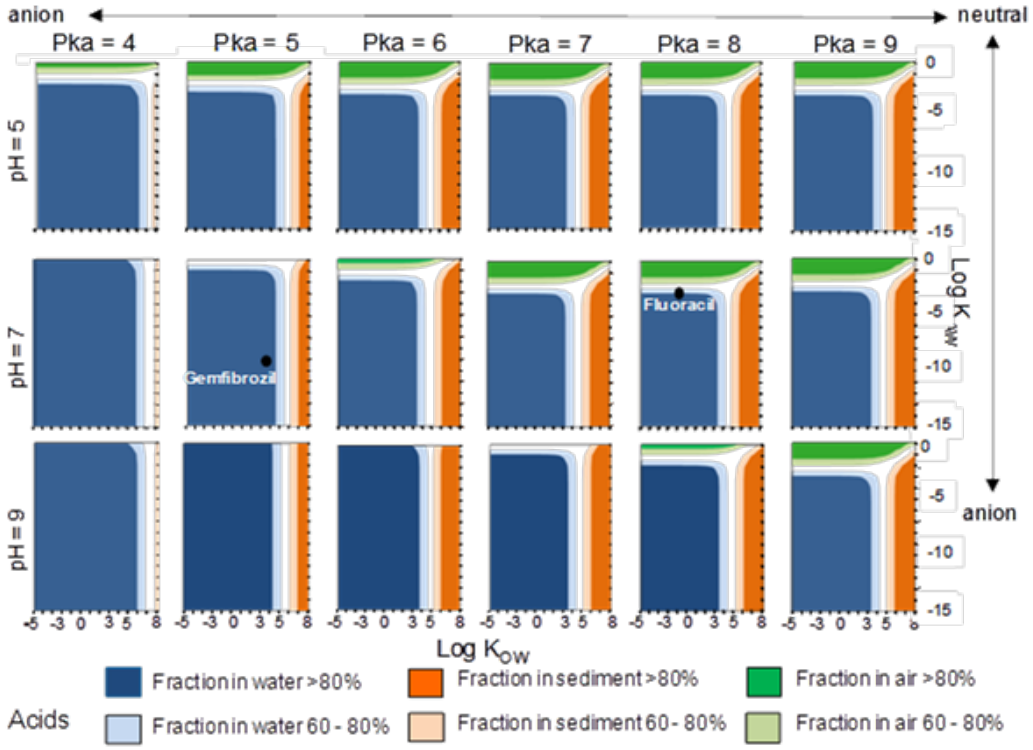
Recently, there have been a number of studies that have attempted to improve the applicability domain of multimedia fate models to include ionisable organic compounds. Franco and Trapp (2010), for instance, have developed a multimedia fate model for ionisable organic compounds based on the use of chemical activities. The model includes pH and ionic strength dependence as well as species specific estimates of partition coefficients based on chemical specific pK_a values, and estimates sorption behaviour based on both hydrophobic and electronic interactions (Franco and Trapp, 2010). Their "Multimedia Activity Model for Ionics" (MAMI) (Franco and Trapp, 2010) thus represents a promising framework for enhancing the applicability domain of multimedia fate models used for the ERA of ionisable organic compounds. This

chapter explores how multimedia models based on the activity approach might be used to enhance the risk assessment of ionisable organic compounds.

4.1 Evaluative assessment of the equilibrium 'chemical space' for ionisable organic compounds

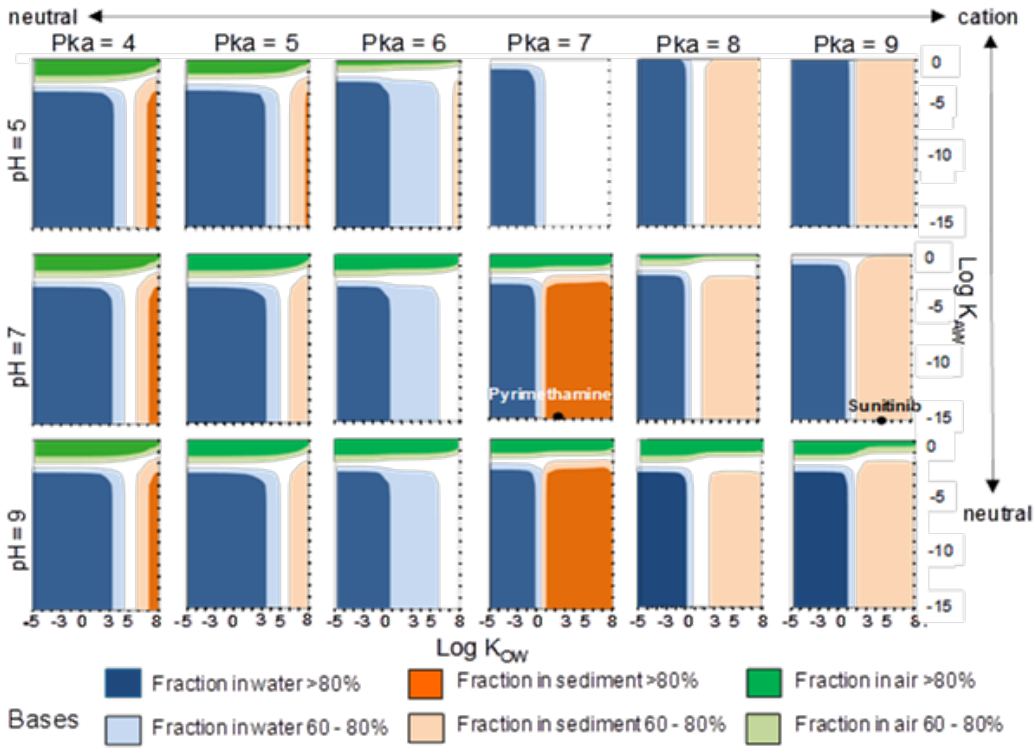
Evaluating the equilibrium or steady-state partitioning of ionisable organic compounds between various environmental media, such as air, water, soil, and biota, can provide useful insight regarding which media the environmental risks for a chemical with a specific set of physical-chemical properties may be most important. This information can then be used to prioritise ecotoxicological testing and/or environmental monitoring aimed at better quantifying exposure and providing a more relevant assessment of the risk associated with that substance. (Trapp et al. 2010) have described the parameterisation for a multimedia model based on the activity approach applied to a lake system, with a surface area of 10^6 m^2 and a depth of 3 m; sediment depth of 0.03m; atmospheric height of 500 m; and 1000 kg of biota. Using this modelling framework, the Task Force have adopted a 'chemical space' approach for evaluating the steady-state, equilibrium partitioning of chemicals, with an emphasis on assessing how the partitioning behaviour of chemicals might change as a function of pH, pK_a, and their partitioning coefficients. To do this, the Task Force have selected a chemical space that covers the region of $-5 < \log K_{OW} < 8$, and $-10 < \log K_{AW} < 0$ on a grid of 1 log unit, while holding the pK_a at 4, 5, 6, 7, 8, 9 and pH at 5, 7, and 9, for both acids and bases, respectively. This evaluative approach thus produces 36 separate chemical space plots (Figures 14 and 15).

Figure 14: Plots of log K_{AW} versus log K_{OW} as a function of pH and pK_a, illustrating the partitioning behaviour of organic acids



[a] Based on output obtained from the multimedia environment described by Trapp et al (2010)

Figure 15: Plots of log K_{AW} versus log K_{OW} as a function of pH and pK_a, illustrating the partitioning behaviour of organic bases



[a] Based on output obtained from the multimedia environment described by Trapp et al (2010)

The results illustrated in Figures 14 and 15 demonstrate how the behaviour of acids and bases differ from one another, with the suggestion that the sorption of ionised bases (i.e. cationics) being significantly greater than that of the ionised acids (i.e. anionics). This observation is based on regressions defined within the multimedia model that estimate the sorption behaviour of cations differently from anions (see Table 4, chapter 3). The observations illustrated in Figures 14 and 15 are useful in that they suggest that cationic materials with relatively low log K_{OW} values (i.e. > 1) may partition to a relatively significant extent, and thus sorption to solids can be an important fate process, whereas ionised acids even with relatively large log K_{OW} values may show limited partitioning to solids. Consequently, assessing the removal processes for acids and bases within an ERA when deriving a PEC estimate should be handled separately, adopting the appropriate regressions. Currently, within SimpleTreat and SimpleBox, for instance, this is not the case. The current approach assumes that the ionised species of an acid or base is present entirely in the dissolved phase, which can lead to an overestimate of the PEC, particularly for the charged species of bases.

To further illustrate how Figures 14 and 15 can be used to help prioritize ecotoxicological testing strategies for a particular substance, the position of four APIs was plotted within the chemical space. The properties of two acids (gemfibrozil and fluoracil) and two bases (pyrimethamine and sunitinib) taken from the Appendix have been selected. Gemfibrozil is a monoprotic acid with a pK_a value of 8 and a measured log K_{OW} (neutral species) of 3.9. Based on a log K_{OW} >3.5 it is possible that concerns regarding the potential for bioaccumulation could be raised under some jurisdictions, which could trigger BCF testing. Using the chemical space illustrated in Figure 14, however, it can be demonstrated that the equilibrium partitioning of gemfibrozil is projected to be >80% to the aqueous phase. This would imply that the fate of gemfibrozil will be largely governed by its fate in the aqueous phase. This appears to be supported by observations by Ra et al. (J. S. Ra, S. Y. Oh, B. C. Lee, and S. D. Kim. The effect of suspended particles coated by humic acid on the toxicity of pharmaceuticals, estrogens, and phenolic compounds. Environment International 34 (2):184-192, 2008.) who observed negligible sorption of gemfibrozil to suspended particles. In this instance, the presence of humic acids thus had no influence on bioavailability and therefore did not modify the toxicity (Ra et al, 2008). On the other hand, the physical-chemical properties of pyrimethamine, a monoprotic base with a log K_{OW} (neutral) of 2.69 and a pK_a of about 7, places it in Figure 15 in a region where this substance has the potential to show equilibrium partitioning that would favour the sediment phase. Testing for this substance should thus consider the influence of humic acids on bioavailability, as this may likely have an influence on the results of aquatic toxicity testing. Additionally, it may be of interest to assess the toxicity of pyrimethamine to sediment dwelling organisms. A similar strategy should be employed for sunitinib shown in Figure 15 to have the potential for significant partitioning to sediment. Consequently, the equilibrium partitioning illustrated in Figures 14 and 15, for acids and bases respectively, can provide an initial screen regarding the potential exposure scenario. As expected, acids and bases will be influenced by different processes, and should thus be considered independently from one another. Although the output from the model developed by Trapp et al. (2010) is illustrated in a graphical form, this model and the MAMI model would typically be used to provide more specific information regarding the environmental fate and behaviour of individual chemicals.

The projected partitioning illustrated in Figures 14 and 15 are strongly influenced by the regression coefficients that define partitioning to organic carbon (K_{OC}). The regressions used in this instance are those defined by Trapp et al. (2010), and are summarised as:

For acids, neutral molecules: $\log K_{OC} = 0.54 \times \log K_{OW,n} + 1.11$ ..... ***(Eq. 29)***

For acids, anion: $\log K_{OC} = 0.11 \times \log K_{OW,n} + 1.54$ ..... ***(Eq. 30)***

For bases, neutral molecules: $\log K_{OC} = 0.37 \times \log K_{OW,n} + 1.70$ ..... ***(Eq. 31)***

For bases, cation (1): $\log K_{OC} = 0.42 \times \log K_{OW} + 2.19$ ..... ***(Eq. 32)***

For bases, cation (2): $\log K_{OC} = pK_a^{0.65} \times f^{0.14}$ ..... ***(Eq. 33)***

Where log KOW,n is the octanol-water partition coefficient of the neutral molecule, and f is calculated from the apparent KOW at pH 7 (the DpH=7): f = D/(D+1).

For cations (1) the regression is obtained by log-linear regression, and considers only hydrophobic interactions, whereas for cations (2) a non-linear fit to the data has been obtained, which attempts to account for the electrical properties of the cation (Trapp et al, 2010). We highlight exactly how projections of partitioning to the sediment compartment have been made because the regressions derived are critical for projecting freely dissolved concentrations. The importance of developing more robust and reliable estimates of K_{OC} is explored in greater detail in the next Section and is further emphasised based on the learnings from the agrochemicals industry.

4.2 Towards an improved regression for the sorption of ionisable organic compounds to sludge

The applicability of existing methods to estimate sorption processes for ionisable organic compounds, particularly in a waste water treatment system, need to be re-examined within a regulatory context. Regressions for K_{OC} recently proposed by Franco and Trapp (2008) (Table 10, Section 3.2.4) for monovalent acids and bases, for instance, developed from soil-water sorption studies, provide a basis for addressing this need. Given the different composition and electrical properties of sewage sludge compared to soils, it is possible that the partitioning behaviour within a waste water treatment plant may differ from sorption to soils. As discussed above, derivation of improved estimates for the K_{OC} of sludge are likely to be particularly important for bases.

It is reasonable to assume, given the high concentration of organic matter characteristic of primary and secondary sludge solids, that normalisation to organic carbon to describe partitioning ($K_d = K_{OC} \times OC$), even for ionisable organic compounds, could represent a valid approach when attempting to improve estimates of partitioning to solids in a waste water treatment system. Based on this assumption secondary sludge-water partition coefficients normalised to organic carbon (K_{OC},sludge) for a number of monovalent bases with pK_a values > 5 were collected from the recent scientific literature. In total 66 K_{OC} measurements were collected for 48 substances, including 3 biocides, 7 industrial chemicals and 38 pharmaceuticals, some of which were measured in different studies and sludges. The database is presented in Table 14, together with the D_{OW} values estimated with either SPARC or ACD at pH 7.

Table 14: Measured log K_{OC} values in secondary sludge and SPARC-estimated log D_{OW} values at pH 7

Substance	log D_{OW} (calculated at pH 7)	log K_{OC} (measured)	T (°C)	pH	OC	Reference
Imazalil	3.87	4.01	NS	6.8	0.29	Wick et al, 2011
Fenpropimorph	4.6	3.71				
Tridemorph	6.14 [a]	4.82				
Clotrimazol	6.16	4.93	4	7	0.4	Hörsing et al, 2011
Trimethoprim	0.54	3.02				
Loperamide	4.27	4.14				
Haloperidol	3.32	3.86				
Cyproheptadine	3.79	3.95				
Orphenadrine	2.52	3.20				
Sertraline	3.16	4.63				
Clomipramine	3.28	4.22				
Donepezil	1.86	3.38				
Bisoprolol	0.52	2.44				
Amitryptiline	3.88	3.85				
Fluoxetine	1.66	4.18				
Verapamil	1.52	3.00				
Tramadol	0.79	2.68				
Citalopram	1.78	2.72				
Paroxetine	1.41	4.32				
Biperiden	1.18	3.27				
Venlafaxine	0.13	2.40				
Dicycloverin	3.56	3.63				
Alfuzosin	1.52	3.48				
Duloxetine	3.05	3.86				
Chloprothixene	4.19	4.70				
Maprotiline	2.20	4.05				
Tizotifen	5.37	3.89				
Mianserin	2.52	3.36				
Ketoconazole	4.62	4.33				
Risperidone	1.31	3.21				
Alprazolam	2.23	3.27				
Nefazodone	5.68	4.32				
Hydroxyzine	3.53	3.26				
Desloratidine	2.19	3.86				

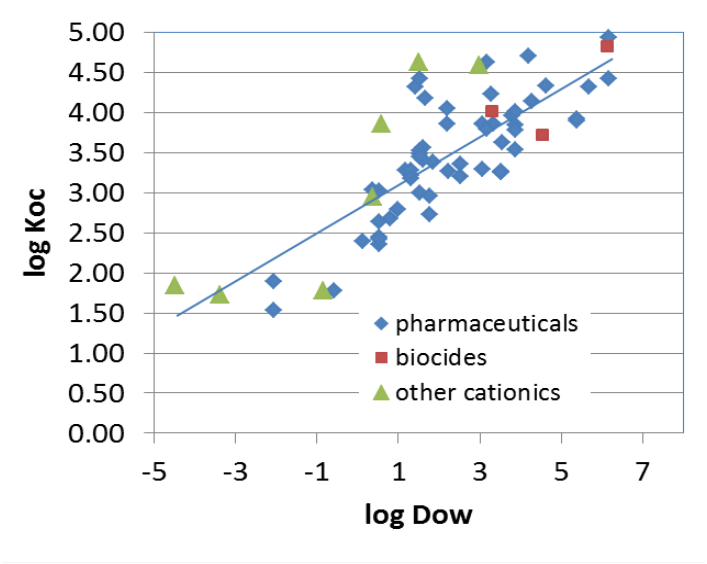
Substance	log D_{OW} (calculated at pH 7)	log K_{OC} (measured)	T (°C)	pH	OC	Reference
Amitryptiline	3.88	3.53	20 - 25	6.3	0.31	Barron et al, 2009
Atenolol	−2.05	1.53				
Citalopram	1.78	2.96				
Clotrimazole	6.16	4.42				
Doxazosin	1.52	4.42				
Erithromycin	0.98 [a]	2.79				
Metoprolol	−0.58	1.78				
Nortryptiline	3.06	3.29				
Propanolol	0.38	3.03				
Sertraline	3.16	3.79				
Tamoxifen	5.39	3.92				
Trimethoprim	0.54	2.35				
Amitriptyline	3.88	4.01	4	7.6	0.44	Stevens-Garmon et al, 2011
	3.88	3.78				
Clozapine	1.6	3.56				
	1.6	3.41				
Verapamil	1.52	3.52				
	1.52	3.44				
Risperidone	1.31	3.28				
	1.31	3.17				
Hydroxyzine	3.53	3.26				
	3.53	3.25				
Trimethoprim	0.54	2.42				
	0.54	2.63				
Atenolol	−2.05	1.89				
(3-Chloro-2-hydroxypropyl)-trimethyl-ammoniumchloride	−4.48	1.84	NS	NS	NS	ECHA registration dossier, 2012
2,3-Epoxypropyl-trimethyl-ammoniumchloride	−3.39	1.73				
Oxadiazinamine	−0.84	1.77				
Dodecyl-trimethyl-ammoniumchloride	0.36	2.94	22	7.33	0.37	Ismail et al, 2010
Exadecyl-trimethyl-ammoniumchloride	1.5	4.62				
Dodecyl-benzyl-dimethyl ammoniumchloride	0.59	3.85				
Hexadecyl-benzyl-dimethyl-ammoniumchloride	2.97	4.58				

NS Not stated

[a]Calculated with ACD

When the estimates for log D_{OW} in Table 14 were plotted against measured log K_{OC} values, a positive slope with a coefficient of determination r^2 = 0.64 was observed (Figure 16). The line represents the linear regression.

Figure 16: Relationship between measured log K_{OC} and estimates of log D_{OW} for the compounds in Table 14



The observation of a potential relationship between K_{OC} and D_{OW} observed in Figure 16 is in contrast to a similar attempt to correlate these properties by Hörsing et al (2011), who failed to observe any significant correlation. The inconsistency between the data shown here and that of Hörsing et al (2011) can be partly explained by the poor estimates of D_{OW} (i.e. based on KOWWIN), in combination with the inclusion of substances with different electrical charge used in their interpretation. The current assessment, however, utilised a more robust estimation programme for D_{OW} estimates, and reduced variability in the interpretation by focusing the analysis on monovalent bases with $pK_a > 5$. This is because the inclusion of acids, for which sorption to solids are less important than for bases, as illustrated in Figures 14 and 15, has the potential to introduce a significant level of variability in the potential relationships.

The observation that a relatively good correlation can be observed for monovalent bases, suggests that the derivation of a simple linear regression model, based on D_{OW} (calculated at pH 7), is possible. This relationship has thus been calibrated to estimate the K_{OC} (sludge) for bases:

$$\log K_{OC} = 0.31 \log D_{OW} + 2.78 \quad \text{..... } \textit{(Eq. 34)}$$

The equation has a mean square error of 0.38 on the log K_{OC}. The regression may thus be used as a lower tier estimate of the K_{OC} of monovalent bases. This analysis has consequently resulted in a revision to the SimpleTreat model, whereby inclusion of equation 34 has recently been proposed as replacement for the default assumption of $K_{OC} = 0$ for cationics in models such as SimpleTreat (Franco et al, 2013). However, the regression reported in Figure 16 (r^2 = 0.64) does not explain all the variance observed. This is not unexpected, since it is reasonable to expect that factors, other than hydrophobicity, may strongly influence sorption of cationic organic compounds to sludge. For instance, it is probable that in some instances electronic interactions between the positively charged chemical and negatively charged surfaces in the environment can result in significant interactions. These interactions, however, will likely require that the electric charge of the chemical and that of the surface are free to interact, and therefore are not prone to steric hindrance. It can also be observed that the correlation shown in Figure 16 appears to be less significant at log $D_{OW} < 0$, where hydrophobic interactions are likely to be relatively weak.

5. EXPERIENCES FROM THE AGROCHEMICALS INDUSTRY

Synthetic pesticides are amongst the most heavily regulated chemicals worldwide. Although approaches in world regions differ, the regulations generally focus on demonstrating biological efficacy on the target organism(s), apart from information on the toxicology and ecotoxicology (to non-target organisms), dietary and operator exposure, behaviour in the environment, physical chemistry and analytical chemistry.

The behaviour of a pesticide in the environment is determined by the physical properties and metabolism/degradation of the compound. As highlighted above for ionisable organic compounds, one of the most important physical properties involved in environmental processes is soil adsorption. In this chapter the experiences gained by the agrochemicals industry whilst investigating the soil adsorption characteristics of synthetic pesticides are summarised.

5.1 The concept of soil adsorption and desorption

When organic compounds come into contact with soils and sediments they can be taken up by organisms, be degraded by biotic and abiotic mechanisms or transported within the aqueous phase (sediments) or both the aqueous and gaseous phases (soils). All of these processes are controlled to a large extent by the propensity of the compound to sorb to and desorb from constituents of the solid phase.

The extent to which adsorption to soil and sediments takes place is generally described by the adsorption-desorption distribution coefficient (K_d) (Section 2.3). Classically, sorption has been conceptualised as a rapid and reversible process involving partitioning of the compound between the liquid and solid phases: water and organic matter. To reflect this, the K_d value is often normalised to the organic carbon (OC) content of the soil or sediment to give a value termed the K_{OC} (Hamaker and Thompson, 1972) (Section 3.2.4). K_{OC} is often regarded as a universal parameter related to the hydrophobicity of the molecule, which applies to a given chemical in all soils.

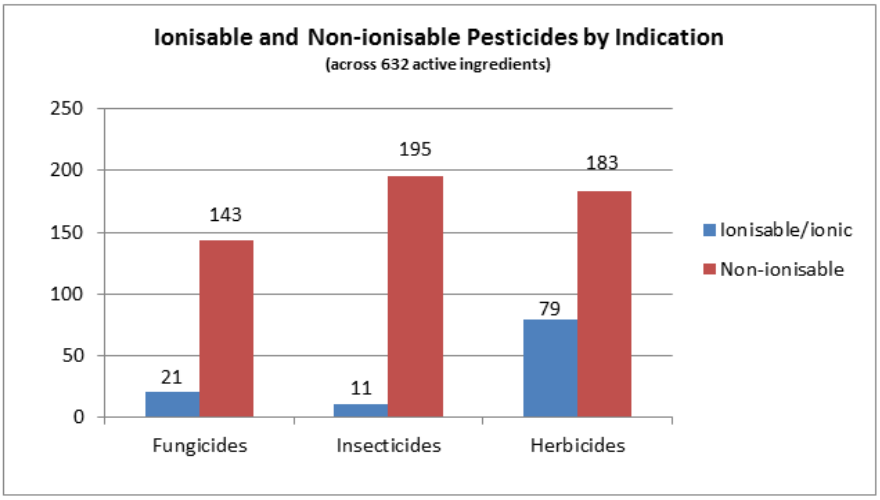
However, in recent years it has become clear that sorption processes are more complex than this. Depending on the properties of the chemical, other matrix constituents such as clays (Bailey et al., 1968; Aharonson and Kafkafi, 1975; Cox et al, 1998; Tolls, 2001) and sesquioxides (Leone et al., 2002; Kahle and Stamm, 2007) can be important sorbents (Calvet, 1989). Studies conducted over longer timescales have demonstrated that while adsorption is often initially rapid it can also continue to slowly increase over a period of many weeks. This has been suggested to result from the diffusion of the compound into organic matter and intraparticle nanopores (Pignatello and Xing, 1995).

5.2 The synthetic pesticide 'chemical space'

Pesticides can be generally separated into three main categories (indications) for use: insecticide, fungicide or herbicide. In order to be effective against the three target organisms, each of these categories of pesticides require different physical and chemical characteristics. When examining the 'chemical space' occupied by these compounds, it is therefore sensible to review the indications separately.

From a review of pesticides listed in the 12th Edition of the Pesticide Manual (Delaney et al, in Tomlin, 2000), the following statistical distributions for each indication can be presented (Figure 17).

Figure 17: Ionisable and non-ionisable pesticides by indication [a]



[a] Across 632 active ingredients

The fact that ionisable compounds are more likely to be within the herbicide indication is not an accident. Weak acids (within a certain log K_{OW} range) tend to have the most favourable properties for leaf uptake, concentration in the phloem of the target plant and translocation to the roots. Therefore many foliar applied, systemic herbicides are weak acids.

5.2.1 General trends in the soil availability of pesticides

To a large extent, the soil availability (determined by adsorption and desorption) of pesticides is determined by the intended use of the molecule. For example, pre-emergence herbicides (that prevent germination of seeds) should be designed such that, when the herbicide is applied to soil, a sufficient quantity of the active ingredient is available to the target organisms (i.e. not predominantly bound to the soil). These compounds usually have lower K_d values. Contact fungicides or insecticides designed to protect without entering the vascular tissue of a crop tend to have higher K_d values. Systemic herbicides, fungicides or insecticides designed to move within the vascular tissue of a plant have again lower K_d values. Pesticides containing cationic charges or basic functionality require higher K_d values

The K_d of pesticides can therefore cover a very wide range of values. The relationship between K_d and soil parameters in addition to the organic matter content can be an important consideration when assessing the environmental behaviour of pesticides. These parameters include:

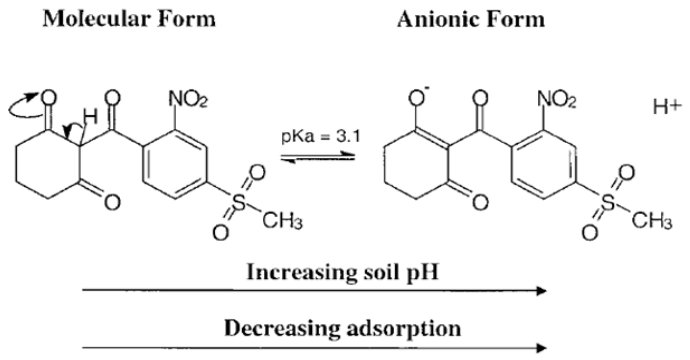
- the soil pH, the soil clay content as determined mineralogically
- the nature, proportion and location of metal ions within the soil matrix, and the chemical nature of the soil organic matter

5.2.2 Soil adsorption and soil pH

Since weak acids constitute a significant proportion of herbicides, the behaviour of anions in soil is and has been an important consideration for the pesticide industry. The pK_a of the acid can be used to calculate the proportion of the deprotonated and protonated species present in soil and this can be related back to K_d.

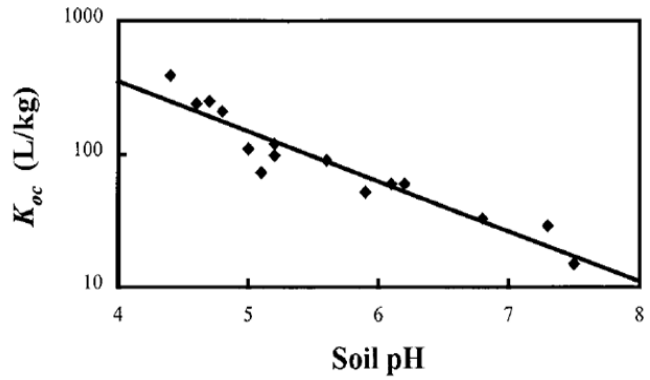
For example, Dyson et al, (2002) described the behaviour of the systemic herbicide mesotrione in soil. The following is a summary of their findings with respect to soil adsorption of the compound (Figure 18).

Figure 18: Soil behaviour of the systemic herbicide mesotrione



The K_d of mesotrione was clearly shown to decrease with increasing soil pH (Figure 19).

Figure 19: K_{OC} decreases with increasing soil pH for mesitrione



Indeed, when a regression line was constructed from the same data, the equation was:

$$\log_{10}(K_{OC}) = -0.376\ pH + 4.05 \quad \text{..... } \textit{(Eq. 35)}$$

Dyson et al concluded that both soil organic matter and soil pH were instrumental in determining the soil adsorption characteristics of mesotrione.

Similar soil behaviour was observed for imazethapyr, another systemic herbicide, which was also sorbed to a greater extent at low pH than at high pH. However, at high pH, desorption was less, reducing the availability of imazethapyr residues to plant. At low pH, the compound was more readily desorbed and hence was available to be taken up by crops resulting in injury (Bresnahan et al., 2000).

Where bases are concerned, the behaviour can be very different, because the cationic form can be bound to soil to a greater extent than the unprotonated compound. The interaction of cations with soil can be described by considering the soil adsorption of the herbicide. For example for Paraquat, the experimentally determined soil K_d was vastly in excess of what would be predicted by considering the log K_{OW} or solubility of the compound. The authors concluded that the interactions between Paraquat and the organic matter content of the soil were of little relevance compared to the electrostatic interactions of the cation with the anionic soil matrix.

The soil sorption behaviour of acids and bases can also be calculated departing from their physical properties. Several estimation tools exist, as discussed above (Chapter 3).

5.2.3 Soil adsorption and clay mineralogy

Strong correlations between the sorption of nonpolar compounds and soil organic matter content has led to the near ubiquitous use of K_{OC} as soil partitioning coefficient (Section 3.2.3, 5.1). A growing body of evidence is, however, emerging to indicate that interactions with soil clay minerals can make an important contribution to the sorption of a range of polar and aromatic compounds. In particular, expandable 2:1 silicate clays (e.g. montmorillonite and vermiculite) are of significance because of their large specific surface area and big cation exchange capacity (Green, 1974). These minerals are generally found in less heavily weathered soils. Kaolinite, a 1:1 non-expanding clay which can carry a net positive charge at low pHs, is often present in weathered soils. The contrasting surface charge properties of these soils can result in differences in the sorption behaviour of pesticide compounds.

The use of simplified xenobiotic-clay-water systems has provided useful insights into the nature of the sorption processes that take place. In soils, clay minerals are intimately associated with organic matter and hence findings in model systems cannot be directly extrapolated to whole soil systems. Polar and aromatic compounds can interact with clay minerals through a variety of mechanisms. Cationic herbicides such as paraquat and diquat are completely ionised in water. They readily replace inorganic cations from the surface of clays resulting in extensive sorption, especially to expandable clays (Weber and Weed, 1968). This mechanism is important for weak organic bases such as the herbicide s-triazine (1,3,5 triazine) (Celis et al, 1998). These compounds are protonated at pHs below their pK_a resulting sorption to clay surfaces. It is important to note that the acidity at the clay surface is often higher than in the bulk solution; that can result in higher sorption than would be predicted from the pH of the bulk solution. The type of exchangeable

cation present can also have a significant influence on the extent and mechanism of sorption observed. Some cations are more easily displaced by competing organic compounds and cations with relatively small hydration spheres such as K^+, and can facilitate hydrophobic interactions with the uncharged siloxane surface of the clay (Li, 2004). Hydrophobic interactions were suggested to contribute to the sorption of dicamba, atrazine, simazine and prosulfuron (Zhao et al., 1996; Cox et al, 2000; Sheng et al., 2001; Hyun and Lee, 2004). There is also evidence that a prevalence of trivalent cations such as Al^{3+} on clay surfaces can enhance the polarisation of water molecules facilitating increased sorption as a result of hydrogen bonding. Hydrogen bonding mediated sorption has been proposed for primisulfuron and 2,4-dichlorophenoxyacetic acid (2,4-D) among others (Hermosin and Cornejo, 1993; Pusino et al, 2004). In the case of aromatic compounds, it is hypothesised that the presence of delocalised pi electron clouds can produce electron rich, donating (−ve) or electron deficient, accepting (+ve) aromatic ring structures, respectively. Such compounds can then interact with surfaces of the opposite nature such as polarised and charged mineral surfaces (Keiluweit and Kleber, 2009)

Interactions of a pesticide (agrochemical) with clay minerals can have a significant influence on their agronomic performance and environmental impact. Some of the sorption mechanisms outlined above can result in irreversible sorption to clays as observed in the case of nicosulfuron (Ukrainczyk and Rashid, 1995). This could result in reduced availability of compounds in some soil types which could reduce the duration of effect of soil applied compounds and would result reduced mobility in soil than would be predicted from an estimated K_{OC} value.

5.2.4 Soil adsorption and metal chelation

There is a discrete class of organic compounds that have the ability to chelate metals, by ligand binding of the metal ions. The so-formed chelate metal complexes can sometimes play an important role in the mode of action of a pesticide, for example HPPD inhibition. In such examples, the same metal chelating properties that drive pesticide efficacy can also result in increased soil adsorption through chelation of metals located on/in the surface of the soil matrix. In the case of mesotrione (Section 5.2.2), a simple comparison of the measured K_{OC} of mesotrione with an estimate derived from the relationship between log K_{OW} and soil adsorption (such as that proposed by Briggs, 1981) will reveal that the actual soil adsorption is much higher than if it were determined by hydrophobicity alone. Therefore, estimations of soil adsorption for compounds with the ability to chelate metals are often inaccurate.

5.2.5 Soil adsorption and the chemical nature of the soil organic matter

In 1998, Evanko and Dzombak published research which has parallels with some pesticides and their metabolites/degradation products. In summary, organic acids can be much more highly sorbed to soil than would be expected given the log K_{OW} (log D_{OW}) of their deprotonated forms. The extent to which this occurs can be directly related back to the number, type and configuration of the functional groups. Examples of such behaviour can be and have been found in current commercial pesticide (and non-pesticide) chemistry.

5.3 Conclusion

Although various purportedly reliable methods exist for calculating soil sorption properties of chemicals, these methods usually relate K_{OW} directly to K_{OC}. Whilst the resulting estimates may be acceptable for many simple, non-ionisable organic compounds, in the case of pesticides many alternative soil sorption mechanisms exist. These can be significant or even dominant over the established concept of hydrophobic interactions/binding. Indeed, incidents of "atypical" soil behaviour of pesticides are in fact relatively common. Since soil adsorption is simple and relatively inexpensive to determine experimentally, measurement of this important environmental property is preferred. Estimation is less suitable, unless (for a given chemistry series) it has already been demonstrated that hydrophobic-driven soil sorption is dominant.

6. REGULATORY IMPLICATIONS AND RECOMMENDATIONS

Based on activity undertaken as part of this task force it is suggested that multimedia models based on the activity approach provide a promising framework for ERA of ionisable organic compounds with a down-the-drain emission scenario. In the interim there is a need for improved regressions implemented into existing tools for describing the partitioning behaviour of ionisable organic compounds to solids, such as described above, an observation that is consistent with the experiences of the agrochemicals industry. Whereas it is suggested that preliminary activity along these lines can lead to low-tiered improvements in model parameterisation with respect to handling ionisable organic compounds, there remains the need for additional data aimed at improving mechanistic understanding of processes that may be influencing environmental fate and behaviour. For instance, there is a need for additional work on the sorption of cationic materials to sludge, and improved understanding needed for extrapolating data between sludge, soil, and sediment, which will enable the derivation of more environmentally relevant PECs.

As a general observation it is possible to define a generic model environment for use in lower-tiered predictive risk assessment, based on work described by Franco and Trapp (2010). As an initial screen, Figures 13 and 14 can be used to assess the relative influence of humic acids on the bioavailability of a chemical substance, information that could then be used in the design of ecotoxicological testing. The environmental exposure of organisms and humans to chemicals is implemented in the EU tool for the chemical safety assessment (EUSES). The fate of a chemical released to the environment is predicted via a regional Level III multimedia model (SimpleBox), which is linked to output from SimpleTreat described above. Activity related to this task force has helped initiate an update to the SimpleTreat model that will allow for better handling of ionisable organic compounds (Franco et al. 2013). The updated version of SimpleTreat should be used to derive the concentration in effluent ($Clocal_{eff}$), which can then be used to provide an improved estimate of local concentration in surface water ($Clocal_{water}$). In the EU TGD $Clocal_{water}$ is derived as:

$$Clocal_{water} = Clocal_{eff} / ((1 + Kp_{susp} \times SUSP_{water} \times 10^{-6}) \times DILUTION) \quad \textit{(Eq. 36)}$$

Where $SUSP_{water}$ is the concentration of suspended matter in the river, DILUTION is the dilution factor, and Kp_{susp} is the solids-water partitioning coefficient of suspended matter, and is estimated from the K_{OC} of the substance. As discussed above, caution should be taken in the derivation of Kp_{susp}. Consequently, improving estimates of partitioning with solids for ionisable organic compounds is recommended as a critical component towards improved projections of bioavailable concentrations in surface waters.

Where refinement of the risk assessment is required, it is suggested that current understanding of mechanistic interactions involving the ionised species of an organic chemical with various environmental matrices are currently not sufficient to provide a definitive ERA.

Thus, in addressing the question defined in the terms of reference for this task force, i.e.: Can recommendations be made regarding what pH and soil properties are most useful for accurately predicting environmental concentrations, i.e. is it possible to define a generic model environment for use in a predictive risk assessment? Is it possible to advise the most appropriate testing conditions? The response would be

that it is possible at low-tier assessments, using refinements to existing tools, such as demonstrated by equation 1, or utilising the activity approach to multimedia modelling described by Franco and Trapp (2010). Additionally, empirical studies aimed at assessing the partitioning behaviour of ionisable organic compounds, such as APIs, should be conducted with various different types of sludge, at varying pH, analogous to the approach adopted in the agrochemicals industry. Furthermore, there is a need for improved understanding regarding the extrapolation of data obtained from soil sorption studies towards estimating sorption to sludge or to sediment, as these matrices may have properties that are very different from soils. Again, this is analogous to the approach taken by the agrochemicals industry, whereby sorption behaviour between different types of soils is conducted, and attempts are made towards an improved understanding regarding the mechanisms that are most important for influencing sorption.

Clearly, improved mechanistic understanding is essential to support high-tiered assessments. It is suggested, for instance, that the key factor influencing bioavailability, and therefore the PEC, is sorption to different environmental matrices. Based on the current paradigm this is typically based on measurements or estimates of K_{OC}, which assume that hydrophobic interactions are the dominant sorption process. As illustrated above in Figure 16 (Section 4.2), relationships based on K_{OC} regressed against D_{OW} for ionisable organic compounds, are sufficient to address interactions dominated by hydrophobic interactions, but the correlation is not entirely satisfactory. Thus, there is a need to assess how other parameters might be used to improve the understanding of sorption. For instance, the charge surface area of the molecule might help to differentiate the relative importance of the hydrophobic component of the molecule versus the charge; a complex molecule with significant branching may provide steric hindrance to the charge, resulting in greater hydrophobic behaviour being possible. Whereas the sorption behaviour of a relatively simple molecule with one or more charged functional groups not shielded by hydrophobic chains may likely be more strongly influenced by electronic interactions. Thus introduction of additional parameters such as charged surface area in combination with D_{OW} and the cationic exchange capacity of the sorbent may lead to improved PEC estimates. Additional research directed at improving the ability to predict sorption of ionisable organic compounds to various environmental matrices is thus needed.

6.1 The role of D_{OW} versus K_{ow}

An additional observation made within this report is the need to differentiate between acids and bases, particularly when considering the relative importance of trigger values. This also relates to likely differences in sorption behaviour of the two different classes of chemicals, which will likely result in significant differences in bioavailability. Based on the data presented in Figures 14 and 15 (Section 4.1), the anionics, even with relatively large D_{OW} may have a greater PEC than cationics with similar D_{OW}. Consequently, the trigger value for the acid and base should be represented accordingly.

It is assumed that the trigger values, based on K_{OW} and summarised in Table 5 of Section 2.2.3, for bioconcentration testing are meant to assess the bioconcentration potential of chemicals based on their potential for enhanced hydrophobic interactions. There has been an historic reliance on the use of octanol as a surrogate for biological lipids (Leo et al, 1971), and therefore exposure to chemicals with K_{OW} values > 1,000 can be used as a means for screening chemicals that may have the potential to accumulate in

biological lipids. The assumption appears to be generally applicable to neutral organic compounds, but there are concerns regarding the applicability of using K_{OW} as a trigger value for bioconcentration testing for ionisable organic compounds. The main concern regards the relative importance of hydrophobic interactions for ionisable organic compounds, versus other potential mechanisms of interaction. As a preliminary step towards addressing this concern, it is suggested that D_{OW}, reported at pH 7, represents a better metric as a trigger value, than does K_{OW}, since it should account for the ionisation state of the chemical. Unfortunately, there is a paucity of data to definitively demonstrate the utility of using D_{OW} as opposed to K_{OW}. It is acknowledged, however, that the current trigger values listed in Table 5, Section 2.2.3, appear to be responsible for a relatively significant increase in the number of bioconcentration tests being commissioned by pharmaceutical companies. Thus, analogous to data illustrated in Figure 16, which attempts to provide a low-tiered approach for estimating the sorption of monoprotic bases to sludge solids, based on a relationship with D_{OW}, it may be possible to acquire data that could be used to demonstrate the role that D_{OW} might play in screening ionisable organic compounds for bioconcentration. The Task Force thus recommends that data being generated regarding the bioconcentration of ionisable organic compounds are made publicly available to allow greater transparency which would help to improve the mechanistic understanding with respect to BCF, and strengthen the argument of using D_{OW} as opposed to K_{OW} as a more appropriate trigger value. The recent CEFIC-LRI request for proposal (LRI-ECO21) pertaining to the development of a mechanistic model for the bioaccumulation of ionisable organic compounds in fish, may lead to timely insight towards an improved understanding.

6.2 Future needs

There remains a paucity of data directed at improving the mechanistic understanding of sorption, which is critical for improving the understanding of bioavailability and potential for bioconcentration and bioaccumulation. It would thus be prudent to focus future research needs on the development of improved mechanistic understanding. Boxall et al (2012), for instance, provide 20 priority questions that need to be addressed to elucidate the environmental risks associated with pharmaceuticals. The 20 questions represent seven different categories: 1) prioritisation of substances for assessment; 2) pathways of exposure; 3) bioavailability and uptake; 4) effects characterisation; 5) risk and relative risk; 6) antibiotic resistance; and 7) risk management. The questions identified around pathways of exposure and bioavailability is consistent with areas where research would be needed. Specifically:

- What are the environmental exposure pathways for organisms (including humans) to pharmaceutical and personal care products (PPCPs) in the environment and are any of these missed in current risk assessment approaches?
- How can the uptake of ionisable PPCPs into aquatic and terrestrial organisms and through food chains be predicted?
- What is the bioavailability of non-extractable residues of PPCPs?

While this task force has focused on questions pertaining to bioavailability (exposure), there remains a need for improved hazard assessment of ionisable organic compounds. From the 20 questions identified by Boxall et al (2012) the following were related to hazard assessment, including leading effects and dose-response:

- How can pharmaceutical preclinical and clinical information be used to assess the potential for adverse environmental impacts of pharmaceuticals?
- What can be learned about the evolutionary conservation of PPCP targets across species and life stages in the context of potential adverse outcomes and effects?
- How can ecotoxicological responses, such as histological and molecular-level responses, observed for PPCPs, be translated to traditional ecologically important end-points such as survival, growth and reproduction of a species?
- How can ecotoxicity test methods, which reflect the different modes of actions of active PPCPs, be developed and implemented in customised risk assessment strategies?
- How can effects from long-term exposure to low concentrations of PPCP mixtures on non-target organisms be assessed?
- Can non-animal testing methods be developed that will provide equivalent or better hazard data compared to current in vivo methods?

6.3 Recommendation

In summary, the Task Force recommends that the ERA of ionisable organic compounds emphasise a need for projecting robust and reliable estimates and/or measurements of bioavailability. Specifically:

- Testing strategies, particularly those aimed at quantifying K_{OW}, D_{OW} and K_{OC} need to ensure that they account for the potential for ionisation during the test, and the implications of ionisation with respect to modelling $Clocal_{water}$ within the EU TGD framework are appropriately captured.
- With regard to analytical methods, the finalisation of OECD test guideline 122 for measuring pK_a, K_{OW} and D_{OW} is encouraged.
- The use of QSARs to estimate K_{OW}, D_{OW}, and K_{OC} need to be checked for their applicability towards the chemical under investigation. Based on observations from data scrutinised within this report, greater confidence in estimation methods appear to be warranted for acids than for bases.
- It is recommended that users compare output from more than one estimation method, for instance between SPARC and ACD with respect to estimates of D_{OW}.
- There is a need for a wider debate regarding the relevance of regulatory triggers, such as K_{OW}, in screening ionisable organic chemicals for their potential to be persistent and bioaccumulative.
- Are there surrogates, other than octanol, that could be better used as a metric for bioaccumulation.

Given the recent interest in ionisable organic compounds, such as those used as APIs, it is of great importance to improve mechanistic understanding of their sorption to various environmental matrices. Research is thus needed to transition current understanding, which is largely based on interactions associated with neutral organic compounds with organic carbon, to an improved framework for assessing the electronic interactions of a charged molecule with charged solid surfaces. In particular:

- Encourage updates to ERA tools, such as SimpleBox and SimpleTreat, to better project concentrations of ionisable organic compounds.

- To complement knowledge gained towards an improved assessment of exposure, there is a need to encourage support to address the relevance of ecotoxicological testing strategies for ionisable organic compounds.

ABBREVIATIONS

ACD/Labs	Advanced Chemistry Development (company)
APIs	Active pharmaceutical ingredient
BCF	Bioconcentration factor
BIOWIN	The biodegradation probability program
COD	Chemical oxygen demand
Da	Dalton, unified atomic mass unit
DOC	Dissolved organic carbon
D_{OW}	Distribution coefficient, octanol-water
DT50	Half-life, depuration (time needed to eliminate 50% of the substance) (IUPAC, 2009)
DT90	Time to 90% depuration (IUPAC, 2009)
ECHA	European Chemicals Agency
EMEA	European Medicines Agency
EPA	Environmental Protection Agency
EPI	Exposure/potency index
ERA	Environmental risk assessment
EU	European Union
EUSES	European unified system for the evaluation of substances
GREAT-ER	Geographically-referred regional exposure assessment tool for European rivers
HPLC	High performance liquid chromatography
K_a	Acid dissociation (acidity) constant
Kbiol	Rate constant, biological degradation
K_{OW}	Octanol-water partition coefficient
LRI	Long-range Research initiative
LFERs	Linear free energy relationships
LSERs	Linear solvation energy relationship
MAMI	Multimedia activity model for (organic neutral and) ionisable chemicals
MoA	Mode of action
NER	Non-extractable residue
OC	Organic carbon
OECD	Organisation for Economic Co-operation and Development
OPPTS	Office of Prevention, Pesticides and Toxic Substances
PBT	Persistent, bioaccumulative, toxic
PEC	Predicted environmental concentration
pH	–log (H+ concentration)
pK_a	–log (acid dissociation constant)
PMO	Perturbed molecular orbital
PNEC	Predicted no effect concentration
PPCP	Pharmaceutical and personal care product
QSAR	Quantitative structure activity relationship
RCR	Risk characterisation ratio
SPARC	SPARC performs automated reasoning in chemistry
SRC	Syracuse Research Corporation
TGD	Technical guidance document

APPENDIX A: MEASUREMENT OF ACIDITY (pK_A)

Potentiometric titration

Historically, potentiometric titration was the standard method for pK_a measurement. In a potentiometric titration, a sample is titrated with acid or base using a pH electrode to monitor the course of titration. The equivalence point is the volume at which the slope is greatest, or at which the inflection point occurs, where the line changes from upward curvature to downward curvature.

The pK_a value is calculated from the change in shape of the titration curve compared with that of a blank titration, i.e. without a sample present. Potentiometric titration is a high-precision technique for determining the pK_a values of substances. It is commonly used due to its accuracy and the commercial availability of fast, automated instruments. However, the shortcomings of the method include the requirements to use a milligram of pure compounds and a mixture of aqueous buffers. Solutions of at least 10^{-4} M are required in order to detect a significant change in shape of the titration curve. To avoid errors, especially for measurements at neutral-to-high pH, carbonate-free solutions must be prepared (Babic et al, 2007). Although potentiometric titration of sparingly soluble compounds may be done in the presence of co-solvents such as methanol, the resulting acid dissociation constants refers only to the particular solvent medium employed, and extrapolation procedures, such as the Yasuda-Shedlovsky method, are required to deduce the pK_a values at zero co-solvent (Takács-Novák et al, 1997).

Spectrophotometry

UV-Vis spectrophotometry is used to study the dissociation of weak electrolytes. UV–VIS spectrophotometry can handle compounds with lower solubility and lower sample concentrations compared to titration methods. The main advantage is higher sensitivity (> 10^{-6} M) to compounds with favourable molar absorption coefficients. However, in such a case, a compound must contain a UV-active chromophore close enough to the site of the acid–base function in the molecule. Spectral data are recorded continuously during the course of titration by a spectrometer. The absorption spectra of the sample changes during the course of the titration to reflect the concentration of neutral and ionised species present. The largest change in absorbance occurs at the pH corresponding to a pK_a value. These changes are usually identified from the first derivative of the absorbance against time plot or from overlay plots of the different spectra.

The determination of pK_a values by UV–VIS assumes that the solute of interest is pure or that its impurities do not absorb in the UV–VIS range, since the spectra of impurities can overlap with those corresponding to the solutes of interest. Spectrophotometric methods offer excellent precision, as in potentiometry, but they require different spectra for different species at experimentally suitable wavelengths (generally above 220 nm). Traditionally, spectral data at a single analytical wavelength are acquired from a sample in a series of buffer solutions with known pH values, after which the pK_a is determined. To use this method, the absorption spectra of individual species must be characterised beforehand and the molar absorptivities of protonated and deprotonated species are thus required. These measurements are non-trivial if acid-base equilibria comprise more than two ionisation steps or if reacting components are not stable within two pH units of the pK_a value, so a multi-wavelength spectrophotometric approach has been developed to determine acid dissociation. Target-factor analysis has been applied to deduce pK_a values from the multi-

wavelength UV absorption data recorded at different pH values (Allen et al, 1998; Babic et al, 2007). The method is suited for compounds with either very high or very low pK_a values.

Conductometry

Since the conductance of a solution of is a measure of the concentration of H^+ and A^- ions, a measurement of conductance of a solution of known [HA] concentration allows to calculate the degree of dissociation of the compound (dissociated fraction = α) as the ratio of molar electric conductivity at a given concentration (Λ_c) to the maximum molar electric conductivity (Λ_∞).

The conductometric method is applied by measuring the conductivity of a 0.1 M solution of the test substance in distilled water, followed by measurements on a series of sequentially diluted solutions. The equivalent conductance is calculated for each acid concentration and for each concentration of a mixture of one equivalent of acid, plus 0.98 equivalents of sodium hydroxide. Values of $1/\Lambda c$ are plotted against $\sqrt{C}$ and $\Lambda\infty$ (Kohlrausch law: $\Lambda=\Lambda\infty - a\sqrt{C}$, where $\Lambda\infty$: equivalent conductance at infinite dilution, c: concentration; a: constant). The pK_a can be calculated from $\alpha = \Lambda c/\Lambda\infty$ and $K_a = \alpha 2 /(1-\alpha)$.

The conductivity of a solution is dependent on several factors, including the concentration of the solute, the degree of dissociation of the solute, the valence of the ion(s) present in the solution, the temperature, and the mobility of the ions in the solution.

Since the charge of ions in solution facilitates the conductance of electrical current, the conductivity of a solution is proportional to its ion concentration. In some situations, however, conductivity may not correlate directly to concentration. For strong electrolytes, such as salts and strong acids and bases, molar conductivity varies little with concentration, but for weak electrolytes, such as weak acids, molar conductivity depends strongly on concentration, being exponentially smaller with smaller concentration. Molar conductivity or equivalent conductance of a solution changes with the concentration of the solution:

In practice this method is more laborious than the potentiometric method and more calculations are needed. The method is especially suited for acids with pK_a values between 1.9 and 5.2. It is less reliable in the study of very weak electrolytes; i.e. very high pK_a values.

APPENDIX B: MEASUREMENT OF PARTITIONING (K_{OW})

OECD 107 - Partition coefficient (n-octanol/water): Shake flask

This method is appropriate for the determination of the partition coefficient of substances with log K_{OW} values in the range of −2 to 4 (OECD, 1995a). Measurements of the partition coefficient should be made on ionisable substances only in their non-ionised (neutral) state and this can be achieved by the use of an appropriate buffer with a pH of at least two units below (free acid) or above (free base) the pK_a.

In order to determine a partition coefficient duplicate samples of water, n-octanol and test compound are equilibrated with each other via mechanical shaking. The two solvent phases are then separated by centrifugation and the concentrations of the test compound in the two phases, aqueous and octanol, are determined using an appropriate analytical technique. In total there should be three duplicate runs with different solvent ratios, and the six K_{OW} values should be within a factor of two of each other.

Briefly, this method was developed for measuring K_{OW} of neutral compounds and is of limited value when dealing with ionisable or multi-protic compounds.

OECD 107 - Partition coefficient (n-octanol/water): Shake flask at pH 5, 7 and 9

The shake flask method conducted @ pH 5, 7 and 9 is a variation of the OECD 107 method and takes account of the partitioning behaviour of ionisable compounds over the environmentally relevant pH range (pH 5-9). Typically, three pH values (pH 5, 7 and 9) are employed. The principle of the test is the same except that three flasks, each buffered at a specific pH, are employed rather than a single flask buffered to ensure that only the neutral form of the molecule is present. Depending on the pK_a of the compound, changes in pH will alter the proportion of non-ionised and ionised species distributed between the two different solvent phases. The reported value from this method is D_{OW}, and should always be associated with the relevant pH value at which it was measured. Unfortunately, much of the scientific literature has conflated the terms K_{OW} and D_{OW} and it is not unusual for the distribution coefficient to be expressed as K_{OW} at pH 7 rather than log D_{OW} at pH 7. This can lead to potential confusion, since K_{OW} should strictly refer to the neutral species, which may or may not exist at pH 7. Importantly, D_{OW} varies with pH in accordance with the relative extent of speciation whereas K_{OW} is a constant value based upon the neutral undissociated form of the compound. The value for the dissociated molecule determined around a pH of 7 is considered more realistic for PBT and chemical safety assessment (ECHA, 2008b).

OECD 117 - Partition coefficient (n-octanol/water): High performance liquid chromatography (HPLC)

This is a relatively quick way of estimating K_{OW}. It is not measured directly, but from a correlation between log k (capacity factor) and a series of reference chemicals with known log K_{OW} values (OECD, 2004). It therefore depends on the quality of the log K_{OW} measurement of the reference chemicals (often measured by the shake flask method). A series of reference compounds with similar chemical functionality to the test material should be used to generate the correlation between log k and log K_{OW}. The test material is injected onto a reverse phase column and partitions between the mobile solvent phase and the hydrocarbon stationary phase as it is transported along the column by the mobile phase. The chemicals are retained in proportion to their hydrocarbon-water partition coefficient, with hydrophilic chemicals eluted first and

hydrophobic chemicals last. The retention time is used to derive log K, which is then used to calculate log K_{OW} of the test substance, based on linear regression analysis of log K with the log K_{OW} values of the reference substances.

In general, the HPLC method is less sensitive to impurities than the shake flask method. The HPLC method is also very suitable for measuring the K_{OW} of mixtures of chemical homologues. However, charged molecules have more complex retention behaviour than the neutral species, and therefore this method is not recommended as being suitable for determining the K_{OW} of ionisable compounds.

OECD 122 - Partition coefficient (n-octanol/water): pH-Metric for ionisable substances

This is the method of choice for determining the partitioning behaviour of multiprotic or ionisable substances with log K_{OW} values between -2 to 7 (OECD, 2000a). A derived estimation of log K_{OW} is based on the apparent shift in pK_a when n-octanol is added to a solution of the test substance in water. The pH-metric technique consists of two linked potentiometric titrations. The pK_a of the test substance is determined by acid-base titration of an aqueous solution of the substance using potentiometric measurement of pH. To measure the log K_{OW}, one or more additional titrations are done. In these additional titrations, n-octanol is added to a solution of the substance in water and the apparent pK_a of the substance in the two-phase system is measured. This apparent pK_a value is denoted by the term poK_a. The pK_a values derived from the aqueous and the two-phase titration curves are different and this difference is related to the value of log K_{OW}. Using established equations, an estimation of the partition coefficient is obtained. This method derives values for pK_a, log K_{OW} and log D_{OW} across the ionisable pH range and therefore represents the most comprehensive data outputs of all methods reviewed here and has been recommended by the EMA ERA guideline Q+A technical review (EMA, 2010). For ionisable solutes, a major advantage of the method over the shake-flask procedure is that it affords a distribution profile (i.e., a pH-log D_{OW} curve) rather than single points. However, the method requires sophisticated analytical technology and there appears to be limited availability at Contract Research Organisations. The method also struggles with insoluble compounds and self-evidently is not suitable for neutral compounds.

OECD 123 - Partition coefficient (n-octanol/water): Slow-stirring

The ‘shake-flask' method (OECD 107) is prone to artefacts due to transfer of octanol micro droplets into the aqueous phase. With increasing values of K_{OW} the presence of these droplets in the aqueous phase leads to an increasing overestimation of the concentration of the test substance in the water. Therefore, the use of the shake flask method is limited to substances with log $K_{OW} < 4$. The experimental difficulties associated with the formation of micro droplets can be overcome in the slow-stirring method (OECD, 2006). In this method, water, octanol and the test compound are equilibrated in a stirred reactor. Exchange between the phases is accelerated by stirring. In that manner turbulence is introduced and the exchange between octanol and water is enhanced without micro droplets being formed. The time to equilibrium, however, will vary depending on the hydrophobicity of the test substances. For very hydrophobic substance the time to equilibrium may take several days. Once equilibrium is reached the K_{OW} is determined directly as in the shake flask method. In comparison with the shake flask method, this method may also be adapted to investigate the D_{OW} of ionisable substances at pH 5, 7 and 9.

OECD 107/EU A.8 - Estimation of log K_{OW} from saturated solutions

Due to the low solubility and the multi-protic nature of some substances, conventional methods for determining K_{OW}, such as the shake flask procedure or the HPLC screen, are not technically feasible or considered appropriate. For substances with K_{OW} values outside the range of applicability, test methods that utilise the saturation solubility values in octanol and water, which are determined by visual inspection and which may be supported by turbidity measurements, may be appropriate. In these instances, K_{OW} can be estimated based on the ratio of the solubility of the chemical in octanol and water at saturation.

This estimation method does have a serious drawback in that K_{OW} is not based on an interaction between water and solvent (octanol) and as a consequence the correlation between octanol solubility and K_{OW} may be perceived as insufficient. In the event of insurmountable technical challenges this is an acceptable alternative to the shake flask method, but it is recommended that data obtained using the solubility approach be treated with caution.

APPENDIX C: MEASUREMENT OF SORPTION (K_d)

OECD 106 – Adsorption-desorption using batch equilibrium (OECD, 2000b)

This batch equilibrium method is appropriate for the determination of the adsorption-desorption distribution coefficient of ionisable and neutral substances that have a variety of functional groups, pK_a values and log K_{OW} values. The OECD 106 was originally intended to evaluate the sorption characteristics in 5 standardised soil types, but can be easily modified for the analysis of sediment and wastewater treatment sludge. The method may be limited in part by compounds that have low solubility, or that significantly bind to the test apparatus. The method is amenable to ^{14}C-labeled test materials thereby facilitating analyses at low concentrations and a complete mass balance/ internal validation of the experiment. The test protocol is conducted in phases that allow for: 1) the optimisation of solids levels to ensure appropriate analytical sensitivity for measurement of test substance in both the solid and aqueous phases; 2) confirmation of the equilibrium period required for the test substance to be in equilibrium between the solid and aqueous phases; and 3) confirmation that the test substance is stable during the equilibrium period. Once fully optimised, the sorption- desorption properties of the test substance is then evaluated over a concentration range to construct the sorption- desorption isotherm. The isotherm relates the amount of substance adsorbed to the concentration of the substance in solution at equilibrium.

To determine a sorption distribution coefficient, replicate samples of 0.01 M $CaCl_2$, sorbent and test compound are equilibrated with each other via mechanical shaking. The two phases are then separated by centrifugation and the concentrations of the test compound in the two phases, aqueous and solid phase, are determined using an appropriate analytical technique.

While the standardisation of measuring soil pH in 0.01 M $CaCl_2$ is well known and established (ISO, 1995; Nilsson et al, 2005), and that it approximately represents the ionic strength characteristic of soils (Nilsson et al, 2005) and is used in the method to improve centrifugation and minimise cation exchange (OECD 106), it should be recognised that the approach has the potential to underestimate sorption for those compounds where cation exchange is the main mechanism of sorption (Nicholls and Evans,1991) by displacing cationic compounds at surface of the sorbent. For such cases it may be helpful to conduct sorption determinations in both distilled water and 0.01 M $CaCl_2$ to assess whether a potential cation exchange mechanism is relevant.

OPPTS 835.1110 – Activated sludge sorption isotherm (US EPA, 1998)

This batch equilibrium method follows that of the OECD 106 in respect to the underlying principles, how the test is generally conducted and any potential restrictions. The method provides pragmatic guidance on how to collect and prepare activated sludge for the sorption test that is not found in the OECD 106 guidance. Activated sludge is settled, washed and then lyophilised prior to its use to remove unwanted matrix related materials and to limit the microbial activity of the matrix.

OECD 121 – Estimation of adsorption coefficient (K_{OC}) on soil and sewage sludge using high pressure liquid chromatography (HPLC) (OECD, 2001)

This HPLC method ‘estimates' the sorption coefficient of a test material based on its retention (capacity factor) in a standard HPLC column. The test material interacts with the polar and non-polar sites on the

column in a similar fashion as with the organic matter in soil and sludge matrices. This relationship allows for the correlation of the capacity factor to K_{OC} as established by the use of reference substances in a calibration curve. While this method does not require the use of ^{14}C-labeled test material, it does require the material to have some chromophore or other moiety detectable by standard HPLC detection systems; and the material must be stable in solvent/ buffer systems used in the HPLC. For ionisable substances, the retention should be evaluated under at least two conditions where the substance is non-ionised and where it's at least 10% ionised to fully assess the impact of pH on sorption. The method does not adequately estimate sorption coefficients when the mechanism of sorption is predominately associated with clay and/ or other soil constituents (OECD 121). It assumes that K_d normalised by the fraction of organic content is appropriate for reading across from soil and sludge matrices when applied to ionisable substances. This method may be of particular value for estimating K_{OC} when the test substance is volatile, highly sorptive to the test chamber, or very insoluble.

APPENDIX D: MEASUREMENT OF HYDROLYSIS

OECD 111 – Hydrolysis as a function of pH (OECD, 2004b)

This Test Guideline describes a laboratory test method to assess abiotic hydrolytic transformations of chemicals in aquatic systems at pH values normally found in the environment (pH 4 – 9). This Guideline is designed as a tiered approach; each tier is triggered by the results of the previous tier.

Sterile aqueous buffer solutions of different pH values (pH 4, 7 and 9) are treated with the non-labelled or labelled test substance (only one concentration, which should not exceed 0.01 M or half of the saturation concentration). They are incubated in the dark under controlled laboratory conditions (at constant temperatures). After appropriate time intervals, buffer solutions are analysed for the test substance and for hydrolysis products. The preliminary test should be carried out for 5 days at 50 ± 0.5°C and pH 4.0, 7.0 and 9.0. The second tier consists of the hydrolysis of unstable substances, and the third tier is the identification of hydrolysis products. The higher Tier tests should be conducted until 90 % hydrolysis of the test substance is observed or for 30 days whichever comes first.

OPPTS 835.2120 – Hydrolysis (US EPA, 2008)

This harmonised OPPTS test guideline is based largely on OECD Guidelines for the Testing of Chemicals, OECD 111 hydrolysis as a function of pH (OECD, 2004b) with clarifications derived from 40 CFR 796.3500 hydrolysis as a function of pH at 25 ºC and OPP 161-1 hydrolysis studies Pesticide Assessment Guidelines Subdivision N - Chemistry: Environmental Fate (EPA report 540/9-82-021, October 1982) for testing under TSCA and FIFRA, respectively.

OPPTS 835.2130 – Hydrolysis as a function of pH and temperature (US EPA, 1998)

The source material used in developing this harmonised OPPTS test guideline are OPPT 796.3510, OPP 161–1 Hydrolysis Studies, and OECD 111 Hydrolysis as a Function of pH (OECD, 2004b). This guideline was developed to determine the hydrolysis rate constants and half-live of substances at any environmentally relevant pH and temperature anywhere in the United States.

To determine the rates of hydrolysis at a fixed temperature hydrolysis experiments are carried out at three pH values (typically 3, 7 and 11)

To determine the rates of hydrolysis as a function of temperature, hydrolysis experiments are carried out at 3 pH values as above but at three different temperatures. From these data the half-life of the compound can be determined at any relevant environmental pH and temperature.

APPENDIX E: MEASUREMENT OF BIODEGRADATION

OECD 301 – Ready biodegradation (OECD, 1992b)

The Ready Biodegradation test is the first step or tier in biodegradation screening. It utilises 'stringent' (low biomass) test conditions where positive test results (pass) of 'readily biodegradability' one may infer the chemical will undergo rapid and complete mineralisation (CO2 evolution). The Ready Biodegradation test is available in several standard options (A-F) that accommodates DOC, DO, CO_2 evolution and O_2 uptake as endpoints and for chemicals of differing solubility, volatility and sorptive characteristics. Biosolid levels are usually at ≤ 30 mg/l; test concentration range of 2 to 100 mg/l and may use chemical specific analysis as needed. Pass criteria for the test are generally noted as 70% DOC removal (A, E); 60% $ThCO_2$ (B); 60% ThOD (C, D, F) within a 10-day window of the 28-day test.

The main output of the test is for classification purposes. Passing this test, however, supports action criteria that 'no further testing' is required as found in most if not all regulatory environmental assessment frameworks. A chemical not passing the test does not mean the chemical will persist in the environment. This result typically indicates further testing is needed at one of the higher tiers, such as the OECD 302 Inherent test, or one of the simulation tests, such as OECD 314, 303, 308 or 309 depending on what compartment is of interest.

The test is applicable to most chemical substances and is not uniquely sensitive or insensitive to ionic substances as such. The test is often not selected for chemicals that typically fail the 'Ready Biodegradation' test, such as pharmaceuticals, in lieu of initiating testing at a higher tier. This strategy is often employed as such to better characterise the emissions of compounds whose main route of entry into the environment is the wastewater treatment plant.

OECD 302 – Inherent biodegradation (OECD, 1981b,c, 1991, 1992a)

The inherent biodegradation tests (OECD 302 A-C) constitute the second step or tier in screening. The tests are not as stringent as the ready biodegradation series, typically using biomass concentrations ranging from 100 mg/l up to STP realistic concentrations of 1,000 to 2,000 mg/l. Chemical specific analysis is employed to monitor loss of parent substance (primary degradation), along with other general endpoints such as DOC or O_2 uptake. Biodegradation above 20% theoretical may be evidence of inherent primary biodegradation; biodegradation above 70% of theoretical may be evidence of inherent ultimate biodegradation.

As an intermediate level test, it does not provide the assurance of rapid and complete mineralisation as 'passing' a ready biodegradation test, nor provide the accurate kinetics of a simulation test for refining a predicted environmental concentration. The inherent tests may eliminate the need for additional simulation testing if conducted longer than 28 days in the Modified SCAS test; and may extrapolate kinetics for STP removal when the chemical passes 70% degradation in a Zahn-Wellens test within 7 day period.

As with the 'ready biodegradation' tests, there are no specific limitations to ionisable substances. Inherent tests may not be selected for those compounds that are not readily biodegradation in lieu of a simulation test. For those tests not utilising radiolabel ^{14}C- test material one should take care in interpreting degradation losses where volatility or non-specific adsorption may occur in the test system. Without the use

of chemical specific analyses the test is of little value when the main route of depletion is primary rather than ultimate degradation.

OECD 303A – Simulation of aerobic sewage treatment: Activated sludge (OECD, 2001)

OPPTS 835.3220 – Activated sludge (EPA, 2008a) **or OPPTS 835.3220 – Porous pot test** (EPA, 1998)

The OECD 303 Sewage Treatment Plant (STP) simulation is designed to provide aerobic removal kinetic data to simulate those results of a typical treatment plant either with activated sludge units or biofilters. The test systems are designed to be continuous, with various options available for settling sludge in the aerobic sludge units (porous candle, settling vessel, etc.) to simulate STP clarifier. Biomass and test concentrations are at more realistic conditions than ready or inherent tests; i.e. biomass around 2000 mg/l and test material concentrations ranging from µg/l to mg/l levels. Specific analysis for test material, along with general endpoints of DOC and COD may be measured on influent and effluent. The system is run with hydraulic and solids retention times of typical public sewage treatment plants of 6 hours and 6-10 days respectively. The study may be conducted with control units to assess the potential inhibitory effects of the test material, or potential problems with settleability; or potential abiotic depletion mechanisms. Use of radiolabel ^{14}C-test material would allow for mass balance determination and assessment of mineralisation.

The main output of the test is the removal kinetics, first order decay elimination rate for assessing removal during a typical 6-hour hydraulic retention time. The kinetic data is essential to revising predicted environmental surface water concentration as a result of sewage treatment.

There are no specific limitations to ionisable substances. The study does allow for the measurement of test material sorbed to the wasted sludge, allowing for a direct measurement of removal on wasted sludge. As the test is conducted at realistic solids levels, any impact of sorption to the availability of the test material to biodegradation may be realistically evaluated. This may be of particular interest for ionisable substances, given the variety of ionic mechanisms of sorption prevalent for many of these substances. It is essential that activated sludge collected in the test is collected when the STP is operating normally without any upsets (poor settleability) or when COD removal is diminished. Information as to whether any ionic surfactants have been used in the STP for control of flocculation is very helpful in the assessment, as that may also influence sorption. It is not well characterised as to what extent synthetic feed influences the microbial diversity over time and to what extent the original microbial population changes. It may in fact be surmised (by the authors) that it helps standardise the sludge microbial population from one test to the next.

OECD 303B – Simulation of aerobic sewage treatment: Biofilms (OECD, 2001) **or OPPTS 835.3260** (EPA, 2006)

In biofilms, synthetic or domestic sewage, and the test substance, in admixture or alone, are applied to the internal surface of a slowly rotating inclined tube. A layer of microorganisms is built up on the internal surface. Effluent from the tube is collected and either settled and/or filtered before analysis for DOC and/or the test substance by a specific method. Control units are operated in parallel under the same conditions.

The difference between the concentrations of DOC/COD in the effluent from the test and control units is assumed to be due to the test substance although specific compound analysis is often carried out before and after treatment. This difference is compared with the concentration of the added test substance to calculate

the elimination of the test substance. Biodegradation may normally be distinguished from bio-adsorption by careful examination of the elimination-time curve.

OECD 314 – Simulation of chemicals discharged in wastewater: Mixing zone and river die-away (OECD, 2008)

The OECD 314 series of simulation tests are designed to provide the extent and kinetics of degradation (primary and ultimate) for 5 potential scenarios related to those chemicals discharged through a sewage treatment plant. Individual test guidance is provided for wastewater during sewer transit, activated sludge, anaerobic sludge, effluent in mixing zone and untreated effluent directly discharged to surface water. The test methods are either open batch or closed gas flow through batch systems allowing for the use of ^{14}C-labeled test materials. Like the OECD 303 simulation, biomass and test concentrations are at more realistic conditions than ready or inherent tests; i.e. biomass for activated sludge around 2000 mg/l and test material concentrations ranging from µg/l to mg/l levels. Specific analysis for test material, along with general endpoints of DOC and COD may be measured on influent and effluent. The simulations are conducted as a die-away test with no additional synthetic feed used as with the OECD 303. Sewage and river inocula are used within 24 hours of collection. As no additional feed is provided other than the COD that is present in those samples, the study should be initiated within that 24 hour period and continued no longer than required for the particular protocol.

The main output of the test is the first order decay elimination rate for assessing removal. The kinetic data is essential to revising predicted environmental concentrations for the various environmental scenarios outlined in the protocols.

There are no specific limitations to ionisable substances. The study conducted as batch studies provides easier maintenance of test systems compared to those of the OECD 303 thereby minimising some of the associated study costs. Otherwise most comments noted in the OECD 303 are applicable here as well.

OECD 308 – Simulation in aquatic sediment system (OECD, 2002)

The OECD 308 Aerobic and Anaerobic Water-Sediment Biodegradation test is designed to provide kinetic degradation rates for the water phase, sediment phase and the total test system, ultimate kinetic degradation rate for mineralisation of total test system, mass balance, distribution of activity between the phases and identification of transformation products as needed. It is designed to use ^{14}C-labeled test material to follow the complete fate of the test material in the test system. Originally to represent over spray of pesticides/biocides in irrigation ditches, the method over time has been adopted by veterinary and human medicine regulatory frameworks as well to represent fate of pharmaceuticals in surface waters and sediments. The test uses 2 water-sediment samples in a ratio of 3:1 representing high and low organic content. Test concentration applied to the water phase is typically approximately 1 mg/l to allow for sufficient quantification of ^{14}C-test material in all phases throughout the study period.

The main output of the test is the first order decay elimination rate of the total test system (primary degradation); along with mass balance, distribution of residues between the phases, metabolite ID if > 10% dose and dissipation of residues from the aqueous phase. Determination of the kinetic degradation data from the sediment phase alone is often not achievable due to the concurrent processes of sorption and degradation that occur, especially for those compounds that become highly bound to sediment, such as

cationic compounds. This is true for most pharmaceuticals. The anaerobic phase of the test is typically not required for human pharmaceuticals as its been found the outcomes are similar to the aerobic phase except the degradation rates are slower with no new observation of transformation products than what is seen in the aerobic study[13]. For human pharmaceuticals it is a standalone test and primarily used to note the occurrence of transformation products. Kinetic data is not used to revise PEC estimates for water or sediment. For veterinary medicines and pesticides the kinetic data for total system half-life may be used in surface water models (EXPRESS; FOCUS; EUSES) to revise PEC surface water. For these products both aerobic and anaerobic studies are required by their respective regulatory authorities.

There are no specific limitations to ionic compounds, though the outcome is highly influenced by the type of ionic species present in these water-sediment systems. Cations in particular are shown to highly bind to sediments when compared to neutral and anionic compounds when evaluating 36 pharmaceuticals (Ericson, 2007); 55% irreversibly bound compared to 33% and 29% respectively. Similarly, cations typically show less biotransformation than neutral and anionic compounds, potentially inferring that cations are less bioavailable for degradation; half-life of 87 days compared to 29 and 30 days respectively. It is not clear whether these half-lives and the amount found to be bound are truly representative of fresh water-sediment systems as found downstream of sewage treatment plants.

OECD 309 – Simulation in surface waters: River die-away (OECD, 2004a)

The OECD 309 is an aerobic surface water biodegradation test and provides the kinetic degradation data for primary and ultimate degradation. It follows the OECD 314 river die-away test in that it is designed as a batch test to use ^{14}C-labeled test material, run at relatively low concentrations in the range of 1 to 100 µg/l range and may be run with surface water as is (pelagic) or amended at low solids levels of 0.01 but up to 1 g/l to represent a suspended sediment system. Unlike the OECD 314 river die-way, it is run at multiple concentrations. Test duration may be run for an extended period out to 90 days only if degradation has started within the first 60 days. Should the test run for an extended period, the test system may be renewed with a portion of the water or suspension allowing for a semi-continuous operation.

The main output of the test is the first order decay elimination rate for assessing removal. The kinetic data is essential to revising predicted environmental concentrations for the surface water scenarios outlined in the protocol.

The test is applicable to most test substances and has no specific limitations to ionisable substances.

APPENDIX F: IONISABLE COMPOUNDS DATA

The available data are laid out in Mackay's handbook format (Mackay et al, 2006).

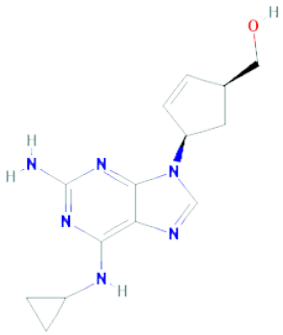
Information on structure, IUPAC name, SMILES code and formula was taken from the NLM databank (www.ncbi.nlm.nih.gov/sites/entrez), consulted on-line in October 2010. Alternatively, the data were found in the European chemical substances information system (ESIS) (http://ecb.jrc.ec.europa.eu/esis/) or SPARC (http://sparc.chem.uga.edu/sparc/search/searchcas.cfm).

The values were experimentally determined (measured) or estimated, e.g. calculated using a mathematical SAR model, at 25°C (room temperature) unless indicated otherwise.

Contents

Abacavir

Structure:



IUPAC name: {(1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]cyclopent-2-en-1-yl}methanol
CAS registry number: 136470-78-5
SMILES code: C1CC1NC2=NC(=NC3=C2N=CN3C4CC(C=C4)CO)N
Molecular formula: $C_{14}H_{18}N_6O$
Molecular weight: 286.33
Dissociation constant, pK_a: Acid 5.08; base:
Melting point (°C): 184

Water solubility (g/m^3 or mg/l): 22,400
Vapour pressure (Pa): 8.60E-10
g/l Henry's law constant (Pa m^3/mol): 8.5E-12
Octanol/water partition coefficient, log K_{OW} (neutral species): 1.2
Distribution coefficient, log D_{OW} (at reported pH): 0.88 pH 5; 1.18 pH 7; 1.2 pH 9
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 2.17 sandy loam; 2.47 clay loam; 2.97 sandy silt loam

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

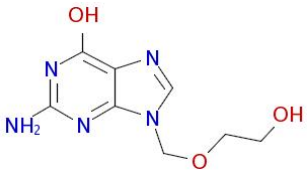
- Volatilisation:
- Photolysis:
- Oxidation:
- Hydrolysis:
- Biodegradation: 96%, 2 d, Modified Zahn-Wellens, primary biodegradation, loss of parent, activated sludge
- Biotransformation:

Half-lives in the environment:

- Air
- Water: > 8,760 h
- Soil
- Sediment:

K biomass in sludge, log Kb: 1.89 - 2.70 (est)
Pagga method, log Kb: 2.19 (154 after 3 h)

Acyclovir

Structure: 

IUPAC name: 2-Amino-1,9-dihydro-9-(2 hydroxyethoxy) methyl-6h-purin-6-one
CAS registry number: 59277-89-3
SMILES code: O=C2NC(=Nc1c2(ncn1COCCO))N
Molecular formula: $C_8H_{11}N_5O_3$
Molecular weight: 225.21
Dissociation constant, pK_a: Acid 2.27, 9.25; base:
Melting point (°C): 256.5 - 257

Water solubility (g/m^3 or mg/l): 1,450 pH 4.9; 1,410 pH 7; 3,280 pH 9; 1,250 dist H_2O
Vapour pressure (Pa): < 1.33E-5
Henry's law constant (Pa m^3/mol): 3.22E-17 (3.18 E-22 atm·m^3/mol)
Octanol/water partition coefficient, log K_{OW} (neutral species): −1.2 pH 7
Distribution coefficient, log D_{OW} (at reported pH): −1 pH 7.4
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 2.63 sandy loam; 2.60 loam; 2.64 silt loam

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

- Volatilisation:
- Photolysis:
- Oxidation:
- Hydrolysis: > 8,760 h
- Biodegradation: Aerobic – Ready (percent degradation): 0.7%, 28 d, Sturm test
  Aerobic – Inherent (percent degradation): 50%, < 1 day, Modified Zahn-Wellens, activated sludge
- Biotransformation:

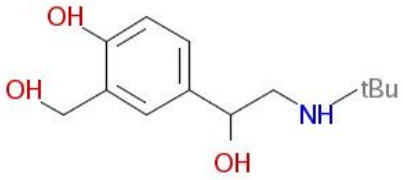
Half-lives in the environment:

- Air:
- Water: 3.55 h (pH 7 buffer)
- Soil:
- Sediment

Other information:
K biomass in sludge, log K_b: 2.33 - 2.37 (est)
Pagga method, log K_b: Biodegrades too fast to measure

Albuterol (Salbutamol)

Structure:



IUPAC name: 4-[2-(tert-Butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol
CAS registry number: 18559-94-9
SMILES code: Oc1ccc(cc1CO)C(O)CNC(C)(C)C
Molecular formula: $C_{13}H_{21}NO_3$
Molecular weight: 239.31
Dissociation constant, pK_a: Acid 9.14, 10.6; base:
Melting point (°C):

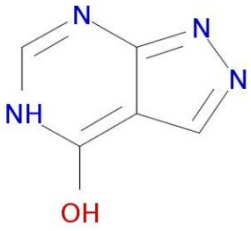
Water solubility (g/m^3 or mg/l): 249,000 pH 5; 245,000 pH 7; 32,400 pH 9
Vapour pressure (Pa): 6E-6
Henry's law constant (Pa m^3/mol): 5.00E-14
Octanol/water partition coefficient, log K_{OW} (neutral species):
Distribution coefficient, log D_{OW} (at reported pH): −1.5 pH 5, −2.8 pH 7, −2.8 pH 9
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: −1.4 sandy loam; −1.15 clay loam; −0.6 sandy silt loam

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

- Volatilisation:
- Photolysis:
- Oxidation:
- Hydrolysis:
- Biodegradation: Aerobic – Ready (percent degradation): 1%, 28 d, Modified Sturm test
  Aerobic – Soil (percent degradation): 1.3 - 38.7%, 64 d
- Biotransformation:

Half-lives in the environment:

Allopurinol

Structure: 

IUPAC name: 1,2-Dihydropyrazolo[3,4-d]pyrimidin-4-one
CAS registry number: 315-30-0
SMILES code: Oc1ncnc2[nH]ncc12
Molecular formula: $C_5H_4N_4O$
Molecular weight: 136.12
Dissociation constant, pK_a: Acid 9.4, 10.2; base:
Melting point (°C): > 350, 360

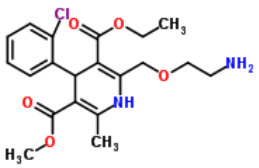
Water solubility (g/m^3 or mg/l): 483, 569 ,748; > 400 with slow dissolution in algal t (est)
Vapour pressure (Pa): 1.6E-6
Henry's law constant (Pa m^3/mol): 1.70E-13
Octanol/water partition coefficient, log K_{OW} (neutral species): –0.55; 0.32
Distribution coefficient, log D_{OW} (at reported pH): 0.33 pH6
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: < 1.25; log K_d 3.20 (K_d 1,575 l/kg 24 h, 0 l/kg 28 d) OECD 301F with HPLC

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation: Aerobic – Inherent (percent degradation): 2%, 28 d, Modified Zahn-Wellens, activated sludge
Biotransformation:

Half-lives in the environment:

Amlodipine



Structure:

IUPAC name: 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate
CAS registry number: 111470-99-6
SMILES code: Clc1ccccc1C2C(=C(/N/C(=C2/C(=O)OCC)COCCN)C)\C(=O)OC
Molecular formula: $C_{20}H_{25}ClN_2O_5$
Molecular weight: 408.8759
Dissociation constant, pK_a: 9.02
Melting point (°C): 200.57 (est)

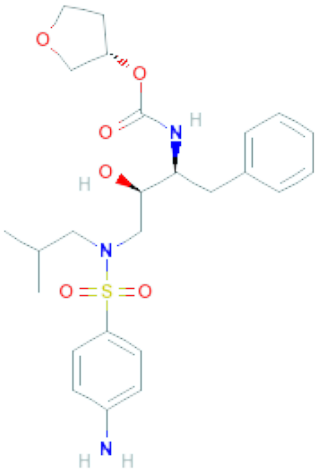
Water solubility (g/m^3 or mg/l): 75.32 (est)
Vapour pressure (Pa): 1.6E-7 (est)
Henry's law constant (Pa m^3/mol): 2.91E-017 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 3.0 (exp)
Distribution coefficient, log D_{OW} (at reported pH): 1.3 pH 5; 1.33 pH 7; 3.15 pH 9
Bioconcentration factor, log BCF: 1.61 (est)
Sorption partition coefficient, log K_{OC}: 0.52 (exp); log k_d = 0.45 (exp)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Amprenavir (Agenerase)

Structure:



IUPAC name: [(3S)-oxolan-3-yl]N-[(2S,3R)-4-[(4-aminophenyl)sulfonyl-(2-methylpropyl) amino]-3-hydroxy-1-phenylbutan-2-yl]carbamate
CAS registry number: 161814-49-9
SMILES code: CC(C)CN(CC(C(CC1=CC=CC=C1)NC(=O)OC2CCOC2)O)S(=O)(=O)C3=CC=C(C=C3)N
Molecular formula: $C_{25}H_{35}N_3O_6S$
Molecular weight: 505.63
Dissociation constant, pK_a: Acid 2.05; base:
Melting point (°C): 118-134

Water solubility (g/m^3 or mg/l): 59 pH 5; 66 pH 7; 68 pH 9
Vapour pressure (Pa): < 1.0E-06 Pa
Henry's law constant ($Pa\ m^3/mol$): < 1.0E-08
Octanol/water partition coefficient, log K_{OW} (neutral species): 2.5 pH 7; 2.4 pH 6
Distribution coefficient, log D_{OW} (at reported pH):
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 2.28 pH 4.9; 2.66 pH 6.0; 2.26 pH 8.2

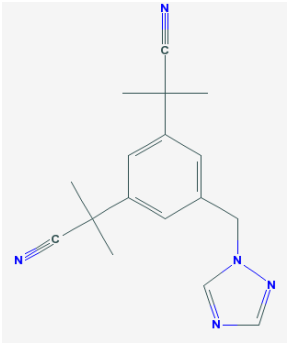
Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation: Aerobic – Ready (percent degradation): < 1.5%, 28 d, Modified Sturm test
Biotransformation:

Half-lives in the environment:

Air
Water: > 8,760 h
Soil
Sediment

Anastrozole

Structure: 

IUPAC name: 1,3-Benzenediacetonitrile, a, a, a', a'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)
CAS registry number: 120511-73-1
SMILES code: N#CC(c1cc(cc(c1)C(C#N)(C)C)Cn2ncnc2)(C)C
Molecular formula: $C_{17}H_{19}N_5$
Molecular weight: 293.37
Dissociation constant, pK_a: Acid 2.01; base:
Melting point (°C): 187.64

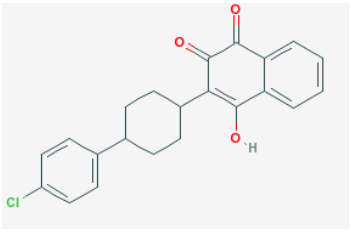
Water solubility (g/m^3 or mg/l):
Vapour pressure (Pa): 1.59E-06
Henry's law constant (Pa m^3/mol): 2.28E-10
Octanol/water partition coefficient, log K_{OW} (neutral species): 1.59
Distribution coefficient, log D_{OW} (at reported pH):
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 5.368

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

- Volatilisation:
- Photolysis:
- Oxidation:
- Hydrolysis:
- Biodegradation: Not readily biodegradable
- Biotransformation:

Half-lives in the environment:

Atovaquone

Structure: 

IUPAC name: 3-[4-(4-chlorophenyl)cyclohexyl]-4-hydroxynaphthalene-1,2-dione
CAS registry number: 95233-18-4
SMILES code: O=C1C(O)=C(C(=O)c2ccccc12)C4CCC(c3ccc(cc3)Cl)CC4
Molecular formula: $C_{22}H_{19}ClO_3$
Molecular weight: 366.84
Dissociation constant, pK_a: Acid not ionisable at pH 5 - 9; base:
Melting point (°C):

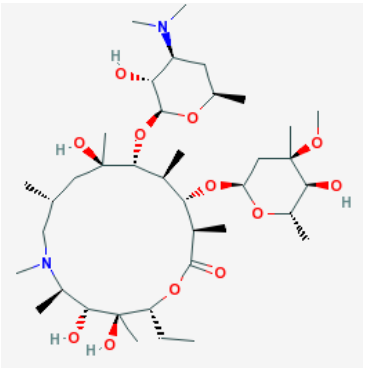
Water solubility (g/m^3 or mg/l): < 0.001 pH 5; < 0.001 pH 7; 0.61 pH 9
Vapour pressure (Pa): 1.73E-12
Henry's law constant (Pa m^3/mol): 1.70E-13
Octanol/water partition coefficient, log K_{OW} (neutral species):
Distribution coefficient, log D_{OW} (at reported pH): 4.6 pH 5; 4.6 pH 7; 4.6 pH 9
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 4.58 sandy loam; 4.18 loam; 4.27 silt loam

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Other Information:
K biomass in sludge, log K_b: 3.91 - 4.31 (est)

Azithromycin

Structure: 

IUPAC name: (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-[(2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-2-ethyl-3,4,10-trihydroxy-13-[(2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-azacyclopentadecan-15-one

CAS registry number: 83905-01-5

SMILES code:
O=C3OC(CC)C(O)(C)C(O)C(N(C)CC(C)CC(O)(C)C(OC1OC(C)CC(N(C)C)C1(O))C(C)C(OC2OC(C)C(O)C(OC)(C)C2)C3C)C

Molecular formula: $C_{38}H_{72}N_2O_{12}$

Molecular weight: 748.99

Dissociation constant, pK_a: Acid 8.74; base:

Melting point (°C): 114

Water solubility (g/m^3 or mg/l): 510 - 25380

Vapour pressure (Pa):

Henry's law constant (Pa m^3/mol):

Octanol/water partition coefficient, log K_{OW} (neutral species)

Distribution coefficient, log D_{OW} (at reported pH): 0.534 pH 7

Bioconcentration factor, log BCF:

Sorption partition coefficient, log K_{OC}: 74.2 - 96.3% in sediment following OECD 308; K_d 1.4 l/gss in small MBR

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:

Photolysis:

Oxidation:

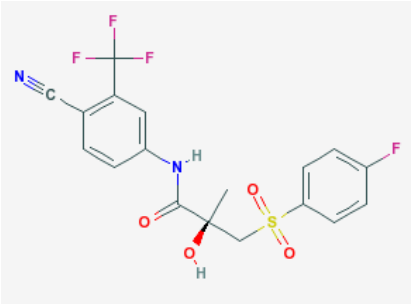
Hydrolysis:

Biodegradation: k_{biol} 0.17 l/gss/d in small MBR

Biotransformation:

Half-lives in the environment:

Bicalutamide

Structure: 

IUPAC name: (2R)-N-[4-cyano-3-(trifluoromethyl)phenyl]-3-(4-fluorophenyl)sulfonyl-2-hydroxy-2-methylpropanamide
CAS registry number: 90357-06-5
SMILES code: CC(CS(=O)(=O)C1=CC=C(C=C1)F)(C(=O)NC2=CC(=C(C=C2)C#N)C(F)(F)F)O
Molecular formula: $C_{18}H_{14}F_4N_2O_4S$
Molecular weight: 430.37
Dissociation constant, pK_a: Acid not ionisable pH 4 - 10; base:
Melting point (°C): 243.30

Water solubility (g/m^3 or mg/l):
Vapour pressure (Pa): 1.13E-15
Henry's law constant (Pa m^3/mol): 3.76E-13
Octanol/water partition coefficient, log K_{OW} (neutral species): 2.54
Distribution coefficient, log D_{OW} (at reported pH):
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 2.62

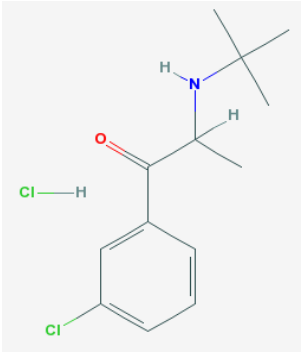
Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

- Volatilisation:
- Photolysis:
- Oxidation:
- Hydrolysis:
- Biodegradation: Not readily biodegradable
- Biotransformation:

Half-lives in the environment:

- Air
- Water: > 8,760 h
- Soil
- Sediment

Bupropion hydrochloride

Structure: 

IUPAC name: 2-(tert-butylamino)-1-(3-chlorophenyl)propan-1-one hydrochloride
CAS registry number: 31677-93-7
SMILES code: CC(C(=O)C1=CC(=CC=C1)Cl)NC(C)(C)C.Cl
Molecular formula: $C_{13}H_{18}ClNO.ClH$
Molecular weight: 276.19
Dissociation constant, pK_a: Acid 8.35; base:
Melting point (°C): 220

Water solubility (g/m^3 or mg/l): 312
Vapour pressure (Pa): 4.93E-05 Pa
Henry's law constant (Pa m^3/mol): 7.40E-07
Octanol/water partition coefficient, log K_{OW} (neutral species):
Distribution coefficient, log D_{OW} (at reported pH): −0.6 pH 1.2; −0.91 pH 6; 1.54 pH 7.4
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 2.93

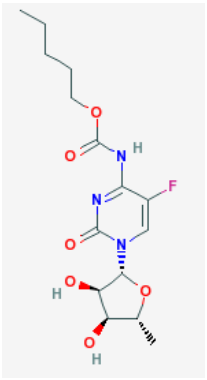
Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation: Aerobic – Ready (percent degradation): 1.21%, 14 d
Aerobic – Inherent (percent degradation): 96%, 14 d, Modified Zahn-Wellens, activated sludge
Biotransformation:

Half-lives in the environment:

Other Information:
K biomass in sludge, log K_b: 1.79

Capecitabine

Structure: 

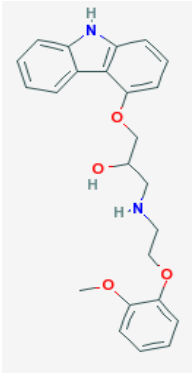
IUPAC name: Pentyl N-[1-[(2R,3R,4S,5R)-3,4-dihydroxy-5-methyloxolan-2-yl]-5-fluoro-2-oxopyrimidin-4-yl]carbamate
CAS registry number: 154361–50–9
SMILES code: O=C1N=C(NC(=O)OCCCCC)C(F)=CN1C2OC(C)C(O)C2(O)
Molecular formula: $C_{15}H_{22}FN_3O_6$
Molecular weight: 359.34
Dissociation constant, pK_a: Acid 8.8; base:
Melting point (°C): 116, 120

Water solubility (g/m^3 or mg/l): 26,000 H_2O; 24,000 pH 4.5, 6.0; 23,000 pH 7.3; 27,000 pH 8.3, 45,000 pH 9.5
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species):
Distribution coefficient, log D_{OW} (at reported pH): 4.4 pH 5.0, 4.6 pH 6.0, 4.5 pH 7.4, 3.5 pH 8.3, 0.98 pH 9.5
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: K_d 272 l/kg 3 h parallel flask in "MITI II" test, medium mobility, medium adsorption; no adsorption as per DOC, 3 h and 24 h, parallel flask to respiratory inhibition test

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Carvedilol

Structure: 

IUPAC name: 1-(9H-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)ethylamino]propan-2-ol
CAS registry number: 72956-09-3
SMILES code: OC(COc2cccc3[nH]c1ccccc1c23)CNCCOc4ccccc4(OC)
Molecular formula: $C_{24}H_{26}N_2O_4$
Molecular weight: 406.47
Dissociation constant, pK_a: Acid 7.8, base:
Melting point (°C): 112, 117 - 120, 113

Water solubility (g/m^3 or mg/l): 30.8
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol): 3.90E-07
Octanol/water partition coefficient, log K_{OW} (neutral species): 4.19
Distribution coefficient, log D_{OW} (at reported pH): 1.98 pH 5; 2.73 pH 7; 3.06 pH 9
Bioconcentration factor, log BCF: 1.9, 2.37 (BCF 79.87 l/kg, 232.79 Kint/Kout) both 48 h *Gammarus pulex*
Sorption partition coefficient, log K_{OC}: 57% ads to activated sludge 24 h, 96% ads 28 d (OECD 301F + HPLC); soil/sediment log K_{OC} 4.37 - 4.61 measured (K_{OC} 23,442 - 40,738 l/kg), activated sludge log K_d 3.74 - 4.31 measured (K_d 5,495 - 20,417 l/kg); log K_{OC} > 5.63 measured

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

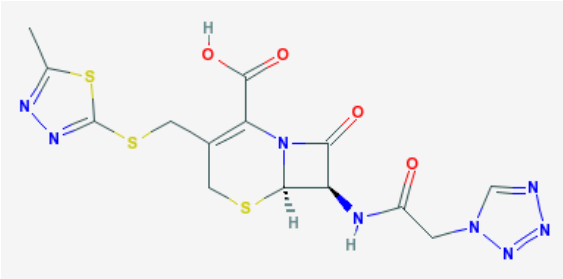
Volatilisation:
Photolysis: $t_{1/2}$ aqueous: 1.48 h Oxidation:
Hydrolysis:
Biodegradation: Aerobic – Ready (percent degradation): 25%, 28 d, OECD 301B, CO_2 evolution, activated sludge
Aerobic – Inherent (percent degradation): 50%, 28 d, batch activated sludge
Biotransformation:

Half-lives in the environment:

Air
Water: 1.48 h (photolysis, aqueous)
Soil
Sediment

K biomass in sludge, log K_b: 3.74 - 4.31

Cefazolin

Structure: 

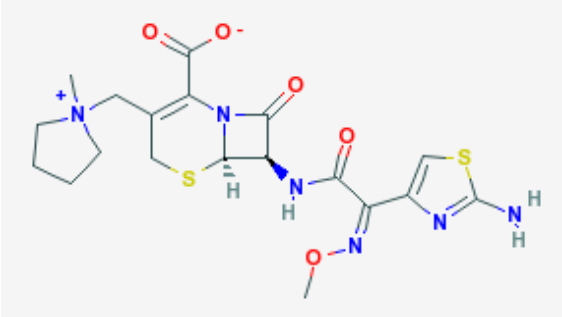
IUPAC name: (6R,7R)-3-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanylmethyl]-8-oxo-7-[[2-(tetrazol-1-yl)acetyl]amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
CAS registry number: 25953-19-9
SMILES code: CC1=NN=C(S1)SCC2=C(N3C(C(C3=O)NC(=O)CN4C=NN=N4) SC2)C(=O)O
Molecular formula: $C_{14}H_{14}N_8O_4S_3$
Molecular weight: 454.51
Dissociation constant, pK_a: Acid, acidic group 2.33; base:
Melting point (°C): 198 - 200

Water solubility (g/m^3 or mg/l):
Vapour pressure (Pa): 1.50E-18
Henry's law constant (Pa m^3/mol): 2.01E-23
Octanol/water partition coefficient, log K_{OW} (neutral species): -0.58
Distribution coefficient, log D_{OW} (at reported pH): pH 5 = −4.68; pH 7 = −5.76; pH 9 = −5.81
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Cefepime

Structure: 

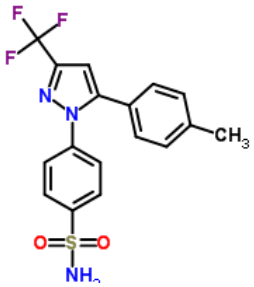
IUPAC name: (6R,7R)-7-[[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetyl]amino]-3-[(1-methylpyrrolidin-1-ium-1-yl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
CAS registry number: 88040–23–7
SMILES code: C[N+]1(CCCC1)CC2=C(N3C(C(C3=O)NC(=O)C(=NOC)C4=CSC(=N4)N)SC2)C(=O)[O-]
Molecular formula: $C_{19}H_{24}N_6O_5S_2$
Molecular weight: 480.57
Dissociation constant, pK_a: Acid 1.39, 3.26; base:
Melting point (°C):

Water solubility (g/m^3 or mg/l): 0.7 Vapour pressure (Pa): 1.68E–5
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species):
Distribution coefficient, log D_{OW} (at reported pH): 2.5 pH 5, 2.6 pH 9
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: K_d soils 1 - 5, K_{OC} 150 - 325

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Celecoxib



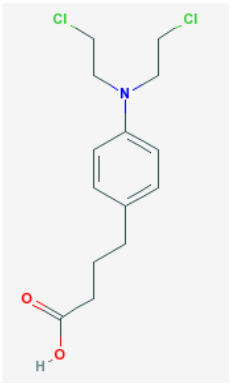
IUPAC name: 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide
CAS registry number: 169590-42-5
SMILES code: O=S(=O)(c3ccc(n1nc(cc1c2ccc(cc2)C)C(F)(F)F)cc3)N
Molecular formula: $C_{17}H_{14}F_3N_3O_2S$
Molecular weight: 381.37
Dissociation constant, pK_a: 11.1
Melting point (°C): 158 (exp)

Water solubility (g/m^3 or mg/l): 4.305 (est)
Vapour pressure (Pa): 1.6E-7 (est)
Henry's law constant (Pa m^3/mol): 7.75E-13 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 3.53
Distribution coefficient, log D_{OW} (at reported pH): 2.91 pH 5; 3.18 pH 7; 2.69 pH 9
Bioconcentration factor, log BCF: 2.04
Sorption partition coefficient, log K_{OC}: 0.51 - 0.56 (exp)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Chlorambucil

Structure: 

IUPAC name: 4-[4-[bis(2-chloroethyl)amino]phenyl]butanoic acid
CAS registry number: 305-03-3
SMILES code: O=C(O)CCCc1ccc(cc1)N(CCCl)CCCl
Molecular formula: $C_{14}H_{19}Cl_2NO_2$
Molecular weight: 304.21
Dissociation constant, pK_a: Acid 5.75; base:
Melting point (°C): 65 - 69

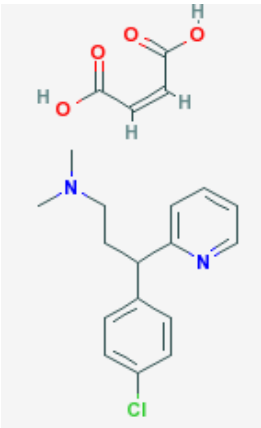
Water solubility (g/m^3 or mg/l):
Vapour pressure (Pa): 7.60E-06
Henry's law constant (Pa m^3/mol): 2.74E-05 (2.70E-10 atm·m^3/mol)
Octanol/water partition coefficient, log K_{OW} (neutral species): 3.17
Distribution coefficient, log D_{OW} (at reported pH): 3.30 pH 5; 1.49 pH 7; −0.15 pH 9; 0.61 pH 7.4
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Other Information

Chlorpheniramine maleate

Structure: 

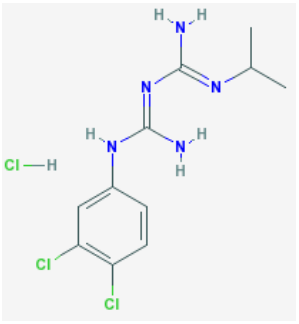
IUPAC name: (Z)-but-2-enedioic acid;
3-(4-chlorophenyl)-N,N-dimethyl-3-pyridin-2-ylpropan-1-amine
CAS registry number: 113-92-8
SMILES code: CN(C)CCC(C1=CC=C(C=C1)Cl)C2=CC=CC=N2.C(=CC(=O)O)C(=O)O
Molecular formula: $C_{16}H_{19}ClN_2.C_4H_4O_4$
Molecular weight: 390.85
Dissociation constant, pK_a: Acid 4.0, 9.2; base:
Melting point (°C): 130 - 135

Water solubility (g/m^3 or mg/l): 160,000
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species):
Distribution coefficient, log D_{OW} (at reported pH): −3.24 pH 5; -2.99 pH 7; -1.21 pH 9
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Chlorproguanil hydrochloride

Structure: 

IUPAC name: (1E)-1-[amino-(3,4-dichloroanilino)methylidene]-2-propan-2-ylguanidine hydrochloride
CAS registry number: 15537-76-5
SMILES code: CC(C)N=C(N)N=C(N)NC1=CC(=C(C=C1)Cl)Cl.Cl
Molecular formula: $C_{11}H_{16}Cl_3N_5$
Molecular weight: 324.64
Dissociation constant, pK_a: Acid 3.24; base:
Melting point (°C): 256

Water solubility (g/m^3 or mg/l): 4,480 pH 5 acetate buffer; 550 pH 7 phosphate buffer; 4,450 pH11 (NaOH); 5,290 water
Vapour pressure (Pa):
Henry's law constant ($Pa\ m^3/mol$):
Octanol/water partition coefficient, log K_{OW} (neutral species): 3.22
Distribution coefficient, log D_{OW} (at reported pH): 1.39 pH 5; 1.39 pH 7; 1.81 pH 9
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

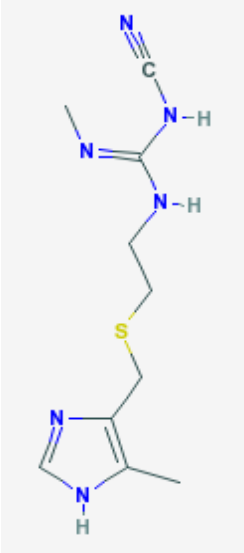
Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation: Aerobic – Inherent (percent degradation): < 5%, 14 d, Modified Zahn-Wellens, activated sludge
Biotransformation:

Half-lives in the environment:

Other Information
K biomass in sludge, log K_b: 3.19

Cimetidine

Structure: 

IUPAC name: 1-cyano-2-methyl-3-[2-[(5-methyl-1H-imidazol-4-yl)methylsulfanyl]ethyl]guanidine
CAS registry number: 51481-61-9
SMILES code: N#CNC(=NCCSCc1nc[nH]c1C)NC
Molecular formula: $C_{10}H_{16}N_6S$
Molecular weight: 252.35
Dissociation constant, pK_a: Acid 6.9; base:
Melting point (°C): 143-144

Water solubility (g/m^3 or mg/l): 14,203 - 14,510 pH 5; 7,807 - 8,098 pH 7; 4,996 - 5,009 pH 9
Henry's law constant (Pa m^3/mol): < 1.0E-11
Vapour pressure (Pa): 7.5E-7 Pa
Octanol/water partition coefficient, log K_{OW} (neutral species):
Distribution coefficient, log D_{OW} (at reported pH): −1.14 pH 5; 0.199 pH 7; 0.433 pH 9
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 3.03 - 3.62

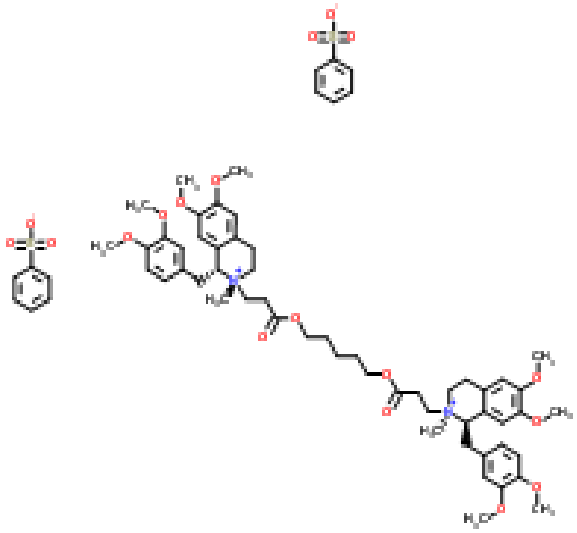
Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

- Volatilisation:
- Photolysis:
- Oxidation:
- Hydrolysis:
- Biodegradation: Aerobic – Inherent (percent degradation): 50%, 3 d, batch activated sludge
- Biotransformation:

Half-lives in the environment:

- Air
- Water: Neutral: > 1 month, measured (photolysis) in deionised water; Aqueous: 2 - 200 h, measured in lake water
- Soil
- Sediment

cis-Atracurium besylate



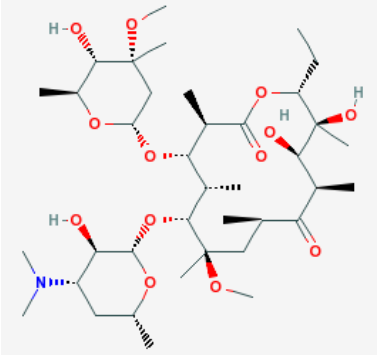
Structure:
IUPAC name: (1R,2R,1'R,2'R)-2,2'-{pentane-1,5-diylbis[oxy(3-oxopropane-3,1-diyl)]}bis[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium] bisbenzenesulfonate
CAS registry number: 96946-42-8
SMILES code: O-]S(=O)(=O)c1ccccc1.[O-]S(=O)(=O)c1ccccc1.O=C(OCCCCCOC(=O)CC[N@@+]2([C@@H](c1c(cc(OC)c(OC)c1)CC2)Cc3ccc(OC)c(OC)c3)C)CC[N@+]5(C)[C@@H](c4cc(OC)c(OC)cc4CC5)Cc6ccc(OC)c(OC)c6
Molecular formula: $C_{65}H_{82}N_2O_{18}S_2$
Molecular weight: 1243.48
Dissociation constant, pK_a: Not ionisable pH 5 - 9
Melting point (°C):

Water solubility (g/m^3 or mg/l):
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species): −2.12
Distribution coefficient, log D_{OW} (at reported pH): 2.68 pH 5; 2.68 pH 7; 2.68 pH 9
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Clarithromycin

Structure: 

IUPAC name: (3R,4S,5S,6R,7R,9R,11R,12R,13S,14R)-6-[(2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-14-ethyl-12,13-dihydroxy-4-[(2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-7-methoxy-3,5,7,9,11,13-hexamethyl-oxacyclotetradecane-2,10-dione
CAS registry number: 81103–11–9
SMILES code: O=C3OC(CC)C(O)(C)C(O)C(C(=O)C(C)CC(OC)(C)C(OC1OC(C)CC(N(C)C)C1(O))C(C)C(OC2OC(C)C(O)C(OC)(C)C2)C3C)C
Molecular formula: $C_{38}H_{69}NO_{13}$
Molecular weight: 747.96
Dissociation constant, pK_a: Acid 8.99; base:
Melting point (°C): 220

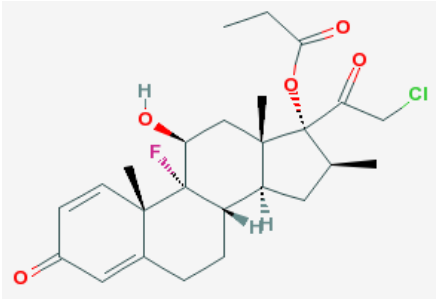
Water solubility (g/m^3 or mg/l): 130 - 130,000
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species): 3.16
Distribution coefficient, log D_{OW} (at reported pH): 1.66 pH 8
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: K_d 0.73&1.2 l/gss in small MBR

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

- Volatilisation:
- Photolysis:
- Oxidation:
- Hydrolysis:
- Biodegradation: k_{biol} 0.034, 0.2 l/gss/d in small MBR
- Biotransformation:

Half-lives in the environment:

Clobetasol propionate

Structure: 

IUPAC name: [(8S,9R,10S,11S,13S,14S,16S,17R)-17-(2-chloroacetyl)-9-fluoro-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl] propanoate
CAS registry number: 25122-46-7
SMILES code: O=C1C=CC3(C(=C1)CCC2C4CC(C)C(OC(=O)CC)(C(=O)CCl)C4(C)(CC(O)C23(F)))(C)
Molecular formula: $C_{25}H_{32}ClFO_5$
Molecular weight: 466.95
Dissociation constant, pK_a: Acid not ionisable pH 5 to9; base:
Melting point (°C): 195

Water solubility (g/m^3 or mg/l): 2
Vapour pressure (Pa): 3.63E-11
Henry's law constant ($Pa\ m^3/mol$): 2.32E-14
Octanol/water partition coefficient, log K_{OW} (neutral species): 3.5
Distribution coefficient, log D_{OW} (at reported pH): 3.86 pH 5; 3.86 pH 7; 3.86 pH 9
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

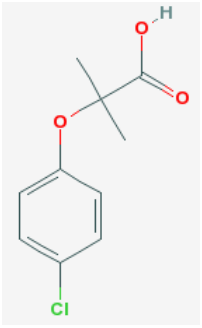
Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation: Aerobic – Inherent (percent degradation): < 5%, 14 d, Modified Zahn-Wellens, primary biodegradation, loss of parent, activated sludge
Biotransformation:

Half-lives in the environment:

Other Information
K biomass in sludge, log K_b: 2.21 (K_b 163)

Clofibric acid, Clofibrinic acid

(metabolite of Clofibrate, Etofibrate and Theofibrate)

Structure: 

IUPAC name: 2-(p-chlorophenoxy)-2-methylpropionic acid
CAS registry number: 882-09-7
SMILES code: O=C(O)C(Oc1ccc(cc1)Cl)(C)C
Molecular formula: $C_{10}H_{11}ClO_3$
Molecular weight: 214.65
Dissociation constant, pK_a: Acid 2.95; base:
Melting point (°C): 118 - 119

Water solubility (g/m^3 or mg/l): 582.5
Vapour pressure (Pa): 0.00015
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species): 3.65, 2.57; 2.84; 2.88
Distribution coefficient, log D_{OW} (at reported pH): 3.39 pH7.4
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: K_{OC} in high-organic soil 76 (ads), 135 (des) l/kg, in low-organic soil too low to measure (all in aqueous phase) OECD 106, high leaching rate in lysimeter; log K_{OC} 0.9 -1.36 in column experiments; K_d 0.005 l/gss in small MBR

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation 1: 51% removal in STP 6 d (Ternes, 1998); 35% elimination in STP activated sludge Hamburg; no elimination in two unadapted biofilm reactors for 3 wk; < 10% elimination in pilot STP 10 µg/l flow-through 21 d; 0% in biofilm reactor 10 µg/l flow-through 120 d, aerobic and anaerobic
Biodegradation 2: No degradation during soil (anaerobic) transport; 2 - 6% elimination in pilot STP; 1 - 5% elimination in oxic biofilm reactor, 26 - 30% elimination in anoxic biofilm reactor
Biodegradation 3: DT_{50} 82 d in water, DT90 274 d in water, 100 - 150 ng/g in sediment (OECD 308); 30% average removal in 6 Italian STPs in winter (in summer not detectable in influent and effluent)
Biodegradation 4: 71.8 ± 30.9% average removal in Spanish STP with MBR, 27.7 ± 46.9% with CAS; 29% removal in pilot STP after 9 d; DT_{50} 251 d in aqua dest (dark); 0 - 44%, 0 - 76%, 0 - 59%, 0 - 99%, 0 - 64%, 0 - 70% removal in 6 German STPs
Biodegradation 5: k_{biol} 0.09 l/gss/d in small MBR

Biodegradation 6: < 50 ng/l in STP effluent (Valenton, France) (0/3samples, limit of quantification 50 ng/l)

Biotransformation:

Half-lives in the environment:

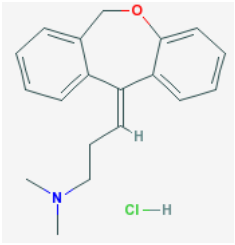
Air

Water: DT_{50} 82 d in water, DT_{90} 274 d in water, 100 - 150 ng/g in sediment (OECD 308); DT_{50} 251 d in aqua dest (dark)

Soil

Sediment

Doxepin hydrochloride

Structure: 

IUPAC name: 3-(6H-benzo[c][1]benzoxepin-11-ylidene)-N,N-dimethylpropan-1-amine hydrochloride
CAS registry number: 1229-29-4
SMILES code: O3c1ccccc1C(c2ccccc2C3)CCCN(C)C
Molecular formula : $C_{19}H_{21}NO.ClH$
Molecular weight: 315.84
Dissociation constant, pK_a: Acid: ; base 9.0
Melting point (°C): 184

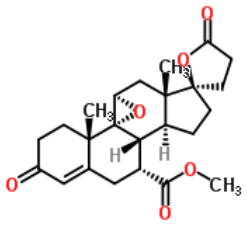
Water solubility (g/m^3 or mg/l): 666,600; 110, 31.6, 4.9 (free doxepin base)
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species): 4.29; 3.88 (free doxepin base)
Distribution coefficient, log D_{OW} (at reported pH): 2.4 pH 7.4 (free base)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 2.75 (K_{OC} 566 ± 93); log K_d 2.14 (K_d 139 ± 23) (both are average values at 2.5, 5, 14 h. No adsorption OECD 301F

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation: k_{biol} 0.29 ± 0.06 l/gSS/d (March), 0.68 ± 0.12 l/gSS/d (Oct)
Biotransformation:

Half-lives in the environment:

Eplerenone



Structure:

IUPAC name: Methyl (4aS,4bR,5aR,6aS,7R,9aS,9bR,10R)-4a,6a-dimethyl-2,5'-dioxo-2,4,4',4a,5',5a,6,6a,8,9,9a,9b,10,11-tetradecahydro-3H,3'H-spiro[cyclopenta[7,8]phenanthro[4b,5-b]oxirene-7,2'-furan]-10-carboxylate

CAS registry number: 107724-20-9

SMILES code:

COC(=O)[C@@H]4C\C1=C\C(=O)CC[C@]1(C)[C@@]65O[C@@H]6C[C@@]3(C)[C@@H](CC[C@]23CCC(=O)O2)[C@H]45

Molecular formula: $C_{24}H_{30}O_6$

Molecular weight: 414.49

Dissociation constant, pK_a: 7

Melting point (°C): 216.7 (est)

Water solubility (g/m^3 or mg/l): 4.128 (est)

Vapour pressure (Pa): 2E-8 (est)

Henry's law constant (Pa m^3/mol): 3.93E-13 (est)

Octanol/water partition coefficient, log K_{OW} (neutral species): 3.26 (est)

Distribution coefficient, log D_{OW} (at reported pH): 1 pH 5; 1.02 pH 7 (exp); 0.991 pH 9

Bioconcentration factor, log BCF: 1.807 (est)

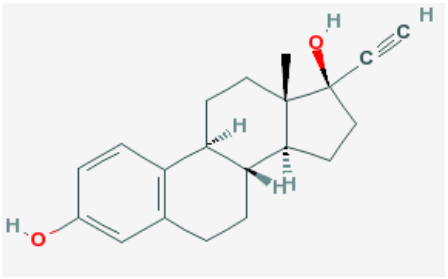
Sorption partition coefficient, log K_{OC}: 2.13 - 2.80

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Ethinyl oestradiol

Structure:



IUPAC name: (8R,9S,13S,14S,17R)-17-Ethynyl-13-methyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[a]phenanthrene-3,17-diol

CAS registry number: 57-63-6

SMILES code: C#CC3(O)(CCC2C4CCc1cc(O)ccc1C4(CCC23(C)))

Molecular formula: $C_{20}H_{24}O_2$

Molecular weight: 296.41

Dissociation constant, pK_a: Acid 10.4, 10.21; base:

Melting point (°C): 142 – 146, 186, 146; 180.3

Water solubility (g/m^3 or mg/l): 16.9 pH 5, 18.6 pH 7, 18.2 pH 9; 4.7, 4.83, 9.8, , 4.745; 5–6 g/l; 14.9; 4.8

Vapour pressure (Pa): 6E–11

Henry's law constant (Pa m^3/mol):

Octanol/water partition coefficient, log K_{OW} (neutral species): 3.67, 4.15, 4.2, 6.5

Distribution coefficient, log D_{OW} (at reported pH): 4.17 pH 5; 4.2 pH 7; 4.15 pH 9

Bioconcentration factor, log BCF: 635 (610–660) Ppromelas; sediment BCF(lipid/OC) 75±12 BCF(ww/ww) 90±14 35d (end of study), 84% found as glucuronides!, extrapolated BCF(lipid/OC) 191±50 extrBCF(ww/ww) 230±60 350d, DT_{50} 10d, extrapolated DT90 30d Lvariegatus [^{14}C]EE2; BAFwater 18±3.1 – 215±61.1 21d at 0.02-3.1mg/l, max BAF at 0.56mg/l Ctentans, BSAFsed/water 0.8±0.05 21d at 1.5mg/kg sed Ctentans; BAFwater 34±0.7 – 142±11.6 21d at 0.02-0.91mg/l, max BAF at 0.02mg/l Hazteca, BSAFsed/water 0.3±0.002 21d at 1.5mg/kg sed Hazteca;

Sorption partition coefficient, log K_{OC}: 6310; Kp calc = 5250 l/kg; 68% adsorpt to sludge at 3 h; logKd = 2.58–2.62, K_d = 280–417;logKd 2.84< -> K_d 692 l/kgTSS, logKom 3.03< -> Kom 1072 l/kgVSS, logK_{OC} 3.31< -> K_{OC} 2042, logKF –0.3143, 1/n 0.9337, ads pH-dependent; 20% (statist insign) sorption (exp) in batch activated sludge at 1mg/l (48h) and 1µg/l (24 h); K_d 350 l/kg sec sludge, 262–278 l/kg prim sludge ^{14}C-labelled EE2; K_d(primS) 350, K_d(secAS) 270 l/kg, sorption: 8% in raw WW, 5% in prim Sludge, 3% in secAS (0.4gAS/l, Ar inertisation); soil K_d 12.3–246.1, avg log K_{OC} = 2.9±0.32 (6 NZ soils); K_d 300 l/kg (AS, only graph), < 10% sorption in STP; small MBR K_d > 0.5&> 0.3 l/gss

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:

Photolysis:

Oxidation:

Hydrolysis:

Biodegradation: > 90% elimination in STP mainly due to aerobic biodeg; 85±14% removal in STP; no loss 7d spiked treated sewage; no genuine degr (exp) in batch activated sludge 1mg/l (48 h) and 1µg/l (24 h);

glucuronide cleavage/transformation, STP mass flux, no detect GW, ozonation, bound residues Ternes; k_{biol} = 5.3–6 l/gSS/d => > 70% biodegr; 65% removal STP models, both activated sludge and MBR; smallMBR k_{biol}> 0.5&> 0.7 l/gss/d, rem 90%biodeg&2%sorpt;

Biotransformation:

Half-lives in the environment:

Air

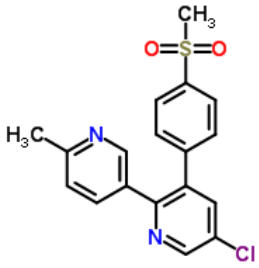
Water: 158 ng/l dosed to nonsterile mineral water lost 30% (resid 110 ng/l) over 48 d in the dark at 28°C; $t_{½}$ surface waters = 50 d;

Soil

Sediment

Etoricoxib

Structure:



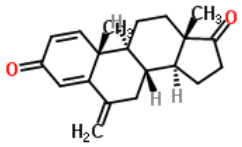
IUPAC name: 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine
CAS registry number: 202409-33-4
SMILES code: O=S(=O)(c3ccc(c2cc(Cl)cnc2c1cnc(cc1)C)cc3)C
Molecular formula: $C_{18}H_{15}ClN_2O_2S$
Molecular weight: 358.84
Dissociation constant, pK_a:
Melting point (°C): 220.98 (est)

Water solubility (g/m^3 or mg/l): 18.08 (est)
Vapour pressure (Pa): 1.08E-8 (est)
Henry's law constant (Pa m^3/mol): 1.03E-014 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 2.28
pK_a: 4.3
Distribution coefficient, log D_{OW} (at reported pH): 2.02 (pH 5); 2.3 (pH 7); 2.2 (pH 9)
Bioconcentration factor, log BCF: 1.537 (est)
Sorption partition coefficient, log K_{OC}: 0.32 – 0.48

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Exemestane



Structure:

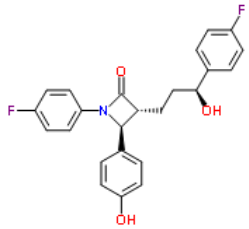
IUPAC name: 6-methylideneandrosta-1,4-diene-3,17-dione
CAS registry number: 107868-30-4
SMILES code: O=C\1\C=C/[C@]3(C(=C/1)/C(=C)C[C@H]4[C@@H]2CCC(=O)[C@]2(CC[C@H]34)C)C
Molecular formula: $C_{20}H_{24}O_2$
Molecular weight: 296.40
Dissociation constant, pK_a: 7
Melting point (°C): 155.13 (est)

Water solubility (g/m^3 or mg/l): 38.69 (est)
Vapour pressure (Pa): 1.4E-4 (est)
Henry's law constant (Pa m^3/mol): 1.64E-8 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 2.95 (est)
Distribution coefficient, log D_{OW} (at reported pH): 2.55 (pH 4); 2.5 (pH 7) (exp); 2.33 (pH 10)
Bioconcentration factor, log BCF: 1.574 (est)
Sorption partition coefficient, log K_{OC}: 3.2 – 3.82

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Ezetemibe



Structure:

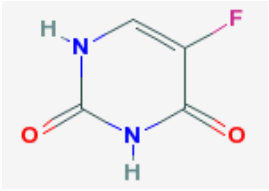
IUPAC name: (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one
CAS registry number: 163222-33-1
SMILES code: Fc1ccc(cc1)[C@@H](O)CC[C@H]4C(=O)N(c2ccc(F)cc2)[C@@H]4c3ccc(O)cc3
Molecular formula: $C_{24}H_{21}F_2NO_3$
Molecular weight: 409.43
Dissociation constant, pK_a:
Melting point (°C): 239.62 (est)

Water solubility (g/m^3 or mg/l): 4.406 (est)
Vapour pressure (Pa): 1.96E-12 (est)
Henry's law constant (Pa m^3/mol): 4.41E-018 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 4.36
pK_a: 9.8
Distribution coefficient, log D_{OW} (at reported pH): 4.27 (pH 5); 4.36 (pH 7); 4.54 (pH 9)
Bioconcentration factor, log BCF: 1.683 (est)
Sorption partition coefficient, log K_{OC}: 0.55 – 0.64

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Fluorouracil, 5-

Structure: 

IUPAC name: 5-Fluoro-1H-pyrimidine-2,4-dione
CAS registry number: 51–21–8
SMILES code: O=C1NC=C(F)C(=O)N1
Molecular formula: $C_4H_3FN_2O_2$
Molecular weight: 130.08
Dissociation constant, pK_a:
Melting point (°C): 282

Water solubility (g/m^3 or mg/l): 10,000/12,140; 12,000
Vapour pressure (Pa): 7.12E–8 mmHg = 9.5E–6Pa
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species): –0.89;–0.89; logD –1 pH 7.4
Acid pK_a: 8.0, 13.0
Base pK_a:
Distribution coefficient, log D_{OW} (at reported pH):
Bioconcentration factor, log BCF: 6.75 (Kint/Kout) 48h Gpulex
Sorption partition coefficient, log K_{OC}: no adsorption to activated sludge after 3 h in Zahn-Wellens test; low ads to raw wastewater (< 10%, MLSS 12–15g/l) and to AS (2–5%) 24 h at 5 and 500 µg ^{14}C-FU/l; no adsoprtion to activated sludge but rapid biodegradation

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation: 00% elimination activated sludge/bioreactor system 24 h at 5 and 500 µg ^{14}C-FU/l

FU/l

Biotransformation:

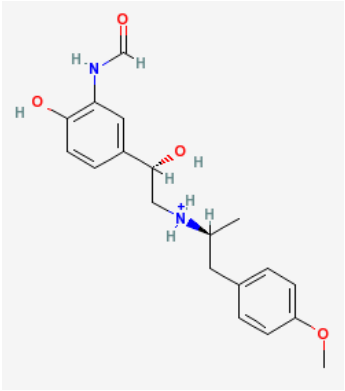
Half-lives in the environment:

Air
Water: $t_{½}$ environment 1–19 d; $t_{½}$ natural water/sediment systems ≤ 2 d OECD308 (both pond and river water/sediments), $t_{½}$ nat river water 9–10 d (20°C, mineralisation, $^{14}CO_2$)
Soil

Sediment: $t_{½}$ environment 1–19 d; $t_{½}$ natural water/sediment systems ≤ 2 d OECD308 (both pond and river water/sediments), $t_{½}$ nat river water 9–10 d (20°C, mineralisation, $^{14}CO_2$); 100% elimination in activated sludge/bioreactor system 24 h at 5 and 500 µg ^{14}C-FU/l

Other Information

Formoterol fumarate dihydrate

Structure: 

IUPAC name: [(2S)-2-(3-formamido-4-hydroxyphenyl)-2-hydroxyethyl]-
[(2S)-1-(4-methoxyphenyl)propan-2-yl]azanium
CAS registry number: 43229-80-7
SMILES code: CC(CC1=CC=C(C=C1)OC)[NH2+]CC(C2=CC(=C(C=C2)
O)NC=O)O
Molecular formula: $C_{19}H_{25}N_2O_4^+$
Molecular weight: 840.91
Dissociation constant, pK_a:
Melting point (°C):

Water solubility (g/m^3 or mg/l):
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species):
Acid pK_a: 7.9, 9.2
Base pK_a:
Distribution coefficient, log D_{OW} (at reported pH): 0.41 (pH 7.4)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

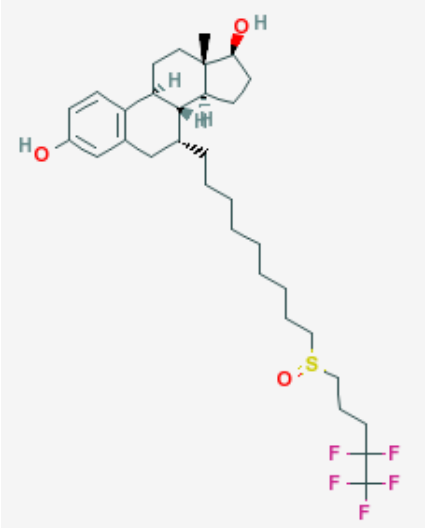
Environmental fate rate constants, k, and half-lives, $t_{1/2}$:
Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation: Not readily biodegradable
Biotransformation:

Half-lives in the environment:

Other Information

Selenastrum capricornutum 72 h EbC_{50} 46 mg/l

Fulvestrant

Structure: 

IUPAC name: 7R,8R,9S,13S,14S,17S)-13-methyl-7-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)nonyl]-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthrene-3,17-diol

CAS registry number: 129453-61-8

SMILES code: CC12CCC3C(C1CCC2O)C(CC4=C3C=CC(=C4)O)CCCCCCCCCS(=O)CCCC(C(F)(F)F)(F)F

Molecular formula: $C_{32}H_{47}F_5O_3S$

Molecular weight: 606.80

Dissociation constant, pK_a:

Melting point (°C):

Water solubility (g/m^3 or mg/l):

Vapour pressure (Pa): 5.27E+21

Henry's law constant (Pa m^3/mol):

Octanol/water partition coefficient, log K_{OW} (neutral species):

Acid pK_a: 10.4

Base pK_a:

Distribution coefficient, log D_{OW} (at reported pH): pH 7 = 7.67

Bioconcentration factor, log BCF:

Sorption partition coefficient, log K_{OC}: 5.68 (pH 7.4)

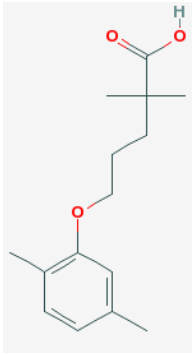
Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

BCF = 342

Half-lives in the environment:

Other Information

Gemfibrozil

Structure: 

IUPAC name: 5-(2,5-Dimethylphenoxy)-2,2-dimethylpentanoic acid
CAS registry number: 25812–30–0
SMILES code: O=C(O)C(C)(C)CCCOc1cc(ccc1C)C
Molecular formula: $C_{15}H_{22}O_3$
Molecular weight: 250.33
Dissociation constant, pK_a:
Melting point (°C): 58–61 OECD102

Water solubility (g/m^3 or mg/l): 18.6 OECD105
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species): 3.9
Acid pK_a: 4.7
Base pK_a:
Distribution coefficient, log D_{OW} (at reported pH): 4.17 pH3
Bioconcentration factor, log BCF: BCF 113 at 1.5 µg/l NC (= BCF 500 at 0.34 µg/l MMC), BCF 52 at 1500 µg/l NC (= BCF 92 at 851.9 µg/l MMC), depuration $t_{½}$ subs to ip injection 19h; 14-d subchronic effect of gemfibrozil exposure at both concs was reduced testosterone levels; not detected in fish muscle, but detected and quantified in 2/5 fish liver sampling locations in the USA, means = 70 (range 25 LOD –90), 27.1 (2/6samples; 25–27.3) ng/g
Sorption partition coefficient, log K_{OC}: sludge K_d = 3.25E–4

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation: 44% in STP, average value of Stumpf and Ternes; STP pseudo-first-iorder kinetics, biodegradable; sign degr STP, k 5 l/gSS/d, limit for sign k=0.1; avg rem Spanish STP with MBR 89.6±23.3%, with CAS 38.8±16.9%; 7STPs EU rem < 10–75%; STEP Valenton F: effl 147ng/l, 2/3samples, LoQ 25ng/l, rem 69%; STP avg rem 67±48%(range 30–99%) 7 STPs Ebro basin, SP;

Biotransformation:

Half-lives in the environment:

Air

Water: simplified 308-like system, result for water, DT_{50} 20–70 h, result given as graph only

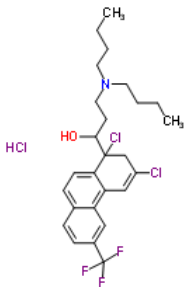
Soil

Sediment

Other Information

Halofantrine hydrochloride

Structure:



IUPAC name: 3-(dibutylamino)-1-[1,
3-dichloro-6-(trifluoromethyl)phenanthren-9-yl]propan-1-ol hydrochloride
CAS registry number: 36167-63-2
SMILES code: Cl.CCCCN(CCCC)CCC(O)C3(Cl)CC(/Cl)=C\c2c3ccc1ccc(cc12)C(F)(F)F
Molecular formula: $C_{26}H_{33}Cl_3F_3NO$
Molecular weight: 536.86
Dissociation constant, pK_a:
Melting point (°C): 199 – 202 (exp)

Water solubility (g/m^3 or mg/l): 6.1 (pH 5) (exp); 0.5 (pH 7) (exp); < 0.05 (pH 9) (exp)
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species):
pK_a: 9.7 (exp)
Distribution coefficient, log D_{OW} (at reported pH): 3.66 (pH 5) (exp); 3.78 (pH 7) (exp); 3.80 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

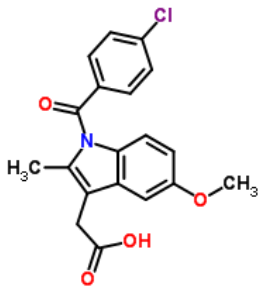
Half-lives in the environment:

Other Information:

K biomass in sludge, log K_b: 4.34 (K_b 21,878)

Indomethacin, Indometacin

Structure:



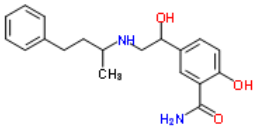
IUPAC name: [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid
CAS registry number: 53–86–1
SMILES code: Cc1c(c2cc(ccc2n1C(=O)c3ccc(cc3)Cl)OC)CC(=O)O
Molecular formula: $C_{19}H_{16}ClNO_4$
Molecular weight: 357.79
Dissociation constant, pK_a:
Melting point (°C): 158

Water solubility (g/m^3 or mg/l): 0.9378
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species): 3.08
pK_a: 4.5
Distribution coefficient, log D_{OW} (at reported pH):4.27 (pH 2), 0.91 pH 7.4
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Labetalol



Structure:

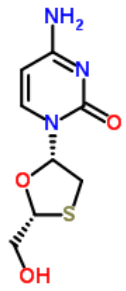
IUPAC name: 2-hydroxy-5-[1-hydroxy-2-(4-phenylbutan-2-ylamino)ethyl]benzamide
CAS registry number: 36894-69-6
SMILES code: O=C(c1cc(ccc1O)C(O)CNC(C)CCc2ccccc2)N
Molecular formula: $C_{19}H_{24}N_2O_3$
Molecular weight: 328.41
Dissociation constant, pK_a:
Melting point (°C): 136 - 139 (exp)

Water solubility (g/m^3 or mg/l): 72.9 (est)
Vapour pressure (Pa): 1.10E-13 (est)
Henry's law constant (Pa m^3/mol): 6.63E-19 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 3.09 (exp)
pK_a: 9.3 (exp)
Distribution coefficient, log D_{OW} (at reported pH): -0.47 (pH 5) (exp); -0.43 (pH 7) (exp); -0.16 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 3.75 (est)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Lamivudine

Structure: 

IUPAC name: 4-amino-1-[(2S,5R)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2-one
CAS registry number: 134678-17-4
SMILES code: O=C1/N=C(/N)\C=C/N1[C@H]2O[C@H](SC2)CO
Molecular formula: $C_8H_{11}N_3O_3S$
Molecular weight: 229.26
Dissociation constant, pK_a:
Melting point (°C): 178 - 182 (exp)

Water solubility (g/m^3 or mg/l): 135,000 (pH 5) (exp); 77,200 (pH 7) (exp); 84,400 (pH 9) (exp)
Vapour pressure (Pa): 4.5E-6 (exp)
Henry's law constant (Pa m^3/mol): 1.E-13 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): -0.7 (exp)
pK_a: 4.26 (exp)
Distribution coefficient, log D_{OW} (at reported pH): -1.86 (pH 5) (exp); -1.44 (pH 7) (exp); -1.17 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: clay loam 1.51 (exp); sandy loam 1.48 (exp); sandy silt loam 2.03 (exp)

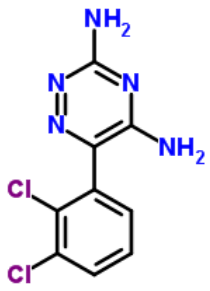
Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

- Air
- Water > 365 d (exp)
- Soil [Query: refer to spreadsheet]
- Sediment

Lamotrigine (Lamictal)

Structure:



IUPAC name: 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine
CAS registry number: 84057-84-1
SMILES code: Clc2c(Cl)c(c1nnc(nc1N)N)ccc2
Molecular formula: $C_9H_7Cl_2N_5$
Molecular weight: 256.09
Dissociation constant, pK_a:
Melting point (°C): 216 - 220 (exp)

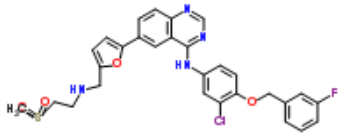
Water solubility (g/m^3 or mg/l): 170 (exp)
Vapour pressure (Pa): 4E-06 (est)
Henry's law constant (Pa m^3/mol): 2.20E-11 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 1.4 (exp)
pK_a: 5.7 (exp)
Distribution coefficient, log D_{OW} (at reported pH): < 1 (pH 5) (exp); 1.4 (pH 7) (exp); 1.4 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

K biomass in sludge, log K_b: 1.15 (K_b: 14)

Lapatinib free base



Structure:

IUPAC name: N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[(2-methylsulfonylethylamino)methyl]furan-2-yl]quinazolin-4-amine
CAS registry number: 231277-92-2
SMILES code: CS(=O)(=O)CCNCc1ccc(o1)c2ccc3c(c2)c(ncn3)Nc4ccc(c(c4)Cl)OCc5cccc(c5)F
Molecular formula: $C_{29}H_{26}ClFN_4O_4S$
Molecular weight: 587.07
Dissociation constant, pK_a:
Melting point (°C): 142 – 143 (exp)

Water solubility (g/m^3 or mg/l): 0.007 (pH 4) (exp)
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species): 6 (est)
pK_a: 4.6 (exp); 6.7 (exp)
Distribution coefficient, log D_{OW} (at reported pH):
Bioconcentration factor, log BCF: 2.12 – 2.15 (exp)
Sorption partition coefficient, log K_{OC}: Clay loam = 5.13 ; silt clay loam = 5.21; clay loam = 4.65) loamy sand = 6.12

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation:

Aerobic - Ready

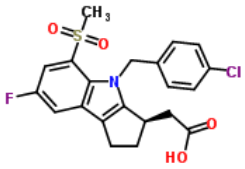
Percent degradation: 14%, 28 d, Closed bottle test
Aerobic – Soil
Percent degradation: 0.2%, 64 d, OECD 304

Biotransformation:

Half-lives in the environment:

Other Information
K Biomass in Sludge: 181970 (exp)

Laropiprant



Structure:

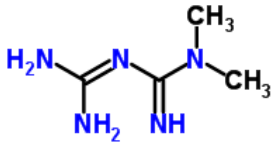
IUPAC name: [(3R)-4-(4-chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl]acetic acid
CAS registry number: 571170-77-9
SMILES code: O=S(=O)(c1cc(F)cc2c1n(c3c2CC[C@@H]3CC(=O)O)Cc4ccc(Cl)cc4)C
Molecular formula: $C_{21}H_{19}ClFNO_4S$
Molecular weight: 435.90
Dissociation constant, pK_a:
Melting point (°C): 242.75 (est)

Water solubility (g/m^3 or mg/l): 0.4261 (est)
Vapour pressure (Pa): 3.6E-10 (est)
Henry's law constant (Pa m^3/mol): 7.00E-015 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 2.4
pK_a: 7
Distribution coefficient, log D_{OW} (at reported pH): 2.1 (pH 7)
Bioconcentration factor, log BCF: 0.5 (est)
Sorption partition coefficient, log K_{OC}: 0.47 - 0.52

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Metformin (hydrochloride)



Structure:

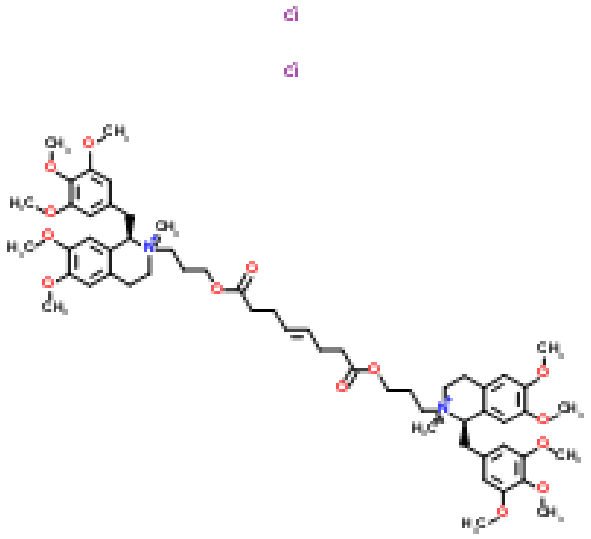
IUPAC name: 3-(diaminomethylidene)-1,1-dimethylguanidine
CAS registry number: 657–24–9
SMILES code: [N@H]=C(\N=C(/N)N)N(C)C
Molecular formula: $C_4H_{11}N_5$
Molecular weight: 129.16
Dissociation constant, pK_a:
Melting point (°C): 225

Water solubility (g/m^3 or mg/l): 300,000; 500,000 (20°C)
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species):
Acid pK_a: 2.8
Base pK_a: 11.5
Distribution coefficient, log D_{OW} (at reported pH): pH 5 = -2.0; pH 7 = -2.0 ; pH 9 = -2.13
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 0.26 – 0.63

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Mivacurium chloride (Mivacron)



Structure:

IUPAC name: (1R,1'R)-2,2'-{[(4E)-1,8-dioxooct-4-ene-1,8-diyl]bis(oxypropane-3,1-diyl)}bis[6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolinium] dichloride
CAS registry number: 106791-40-6
SMILES code: [Cl-].[Cl-].O=C(OCCC[N+]2(C)[C@@H](c1cc(OC)c(OC)cc1CC2)Cc3cc(OC)c(OC)c(OC)c3)CC/C=C/CCC(=O)OCCC[N+]5([C@@H](c4c(cc(OC)c(OC)c4)CC5)Cc6cc(OC)c(OC)c(OC)c6)C
Molecular formula: $C_{58}H_{80}Cl_2N_2O_{14}$
Molecular weight: 1100.3
Dissociation constant, pK_a:
Melting point (°C):

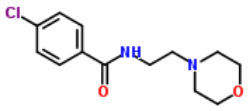
Water solubility (g/m^3 or mg/l): 1080000 (pH 5) (20°C) (exp); 1050000 (pH 7) (20°C) (exp); 1200000 (pH 9) (20°C) (exp)
Vapour pressure (Pa): 1E-10 (est)
Henry's law constant (Pa m^3/mol): 1.00E-16 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): -1.82 (exp)
pK_a: > 13 (exp); No dissociation occurs within the range of 2 – 13 (exp)
Distribution coefficient, log D_{OW} (at reported pH):
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: silty clay loam > 4.5 (pH 4.9) (exp); sandy loam > 4.32 (pH 5.8) (exp); sandy loam > 4.30 (pH 8.2) (exp)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

- Air
- Water
- Soil [Query: refer to spreadsheet]
- Sediment

Moclobemide



Structure:

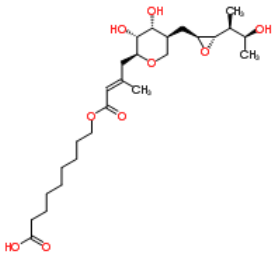
IUPAC name: 4-chloro-N-[2-(morpholin-4-yl)ethyl]benzamide
CAS registry number: 71320–77–9
SMILES code: Clc1ccc(cc1)C(=O)NCCN2CCOCC2
Molecular formula: $C_{13}H_{17}ClN_2O_2$
Molecular weight: 268.74
Dissociation constant, pK_a:
Melting point (°C): 138

Water solubility (g/m^3 or mg/l): 4000
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species):
pK_a: 6.2
Distribution coefficient, log D_{OW} (at reported pH):1.61 (pH 7.4)
Bioconcentration factor, log BCF: 4.2 – is this a log value?
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Mupirocin

Structure: 

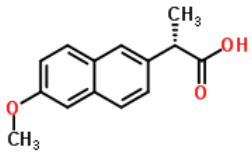
IUPAC name: 9-[(E)-4-[(2S,3R,4R,5S)-3,4-dihydroxy-5-[[(2S,3S)-3-[(2S,3S)-3-hydroxybutan-2-yl]oxiran-2-yl]methyl]oxan-2-yl]-3-methylbut-2-enoyl]oxynonanoic acid
CAS registry number: 12650-69-0
SMILES code:
O=C(O)CCCCCCCCOC(=O)\C=C(/C)C[C@@H]2OC[C@H](C[C@@H]1O[C@H]1[C@@H](C)[C@@H](O)C)[C@@H](O)[C@H]2O
Molecular formula: $C_{26}H_{44}O_9$
Molecular weight: 500.62
Dissociation constant, pK_a:
Melting point (°C): 79 – 80 (exp)

Water solubility (g/m^3 or mg/l): 1000 (exp)
Vapour pressure (Pa): 2.1E-16 (est)
Henry's law constant (Pa m^3/mol): 2.0E-19 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species):
pK_a: 4.9 (exp)
Distribution coefficient, log D_{OW} (at reported pH): 0.6 (pH 7) (exp); 2.28 (pH 5) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Naproxen



Structure:

IUPAC name: (2S)-2-(6-methoxynaphthalen-2-yl)propanoic acid
CAS registry number: 22204–53–1
SMILES code: C[C@@H](c1ccc2cc(ccc2c1)OC)C(=O)O
Molecular formula: $C_{14}H_{14}O_3$
Molecular weight: 230.26
Dissociation constant, pK_a:
Melting point (°C): 154 – 156 (exp);

Water solubility (g/m^3 or mg/l): 15.9 (exp);
Vapour pressure (Pa): 2.52E-04 (est)
Henry's law constant (Pa m^3/mol): 4.52E-08 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 3.18 (pH 2.18) (exp);
pK_a: 4.2
Distribution coefficient, log D_{OW} (at reported pH): pH 7 = 0.64; pH 9 = -1.16
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 2.543 (est)

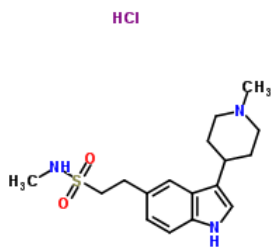
Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

- Air
- Water 336 h (exp)
- Soil
- Sediment

Naratriptan hydrochloride

Structure:



IUPAC name: N-methyl-2-[3-(1-methylpiperidin-4-yl)-1H-indol-5-yl]ethanesulfonamide hydrochloride (1:1)
CAS registry number: 143388-64-1
SMILES code: Cl.O=S(=O)(NC)CCc3ccc1c(c(cn1)C2CCN(C)CC2)c3
Molecular formula: $C_{17}H_{26}ClN_3O_2S$
Molecular weight: 371.92
Dissociation constant, pK_a:
Melting point (°C): 248 (exp)

Water solubility (g/m^3 or mg/l): 18000 (pH 5) (exp); 20000 (pH 7) (exp); 16000 (pH 9) (exp)
Vapour pressure (Pa): 8.30E-04 (exp)
Henry's law constant (Pa m^3/mol): 2.4E-21 - 3.4E-21 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 1.97 (exp)
pK_a: 9.03 (exp)
Distribution coefficient, log D_{OW} (at reported pH): -1.7 (pH 5) (exp); -0.62 (pH 7) (exp); 1.1 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 3.36 (pH 6) (exp); 3.51 (pH 6.2) (exp); 3.18 (pH 8.2) (exp)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

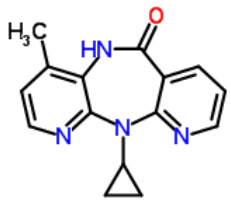
Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation: Aerobic - Ready

Percent degradation: < 1%, 28 d, Modified Sturm test.
Aerobic - Inherent
Percent degradation: 27%, 28 d, Modified Zahn-Wellens, primary biodegradation, loss of parent., Activated sludge
Aerobic - Inherent
Percent degradation: 3%, 28 d, Modified Zahn-Wellens, DOC removal., Activated sludge

Biotransformation:

Half-lives in the environment:

Nevirapin



Structure:

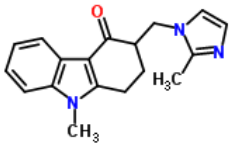
IUPAC name: 11-cyclopropyl-4-methyl-5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one
CAS registry number: 129618–40–2
SMILES code: O=C2Nc1c(ccnc1N(c3ncccc23)C4CC4)C
Molecular formula: $C_{15}H_{14}N_4O$
Molecular weight: 266.30
Dissociation constant, pK_a:
Melting point (°C): 247 – 249

Water solubility (g/m^3 or mg/l): 100
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species): 1.81 (pH 4.9)
pK_a: 2.8
Distribution coefficient, log D_{OW} (at reported pH):
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 1.84 – 2.49 (exp)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Ondansetron



Structure:

IUPAC name: 9-methyl-3-[(2-methylimidazol-1-yl)methyl]-2,3-dihydro-1H-carbazol-4-one
CAS registry number: 99614-02-5
SMILES code: O=C3c2c1ccccc1n(c2CCC3Cn4ccnc4C)C
Molecular formula: $C_{18}H_{19}N_3O$
Molecular weight: 293.36
Dissociation constant, pK_a:
Melting point (°C): 243 (exp)

Water solubility (g/m^3 or mg/l): 2510 (pH 5) (exp); 68.1 (pH 7) (exp); 10.3 (pH 9) (exp)
Vapour pressure (Pa): 2.5E-5 (exp); 1.9E-5 (20°C) (exp)
Henry's law constant (Pa m^3/mol): 8.3E-10 (exp)
Octanol/water partition coefficient, log K_{OW} (neutral species):
pK_a: 5.81 (exp)
Distribution coefficient, log D_{OW} (at reported pH): 0.226 (pH 5) (exp); 0.994 (pH 7) (exp); 1.26 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 4.22 - 4.51 (exp)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

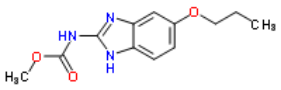
Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation:

Aerobic - Ready
Percent degradation: 18.9%, 28 d, Semi-continuous activated sludge (SCAS),
Activated sludge
Aerobic - Soil
Percent degradation: 20.3 - 99.9%, 64 d, , Soil

Biotransformation:

Half-lives in the environment:

Oxibendazole



Structure:

IUPAC name: methyl N-(6-propoxy-1H-benzimidazol-2-yl)carbamate
CAS registry number: 20559-55-1
SMILES code: O=C(OC)Nc2nc1ccc(OCCC)cc1n2
Molecular formula: $C_{12}H_{15}N_3O_3$
Molecular weight: 249.27
Dissociation constant, pK_a:
Melting point (°C): 226 (exp)

Water solubility (g/m^3 or mg/l): 62 (pH 5) (exp); 73 (pH 7) (exp); 30 (pH 8) (exp)
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species): 1.74 (exp)
Acid pK_a: 4.45 (exp)
Base pK_a: 10.8 (exp)
Distribution coefficient, log D_{OW} (at reported pH): 0.81 (pH 0.36) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

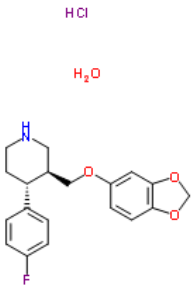
Environmental fate rate constants, k, and half-lives, $t_{1/2}$:
- Volatilisation:
- Photolysis: 1.8 – 10.2 d (exp)
- Oxidation:
- Hydrolysis:
- Biodegradation: Aerobic - Inherent

Percent degradation: 91%, 14 d, Modified Zahn-Wellens, primary biodegradation, loss of parent., Activated sludge
- Biotransformation:

Half-lives in the environment:

K biomass in sludge, log K_b: 2.09 (K_b 122)

Paroxetine hydrochloride hemihydrate

Structure: 

IUPAC name: (3S,4R)-3-(1,3-benzodioxol-5-yloxymethyl)-4-(4-fluorophenyl)piperidine hydrochloride hemihydrate
CAS registry number: 110429-35-1
SMILES code: Cl.Fc1ccc(cc1)[C@@H]2CCNC[C@H]2COc3ccc4OCOc4c3.O
Molecular formula: $C_{19}H_{23}ClFNO_4$
Molecular weight: 374.82
Dissociation constant, pK_a:
Melting point (°C): 136 – 137 (exp)

Water solubility (g/m^3 or mg/l): 5696 - 7881 (pH 5) (exp); 1132 - 1133 (pH 7) (exp); 318 - 341 (pH 9) (exp)
Vapour pressure (Pa): < 1.10E-03 (est)
Henry's law constant (Pa m^3/mol): 3.40E-10 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species):
pK_a: 9.6 (exp)
Distribution coefficient, log D_{OW} (at reported pH): 1.12 (pH 5) (exp); 1.32 (pH 7) (exp); 3.27 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 4.02 - 4.93 (exp)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

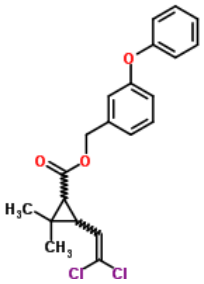
- Volatilisation:
- Photolysis:
- Oxidation:
- Hydrolysis: 2.4 h (exp)
- Biodegradation:
- Biotransformation:

Half-lives in the environment:

- Air
- Water > 1 year (exp)
- Soil
- Sediment

K biomass in sludge, log K_b: 2.94 (K_b 871)

Permethrin

Structure: 

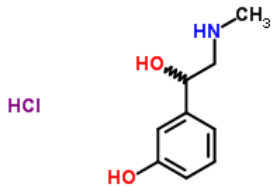
IUPAC name: (3-phenoxyphenyl)methyl
3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate
CAS registry number: 52645-53-1
SMILES code: Cl/C(Cl)=C/C3C(C(=O)OCc2cccc(Oc1ccccc1)c2)C3(C)C
Molecular formula: $C_{21}H_{20}Cl_2O_3$
Molecular weight: 391.29
Dissociation constant, pK_a:
Melting point (°C):

Water solubility (g/m^3 or mg/l): 0.2 (exp); 0.050 (seawater) (exp)
Vapour pressure (Pa): 3.8E-04 (exp)
Henry's law constant (Pa m^3/mol): 2.5E-09 (exp)
Octanol/water partition coefficient, log K_{OW} (neutral species): 5.75 (trans isomer) (exp); 6.01 (cis isomer) (exp)
pK_a: Not ionisable
Distribution coefficient, log D_{OW} (at reported pH): 5.57 (pH 5) (exp); 5.57 (pH 7) (exp); 5.57 (pH 9) (exp)
Bioconcentration factor, log BCF: 3.28 (exp)
Sorption partition coefficient, log K_{OC}: 4.02 - 4.93 (exp)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:
Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation: Aerobic - Inherent
Percent degradation: 50 - 85%, 28 d, , Lake water
Aerobic - Soil
Percent degradation: > 50%, 28 d
Biotransformation:

Half-lives in the environment:
Air
Water 50 d (exp)
Soil
Sediment

Phenylephrine hydrochloride



Structure:

IUPAC name: 3-[(1R)-1-hydroxy-2-(methylamino)ethyl]phenol hydrochloride
CAS registry number: 61-76-7
SMILES code: Cl.OC(c1cc(O)ccc1)CNC
Molecular formula: $C_9H_{14}ClNO_2$
Molecular weight: 203.66
Dissociation constant, pK_a:
Melting point (°C): 143 (exp)

Water solubility (g/m^3 or mg/l):
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species): -0.31 (exp)
pK_a: 8.86 (exp)
Distribution coefficient, log D_{OW} (at reported pH): -2.53 (pH 5) (exp); -2.21 (pH 7) (exp); -0.61 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

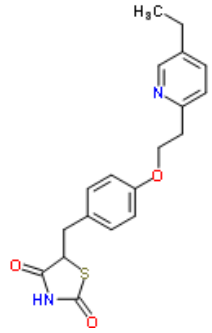
Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation:

Aerobic - Inherent
Percent degradation: 99%, 7 d, Modified Zahn-Wellens, primary biodegradation, loss of parent., Activated sludge
Aerobic - Inherent
Percent degradation: 81%, 28 d, Modified Zahn-Wellens, DOC removal., Activated sludge

Biotransformation:

Half-lives in the environment:

Pioglitazone

Structure: 

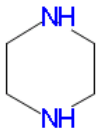
IUPAC name: 5-{4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl}-1,3-thiazolidine-2,4-dione
CAS registry number: 111025-46-8
SMILES code: O=C1NC(=O)SC1Cc3ccc(OCCc2ncc(cc2)CC)cc3
Molecular formula: $C_{19}H_{20}N_2O_3S$
Molecular weight: 356.44
Dissociation constant, pK_a:
Melting point (°C): 271.69 (est)

Water solubility (g/m^3 or mg/l): 46.85 (est)
Vapour pressure (Pa): 3.84E-12 (est)
Henry's law constant (Pa m^3/mol): 1.72E-012 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 3.4
pK_a 1: 3.8
pK_a 2: 6.3
Distribution coefficient, log D_{OW} (at reported pH): 3.17 (pH 5); 3.18 (pH 5); 3.40 (pH 7); 3.32 (pH 7); 1.5 (pH 9)
Bioconcentration factor, log BCF: 2.35 (est)
Sorption partition coefficient, log K_{OC}: 0.46 – 0.57

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Piperazine



Structure:

IUPAC name: piperazine ;
CAS registry number: 110-85-0
SMILES code: C1CNCCN1
Molecular formula: $C_4H_{10}N_2$
Molecular weight: 86.14
Dissociation constant, pK_a:
Melting point (°C):

Water solubility (g/m^3 or mg/l): 150000 (pH 12) (20°C) (exp)
Vapour pressure (Pa): 1.60E-1 (20°C) (exp)
Henry's law constant (Pa m^3/mol): 2.20E-9 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): -1.5
Acid pK_a: 4.19 (exp)
Base pK_a: 9.73 (exp)
Distribution coefficient, log D_{OW} (at reported pH): -4.18 (pH 5) (exp); -3.47 (pH 7) (exp); -1.95 (pH 9) (exp)
Bioconcentration factor, log BCF: < 0.3 (exp)
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

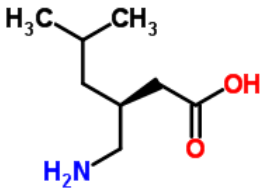
Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation:

Aerobic - Inherent
Percent degradation: > 90%, 28 d, Modified Zahn-Wellens, DOC removal., Activated sludge

Biotransformation:

Half-lives in the environment:

Pregabalin



Structure:

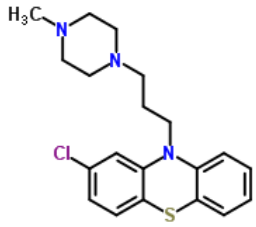
IUPAC name: (3S)-3-(aminomethyl)-5-methylhexanoic acid
CAS registry number: 148553-50-8
SMILES code: O=C(O)C[C@H](CC(C)C)CN
Molecular formula: $C_8H_{17}NO_2$
Molecular weight: 159.23
Dissociation constant, pK_a:
Melting point (°C): 282.51 (est)

Water solubility (g/m^3 or mg/l): 1.963E4 (est)
Vapour pressure (Pa): 2.7E-7 (est)
Henry's law constant (Pa m^3/mol): 3.08E-010 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): -1.9
pK_a 1: 4.2
pK_a 2: 10.6
Distribution coefficient, log D_{OW} (at reported pH): -1.43 (pH 4); -1.35 (pH 7.4)
Bioconcentration factor, log BCF: 0.5 (est)
Sorption partition coefficient, log K_{OC}: 1.62 – 2.04

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Prchlorperazine



Structure:

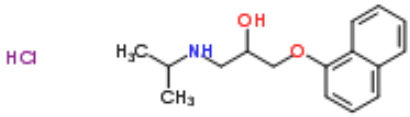
IUPAC name: 2-chloro-10-[3-(4-methylpiperazin-1-yl)propyl]-10H-phenothiazine
CAS registry number: 58-38-8
SMILES code: Clc2cc1N(c3c(Sc1cc2)cccc3)CCCN4CCN(C)CC4
Molecular formula: $C_{20}H_{24}ClN_3S$
Molecular weight: 373.93
Dissociation constant, pK_a:
Melting point (°C):

Water solubility (g/m^3 or mg/l): 14.96 (est)
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species): 4.88 (exp)
Base pK_a: 8.34 (exp); 6.3 (exp)
Distribution coefficient, log D_{OW} (at reported pH): -0.65 (pH 5) (exp); 2.39 (pH 7) (exp); 3.74 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Propranolol hydrochloride



Structure:

IUPAC name: 1-(naphthalen-1-yloxy)-3-(propan-2-ylamino)propan-2-ol hydrochloride (1:1)
CAS registry number: 318-98-9
SMILES code: Cl.OC(CNC(C)C)COc2cccc1ccccc12
Molecular formula: $C_{16}H_{22}ClNO_2$
Molecular weight: 295.80
Dissociation constant, pK_a:
Melting point (°C): 162 (exp)

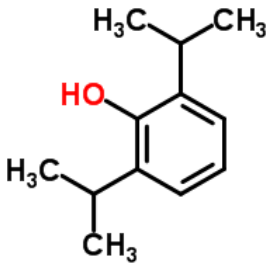
Water solubility (g/m^3 or mg/l): 97900 (exp)
Vapour pressure (Pa): 3.31E-06 (est)
Henry's law constant (Pa m^3/mol): 8.13E-18 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 0.772 (exp)
pK_a: 9.53
Distribution coefficient, log D_{OW} (at reported pH): pH 5 = 1.4; pH 7 = 0.72; pH 9 = 2.7
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 1.24 (pH 7.4) (est)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Proprofol

Structure:



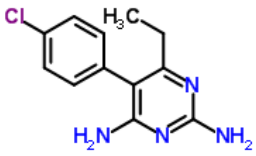
IUPAC name: 2,6-di(propan-2-yl)phenol
CAS registry number: 2078-54-8
SMILES code: Oc1c(cccc1C(C)C)C(C)C
Molecular formula: $C_{12}H_{18}O$
Molecular weight: 178.27
Dissociation constant, pK_a:
Melting point (°C): 18 (exp)

Water solubility (g/m^3 or mg/l): 174 (exp)
Vapour pressure (Pa): 3.33 (exp)
Henry's law constant (Pa m^3/mol): 2.83E-04 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 3.889 (pH 8) (exp)
Acid pK_a: 11.13
Base pK_a:
Distribution coefficient, log D_{OW} (at reported pH):
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: 2.49 (exp)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Pyrimethamine



Structure:

IUPAC name: 5-(4-chlorophenyl)-6-ethylpyrimidine-2,4-diamine
CAS registry number: 58-14-0
SMILES code: Clc2ccc(c1c(nc(nc1CC)N)N)cc2
Molecular formula: $C_{12}H_{13}ClN_4$
Molecular weight: 248.71
Dissociation constant, pK_a:
Melting point (°C): 238 - 241 (exp)

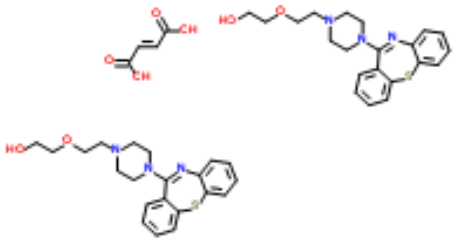
Water solubility (g/m^3 or mg/l): insoluble (exp)
Vapour pressure (Pa): 6.23E-08 (est)
Henry's law constant (Pa m^3/mol): 1.08E-10 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 2.69 (exp)
pK_a: 7.34 (20°C) (exp)
Distribution coefficient, log D_{OW} (at reported pH): 1.81 (pH 5) (exp); 3.02 (pH 7) (exp); 3.09 (pH 9) (exp); 2.44 (pH 7.4) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:
- Volatilisation:
- Photolysis:
- Oxidation:
- Hydrolysis:
- Biodegradation: Aerobic - Inherent

Percent degradation: 2%, 28 d, Modified MITI (II) Test., Activated sludge
- Biotransformation:

Half-lives in the environment:
- Air
- Water 6 months (exp)
- Soil
- Sediment

Quetiapine fumarate



Structure:

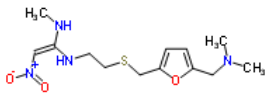
IUPAC name: 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-ylpiperazin-1-yl)ethoxy]ethanol (2E)-but-2-enedioate (2:1) (salt)
CAS registry number: 111974-72-2
SMILES code:
O=C(O)\C=C\C(=O)O.OCCOCCN4CCN(/C2=N/c3ccccc3Sc1ccccc12)CC4.N\1=C(\c3c(Sc2c/1cccc2)cccc3)N4CCN(CCOCCO)CC4
Molecular formula: $C_{46}H_{54}N_6O_8S_2$
Molecular weight: 883.0864
Dissociation constant, pK_a:
Melting point (°C):

Water solubility (g/m^3 or mg/l):
Vapour pressure (Pa): 4.29E-11 (est)
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species):
Acid pK_a: 3.32, 6.83 (exp)
Base pK_a:
Distribution coefficient, log D_{OW} (at reported pH): pH 5 = 1.4 (exp); pH 7 = 2.7 (exp); pH 9 = 2.6 (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:
Nebo soil (28% clay,18% sand, 54% silt, 1.6% organic carbon) : 5.34 (exp)
East jubilee soil (13% clay, 70% sand, 17% silt, 2.2% organic carbon): 3.90 (exp)
Kenny hill soil (14% clay, 78% sand, 8% silt, 3.1% organic carbon): 3.15 (exp)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Ranitidine



Structure:

IUPAC name: (E)-1-N'-[2-[[5-(dimethylaminomethyl)furan-2-yl]methylsulfanyl]ethyl]-1-N-methyl-2-nitroethene-1,1-diamine
CAS registry number: 66357-35-5
SMILES code: [O-][N+](=O)\C=C(\NC)NCCSCc1oc(cc1)CN(C)C
Molecular formula: $C_{13}H_{22}N_4O_3S$
Molecular weight: 314.40
Dissociation constant, pK_a:
Melting point (°C): 72 (exp)

Water solubility (g/m^3 or mg/l): soluble (exp)
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol): 2.3E-11 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species):
pK_a: 8.29 (pH 10) (exp)
Distribution coefficient, log D_{OW} (at reported pH): -2.5 (pH 5) (exp); -1.1 (pH 7) (exp); 0.14 (pH 9) (exp); -0.53 (pH 7.4) (exp) literature value
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: silty clay loam 4.49 (exp); sandy loam 3.15 (exp); sandy loam 2.51 (exp)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation:

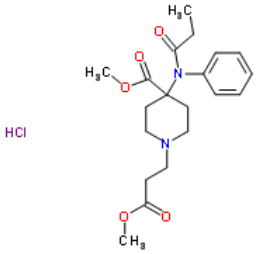
Aerobic - Ready
Percent degradation: < 1%, 28 d, Modified Sturm test.
Aerobic - Inherent
Percent degradation: 43%, 28 d, Modified Zahn-Wellens, primary biodegradation, loss of parent., Activated sludge
Aerobic - Inherent
Percent degradation: 2%, 28 d, Modified Zahn-Wellens, DOC removal., Activated Sludge
Anaerobic – Soil Percent degradation: 12%, 35 d
Aerobic – Soil Percent degradation: 3 - 10%, 67 d

Biotransformation:

Half-lives in the environment:

Remifentanil hydrochloride

Structure:



IUPAC name: methyl
1-(3-methoxy-3-oxopropyl)-4-(N-propanoylanilino)piperidine-4-carboxylate
hydrochloride
CAS registry number: 132539-07-2
SMILES code: Cl.O=C(OC)C2(N(c1ccccc1)C(=O)CC)CCN(CCC(=O)OC)CC2
Molecular formula: $C_{20}H_{29}ClN_2O_5$
Molecular weight: 412.91
Dissociation constant, pK_a:
Melting point (°C): 205 (exp)

Water solubility (g/m^3 or mg/l): 150000 (pH 5) (exp); 315000 (pH 7) (exp); 1610 (pH 9) (exp)
Vapour pressure (Pa): 3.5E-08 (exp)
Henry's law constant (Pa m^3/mol): 1.40E-15 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species):
pK_a: 7.18 (exp)
Distribution coefficient, log D_{OW} (at reported pH): -0.19 (pH 5) (exp); 1.36 (pH 7) (exp); 1.61 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: Clay loam 1.97 (pH 6.5) (exp) ; sandy loam 2.41 (pH 6.1)(exp) ; sandy silt loam 2.99 (pH 4.5) (exp)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation:

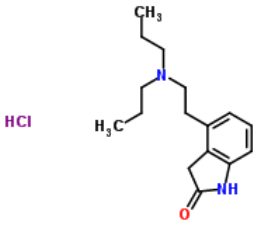
Aerobic - Ready
Percent degradation: 4%, 28 d, Modified Sturm test., Activated sludge
Aerobic – Soil Percent degradation: 22.62 - 30.41%, 64 d

Biotransformation:

Half-lives in the environment:

Air
Water 9.5 h (exp)
Soil
Sediment

Ropinirole hydrochloride



Structure:

IUPAC name: 4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one hydrochloride (1:1)
CAS registry number: 91374-20-8
SMILES code: Cl.O=C2Nc1cccc(c1C2)CCN(CCC)CCC
Molecular formula: $C_{16}H_{25}ClN_2O$
Molecular weight: 296.84
Dissociation constant, pK_a:
Melting point (°C): 245 – 246 (exp)

Water solubility (g/m^3 or mg/l): 133000 (exp)
Vapour pressure (Pa): 8.4E-6 (est)
Henry's law constant (Pa m^3/mol): 5.10E-12 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 2.84 (exp)
pK_a: pK_a1 9.5 (exp); pK_a2 11.6 (exp)
Distribution coefficient, log D_{OW} (at reported pH): 2.33 (pH 8.4) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

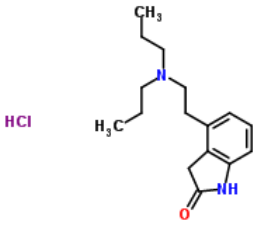
- Volatilisation:
- Photolysis: 433 – 13700 d (exp)
- Oxidation:
- Hydrolysis:
- Biodegradation:
- Biotransformation:

Half-lives in the environment:

- Air
- Water 163 d (exp)
- Soil
- Sediment

K biomass in sludge, log K_b: 1.92 (K_b 83.18)

Ropivacaine hydrochloride monohydrate



Structure:

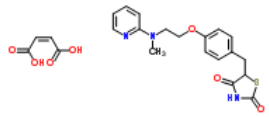
IUPAC name: 4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one hydrochloride (1:1)
CAS registry number: 132112-35-7
SMILES code: Cl.O=C2Nc1cccc(c1C2)CCN(CCC)CCC
Molecular formula: $C_{16}H_{25}ClN_2O$
Molecular weight: 328.88
Dissociation constant, pK_a:
Melting point (°C):

Water solubility (g/m^3 or mg/l): 53800 (est)
Vapour pressure (Pa): 8.17E-05 (est)
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species): 2.06 (exp)
Acid pK_a: 8.2
Base pK_a:
Distribution coefficient, log D_{OW} (at reported pH): pH = 7.4 = 2.06
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Rosiglitazone maleate



Structure:

IUPAC name: (Z)-but-2-enedioic acid;
5-[[4-[2-[methyl(pyridin-2-yl)amino]ethoxy]phenyl]methyl]-1,
3-thiazolidine-2,4-dione
CAS registry number: 155141-29-0
SMILES code: O=C1NC(=O)SC1Cc3ccc(OCCN(c2ncccc2)C)cc3.O=C(O)\C=C/C(=O)O
Molecular formula: $C_{22}H_{23}N_3O_7S$
Molecular weight: 473.50
Dissociation constant, pK_a:
Melting point (°C): 122 – 123 (exp)

Water solubility (g/m^3 or mg/l): 9100 (pH 2.3) (exp); 2000 (pH 3.5) (exp); 430 (pH 6.4) (exp)
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species):
pK_a: pK_a1 6.08 (exp); pK_a2 6.8 (exp)
Distribution coefficient, log D_{OW} (at reported pH): 1.80 (pH 4.8) (exp); 2.52 (pH 6.8) (exp); 0.99 (pH 9.1) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation:

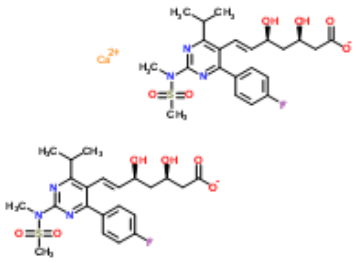
Aerobic - Inherent
Percent degradation: 50%, 1 d, batch activated sludge

Biotransformation:

Half-lives in the environment:

K biomass in sludge, log K_b: 2.80 (K_b 631)

Rosuvastatin calcium



Structure:

IUPAC name: calcium bis[(3R,5S,6E)-7-{4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoate]
CAS registry number: 147098-20-2
SMILES code: [Ca+2].O=S(=O)(N(c1nc(c(c(n1)C(C)C)/C=C/[C@@H](O)C[C@@H](O)CC([O-])=O)c2ccc(F)cc2)C)C.[O-]C(=O)C[C@H](O)C[C@H](O)/C=C/c2c(nc(nc2c1ccc(F)cc1)N(C)S(=O)(=O)C)C(C)C
Molecular formula: $C_{44}H_{54}CaF_2N_6O_{12}S_2$
Molecular weight: 1001.14
Dissociation constant, pK_a:
Melting point (°C):

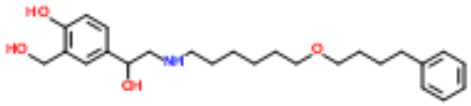
Water solubility (g/m^3 or mg/l):
Vapour pressure (Pa): 3.17E-21 (est)
Henry's law constant (Pa m^3/mol): 2.00E-14 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species):
Acid pK_a: 4.76
Base pK_a:
Distribution coefficient, log D_{OW} (at reported pH): pH 5 = 1.8; pH 7 = 0.28; pH 9 = -0.94
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:
Sandy loam (68% sand; 17% silt; 15% clay OC 1.3%) : 2.11
silty clay loam (12% sand; 57% silt; 31% clay, OC 2.1%) : 2.15
clay loam (42% sand; 22% silt; 36% clay, OC 3.9%) : 1.83

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Air
Water > 8,760 h (exp)
Soil
Sediment

Salmeterol



Structure:

IUPAC name: 2-(hydroxymethyl)-4-[1-hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl] phenol
CAS registry number: 89365-50-4
SMILES code: OCc1cc(ccc1O)C(O)CNCCCCCCOCCCCc2ccccc2
Molecular formula: $C_{25}H_{37}NO_4$
Molecular weight: 415.15
Dissociation constant, pK_a:
Melting point (°C): 80 (exp)

Water solubility (g/m^3 or mg/l): 0.9 (exp)
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol): 3.9E-17 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 2.1 (exp)
pK_a: pK_a1 9.1 (exp); pK_a2 9.55 (exp)
Distribution coefficient, log D_{OW} (at reported pH): 2.06 (pH 5) (exp); 1.71 (pH 7) (exp); 1.32 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}: Kansas 3.84 (exp); California 3.87 (exp); Iowa 4.52 (exp)

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation:

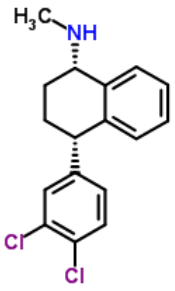
Aerobic - Inherent
Percent degradation: 50%, 12.8 d, Modified Zahn-Wellens, primary biodegradation, loss of parent.
Aerobic - Soil
Percent degradation: 29.9 - 49.9%, 64 d

Biotransformation:

Half-lives in the environment:

Air
Water > 1 year (exp)
Soil
Sediment

Sertraline

Structure: 

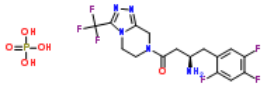
IUPAC name: (1S,4S)-4-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine
CAS registry number: 79559-97-0
SMILES code: Clc1ccc(cc1Cl)[C@H]3c2c(cccc2)[C@@H](NC)CC3
Molecular formula: $C_{17}H_{17}Cl_2N$
Molecular weight: 306.23
Dissociation constant, pK_a:
Melting point (°C): 139.73 (est)

Water solubility (g/m^3 or mg/l): 3.517 (est)
Vapour pressure (Pa): 1.56E-4 (est)
Henry's law constant (Pa m^3/mol): 5.10E-8 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 5.29 (est)
pK_a: 9.48 – 9.58
Distribution coefficient, log D_{OW} (at reported pH): 2 (pH 5); 2.9 (pH 7); 4.4 (pH 9) (exp)
Bioconcentration factor, log BCF: 3.37 (est)
Sorption partition coefficient, log K_{OC}: 3.54

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Sitagliptin phosphate



Structure:

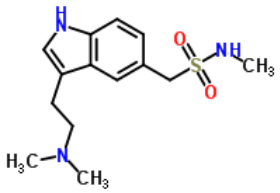
IUPAC name: (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine phosphate
CAS registry number: 65467-77-9
SMILES code: O=P(O)(O)O.Fc1cc(c(F)cc1F)C[C@@H](N)CC(=O)N3Cc2nnc(n2CC3)C(F)(F)F
Molecular formula: $C_{16}H_{18}F_6N_5O_5P$
Molecular weight: 505.31
Dissociation constant, pK_a:
Melting point (°C):

Water solubility (g/m^3 or mg/l):
Vapour pressure (Pa): 3.45E-9 (est)
Henry's law constant ($Pa\ m^3/mol$):
Octanol/water partition coefficient, log K_{OW} (neutral species): -0.03
pK_a: 7.0
Distribution coefficient, log D_{OW} (at reported pH): -1.08 (pH 5); -0.33 (pH 7); 1.11 (pH 9)
Bioconcentration factor, log BCF: 1 (pH 5.5) (est); 4.3 (pH 7.4) (est)
Sorption partition coefficient, log K_{OC}: 0.10 – 0.66

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Sumatriptan base



Structure:

IUPAC name: 1-[3-(2-dimethylaminoethyl)-1H-indol-5-yl]-N-methylmethanesulfonamide
CAS registry number: 103628-46-2
SMILES code: O=S(=O)(NC)Cc1cc2c(cc1)ncc2CCN(C)C
Molecular formula: $C_{14}H_{21}N_3O_2S$
Molecular weight: 295.40
Dissociation constant, pK_a:
Melting point (°C): 175 (exp)

Water solubility (g/m^3 or mg/l): 1000 (20°C) (exp)
Vapour pressure (Pa): 5.03E-03 (exp)
Henry's law constant (Pa m^3/mol): < 9.0E-13 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 0.93 (exp)
pK_a: 9.51 (exp)
Distribution coefficient, log D_{OW} (at reported pH): -1.42 (pH 5) (exp); -1.91 (pH 7) (exp); 0.389 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

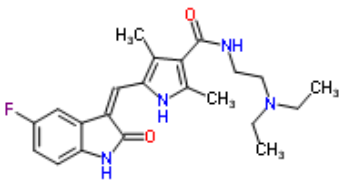
Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation:

Aerobic - Ready
Percent degradation: 1%, 28 d
Aerobic - Inherent
Percent degradation: 100%, 28 d, Modified Zahn-Wellens, primary biodegradation, loss of parent., Activated sludge.
Aerobic - Soil
Percent degradation: 32.1 - 40.2%, 64 d

Biotransformation:

Half-lives in the environment:

Sunitinib



Structure:

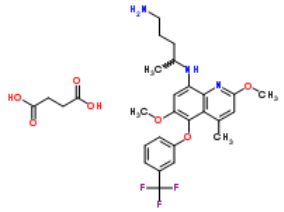
IUPAC name: N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-indolin-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide
CAS registry number: 341031-54-7
SMILES code: CCN(CC)CCNC(=O)c1c(c([nH]c1C)/C=C\2/c3cc(ccc3NC2=O)F)
Molecular formula: $C_{22}H_{27}FN_4O_2$
Molecular weight: 398.47
Dissociation constant, pK_a:
Melting point (°C): 276.63 (est)

Water solubility (g/m^3 or mg/l): 17.93 (est)
Vapour pressure (Pa): 1.78E-12 (est)
Henry's law constant ($Pa\ m^3/mol$): 2.64E-18 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 4.2
pK_a: 8.95
Distribution coefficient, log D_{OW} (at reported pH): 2.2 (pH 7.4)
Bioconcentration factor, log BCF: 1.321 (est)
Sorption partition coefficient, log K_{OC}: 3.76 – 5.82

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Tafenoquine



Structure:

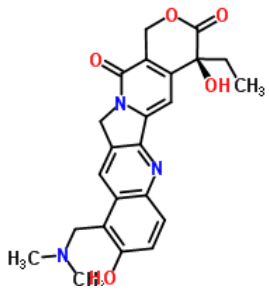
IUPAC name: N^4-{2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinolin-8-yl}pentane-1,4-diamine butanedioate (1:1)
CAS registry number: 106635-81-8
SMILES code: O=C(O)CCC(=O)O.FC(F)(F)c3cc(Oc1c(OC)cc(NC(C)CCCN)c2nc(OC)cc(c12)C)ccc3
Molecular formula: $C_{28}H_{34}F_3N_3O_7$
Molecular weight: 581.57
Dissociation constant, pK_a:
Melting point (°C): 149 (exp)

Water solubility (g/m^3 or mg/l): 37 - 50 (pH 6.5) (exp)
Vapour pressure (Pa):
Henry's law constant (Pa m^3/mol):
Octanol/water partition coefficient, log K_{OW} (neutral species):
pK_a: 9.5 (amine) (exp); 5.6 (succinate) (exp); 3.7 (quinoline) (exp)
Distribution coefficient, log D_{OW} (at reported pH): 2.70 (pH 5) (exp); 2.90 (pH 7) (exp); 4.60 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:
Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation:
Aerobic - Inherent
Percent degradation: > 99%, 5 d, Continuous activated sludge (CAS)
Biotransformation:

Half-lives in the environment:

Topotecan (hydrochloride)

Structure: 

IUPAC name: (s)-10-((dimethylamino)methyl)-4-ethyl-4,9-dihydroxy-1h-pyrano(3,4:6,7)indolizino(1,2-b)quinoline-3,14(4h,12h)-dinone, monohydrochloride
CAS registry number: 119413-54-6
SMILES code: O=C\1N4\C(=C/C2=C/1COC(=O)[C@]2(O)CC)c3nc5c(cc3C4)c(c(O)cc5)CN(C)C
Molecular formula: $C_{23}H_{23}N_3O_5$
Molecular weight: 457.91
Dissociation constant, pK_a:
Melting point (°C):

Water solubility (g/m^3 or mg/l): 420 (pH 5) (exp); 80000 (pH 2 – 3) (20°C) (exp)
Vapour pressure (Pa): 4.7E-16 (est)
Henry's law constant ($Pa\ m^3/mol$): 1.59E-24 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species):
pK_a: pK_a1 6.35 (exp); pK_a2 10.1 (exp)
Distribution coefficient, log D_{OW} (at reported pH): -0.22 (pH 5.1) (exp); -0.3 (pH 7.4) (exp); -0.59 (pH 9.3) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis: 2.51 min (exp)
Oxidation:
Hydrolysis:
Biodegradation:

Aerobic - Ready
Percent degradation: 0%, 28 d, batch activated sludge

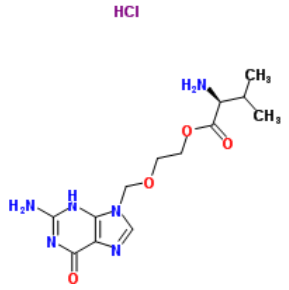
Biotransformation:

Half-lives in the environment:

Air
Water 35 years (exp)
Soil
Sediment

K biomass in sludge: K_b = 191

Valacyclovir hydrochloride

Structure: 

IUPAC name: 2-[(2-amino-6-oxo-3H-purin-9-yl)methoxy]ethyl
(2S)-2-amino-3-methylbutanoate hydrochloride
CAS registry number: 124832-27-5
SMILES code: Cl.O=C(OCCOCn1c2N\C(=N/C(=O)c2nc1)N)[C@@H](N)C(C)C
Molecular formula: $C_{13}H_{21}ClN_6O_4$
Molecular weight: 360.80
Dissociation constant, pK_a:
Melting point (°C): 221 – 225 (exp)

Water solubility (g/m^3 or mg/l): 34,500 (pH 5) (exp); 6,100 (pH 7) (exp); 174,000 (exp)
Vapour pressure (Pa): 4.0E-8 (est)
Henry's law constant (Pa m^3/mol): 9.9E-23 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): -2.16 (pH 5) (exp); -1.29 (pH 7) (exp); H_2O -3.31 (exp)
pK_a: pK_a1 1.9 (exp); pK_a2 7.47 (exp); pK_a3 9.43 (exp)
Distribution coefficient, log D_{OW} (at reported pH):
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Volatilisation:
Photolysis:
Oxidation:
Hydrolysis:
Biodegradation:

Aerobic - Ready
Percent degradation: 0.08%, 28 d, Modified Sturm test.
Aerobic - Inherent
Percent degradation: 100%, 14 d, Modified Zahn-Wellens, Activated sludge

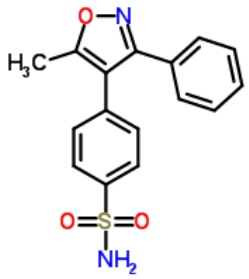
Biotransformation:

Half-lives in the environment:

Air
Water 55.92 h (exp)
Soil
Sediment

Valdecoxib

Structure:



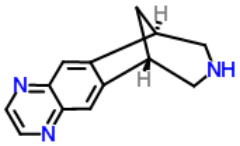
IUPAC name: 4-(5-methyl-3-phenyl-1,2-oxazol-4-yl)benzenesulfonamide
CAS registry number: 181695-72-7
SMILES code: O=S(=O)(N)c3ccc(c2c(onc2c1ccccc1)C)cc3
Molecular formula: C16H14N2O3S
Molecular weight: 314.36
Dissociation constant, pKa:
Melting point (°C): 209.25 (est)

Water solubility (g/m3 or mg/l): 53.34 (est)
Vapour pressure (Pa): 6.12E-8 (est)
Henry's law constant (Pa m3/mol): 2.22E-11 (est)
Octanol/water partition coefficient, log KOW (neutral species): 2.67 (est)
pKa: 10
Distribution coefficient, log DOW (at reported pH): 2.58 (pH 5); 26. (pH 7); 2.53 (pH 9)
Bioconcentration factor, log BCF: 1.354 (est)
Sorption partition coefficient, log KOC: 2.81 – 2.98

Environmental fate rate constants, k, and half-lives, t1/2:

Half-lives in the environment:

Varenicline



Structure:

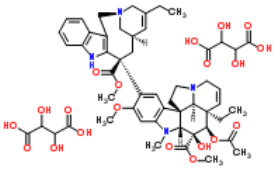
IUPAC name: (6R,10S)-7,8,9,10-tetrahydro-6H-6,10-methanoazepino[4,5-g]quinoxaline
CAS registry number: 375815-87-5
SMILES code: n1c2cc3c(cc2ncc1)[C@@H]4CNC[C@H]3C4
Molecular formula: $C_{13}H_{13}N_3$
Molecular weight: 211.26
Dissociation constant, pK_a:
Melting point (°C): 143.74 (est)

Water solubility (g/m^3 or mg/l): 5.155E4 (est)
Vapour pressure (Pa): 6.2E-4 (est)
Henry's law constant (Pa m^3/mol): 2.68E-11 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 1.03 (est)
pK_a: 9.2
Distribution coefficient, log D_{OW} (at reported pH): -1.23 (pH 5); -0.817 (pH 7); 0.758 (pH 9)
Bioconcentration factor, log BCF: 0.092 (est)
Sorption partition coefficient, log K_{OC}: 3.84 – 4.22

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Vinorelbine tartrate



Structure:

IUPAC name: 3',4'-didehydro-4'-deoxy-c'-norvincaleukoblastine
[r-(r*,r*)-2,3-dihydroxybutanedioate
CAS registry number: 125317-39-7
SMILES code:
OC(=O)C(O)C(O)C(O)=O.OC(=O)C(O)C(O)C(O)=O.COC(=O)[C@@]2(C[C@@H]4/C=C(/CC)C[N@](Cc1c3ccccc3nc12)C4)c5cc9c(cc5OC)N(C)[C@@H]6[C@]98CCN7C\C=C/[C@@](CC)([C@@H](OC(C)=O)[C@]6(O)C(=O)OC)[C@H]78
Molecular formula: C53H66N4O20
Molecular weight: 1079.13
Dissociation constant, pKa:
Melting point (°C): 210 (exp)

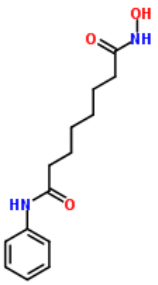
Water solubility (g/m3 or mg/l): > 1,000,000 (H2O) (exp); > 250,000 (pH 5) (exp); 1,000 (pH 7) (exp); 50 - 1,000 (pH 9) (exp)
Vapour pressure (Pa): 1.03E-65 (exp)
Henry's law constant (Pa m3/mol):
Octanol/water partition coefficient, log KOW (neutral species):
pKa: vinorelbine pKa1 5.09 (exp); pKa2 9.05 (exp); pKa3 10.45 (exp)
Distribution coefficient, log DOW (at reported pH): -0.2 (pH 5) (exp); 2.1 (pH 7) (exp); 3.8 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log KOC:

Environmental fate rate constants, k, and half-lives, t1/2:
- Volatilisation:
- Photolysis:
- Oxidation:
- Hydrolysis:
- Biodegradation:

Aerobic - Ready
Percent degradation: 9.24%, 28 d, Modified Sturm test.
Aerobic - Ready
Percent degradation: 17.8% 63 d, Modified Sturm test.
- Biotransformation:

Half-lives in the environment:
- Air
- Water > 1 year (exp)
- Soil
- Sediment

Vorinostat

Structure: 

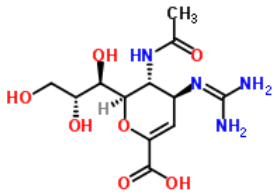
IUPAC name: N-hydroxy-N'-phenyloctanediamide
CAS registry number: 149647-78-9
SMILES code: O=C(Nc1ccccc1)CCCCCCC(=O)NO
Molecular formula: C14H20N2O3
Molecular weight: 264.32
Dissociation constant, pKa:
Melting point (°C): 223.71 (est)

Water solubility (g/m3 or mg/l): 1167 (est)
Vapour pressure (Pa): 3.47E-11 (est)
Henry's law constant (Pa m3/mol): 1.23E-14 (est)
Octanol/water partition coefficient, log KOW (neutral species): 1.42
pKa: 9.2
Distribution coefficient, log DOW (at reported pH): 1.2 (pH 5); 1.42 (pH 7); 0.47 (pH 9)
Bioconcentration factor, log BCF: 0.406 (est)
Sorption partition coefficient, log KOC: 0.40 – 0.53

Environmental fate rate constants, k, and half-lives, t1/2:

Half-lives in the environment:

Zanamivir



Structure:

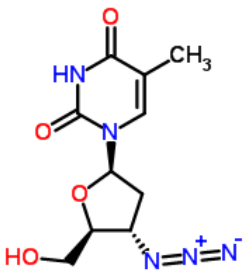
IUPAC name: (2R,3R,4S)-3-acetamido-4-(diaminomethylideneamino)-2-[(1R,2R)-1,2,
3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid
CAS registry number: 139110-80-8
SMILES code: O=C(O)C=1O[C@@H]([C@H](O)[C@H](O)CO)[C@H](NC(=O)C)[C@@H](/N=C(\N)N)C=1
Molecular formula: C12H20N4O7
Molecular weight: 332.31
Dissociation constant, pKa:
Melting point (°C):

Water solubility (g/m3 or mg/l): 18,000 (exp)
Vapour pressure (Pa): 1 E-7 (exp)
Henry's law constant (Pa m3/mol): 2.0E-14 (exp)
Octanol/water partition coefficient, log KOW (neutral species): -7.082 (exp)
pKa: 2.48 (exp)
Distribution coefficient, log DOW (at reported pH): -5.52 (pH 5) (exp); -5.50 (pH 7) (exp); -5.50 (pH 9) (exp)
Bioconcentration factor, log BCF:
Sorption partition coefficient, log KOC:
clay loam 0.92 (pH 6) (exp); sandy loam < 1.18 (pH 6.2) (exp); sandy loam < 0.82 (pH 8.2) (exp)

Environmental fate rate constants, k, and half-lives, t1/2:

Half-lives in the environment:

Zidovudine

Structure: 

IUPAC name: 3'-azido-3'-deoxythymidine
CAS registry number: 30516–87–1
SMILES code: O=C/1NC(=O)N(\C=C\1C)[C@@H]2O[C@@H]([C@@H](\N=[N+]=[N-])C2)CO
Molecular formula: $C_{10}H_{13}N_5O_4$
Molecular weight: 267.24
Dissociation constant, pK_a:
Melting point (°C): 113 – 115; 106 – 112

Water solubility (g/m^3 or mg/l): 24,000 (pH 7) (exp); 22600 (pH 4) (exp); 23100 (pH 8) (exp); 22200 (water pH 5.7) (exp)
Vapour pressure (Pa): 6.70E-06 (est)
Henry's law constant (Pa m^3/mol): 3.47E-025 (est)
Octanol/water partition coefficient, log K_{OW} (neutral species): 0.06 (exp)
pK_a: 9.72 (exp)
Distribution coefficient, log D_{OW} (at reported pH):
Bioconcentration factor, log BCF:
Sorption partition coefficient, log K_{OC}:

Environmental fate rate constants, k, and half-lives, $t_{1/2}$:

Half-lives in the environment:

Air
Water > 1 year (exp)
Soil
Sediment

K biomass in sludge: K_b = 59.12

The available data are presented in Mackay handbook format (Mackay et al, 2006).

BIBLIOGRAPHY

References quoted

The following references were consulted by the Task Force and they are quoted in the report

Aharonson N, Kafkafi U. 1975. Adsorption of benzimidazole fungicides on montmorillonite and kaolinite clay surfaces. J Agric Food Chem 23:434-437.

Allen RI, Box KJ, Comer JE, Peake C, Tam KY. 1998. Multiwavelength spectrophotometric determination of acid dissociation constants of ionizable drugs. J Pharm Biomed Anal 17:699-712.

Avdeef A. 1996. Assessment of distribution-pH profiles. Lipophilicity in drug action and toxicology. Wiley-VCH, Weinheim, Germany pp 109-139.

Avdeef, A. 2001. Physicochemical profiling (solubility, permeability and charge state). Curr Top Med Chem 1:277-351.

Babic S, Horvat AJ, Pavlovic DM, Kastelan-Macan M. 2007. Determination of pK(a) values of active pharmaceutical ingredients. TrAC 26:1043-1061.

Bailey GW, White JL, Rothberg T. 1968. Adsorption of organic herbicides by montmorillonite: role of pH and chemical character of adsorbate. Soil Sci Soc Am J 32:222-234.

Balogh GT, Gyarmati B, Nagy B, Molnar L, Keseru GM. 2009. Comparative evaluation of in silico pK(a) prediction tools on the gold standard dataset. QSAR Comb Sc 28:1148-1155.

Barron L, Purcell M, Havel J, Thomas K, Tobin J, Paull B. 2009. Occurrence and fate of pharmaceuticals and personal care products within sewage sludge and sludge-enriched soils (2005-FS-30-M1). STRIVE report series no. 34. Dublin City University, Norwegian Institute for Water Research (NIVA), Masaryk University, Czech Republic. Environmental Protection Agency (EPA), Wexford, Ireland.

Bowmer T, Leopold A. 2004. Strategies for selecting biodegradation simulation tests and their interpretation in persistence evaluation and risk assessment. Simulation testing of environmental persistence (STEP): Report of a two-day workshop held in Rotterdam, 4 and 5 October, 2004. The Netherlands Organization for Applied Scientific Research (TNO) Zeist, Netherlands.

Boxall A, Fogg LA, Blackwell PA, Kay P, Pemberton EJ, Croxford A. 2004. Veterinary medicines in the environment. Rev Eviron Contam Toxicol 180:1-91.

Boxall ABA, Rudd MA, Brooks BW, Caldwell DJ, Choi K, Hickmann S, Innes E, Ostapyk K, Staveley JP, Verslycke T, Ankley GT, Beazley KF, Belanger SE, Berninger JP, Carriquiriborde P, Coors A, DeLeo PC, Dyer SD, Ericson JF, Gagné F, Giesy JP., Gouin T, Hallstrom L, Karlsson MV, Larsson DG, Lazorchak JM, Mastrocco F, McLaughlin A, McMaster ME, Meyerhoff RD, Moore R, Parrott JL, Snape JR, Murray-Smith R, Servos MR, Sibley PK, Straub JO, Szabo ND, Topp E, Tetreault GR, Trudeau VL, Van Der Kraak G. 2012. Pharmaceuticals and personal care

products in the environment: What are the big questions? Environ Health Perspect http://dx.doi.org/10.1289/ehp.1104477.

Bresnahan GA, Koskinen WC, Dexter AG, Lueschen WE. 2000. Influence of soil pH-sorption interactions on imazethapyr carry-over. J Agric Food Chem 48:1929-1934.

Briggs GG. 1981. Theoretical and experimental relationships between soil adsorption, octanol-water partition coefficients, water solubilities, bioconcentration factors and the parachor. J Agric Food Chem 29:1050-1059.

Calvet R. 1989. Adsorption of organic chemicals in soils. Environ Health Perspect 83:145-177.

Celis R, Cornejo J, Hermosin MC, Koskinen WC. 1998. Sorption of atrazine and simazine by model soil colloids. Soil Sci Soc Am J 62:165-171.

Chamberlain K, Evans AA, Bromilow RH. 1996. 1-Octanol/water partition coefficient (K-ow) and pK(a) for ionisable pesticides measured by a pH-metric method. Pestic Sci 47:265-271.

Choubert JM, Pomies M, Ruel SM, Coquery M. 2011. Influent concentrations and removal performances of metals through municipal wastewater treatment processes. Water Sci Technol 63:1967-1973.

Comer J, Tam K. 2007. Lipophilicity profiles: Theory and measurement. In Testa B, van de Waterbeemd H, Folkers G, Guy RH, eds. Pharmacokinetic optimization in drug research: Biological, physicochemical and computational strategies. Helvetica Chimica Acta, Zürich, Switzerland 275-304.

Cox l, Koskinen WC, Celis R, Yen PY, Hermosin MC, Cornejo J. 1998. Sorption of imidacloprid on soil clay mineral and organic components. Soil Sci Soc Am J 62:911-915.

Cox L, Celis R, Hermosin MC, Cornejo J. 2000. Natural soil colloids to retard simazine and 2,4,-D leaching in soil. J Agric Food Chem 48:93-99.

Cronin MT, Walker JD, Jaworska JS, Comber MH, Watts CD, Worth AP. 2003. Use of QSARs in international decision-making frameworks to predict ecologic effects and environmental fate of chemical substances. Environ Health Perspect 111:1376-1390.

Csizmadia F, Tsantili-Kakoulidou A, Panderi I, Darvas F. 1997. Prediction of distribution coefficient from structure 1. Estimation method. J Pharm Sci 86:865-871.

Dean J. 1999. Lange's handbook of chemistry, fifteenth edition. McGraw-Hill, New York, NY, USA 8.24-8.72.

Delaney J et al. 12th Edition of the Pesticide Manual (CDS Tomlin, BCPC) (Syngenta).

Doucette WJ. 2003. Quantitative structure-activity relationships for predicting soil-sediment sorption coefficients for organic chemicals. Environ Toxicol Chem 22:1771-1788.

Dyson JS, Beulke S, Brown CD, Lane MCG. 2002. Adsorption and degradation of the weak acid mesotrione in soil and environmental fate implications. J Environ Qual 31:613-618.

EC. 1996. Technical guidance document in support of the Commission Directive 93/67/EEC on risk assessment for new notified substances and Commission Regulation (EC) No 1488/94 on risk assessment for existing substances. Parts 1-4. Office for Official Publications of the European Communities, Luxembourg, Luxembourg.

EC. 2003. Technical guidance document in support of Commission directive 93/67/EEC on risk assessment of new notified substances and Commission Regulation (EC) no. 1488/94 on risk assessment for existing chemicals and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. Office for Official Publications of the European Communities, Luxembourg, Luxembourg.

ECETOC. 2003b. (Q)SARs: Evaluation of the commercially available software for human health and environmental endpoints with respect to chemical management applications. Technical report no. 89. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium.

ECETOC. 2003a. Environmental risk assessment of difficult substances. Technical report no. 88. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium.

ECHA. 2008a. Endpoint specific guidance. In: Guidance on information requirements and chemical safety assessment. Chapter R.7b. European Chemicals Agency, Helsinki, Finland.

ECHA. 2008b. n-Octanol/water partition coefficient. Guidance on information requirements and chemical safety assessment. Chapter R7a, Section R.7.1.8, pp 100-112. European Chemicals Agency, Helsinki, Finland.

ECHA. 2008c. PBT Assessment. In: Guidance on information requirements and chemical safety assessment. Chapter R.11. European Chemicals Agency, Helsinki, Finland.

EMA. 2010. Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'. EMA/CHMP/SWP/44609/2010. Committee for Medicinal Products for Human Use (CHMP), London, UK.

EMEA. 2006. Guideline on the environmental risk assessment of medicinal products for human use. CPMP/SWP/4447/00 corr 1. European Medicines Agency, London, UK.

Ericson JF. 2007. An evaluation of the OECD 308 water/sediment systems for investigating the biodegradation of pharmaceuticals. Environ Sci Technol 41:5803-5811.

Ericson JF. 2012. Water-sediment biodegradation: Challenges in modeling and screening for pharmaceutical products. Presented at SETAC 6th World Congress, May 2012, Berlin, Germany. Pfizer, Westerly, Richmond, USA.

EU. 2001. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Off J EC L311:67-128.

Evanko CR, Dzombak, DA. 1998. Influence of structural features on sorption of NOM-analogue organic acids to goethite. Environ Sci Technol 32:2846-2855.

Fass. 2007. Environmental classification of pharmaceuticals in www.fass.se, guidance for pharmaceutical companies. Farmacevtiska specialiteter i Sverige [Pharmaceutical specialties in Sweden]. www.fass.se/environment.

FDA. 1998. Environmental assessment of human drug and biologics applications. Guidance for industry, report CMC 6, revision 1. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Office of Training and Communications, Division of Communications Management, Drug Information Branch, Rockville, MD, USA.

Franco A, Trapp S. 2008. Estimation of the soil-water partition coefficient normalized to organic carbon for ionizable organic chemicals. Environ Toxicol Chem. 27:1995-2004.

Franco A, Trapp S. 2010. A multimedia activity model for ionizable compounds: Validation study with 2,4-dichlorophenoxyacetic acid, aniline, and trimethoprim. Environ Toxicol Chem 29:789-799.

Franco A, Ferranti A, Davidsen C, Trapp S. 2010. An unexpected challenge: ionizable compounds in the REACH chemical space. Int J Life Cycle Assess 15:321-325.

Franco A, Hauschild M, Jolliet O, Trapp S. 2011. Atmospheric fate of non-volatile and ionizable compounds. Chemosphere 85:1353-1359.

Franco A, Struijs J, Gouin T, Price OR. 2013. Evolution of the sewage treatment plant model SimpleTreat: Applicability domain and data requirements. Integr Environ Assess Manag 4:560-568.

Gao J, Ellis L, Wackett L. 2010. The University of Minnesota Biocatalysis/Biodegradation Database: improving public access. Nucleic Acids Research 38:D488-D491.

Giles CH, MacEwan TH, Nakhwa SN, Smith D. 1960. Studies in adsorption. Part XI. A system of classification of solution adsorption isotherms, and its use in diagnosis of adsorption mechanisms and measurement of specific surface area of solids. J. Chem Soc 3973-3992.

Green RE. 1974. Pesticide-clay-water-interactions. Soil Sci Am 3-37. Journal Series No. 1704 of the Hawaii Agricultural Experiment Station.

Hamaker JW, Thompson JM. 1972. Diffusion and volatilization. In Goring CAI, Hamaker JW, eds, Organic chemicals in the soil environment, Vol I. Marcel Dekker, New York, NY, USA, pp 49–143.

Hammett L. 1940. Physical organic chemistry. McGraw-Hill Company, New York.

Hansch D, Leo A. 1979. Substituent constants for correlation analysis in chemistry and biology. Wiley-Interscience, New York, NY, USA.

Harries JE, Sheahan DA, Jobling S, Matthiessen P, Neall M, Sumpter JP, Taylor T, Zaman, N. 1997. Estrogenic activity in five United Kingdom rivers detected by measurement of vitellogenesis in caged male trout. Environ Toxicol Chem 16:534-542.

Harries JE, Sheahan DA, Jobling S, Matthiessen P, Neall P, Routledge EJ, Rycroft R, Sumpter JP, Tylor T. 1996. A survey of estrogenic activity in United Kingdom inland waters. Environ Toxicol Chem 15:1993-2002.

Harris JC, Hayes MJ. 1990. Acid dissociatino constant. In Lyman WJ, Reehl WF, Rosenblatt DH, eds, Handbook of chemical property estimation methods, American Chemical Society, Washington, DC, USA.

Hermosin MC, Cornejo J. 1993. Binding mechanism of 2, 4-dichlorophenoxyacetic acid by organo-clays. J Environ Qual 22:325-331.

Hilal S, Carreira LA, Baughman GL. Karickhoff SW, Melton CM. 1994. Estimation of Ionization-Constants of Azo Dyes and Related Aromatic-Amines. Environ Implication Journal of Physical Organic Chemistry 7:122-141.

Hilal SH, El-Shabrawy Y, Carreira LA, Karickhoff SW, Toubar SS., Rizk M. 1996. Estimation of the ionization pK(a) of pharmaceutical substances using the computer program SPARC. Talanta 43:607-619.

Hilal SH, Karickhoff SW, Carreira LA. 1995. A rigorous test for SPARC's chemical reactivity models: Estimation of more than 4300 ionization pK(a)s. Quantitative Structure-Activity Relationships 14:348-355.

Hilal SH, Karickhoff SW, Carreira LA. 2004. Prediction of the solubility, activity coefficient and liquid/liquid partition coefficient of organic compounds. Qsar & Combinatorial Science 23:709-720.

Hörsing M, Ledin A, Grabic R, Fick J, Tysklind M, la Cour Jansen J, Andersen HR. 2011. Determination of sorption of seventyfive pharmaceuticals in sewage sludge. Water Res 10.1016.

Hyun S, Lee LS. 2004. Factors controlling sorption of prosulfuron by variable-charge soils and model sorbents. J Environ Qual 33:1354-1361.

Ismail ZZ, Tezel U, Pavlostathis SG. 2010. Sorption of quaternary ammonium compounds to municipal sludge. Water Res 44:2303-2313.

ISO. Soil quality: Measurement of pH. ISO 10390-1. 1995. International Organisation for Standardisation, Geneva, Switzerland.

Kah M, Brown CD. 2008. LogD: Lipophilicity for ionisable compounds. Chemosphere 72:1401-1408.

Kahle M, Stamm C. 2007. Time and pH-dependent sorption of the veterinary antimicrobial sulfathiazole to clay minerals and ferrihydrite. Chemosphere 68:1224-1231.

Keiluweit M, Kleber M. 2009. Molecular-level interactions in soils and sediments: The role of aromatic π-systems. Eviron Sci Technol 43:3421-3429.

Keller V. 2006. Risk assessment of "down-the-drain" chemicals: Search for a suitable model. Sci Total Environ 360:305-318.

Kipka U, Di Toro DM. 2011b. A linear solvation energy relationship model of organic chemical partitioning to dissolved organic carbon. Environ Toxicol Chem 30:2023-2029.

Kipka U, Di Toro DM. 2011a. A linear solvation energy relationship model of organic chemical partitioning to particulate organic carbon in soils and sediments. Environ Toxicol Chem 30:2013-2022.

Kolpin DW, Furlong ET, Meyer MT, Thurman EM, Zaugg SD, Barber LB, Buxton HT. 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in US streams, 1999-2000: A national reconnaissance. Environ Sci Technol 36:1202-1211.

Kortüm G, Vogel W, Andrussow K. 1960. Dissociation constants of organic acids in aqueous solution. Pure Appl. Chem 1:187-536.

Lee AC, Crippen GM. 2009. Predicting pK(a). J Chem Inf Model 49:2013-2033.

Leo A, Hansch C, Elkins D. 1971. Partition coefficients and their uses. Chem Rev 71:525-616.

Leone P, Negre M, Gennari M, Boero V, Celis R and Cornejo J. 2002. Adsorption of imidazolinone herbicides on smectite-humic acid and smectite-ferrihydrite Associations. J Agric Food Chem 50:291-298.

Li H, Teppen BJ, Laird DA, Johnston CT, Boyd SA. 2004. Geochemical modulation of pesticide sorption on smectite clay. Environ Sci Technol 38:5393-5399.

Liao C, Nicklaus MC. 2009. Comparison of nine programs predicting pK_a values of pharmaceutical substances. J Chem Inf Model 49:2801-2812.

Lide D. 1995. CRC Handbook of Chemistry and Physics, 76th ed. CRC Press, Boca Raton, FL, USA.

Livingstone DJ. 2003. Theoretical property predictions. Current Topics in Med Chem 3:1171-1192.

Manallack DT. 2009. The acid-base profile of a contemporary set of drugs: implications for drug discovery. SAR QSAR Environ Res 20:611-655.

Manchester J, Walkup G, Rivin O, You ZP. 2010. Evaluation of pK(a) Estimation Methods on 211 Drug like Compounds. J Chem Inf Model 50:565-571.

Mannhold R, Poda GI, Ostermann C, Tetko IV. 2009. Calculation of Molecular Lipophilicity: State-of-the-Art and Comparison of log P Methods on More Than 96,000 Compounds. J Pharm Sci 98:861-893.

Meloun M, Bordovska S. 2007. Benchmarking and validating algorithms that estimate pK(a) values of drugs based on their molecular structures. Anal Bioanal Chem 389:1267-1281.

Meylan WM, Howard PH. 1995. Atom Fragment Contribution Method for Estimating Octanol-Water Partition-Coefficients. J Pharm Sc 84:83-92.

Meylan WM, Howard PH. 2000. Estimating log P with atom/fragments and water solubility with log P. Perspect Drug Discov Des 19:67-84.

Meylan WM, Howard PH, Boethling RS. 1996. Improved method for estimating water solubility from octanol water partition coefficient. Environ Toxicol Chem 15:100-106.

Nguyen TH, Goss KU, Ball WP. 2005. Polyparameter linear free energy relationships for estimating the equilibrium partition of organic compounds between water and the natural organic matter in soils and sediments. Environ Sci Technol 39:913-924.

Nicholls PH, Evans AA. 1991. Sorption of ionisable organic compounds by field soils. Part 1: Acids. Pestic Sci 33:319-330.

Nilsson SI, Johnsson L, Jennische P. 2005. A horizontal standard for pH measurements - The influence on pH measurements of sample pretreatment, ionic composition / ionic strength of the extractant and centrifugation / filtration. Horizontal 15-1 pH. Swedish University of Agricultural Sciences, Uppsala, Sweden.

OECD. 1981a. Dissociation constants in water (titration method - spectrophotometric method - conductometric method). OECD Guideline for the testing of chemicals 112. Organisation for Economic Cooperation and Development, Paris, France.

OECD. 1981b. Inherent biodegradability: Modified SCAS test. OECD Guideline for the testing of chemicals 302A. Organisation for Economic Cooperation and Development, Paris, France.

OECD. 1981c. Inherent biodegradability: Modified MITI Test (II). OECD Guideline for the testing of chemicals 302C. Organisation for Economic Cooperation and Development, Paris, France.

OECD. 1992a. Zahn-Wellens/EMPA test. OECD Guideline for the testing of chemicals 302B.. Organisation for Economic Cooperation and Development, Paris, France.

OECD. 1992b. Ready biodegradability. OECD Guidline for the testing of chemicals 301 A-F. Organisation for Economic Cooperation and Development, Paris, France.

OECD. 1995a. Partition coefficient (n-octanol/water): Shake flask method. OECD Guideline for the testing of chemicals 107. Organisation for Economic Cooperation and Development, Paris, France.

OECD. 2000a. log K_{OW} pH-metric method for ionisable substances. OECD Guideline for the testing of chemicals, proposal for a new test guideline 122 (draft). Organisation for Economic Cooperation and Development, Paris, France.

OECD. 2000b. Adsorption - desorption using a batch equilibrium method. OECD Guideline for the testing of chemicals 106. Organisation for Economic Cooperation and Development, Paris, France.

OECD. 2001. Estimation of the adsorption coefficient (K_{OC}) on soil and on sewage sludge using high performance liquid chromatography (HPLC). OECD Guideline for the testing of chemicals, Section 1: Physical-chemical properties, test no. 121. Organisation for Economic Cooperation and Development, Paris, France.

OECD. 2001. Simulation test - Aerobic sewage treatment: 303A: Activated sludge unites - 303B: Biofilms. OECD Guideline for the testing of chemicals 303. Organisation for Economic Cooperation and Development, Paris, France.

OECD. 2002. Aerobic and anaerobic transformation in aquatic sediment systems. OECD Guideline for the testing of chemicals 308. Organisation for Economic Cooperation and Development, Paris, France.

OECD. 2004. Partition coefficient (n-octanol/water), high performance liquid chromatography (HPLC) method. OECD Guideline for the testing of chemicals 117. Organisation for Economic Cooperation and Development, Paris, France.

OECD. 2004a. Aerobic mineralisation in surface waters - Simulation biodegradation test. OECD Guideline for the testing of chemicals 309. Organisation for Economic Cooperation and Development, Paris, France.

OECD. 2004b. Hydrolysis as a function of pH. OECD Guidelines for the testing of chemicals 111. Organisation for Economic Cooperation and Development.

OECD. 2006. Partition coefficient (n-octanol/water): Slow stirring method. OECD Guideline for the testing of chemicals 123. Organisation for Economic Cooperation and Development, Paris, France.

OECD. 2008. Simulation tests to assess the biodegradability of chemicals discharged in wastewater. OECD Guideline for the testing of chemicals 314 A-E. Organisation for Economic Cooperation and Development, Paris, France.

Onesios KM, Yu JT, Bouwer EJ. 2009. Biodegradation and removal of pharmaceuticals and personal care products in treatment systems: a review. Biodegradation 20:441-466.

Oulton RL, Kohn T, Cwiertny DM. 2010. Pharmaceuticals and personal care products in effluent matrices: A survey of transformation and removal during wastewater treatment and implications for wastewater management. J Environ Monit 12:1956-1978.

Pavan M, Worth AP. 2008. Review of estimation models for biodegradation. Qsar Comb Sci 27:32-40.

Perrin DD. 1965. Dissociation constants of organic bases in aqueous solution. Butterworths, London, UK.

Petrauskas AA, Kolovanov EA. 2000. ACD/log P method description. Perspectives in Drug Discovery and Design 19:99-116.

Pignatello JJ, Xing B. 1995. Mechanisms of slow sorption of organic chemicals to natural particles. Environ Sci Technol 30:1-11.

Pusino A, Petretto S, Gessa C. 2004. Sorption of primisulfuron on soil and inorganic and organic colloids. Euro J Soil Sci 55:175-182.

Rayne S, Forest K. 2010. D_{ow} and K_{aw}, eff vs. K_{OW} and K_{aw} degrees: acid/base ionization effects on partitioning properties and screening commercial chemicals for long-range transport and bioaccumulation potential. J Environ Sci Health A Tox Hazard Subst Environ Eng 45:1550-1594.

Renner R. 2002. The K_{OW} controversy. Environ Sci Technol 36:410A-413A.

Richardson ML, Bowron JM. 1985. The fate of pharmaceutical chemicals in the aquatic Environment. J Pharm Pharmacol 37:1-12.

Richardson SD, Ternes TA. 2011. Water Analysis: Emerging Contaminants and Current Issues. Anal Chem 83:4614-4648.

Sabljic A. 1987. On the Prediction of Soil Sorption Coefficients of Organic Pollutants from Molecular-Structure - Application of Molecular Topology Model. Environ Sci Technol 21:358-366.

Schmitt H, Boucard T, Garric J, Jensen J, Parrott J, Péry A, Römbke J, Straub JO, Hutchinson TH, Sánchez-Argüello P, Wennmalm A, Duis K. 2010. Recommendations on the environmental risk assessment of pharmaceuticals: Effect characterization. Integr Environ Assess Manag 6:588-602.

Schuurmann G, Ebert RU, Kuhne R. 2006. Prediction of the sorption of organic compounds into soil organic matter from molecular structure. Environ Sci Technol 40:7005-7011.

Serjeant E, Dempsey B. 1979. Ionisation constants of organic acids in aqueous solution. Pergamon Press, Oxford, UK.

Sheng G, Johnston CT, Teppen BJ, Boyd SA. 2001. Potential contributions of smectite clays and organic matter to pesticide retention in soils. J Agric Food Chem 49:2899-2907.

Slater B, Mccormack A, Avdeef A, Comer JEA. 1994. pH-metric log-P. 4. Comparison of partition-coefficients determined by hplc and potentiometric methods to literature values. J Pharm Sci 83:1280-1283.

Sposito G. 1984. The surface chemistry of soils. Oxford Univ Press. New York, USA.

Stevens-Garmon J, Drewes JE, Khan SJ, McDonald JA, Dickenson ER. 2011. Sorption of emerging trace organic compounds onto wastewater sludge solids. Water Res 45:3417-3426.

Takács-Novák K, Avdeef A. 1996. Interlaboratory study of log P determination by shake-flask and potentiometric methods. J Pharm Biomed Anals 14:1405-1413.

Takács-Novák K, Box KJ, Avdeef A. 1997. Potentiometric pK(a) determination of water-insoluble compounds: Validation study in methanol/water mixtures. Int J Pharm 151:235-248.

Tarazona JV, Escher BI, Giltrow E, Sumpter J, Knacker T. 2009. Targeting the environmental risk assessment of pharmaceuticals: Facts and fantasies. Integr Environ Assess Manag 6S1:603-613.

ter Laak T, Gebbink WA, Tolls J. 2006. Estimation of soil sorption coefficients of veterinary pharmaceuticals from soil properties. Environ Toxicol Chem 25:933-941.

Tetko IV. 2002. Neural network studies. 4. Introduction to associative neural networks. J Chem Inf Comput Sci 42:717-728.

Tetko IV, Tanchuk VY. 2002. Application of associative neural networks for prediction of lipophilicity in ALOGPS 2.1 program. J Chem Inf Comput Sci 42:1136-1145.

Tolls J. 2001. Sorption of veterinary pharmaceuticals in soils: A review. Environ Sci Technol 35:3397-3406.

Trapp S, Franco A, Mackay D. 2010. Activity-Based Concept for Transport and Partitioning of Ionizing Organics. Environ Sci Technol 44:6123-6129.

Tomlin CDS, ed. 2000. The pesticide manual, a world compendium, 12th ed. British Crop Protection Council, Farnham, Surrey, UK.

Ukrainczyk l, Rashid N. 1995. Irreversible sorption of nicosulfuron on clay minerals. J Agric Food Chem, Short Communications 43:855-857.

US EPA. 2008. Hydrolysis. Fate, transport, and transformation test guidelines, OPPTS 835.2120. United States Environmental Protection Agency, Washington DC, USA.

US EPA. 1998. Activated sludge sorption isotherm. Fate, transport, and transformation test guidelines, OPPTS 835.1110. United States Environmental Protection Agency, Washington DC, USA.

US EPA. 1998. Hydrolysis as a function of pH and temperature. Fate, transport, and transformation test guidelines, OPPTS 835.2130. United States Environmental Protection Agency, Washington DC, USA.

US EPA. 1996. Dissociation constants in water. Product properties test guidelines, OPPTS 830.7370. United States Environmental Protection Agency, Washington DC, USA.

van Leeuwen CJ, Hermens JLM. 1995. Risk assessment of chemicals: An introduction. Kluwer Academic, Dordrecht, Netherlands.

van Leeuwen CJ, Vermeire T. 2007. Risk assessment of chemicals: An introduction, 2nd edn. Springer, Dordrecht, Netherlands.

Wauchope RD, Yeh S, Linders JB, Kloskowski R, Tanaka K, Rubin B, Katayama A, Kördel W, Gerstl Z, Lane M, Unsworth JB. 2002. Pesticide soil sorption parameters: theory, measurement, uses, limitations and reliability. Pest Manag Sci 58:419-445.

Weber JB and Weed SN. 1968. Adsorption and desorption of diquat, paraquat, and prometone by montmorillonitic and kaolinitic clay minerals. Soil Sci Soc Am Proc 32: 485–487.

Webster EM, Ellis DA. 2011. Equilibrium Modeling: A pathway to understanding observed perfluorocarboxylic and perfluorosulfonic acid behavior. Environ Toxicol Chem 30:2229-2236.

Wells MJ. 2006. log D_{OW}: Key to understanding and regulating wastewater-derived contaminants. Environ Chem 3:439-449.

Wen Y, Su LM, Qin WC, Fu L, He J, Zhao YH. 2012. Linear and non-linear relationships between soil sorption and hydrophobicity: Model, validation and influencing factors. Chemosphere 86:634-640.

Wick A, Marincas O, Moldovan Z, Ternes TA. 2011. Sorption of biocides, triazine and phenylurea herbicides, and UV-filters onto secondary sludge. Water Res 45:3638-3652.

Yu H, Kühne R, Ebert RU., Schüürmann G. 2011. Prediction of the Dissociation Constant pK_a of Organic Acids from Local Molecular Parameters of Their Electronic Ground State. J Chem Inf Model 51:2336-2344.

Zhao H, Jaynes WF, Vance GF. 1996. Sorption of the ionizable organic compound, dicamba (3,6-dichloro-2-methoxy benzoic acid), by organo-clays. Chemosphere 33:2089-2100.

References not quoted

The following references were consulted by the Task Force, but are not quoted for various reasons such as secondary review, abstract only or covered by another reference.

*Al-Odaini NA, Zakaria MP, Yaziz MI, Surif S. 2010. Multi-residue analytical method for human pharmaceuticals and synthetic hormones in river water and sewage effluents by solid-phase extraction and liquid chromatography-tandem mass spectrometry. J Chromatogr A 1217:6791-6806.

*Armitage JM, Arnot JA, Wania F, Mackay D. 2011. The development and evaluation of a mass balance bioaccumulation model for ionogenic chemicals in fish. Poster at SETAC Milano, Italy. University of Toronto, Scarborough, Ontario, Canada.

*Barron L, Havel J, Purcell M, Szpak M, Kelleher B, Paull B. 2009. Predicting sorption of pharmaceuticals and personal care products onto soil and digested sludge using artificial neural networks. Analyst 134:663-670. DOI: 10.1039/b817822d.

*Batt AL, Kim S, Aga DS. 2007. Comparison of the occurrence of antibiotics in four full-scale wastewater treatment plants with varying designs and operations. Chemosphere 68:428-435.

*Bendz D, Paxéus NA, Ginn TR, Loge FJ. 2005. Occurrence and fate of pharmaceutically active compounds in the environment, a case study: Höje River in Sweden. J Hazard Mater 122:195-204.

*Boethling, B, Lynch DG, Jaworska JS, Tunkel JL, Thom GC, Webb S. 2004. Using BIOWIN, Bayes and batteries to predict ready biodegradability. Environ Sci Technol 23:911-920.

*Box KJ, Comer JEA. 2008. Using measured pK_a, logP and solubility to investigate supersaturation and predict BCS class. Curr Drug Metab 9:869-878.

*Brooks BW, Valenti TW, Cook-Lindsay BA, Forbes MG, Doyle RD, Scott JT, Stanley JK. 2011. Influence of climate change on reservoir water quality assessment and management. In Linkov I, Bridges TS (eds). Climate: Global change and local adaptation. Springer, Netherlands, pp 495-528.

*Brown JN, Paxéus N, Förlin L, Larsson DGJ. 2007. Variations in bioconcentration of human pharmaceuticals from sewage effluents into fish blood plasma. Environ Toxicol Pharmacol 24:267-274.

*Calisto V, Esteves VI. 2009. Psychiatric pharmaceuticals in the environment. Chemosphere 77:1257-1274.

*Carballa M, Fink G, Omil F, Lema JM, Ternes T. 2008. Determination of the solid-water distribution coefficient (K_d) for pharmaceuticals, estrogens and musk fragrances in digested sludge. Water Res 42:287-295.

*Casey F, Larsen GL, Hakk H, Simunek J. 2003. Fate and transport of 17β-estradiol in soil-water systems. Environ Sci Technol 37:2400-2409.

*Choi K, Kim Y, Park J, Park CK, Kim M, Kim HS, Kim P. 2008. Seasonal variations of several pharmaceutical residues in surface water and sewage treatment plants of Han River, Korea. Sci Total Environ 405:120-128.

*Cowan-Ellsberry CE, Dyer SD, Erhardt S, Bernhard MJ, Roe AL, Dowty ME, Weisbrod AV. 2008. Approach for extrapolating in vitro metabolism data to refine bioconcentration factors estimates. Chemosphere 70:1804-1817.

*Dimitrov S, Dimitrova N, Georgieva D, Vasilev K, Hatfield T, Straka J, Mekenyan O. 2011. Simulation of chemical metabolism for fate and hazard assessment III. New developments of the bioconcentration factor base-line model. SAR QSAR Environ Res 23:17-36.

*Dimitrov S, Pavlov T, Dimitrova N, Georgieva D, Nedelcheva D, Kesova A, Vasilev R, Mekenyan O. 2011. Simulation of chemical metabolism for fate and hazard assessment II. CATALOGIC simulation of abiotic and microbial degradation. SAR QSAR Environ Res 22:719-755.

*Dimitrov S, Pavlov T, Veith G, Mekenyan O. 2011. Simulation of chemical metabolism for fate and hazard assessment I. Approach for simulating metabolism. SAR QSAR Environ Res 22:699-718.

*Droge S, Goss KU. 2011a. How to model the sorption affinity of cationic organic compounds to natural organic matter? Presented at SETAC Milano, Italy. Helmholtz Centre for Environ Res – UFZ, Leipzig, Germany.

*Droge S, Goss KU. 2011b. Sorption of cationic organic compounds in soil: do clay minerals matter compared to organic matter? Poster at SETAC Milano, Italy. Helmholtz Centre for Environ Res – UFZ, Leipzig, Germany.

*ECETOC. 2003. Environmental risk assessment of Difficult Substances. Technical Report 88. ECETOC, Brussels.

*Erickson RJ, Mckim JM, Lien GJ, Hoffman AD, Batterman SL. 2006a. Uptake and elimination of ionizable organic chemicals at fish gills: I. Model formulation, parameterization, and behavior. Environ Toxicol Chem 25:1512-1521.

*Erickson RJ, Mckim JM, Lien GJ, Hoffman AD, Batterman SL. 2006b. Uptake and elimination of ionizable organic chemicals at fish gills: II. Observed and predicted effects of pH, alkalinity, and chemical properties. Environ Toxicol Chem 25:1522-1532.

*Ericson JF, Huggett DB, Constantine LA. 2005. Environmental fate testing for new human pharmaceutical candidates. Pfizer Global Research and Development, Groton, Connecticut, USA. Presented at SETAC.

*EU. 2003. Directive 2001/83/EC of the European parliament and of the council of 6 November 2001 on the community code relating to medicinal products for human use.

*FDA. 2001. Guidance for Industry: Environmental impact assessments (EIA's) for veterinary medicinal products (VMP's) - Phase I VICH GL6 final guidance. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Veterinary Medicine, Rockville, MD, USA.

*FDA. 2006. Environmental impact assessments (EIA's) for veterinary medicinal products (VMP's) - Phase II VICH GL38 final guidance. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Veterinary Medicine, Rockville, MD, USA.

*Fent K, Weston AA, Caminada D. 2006. Ecotoxicology of human pharmaceuticals. Aquat Toxicol 76:122-159.

*Franco A, Fu W, Trapp S. 2009. Influence of soil pH on the sorption of ionizable chemicals: modeling advances. Environ Toxicol Chem 28:458-464.

*Franco A, Legind C, Trapp S. 2010. ERA of ionizable compounds: Physicochemical properties and environmental partitioning. Department of environmental engineering, Technical University of Denmark. http://homepage.env.dtu.dk/stt/Homepage%20anf/Website.htm.

*Fu WJ, Franco A, Trapp S. 2009. Methods for estimating the bioconcentration factor of ionizable organic chemicals. Environ Toxicol Chem 28:1372-1379.

*Gawlik BM, Feicht EA, Karcher W, Kettrup A, Muntau H. 1998. On the presence of PCDD/Fs and other chlorinated hydrocarbons in the second generation of the European Reference Soil Set – the EUROSOILS. Fresen J Anal Chem 368:407-411.

*Gawlik BM, Kettrup A, Muntau H. 2000. Estimation of soil adsorption coefficients of organic compounds by HPLC screening using the second generation of the European reference soil set. Chemosphere 41:1337-1347.

*Ghasemi J, Saaidpour S. 2007. Quantitative structure-property relationship study of n-octanol-water partition coefficients of some of diverse drugs using multiple linear regression. Anal Chim Acta 604:99-106.

*Golmohammadi H. 2009. Prediction of octanol-water partition coefficients of organic compounds by multiple linear regression, partial least squares, and artificial neural network. J Compt Chem 30:2455-2465.

*Gros M, Pizzolato TM, Petrović M. 2008. Trace level determination of β-blockers in waste waters by highly selective molecularly imprinted polymers extraction followed by liquid chromatography-quadrupole-linear ion trap mass spectrometry. J Chromatogr A 1189:374-384.

*Gruber V, Halley B, Hwang SC, Ku CC. 1990. Mobility of avermectin B1a in soil. J Agric Food Chem 38:886-890.

*Guideline on the environmental risk assessment of medicinal products for human use. EMEA.

*Gurr CJ, Reinhard M. 2006. Harnessing natural attenuation of pharmaceuticals and hormones in rivers. Environ Sci Technol 40:2872-2876.

*Heberer T. 2002. Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: A review of recent research data. Toxicol Lett 131:5-17.

*Hilal SH, Carreira LA, Karickhoff SW. 1994. Estimation of chemical reactivity parameters and physical properties of organic molecules using SPARC. In Politzer P, Murray JS, eds. Theoretical and computational chemistry, quantitative treatment of solute/solvent interactions. Elsevier, Amsterdam, Netherlands.

*Hoerger CC, Dörr B, Schlienger C, Straub JO. 2009. Environmental risk assessment for the galenical formulation of solid medicinal products at Roche Basle, Switzerland. Integr Environ Assess Manag 5:331-337.

*Howard PH, Muir DCG. 2011. Identifying new persistent and bioaccumulative organic compounds among chemicals in commerce II: Pharmaceuticals. Environ Sci Technol 45:6938-6946.

*Huerta-Fontela M, Galceran MT, Ventura F. 2010. Fast liquid chromatography-quadrupole-linear ion trap mass spectrometry for the analysis of pharmaceuticals and hormones in water resources. J Chromatogr A 1217:4212-4222.

*Jelić A, Gros M, Ginebreda A, Cespedes-Sánchez R, Ventura F, Petrovic M, Barcelo D. 2011. Occurrence, partition and removal of pharmaceuticals in sewage water and sludge during wastewater treatment. Water Res 45:1165-1176.

*Jelić A, Petrović M, Barcelo D. 2009. Multi-residue method for trace level determination of pharmaceuticals in solid samples using pressurized liquid extraction followed by liquid chromatography/quadrupole-linear ion trap mass spectrometry. Talanta 80:363-371.

*Jones OAH, Voulvoulis N, Lester JN. 2002. Aquatic environmental assessment of the top 25 English prescription pharmaceuticals. Water Res 36:5013-5022.

*Jones OAH, Voulvoulis N, Lester JN. 2006. Partitioning behavior of five pharmaceutical compounds to activated sludge and river sediment. Arch Environ Contam Toxicol 50:297-305.

*Kah M, Brown CD. 2007. Prediction of the adsorption of ionisable pesticides in soils. J Agric Food Chem 55:2312-2322.

*Kay P, Blackwell PA, Boxall ABA. 2004. Fate of veterinary antibiotics in a macroporous tile drained clay soil. Environ Toxicol Chem 23:1136-1463.

*Khan B, Xianliang Qiao, Lee SE. 2009. Stereoselective sorption by agricultural soils and liquid-liquid partition of trenbolone (17α and 17β) and trendione. Environ Sci Technol 43:8827-8833.

*Knacker T, Metcalfe C. 2010. Special issue: Environmental risk assessment of pharmaceuticals (ERAPharm). Integr Environ Assess Manag 6S1:511-613. www.setacjournals.org/view/0/ieamspecialerapharm.html.

*Kondo T, Yamamoto H, Tatarazako N, Kawabe K, Koshio M, Hirai N, Morita M. 2005. Bioconcentration factor of relatively low concentrations of chlorophenols in Japanese medaka. Chemosphere 61:1299-1304.

*Kreuzig R, Blümlein K, Höltge S. 2007. Fate of the benzimidazole antiparasitic flubendazole and fenbendazole in manure and manured soils. Clean 35:488-494.

*Kuhnt G, Muntau H, eds. 1994. EURO-soils: Identification, collection, treatment, characterization. Geographisches Institut, Kiel, JRC Ispra, European Commission. Special Publication No. I.94.60. EC Environment Institute, Ispra, Italy.

http://eusoils.jrc.ec.europa.eu/esdb_archive/eusoils_docs/Various/EURO_SOILS.pdf

*Läkemedelsfakta, miljöinformation. Läkemedelsindustriföreningens Service, Höganäs, Sweden. www.fass.se/LIF/home/index.jsp

*Lee L, Strock TJ, Sarmah AK, Rao PSC. 2003. Sorption and dissipation of testosterone, estrogens and their primary transformation products in soils and sediment. Environ Sci Technol 37:4098-4105.

*Legind CN, Franco A, Trapp S. 2010. Bioaccumulation of ionisable compounds. DTU Environment, Technical University of Denmark. Presented at TF meeting, 8-9 September 2010, Brussels. http://homepage.env.dtu.dk/stt/Homepage%20anf/Website.htm <pptx>

*Le-Minh N, Khan SJ, Drewes JE, Stuetz RM. 2010. Fate of antibiotics during municipal water recycling treatment processes. Water Res 44:4295-4323.

*Letinski D, Lampi M, Febbo E, Manning R, Knarr T, Butler J, Connelly M, Paumen ML, Parkerton T. 2010. Use of a passive dosing system to determine bioconcentration factors of multiple, sparingly soluble hydrocarbons in fish. Poster presented at SETAC Seville, Spain.

*Loganathan B, Phillips M, Mowery H, Jones-Lepp TL. 2007. Contamination profiles and mass loadings of macrolide antibiotics and illicit drugs from a small urban wastewater treatment plant. Chemosphere 75:70-77.

*Lombardo F, Shalaeva MY, Tupper KA, Gao F. 2001. ElogDoct: A tool for lipophilicity determination in drug discovery. 2. Basic and neutral compounds. J Med Chem 44:2490-2497.

*Mackay D, Shiu WY, Ma KC, Lee SC. 2006. Handbook of physical-chemical properties and environmental fate for organic chemicals second edition. Volume 1: Introduction and hydrocarbons, 2: Halogenated hydrocarbons, 3: Oxygen containing compounds, 4: Nitrogen and sulfur containing compounds and pesticides. CRC Press, Taylor & Francis Group, Boca Raton, Florida, USA.

*MacLeod SL, Sudhir P, Wong CS. 2007. Stereoisomer analysis of wastewater-derived β-blockers, selective serotonin re-uptake inhibitors, and salbutamol by high-performance liquid chromatography-tandem mass spectrometry. J Chromatogr A 1170:23-33.

*Metcalfe CD, Chu SG, Judt C, Li HX, Oakes KD, Servos MR, Andrews DM. 2010. Antidepressants and their metabolites in municipal wastewater, and downstream exposure in an urban watershed. Environ Toxicol Chem:29:79-89.

*Monteiro S, Qin K, Boxall A, Topp E, Metcalfe C. 2008. Fate of human pharmaceuticals in the soil environment. Central Science Laboratory, York, UK; University of York, UK; ERA Pharm. Presented at SETAC Europe Annual Meeting 2008, Warsaw, Poland.

*Monteiro SC, Boxall ABA. 2010. Occurrence and fate of human pharmaceuticals in the environment. Rev Environ Contam Toxicol 202:53-154.

*Mowery HR, Loganathan BG. 2007. Persistent organic compounds in wastewater: Azithromycin and Urobilin concentrations in wastewater treatment plant samples from Murray, Kentucky, USA. Organohalogen Compounds 69:2961-2964.

*Nakamura Y, Yamamoto H, Sekizawa J, Kondo T, Hirai N, Tatarazako N. 2008. The effects of pH on fluoxetine in Japanese medaka (*Oryzias latipes*): Acute toxicity in fish larvae and bioaccumulation in juvenile fish. Chemosphere 70:865-873.

*Netherton M, Boxall A. Raffaelli D. 2007. Uptake of human pharmaceuticals in Gammarus pulex. Poster presented at ERAPharm2007 Conference. Central Science Laboratory, York, UK; University of York, UK. <ppt>

*Nicholls PH, Evans AA. 1991. Sorption of ionisable organic compounds by field soils. Part 2: Cations, bases and zwitterions. Pestic Sci 33:339-345.

*Nichols J, Erhardt S, Dyer S, James M, Moore M, Plotzke K, Segner H, Schultz I, Thomas K, Vasiluk L, Weisbrod A. 2007. Use of in vitro absorption, distribution, metabolism, and excretion (ADME) data in bioaccumulation assessment for fish. Hum Ecol Risk Assess 13:1164-1191.

*Nowara A, Burhenne J, Spiteller M. 1997. Binding of fluoroquinolonecarboxylic acid derivatives to clay minerals. J Agric Food Chem 45:1459-1463.

*Öllers S, Singer HP, Fässler P, Müller SR. 2001. Simultaneous quantification of neutral and acidic pharmaceuticals and pesticides at the low-ng/ l level in surface and waste water. J Chromatogr A 911:225-234.

*Pan B, Ning P, Xing B. 2009. Humic substances review series part V – Sorption of pharmaceuticals and personal care products. Environ Sci Pollut Res 16:106-116.

*Paterson G, Metcalfe CD. 2008. Uptake and depuration of the anti-depressant fluoxetine by the Japanese medaka (Oryzias latipes). Chemosphere 74:125-130.

*Pavan M, Worth AP, Netzeva TI. 2006. Review of QSAR models for bioconcentration. Report EUR 22327 EN. European Commission Directorate General Joint Research Centre, Institute for Health and Consumer Protection, Toxicology and Chemical Substances Unit, European Chemicals Bureau, Ispra, Italy.

*Rabølle M, Spliid NH. 2000. Sorption and mobility of metronidazole, aloquindox, oxyteteracycline and tylosin in soil. Chemosphere 40:715-722.

*Ramirez AJ, Brain RA, Usenko S, Mottaleb MA, O'Donnell JG, Stahl LL, Wathen JB, Snyder BD, Pitt JL, Perez-Hurtado P, Dobbins LL, Brooks BW, Chambliss CK. 2009. Occurrence of pharmaceuticals and personal care products in fish: Results of a national pilot study in the United States. Environ Toxicol Chem 28:2587-2597.

*Rayne S, Forest K. 2010. D_{OW} and K_{aw},eff vs. K_{OW} and Koaw: Acid/base ionization effects on partitioning properties and screening commercial chemicals for long-range transport and bioaccumulation potential. J Environ Sci Health A45:1550-1594.

*Richter O, Kullmer C, Kreuzig R. 2007. Metabolic fate modeling of selected human pharmaceuticals in soils. Clean 35:495-503.

*Roberts G, Boethling B, Ericson J, Lewis F, Marshall S, Holt H, Galay Burgos M. 2010. Environmental risk assessment of bound residues. Poster SETAC Seville, May.

*Rosal R, Rodrıguez A, Perdigon-Melon JA, Petre Eloy Garcıa-Calvoa A, José Gomez M, Agüera A, Fernandez-Alba AR. 2010. Occurrence of emerging pollutants in urban wastewater and their removal through biological treatment followed by ozonation. Water Res 44:578-588.

*Sassman SA, Lee LS. 2007. Sorption and degradation in soils of veterinary ionophore antibiotics: monensin and lasalocid. Environ Toxicol Chem 26:1614-1621.

*Scheytt T, Mersmann P, Lindstädt R, Heberer T. 2005. 1-Octanol/water partition coefficients of 5 pharmaceuticals from human medical care: Carbamazepine, Clofibric acid, Diclofenac, Ibuprofen, and Propyphenazone. Water Air Soil Pollut 165:3-11.

*Stackelberg P, Gibs J, Furlong ET, Meyer MT, Zaugg SD, Lippincott RL. 2007. Efficiency of conventional drinking-water-treatment processes in removal of pharmaceuticals and other organic compounds. Sci Total Environ 377:255-272.

*Straub JO, Stewart JM. 2007. Deterministic and probabilistic acute-based environmental risk assessment for Naproxen for western europe. Environ Toxicol Chem 26:795–806.

*Straub JO. 2010. Combined environmental risk assessment for 5-Fluorouracil and Capecitabine in Europe. Integr Environ Assess Manag 6S1:540-566.

*Teijon G, Candela L, Tamoh K, Molina-Díaz A, Fernández-Alba AR. 2010. Occurrence of emerging contaminants, priority substances (2008/105/CE) and heavy metals in treated wastewater and groundwater at Depurbaix facility (Barcelona, Spain). Sci Total Environ 408:3584-3595.

*Tetko I, Poda GI. 2004. Application of ALOGPS 2.1 to predict log D distribution coefficient for Pfizer Proprietary compounds. J Med Chem 47:5601-5604.

*Tolls J. 2001. Sorption of veterinary pharmaceuticals in soils: A review. Environ Sci Technol 35:3397-3406.

*Trapp S. 2010. Cytoplasm lysosome mitochondria nucleus & lipids. DTU Environment, Technical University of Denmark. Presented at TF meeting, 8-9 September 2010, Brussels.

*Tülp H, Fenner K, Schwarzenbach RP, Goss KU. 2009. pH-dependent sorption of acidic organic chemicals to soil organic matter. Environ Sci Technol 43:9189-9195.

*Valenti TW, Perez-Hurtado P, Chambliss CK, Brooks BW. 2009. Aquatic toxicity of sertraline to Pimephales promelas at environmentally relevant surface water pH. Environ Toxicol Chem 28:2685-2694.

*Valenti TW, Taylor JM, Back JA, King RS, Brooks BW. 2010. Influence of drought and total phosphorus on diel pH in wadeable streams: Implications for ecological risk assessment of ionizable contaminants. Integr Environ Assess Manag 7:636-647.

*Von Oepen B, Kördel W, Klein W. 1991. Sorption of polar and nonpolar compounds to soils: Processes and measurements and experience with the applicability of the modified OECD Guideline 106. Chemosphere 22:285-304.

*Voutsas E, Magoulas K, Tassios D. 2002. Prediction of the bioaccumulation of persistent organic pollutants in aquatic food webs. Chemosphere 48:645-651.

*Weisbrod A, Sahi J, Segner H, James MO, Nichols J, Schultz I, Erhardt S, Cowan-Ellsberry C, Bonnell M, Hoeger B. 2009. The state of in vitro science for use in bioaccumulation assessments for fish. Environ Toxicol Chem 28:86-96.

*Williams M, Ong PL, Williams DB, Kookana RS. 2009. Estimating the Sorption of pharmaceuticals based on their pharmacological distribution. Environ Toxicol Chem 28:2572-2579.

*Williams M, Saison CLA, Williams DB, Kookana RS. 2006. Can aquatic distribution of human pharmaceuticals be related to pharmacological data? Chemosphere 65:2253-2259.

*Yeager R, Halley BA. 1990. Sorption/desorption of [14C]efrotomycin with soils. J Agric Food Chem 38:883-886.

*Yu Z, Xiao B, Huang W, Peng P. 2004. Sorption of steroid estrogens to soils and sediments. Environ Toxicol Chem 23:531-539.

*Yu-Chen Lin A, Tsung-Hsien Yu, Shaik Khaja Lateef. 2009. Removal of pharmaceuticals in secondary wastewater treatment processes in Taiwan. J Hazard Mater 167:1163-1169.

*Zhang X, Oakes KD, Cui S, Bragg L, Servos MR, Pawliszyn J. 2010. Tissue-specific in vivo bioconcentration of pharmaceuticals in rainbow trout (Oncorhynchus mykiss) using space-resolved solid-phase microextraction. Environ Sci Technol 44:3417-3422.

MEMBERS OF THE TASK FORCE

T. Gouin (Chairman)	Unilever UK - Bedford
V. Coombe[a]	Astra Zeneca UK - Brixham
J. Ericson	Pfizer USA - Westerly
B. Hidding	BASF D - Ludwigshafen
J. Ryan	GlaxoSmithKline UK - Ware
K. Silverman[b]	MSD USA - New Jersey
B. Simon-Hettich	Merck D - Darmstadt
N. Sorokin[b]	Reckitt Benckiser UK - Hull
J. Straub[b]	F. Hoffmann-La Roche CH - Basel
H. Vrijhof Scientific Secretary	ECETOC B - Brussels

Acknowledgement

The Task Force wishes to thank A. Seville and R. Oliver (both at Syngenta, UK - Bracknell, Berkshire) for their contribution (Chapter 5).

[a] Retired

[b] Part-time, resigned

MEMBERS OF THE SCIENTIFIC COMMITTEE

(Peer Review Committee)

F. Lewis (Chairman)[a] Global Platform Lead	Syngenta UK - Bracknell
B. van Ravenzwaay (Vice-Chairman) Senior Vice President - Experimental Toxicology & Ecology	BASF D - Ludwigshafen
R. Bars Team Leader, Toxicology Research	Bayer CropScience F - Sophia Antipolis
D. Farrar Occupational Health Business Manager	Ineos Chlor UK - Runcorn
A. Flückiger Chief Occupational Health Officer	F. Hoffmann - La Roche CH - Basel
H. Greim Institute of Toxicology and Environmental Hygiene	Technical University München D - München
G. Malinverno Global Government and Regulatory Affairs Manager	Solvay B - Brussels / I - Milano
L. Maltby Professor of Environmental Biology	University of Sheffield UK - Sheffield
S. Marshall Environmental Science Leader	Unilever SEAC UK - Bedford
M-L. Meisters Manager Health and Environmental Sciences EMEA	DuPont de Nemours B - Mechelen
C. Money Distinguished Scientific Associate	ExxonMobil UK - Hythe
M. Pemberton Director	Systox UK - Wilmslow

[a] Responsible for primary peer review

MEMBERS OF THE SCIENTIFIC COMMITTEE (cont'd)

C. Rodriguez Principal Toxicologist, Corporate Central Product Safety	Procter and Gamble B - Strombeek-Bever
L. Rushton Principal Research Fellow	Imperial College London UK - London
D. Salvito[a] Vice President, Environmental Sciences	RIFM USA - Woodcliff Lake, NJ
J. Snape Principal Scientist	AstraZeneca UK - Brixham
G. Swaen Senior Epidemiologist	Dow Europe NL - Terneuzen
J. Tolls Director Environmental Safety Assessment	Henkel D - Düsseldorf
S. van der Vies Professor of Biochemistry	VU Medical Center NL - Amsterdam
C.J. van Leeuwen Principal Scientist	KWR Watercycle Research Institute NL - Nieuwegein
H.-J. Wiegand Head, Product Safety Department	Evonik Industries D - Essen

[a] Responsible for primary peer review

ECETOC PUBLISHED REPORTS

The full catalogue of ECETOC publications can be found on the ECETOC website:
http://www.ecetoc.org/publications

Responsible Editor:
Dr Alan Poole
ECETOC AISBL
Av. E. Van Nieuwenhuyse 2 (box. 8)
B-1160 Brussels, Belgium
VAT: BE 0418344469
www.ecetoc.org
D-2013-3001-235

Established in 1978, ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) is Europe's leading industry association for developing and promoting top quality science in human and environmental risk assessment of chemicals. Members include the main companies with interests in the manufacture and use of chemicals, biomaterials and pharmaceuticals, and organisations active in these fields. ECETOC is the scientific forum where member company experts meet and co-operate with government and academic scientists, to evaluate and assess the available data, identify gaps in knowledge and recommend research, and publish critical reviews on the ecotoxicology and toxicology of chemicals, biomaterials and pharmaceuticals.