PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

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Review

Cite this article: Kookana RS *et al*. 2014 Potential ecological footprints of active pharmaceutical ingredients: an examination of risk factors in low-, middle- and high-income countries. *Phil. Trans. R. Soc. B* **369**: 20130586. http://dx.doi.org/10.1098/rstb.2013.0586

One contribution of 18 to a Theme Issue 'Assessing risks and impacts of pharmaceuticals in the environment on wildlife and ecosystems'.

Subject Areas:
environmental science

Keywords:
antibiotics, developing countries, ecological risks, wastewater, sewage

Author for correspondence:
Rai S. Kookana
e-mail: rai.kookana@csiro.au

Potential ecological footprints of active pharmaceutical ingredients: an examination of risk factors in low-, middle- and high-income countries

Rai S. Kookana[1], Mike Williams[1], Alistair B. A. Boxall[2], D. G. Joakim Larsson[3], Sally Gaw[4], Kyungho Choi[5], Hiroshi Yamamoto[6], Shashidhar Thatikonda[7], Yong-Guan Zhu[8] and Pedro Carriquiriborde[9]

[1]CSIRO, Private Mail Bag No 2, Glen Osmond, South Australia 5064, Australia
[2]Environment Department, University of York, Heslington, York YO10 5DD, UK
[3]Department of Infectious Diseases, Institute for Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[4]Department of Chemistry, University of Canterbury, Christchurch 8140, New Zealand
[5]School of Public Health, Seoul National University, Seoul, South Korea
[6]Faculty of Integrated Arts and Sciences, The University of Tokushima, Tokushima 770-8502, Japan
[7]Department of Civil Engineering, Indian Institute of Technology, Hyderabad, India
[8]General Institute of Urban Environment, Chinese Academy of Sciences, 1799 Jimei Road, Xiamen 361021, People's Republic of China
[9]Centro de Investigaciones del Medio Ambiente Facultad de Ciencias Exactas, Universidad Nacional de la Plata Calle, Buenos Aires, Argentina

Active pharmaceutical ingredients (APIs) can enter the natural environment during manufacture, use and/or disposal, and consequently public concern about their potential adverse impacts in the environment is growing. Despite the bulk of the human population living in Asia and Africa (mostly in low- or middle-income countries), limited work relating to research, development and regulations on APIs in the environment have so far been conducted in these regions. Also, the API manufacturing sector is gradually shifting to countries with lower production costs. This paper focuses mainly on APIs for human consumption and highlights key differences between the low-, middle- and high-income countries, covering factors such as population and demographics, manufacture, prescriptions, treatment, disposal and reuse of waste and wastewater. The striking differences in populations (both human and animal), urbanization, sewer connectivity and other factors have revealed that the environmental compartments receiving the bulk of API residues differ markedly between low- and high-income countries. High sewer connectivity in developed countries allows capture and treatment of the waste stream (point-source). However, in many low- or middle-income countries, sewerage connectivity is generally low and in some areas waste is collected predominantly in septic systems. Consequently, the diffuse-source impact, such as on groundwater from leaking septic systems or on land due to disposal of raw sewage or septage, may be of greater concern. A screening level assessment of potential burdens of APIs in urban and rural environments of countries representing low- and middle-income as well as high-income has been made. Implications for ecological risks of APIs used by humans in lower income countries are discussed.

1. Introduction

Public concerns about the potential adverse impact of active pharmaceutical ingredient (API) residues in the environment have increased during the past decade. In addition to sub-lethal effects, such as in the case of endocrine disruption in fish [1,2], direct toxic effects of APIs on exposed organisms, with

Electronic supplementary material is available at http://dx.doi.org/10.1098/rstb.2013.0586 or via http://rstb.royalsocietypublishing.org.

population level impacts, have been noted. Exposure to residues of the non-steroidal anti-inflammatory drug (NSAID) diclofenac in tissues of cattle in Asia resulted in massive declines (more than 95%) in the populations of some species of vultures in Asia [3]. As a result, diclofenac was withdrawn from veterinary use in India [4,5]. The 'Asian vulture crisis', provides an example of an unexpected acute exposure route that highlighted the potential ecological impact of these biologically active compounds. Another area of concern relates to ecological risks associated with environmental contamination by antibiotics, with potential for direct toxicity to aquatic microorganisms and indirect impacts through proliferation of antibiotic resistance [6]. Despite these examples, there has been a notable lack of studies that demonstrate effects of APIs based on ecologically relevant assessments, with respect to appropriate exposure concentrations and duration, ecotoxicological endpoints and implications of mixture effects [7,8]. However, where ecologically appropriate exposures were used, APIs have been demonstrated to cause effects in organisms, such as behaviour and reproduction, which may have broader ecological consequences [7,9–14].

APIs used to treat diseases in humans (and animals) can enter the natural environment during the manufacturing process [15] or, following therapeutic use, via some form of wastewater collection and treatment system [16]. The excretion or application of animal manures to agricultural land or waterways occur following veterinary/aquaculture use [17,18]. Generally, wastewater undergoes some level of treatment which can be variably effective in removing APIs. However, discharges of high concentrations of APIs in the environment may occur due to lack or inefficiency of treatment facilities or inappropriate disposal practices. A range of APIs have been detected in different environmental compartments over the years [19–22]. Some of these compounds (e.g. carbamazepine, fluoxetine, fluroquinolones and tetracycline antibiotics) may persist in the environment [23]. Consequently, increasing attention is being placed globally on the impacts of APIs that are present in the environment.

Despite the fact that a vast majority of the human population live in Asia and Africa, the majority of research (≈75%) and most of the regulatory developments on APIs in the environment have focused on the North American and European situations [20]. A significant amount of work has also been done in some Asian countries (e.g. China, Japan and South Korea). However, much less information is available for other regions of the world such as Oceania, Africa, South America and parts of Asia. In addition to the huge population pressure in these regions, there has been a gradual shift in the global API manufacturing sector over recent years due to outsourcing of drug manufacturing to lower income countries [24].

A number of factors will determine the environmental exposure of an API including: (i) population and demographics, (ii) access to health systems, (iii) size and nature of the manufacturing sector, (iv) connectivity to sewerage and sewage treatment systems, (v) ecology of the receiving environment and (vi) the availability and effectiveness of regulatory frameworks. These factors are likely to differ between high- and lower income economies, and consequently as are the environmental risks of APIs.

In this paper, we examine the key differences between some of the above risk factors relating to environmental exposure in low-, middle- (e.g. in Asia, South America) and high-income countries (e.g. from Australasia, North America and Europe). We initially consider differences in factors driving the use of APIs and their release into the environment, then move on to discuss differences in pathways into the environment and the evidence for environmental contamination by APIs in lower income countries. Finally, we make a relative assessment of the likely differences in factors among selected low-, middle- and high-income countries contributing to the environmental risk of APIs. As published data relating to the presence of APIs in the aquatic environment have been dominated by research from Europe and North America [8,20,25], this paper focuses on low- and middle-income countries as a means of comparing and contrasting with high-income countries, the factors which can influence the level of API residues in the environment. We provide selected examples of sources and pathways of exposure and effects of human APIs on ecosystem health to illustrate the most important differences between low- and high-income nations.

2. Key contributing factors to ecological risks associated with active pharmaceutical ingredients in lower income countries

(a) Population and demographics

One of the key factors governing the total demand for APIs is the size of the human population of a country and the accessibility to healthcare. Some of the world's most populous countries are located in growing economies in the continents of Asia, Africa and South America (electronic supplementary material, table S1). Here, the contrast is the greatest between low- to middle- and high-income nations. Nearly 78% of the total global population is located in Asia and Africa, whereas only about 16% is present in Europe and North America. Indeed, nearly 40% of the global population lives in three Asian countries, namely China, India and Indonesia (electronic supplementary material, table S1).

On the basis of concentration of human population, one would assume that the overall demand for APIs would be higher in Asia and consequently expect a greater environmental risk from a greater presence of APIs. The population pressure (or lack of it) does not, however, directly translate into environmental impact as there are other factors that can moderate it. For example, the population density of Australia is low but most of the population is congregated in cities, leading to the concentration of waste streams. Similarly, 13 of the 100 most populated urban agglomerations in the world are located in South America (eight in Brazil) with more than 3.5 million people in each of these. The degree of urbanization (electronic supplementary material, table S1) may be a good indicator of areas where discharge of APIs to the environment is likely to be concentrated.

Age demographic is an important factor in determining demand for pharmaceuticals. While the *per capita* demand for medication increases with increasing age, the overall use of APIs is a complex phenomenon. Not only the amount but also the combination of particular pharmaceuticals that are used are expected to be different for the ageing population than that for a younger population. While only 7.1% of the total population in Asia is currently more than 65 years old, the proportion of this group is 13.4% in North America and more than double in Europe (16.4%). Most

high-income countries, with the notable exception of the USA (where growth is largely due to immigration), have sub-replacement growth rates (electronic supplementary material, table S1). By contrast, the populations in lower income economies are growing relatively rapidly. The population growth rate during the past decade has been highest in Africa followed by Asia and Latin America [26]. The population pyramids of selected countries demonstrate the distribution of age groups in low- (Bangladesh), lower middle- (India), upper middle- (China) and high- (Australia, UK, USA) income countries (electronic supplementary material, figure S1). As the nature and extents of APIs used by young or ageing populations are different, so may be their potential ecological footprints.

(b) Factors influencing consumption patterns of active pharmaceutical ingredients

The ecological risk associated with an API is dependent on its consumption volume and pattern of use. Consumption patterns and overall use of APIs within a country are influenced by a range of country-specific factors, such as demographics, economics, disease burdens, government policies and cultural tendencies. It is important to note that a greater extent of resources available in high-income nations allows better monitoring and regulation of API use, compared with low-income nations.

There is no single method that allows an unbiased assessment of the use of APIs in different nations, let alone the use of APIs that are used illegally. However, a number of ways of estimating consumption of APIs within a country has been attempted. These include marketing data, surveys of APIs dispensations, wastewater data [27], as well as estimation of total volume available of an API (i.e. sum of manufactured and imported APIs, minus exported APIs). Regional API consumption has been estimated by monitoring concentrations of APIs in sewerage systems and 'back-calculating' to get a figure relating to the average consumption in the area serviced by the sewerage network. This approach has been applied for estimating the usage of illicit drugs [28,29], for example. However, this approach would become less viable in areas where connectivity to sewers is low, which is often the case in low-income countries (electronic supplementary material, table S1). The other approaches to estimating API consumption also have their own advantages and disadvantages [27], with some able to provide a better estimation than others. For example, while data relating to the sales of APIs in monetary terms are readily available, this type of information is highly dependent on a number of variables and is therefore not easily translatable into the mass of APIs consumed.

Prescription numbers can provide a useful measure, especially when the amount of API within a prescription is known. Total volumes sold within a country can similarly be converted into number of doses consumed within a country. The use of the defined daily dose (DDD) or DDD *per capita* concept, used by the World Health Organization (WHO), allows a comparative measure that takes into account the different potency of drugs (in humans) and of drug consumption between population groups. One downfall of estimating inputs into the environment based on volumes consumed within a country is that adherence to API therapy, especially for long-term treatment, is around 50% in high-income countries and even less in lower income economies [30]. Although this measure may therefore represent an overestimation of API use, many of these unused APIs can still be disposed of in a way that will ultimately lead to environmental contamination [31].

(i) Differences in disease burdens

It is generally accepted that as a country's population ages, the demand for APIs increases [32]. Higher levels of urbanization are associated with changes in lifestyle, along with a higher *per capita* income, which is an important factor in the access to and use of APIs. Increased affluence, through urbanization and wealth, also influences the pattern of disease burden with a subsequent occurrence of chronic or non-communicable diseases comprising a higher burden, relative to acute or infectious diseases, in higher income countries [32]. Some chronic diseases such as diabetes are becoming prevalent in a number of lower income countries [32] and APIs will become an increasingly important mitigating factor in reducing the disease burden. For example, more than 80% of mortality worldwide attributable to diabetes occurs in low- and middle-income countries [33]. According to projections by WHO, the number of deaths due to diabetes will double between 2005 and 2030. Mass drug administration (MDA) programmes which target whole communities are being used to target neglected tropical diseases such as lymphatic filiariasis and leprosy. These MDA programmes are occurring in Asian, African, Latin American and Pacific nations [34] and may result in increasing seasonal discharges of APIs to the environment [35], resulting in greater exposure and impact during such campaigns.

(ii) Healthcare policy

Healthcare policy, both internationally and nationally, is also an important factor in preferential use of APIs. An essential medicines list (EML) is published biennially by the WHO, which includes APIs that are determined to be the minimum number required for basic healthcare needs within a country. The selection of APIs is based on their efficacy, safety and cost-effectiveness in treating priority conditions. Individual countries also publish their own EML, which often includes additional APIs from the WHO EML. Non-steroidal and non-opioid analgesics, for example, that are listed in the WHO EML include acetylsalicylic acid, ibuprofen and paracetamol, while the majority of the 100 countries with published EMLs had at least six APIs listed under this category, commonly including diclofenac and indomethacin [36]. This is reflected in the relatively high proportion of diclofenac use in a number of countries, within the class of NSAIDs (figure 1). Inclusion on the EML, however, does not always reflect use of an API, as some NSAIDs such as mefenamic acid have been found to be used in a greater proportion in countries such as Indonesia and Pakistan (figure 1). The above adds to the complexity involved in establishing regional trends in API consumption.

(iii) Economic cost of active pharmaceutical ingredients

Cost may carry a disproportionate weighting in the selection and use of APIs. Global health expenditure and API use is highly inequitable, with more than 80% of global expenditure on APIs occurring in high-income countries which represent 18% of the global population. The median *per capita* consumption of APIs in 2008 was 1042 standard units of API in

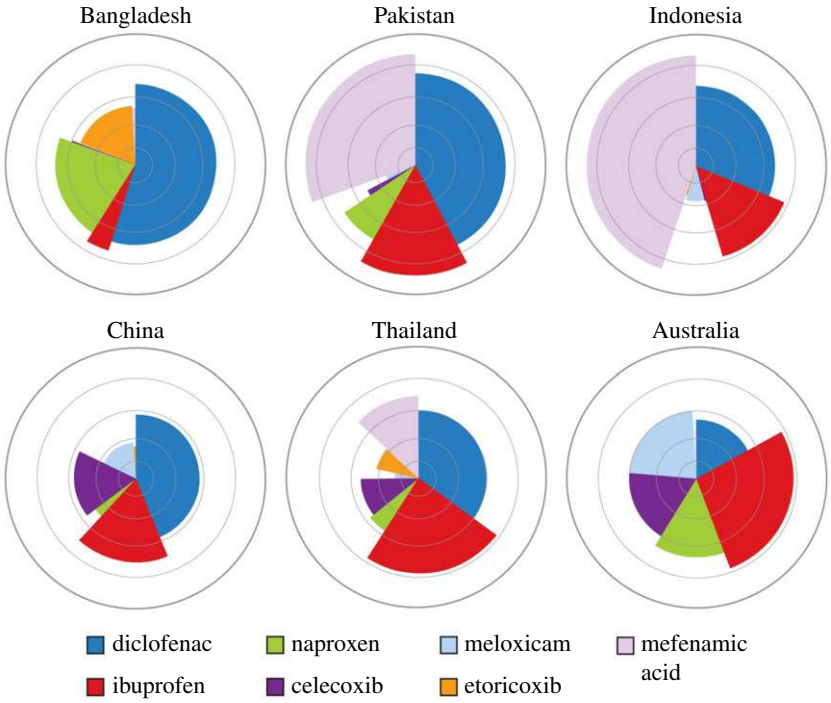

Figure 1. The relative proportion and volumes of seven common NSAIDs in some Asian countries and Australia. Note: Each ring represents a logarithmic increase, with the innermost ring representing 0.1 tonnes and the outermost ring representing 1000 tonnes. (Adapted from McGettigan & Henry [36].)

high-income countries compared with 135–214 standard units (a standardized measure of volume that can be converted to a DDD) of API in low- and lower/middle-income countries [32]. Out-of-pocket expenses paid by patients in high-income countries are less than 10% in European countries such as France, the Netherlands and the UK [32]. Conversely, out-of-pocket expenses in India range from 83% in rural areas to 77% in urban areas, and 98% of API consumption in Pakistan is covered by individuals [32]. Many other local factors, such as procurement and distribution practices and cultural preferences, will also influence API consumption [32]. In the case of NSAIDs, for example, the median supply price of diclofenac is as low as $US 0.0055 per tablet compared with $US 0.033 per tablet for mefenamic acid [37] which is not reflected in their proportionate use in Pakistan and Indonesia, in particular (figure 1). Indeed, in Indonesia, phenylbutazone, mefenamic acid and piroxicam make up nearly 72% of total NSAID use [36], which all have higher median supply prices compared with diclofenac and ibuprofen [37].

(iv) Self-medication and over-prescription

In many lower income countries most APIs can be purchased without a prescription (so-called 'self-medication'). WHO defines 'self-medication' as the selection and use of APIs by individuals to treat self-recognized illnesses or symptoms [38]. This is a common practice in many lower income nations in Asia, Africa and Latin America, and has been a cause of concern for WHO for a number of reasons including irrational use of antibiotics leading to development of resistance, iatrogenic effects, allergic reactions and poisoning [39]. For example, a survey of API dispensation patterns in three community pharmacies of South India over a two-month period revealed that the 'Schedule H Drugs' (APIs requiring a prescription) were extensively dispensed by these pharmacies without a valid prescription [40]. However, the extent of this practice was highly variable among the surveyed pharmacies (electronic supplementary material, table S2). In addition to self-medication, over-prescription or prescription on perceived patient demand is a problem in lower income countries [41]. A doctor's prescribing decisions may be influenced by other factors including vested interests (links to pharmacy, brand or manufacturing units) and any incentives offered by the pharmaceutical industry [41]. This, however, may not be a problem confined to lower income countries only.

(v) Veterinary use of antibiotics and other active pharmaceutical ingredients

Although the focus of this paper is on human APIs, the veterinary use of APIs is worth noting as there is often an overlap between the two. In lower income countries, and especially those located in Asia, substantial amounts of veterinary antibiotics are used, especially in animal husbandry and aquaculture industries [42,43]. The total number and densities of livestock in some Asian countries, such as China and India, can be very high [44,45]. According to the United Nations Food and Agriculture Organization (FAO), some 90% of the total global aquaculture production comes from Asia, with the majority of this occurring in China [45]. Alongside the comparatively large aquaculture industry in East Asia, a much broader range of APIs, including antimicrobials and parasiticides, have been reported to be used there within the industry [42,43]. The potential risks associated with the use of antibiotics in aquaculture for water quality, as well as the development of microbial resistance, has received considerable attention in recent years (e.g. [18,43,46]).

(vi) Consumption rates of active pharmaceutical ingredients

With respect to total NSAID use, a recent survey in a number of Asia-Pacific countries [36] indicates that the usage patterns (in terms of DDDs/1000/day) in low- or middle-income countries are generally similar to those in high-income

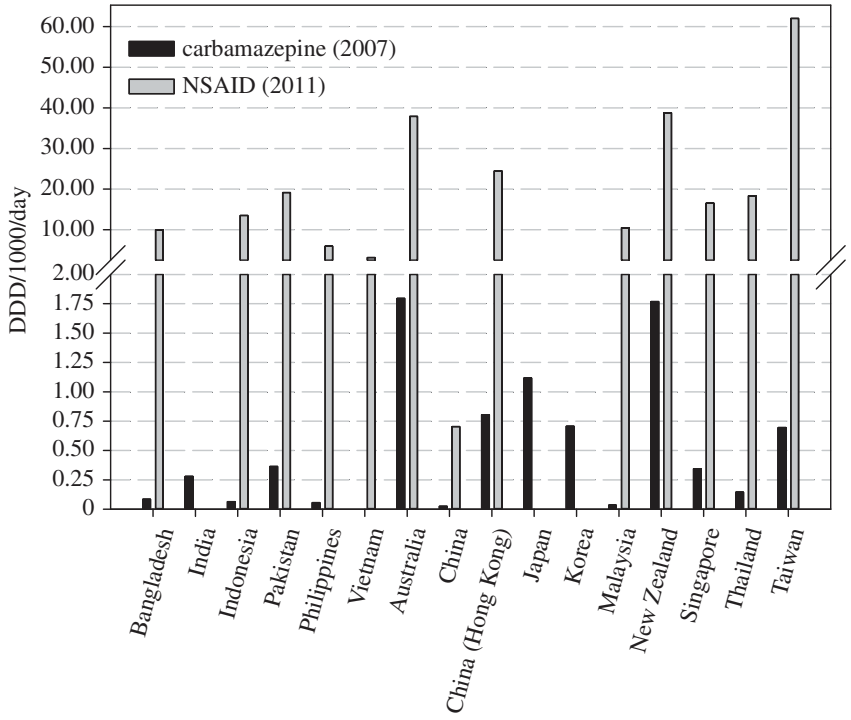

Figure 2. Usage rates of carbamazepine and NSAIDs (total) in a number of Asian and Australasian countries. (No NSAID data are available for India, Japan and Korea.) Lower income countries are represented by Bangladesh to Vietnam and higher income countries by Australia and Taiwan (based on World Bank classification). (Adapted from Zhang & Geißen [47] and World Bank [48].)

countries (figure 2). Comparatively higher use rates are noted for countries such as Australia, New Zealand, China (Hong Kong) and Taiwan. Lower use rates were noted for mainland China, whereas no data were available for India, Japan and Korea. A similar survey conducted in 2007 assessing the usage rates of the antiepileptic carbamazepine [47], shows a greater gap in the prevalence of use in low- and high-income countries, where a substantially greater usage rate is evident in Australia, China (Hong Kong), Japan, Korea, New Zealand and Taiwan (figure 2).

Overuse or other misuses of antibiotics is a global concern due to the potential for increasing antibiotic resistance [32]. A survey on use of antibiotics in Delhi involving 33 000 patients over a 1-year period in 2008 [49], when compared with the national-level statistics on dispensed API consumption in Australia in that year [50], indicated that a number of similarities may exist between lower middle-income and high-income countries (electronic supplementary material, table S3). The comparison revealed that despite significant differences between usage rates of some antibiotics, the overall usage rates in Delhi and Australia were similar, with 16.5 and 17.5 DDD/1000/day consumed, respectively (electronic supplementary material, table S3). Similarly, in non-hospitalized Swedish patients, the use of antibiotics in 2008 totalled 13.53 DDD/1000/day [51]. Caution should be exercised in making a direct comparison between countries, as the Swedish data include all antibiotics used, whereas the Australian and New Delhi data do not. Besides the Delhi survey is unlikely to be representative of Indian rural population. When the usage rate of APIs is converted into total volume consumed within a country [52], however, the trends observed with usage patterns are often reversed (figure 2). For example, although the usage rates (DDD/1000/day) of diclofenac in Australia, Bangladesh and Pakistan are similar, the number of tonnes of diclofenac consumed in Bangladesh and Pakistan in 2011 were five and 10 times greater than in Australia, respectively (electronic supplementary material, table S4). Constructing a clear picture of trends in API utilization in lower income nations, however, is considerably more challenging [27]. The same is true for those high-income countries where national-level statistics on dispensed APIs are not maintained.

(vii) Non-conventional active pharmaceutical ingredients: the contribution of complementary and alternative medicines

Populations in the Asia region are much more reliant on natural remedies than elsewhere in the world. Alternative therapies using herbal medicines, such as Chinese traditional medicines or Indian Ayurvedic medicines, are commonly practiced in Asia. According to WHO [53], 80% of the population may rely on complementary and alternative medicines (CAMs) for primary healthcare, while also becoming increasingly popular in high-income countries. The total sale of herbal medicine in China was equivalent to US$ 14 billion in 2005 and the revenue in Western Europe reached US$ 5 billion in 2003–2004. According to an estimate [54], annual sale of four key CAMs products in the UK was approximately £36 million per year with corresponding estimate of usage of the CAMs ranging from 3 to 32 tons per year (electronic supplementary material, table S5). The implications of CAM residues in the environment with respect to ecosystem health are currently not well understood.

(viii) Shifting global manufacturing base to Asia and other regions

Some lower income countries are manufacturing APIs for the international market. The manufacturing activities, including synthesis of APIs and formulation into doses, can create point-source problems related to APIs' residues through the industrial waste discharges, for example, to

the riverine environment [55,56]. The Asian API market is growing at 10–15%, which is double the rate of the G7 countries [24]. India's domestic API market is the 14th largest globally with an annual turnover of US$20 billion and about 80% of the APIs used in India are produced in the country [57]. According to an estimate, India supplies some 22% (in terms of sale value) of the world's generic APIs, while about 36% of the total global APIs are exported by China [58]. Indeed, there has been a gradual yet consistent shift in the global API manufacturing sector over recent years due to the expansion of low cost manufacturing in Asia. Contract manufacturing was worth US$22 billion in 2009 and is expected to grow at about 11–12% this year [59]. While the so-called BRIC countries (Brazil, Russia, India and China) are considered established contract manufacturers, countries such as Vietnam, South Korea and Bangladesh are rapidly emerging contract manufacturing destinations for American and European markets [59].

It is also a common practice to discharge untreated or poorly treated industrial wastewater into domestic wastewater channels in some Asian countries [60,61]. This is for at least two reasons, namely the lack of adequate treatment facilities and/or poor regulatory enforcement. Larsson *et al.* [62] and Fick *et al.* [55] published studies on wastewater quality from the Patancheru Industrial Estate in Hyderabad, India. This industrial estate has around 90 units manufacturing bulk APIs which collectively produce about 1.5 megalitres of wastewater daily. The treatment plant on the site mixes the effluent with domestic wastewater to enhance biodegradation. The water downstream of the treatment plants as well as lakes in the region were found to contain very high levels of API residues, in the order of $\mathrm{mg\,l^{-1}}$ [52], as opposed to $\mathrm{ng\,l^{-1}}$ levels commonly reported in Europe and North America. This is indicative of the inefficient wastewater treatment as well as unauthorized discharges [55]. Similar reports are available from other countries such as China [63], Taiwan [64] and Pakistan [55]. The presence of industrial wastewater in the sewage stream can be a significant contributor to the environmental load of APIs not only in lower income nations [60,62], but also globally [15,65]. A companion paper in this issue [15] discusses this aspect in the global context and demonstrates the point-source pollution implications of the API manufacturing sector.

(c) Exposure-related factors

From human therapeutic use alone, it would be expected that for many APIs the potential environmental loadings would be considerably greater in lower income countries based on the relatively large populations compared with high-income nations. The total volume of APIs entering the environment is not only dependent on the total volume used within a population but also the ratio of API that is consumed relative to total sales, pharmacokinetics, wastewater flows and treatment efficiency [47,66]. The absence of sewerage systems or rudimentary treatment technologies can significantly affect API exposure pathways. Where a high proportion of sewerage connectivity exists, the entry of APIs into the environment is principally a point-source issue, with discharge into surface waters. Other environmental compartments, such as groundwater and the terrestrial environment, may become proportionately more impacted in lower income nations where sewer connectivity is less common and reliance on septic systems or use of raw sewerage for irrigation and fertilization is greater.

(i) Urbanization and sewer connectivity

Despite major improvements in sanitation and the hygiene situation in lower income countries over two decades (especially in Eastern Asia), in 2011 there were still about 2.5 billion people that did not have access to improved sanitation facilities and close to 15% of the total population continued to defaecate in the open [67]. Improved sanitation facilities include flush/pour flush to piped sewer systems, septic tanks or pit latrines. As shown in the electronic supplementary material, table S1, many countries in Africa and Asia have half or more of their urban populations without access to improved sanitation. The pathways of release of excreta to the receiving environment (and, by inference, residues of APIs) are complex and unlike those from treated wastewater effluents in high-income nations.

One of the key factors that differentiates the growing economies from the high-income nations is the degree of urbanization and the extent of sewer connectivity. Urban population centres in high-income nations, being connected to the sewerage system, produce concentrated waste streams resulting in a point-source pollution problem. The opposite (diffuse-source) is usually the case in countries with predominantly rural populations and/or where sewer connectivity in urban areas is low. This has a major implication on the distribution and loadings of APIs in the environment. While the urbanization in lower income South American countries, namely Argentina and Brazil, is on par (85–90%) with high-income countries, the highly populated countries in Asia (Bangladesh, India, Pakistan and Vietnam) have a much smaller proportion of population (28–36%) living in urban centres (electronic supplementary material, table S1).

In terms of sewer connectivity, the contrast between the lower and high-income countries is again stark. Unlike high-income nations where more than 90% of the populations are connected with sewers (e.g. Australia, USA, UK, Japan and Korea), a much smaller fraction of the populations in lower income countries is connected to sewerage systems. In several lower income countries in Asia (e.g. Bangladesh, India, Pakistan and Thailand), even the urban population has less than 30% connectivity to sewers (electronic supplementary material, table S1). Indonesia and Vietnam have extremely low sewer connectivity of 2% and 4%, respectively, due to their reliance on septic systems. Some 60–90% of the urban population in Vietnam, Sri Lanka, Indonesia, Thailand and the Philippines rely on septic systems [68]. The sum of populations in these three countries (338 million) is equivalent to about 40% of the total European population. In South America, connectivity levels vary from high (more than 80%) in Chile and Peru, to intermediate (more than 40%) in Brazil, Argentina and Bolivia, and to low (less than 20%) in Paraguay and Guyana [69,70]. The low degree of sewer connectivity in lower income countries, therefore, makes a very different release scenario of APIs in these countries, in comparison with high-income nations.

(ii) Sewage treatment infrastructure and efficiency

Treatment of sewage or septage (waste stored in septic systems) from domestic sources or effluents from the API manufacturing industry may play a major role in determining the extent of environmental exposure to APIs, as some compounds can be

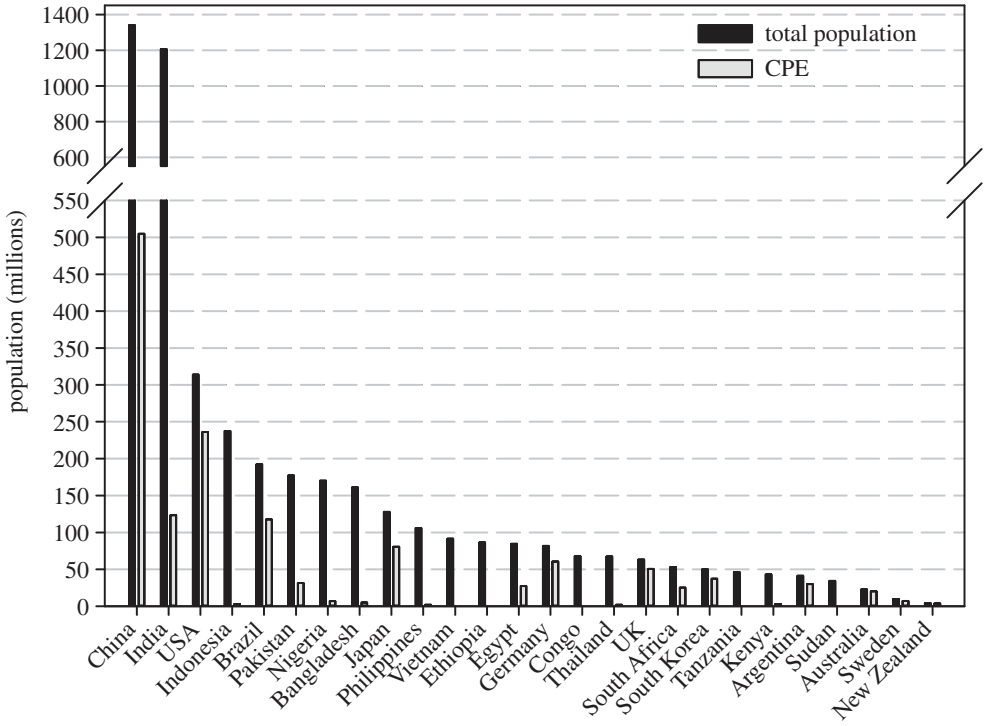

Figure 3. A comparison of total populations of selected countries with those that are likely to contribute to point-source discharge of APIs through sewage treatment plants. The CPE is calculated as a multiple of total population × urbanization × sewer connectivity. Note: Some countries such as Indonesia and Vietnam rely on septic-tank systems rather than sewerage systems. For data sources, please refer to table 1. (Adapted from [36,47].)

quite effectively removed during treatment. Rojas *et al.* [71] found that while some of the APIs (such as acetaminophen and caffeine) are very susceptible to removal during treatment (near 100%), others (e.g. carbamazepine and diclofenac) are generally poorly removed (less than 50%). In a recent study on six wastewater effluents of Argentina, where sewage treatment is poor or absent, the ratio of caffeine/carbamazepine was found to be more than 10 [72]. Treatment efficiencies of sewage treatment plants (STPs) depend on the treatment technology employed, the physico-chemical properties of the APIs and the prevailing operating conditions [67,69]. In a comparative study on removal efficiencies of APIs in STPs from Canada, Germany and Brazil, Ternes *et al.* [73] found that Brazilian STPs were more effective than the other two countries, probably because of the warmer conditions prevailing during treatment. While many of the lower income countries are located in the tropics, the STPs in these regions may not necessarily be more effective [58].

In lower income countries, the centralized treatment infrastructures found in Europe and North America may either be non-existent or ineffective. A study on water quality treatment efficiency of STPs in Delhi by Jamwal *et al.* [74] found that the effluent released from these STPs usually failed faecal coliform criteria. Furthermore, this study highlighted the fact that only about 50% of the total design capacity was used by the 17 surveyed STPs, which serviced around 11.7 million people. Irregular power supply was identified as one of the factors which may be a common problem in the countries with poor infrastructure investment in utilities. Similarly, for the septage collected from septic systems, only a small fraction of septage is currently treated (0–5%) [68]. The exceptions to this are Malaysia, where 100% of the septage is treated, and Thailand (30% treatment). In India, there is no treatment of the septage from more than 160 million onsite sanitation systems, which are mainly composed of septic systems [68].

(d) Populations contributing to the point-source pollution

In terms of point source of API residues in the environment, the average footprint of the urban population could perhaps be assessed on the basis of sewer connectivity. The contributing population equivalents (CPEs) to this source can be calculated as a multiple of three factors: i.e. population × urbanization fraction × sewer connectivity fraction (electronic supplementary material, table S1). These CPEs have been compared against their total population in figure 3. This demonstrates that many low- and middle-income countries, despite their huge populations, rank much lower than less populous high-income nations. For example, Indonesia, Vietnam, Nigeria and Bangladesh have very low CPEs, with only 1–4% of the total population contributing to point-source emissions. India has a much lower CPE than the USA due to the lower extent of urbanization and sewer connectivity, where only about 10% of the urban population contributes to the point source. In fact, with the exception of Argentina and Brazil, most of the lower income countries listed in the electronic supplementary material, table S1, have less than 10% of the total population contributing to the point-source problem. The lower income economies of Asia and Africa together have lesser total population contributing to the point-source footprint than the USA alone. This is because many countries in Asia (such as Indonesia, Vietnam and Thailand) and Africa (such as Nigeria, Ethiopia, Democratic Republic of Congo, Tanzania and Sudan) have less than 10% sewer connectivity for the urban population [67]. The estimated CPEs for point-source contribution of the top five populous countries of Africa (Nigeria, Ethiopia, Egypt, Democratic Republic of Congo and South Africa) are about the same as that of the UK alone. This factor has not been fully appreciated in the current literature, which has mainly focused on monitoring of APIs in treated effluents

and associated receiving environments. However, this does not mean the risk to the environment is lower in low- to middle-income nations, but the pathways of release or the receiving environments may be very different than those of high-income countries. This aspect is further discussed in §2e below.

(e) Receiving environments

(i) Surface water

Many lower income countries have major population centres, with a population of more than 750 000, in landlocked regions [75]. The two most populous countries in Asia, i.e. India and China, have the majority of their urban agglomerations in landlocked areas (electronic supplementary material, table S1). When treatment levels of sewage discharges are poor in these urban agglomerations then there is considerable pressure on freshwater systems. Even in the case where major population centres are located in coastal regions and dilution rates are considerable, residues of APIs such as antibiotics can still be measured in water at relatively high concentrations [46,76,77]. Also, while high dilution levels occur in marine and some freshwater systems, association of APIs with sediments can make a significant contribution to their overall environmental loading [78–81].

It is a common practice in many low- and middle-income countries to discharge untreated sewage to rivers and other water bodies, and to use these sewage-affected waters for irrigation. According to a study conducted in 71 Indian cities in 2009 [82], only 22% of the total 38 255 megalitres of sewage generated per day in these cities was treated and 78% of untreated sewage was disposed of in rivers, lakes and groundwater. Most of Delhi's 20 drains and effluent from 17 STPs is discharged into the Yamuna River and is used for irrigation downstream. With the exception of the monsoon season, the river essentially becomes a drain for treated and untreated wastewater. In Thailand, effluents from septic systems enter waterways via urban canals and it is estimated that 86% of sewage and 70% of septage are disposed of in waterways or on land [68]. In some countries, like Argentina, costal and riverside cities have good sewerage connectivity systems but sewage is released (mainly raw or poorly treated) through point sources into the surface receiving waters (i.e. Mar del Plata, Buenos Aires, Rosario). In Buenos Aires, only 14% of the total volume of effluent discharged into La Plata River estuary during 2011 was treated [83].

Discharge of raw sewage is not just a problem for low- and middle-income nations. Unintentional discharges of raw sewage may occur in high-income countries due either to the treatment system not being able to cope with the high flow of wastewater or floods (e.g. Australia and USA), or through damage to the infrastructure due to earthquakes (e.g. Japan and New Zealand). For example, in a recent study on antibiotic-resistant bacteria in the waterways of New York, Young *et al.* [84] found a strong link between the abundance of antibiotic-resistant bacteria and sewage-associated bacteria in Hudson River, indicating the presence of the untreated sewage. Combined sewer overflow can be a problem in any large cities with centralized sewage treatment and it is estimated that some 27 billion gallons of raw sewage and rainwater is discharged every year into the Hudson River.

(ii) Groundwater

In some lower income countries, which rely heavily on septic systems for sanitation, groundwater may be impacted by APIs. In many situations, septic systems have open or leaky bottoms and are only emptied sporadically. In Indonesia, as much as 70% of the country's groundwater contamination is caused by leaking septic tanks and disposal of septage [68]. Small inland cities in Argentina are dominated mainly by septic systems and cesspools mainly diffusely impacting chiefly on groundwaters. Even where septage from septic systems is collected, the question arises as to where the septage is disposed of and where the residues of APIs end up. According to a major study on several Asian countries [68], the management of septage or the sludge that has accumulated in septic systems is not a top priority for most countries. The study found that, in the absence of public services, septage is often collected once in 3–5 years and is disposed of in drains, waterways, open land and agricultural fields. Clearly, the groundwaters in countries depending on septic systems are likely to be at a greater risk of contamination with API residues than in those that are well connected to a sewerage system.

(iii) Land

It is estimated that about 20 million ha of agricultural land worldwide is irrigated with wastewater (treated and untreated) and it is common practice in low- to middle-income countries to use untreated or heavily polluted wastewater for irrigation [85]. In dry areas of South America, treated or poorly treated effluents are commonly used for irrigation; for example, primarily treated sewage effluents are used for irrigation in Mendoza City (Argentina) [86]. API-contaminated water used for irrigation has led to concerns related to uptake in plants and soil organisms [87,88], as well as potential for development and transfer of resistance genes in soil-based pathogens [89]. Septage collected from septic systems is often disposed of on open land or agricultural fields [68]. In squatter settlements that are inaccessible to vehicles, septage may be manually collected and disposed of close to habitations. The disposal of untreated septage is generally uncontrolled in many of these countries. Biosolids collected from STPs or animal manures are applied to land as fertilizers or soil amendments in some medium- and high-income nations (e.g. Australia, Japan and China). However, some other nations (e.g. Korea) do not allow biosolids or sewage sludge on food producing agricultural lands [90]. The impact of disposal of raw sewage on land has potential human and ecological health implications through contamination of food and groundwater.

3. Environmental monitoring of active pharmaceutical ingredients in lower income countries

(a) Environmental monitoring studies in Asia and South America

Comparatively few environmental surveys monitoring APIs in STPs and receiving waters have been undertaken in Asia-Pacific countries relative to North America and, in particular, Europe. A recent comprehensive review of 236 monitoring studies in peer-reviewed journals undertaken by Hughes *et al.* [20] highlighted this regional bias. For example, from a subset of 155 studies, 16% were based in Asia and, of these, the majority were based in the Guangdong province of China and mainly

included analysis of antibiotic residues [20,79,91]. A bias towards high-income countries was also noted in a review of anti-infectives by Segura *et al.* [6], which found that of 159 papers reviewed, only 16% represented low- to middle-income countries (which includes China). Along with this regional/economic bias, it was also noted that there was a distinct emphasis on monitoring APIs within the therapeutic categories of the cardiovascular system, anti-infectives (specifically antibiotics), nervous system (including antiepileptics and analgesics) and the musculoskeletal system (specifically NSAIDs) [20]. In the case of antiepileptics, this refers in particular to carbamazepine, which is the most commonly detected API in Europe and North America and among the most commonly represented API in the Asian region (figure 4). Indeed, Hughes *et al.* [20] noted that more than 50% of the studies they reviewed were represented by only 14 APIs. More recent studies published after this review [20] tend to highlight the focus on antibiotics within their monitoring programmes [18,79,91–97]. This is likely to be related to the perceived irrational use of antibiotics in many Asian countries [79,98]. A monitoring study on antibiotics in five tropical Asian countries (India, Indonesia, Vietnam, Malaysia and the Philippines) found concentrations of sulfamethoxazole that were considerably higher than those reported in Europe, USA, Australia and Canada [18]. The study estimated that some 12 tons of sulfamethoxazole was annually discharged from the Mekong River into the South China Sea. Indeed, similar masses of antibiotics were also estimated to be carried by a number of rivers in China, amounting to hundreds of tonnes of combined antibiotics likely to be discharged per year [77,99]. With a number of large river systems present in Asia, such as the Yellow River with a flow of around $200 \times 10^8\ m^3\ yr^{-1}$ considerations to both comparative concentrations and amounts are important in estimating potential risks.

The concentrations of the most frequently detected antibiotic and non-antibiotic APIs in China are similar to those in other Asian countries (e.g. Taiwan, Japan and South Korea), South America [100] as well as the rest of the world (figure 4) [20,79,91]. While non-antibiotic APIs are generally at $ng\ l^{-1}$ concentrations; salicylic acid, a metabolite of acetylsalicylic acid or aspirin, has been detected at a number of locations at low $\mu g\ l^{-1}$ concentrations in surface waters [79]. As both salicylic acid and acetylsalicylic acid are highly susceptible to removal (more than 90%) during wastewater treatment (especially during secondary and higher treatment) [101,102], their $\mu g\ l^{-1}$ concentrations in surface water may be indicative of either an extremely high level entering a STP or of a low efficiency of treatment [103]. In South America (Argentina and Brazil) also, APIs in surface waters are ubiquitous and residues have been detected in the range from below the limit of quantitation to about $10 \mu g\ l^{-1}$ depending on the compound and sewage treatment, sometimes several kilometres downstream of discharge points [94,97–100].

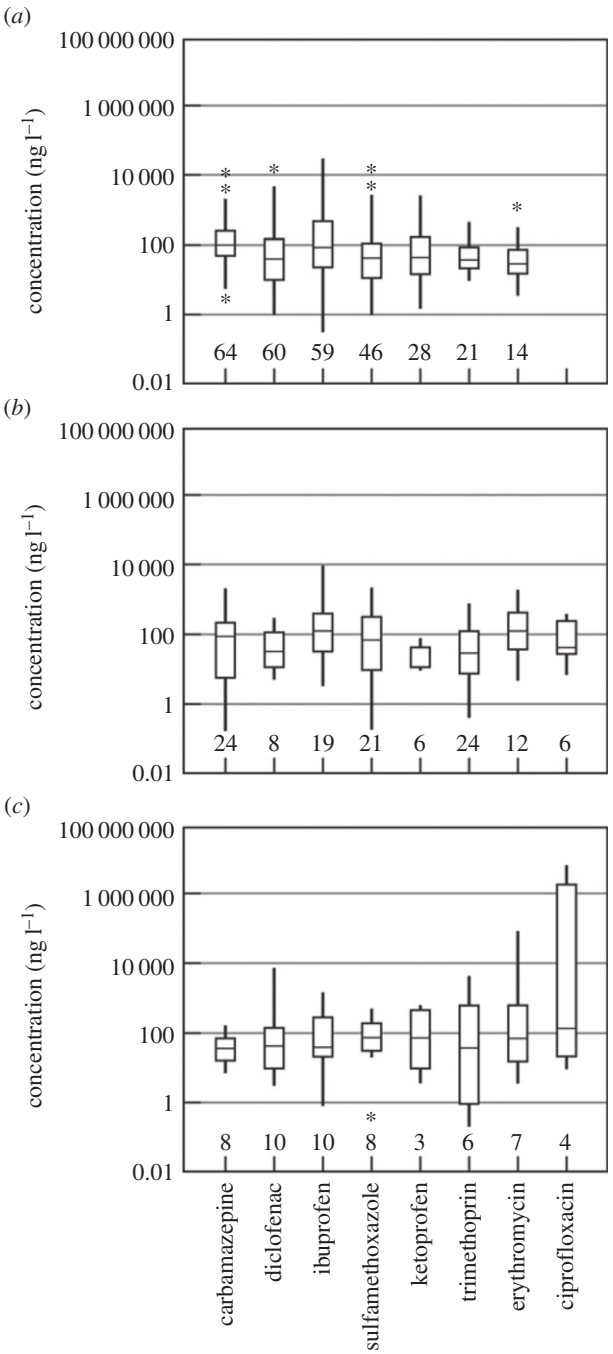

Figure 4. Box plots of monitoring data of selected APIs in the receiving environments (surface water) in Asia in comparison with Europe and North America; panel (*a*) represents European region, panel (*b*) represents North America and panel (*c*) represents Asia. The horizontal line represents the median value, box represents the interquartile range, whiskers show the data range and asterisk the outlier. The values on *x*-axes represent the number of records used. (Adapted from Hughes *et al.* [20] with permission from the American Chemical Society 2013.)

(b) Implications for understanding surface water concentrations of active pharmaceutical ingredients in Asia

The studies reviewed in §3a, especially those reporting very high concentrations in surface waters (e.g. [15]) raise two important points. First, the potential for inputs into surface waters from manufacturing sources may be disproportionately high relative to inputs from either human post-therapeutic use or from other sources, such as veterinary inputs. Second, based on the limited number of studies available, it is difficult to surmise whether such extreme levels are indicative of a general trend or not. This is highlighted by the notable bias in the relatively few published monitoring studies, where STPs servicing more densely populated areas were targeted. This bias is entirely understandable since researchers are usually attempting to identify whether APIs are also present in their particular region, where there may be limited or no precedent. Following well-developed sampling

protocols, through monitoring urban municipal wastewater discharges for a constrained set of target APIs, would therefore be more likely to reveal similar trends between high- and lower income countries. Indeed, the concentrations of the most commonly targeted APIs can be seen to be reasonably consistent when comparing between the European, North American and Asian regions (figure 4). The notable exception is ciprofloxacin, which is heavily skewed by Indian sites [20,62,104], although other manufacturing facilities in China, Taiwan and Pakistan have also contributed to concentrations of antibiotics, analgesics and NSAIDs being higher than expected [63,64,105]. With the recent proliferation of manufacturing activity occurring in countries with a lower quality of water treatment capacity, a greater number of broadly representative monitoring studies need to be undertaken to assess environmental concentrations of APIs in Asia. Representative monitoring would need to take into account spatial and temporal variations in concentrations of APIs, sources of inputs and a broader range of APIs [106]. This, however, remains a challenging goal, considering the number of years of research effort by relatively well-resourced European and North American laboratories to generate a reasonably limited representation of marketed APIs that are presently detectable in surface waters. Furthermore, the focus on monitoring concentrations of APIs in aquatic systems in both high- and lower income nations has resulted in a correspondingly low level of understanding relating to exposure to APIs in terrestrial ecosystems [7]. Where there has been an assessment of APIs in soils, the emphasis has been on antibiotics, particularly in sewage sludge [78,91], which can be used as fertilizer to an appreciable extent [107,108].

4. Implications for ecological risk of active pharmaceutical ingredients in lower income countries

The comparison of the limited published monitoring data currently available in lower income countries does not suggest a major difference in the average concentrations of human API residues. There are a number of points, however, that would suggest this may not be considering the broader picture of the comparative burden of discharged APIs in different countries. As was discussed in §3a, the studies targeting APIs in low-income countries have been relatively few in number and geographically constrained. Furthermore, the majority of these studies focused on 14 APIs, which is a substantial under-representation of marketed APIs [20]. This narrow focus would suggest that definitive evidence for comparative environmental loads of APIs and associated ecological risks, requires a considerably broader assessment of the presence of APIs, both in terms of the class of API and their loadings in geographical regions [106]. The identification of obvious differences in use patterns of some APIs (e.g. [36,47]) and environmental concentrations of APIs [62] highlights the need for a broader assessment to determine whether these are anomalies or part of a general trend.

(a) A qualitative assessment of ecological risks in lower income countries

An integrated assessment based on key factors discussed in this paper in §§2 and 3 has been summarized in table 1 as a means of estimating the potential extent of API inputs into the environment, and the implications for ecological risk, in a selection of low-, middle- and high-income countries. This table represents a qualitative assessment of a number of factors that are likely to contribute to the environmental input of APIs, irrespective of class of API, and includes factors that influence consumption rates, removal of APIs from wastewater streams post therapy and the general state of the environment into which APIs may be discharged. Each factor presented in table 1 may also take into consideration a number of other factors. For example, while sewage connectivity is important for general sanitation, it can also cause environmental inputs of APIs to shift from a diffuse-source to point-source situation. Where a point-source situation exists, a consistently high degree of treatment is necessary to mitigate entry of APIs into environments receiving discharges. While the issue of inputs of veterinary APIs was only briefly discussed, this is highlighted in table 1 as it is likely to represent an important input of APIs to rural environments, especially when urbanization can be 50% or less in many low- to middle-income countries (table 1).

In general, high-income countries were the only countries to have a low-risk rating, while China and India were considered to have the conditions that would constitute a high ecological risk from APIs. Because each factor was weighted evenly, however, there was no clear factor, such as income status or population size, that led to the overall risk level. In the case of Australia and New Zealand, a relatively small population in few urban centres, generally discharging highly centralized STPs into the marine environment meant an overall low-risk rating. This is despite an ageing population with high public expenditure on healthcare (electronic supplementary material, table S1). Although the income, age demographics and sewer connectivity of China and India differ, they both have high population pressures, a high proportion of these population centres based in landlocked regions, a large and rapidly expanding API manufacturing industry and a considerable terrestrial and aquatic livestock density.

It would be expected that a considerably greater degree of exposure risk exists where high connectivity to STPs with poor treatment levels leads to highly concentrated effluent streams entering aquatic ecosystems [55] (table 1). Other exposure pathways that have limited parallels in high-income countries also include APIs entering aquatic environments through diffuse sources of poorly treated wastewater or through direct application of untreated or poorly treated wastewater and sludges to terrestrial environments [68]. For example, a substantial proportion of untreated or poorly treated sewage is used for irrigation in the Indian subcontinent. In this region, a greater risk to terrestrial organisms may be expected [87]. The rapidly growing aquaculture and livestock industries of China and Southeast Asia (table 1), relying on the use of antibiotics and anti-infectives [43], is resulting in a greater exposure of aquatic and terrestrial organisms to antibiotics [18,46,81,97,119] with implications for the development of resistance to antibiotics [104]. Tropical regions of Southeast Asia (including Indonesia, Malaysia, the Philippines and Thailand), Africa and South America are recognized biodiversity hot-spots from species richness, threatened species or endemic species standpoints [120,121]. Some of these regions are also identified as having greater API footprints in the terrestrial and aquatic environment (table 1). There is a need for more research in these areas to

Table 1. Summary of the factors that contribute to the potential ecological risk of APIs to aquatic organisms leading to an overall risk rating for selected countries. Each factor summarizes identified pathways into the environment of APIs, such as use patterns, manufacturing activity, sewage systems, veterinary inputs and other environmental stressors, for each country. The relative risks are ranked on the basis of low, medium and high and summarized as an overall ecological risk rating of APIs due to expected exposure levels and the general state of the environment. (Caption overleaf.)

country	urban					rural					
	urban population (% total population) [75][a]	API consumption [48,109][b]	manufacturing sector [110–112][c]	% sewage connectivity/ treatment [67]	receiving environment [67,75][d]	animal population density (terrestrial) [44,113]	aquaculture production [113]	use of veterinary medicines [45,114][e]	use of sewage in agriculture [115–117][f]	overall state of environment[g]	overall risk rating[h]
Argentina	43 million (92%); 4 cities >750 000 population	median age: 31 upper middle income	API manufacturing present	78%; low degree of treatment	majority of discharge to coastal environment (75% coastal)	moderate to high bovine, low poultry, low swine density	0.003×10^6 tonnes produced	moderate animal density, aquaculture production	yes; high volume of water reuse, moderate level of treatment	rank 93rd EPI low level of water stress[c]; low/moderate threat to water security[d]	medium
Australia	20 million (89%); 5 cities >750 000 population	median age: 38 high income	API export value US$1–5 billion (2009) with ~15% growth (2001–2009)	>90%; high degree of treatment	majority of discharge to coastal environment (100% coastal)	moderate bovine, low poultry, low swine density	0.07×10^6 tonnes produced	low animal density; CAFOs [118] present	yes; high volume of water reuse, high level of treatment	rank 3rd EPI high level of water stress; low/moderate threat to water security	low
Bangladesh	43 million (28%); 4 cities >750 000 population	median age: 24 low income	API manufacturing present	11%; low degree of treatment	majority of discharge to coastal environment (100% coastal)	low bovine, moderate to high poultry, low swine density	1.5×10^6 tonnes produced	high poultry density and aquaculture production	no data; poor level of treatment if used	rank 169th EPI high level of water stress; high threat to water security	medium
Brazil	166 million (85%); 26 cities >750 000 population	median age: 30 upper middle income	API manufacturing present	72%;low degree of treatment	majority of discharge to inland environment (42% coastal)	moderate to high bovine, moderate poultry, low swine density	0.63×10^6 tonnes produced	moderate animal density and aquaculture production	yes; high volume of water reuse, moderate level of treatment	rank 77th EPI low level of water stress; low/high threat to water security	medium
China	681 million (51%); 143 cities >750 000 population	median age: 36 upper middle income	API export value >US$5 billion (2009) with ~20% growth (2001–2009)	74%; low degree of treatment	moderate discharge to inland environment (44% coastal)	low to high bovine, low to high poultry, low to high swine density	38.6×10^6 tonnes produced	high animal density and aquaculture production	yes; high volumes of reuse, poor level of treatment	rank 118th EPI low/high level of water stress; high threat to water security	high
India	388 million (31%); 57 cities >750 000 population	median age: 27 lower–middle income	API export value ~US$5 billion (2009) with ~20% growth (2001–2009)	33%; low degree of treatment	majority discharge to inland environment (37% coastal)	high bovine, moderate poultry, low swine density	4.6×10^6 tonnes produced	high bovine density and aquaculture production	yes; high volumes of reuse, poor level of treatment	rank 155th EPI high level of water stress; high threat to water security	high
Indonesia	123 million (51%); 15 cities >750 000 population	median age: 29 lower middle income	API manufacturing present	2%;high reliance on septic tanks	majority discharge to coastal environment (100% coastal)	low bovine, high poultry, low swine density	2.7×10^6 tonnes produced	high bovine density and aquaculture production	no data; poor level of treatment if used	rank 112th EPI low/moderate level of water stress; high threat to water security	medium
Japan	115 million (91%); 8 cities >750 000 population	median age: 46 high income	high value of production (~US$67 billion in 2007)	>95%; high degree of treatment	majority discharge to coastal environment (88% coastal)	moderate bovine, high poultry, low swine density	0.56×10^6 tonnes produced	high poultry density and moderate aquaculture production	yes; high volume of water reuse, high level of treatment	rank 26th EPI low/moderate level of water stress; low threat to water security	medium
Korea (Republic)	40 million (83%); 13 cities >750 000 population	median age: 40 high income	high value of production (~US$21 billion in 2007)	87%; high degree of treatment	majority discharge to inland environment (30% coastal)	moderate to high bovine, high poultry, moderate swine density	0.51×10^6 tonnes produced	high animal density and moderate aquaculture production	no	rank 43rd EPI low level of water stress; moderate/high threat to water security	medium
New Zealand	3.8 million (86%); 1 city >750 000 population	median age: 37 high income	API manufacturing present	>95% (1990 data); high degree of treatment	majority discharge to coastal environment (100% coastal)	moderate bovine, low poultry, low swine density	0.11×10^6 tonnes produced	moderate bovine density and aquaculture production	no	rank 16th EPI low level of water stress; low threat to water security	low
Philippines	46 million (49%); 4 cities >750 000 population	median age: 23 lower middle income	API manufacturing present	37%; low degree of treatment	majority discharge to coastal environment (100% coastal)	moderate bovine, moderate poultry low swine density	0.77×10^6 tonnes produced	moderate animal density and aquaculture production	no data; poor level of treatment if used	rank 114th EPI low level of water stress; high threat to water security	medium
Singapore	5 million (100%); 1 city >750 000 population	median age: 34 high income	API manufacturing present	100%; high degree of treatment and reuse	Majority re-use (100% coastal)	low bovine, high poultry, low swine density	0.004×10^6 tonnes produced	high poultry density and low aquaculture production	tiny agricultural base, high level of treatment	rank 4th EPI low level of water stress; high threat to water security	low
Sweden	8 million (85%); 1 city >750 000 population	median age: 42 high income	high value of production (~€6.5 billion in 2011)	83%;high degree of treatment	majority discharge to coastal environment (100% coastal)	low bovine, low poultry, low swine density	0.013×10^6 tonnes produced	low animal density and aquaculture production	yes	rank 9th EPI low level of water stress; low threat to water security	low
Thailand	24 million (34%); 2 cities >750 000 population	median age: 42 upper middle income	API manufacturing present	9%; high reliance on septic tanks	majority discharge to coastal environment (100% coastal)	moderate bovine, moderate poultry, low swine density	1×10^6 tonnes produced	moderate animal density and high aquaculture production	yes	rank 78th EPI low level of water stress; moderate/high threat to water security	medium
UK	50 million (80%); 7 cities >750 000 population	median age: 40 high income	high value of production (~€20 billion 2011)	>95%; high degree of treatment	moderate discharge to inland environment (55% coastal)	moderate to high bovine, low poultry, low swine density	0.18×10^6 tonnes produced	moderate bovine density and aquaculture production	no	rank 12th EPI low level of water stress; low/moderate threat to water security	medium
USA	43 million (82%); 4 cities >750 000 population	median age: 37 high income	high value of production (~US$179 billion in 2007)	>95%; high degree of treatment	moderate discharge to inland environment (56% coastal)	moderate to high bovine, low to high poultry, low to high swine density	0.4×10^6 tonnes produced	low/high animal density and aquaculture production; CAFOs present	yes; high volume of water reuse, high level of treatment	rank 33rd EPI low/high level of water stress; low/moderate threat to water security	medium
Vietnam	28 million (31%); 5 cities >750 000 population	median age: 29 lower middle income	API manufacturing present	4%; high reliance on septic tanks	majority discharge to coastal environment (100% coastal)	moderate bovine, high poultry, moderate swine density	2.8×10^6 tonnes produced	moderate to high animal density and high aquaculture production	yes; high volumes of reuse, poor level of treatment	rank 136th EPI moderate level of water stress; high threat to water security	medium

[a]The ranking has been based on a combination of level of urbanization, total urban population and number of cities with population more than 750 000.
[b]Based on medicine consumption in high-income countries approximately 2 times greater than upper-middle, approximately 5 times greater than lower-middle and approximately 10 times greater than low income [32].
[c]The ranking has been based on degree of treatment, while sewage connectivity relates to extent of concentration of contaminants in receiving environment.
[d]The percentage discharge relates to the geographical location of major cities (population more than 750 000), although this does not preclude into marine/estuarine discharge of wastewater for landlocked urban centres or freshwater/land discharges for coastal urban centres. A higher likelihood of coastal discharge suggests a higher degree of contaminant dilution in marine ecosystems.
[e]The ranking of the use of veterinary medicines was based on animal density and volumes of aquaculture production.
[f]Ranking is based on level of treatment and volume of use.
[g]Water stress relates to annual average water scarcity in major river basins 1996–2005. Water security relates to cumulative impact of 23 factors on water resources.
[h]Overall ranking: red = 3, amber = 2, green = 1; overall score: 10–16 = low risk, 17–24 = medium risk, more than 24 = high risk.
[i]CAFO = Concentrated animal feeding operation; an agricultural operation where animals are fed and raised in confined situations.
[j]High density relates to eastern China.

develop a better understanding of potential impacts of APIs on the biodiversity of these unique and fragile ecosystems.

Despite being a qualitative assessment, the rating framework used in table 1 may be a useful way of comparing the current relative risks that APIs are likely to pose to the environment and focus future research efforts. As these economies grow further, some of the risk factors may be downgraded, whereas others may be upgraded. For example, the increasing urbanization occurring in many low- to middle-income countries presents two potential outcomes; increased urbanization can lead to the development of point sources of APIs, along with other pressures on surrounding environments, while on the other hand, greater urbanization can lead to greater wealth and subsequent investment in infrastructure and sanitation to mitigate more effectively inputs of APIs. In combination with other proposed strategies for targeting relevant APIs in particular countries, this rating framework could contribute to more effective allocation of resources for the assessment of potential risks of APIs.

(b) Observations on ecological risks in lower income countries

The majority of published literature relating to lower income countries has focused only on the environmental exposure aspects of APIs. Indeed, as discussed in §2c, it is primarily the exposure that is likely to be different in these countries (e.g. volume and type of APIs used, lack of treatment facilities, differences in the size and nature of sources). However, a number of examples, mainly from China and India, demonstrate the comparatively high environmental risk that can occur due to the levels of exposure. Analysis of surface water samples collected in northern China, in conjunction with a review of predicted no-effect concentrations for sensitive species, showed that measured concentrations of 11 of 14 anti-infectives represented a high risk at least once at 13 different sites [119]. Three anti-infectives had concentrations that were considered to be a high risk at all 13 sites. More generally, the highest measured concentrations of two anti-infectives, sulfamethoxazole and ofloxacin, in wastewater and natural waters reviewed in three different regions (Europe, North America and Asia) were at levels close to, or overlapping, lowest observable effect concentrations (LOECs) or 50% effective concentrations (EC_{50}) [6]. While overlap with LOECs and EC_{50} values was more significant in undiluted wastewater samples, the authors suggested that even a weak overlap could have an important impact on the most sensitive species (such as bacteria and algae), as well as contributing to the development of anti-infective resistance [6]. Even in the case where effects specific to a particular mode of action (e.g. effects of antibiotics on microorganisms) are not evaluated, the risks to aquatic organisms can still be high. One of the few examples that assessed the ecotoxicity of wastewaters in a lower income country, containing high ($\mu g\,l^{-1}$ to $mg\,l^{-1}$) concentrations of a range of APIs, demonstrated that clear effects occur during the developmental stages of frogs (*Xenopus tropicalis*) and fish (*Danio rerio*), even at 1 in 500 dilutions of the effluent [122]. Slightly lower dilution levels of this effluent sourced from Indian API manufacturers also had effects on microbes (*Vibrio fisheri*), invertebrates (*Daphnia magna*) and plants (*Lactuca* sativa) [62].

As noted in §3a, it is difficult to determine whether the comparatively high concentrations measured in a limited number of studies in lower income countries are representative of a general trend [6,20]. Based on the summary of risk factors presented in table 1, large urban populations were considered to represent a high-risk situation where pharmaceuticals are released in concentrated streams to receiving aquatic environments. This is particularly the case where there is a high degree of sewage connectivity with a poor level of treatment, as is the case in Argentina, Brazil and China (table 1). The relative impacts of APIs derived from wastewater are also expected to be greater in freshwater systems, compared with marine systems, where there is a lesser degree of dilution or spatial accumulation of impacts [115]. There is, however, a substantial knowledge gap associated with exposure and effects of APIs in marine ecosystems [123], although the exposure factors that have been raised here would suggest a greater relative risk would occur in lower income countries. This is due to factors such as poor wastewater treatment in urban coastal environments and a high volume of aquaculture production, which is especially concentrated in Asian countries (table 1).

So far, comparatively little research has been conducted on environmental fate and exposure of APIs in terrestrial systems, let alone their ecological impacts. Many terrestrial studies relating to toxicity of APIs mainly focus on veterinary APIs, such as antibiotics and parasiticides, which relate to their post-therapeutic use in livestock [124]. It is also recognized that the application of wastewater or sludge on land

can also contribute to APIs entering terrestrial environments where they can be taken up by plants but their ecological implications are unclear [125]. It is likely, however, that the release of APIs through the disposal of poorly treated wastewater and sludges on land may lead to a greater extent of exposure in lower income countries.

Indeed, it is likely that the exposure of organisms in all receiving environments are generally going to be at higher levels in a number of lower income countries than that experienced in high-income countries. This, however, will not be in isolation from other environmental stressors, including overall pollution, unsustainable water use and rapid urbanization, which have contributed to a global decline in biodiversity [115,126]. In lower income countries, such environmental stressors are likely to be considerably greater than in high-income nations [115–117], which will decrease the ecological resilience for coping with the additional burdens of API contamination.

5. Concluding remarks

From the preceding discussion, it is clear that the situation of APIs in the environment in lower income countries is likely to be quite different than in higher income countries. While 78% of the world's population lives in Asia and Africa (mostly in lower income nations) the high population pressure does not directly translate to greater impact of APIs on the environment. In addition to factors such as population density, a myriad of other factors, such as sanitation and hygiene, urbanization and sewer connectivity, treatment chain or lack of it, and the presence of an API manufacturing sector can influence the relative footprint of APIs in these countries. The lack of data on environmental occurrence in emerging economies in comparison to developed countries makes it difficult to understand the exposure pathways and presence of residues of APIs in the environment in lower income countries.

The use of many herbal medicines and natural products, common in Asia, has been demonstrated to have implications for toxicity based on their biological activity or through interactions with other medicines in the realm of human therapy (e.g. [126,127]). These traditional or herbal medicines can contain a vast array of biologically active ingredients, either identified or unidentified [128], sometimes in conjunction with conventional APIs [129]. The potential impact of complementary and alternative medicines on the environment into which they are released is, therefore, unknown and should be taken into consideration in future assessments of environmental risks from APIs [8].

The pace of development in many of the lower income countries is likely to lead to greater wealth, access to the healthcare system and greater spending on healthcare, improvement in sanitation and hygiene and connectivity to centralized sewerage systems in coming years. This would mean there is likely to be a rapid convergence towards a point-source nature of dispersals of APIs in the environment in lower income countries. In the meantime, the increasing global attention being directed towards the issue of APIs in the environment may facilitate research, development and understanding of the risks associated with these compounds and may help the lower income nations more effectively to allocate resources to better manage the problem.

Acknowledgements. We are grateful to Dr Min Qiao of the Chinese Academy of Sciences for her special help in translation of Chinese literature and our colleague Dr Jun Du's efforts in compilation of API use data from various surveys. The authors thank anonymous reviewers (including internal reviewers) for their comments on the manuscript.

Funding statement. The lead authors are grateful to CSIRO Oceans and Atmosphere Flagship for financial support of this project.

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