Drug Saf 2010; 33 (11): 963-968
0114-5916/10/0011-0963/$49.95/0

Ecopharmacovigilance for Better Health

Giampaolo Velo and *Ugo Moretti*

Clinical Pharmacology Unit, University Hospital of Verona, Pharmacovigilance Centre of Veneto Region, Reference Centre for Education and Communication within the WHO Programme for International Drug Monitoring, Verona, Italy

As stated by Al Gore in the *New York Times* in 2007, ''Our home, Earth, is in danger. What is at risk of being destroyed is not the planet itself, but the conditions that have made it hospitable for human beings.''[1] Chemical substances including pharmaceuticals may contribute to this.

In the 2009 Erice Statement about communication, medicines and patient safety, an international group of volunteer professionals stated that:

''The presence of widely dispersed drugs and drug metabolites in the environment poses a potential direct, and indirect, risk to humans.

- The nature and extent of the potential risks must be further investigated and assessed.
- Safe disposal of medicines must be promoted, and appropriate facilities set up and used.
- Further measures may have to be taken to reduce drug discharge into environment, including education.
- The promotion of rational drug use should reduce the volume of medicines finding their way into the environment.''[2]

During the 20th century, thousands of chemicals have been introduced into the market and used in everyday life, in industry and agriculture. This was 'blindly' carried out without considering the direct and indirect consequences on human health, animal species and on the environment. Every year an estimated 100 000 tons of antimicrobials are used all over the world.[3] Many drugs are available on the market and their number keeps growing. Today, approximately 3000 different pharmaceuticals are commonly used in Europe.[4]

Pharmaceutical compounds have been developed for their biological effects and, as they are highly active substances, they can affect both humans and animals by entering the water supplies and the food chain.

Drugs should be taken only if strictly necessary, particularly when considering that they might also cause adverse reactions. The more rational use of drugs would certainly improve the quality of therapy as well as diminishing the quantities used and therefore the levels that finally end up in the environment. Improved and more selective prescribing (e.g. through personalized medicine) and patient education (e.g. by implementing pharmaceutical care programmes) would reduce the amount of drugs that enter the ecosystem.

What about biopharmaceuticals: are they an environmental risk? It seems that the biological medicinal products that are in clinical use do not constitute a risk to the environment as they do not survive the passage through the body and, if they do, their chemical instability in hydrolytic conditions and susceptibility to microbial breakdown render them harmless.[5] Research on the environmental impact of these drugs is at an early stage and further studies are needed.

Ecopharmacovigilance is a new issue of great interest. It can be defined as the science and activities concerning detection, assessment, understanding and prevention of adverse effects or other problems related to the presence of pharmaceuticals in the environment, which affect both human and the other animal species. It derives from a compromise between a highly industrialized

chemical-based society and the need for the protection of the environment.

If we consider human use, the largest flow of drugs into the environment comes from people who are under medical treatment. Drugs are eliminated from the body, either in unchanged form or as metabolites, still partially active, through urine and faeces, and find their way to sewage treatment plants. However, we should not forget that drugs for veterinary use are also an important contributor to drugs in the environment.

Drugs are generally water-soluble. The distribution and behaviour of different drugs in the aqueous phase will differ, both between different pharmaceutical classes and between drugs belonging to the same class. Drugs and their metabolites may be divided into three groups:[6]

- drugs that break down rapidly (e.g. aspirin [acetylsalicylic acid]);
- drugs that are both water-soluble and stable (e.g. bezafibrate and other lipid-lowering drugs);
- drugs that are fat-soluble and stable (e.g. fluoroquinolones).

Since drugs can pollute our environment, we can be exposed to them during our entire life. (figure 1): unexpected toxic effects may occur due to unwanted and unknown consumption of a cocktail of drugs from drinking water and food. These potential effects are difficult to ascribe to a specific compound, as various chemical substances from different sources may be implicated, and drug interactions are highly possible. Antimicrobials are only partially eliminated through sewage treatment plants and can therefore reach surface and ground water, and sediments. They may be an important cause of microbial resistance.[8,9]

1. Drugs in Surface Water

Data regarding the concentrations of drugs in surface waters of different European countries have been published; various drugs in rivers, lakes and soil have been detected. In 2000, *The Lancet* published an important research letter on the matter.[10] Well known examples are fluoxetine in the river Thames, reported by the British Environment Agency, cocaine in the Po river found by Istituto Mario Negri in Italy,[11] and antidepressants, antiepileptics and statins in the Niagara river and Lakes Ontario and Erie found by the Water Quality Centre of the University of Ontario in Canada.[12] Others drugs have also been detected, such as analgesic/anti-inflammatory agents (aspirin, diclofenac, ibuprofen, indometacin,

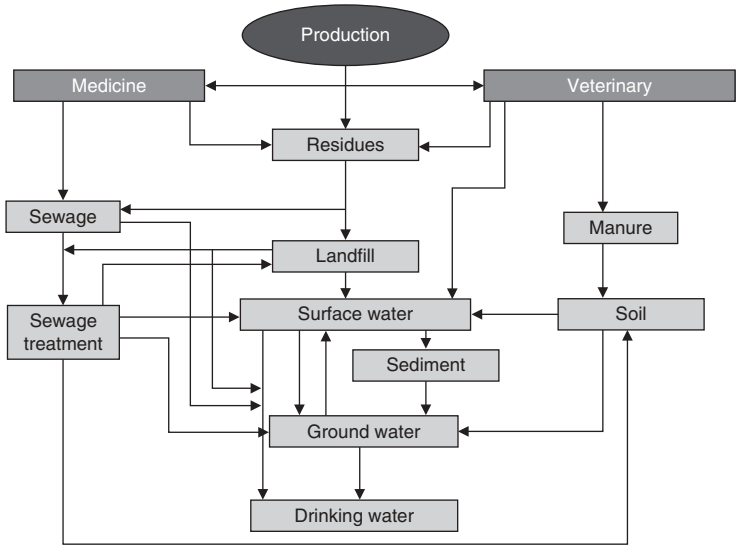

Fig. 1. The fate of drugs (reproduced from Kummerer,[7] with permission).

ketoprofen, naproxen and phenazone), antibacterials (chloramphenicol, erythromycin, lincomycin, roxithromycin, fluoroquinolones, tetracyclines, sulfonamides and trimethoprim), hormone preparations (17-α estradiol, 17-β estradiol, ethinylestradiol, mestranol, 19-norethisterone, progesterone, testosterone and estriol) and antihypertensive agents (β-blockers: atenolol, metoprolol), to mention only a few.[7]

To provide the first nationwide investigation of the occurrence of pharmaceuticals, hormones and other organic wastewater contaminants (OWCs) in water resources, the US Geological Survey measured concentrations of 95 OWCs in water samples from a network of 139 streams across 30 states during 1999 and 2000. Eighty percent of the streams contained traces of drugs.[13] In Northern Europe, contamination with antidepressants and sedatives has been of concern, whereas in Southern Europe, antibacterial contamination is more prevalent. Detectable traces of prescription heart medications and caffeine have even found their way into the Atlantic Ocean.[14]

The problem is a global one, including the less developed countries where there is little or no research or monitoring and which are often used as 'dustbins' by industrialized countries.

2. Drugs in Drinking Water

The first pharmaceutical substance detected in drinking water was clofibric acid, found by a German research group in Berlin 15 years ago.[15] Since then, several drugs such as bezafibrate, phenazone and carbamazepine have been found in drinking water in Germany.[16] Various types of antibacterials have also been detected in drinking water in the US.[17] A list of drugs, such as clofibric acid, carbamazepine, diazepam, diclofenac and ibuprofen detected in drinking water was published a few years ago.[18]

From 2005 to 2007, Stockholm County Council has analysed samples of tap water from airports from a total of 18 countries worldwide in order to detect traces of pharmaceuticals, and found that their occurrence was a global phenomenon. The results of this study have not been published in any scientific journal, but they have been mentioned in various scientific meetings.

3. Effects of Drugs on Environmental Organisms

Although our knowledge regarding the effects of drugs on humans via the ecosystem refers only to potential risks, evidence shows that they may have effects on animal species.

Niels Skakkebaek, a Danish endocrinologist, stated in the *British Medical Journal* that sperm concentrations in men fell by almost 50% from 1940 to 1990.[19] Such news attracted much media attention. A British Broadcasting Corporation (BBC) documentary entitled 'Assault on the Male' suggested a link between the falling sperm counts and the presence in water of chemicals that mimic the sex hormone estrogen: polychlorinated biphenyls, dioxin, pesticides and others. Scientific journals, including the *New England Journal of Medicine*, started discussing this controversial question. A causal connection among humans, environment and chemicals, including drugs, was considered,[20,21] but a definitive conclusion has not been reached. In the UK, male rainbow trout, living in rivers polluted by chemicals with estrogenic effects, produced typically female proteins.[22] In the 1990s, the population of white-backed vultures (*Gyps bengalensis*) in Pakistan declined by more than 95%. This was associated with acute renal failure, attributed to the introduction of large quantities of diclofenac into their diet, as a result of feeding on dead treated livestock.[23]

There is clear evidence of the endocrine disruption effects of hormones on aquatic life. This includes feminization of male fish such as wild roach (*Rutilus rutilus*) living downstream from wastewater treatment works, with intersex individuals and development of ova in the testes.[24]

4. Precautionary Principle

Drug environmental concentrations are well below therapeutic levels of the drugs in the human plasma. Concentrations are very low, decreasing from wastewater (100–1000 ng/L) to surface water (1–100 ng/L) and drinking water

(1–10 ng/L).[7,25] However, sex hormones are active at very low concentrations and antibacterial exposure contributes to bacterial resistance in the environment. It must be remembered that ecosystems do not consist of isolated compartments, and that drugs can enter the food chain. The effect of chronic exposure to very low levels of drugs on humans remains unknown, and we do not know the significance in humans of interactions between multiple drugs at such low concentrations ingested over the whole lifespan. Special populations, such as infants and children, pregnant women, elderly people and patients with particular diseases that could influence the kinetics of drugs, may be especially vulnerable to such exposure. Type B adverse reactions are dose/concentration-independent and may occur at environmental drug concentrations, but this remains to be proved.

We should think and act on a precautionary basis. We should not deny risks simply because they are less than certain. On the contrary, we should know in advance the possible damage to human health and the environment so that we can prevent it. When there are reasonable grounds for concern that potential hazards may affect the environment or human, animal or plant health, and when at the same time the available data preclude a detailed risk evaluation, the precautionary principle has been politically accepted as a risk management strategy in several fields.[26]

We can only agree with what is stated in the booklet 'Environmentally Classified Pharmaceuticals' by Stockholm City Council: ''Since 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, caution is advisable.''[27]

5. What is Going On?

How are we approaching this situation, and what can be done? Directive 2004/28/EC[28] forbids veterinary medicinal product authorization when the environmental risk is unacceptable and managing the risk is not possible. Legislation for human medicinal products is less strict than for veterinary medicinal products. Directive 2004/27/EC of the European Parliament and of the Council of the European Union requires that environmental risk assessment is part of a marketing authorization application.[29]

Related to this, in a report to the European Parliament, Erkki Liikanen, who was a member of the European Commission responsible for enterprise, said: ''The possible effects of the use of medicinal products on the environment are important. The question needed to be addressed carefully as, at the end of the day, the availability of certain medicines is at stake. The compromise amendments, which require an environmental impact assessment and possible mitigating measures, but leave the criteria for granting the marketing authorization untouched is to be seen as a well balanced solution.''[30]

In the so-called 'Pharma package',[31] the European Commission stated that pollution of waters and soils with pharmaceutical residues is an emerging environmental problem and also an emerging public health concern. Several research projects to assess possible environmental and health impacts of pharmaceuticals have been funded. The next step will be focusing on measures that could reduce the potentially harmful impact of pharmaceuticals on the environment and public health, evaluating environmental information on pharmaceuticals collected by the European Medicines Agency and national medicines authorities with a view to integrating this information into the current EU legislative framework.

The Swedish Medical Products Agency investigated environmental effects of the 27 drugs that were most widely used and reported as observed in the environment in Sweden and presented proposals on measures to reduce environmental burden and effects of the products. The study also concluded that chronic environmental toxic effects could not be excluded because of the lack of chronic ecotoxicity data and that the sex hormones estradiol and ethinylestradiol were considered to be associated with possible aquatic environmental risks.[32] Stockholm City Council Environment Department started a drug environmental risk assessment in 2003. By the year

2010, all pharmaceuticals being marketed in Sweden will be assessed for environmental risk.

In response to various reports of trace amounts of pharmaceuticals, including estrogens and codeine, found in New York waterways and around the country, the Environment and Public Works Committee of the US Senate approved in May 2009 an amendment to study the presence of pharmaceutical drugs in drinking water and the long-term health effects on children and families.[33]

Scientific Societies could also play an important role. The International Society of Pharmacovigilance (ISoP) has been very active, organizing workshops and making contact with the Environment Committee of the European Parliament and the Working Party on Pharmaceuticals and Medical Devices. The Society is aiming to act as a bridge between scientists and regulatory and political bodies, and to have ecopharmacovigilance as an integral part of pharmacovigilance.

There is still a lot to think about and even more to do: increased efficacy of sewage treatment plants, better education regarding drug use both for prescribers and consumers, high biodegradability of medicines in the environment and new eco-compatible ways to synthesize drugs ('green pharmaceuticals'). It is important to consider environmental approach when researching and developing new drugs. Biodegradability could also be considered by doctors as added value when they make a prescription.

This is a world in which we swim, but about which we know very little.

Acknowledgements

No sources of funding were used to assist in the preparation of this editorial and the authors have no conflicts of interest that are directly relevant to its content.

References

1. Gore A. Moving beyond Kyoto. The New York Times 2007 Jul 1 [online]. Available from URL: http://www.nytimes.com/2007/07/01/opinion/01gore.html [Accessed 2010 Jun 16]
2. Edwards IR, Hugman B, Lindquist M, et al. Erice Statement 2009: communication, medicines and patient safety. Br J Clin Pharmacol 2010; 69 (2): 207-8
3. Wise R. Antimicrobial resistance: priorities for action. Antimicrob Chemother 2002; 49: 585-6
4. Ternes T, Giger W, Joss A. Introduction in human pharmaceuticals, hormones and fragrances. In: Ternes T, Joss A, editors. The challenge of micropollutants in urban water management. IWA Publishing, 2007: 1-14
5. Kühler TC, Andersson M, Carlin G, et al. Do biological medicinal products pose a risk to the environment? A current view on ecopharmacovigilance. Drug Saf 2009; 32 (11): 995-1000
6. Tysklind M, Fick J, Kallenborn R. The spread of drugs in soil and water. In: Collaboration between Apoteket AB, Stockholm County Council and Stockholm University. Environment and pharmaceuticals. Apoteket AB, 2006: 41-53 [online]. Available from URL: http://www.janusinfo.se/imcms/servlet/GetDoc?meta_id=9564 [Accessed 2010 Jun 16]
7. Kummerer K. Pharmaceuticals in the environment. 3rd ed. Berlin, Heidelberg: Springer-Verlag, 2008
8. Kummerer K. Resistance in the environment. J Antimicrob Chemother 2004; 54: 311-20
9. D'Costa VM, McGrann KM, Hughes DW, et al. Sampling in the antibiotic resistome. Science 2006; 311: 374-7
10. Zuccato E, Calamari D, Natangelo M, et al. Presence of therapeutic drugs in the environment. Lancet 2000; 355: 1789-90
11. Zuccato E, Chiabrando C, Castiglioni S, et al. Cocaine in surface waters: a new evidence-based tool to monitor community drug abuse. Environ Health 2005 Aug 5; 4: 14-20
12. Heberer T. Occurrence, fate, and removal of pharmaceuticals residues in the aquatic environment: a review of recent research data. Toxicol Lett 2002; 131: 5-17
13. Kolpin DW, Furlong ET, Meyer MT, et al. Pharmaceuticals, hormones and other organic wastewater contaminants in U.S. streams, 1999-2000: a national reconnaissance. Environ Sci Technol 2002; 36: 1202-11
14. Dove A. Drugs down the drain. Nat Med 2006; 12 (4): 376-7
15. Stan H, Heberer T, Linkerhagner M. Occurrence of clofibric acid in the aquatic system: is the use in human medical care the source of the contamination of surface, ground, and drinking water? Vom Wasser 1994; D 83: 57-68
16. Ternes TA. Analytical methods for the determination of pharmaceuticals in aqueous environmental samples. Trends Anal Chem 2001; 20: 419-33
17. Ye Z, Weinberg HS, Meyer MT. Trace analysis of trimethoprim and sulfonamide, macrolide, quinolone, and tetracycline antibiotics in chlorinated drinking water using liquid chromatography electrospray tandem mass spectrometry. Anal Chem 2007; 79 (3): 1135-44
18. Jones OA, Lester JN, Voulvonis N. Pharmaceuticals: a threat to drinking water? Trends Biotechnol 2005; 23 (4): 163-7
19. Carlsen E, Giwercman A, Keiding N, et al. Evidence for decreasing quality of semen during past 50 years. BMJ 1992; 305: 609-13
20. Sherins RJ. Are semen quality and male fertility changing? N Engl J Med 1995; 332 (5): 327-8
21. Auger J, Kunstmann JM, Czyglik F, et al. Decline in semen quality among fertile men in Paris during the past 20 years. N Engl J Med 1995; 332: 281-5
22. Knudsen FR, Schou AE, Wiborg ML, et al. Increase of plasma vitellogenin concentration in rainbow trout

(*Oncorhynchus mykiss*) exposed to effluents from oil refinery treatment works and municipal sewage. Bull Environ Contam Toxicol 1997; 59: 802-6

23. Oaks JL, Gilbert M, Virani MZ, et al. Diclofenac residues as the cause of vulture population decline in Pakistan. Nature 2004; 427: 630-3
24. Liney KE, Jobling S, Shears JA, et al. Assessing the sensitivity of different life stages for sexual disruption in roach (*Rutilus rutilus*) exposed to effluents from wastewater treatment works. Environ Health Perspect 2005; 113 (10): 1299-307
25. Boxall ABA. The environmental side effects of medication: how are human and veterinary medicines in soils and water bodies affecting human and environmental health? EMBO Rep 2004; 5 (12): 1110-6
26. European Commission. Communication from the European Commission on the precautionary principle. Brussels; 2000 Feb 02 [online]. Available from URL: http://ec.europa.eu/environment/docum/20001_en.htm [Accessed 2010 Jun 16]
27. Stockholm County Council. Environmentally classified pharmaceuticals 2010 [online]. Available from URL: http://www.janusinfo.se/Global/Miljo%20och%20lakemedel/miljo_broschyr_eng2010.pdf [Accessed 2010 Jun 16]
28. Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the community code relating to veterinary medicinal products [online]. Available from URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32004L0028:EN:HTML [Accessed 2010 Jul 19]
29. Kümmerer K, Velo G. Ecopharmacology: a new topic of importance in pharmacovigilance. Drug Saf 2006; 29 (5): 371-3
30. Liikanen E. Review of the pharmaceutical legislation. Speech/03/615 at the European Parliament Plenary Session, Strasbourg; 2003 Dec 16
31. European Commission. Safe, innovative and accessible medicines: a renewed vision for the pharmaceutical sector, 2008 Dec 10 [online]. Available from URL: http://ec.europa.eu/health/human-use/package_en.htm [Accessed 2010 Jun 16]
32. Carlsson C, Johansson AK, Alvan G, et al. Are pharmaceuticals potent environmental pollutants? Part I: environmental risk assessments of selected active pharmaceutical ingredients. Sci Total Environ 2006; 364: 67-87
33. Press Release of US Senator Kirsten E. Gillibrand, 2009 May 14 [online]. Available from URL: http://gillibrand.senate.gov/newsroom/press/release/?id=a19ef6cc-59e9-4ec1-994d-86ae56f1628e [Accessed 2010 Jun 16]

Correspondence: Professor *Giampaolo Velo*, Clinical Pharmacology Unit, University Hospital of Verona, Policlinico G.B. Rossi, P.le L.A. Scuro 10, 37134 Verona, Italy.
E-mail: gpvelo@sfm.univr.it