A FACTSHEET BY HEALTH CARE WITHOUT HARM EUROPE

Preventing damage to the environment from pharmaceuticals: a primer

The huge quantities of medicines ending up as waste or in aquatic systems are a major environmental health issue. The increasing documentation of low dose effects makes pharmaceuticals a priority area from an environmental health perspective.

One of the most important things purchasing managers, pharmacists and doctors can consider in reducing the environmental impact of medicines is the variation in PBT profile (persistence, bioaccumulation and toxicity) of pharmaceuticals.

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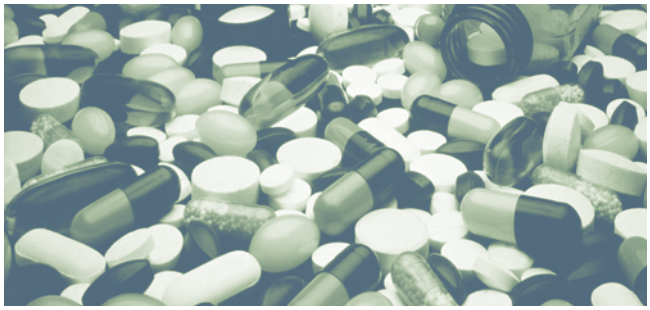
The issue of pharmaceuticals and environmental health is an emerging area.

Whilst patients should be allowed access to the best available pharmaceutical treatment, other things being equal, we should consider the medicine's PBT (Persistence, Bioaccumulation and Toxicity) profile when developing, manufacturing, prescribing, purchasing and disposing of medicines. Our collective aim should be to protect people and the environment from contamination with chemicals which wouldn't otherwise be there.

This factsheet aims to increase our understanding of the issues around pharmaceuticals and suggest ways to reduce their environmental impact. The safe disposal of waste and unused medicines; the design, purchase and prescription of substances with good PBT profile; and the manufacture of pharmaceuticals are factors requiring further societal attention.



Introduction: Pharmaceuticals and the Environment

More than 100 different types of pharmaceuticals or their metabolites have been found in water bodies in Europe and the United States, including drinking water supplies. New research confirms that estrogenic contaminants can contaminate groundwater after being carried by sewage into rivers. Standard water treatment doesn't remove them from waste water effluent, so they pass from treatment plants into rivers. Once in river waters, this research shows they can seep through river sediments and from there potentially into groundwater.[1]

When new medicines are developed their efficacy, safety and convenience are the main criteria researchers consider. However, some molecules have better environmental or PBT (persistence, bio-accumulation and toxicity) profiles than others. Other things being equal, the environmental profile is important to consider when developing a new drug or deciding which molecule to prescribe or purchase.

Society has not yet evolved solutions to the problems, but one of the aims of this document is to explain that different medicines have different PBT profiles which purchasing managers, pharmacists and doctors should consider. Likewise the problem of how to deal with pharmaceutical waste is not yet worked out. This document aims to start a proper debate on this important but neglected area.

Five examples of recent news stories about pharmaceuticals in the environment

Estrogenic compounds in treated sewage water may create exposure risks in drinking water. New research confirms that estrogenic contaminants can seep into sediment after being carried by sewage into rivers. *Environmental Health News*. (8 October 2007)

Flushing medication down the drain no cure for area waterways. Clean up of Fox Valley rivers, lakes, and wetlands over the past 30 years has been extensive and expensive, but it has worked. A danger to our environment continues however, and it's a danger that involves almost every person in our community. *Oshkosh Northwestern, Wisconsin*. (17 September 2007)

Pharmaceutical factories foul waters in India. A treatment plant in India that processes wastewater from pharmaceutical manufacturers discharges water -- containing astronomical amounts of antibiotics, along with high concentrations of other drugs -- into a stream that feeds a major river. *Science News*. (11 August 2007)

A birth control drug interacts with contaminants in sewage waste water to affect reproduction and development in fish. New experiments reveal that the synthetic estrogen used by women for birth control causes wide ranging health effects in minnows, but that the effects differed when the drug was tested alone compared with when it was mixed with wastewater effluent. *Environmental Health News*. (7 September 2007)

The frogs are dying. Although scientists admit that a combination of habitat destruction and increased exposure to harmful ultra-violet rays and pesticides contribute to the free-falling frog populations, recent scientific evidence points an accusatory finger toward a common pharmaceutical taken every day by millions of women: the birth control pill. *Saskatoon StarPhoenix, Canada*. (4 August 2007)

Understanding how pharmaceuticals are developed and prescribed

Patented vs. generic drugs

An innovative pharmaceutical is normally granted a patent lasting 17-20 years. This is to allow companies to recover the cost of discovering and developing a new drug. It typically takes 10 years or more to bring a new medicine to market and costs hundreds of millions of Euros to do so.

A pharmaceutical undergoes pre-clinical testing followed by three phases of clinical testing: Pharmacodynamics (Phase 1); small patient number studies (Phase 2); and large-scale studies (Phase 3). Clinical trials are done for specific diseases (indications). The registered indication for approval can be quite restricted - such as a specific cancer type at a certain stage of development. Companies are not allowed to promote the drug 'off label' in other indications.

Companies promote drugs primarily to doctors, pharmacists and purchasing managers or groups. Factors affecting the decision to use a given drug are: efficacy, safety (including side-effects), price, ease of use (such as injections vs. tablets, number per day, etc.) patient compliance (linked to ease of use, tolerability, etc.), and reimbursement by health authorities and insurance companies. Environmental factors for the most part are not yet part of the decision making criteria to purchase or prescribe a medicine.

At the end of its patent life, a drug becomes 'generic' and can be made and sold by other companies. Here the main economic driver is price: companies with low manufacturing costs are able to compete the most aggressively on price since they have the widest margins to play with. Indian companies have been very successful in the generics sector producing high quality drugs at very low cost.

General Practitioner (GP) vs. Specialist Doctors

GPs are office-based physicians working alone or in group practice. Pharmaceutical companies use very large sales forces to target this audience as they are very spread out and relatively hard to reach. Specialists are either office- or hospital-based and are relatively easy to reach because they are fewer in number. Of the patient population, the majority visit GPs for treatment of common and/or chronic diseases such as respiratory infections, muscular-skeletal diseases, cardiac-vascular diseases and diabetes, plus preventative treatments Thus, the majority of pharmaceuticals are prescribed by GPs.

Medical representatives visiting specialists are highly trained. Specialist doctors are often involved in company clinical trial programmes. The successful outcome of clinical trial is essential for registration and licensing of the medicine. The publication of the trials in high quality medical journals is key to supporting the marketing and promotion of pharmaceuticals. Companies work a lot with specialists. particularly the top-level ones ("opinion leaders"); fewer sales and medical representatives are needed to work with them than with the larger GP audiences and relationships are built up with them over many years.

The World Market

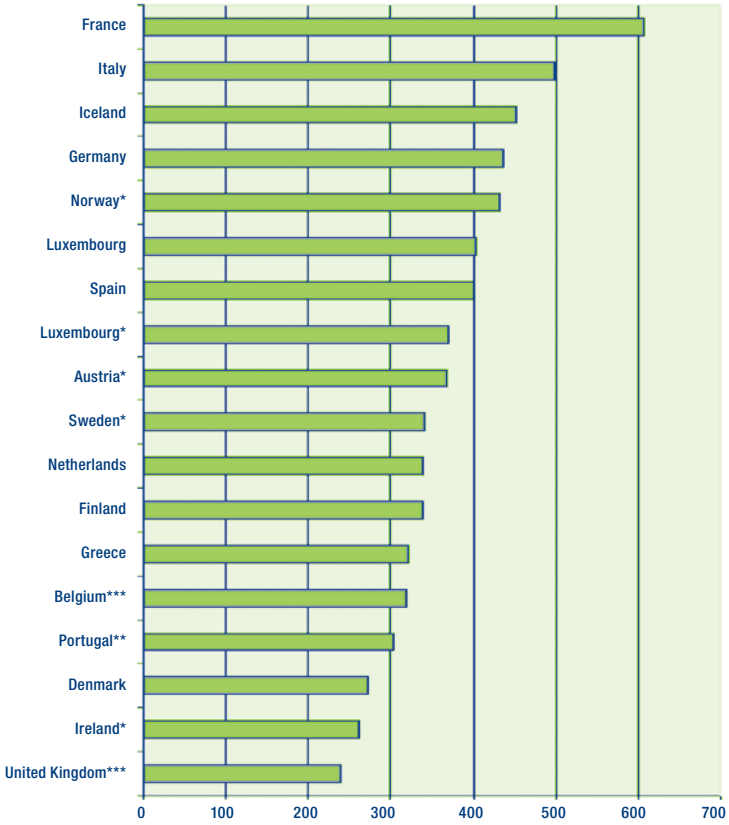
In 2006, the global pharmaceutical market was worth a staggering USD643 billion, up 7% on 2005.[2] In 2004 the total world market for generic prescription drugs was USD39.6bn.[3] Although financially only a relatively small part of the enormous total pharmaceuticals market, the generics sector represents a massive quantity of pharmaceutical consumption.

In 2006 the overall European market ranked second after the US market, representing 30% of global sales:[4]

Country	2005
Europe	29.9%
North America	47.7%
Japan	9.3%
Latin America	4,5%
Africa, Asia and Australia	8,6%

Use of Medicines in Europe

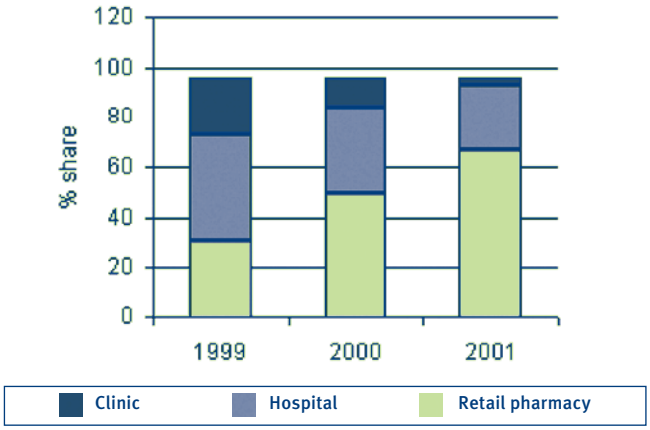
Per capita consumption of pharmaceuticals is highest in France, Italy and Iceland, while it is lowest in Ireland and the United Kingdom.



Consumption of medicines per capita in Western Europe (2003): Figures in US$ based on ex-factory prices.
Source: Talogdata [5]

Generic drugs are by definition cheaper than drugs still on patent. Consequently, their market share in value terms is relatively low - for example in Denmark generic sales represent only about 10% in value. However quantity sales are certainly higher as explained above.

Of particular interest is the declining ratio of hospital sales to retail pharmacy sales. According to a report produced by National Institute of Pharmaceutical Education and Research, "Retail pharmacies' share of pharmaceutical sales more than doubled from 31% in 1999 to over 66% in 2001 at the expense of clinics and hospital outpatient departments. Sales through general practitioner clinics have virtually disappeared, while the shift of outpatients from hospital departments to have their prescriptions filled at retail pharmacies has seen the hospital market share erode from almost 42% to less than 27%.[6]



Pharmaceutical Market Structure by Percentage Share of Value (1999–2001) *Source: IMS Health*

Environmental Impact of Pharmaceuticals

How pharmaceuticals enter the environment

Pharmaceuticals are biologically active compounds which enter the environment through two principal routes:

- By excretion from the patient mainly in urine either as the original compound or as its metabolites
- When the drug is disposed of

According to the excellent advisory booklet Environmentally Classified Pharmaceuticals published by Stockholm County Council (SCC): "Pharmaceuticals are often adapted to resist biodegradation and therefore can remain in the environment for a long time. Some pharmaceuticals have been found in drinking water, which is a warning signal that current handling of them can lead to future health and environmental problems. Access to healthy water is a prerequisite for good health. Since society's use of chemicals, including pharmaceuticals, is continuously rising, the risk is also increasing that these chemicals will return to us in our food and water supply

through nature's ecocycle. We have little knowledge of the effects that continuously supplied trace quantities of pharmaceuticals and other chemicals could have on our development, our ability to resist disease and our wellness in general." [7]

Environmental Hazard Assessment

(i) for persistence	
Readily biodegradable	0
Not readily biodegradable	3
(ii) for potential to bioaccumulation:	
Yes	3
No	0
(iii) for toxicity:	
Very high toxicity	3
High toxicity	2
Moderate toxicity	1
Low toxicity	0

A very useful model for evaluating pharmaceuticals has been developed in Sweden by Stockholm County Council, Apoteket AB and experts in ecotoxicology. The model evaluates molecules according to their ability to persist (P), bioaccumulate (B), and to be toxic (T). Each category (P, B and T) is given a score from 0 to 3. Hence a molecule with a score of 0 would indicate a product of very low ecotoxicity whilst a score of 9 would mean very high ecotoxicity. Physicians and pharmacists should consider these scores when prescribing, purchasing and dispensing pharmaceuticals.

More information about this very useful classification system can be found on the Janus website.[8] Tables listing active principals according to their consumption in defined daily doses (DDD) and PBT scores are listed in the booklet *Environmentally Classified Pharmaceuticals* produced by Stockholm County Council (SCC). You can also find them on the Janus website.[9] A sample list for antibiotics and other drugs used in infectious diseases is shown in the Appendix below.

According to the booklet: "There are examples today of designs of active substances with better environmental properties in the form of a smaller risk of bioaccumulation and persistence than similar active substances.[10] In the development of an active substance, therefore, good environmental properties should be added as an additional design goal for both the drug itself and its packaging".

The following table illustrates volume of use in Sweden of some common medicines and their environmental effects.[11]

Substance	Function	Annual amount in 2002 (kg)	Initial assessment
Atenolol	Beta-blocker	4 500	Risk to aquatic environment cannot be ruled out
Dextropropoxifen	Analgesic	1 800	Risk to soil environment cannot be ruled out
Docusate sodium	Excipient	1 570	Local risk to sediment-living organisms in freshwater environments
Diazepam	Anxiolytic	183	Risk to soil environment cannot be ruled out
Diclofenac	Anti-inflammatory	3 960	Potentially bioaccumulating
Ethinylestradiol	Sex hormone	6.4	Risk to aquatic environment
Ibuprofen	Anti-inflammatory	68 200	Potentially bioaccumulating
Ketoprofen	Anti-inflammatory	62 700	Risk to aquatic environment cannot be ruled out
Norethisterone	Sex hormone	50	Risk to aquatic environment cannot be ruled out
Oxazepam	Anxiolytic	642	Risk to aquatic environment cannot be ruled out
Oxytetracycline	Antibiotic	293	Risk to microorganisms in sewage treatment plants cannot be ruled out
Paracetamol	Analgesic	418 000	Risk to aquatic environment
Ranitidine	Antiulcer	8 360	Risk to soil environment cannot be ruled out
Simvastatin	Lipid-lowering	1 430	Risk to aquatic and soil environments cannot be ruled out; also potentially bioaccumulating
Tetracycline	Antibiotic	2 400	Risk to microorganisms in sewage treatment plants cannot be ruled out
Estradiol	Sex hormone	153	Risk to aquatic environment
Estriol	Sex hormone	38	Risk to aquatic environment

Commonly used pharmaceuticals, herbal preparations and nutritional supplements may also be significant sources of phthalate exposure in the general population.[12]

Disposal of Medicines and Waste

Pharmaceuticals need to be disposed of when they are unused or when the expiry date has been passed. Hospitals have collection systems and pharmaceutical waste is generally incinerated. Whether or not this is the best solution for all drugs warrants further investigation.

The safe disposal of medicines used at home is more problematic. Old, unused preparations often end up in the rubbish bin (going to land-fill or incineration) or flushed down the toilet. In theory, people should return unused medicines to their local pharmacy or medical centre but often this does not happen, either through people not be properly informed or a lack of motivation.

Legal Requirement for the disposal of waste

The European Union Directive 2004/27/EC (31 March 2004) states in Article 127b that "Member States shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired."

This may in principal be the case but many citizens are totally uninformed about what they should do with expired or unused medicines.

Packaging

Pharmaceutical preparations are packed in a variety of ways. Regulations concerning packaging and information differs between countries. For safety reasons, one-dose-packaging is becoming more common, which contributes to increasing waste. Common materials used in packaging are paper, aluminium and plastic, often mixed, which makes waste sorting difficult. Plastic, which is not reused, is replacing glass.

Nonetheless, an estimated 77% of pharmaceutical packaging is recyclable. Different constituents are used in packaging: paper/cardboard (38%), glass (32%), plastic (23%) and aluminium (7%).[13] Halogenated plastics (e.g. PVC or PVdC) are predominantly found in common blister packs. These chemicals have an adverse impact on the environment during manufacture, may contain harmful additives and, when incinerated, form chlorinated dioxins. Alternative plastic materials such as polypropylene or polyester produce carbon dioxide and water when incinerated, and some manufacturers are looking to substitute PVC packaging with more environmentally friendly materials.

Manufacturing as a source of harm

A recent study in India analysed pharmaceuticals in the effluent from a waste water treatment plant serving about 90 bulk drug manufacturers in Patancheru, near Hyderabad, which is a major production site of generic drugs for the world market. The samples contained by far the highest levels of pharmaceuticals reported in any effluent. The high levels of several broad-spectrum antibiotics raises concerns about resistance development. The concentration of the most abundant drug, ciprofloxacin (up to 31,000 g/L) exceeds levels toxic to some bacteria by over 1000 times.[14]

Excretion

Large quantities of pharmaceuticals and their metabolites end up in sewage systems and ground water, mainly from urine. Although water processing plants have methods for removing some organic waste, pharmaceuticals and their active metabolites still end up in sludge. This is of concern especially when sludge is spread on fields as agricultural fertiliser or gets burnt as pellets.

A 2002 US Geological survey analysed 139 rivers and found that 80% contained non prescription drugs and 50% contained measurable levels of antibiotics and oestrogens. In Berlin (2000), the WWF found measurable levels of pharmaceuticals (anti-inflammatories, anti-epileptics, and lipid lowering agents) in rivers and underground water systems.[15]

Stockholms läns landsting

Pharmaceutical residues in Stockholm tap water April 5, 2005 (ng/l)

Generic name	Plant N intake	Plant L intake	Plant G intake	Plant N outlet	Plant L outlet	Plant G outlet
Citalopram	0.1	0.4	1.1	<0.1	0.3	<0.1
Ethinyl oestradiol	<0.3	0.7	<0.3	<0.3	<0.3	0.4
Metoprolol	1.0	1.0	1.0	0.8	0.8	0.3
Naproxen	0.9	0.8	0.9	0.4	0.3	0.6
Oxazepam	1.3	1.7	1.2	1.5	1.4	0.8
Propoxyphen	0.2	0.3	0.7	0.1	0.2	0.1
Trimetoprim	0.2	0.2	0.6	<0.1	0.1	<0.1

Resources

1. Pharmaceutical consumption in Europe: http://www.talogdata.dk/sw241.asp
2. http://h2e-online.org/
3. http://www.noharm.org/europe/pharmaceuticals
4. www.janusinfo.se
5. Environment and Pharmaceuticals: http://www.janusinfo.se/imcms/servlet/GetDoc?meta_id=7237

Appendix

Examples of substances profiled by Stockholm County Council for persistence, bioaccumulation and toxicity.

Substance	Risk	Total PBT Score	Persistence	Bioaccumulation	Toxicity	Volume in DDD	ATC
Antibacterials for systemic use							
oxytetracycline	-	6	3	0	3	18 022	J01A A06
tetracycline	cannot be excluded	5	3	0	2	228 911	J01A A07
ampicillin	cannot be excluded	3	3	0	0	11 699	J01C A01
amoxicillin	moderate	6	3	0	3	1 121 950	J01C A04
benzylpenicillin	cannot be excluded	4	3	0	1	24 613	J01C E01
flucloxacillin	cannot be excluded	-	-	0	-	932 685	J01C F05
piperacillin	insignificant	5	3	0	2	10 403	J01C R05
cefuroxime	insignificant	3	3	0	0	114 760	J01D C02
cefadroxil	cannot be excl	-	-	-	-	153 283	J01D B05
cefotaxime	insignificant	3	3	0	0	21 520	J01D D01
cephtazidime	low	6	3	0	3	10 667	J01D D02
Antivirals for systemic use							
aciclovir	insignificant	3	3	0	0	85 722	J05A B01
ribavirin	insignificant	3	3	0	0	53 550	J05A B04
valacyclovir	insignificant	4	3	0	1	167 879	J05A B11
valganciklovir	insignificant	3	3	0	0	4 170	J05A B14
foscarnet	insignificant	3	3	0	0	306	J05A D01
saquinavir	insignificant	7	3	3	1	3 593	J05A E01
indinavir	insignificant	5	3	0	2	4 140	J05A E02
nelfinavir	insignificant	6	3	3	0	47 395	J05A E04
amprenavir	cannot be excluded	4	3	0	1	-	J05A E05
atazanavir	insignificant	5	3	0	2	101 990	J05A E08
zidovudine	cannot be excluded	4	3	0	1	23 638	J05A F01
didanosine	Insignificant	3	3	0	0	46 045	J05A F02

1 Pierre Labadie et al, (2007) *Evidence for the Migration of Steroidal Estrogens through River Bed Sediments*, Environ. Sci. Technol., 41 (12), pp. 4299-4304
2 IMS World Review 2005
3 Ibid.
4 IMS World Review 2006
5 OECD Health Data 2005; Note: *2002-data, **1998-data, ***1997-data. Chart from Talogdata http://www.talogdata.dk/sw241.asp
6 Chawla HPS et al. (2004) *Emerging Trends in the World Pharmaceutical Market – A Review.* (Business Briefing: North American Pharmacotherapy) www.touchbriefings.com/pdf/790/8-chawla.pdf
7 Apoteket AB and Stockholm County Council.(2006) *Environment and Pharmaceuticals* (Apoteket AB) http://www.janusinfo.se/imcms/servlet/GetDoc?meta_id=7237
8 http://www.janusinfo.se/imcms/servlet/GetDoc?meta_id=7239
9 http://www.janusinfo.se/imcms/servlet/GetDoc?meta_id=7238
10 Kummerer K, Al-Ahmad A, Bertram B, Wiessler M (2000). *Biodegradability of antineoplastic compounds in screening tests: influence of glucosidation and of stereochemistry.* Chemosphere 40: 767-773.
11 *Environment and Pharmaceuticals*
12 Schettler, T. (2006) *Human exposure to phthalates via consumer products.* International Journal of Andrology 29, pp. 134–139.
13 Data from WWF France, private communication
14 Joakim Larsson, DG. de Pedro, C. Paxeus, N. (2007). *Effluent from drug manufactures contains extremely high levels of pharmaceuticals.* Journal of Hazardous Materials (Volume 148, Issue 3) Pages 751-755
15 Data from WWF France, private communication

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