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Pharmaceuticals in soils of lower income countries: physico-chemical fate and risks from wastewater irrigation

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Abstract

Population growth, increasing affluence, and greater access to medicines have led to an increase in active pharmaceutical ingredients (APIs) entering sewerage networks. In areas with high wastewater reuse, residual quantities of APIs may enter soils via irrigation with treated, partially treated, or untreated wastewater and sludge. Wastewater used for irrigation is currently not included in chemical environmental risk assessments and requires further consideration in areas with high water reuse. This study critically assesses the contemporary understanding of the occurrence and fate of APIs in soils of low and lower-middle income countries (LLMIC), to identify gaps in knowledge that addressing would contribute to the development of risk assessments in LLMIC. The physico-chemical properties of APIs and soils vary greatly globally, impacting on API fate, bioaccumulation and toxicity. The impact of pH, clay and organic matter on the fate of organic ionisable compounds are discussed in detail. This study identifies the occurrence and the partitioning and degradation coefficients for APIs in soil:porewater systems, API usage data in LLMICS and removal rates (where used) within sewage treatment plants as key areas where data are missing in order to inform robust environmental risk assessment methodologies.

Keywords: Pharmaceuticals; Soil; Lower and lower middle income countries; Terrestrial risk Assessment; Wastewater; irrigation

1. Introduction

There has been a global increase in the use of active pharmaceutical ingredients (APIs)[1] in recent decades due to population growth, increasing affluence, changes in disease burdens and easier access to medication. In the low and lower-middle income countries (LLMIC) of Asia, Africa and Central and South America, the use of human pharmaceuticals increased by 23-29 % between 2000 and 2011 (WHO 2011). As a consequence, the loadings of residual APIs and other down the drain chemicals (including personal care products) to soils, surface and ground waters of these countries will increase. The major vector of this loading is wastewater (Corcoran et al. 2010; WHO 2006b, c, d). Wastewater is defined as a combination of one or more of blackwater (excreta, urine, faecal sludge), greywater (kitchen and bathing wastewater), commercial and industrial effluent (including hospitals), stormwater and other urban run-off, and agricultural, horticultural and aquacultural effluent. Each may be treated, partially treated or untreated (Corcoran et al. 2010; Jiménez et al. 2010). Difficulties in quantifying the magnitude of wastewater loads, in tandem with a paucity of environmental monitoring data of APIs in LLMIC, makes accurate and precise predictions of temporal trends in API loadings uncertain (Jiménez et al. 2010; Kookana et al. 2014).

Many LLMIC are experiencing physical or economic water scarcity (Fig. 1) with the former particularly important in northern and southern Africa and southern Asia. To counter-act shortages of good quality water in arid and semi-arid regions and to conserve its use, many LLMIC use the wastewater they generate for irrigation of agricultural and horticultural land. The water stressed areas of southern Asia produce wastewater in excess of 10×10^9 m^3 yr^{-1} (Fig. S1) with up to 20 % being used for irrigation. Other countries such as Israel, Jordan, Syria, Iraq and Mexico use more than 40 % of their municipal wastewater for this purpose (Fig. 2(a)). Globally, about 20 million ha of agricultural land is irrigated with wastewater (Scott et al. 2004), with the highest proportions of cultivated areas equipped for irrigation found in the Middle East, southern Asia and western South America, as shown in Fig. 2(b). *Per capita* daily food consumption requires 2 – 5 m^3 of water (Corcoran et al. 2010), making

[1] AEC – Anion exchange capacity
API – Active pharmaceutical ingredient
CDOM – Colloidal dissolved organic matter
CEC – Cation exchange capacity
LLMIC – Lower and lower middle income countries
PEC – Predicted environmental concentration
PNEC – Predicted no effect concentration
POM – Particulate organic matter

agriculture a significant requirement for water, particularly in the extensively irrigated regions noted above (Fig. S2). Irrigation is dominated by untreated and untreated-diluted wastewater, notably in China (> 3.6 million ha), India (> 1 million ha) and Mexico (ca. 190,000 ha), while treated water is extensively used in Chile, Mexico and Egypt (238, 000 ha) (Lautze et al. 2014). Across a range of LLMIC, 80 % of cities use mainly untreated and untreated-diluted wastewater for irrigation (Jiménez et al. 2010). In arid areas, cities such as Dakar (Senegal), Accra (Ghana) and Tamale (Ghana) produce 60-100 % of the consumed leafy vegetables within the city using wastewater irrigation, while 60-80 % of the perishable food for local markets in Hanoi (Vietnam) is produced using diluted wastewater (Corcoran et al. 2010; Drechsel et al. 2006). Water shortages are predicted to become more widespread and acute as human populations increase in number and urbanisation and industrialisation expand, food consumption patterns change, and rainfall distribution and volume alter as a result of climate change (Corcoran et al. 2010; Hanjra and Qureshi 2010). Nevertheless, there appears to be the potential to markedly increase the recovery and re-use of wastewater in many LLMIC, particularly for agricultural use close to highly urbanised areas, given the appropriate incentives (Jiménez et al. 2010; Lautze et al. 2014; WHO 2006c, d).

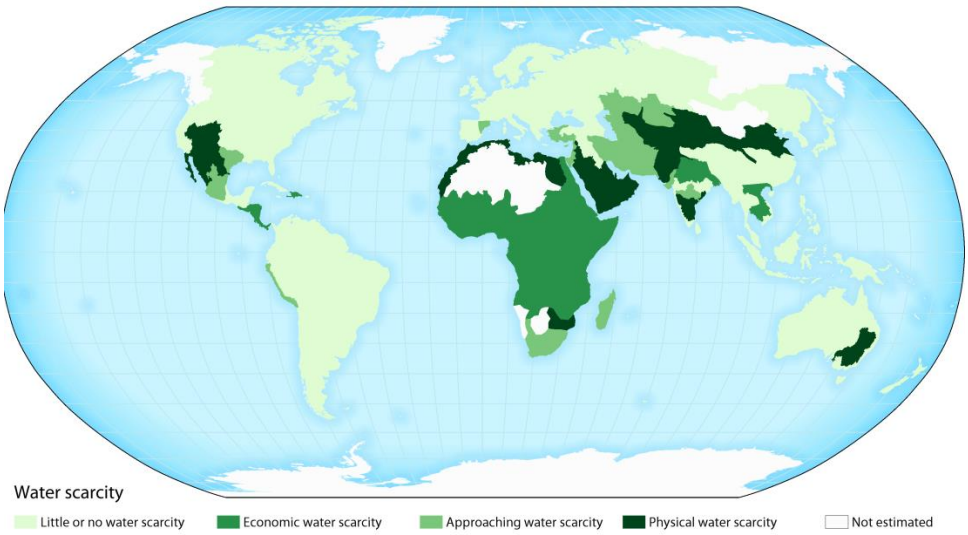
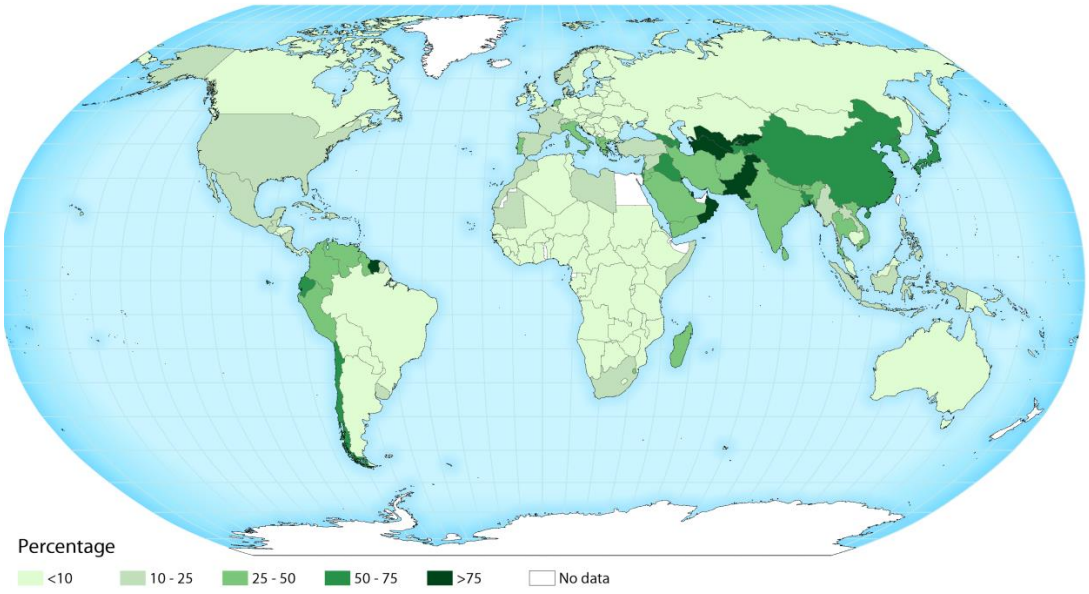


Fig. 1. Regions of physical and economic water scarcity (International Water Management Institute 2006)

(a)



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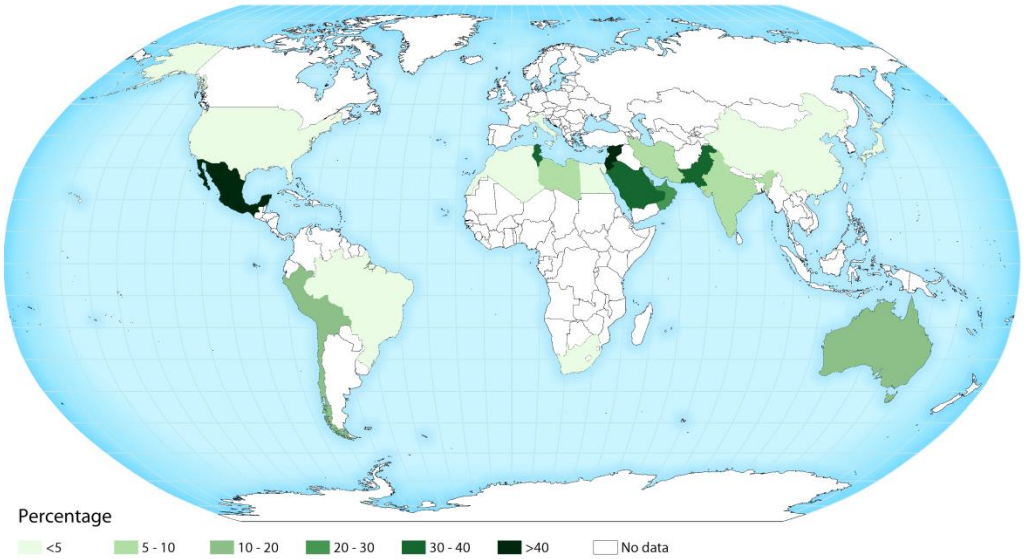


Fig. 2. Global water statistics. (a) Municipal wastewater used for irrigation (%), (b) Cultivated area equipped for irrigation (%). (FAO 2015).

There is currently a lack of public usage data for the amount and type of APIs used in many LLMIC due to poor record keeping, extensive self-medication and the use of non-prescribed APIs over large population numbers (Kookana et al. 2014; Kotwani et al. 2012; Rehman et al. 2013). This knowledge gap is further confounded by inconsistent adherence to therapeutic treatments, particularly for longer-term prescribing (Kookana et al. 2014). For some groups of APIs, *per capita* use may be similar between LLMIC and higher income countries, but owing to larger populations in LLMIC (40 % of the global human population live in China, India, Bangladesh and Pakistan; Rehman et al. 2013) the actual tonnage used is much greater (Kookana et al. 2014). Usage data are often commercially sensitive and thus unavailable to the wider scientific community; however, projected spending patterns indicate continued expansion of API use in LLMIC (Fig. S3). In addition, there has been a marked relocation of pharmaceutical manufacturing from high income countries to LLMIC in recent years, with an annual growth of 10 – 15 %, resulting in ca. 13,000 industrial production units in India and China alone (Cardoso et al. 2014; Rehman et al. 2013). The effluents from these generally poorly regulated sites have been identified as a significant source of APIs to adjacent surface waters and sewage treatment works (Larsson 2014; Liu and Wong 2013; Rehman et al. 2013). This can lead to localised 'hot spots' which are manageable if, *inter alia*, site emissions of APIs are known and safe discharge standards or environmental reference concentrations are developed and enforced (Murray-Smith et al. 2012); nevertheless, there appear to be little data on effluent API loadings (Cardoso et al. 2014). Thus, it is clear that the paucity of data on API environmental loading from consumption and manufacture is a significant obstacle to the wider understanding of API occurrence, fate and impacts in LLMIC. Concerns regarding persistence and antimicrobial resistance of APIs were highlighted as a priority issue in October 2015 at the International Conference on Chemicals Management led by the United Nations Environment Programme, which called for increased global knowledge of pharmaceuticals in all environmental compartments (Nature 2015). This conference backed the need for global cooperation and awareness to overcome the obstacle of the understanding of APIs occurrence and fate in LLMIC.

Guidelines on the safe use of wastewater in LLMIC have been produced since the 1970s, with the most recent published in 2006 (WHO 2006a, b, c, d). The Guidelines are a flexible management framework for safeguarding human health while maximising the benefits of wastewater use in agriculture and aquaculture. The constituents of wastewater addressed with respect to safety in the Guidelines include pathogens, salts, metals, nutrients,

acids and bases, suspended matter, organic matter and toxic organic compounds. The last class includes APIs (WHO 2006b, c), but given that the concern regarding these compounds is recent, regulatory frameworks for controlling API loadings (or indeed, other organic contaminants) to soils and waters are rare in LLMIC (Jiménez et al. 2010; Kookana et al. 2014; Sorensen et al. 2015). Indeed, it is only since 2006 that a comprehensive environmental risk assessment has been required for all new marketing authorisation applications for human medicinal products in the European Union (EMEA, 2006 – now EMA). The underlying assumption for risk assessments is that wastewater is universally treated in sewage treatment plants (as required under EU law), which, as has been described, does not hold for LLMIC. Furthermore, the European environmental risk assessment framework is only concerned with exposure to API following application of sewage biosolids to soil, and does not include additional scenarios, such as irrigation with wastewater and other contaminated water sources which are relevant to LLMIC. Nevertheless, the environmental risk assessment approach would provide a good framework for LLMIC to adopt, including both Phase I and Phase II (Tier A and B assessments). Clearly, the action limits used in Europe (EMEA 2006) for triggering more extensive terrestrial risk assessment by regulators within LLMIC would need to be critically examined to take account of local circumstances. For example, API use and disposal, chemical characteristics and speciation, water re-use, soil physico-chemistry and biology, and climate. It is noteworthy that the appropriateness of some of the action limits in the development of more robust terrestrial risk assessments for APIs in the EU are also under scrutiny, primarily because APIs can exist either as cations, anions or zwitterions within the pH range covering most surface waters (ECETOC 2013a).

The aims of this study are to critically assess contemporary understanding of the occurrence of APIs in soils of LLMIC, to identify API sources to soils, to develop a global overview of key abiotic soil characteristics expected to influence the fate of soil-associated APIs, and highlight the datasets required for the development of a more globally relevant approach to environmental risk assessments that capture exposure scenarios in LLMIC.

2. APIs in LLMIC soils: occurrence, sources and factors controlling their fate

The occurrence, sources and fate of APIs in soils following applications of wastewater and biosolids has been an area of concern and study for at least a decade, but the main focus has been on the high income countries of North America and Europe and antibiotic resistance of soil microbes (BIO Intelligence Service 2013; Kinney et al. 2006; Thiele-Bruhn 2003). Similar studies in LLMIC, with the general exception of China, are much rarer (Kookana et al. 2014; Liu and Wong 2013; Rehman et al. 2013).

2.1 Occurrence in soils

Concentration data for APIs in LLMIC soils are sparse, as shown in Table 1. The majority of APIs identified in studies undertaken were veterinary and human antibiotics (e.g. oxytetracycline, sulfamerazine, norfloxacin), as a result of the combination of high usage in human and animal medicine and concerns about antimicrobial resistance (Chen et al. 2011; Gibson et al. 2010; Li et al. 2011; Rutgersson et al. 2014). Notably, data are missing for LLMIC hosting extensive API manufacturing, including Bangladesh and Pakistan, with only a single dataset available for India. In arid climates, wastewater for irrigation is added continuously throughout the year, which, in principle, can lead to accumulation of API in the soil and leaching of APIs through soil profiles to groundwater even for readily biodegradable compounds. In soils irrigated with untreated wastewater in the Tula Valley (Mexico), Gibson et al. (2010) calculated that carbamazepine and triclosan had accumulated in upper soils horizons by a factor of 603-942 % and 519-858 % respectively. The concentration patterns of both compounds were highly and positively correlated with the soil organic matter concentration, suggesting that this soil component was a critical factor in their accumulation. For other APIs studied (ibuprofen, naproxen and diclofenac) there was no evidence of accumulation, probably due to biodegradation rates exceeding application rates.

Table 1. Concentrations (µg kg^{-1} dry weight) of APIs in soils of low and lower-middle income countries.

Location	API	Concentration (µg kg^{-1})	Reference
Pearl River Delta (China)	Oxytetracycline	9.6 ± 22.9	(Li et al. 2011)
	Sulfamerazine	16.0 ± 20.4	
	Norfloxacin	61.9 ± 33.1	
Hebei (China)	Salicylic acid	4.5 ± 0.8	(Chen et al. 2011)
	Oxytetracycline	6.2 ± 0.2	
	Tetracycline	6.9 ± 0.5	
Tula Valley (Mexico)	Ibuprofen	< 0.1 – 0.30	(Gibson et al. 2010)[a]
	Naproxen	< 0.20 – 2.40	
	Carbamazepine	0.1 – 16.4	
	Triclosan	0.4 – 35.5	
	Diclofenac	< 1.0	
Baithole (India)	Ciprofloxacin	0.014	(Rutgersson et al. 2014)
	Norfloxacin	0.011	
	Ofloxacin	0.019	

[a] Concentration range reflects 5 soils and variable sampling depths

2.2 Wastewater application to soils

In many LLMIC the proportion of the population living in an urban environment is smaller than in high income countries and sewerage connectivity is much lower (Kookana et al. 2014). In addition, sewage treatment plants often underperform or are underused. Little of the non-urban population is connected to sewerage systems, instead relying on septic tanks, pit latrines and other low technology systems. As a consequence, in LLMIC, as a whole, ca. 90 % of untreated and poorly treated wastewater is discharged directly to surface water and soils (Fig. 3) (Kookana et al. 2014; Sorensen et al. 2015; UN Water 2008). The surface water contaminated with wastewater may be subsequently used for irrigation.

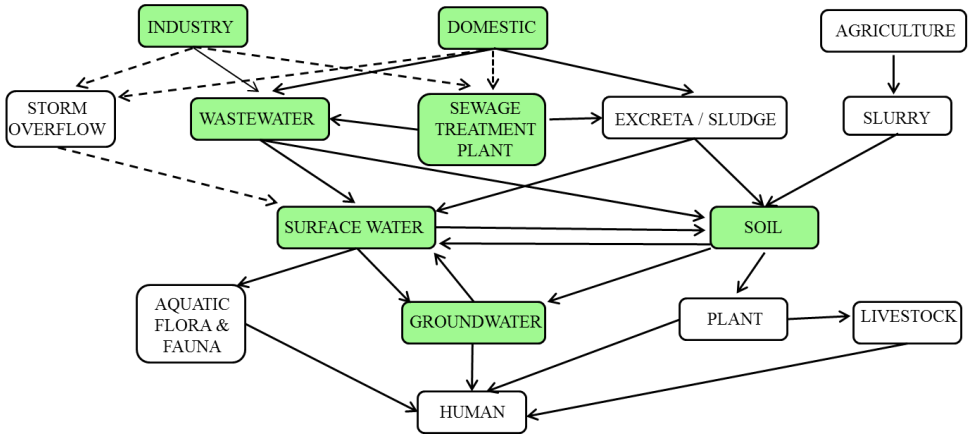


Fig. 3. Potential flows of APIs in the environment from their sources in the industry, domestic and agricultural sectors. Dotted lines indicate less important pathways in LLMICs, shaded areas represent flows discussed in the text (Kookana et al. 2014; Sorensen et al. 2015; UN Water 2008).

Removal efficiencies of APIs in LLMIC sewage treatment plants depend on its concentration in the influent, its physico-chemical properties, the method of treatment and the operating conditions (hydraulic/sludge residence times and the weather/climate during processing). Variation in removal efficiencies can also be the result of experimental factors that need to be assessed before using data for risk assessments or modelling. These include type of sampling (e.g. grab samples or composite sampling schemes) and the inclusion of hydraulic retention times when sampling.

The most commonly reported treatment type is activated sludge as it is one of the most commonly used treatment type used globally (Melvin & Leusch 2016). In Bangkok (Thailand), sewage treatment plants with different activated sludge treatment processes achieved a wide range of API removal efficiencies, from 19-90 % (grab samples). For example, diclofenac showed variable removal (19-60 %) while atenolol removal was higher (76-90%) and more consistent (Tewari et al. 2013). This variation is not confined to LLMIC countries; in European Union countries, 0-98 % removal of APIs has been measured (Castiglioni et al. 2005; Gardner et al. 2013). Seasonal differences in API concentrations in the receiving waters were found between the high flow in January (1-148 ng L^{-1}) and low flow in September (<1-1100 ng L^{-1}) owing to dilution, indicating that climactic variations must also be taken into account when assessing the efficiency of sewage treatment plants and dilution in the receiving environment (Tewari et al. 2013). Korean sewage treatment plants showed a similar variation in API removal efficiencies, with a wide range for carbamazepine removal (42-83%) and a narrow one for naproxen (72-88%) (grab samples) (Sim et al. 2010).

Treatment types commonly used in rural areas globally include lagoons and oxidation ditches (Melvin & Leusch 2016). In rural Australian communities using a series of 10 lagoons for sewage treatment, high removal efficiencies were measured for naproxen (90%) and diclofenac (90%) (composite sampling scheme) (Ying et al 2009). In this study degradation of the APIs was suggested to be the primary removal mechanism due to long residence times and the removal of sludge and solid sedimentation in the early stage lagoons. Whilst Australia is not a LLMIC, sewage processing in rural communities is relevant due to the arid climate and simple sewage infrastructure. It can be concluded that further studies into global removal efficiencies for a wider range of APIs and treatment processes are required.

Concentrations of APIs in effluents from the pharmaceutical industry in LLMIC can be a significant source of APIs if discharges are poorly managed, as API levels in the effluent can be orders of magnitude higher than those in urban sewage effluent (Cardoso et al. 2014; Larsson 2014). In China and Korea, industrial wastewater is often mixed with domestic wastewater prior to discharge to the sewage treatment plant in order to enhance biodegradation of organic contaminants, while in India, Pakistan and Bangladesh, industrial wastewater is more often discharged directly into surface waters (rivers) or domestic sewage systems where these exist (Rehman et al. 2015). Despite the potential for ecotoxicological impacts, there appear to be few data on industrial effluent API loadings in LLMIC (Larsson 2014).

2.3 Physico-chemical factors controlling the fate of APIs in soil

The fate and toxicity of ionisable organic contaminants in soils is significantly influenced by soil pH, the concentration and type of organic matter and clay (and hence ion exchange capacity), the lipophilicity of the API (described by the n-octanol-water partition coefficient (Kow), and its strength as an acid or base (described by the acid dissociation constant, Ka). Nevertheless, other factors, such as soil aeration, moisture content, temperature and patterns of API use, form emitted and mode of emission (episodic or continuous) will also play a role (Dalkmann et al. 2014; Jjemba 2006). For APIs, of which > 80% are ionisable at environmental pH (5-9), predicting how changes in the soil environment influence the ionisation of the molecule and its resulting lipophilicity and hence its behaviour and fate (accumulation, abiotic and biotic degradation, leaching), is an area of ongoing research with respect to exposure assessment and environmental risk assessment (Boxall et al. 2012; ECETOC 2013a). The ambient conditions of soils will vary with location and climate,

which makes the direct knowledge transfer of API behaviour and fate in soils in high income countries, where most studies have been undertaken, to LLMIC less straightforward than perhaps anticipated. In the following sections, API – soil particle interactions and the potential roles of soil pH, clay and organic matter in relation to API fate in wastewater used for irrigation by LLMIC are examined in more detail.

2.3.1 API – soil particle interactions

The range of physico-chemical interactions that may occur between an API and soil particles are summarised in Figure 4 for propanolol. This API has a pKa of 9.45 so at pH 7 the cation will be 282 times more abundant than the neutral form of the molecule. The extent of ionisation and the charge on the ionised molecule will affect the extent to which these reactions occur. In reaction 1, the protonated propranolol molecule forms an ionic bond with a negatively charged surface group on the particle. With reaction 2, a free (i.e. unprotonated) molecule reacts with a functional group on the particle to form a covalent bond. For reaction 3, the naphthoxy side chain of propranolol undergoes hydrophobic interactions with particulate organic matter (POM), or the cation can bond with negatively charged functional groups within the POM. For the final reaction, 4, van der Waals forces and dipole–dipole interactions may be involved in sorption. Other processes which may influence interactions of APIs with particles include ligand exchange and hydrogen bonding (ECETOC 2013b). In contrast to propanolol, naproxen (pKa 4.15) ionises to an anion and at pH 7 the anion will be 708 times more abundant than the neutral molecule; interactions with anionic surface exchange sites would therefore be negligible but it may form a hemi-acetal through carbonyl addition to the reactive surface group.

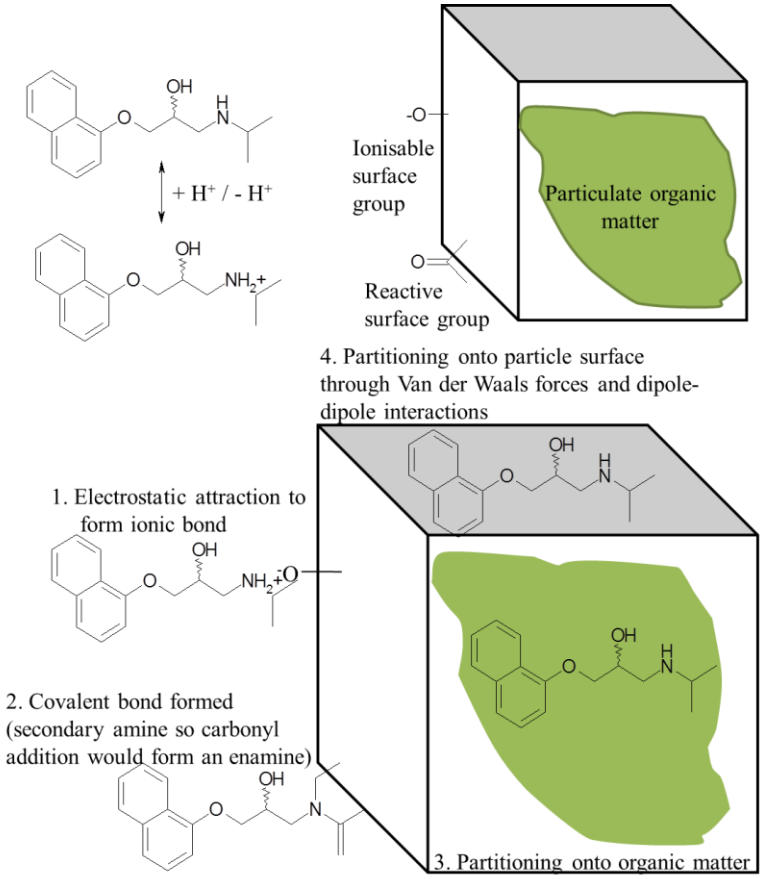


Fig. 4. An example of the possible sorptive interactions between the API propranolol and a heterogeneous soil particle that may control partitioning of the molecule between the dissolved and particulate phases in soils (adapted from Schwarzenbach et al. 1993).

2.3.2 Soil pH

The total potential acidity of a soil essentially comprises the activity of protons in soil pore water plus exchangeable protons at the surfaces of the soil particles (Kah and Brown, 2007). Fig. 5 shows the global distributions of soil pH, determined in a water/soil suspension (FAO/IIASA/ISRIC/ISS-CAS/JRC 2009). While the water method for pH measurement will not necessarily account for exchangeable protons (Kah and Brown 2007), top soils (0-30 cm) in LLMIC using wastewater irrigation (shown in Fig. 2(a)) generally fall into the pH range 5.5-8.5, with soils in southern China, eastern India, and Bangladesh more frequently in the range 4.5–5.5. Wastewater is usually slightly alkaline, which will mitigate the generally acidic nature of the soil environment to some extent (WHO 2006b).

Soil pH will influence the net charge on ionisable APIs and they will be fully ionised (> 99 %) when the pH is at ± 2 pH units from their log K_a (pK_a) values, as shown in Fig. S4; thus many APIs will be significantly ionised at typical soil pH. APIs with more than one pK_a value will exhibit additional charge complexity.

Ionic APIs will be less lipophilic than the neutral forms and hence more water soluble; nevertheless, cationic (basic) APIs may be expected to sorb to negatively charged components within the soil, such as clay and organic matter (Franco et al. 2009; Lertpaitoonpan et al. 2009). With reference to Fig. 4, propranolol (pKa 9.3) will be cationic at most soil pH, and is expected to sorb to the negatively charged components of soils via electrostatic attraction (ter Laak et al. 2006; Schaffer et al., 2012). In contrast, acidic APIs, such as naproxen (pK_a 4.2), will be in anionic form at soil pH higher than the pK_a; thus a reduction in electrostatic sorption at > pH 5 may be the result of repulsion between the anionic API and the negative charge on the soil (Paul et al 2013). Fluoroquinolone antibiotics have two pK_a values (e.g. ofloxacin, pK_a 5.97 and 8.28) which at environmental pH tend to be zwitterionic, but can also be cationic, anionic, or uncharged (Vazquez-Roig et al 2012). At pH $\leqslant$ 5 ciprofloxacin (pK_a 6.18 and 8.76) electrostatic sorption can be hypothesized to increase as pH decreases due to the cationic form of the API interacting with the negatively charged soil surfaces. At pH $\geqslant$ 5, ciprofloxacin sorption will decrease due to diminishing cationic charge and an increase in the anionic carboxylic acid moiety within the net neutral zwitterion, leading to repulsion from the negatively charged soil components (Vasudevan et al 2009).

The more acid soils found in parts of Asia, noted above, are relatively rich in positively charged Al and Fe sesquioxides (FAO 2014) which may provide sorption sites for anionic (acidic) APIs (Hyun and Lee 2004; White 2013). Soil pH will also influence the pH-dependent charge on the organic matter, clay minerals and metal sesquioxide components of the soil, which in turn might be expected to influence API sorption (Hyun and Lee 2004).

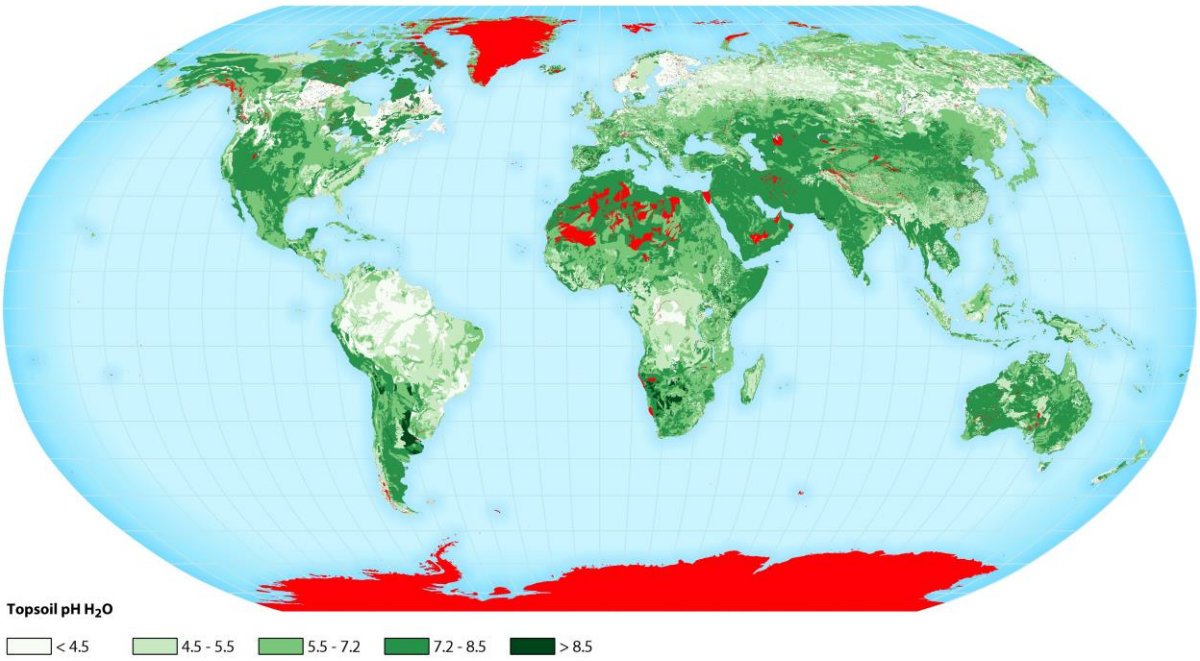
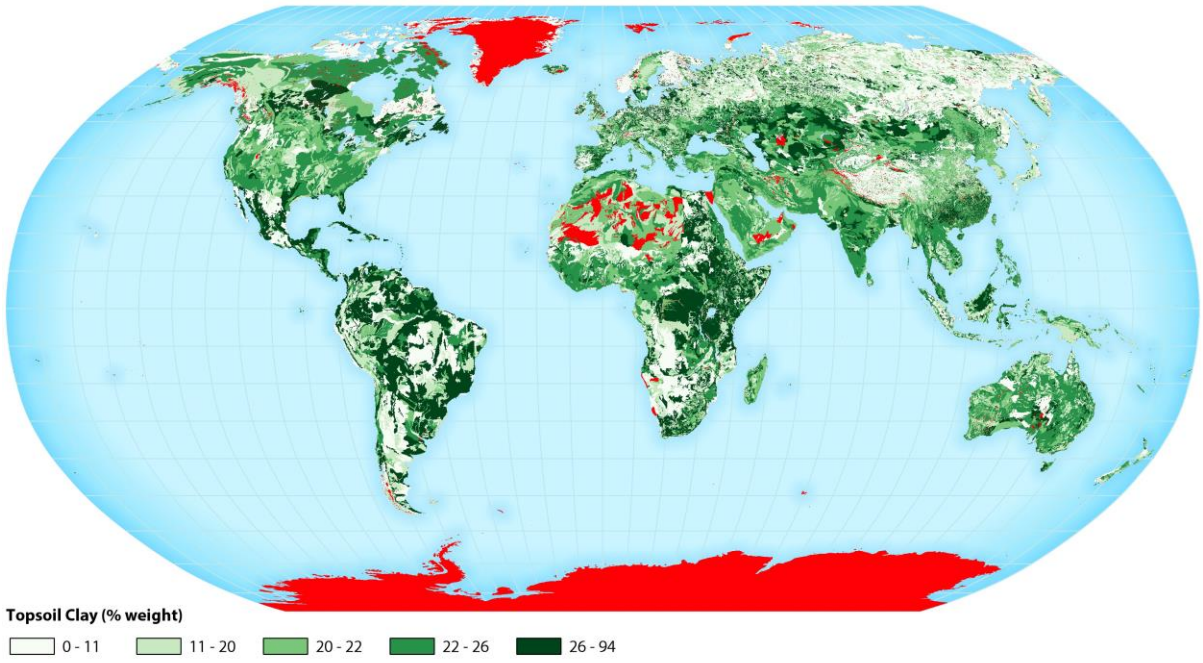


Fig. 5. Global distribution of soil pH (0-30 cm depth) (FAO/IIASA/ISRIC/ISS-CAS/JRC 2009). Coverage in red indicates no data.

2.3.3 Soil clays

Clays are essentially aluminosilicate minerals with a particle size of less than 2 µm. Fig. 6(a) shows the distribution of the clay content in surface soils (defined as 0-30 cm depth) across the globe (FAO/IIASA/ISRIC/ISS-CAS/JRC 2009). The LLMIC that use wastewater for irrigation, as shown in Fig. 2(a), have soils with a wide range of clay content. In China, the southeastern regions have contents of 30-45 %, falling to mainly 15-30 % in the north, while soils with < 15 % clay are more frequent in the western areas. Soils in the central region of India have high clay contents (45-60 %), with some in the 30-45 % range. In the coastal zones of India, in Bangladesh and in parts of Pakistan, 15-30 % clay is more common. Lower clay contents (< 15 %) are found in northern India and central Pakistan. In north Africa, soils with clay contents 15-30 % are common, falling to < 15 % in the eastern areas. Soils along the western coastal zone of South America have clay contents in the range 15-30 %. Elsewhere in the sub-continent and also in Mexico, soils with a wide range of clay content occur.

(a)



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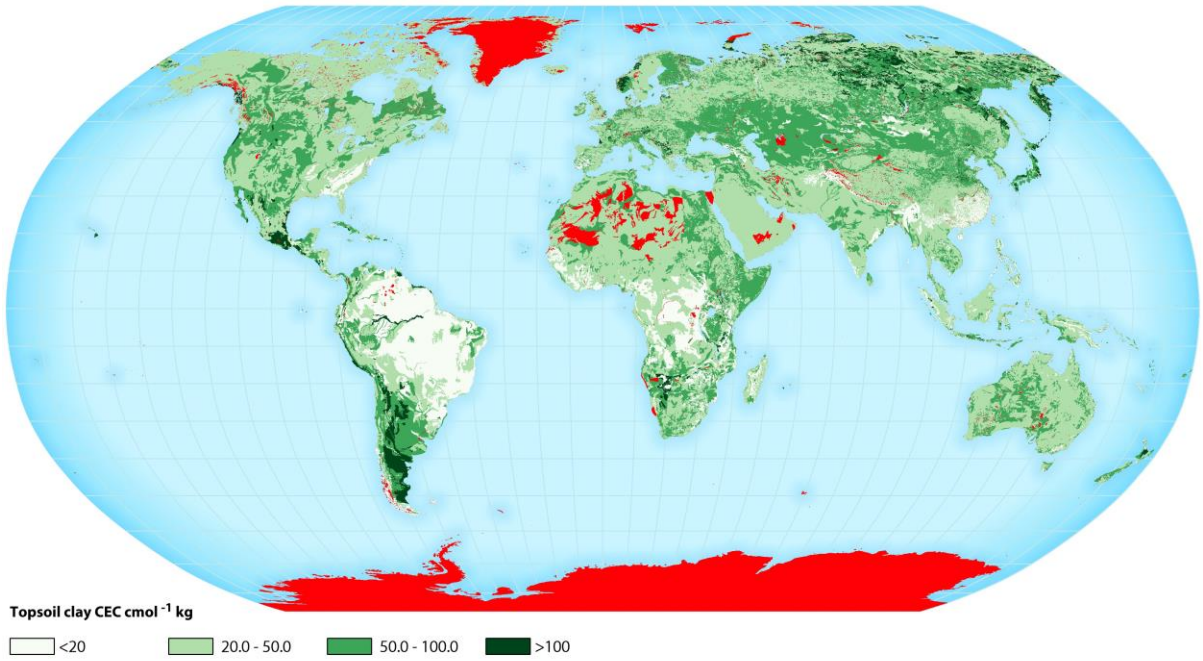


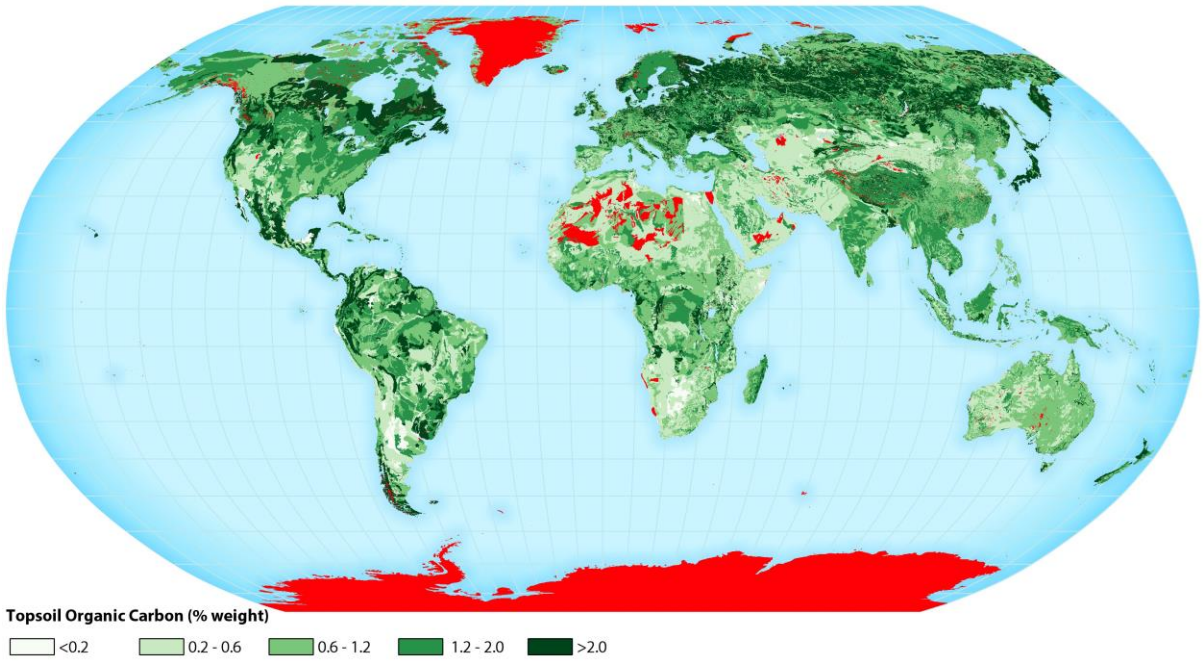
Fig. 6. Global distribution of the (a) clay content (% weight) and (b) clay cation exchange capacity (CEC; cmol^{-1} kg clay) in the top 30 cm of soil (FAO/IIASA/ISRIC/ISS-CAS/JRC 2009).

Clays generally have a cation exchange capacity (CEC) at pH values found in terrestrial systems because of isomorphous substitution (i.e. the replacement in the mineral structure of one cation with another of a different charge) and de-protonation of surface hydroxyl groups (the extent dependent on pore water pH) while the overall magnitude of the CEC value will depend on the type of clay. The higher the CEC value the more sorption sites are potentially available. The distribution of the clay CEC in surface soils across the globe varies considerably (Fig. 6(b)) (FAO/IIASA/ISRIC/ISS-CAS/JRC 2009). Clay CEC values are generally in the range 22-55 $cmol^{-1}$ kg clay (at pH 7) across many of the LLMIC of interest. Values are lower in southeastern China and central South America (< 22 $cmol^{-1}$ kg clay, and often < 10 $cmol^{-1}$ kg clay), and higher in areas of north and western China, central India, the coastal zones of north Africa and western South America. Clays in Mexican soils have some of the highest values (> 104 $cmol^{-1}$ kg clay) observed. In relatively acidic environments however, clays may exhibit an anion exchange capacity (AEC) because of protonation of the surface hydroxyl groups. The AEC:CEC ratio will reflect the difference between the soil pore water pH and the pH of the net zero charge of the particular clay type (Hyun and Lee 2004). Thus, ionic sorption of an API to the clay will be a function of the AEC:CEC ratio, soil solution pH and API pK_a. Clay CEC has been reported to be important for the sorption of some antibiotic APIs (Vasudevan et al. 2009; Yan et al. 2012).

2.3.4 Soil organic matter

Soil organic matter , which represents the variable decomposition products of autochthonous and allochthonous inputs of organic matter (animal, plant, microbial biomass) to soils, is comprised of particulate organic matter (POM) and, in pore water, colloidal dissolved organic matter (CDOM). Fig. 7(a) shows the global distribution of POM, as organic carbon, in surface soils (FAO/IIASA/ISRIC/ISS-CAS/JRC 2009) and most LLMIC that use wastewater for irrigation (Fig. 2a), have soils with organic carbon concentrations above 0.6 % (w/w), indicating fertile soils with, in principle, good contaminant sorption properties. In contrast, soils in northern China, Pakistan and much of North Africa are low in organic carbon (< 0.6 % w/w) and probably need fertiliser to be productive, so wastewater irrigation would likely enhance the organic carbon content of these soils (Qadir et al. 2010).

(a)



(b)

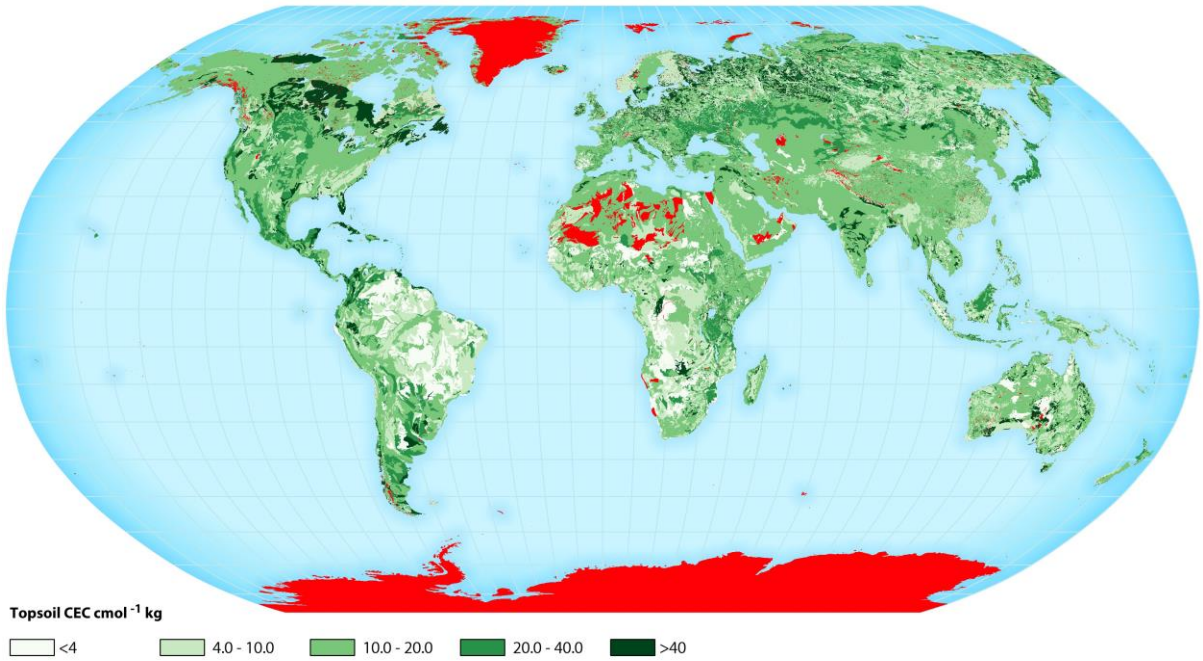


Fig. 7. Global distribution of the (a) organic carbon (% weight) and (b) soil cation exchange capacity (CEC; cmol^{-1} kg soil) in the top 30 cm of soil (FAO/IIASA/ISRIC/ISS-CAS/JRC 2009). Coverage in red indicates no data.

Important fractions of soil POM occur as polymeric macro-molecules with relatively high aromatic and alkyl content (Kleber et al. 2007). Partitioning of hydrophobic contaminants into this fraction has historically been quantified empirically by the organic carbon–water partition coefficient, K_{oc} (ECETOC 2013a), and APIs with aromatic constituents and/or high carbon fraction may partition into the hydrophobic POM fraction and contribute to the API K_{oc} value. A range of APIs (carbamazepine, ibuprofen, naproxen and diclofenac, for example) were generally better retained in soils with relatively high POM and their concentrations were positively correlated with POM concentrations (Chefetz et al. 2008; Drillia et al. 2005; Gibson et al. 2010; Xu et al. 2009). In contrast, partitioning into soil solids of these APIs was less extensive in low POM soils because of reduced hydrophobic interactions with the POM and probable binding of API with CDOM in some cases.

POM also has a CEC because of a pH-dependent net negative surface charge. CEC values of 60 - 300 cmol kg^{-1} organic carbon (at pH 7) may account for 25 - 90% of the total CEC of soils, and in some cases may be more important than clays. Thus transfer of the neutral and cationic forms of all but the most water-soluble APIs from solution to POM will occur (Kinney et al. 2006; Gibson et al. 2010) and it can be concluded that the K_{oc} value will comprise both a hydrophobic and a hydrophilic component. Fig. 7(b) shows the global distribution of top soil CEC due to both organic matter and clay (FAO/IIASA/ISRIC/ISS-CAS/JRC 2009). Soils with CEC values below 10 $cmol^{-1}$ kg soil are considered poor at cation retention, and these occur in southeastern, northern and western China, coastal regions of India, confined areas of North Africa and much of South America. Elsewhere, intermediate (22-55 $cmol^{-1}$ kg soil) values of CEC dominate, with highest values found in parts of central India and throughout Mexico.

In both high and low POM soils, the transport of APIs may be enhanced by irrigation with treated and untreated wastewater (Drillia et al. 2005; Gibson et al. 2010). Thus, the formation of API–CDOM complexes, as discussed below, may contribute to enhanced API solubility and mobility if the CDOM is not surface reactive, but API mobility may decrease if surface sorption occurs (Blackwell et al. 2009; Chefetz et al. 2008). Like POM, CDOM will be comprised of a humic-like hydrophobic fraction and a water-soluble, more polar, component. CDOM generally carries a pH-dependent net negative surface charge due to ionised carboxylic acid and phenolic groups, and the more polar constituents are more abundant at the lower end (< 1 kDa) of the CDOM size range (Yang et al. 2011).

The ability of surface water CDOM or its humic components, to bind organic contaminants has been reported since the 1980s (Chiou et al. 1986; Chiou et al. 1987), although to date there have been very few mechanistic studies of this phenomenon for APIs and wastewater or soil CDOM (Blackwell et al. 2009). The antibiotic ciprofloxacin was reported to partition into humic material CDOM to a much greater extent than into CDOM present in treated municipal wastewater (Carmosini and Lee 2009). The mechanism of sorption to the humic CDOM was pH-dependent cation exchange. Similar partitioning to the polar compound rich wastewater CDOM was not observed because of the relatively high alkalinity of the wastewater. For a range of surface waters (river, estuary) the binding of APIs to CDOM appeared to be dominated by the larger (> 1 kDa) hydrophobic fractions, although the pH dependency of this phenomenon was not explored (Liu et al. 2005; Maskaoui et al. 2007; Yang et al. 2011). The partitioning of the APIs into the estuarine CDOM was 2–4 orders of magnitude higher than into (OC–normalised) suspended matter, emphasising the importance of CDOM to API binding in surface waters (Yang et al. 2011). It has been reported that the character of CDOM (e.g. hydrophobic/hydrophilic balance, molecular size/weight distribution) can change during wastewater treatment, and with type of treatment (Shon et al. 2006). It is likely, therefore, that the binding and reactivity of an API in untreated and treated wastewater may be quite different and perhaps impact on its fate in irrigated soils (Gibson et al. 2010). From these findings it would appear that studies of API–wastewater or API-soil CDOM interactions should become a focus for research.

2.3.5 Clay – organic matter interactions and API sorption

While the clay and soil organic matter constituents have been described separately in order to highlight the global variations in their physico-chemical characteristics, in reality these moieties exist as intimate, and complex, organo-mineral assemblages as a result of solid – solution interactions; indeed, in temperate soils, 50 – 75 % of the soil organic matter is assemblage material (Christensen 2001) In the last two decades an arguably realistic conceptual model of these assemblages has emerged (Kleber et al. 2007). This zonal model, in principle, allows for the chemical bonding mechanisms between APIs and soil components (Fig. 4) that are understood to occur (ECETOC, 2013b). These mechanisms include van der Waals, hydrogen and covalent bonding, ionic and ligand exchange, charge transfer and hydrophobic interactions (Fig. 4). The model also allows for physical sequestration into the soil organic matter matrix. Empirical data are beginning to reveal that the assemblages occur as discrete clusters and that they are the primary sites for interaction with organic matter in

soil pore water. Furthermore, most (ca. 80 %) of the clay mineral surface, which has been generally perceived as reactive to OM, does not interact with the pore water organic matter at all (Vogel et al. 2014). If these findings are corroborated, it may serve to further increase the difficulty in predicting API sorption and fate, and subsequent development of ERAs for LLMIC soils.

2.4 Environmental risk from APIs in soils of LLMIC

In Europe, an API is considered to be a risk to the environment and subject to further testing when its Log K_{ow} is > 4.5, when the surface water PEC exceeds 0.01 µg L^{-1} (lower for compounds with mode of action related concerns), when the surface water PEC:PNEC ratio is > 1, or when the surface water PEC:PNEC (microorganism) ratio is > 0.1 (EMEA 2006). Confidence in this type of assessment is related to the data available and in some cases assumptions are required including worst case scenarios and read across from other environmental compartments. For example, EMEA (2006) does not require the calculation of soil PECs and PNECs for APIs with a Log K_{OC} <4. The soil PNECs reported in Fig. 8 for a range of APIs are predicted from the surface water PNEC using the partition coefficient of the API in soil and the bulk density of wet soils (see Table S1), as described in ECB (2002). These calculations reveal that measured soil concentrations may be higher than the PNECs for fluoxetine, oxytetracycline, triclosan and tetracycline in some cases (Fig. 8). Although soil concentrations of APIs in LLMIC are generally low, the dataset is restricted both spatially and temporally, as shown in Table 1, and so there is uncertainty regarding risk to humans and other biota (Qin et al. 2015). Furthermore, while PNECs are formulated for acute toxicity assessments, chronic effects may be more important, particularly as wastewater irrigation becomes more widespread.

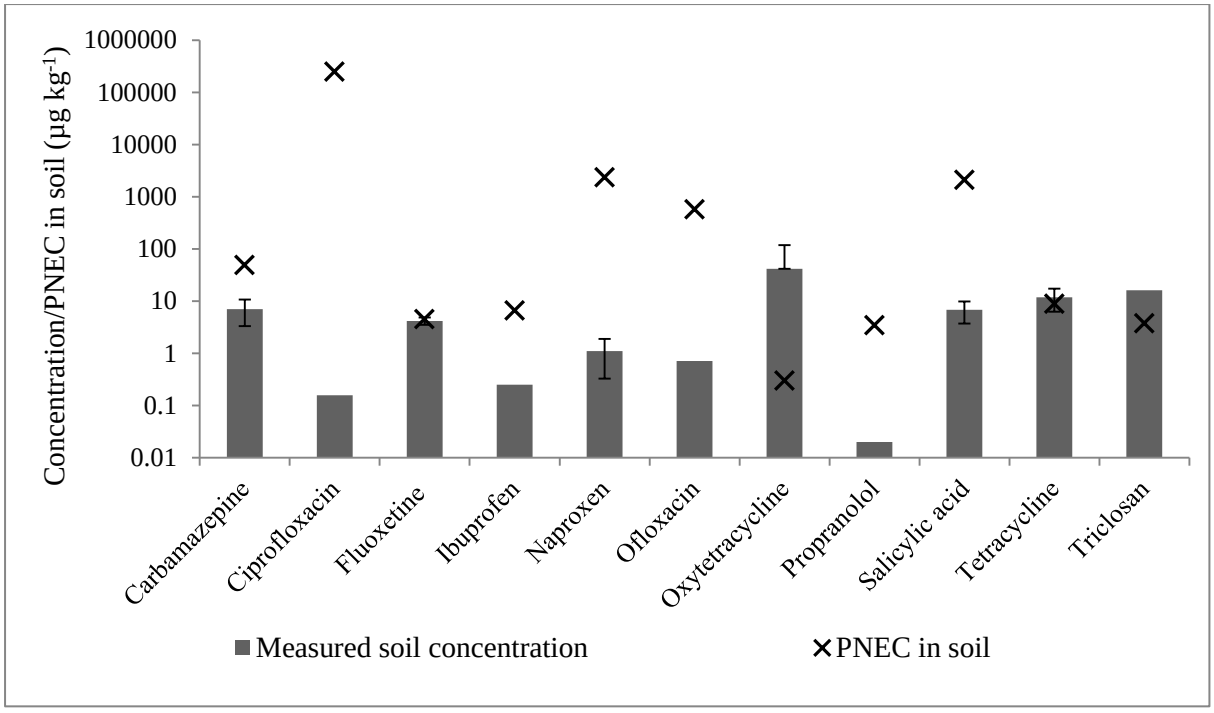


Fig. 8. Concentrations of selected APIs in global soils with the corresponding estimated PNEC in soil. Error bars represent ± standard deviation (n = 3-8). (AstraZeneca 2012; Chen et al. 2011; Durán-Alvarez et al. 2009; Gibson et al. 2010; Jones et al. 2002; Li et al. 2011; Martín et al. 2012; Oakes et al. 2010; Rutgersson et al. 2014; Vazquez-Roig et al. 2012; Wu et al. 2010; Zhao et al. 2010)

Estimates of annual API loading to soils from wastewater irrigation may be obtained by using representative irrigation rates and measured concentrations of APIs in irrigation waters from LLMIC. While this type of calculation has been performed for high income countries (Qin et al. 2015), it is rare for LLMIC because data on API concentrations in irrigation water are not readily measured and/or available. In principle, the resulting maximum concentrations in soils can then be calculated, assuming zero losses (i.e. from lateral run-off, loss to groundwater, biotransformation) and representative infiltration depths and soil densities. Table 2 shows results using this approach for soils in Tula Valley (Mexico), where extensive irrigation using untreated wastewater occurs (Gibson et al. 2010). The calculated maximum soil API concentrations for naproxen, diclofenac and carbamazepine are significantly lower (> order of magnitude) than the predicted no effect concentrations (PNEC) for soil of 2357 µg kg^{-1}, 735 µg kg^{-1} and 48.6 µg kg^{-1}, respectively (PNEC values are reported in Table S1). In contrast, the PNECs for ibuprofen and triclosan, of 3.0 µg kg^{-1} and 3.74 µg kg^{-1}, respectively, are within an order of magnitude of the calculated maximum soil concentrations. Coupled with data on sorption of APIs to soils and API persistence, this type

of analysis is essential for the estimation of predicted environmental concentrations (PECs) of APIs, which are central to the development of robust environmental risk assessments.

Table 2. API loads to soils in Tula Valley, Mexico, from untreated irrigation wastewater and estimated maximum soil concentrations (Gibson et al. 2010)

API	API concentration ($\mu g\ L^{-1}$)	Irrigation rate (L water $m^{-2}\ y^{-1}$)	API annual load (µg)	Infiltration depth (m)	Soil density ($kg\ m^{-3}$)	Soil mass (kg)	Max soil API concentration ($\mu g\ kg^{-1}$ DW[a])
Naproxen	7.3	300	2190	0.3	1500	450	0.114.87
Naproxen	13.6	300	4080	0.3	1500	450	9.07
Ibuprofen	0.74	300	222	0.3	1500	450	0.49
Ibuprofen	1.41	300	423	0.3	1500	450	0.94
Diclofenac	2.05	300	615	0.3	1500	450	1.37
Diclofenac	4.82	300	1446	0.3	1500	450	3.21
Carbamazepine	0.084	300	25.2	0.3	1500	450	0.06
Carbamazepine	0.24	300	72	0.3	1500	450	0.16
Triclosan	0.084	300	25.2	0.3	1500	450	0.06
Triclosan	1.03	300	309	0.3	1500	450	0.69

[a]DW – dry weight of soil

The toxicity of APIs to non-target organisms will depend on, *inter alia*, the speciation of the compound (i.e. the relative amounts of free and bound chemical and their lipophilicities). The amelioration of xenobiotic compound toxicity due to binding with polymeric aromatic humic and fulvic acids has been reported since the 1980s (Chiou et al. 1986, 1987; Oris et al. 1990; Day 1991; Haitzer et al. 1998). For example, fulvic and protein rich CDOM in wastewater effluent reduced endocrine disrupting chemical toxicity to biota; the most effective CDOM was in the < 0.2 µm size fraction, while CDOM in the < 5 kDa fraction did not reduce toxicity of the endocrine disrupting chemical (Lee et al. 2011). The influence of CDOM on the speciation, bioavailability and toxicity of metals in surface waters is now well established (Aiken et al. 2011). The resulting Biotic Ligand Model of CDOM–metal interactions represented a major advance in metal toxicity standards and is now enshrined in EU and USA environmental quality standards (Comber et al. 2008; Aiken et al. 2011). Similar toxicity amelioration experiments of wastewater CDOM or soil solids with APIs have not been reported (Qin et al. 2015). Following the experience with metals, this is

an area of study that clearly merits further effort from the scientific and regulatory communities.

In summary, there is a paucity of information on the potential ecotoxicological impacts of APIs in the terrestrial environments of LLMIC (Kookana et al. 2014). While knowledge transfer from high income countries to LLMICs of API soil biogeochemistry will prove of benefit in some instances, basic datasets on API loadings to the environment, coupled to more systematic measurements of free and bound APIs in soils and waters, are needed so that realistic PECs can be calculated and resultant exposures of biota to contaminant pharmaceuticals elucidated. The development of any subsequent risk assessments, equivalent to the Phase II effects testing of EMEA (2006), should use appropriate test organisms.

3. Conclusions

Water scarcity in LLMICs and the increasing use of APIs globally has led to concerns about the input of APIs and other down the drain chemicals to soils during irrigation with wastewater, a concern that has now been recognised by the International Conference on Chemical Management. Wastewater reuse for irrigation is currently not included in terrestrial environmental risk assessments of APIs and terrestrial assessments are only conducted for APIs with a Log K_{OC} >4, in Europe or elsewhere. For the development of API risk assessment-type frameworks within LLMIC there remains much to do. The datasets missing include accurate API usage in LLMICs, estimates of point and diffuse sources of APIs, (including removal efficiencies during effluent processing in sewage treatment plants, where this occurs), to soils and waters, sludge and irrigation water application rates to land, and the speciation and partitioning of the APIs in those compartments. Soil physico-chemical factors and the chemical structure and behaviour of APIs will influence their fate in soil. A wide range of soil conditions exist in LLMIC globally, making the development of predictive models of soil behaviour, distributions and fate of APIs a challenge. For more extensive assessments of API behaviour and effects, where required, within an environmental risk assessment framework, it is a prerequisite that methods are appropriate. For example, while OECD methods 106 and 307 for determining the fate of ionisable chemicals in soils largely cover the range of soil properties (pH, clay content, soil organic matter concentration) to be found in LLMIC, care must be taken in the selection of soils used for testing to ensure that they are representative for the region of interest.

The development of environmental risk assessments is a resource intensive process. However, without robust monitoring in combination with mechanistic fate data for the partitioning and degradation of APIs in soils of LLMIC countries, it is not possible to address the risk of APIs in the environment. The limited data available for APIs in soil identified here, suggests that within LLMIC, regulators, the wastewater treatment industry, the relevant pharmaceutical sectors, and other stakeholders should co-operate in the development of ERAs in the most cost-effective way.

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Supplementary information

Pharmaceutical contamination of soils in areas with high wastewater reuse

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Table S1. API risk assessment data

API	**Treatment Area**	**% dose excreted**	**Aquatic PEC ($\mu g\ L^{-1}$)**	**Aquatic PNEC ($\mu g\ L^{-1}$)**	**Aquatic PEC/ PNEC**	**Soil PNEC[b] ($\mu g\ kg^{-1}$)**	**pKa**	**Log K_{oc} ($L\ kg^{-1}$)**	**Log K_{ow}**	**K_d soil[b] ($L\ kg^{-1}$)**	**K_d sewage sludge[b] ($L\ kg^{-1}$)**	**Water solubility ($g\ L^{-1}$)**
Atenolol	Cardiovascular		0.68	148	0.0046	1306	9.6	2.6	0.015	7.96	2.95	26.5
Carbamazepine	Neuroscience	1-2[c]	1.23[d]	6.36[d]	0.19[d]	48.6	7[e]	2.56	2.45[i]	5.64	2.09	0.112[i]
Ciprofloxacin	Infection	84[c]	0.035[g]	991[g]	0.0035	248915	6.09[g]	3.1[h]	0.28[i]	427[h]	417[h]	30[i]
Diclofenac	Neuroscience	15[c]	0.8[d]	138.74[d]	0.0058[d]	735	4.15[j]	2.39[k]	4.51[i]	9[k]	105[k]	0.0024[i]
Fluoxetine	Neuroscience	3-11[c]	0.052[l]	0.012[l]	4.3[l]	1.8-4.5	10.06[l]	4.1-4.5[l]	4.26[l]	251.79-632.46	4658-11700	60.3[l]
Ibuprofen	Neuroscience	1-8[c]	4.96[d]	9.06[d]	0.55[d]	3.0	4.91[e]	2.01-2.11[m]	3.97[i]	0.56-3.71[m]	37.86-47.67	0.021[i]
Naproxen	Neuroscience	0-10[n]		21.2[o]		2357	4.2[d]	2.48[k]	3.18[i]	11[k]	36[k]	0.016[i]
Norfloxacin	Infection	50-68[p]	0.24[q]	40[q]	0.006	47-12611	6.30, 8.38[p]	4.8-5.5[p]	-1.03[q]	2-536[r]	23345.42 - 117004.3	0.35[p]
Ofloxacin	Infection		0.05[g]	3.13[g]	0.02	569	6.05, 8.51[g]	4.6[h]	-0.39[i]	309[h]	1.7[h]	28.26[i]
Oxytetracycline	Infection		0.83[d]	0.23[d]	3.6[d]	0.3	3.3, 9.1[j]	1.99[d]	-0.9[i]	1.95	36.16	0.313[i]
Propranolol	Cardiovascular	17	0.044	0.1	0.44	3.4	9.53	3.21[k]	-0.12-2.6	58[k]	600.07	97.9
Salicylic acid	Dermis		1.04[q]	43.1[o]	0.02	2079		3.35[k]	2.26	82[k]	23[k]	2.24[i]
Sulfamethoxazole	Infection	15[c]	0.016[g]	0.21[g]	0.08	0.99	6[g]	2.34[k]	0.89[i]	8[k]	11[k]	0.61[i]
Triclosan	Infection			0.05[r]		3.74	7.8[e]	3.54[k]	4.8[e]	127[k]	1283[k]	0.005[i]

[a] Data with no citation are from AstraZeneca Environmental Risk Assessment Data (AstraZeneca 2012). [b] Soil PNEC, K_d soil and K_d sewage sludge were predicted using the TGD method unless stated otherwise (ECB 2002). [c] (Jjemba 2006). [d] (Jones et al. 2002). [e] (Azzouz and Ballesteros 2012). [f] (Vazquez-Roig et al. 2012). [g] (NCCOS 2006). [h] (Thiele-Bruhn 2003).[i] (Chen et al. 2011). [j] (Berthod et al. 2014). [k] (Barron et al. 2009). [l] (Oakes et al. 2010). [m] (Xu et al. 2009). [n] (Carballa et al. 2008). [o] (Martín et al. 2012). [p] (Peruchi et al. 2015). [q] (Perazzolo et al. 2010). [r] (Chen and Zhou 2014).

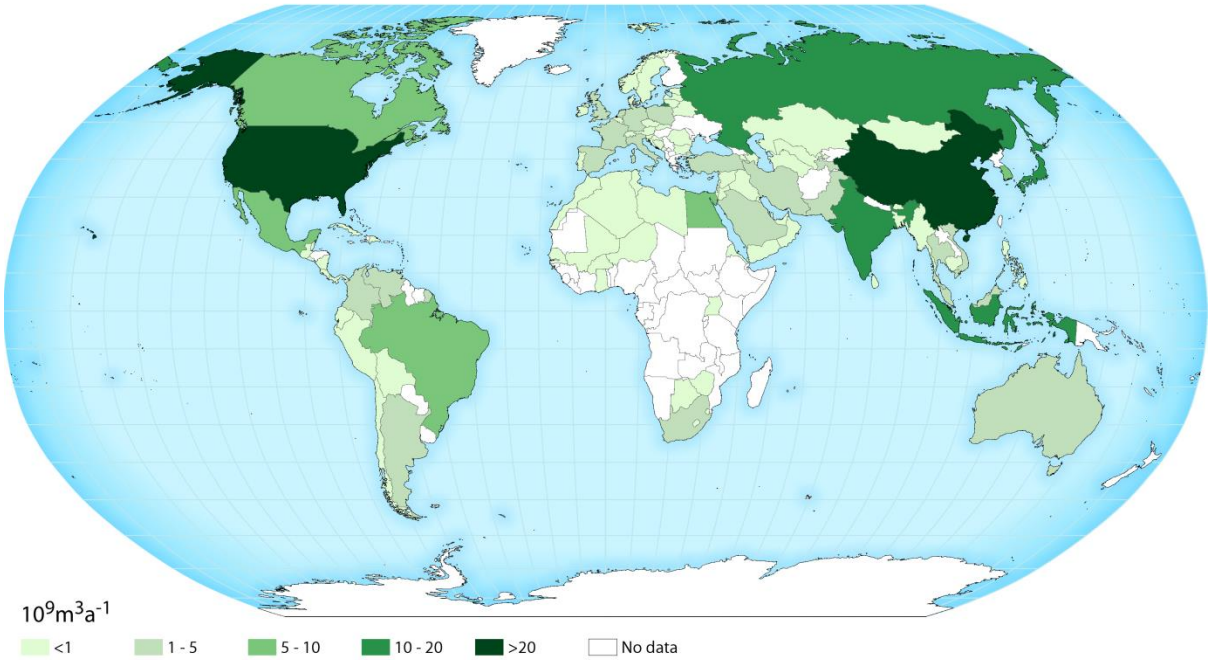

Figure S1. Municipal wastewater production (10^9 m^3a^{-1}) (FAO/IIASA/ISRIC/ISS-CAS/JRC 2009)

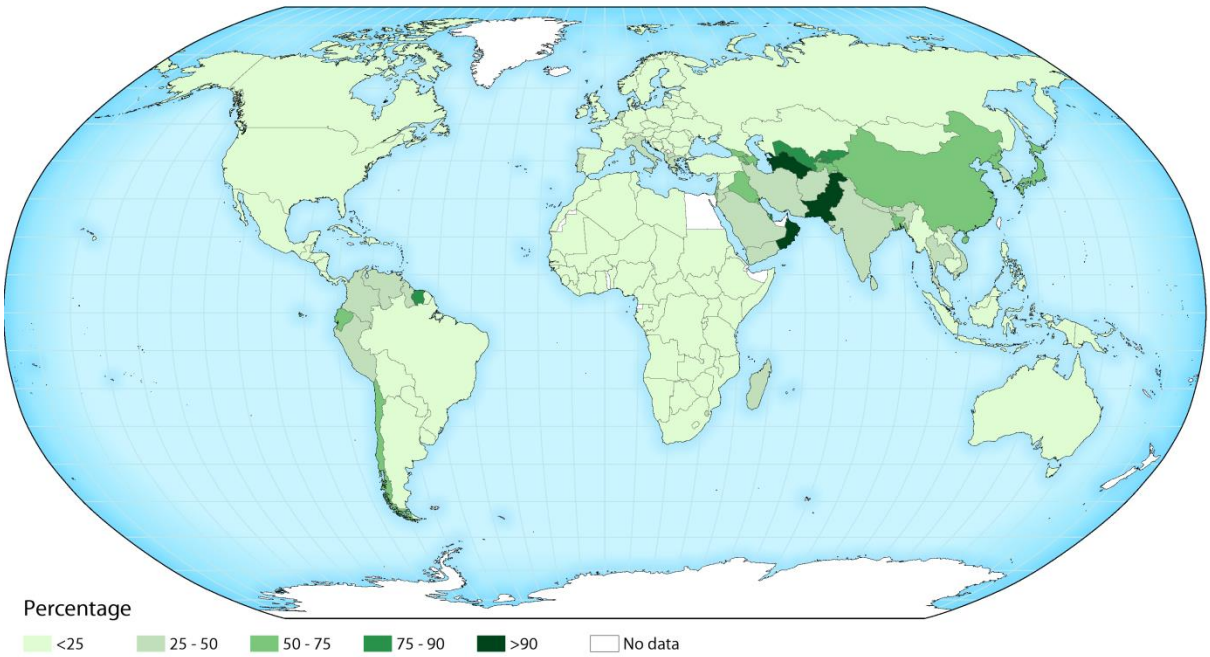

Figure S2. Water withdrawal by agriculture relative to other economic sectors (%) (FAO/IIASA/ISRIC/ISS-CAS/JRC 2009)

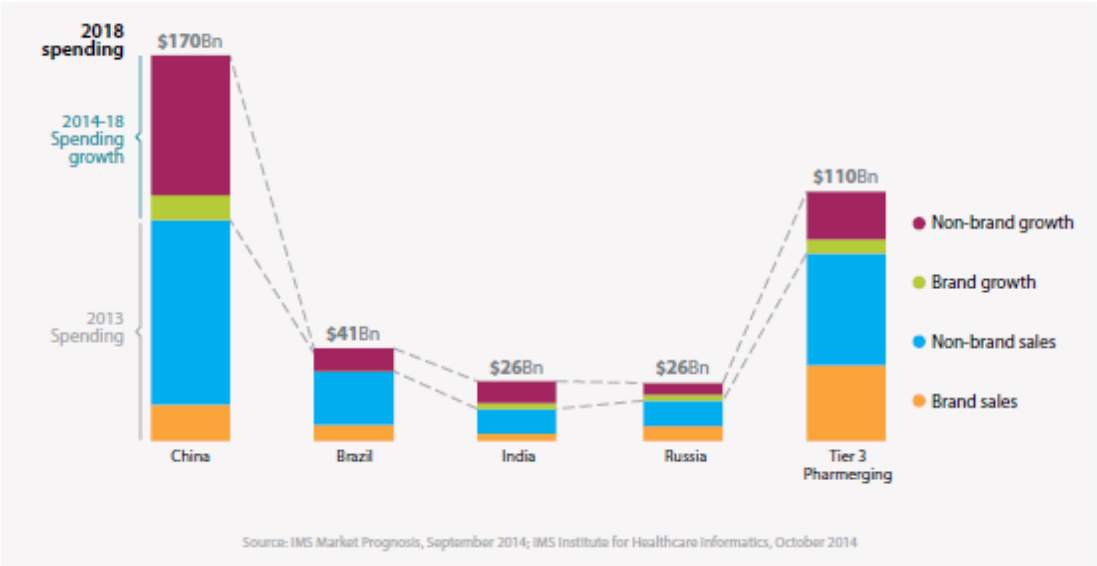

Figure S3. Spending (Billion US dollars) on human medicines in pharmerging countries to 2018. Tier 3 countries include Algeria, Argentina, Colombia, Egypt, Indonesia, Mexico, Nigeria, Pakistan, Poland, Romania, Saudi Arabia, South Africa, Thailand, Turkey, Ukraine, Venezuela, Vietnam (IMS Institute for Healthcare Informatics 2014).

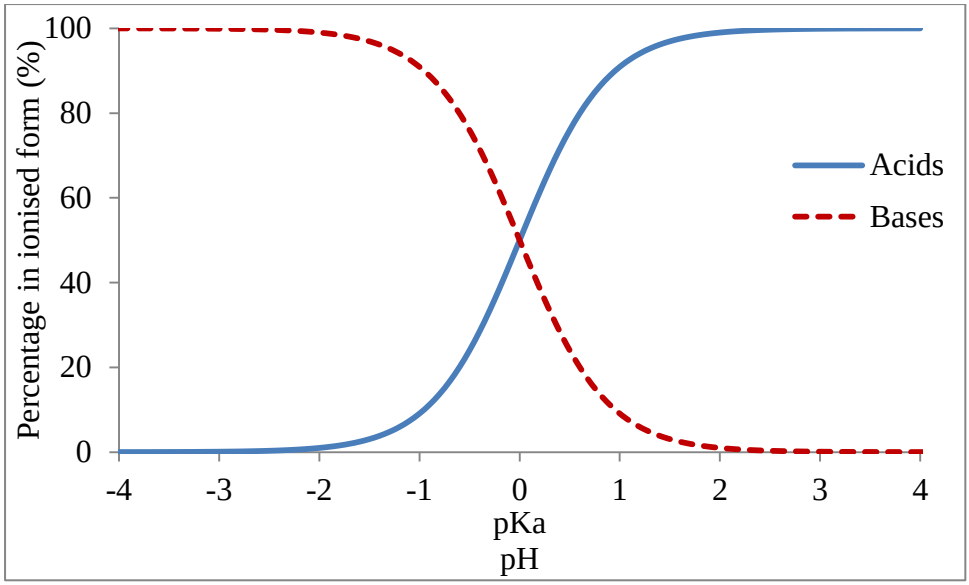

Figure S4. Percentage of acidic or basic API in ionised form as pH varies from less than 4 units to greater than 4 units from the compound pK_a (ECETOC 2013).

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