Ecopharmacology: the Deliberated or Casual Dispersion of Pharmaceutical Principles, Phytosanitary, Personal Health Care and Veterinary Products in Environment Needs a Multivariate Analysis or an Expert Systems for the Control, the Measure and the Remediation.

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Introduction

The dispersion of pharmaceutical products in the environment is well known by researchers from almost 20 years. Many studies in different countries have demonstrated the presence of drugs at trace levels in waters. There are many reasons to explain this dispersion, but the most important are:

- Manufacturing operations in the pharmaceutical industries (but this seems to be the less cause of dispersion in the environment because these releases are usually regulated and carefully observed).
- Metabolic excretion: human metabolism may lower activity or enhance water solubility; however, metabolism is frequently incomplete. This means that in many cases the body does not assimilate a large portion of the drugs and it is excreted as faeces, urine, etc.
- In animal breeding drugs are often used for their biological effects like antibiotics used as growth promoters or as feed additives in fish farms. This form of dispersion is not controlled because in many countries this practice is illegal, but the number of animal farms in the world make us think that this is one of the principal forms of pollution.
- Disposal of unwanted chemicals: many people with their wrong behaviour contribute to the pharmaceutical dispersion in the environment. Complete consume of purchased drugs is an ideal situation. However this is not always the case and so they expire in the hands of the public or health care facilities. Large amounts of pharmaceutical products are discarded as their expiration date passes or they become unwanted. At this time, the correct disposal method of waste product is not clear to the general public. Consequently, waste is discharged through sewage systems or sent to garbage dump.

Even though the impact of pharmaceuticals in the environment at trace levels has not been clearly determined, seems that some active molecules could have a biological effect even down to a few nanograms per litre or give bioaccumulation and provoke effects in the aquatic or terrestrial ecosystems.

For this reason, the precautionary principle calls for action in the face of uncertainty.

Definitions

Because of the complexity of the argument we would give first some definition about terms often used in literature (sometimes in an improper way).

Biopharmacology: it is the branch of pharmacology that studies the production of pharmaceuticals by biotechnology.

Ethnopharmacology: the study and improvement of traditional pharmacopoeia (indigenous knowledge and practices related to curative natural products and medicinal plants) conducted by specialists like medical doctors, pharmacologists, botanists, anthropologists, historians of medicine and pharmacy, etc [1].

Herbal pharmacology: it is the study and the use of medical herbs in particular in Chinese traditions.

Pharmacovigilance: is a feedback system, which is able to control the response of a subject to a given pharmaceutical product. Reading the 2006 report of WHO Programme for International Drug Monitoring [2] we can find "The WHO National Adverse Drug Reaction Monitoring Programme will continue pharmacovigilance efforts by conducting drug safety courses for healthcare professionals and building closer ties with other member countries in the exchange of drug safety information". This is, from our point of view, the correct definition and correlated activity of this term.

Finally *Ecopharmacology*: the study, the knowing and the methods for contrasting the presence in the environment of pharmaceutical products and their metabolites which always interact with the ecosystem in a negative way. Pharmaceuticals cause modifications to the ecosystem by interaction-absorption of drugs, metabolites, excipients, stabilising, thickenings, etc. Environment-Ecopharmacology [3] defines therefore the study of the interaction with the environment of the drugs and, from the obtained results, proposes to the researchers of pharmacovigilance the remedies to reduce the environmental impact. In Ecopharmacology it is necessary to make studies on all those products: personal care, hospital cleaning, disinfectant, antibacterial, plant protection, and veterinary drugs products which are now used in every field.

The word used by Andy Greller "Sri Lanka Rainforest: Birthplace of Ecopharmacology" [4] seems not good for us. It is well known the word "*Biorape*" as the removal of active pharmaceutical ingredients from plants growing in a territory, with no benefit for the people living there.

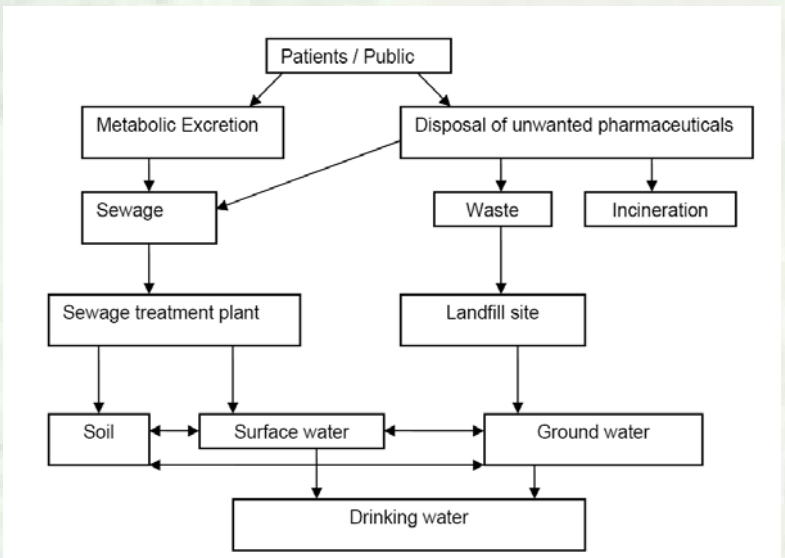

Fig. 1 : Entry paths into the environment for most medical products when prescribed to patients [6,7].

Problems and possible solutions

Pharmaceuticals products do not usually persist in the environment but continuous dispersion keep concentrations relatively constant, usually very small (e.g. ng/l, µg/l). Much is yet to be learned about the effects (particularly those chronic in nature) on humans, plants, and animals exposed to low-level concentrations of active principles. Furthermore, little is known about the potential interactive effects (synergistic or antagonistic toxicity) that may occur from complex mixtures of these compounds in the environment.

It is demonstrated that the extent of usage of antibacterial substances is closely related to the development of antibacterial resistance, so it compromised traditional therapeutic regimens, making treatment of infections more difficult.

Also, hormonally active chemicals, personal care products, and pharmaceuticals are designed to stimulate a physiological response in humans, plants, and animals. Potential concerns from the environmental presence of these compounds include abnormal physiological processes and reproductive impairment, increased incidences of cancer and the potential increased toxicity of chemical mixtures.

Drugs are used for the benefit of humanity but their utilise is expected to increase in future years due to the fact that population is growing, and in many places, such as the US or European countries, is ageing. Also, many new drugs and therapies for otherwise non-treatable illnesses are available every year.

Moreover many factors influence the diffusion of drugs in water systems:

- Development of new and better medicines even more used for specific illness.
- An increased uses of medications for conditions such as high cholesterol, high blood pressure, chronic asthma, and diabetes that requires daily administers of drugs in the years.
- Improvements in drug accesses in the modern country, including growth in insurance coverage for drugs.
- Marketing strategies (sometimes excessive) of pharmaceutical industries.
- Changes in the average age of the population. The older persons usually require more medical attention, more services and consequently a bigger use of drugs for the treatment and management of chronic and acute health conditions.
- Wrong behaviour of patients who don't consume totally the pharmaceuticals and contribute to the their dispersion in the environment.
- Improper uses of drugs for a different target like animal breeding. They ere used as growth promoters or as feed additives in fish farms.
- Use of drugs for doping.

Finding a pharmaceutical in the environment produce high cost (often hidden) for the community. Controlling all these parameters for almost 35,000 active pharmaceutical ingredients in the world, necessarily needs of an Expert System. In the USA something of this kind already exists but promoted by producer itself, the PhATE™ (Pharmaceutical Assessment and Transport Evaluation) model [5].

In the US, the pharmaceutical industry trade association, PhRMA (Pharmaceutical Research and Manufacturers of America) developed a watershed-specific model to predict environmental concentrations from patient use. The PhATE™ (Pharmaceutical Assessment and Transport Evaluation) model is a watershed-based approach and was developed as a tool to estimate concentrations and potential environmental distribution of active pharmaceutical ingredients (APIs) discharged to US surface waters through consumption of medicines. It uses a mass balance approach to model predicted environmental concentrations (PECs) in eleven watersheds that are felt to be representative of most hydrologic regions of the United States. Upon dividing the associated rivers into discrete segments, the model estimates the mass of API that enters a segment from upstream or from sewage treatment works (STWs) and the mass that is subsequently lost from the segment via in-stream loss mechanisms or flow diversions (i.e., manmade withdrawals). STW discharge loads are estimated based on the population served API use per capita, and the mass of the API removed in the STW. Monitoring data generated by the United States Geological Survey were used to corroborate the model. In addition, industry groups working through PhRMA developed human health effects data on the pharmaceutical compounds reported by USGS and used the PhRMA PhATE™ (Pharmaceutical Assessment and Transport Evaluation) model to carry out human health risk assessments for 26 active pharmaceutical ingredients (APIs).

European Projects

The importance of such problems is also highlighted by several initiatives of EU which purpose is monitoring the presence of drugs and other pollutant molecule in the environment and looking for methods for their correct and effective abatement.

a) ERAPharm (Environmental Risk Assessment of Pharmaceuticals): the objective of ERAPharm is to improve and complement existing knowledge and procedures for the environmental risk assessment from human and veterinary pharmaceuticals. It investigated unstudied major routes leading to exposure of the terrestrial and aquatic environment, the fate of pharmaceuticals in surface water and sediment and the effects of antibiotics on microbial communities to the spread of genetically encoded resistance. Duration: 36 months.

b) AquaStress (Mitigation of Water Stress Through new Approaches to Integrating Management): the AquaStress project generated scientific innovations to improve the understanding of water stress and the development of supporting methods and tools to evaluate different mitigation options and their potential interactions with environment. Duration: 48 months.

c) Rempharmawater (Ecotoxicological Assessments and Removal Technologies for Pharmaceuticals in Wastewater): the present project aims at the prevention of pollution of surface-water resources and more generally at the protection of the environment. Therefore the ultimate aim is represented by the achievement of results which can improve living conditions in Europe through the minimisation of environmental impact of wastes posing serious risks to human health. The project focuses on "Ecotoxicological assessments and removal technologies for pharmaceuticals in wastewater", also focus on database development, Pharmafic, to store data (ecotoxicological, physical and chemical properties, etc) on the drugs studied. Duration: 36 months.

d) Eravmis (Environmental Risk Assessment of Veterinary Medicines in Slurry): this report investigates the possibility of defining scenarios for exposure and distribution models for the environmental risk assessment of veterinary medicinal products at registration. A critical component of any modelling procedure is the identification of relevant scenarios to characterise the environmental conditions determining model input parameters. The study is extended to residues of veterinary medicinal products, which reach the environment through spreading of slurry on agricultural soil and animal husbandry. Duration: 36 months.

e) Poseidon: the acronym POSEIDON represents the project "Assessment of Technologies for the Removal of Pharmaceuticals and Personal Care Products in Sewage and Drinking Water Facilities to Improve the Indirect Potable Water Reuse". The project defines the activities of the EU in the field of research, technological development and demonstration for the period of 1998-2004. Duration: 36 months.

f) Triton: the Triton project is related to existing EU projects Poseidon, Rempharmawater and Eravmis, which study the multi-barrier approach to control the indirect and direct discharge of harmful anthropogenic compounds into water bodies. Triton is meant to implement the results obtained by previous projects by providing training for the research players in the research consortia including authorities and end-users and increasing the exchange of information between the EU projects to harmonise the methodologies for tackling the problem in different EU countries. Duration: 24 months.

g) WSSTP (Water Supply and Sanitation Technology Platform): it is a European initiative, open to all stakeholders involved in European water supply and sanitation and major end-user groups. The participants in the platform will together produce a common vision document for the whole European water industry together with a strategic research agenda and an implementation plan for the short (2010), medium (2020) and long term (2030).

Before these projects, there was little available information about environmental concentrations of pharmaceutical products. These EU projects were so far providing the first data at this European scale to assess the presence and effects of antibiotics in the aquatic environment and soils. After these projects many studies are available on impact of some pharmaceuticals in the environment, as well some effective techniques to eliminate these compounds.

drugs	sample1	sample2	sample3
Gemfibrozil	0.81	0.84	4.76
Fenofibrate	0.16	0.10	0.16
Bezafibrate	n.a.	n.a.	0.91
Clofibric acid	0.68	n.a.	0.23
Ibuprofen	0.18	0.02	0.02
Flurbiprofen	n.a.	n.a.	0.34
Naproxen	0.29	0.41	5.22
Diclofenac	0.47	1.48	5.45
Phenazone	n.a.	0.37	n.a.
Acebutolol	0.04	0.02	0.11
Metoprolol	0.01	0.01	0.10
Oxprenolol	0.01	<0.01	0.03
Propranolol	0.01	0.01	0.09
Carbamazepine	0.30	0.34	0.50
Trimetoprim	0.04	0.03	0.13
Sulfamethoxazole	0.01	n.a.	0.03
Ofloxacin	0.58	0.29	0.31
Lomefloxacin	0.32	0.18	0.22
Enoxacin	0.03	0.01	0.03
Norfloxacin	0.07	0.06	0.06
Ciprofloxacin	0.07	0.06	0.04

Tab. 1 : Pharmaceutical residues in STP effluents of Latina (city in south Lazio, Italy). Values are expressed in µg/l. (Project Rempharmawater)

Occurrence of pharmaceutical residues in STP effluents

Compounds	Concentrations (µg/L) median (maximum)			
Antiphlogistics				
Ibuprofen	0.05 (7.11) [a]	0.37 (3.4)[b]	3.09 (27.3) [c]	4.0 (24.6) [d]
Naproxen	1.12 (5.22)	0.30 (0.52)	-	12.5 (33.9)
Ketoprofen	n.d (1.62)	0.2 (0.38)	-	n.d.
Diclofenac	0.68 (5.45)	0.81 (2.1)	0.42 (2.35)	n.d.
β-Blockers				-
Propanolol	0.01 (0.09)	0.17 (0.29)	0.08 (0.28)	-
Metoprolol	0.08 (0.39)	0.73 (2.2)	-	-
Acebutolol	0.06 (0.13)	-	-	-
Oxprenolol	0.02 (0.05)	-	-	-
Lipid regulators			-	-
Gemofibrozil	0.84 (4.76)	0.40 (1.5)	-	1.3 (1.3)
Fenofibrate	0.14 (0.16)	n.d. (0.03)	-	-
Bezafibrate	n.d. (1.07)	2.20 (4.6)	-	-
Clofibric acid	n.d. (0.68)	0.36 (1.6)	-	n.d.
Antiepiliptic			-	-
Carbamazepine	0.87 (1.20)	2.1 (6.3)	-	0.7 (2.3)
Antibiotics			-	-
Trimetroprim	0.04 (0.13)	-	0.07 (1.29)	-
Sulfamethoxazol	0.05 (0.09)	-	<0.05 (0.13)	0.24 (0.87)
Erythromycin	-	-	<0.01 (1.84)	0.08 (0.84)
Reference	1	2	3	4

1) 7 STP in France, Greece, Italy and Sweden (REMPHARMAWATER report)
2) 49 STP Germany, Temes, Wat. Res 1998
3) 5 STP UK, Ashton, Sci. Total Environ. 2004
4) 14 STP Canada, Metcalfe, ET&C, 2003 and ES&T 2004

Tab. 2 : Pharmaceutical residues in STP effluents in different european countries. (Project Rempharmawater)

Conclusion

We do not want to resolve the problem after this work, but we would just give some definitions and an idea, from our point of view, about the method for controlling the environmental pollution.

When the Swiss National Centre (Swissmedic) needed to upgrade their systems of Adverse Drugs Response reporting and feedback, not build a completely new software but develop a national ADR database parallel with the WHO database. This software, called Vigibase Online (VOL), has been made available for other pharmacovigilance centres.

With this paper, we would like to prompt the European Commission to produce a directive and a project for realisation of a "Ecopharmacology Expert System, ExpEcoPhaS", also to answer some trivial questions as "the most sold drug is also the most present in the environment or the most recalcitrance?" or "why in a region we find active pharmaceutical principles?" and so on.

Medical Expert Systems have reached good performance, as "MYCIN, for diagnosing of bacterial infections"; "deDombal`s Leeds Abdominal Pain System"; "Help System, developed at LDS Hospital in Salt Lake City", and we believe this software system stable and quite complex to support all the active pharmaceutical ingredients existing, produced or delivered in Europe.

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