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Ecopharmacology: Deliberated or casual dispersion of pharmaceutical principles, phytosanitary, personal health care and veterinary products in environment needs a multivariate analysis or expert systems for the control, the measure and the remediation

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Abstract

The increasing human and animal use and abuse of drugs as well as of personal health care and gross domestic products, involve disposal and waste problems and, as a consequence, affect the environmental condition. Actually most of the active principles are complex synthesised organic molecules that react, inside human or animal body, by specific biochemical reactions that in no case can reach a 100% yield and produce residues that could be more noxious of the starting compounds. Just reading the indication sheet accompanying any drugs, it is easy to state that no drug can be considered healthy, so, their use constitutes a serious pollution source. The full awareness of this relatively new environmental problem let many researchers to face it from different point of view. Current studies are considering the sources of these substances in the environment, the effects on human health as well as on the flora and fauna species, the recalcitrance and possible degradation methods, analytical techniques able to determine them and their metabolites even at low concentrations and in complex matrices.

Literature on the subject continuously increases and a comparison of all data became more and more difficult both for a single drug and for different ones based on the same or different active principles. This is a typical case in which chemometrics can extract a full information in the easier way, so the design of a European database coupled to suitable expert system software should be strongly suggested.

Keywords: Ecopharmacology; European Project; Expert systems; Dispersion of pharmaceutical; Phytosanitary; Personal health care; Veterinary products; Remediation; Recalcitrance; Degradation

1. Introduction

The unavoidable interaction between the different environmental compartments, lets humans to be the direct or indirect target of the pollution. In fact polluting agents follow a cycle starting and ending to humans. While it is very easy to break the biogeochemical cycles, any attempt to escape from the pollution circle results unsuccessful. In most of the cases, drug consumption is due (or at least is increased) to pathologies related to the environment pollution such as allergies and pulmonary diseases caused by polluted air, stomach diseases caused by polluted foods and so on.

The ageing of the population in technologically advanced society also causes the increase of pollution by drugs. However, it can be stated that a real comparison of the average age of humans as function of the time cannot be done.

The World Health Organization defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".

Therefore the increased pharmaceutical production of the last 10 years cannot be only addressed to the cure of illnesses, but also to contribute to the reaching of this wealth. In addition, the term Ecopharmacology treats (see Definitions section) pharmaceutical active principles, phytosanitary, personal health care and veterinary products. This is correct as very often they have the same origin and, overall, all of them are actually massively used with a scarce knowledge of their negative effects and in

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some cases in an illegal way. With respect to the past, due to the increasing researches on the subject, more strict rules regarding the use of these products are applied and more information to consumers is divulged. In every case this is not enough to solve the problem rising from their dispersion in the environment as, really, the main way by which such products reach the waters is the incomplete metabolisation by the organism, with the consequent excretion of a certain amount of the starting products. Moreover, metabolites that in some cases are more noxious of the starting compounds are also excreted.

Drugs are generally recalcitrant molecules and this is a positive economic factor as they can have a long expiration date. On the contrary this brings to a more serious ecological impact bound to their persistence in different environmental compartments. Depending on their chemical–physical properties, first of all their polarity, they can reach, more or less quickly, the surface-water bodies and the water-bearing stratum. Mainly during the last 20 years many researches treated with the presence of drugs and their metabolites in water bodies [1,2] and, in all the cases contents of the order of nano- and micrograms for litre were found. The toxicity of such compounds was tested on different aquatic and terrestrial organisms and enough data are actually available [3].

Classical remediation methods for wastewater in all the performed researches resulted to have a low efficiency.

2. Definitions

Because of the complexity and relatively newness of the argument, in order to facilitate the literature reading, we would give some definition about the terms often used (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.

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 [4] for International Drug Monitoring 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.

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 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" [5] 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.

ATC/DDD methodology adopted in order to evaluate the population's exposition to drugs. ATC means Anatomical Therapeutic Chemical Classification and allows to divide drugs as a function of the part of the human body affected by disease. DDD means Defined Daily Dose and allows to treat data independently from the different pharmaceutical form and different dose of the active principle.

3. Drug production and consumption

Pharmaceuticals cover a high portion of the worldwide industrial field, due to their use not only for humans but also for animals as additives in foods (example in Table 1).

Europe held an about 30% of the global pharmaceutical market, being second with respect to US (50%) so constituting a source of wealthy and employment; at the same time more than 2000 different pharmaceutical substances are used in EU with a consistent cost for the Sanitary Systems. Just as an example, Fig. 1 shows the total percentage increase of the costs due to the always increasing Defined Daily Dose (DDD, see Definitions section) that never is balanced by the decreasing price of the products.

In Table 2 a comparison of the consumption of some of the most widely used pharmaceuticals in the period 2001–2006 is done. It can be seen that cardiovascular diseases constitute the main source of drug use and had the most consistent increase between 2001 and 2003 while luckily this trend stopped in the next years.

Table 1
Italian consumes of antibacterial drugs. Data from Italian National Health Service

	Tons/year	%
Human medicine	5400	52
Veterinary	5903 [a]	48
Total	10,493	100

[a] 1599 tons/year are used as growth promoters.

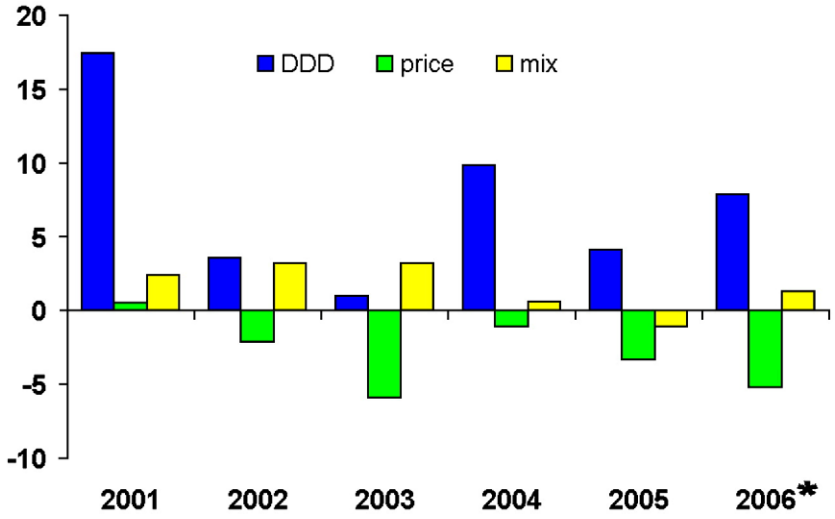

Fig. 1. Trend of the Italian cost for drug starting from 2000. Data from CeVEAS (Center for the evaluation of the efficiency of the Italian Sanitary System. *Calculated on the first 9 months.

As already said, the increasing consumption of pharmaceuticals is mainly due to the ageing of the population, but it must be pointed out that also children are subjected to diseases that often can be attributed to allergies from polluted environment and psychosomatic causes bound to stress (Fig. 2).

4. Pathways of dispersion of drugs into the environment

The high production of pharmaceuticals very often let to exceed the market request so constituting a noticeable amount of products to be wasted. More, as a consequence of the request for an increasing quality production, also due to strict laws, a further increase of the products to be wasted has to be attributed to those not passing the quality control step.

Table 2
Italian consumption of drugs expressed as DDD/1000 residents

ATC (I level)	ATC class	2001	2002	2003	2004	2005	2006[a]
C	Cardiovascular	42.6	45.0	48.0	48.3	48.7	48.7
A	Gastroenteric and metabolism	10.7	11.1	11.4	11.4	11.4	11.8
J	Antimicrobial for systemic use	3.3	3.2	3.3	3.0	3.0	2.8
N	Central nervous	4.5	5.1	5.5	5.6	5.7	5.8
R	Respiratory	8.2	7.5	5.4	5.9	6.0	5.8
B	Blood and emapotopoietic organs	7.3	8.1	8.6	8.7	9.0	9.2
L	Antineoplastic and immunomodulator	0.8	0.8	0.8	0.8	0.8	0.7
G	Genital–urinary and sexual hormones	5.9	5.8	5.8	5.3	5.0	4.7
M	Muscle-skeleton	5.3	5.3	5.2	5.3	5.0	4.7
H	Systemic hormones (no sexual)	3.1	3.2	3.3	3.3	3.4	3.5
S	Sensory organs	2.7	2.6	2.1	2.0	2.0	1.9
D	Dermatologic	1.8	1.5	0.4	0.4	0.4	0.4

Data from CeVEAS (Center for the evaluation of the efficiency of the Italian Sanitary System).
[a] Calculated on the first 9 months.

Characteristics of resistance to the common biotransformation mechanisms are requested to the synthesised drugs, in order to protract the persistence in the organisms of an unchanged pharmacological active substances and also, as above said, to extend the expiration date. This brings to a high cost for the disposal of unsold products that must be added to the one needed to purify the industrial effluents.

As the processes are controlled and ruled by law this is not the main cause of pollution by drugs.

The main cause of dispersion of drugs for human use is instead the not full efficiency of STPs (sewage treatment plants) in their mineralisation. Not metabolised pharmaceuticals and metabolites enter the STPs by excreted urine and faeces from consumers and only in a recent past they are looked for, due to the underestimated risk bound to their presence in the environment [6]. In Table 3 some data relative to the presence in STPs of some of the most common drugs are reported (data source: REMPHARMAWATER European Project) together with some LD_{50} data.

As it regards veterinary products the problem is more serious for no confined farming as the animal's excretions are directly dispersed in the environment; in such case the best life conditions would not require administration of medicines but the administration of growth promoters cannot be excluded.

Further drug dispersion comes from [6,7]:

- uncontrolled draining away, also involuntary, both by the patients and by producers or distributors still unconscious of the problem;
- incorrect use (fraudulent, doping, wrong proportions) by people and through animal breeding in farms;
- advances in medicine and pharmacology that allow to increase the number of drugs looking for higher specificity adverse different diseases as well as different pharmaceutical formulations, (including packaging of the single dose, excipients…) letting to a higher specificity toward different target organs;

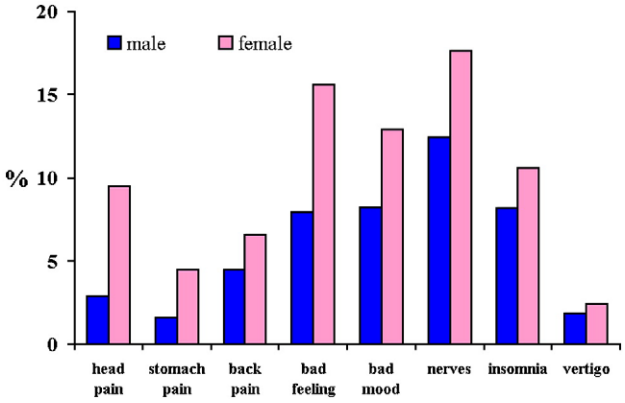

Fig. 2. Main diseases in children of primary scholar age.

- healthier lifestyle that involves an easier access to drugs, health care products, gross domestic disinfectants or similar compositions products.

It would be necessary to add to these the draining with the same ways of veterinary drugs, disinfectant, antibacterial and plant protection products which are now heavily used in every field. Perhaps, some of them may be assimilated to drugs (having molecules with similar structures) and are produced in huge amounts and used almost without control.

These molecules are transported into the food chain and also in superior organisms. The importance of such problems is also highlighted by several initiatives of EU with the purpose to monitor the presence of drugs and other pollutant molecules in the environment and to look for methods for their correct and effective abatement.

Table 3
Results of the HPLC analyses performed on samples coming from different STPs located in the South Lazio (Italy), at the plant exit and some LD_{50}

Drug	Oral LD_{50} (mg/kg)		Concentration (μg/L)		
	Rat	Mouse	Sample 1	Sample 2	Sample 3
Gemfibrozil	4786	3162	0.81	0.84	4.76
Fenofibrate	2000	1600	0.16	0.10	0.16
Bezafibrate	1082	723	–	–	0.91
Clofibric acid	940 (clofibrate)	1220 (clofibrate)	0.68	–	0.23
Ibuprofen	636	740	0.18	0.02	0.02
Flubiprofen	–	–	–	–	0.34
Naproxen	248	360	0.29	0.41	5.22
Diclofenac	53	95	0.47	1.48	5.45
Phenazone	1705	1310	–	0.37	–
Acetobutolol	–	–	0.04	0.02	0.11
Metoprolol	–	–	0.01	0.01	0.10
Oxprenolol	–	–	0.01	0.01	0.03
Propanolol	–	565	0.01	0.01	0.09
Carbamezapine	1957	–	0.30	0.34	0.50
Trimetroprim	7000	–	0.04	0.03	0.15
Ofloxacin	3590	–	0.01	–	0.03
Lomefloxacin	3800	4000	0.32	0.13	0.22
Enoxacin	–	–	0.03	0.01	0.03
Norfloxacin	>4000	–	0.07	0.06	0.06
Ciprofloxacin	>5000	–	0.07	0.06	0.04

5. Persistence and toxicity of drugs and their residues

The fate of any substance in the environment is determined by its capability to undergo biotic (biodegradation) and abiotic (photolysis, photooxidation, hydrolysis processes) degradation.

Due to their specific action, pharmaceuticals are not subjected to microbial degradation, on the contrary they can act reducing the bacterial flora present in the wasting site while, due to their desired stability, also abiotic natural process are scarcely efficient.

In between the last, the process generally called “photo-degradation” can be considered the main, and excluding aqueous oxidant solutions, may be the unique way to eliminate drugs and their residues from the environment. Photodegradation is the process by which the UV component of the solar radiation produce the C–C bond break and, in longer times, the break of the entire molecule.

Such mechanism depend on:

- Recalcitrance of the active principle
- Energy and intensity of the UV radiation that are both low for the solar component reaching the Earth’s surface
- Daily, seasonal and geographical variation allowing to a limited exposition time [8,9]
- Location (outside ground or buried) and physical state (solution, powder, tablet, original market packaging…) of the molecules to be degraded that affect the exposition to the radiation
- Chemical parameters, mainly pH and cationic exchange capacity in the case of soils and sediments; for water bodies, pH and presence of compounds such as nitrate, humate and metals originating powerful oxidizing species like OH radicals and singlet oxygen, must mainly considered
- Physical properties of the wasting site such as aggregation, temperature, humidity.

The presence of drugs in surface and water-bearing stratum demonstrated the inefficiency of the natural degradation process and this involves toxicological and ecological problems [10,11]. As an example in Fig. 3 the trend of photodegradation for Naproxen is reported. It can be seen that to a decrease of the

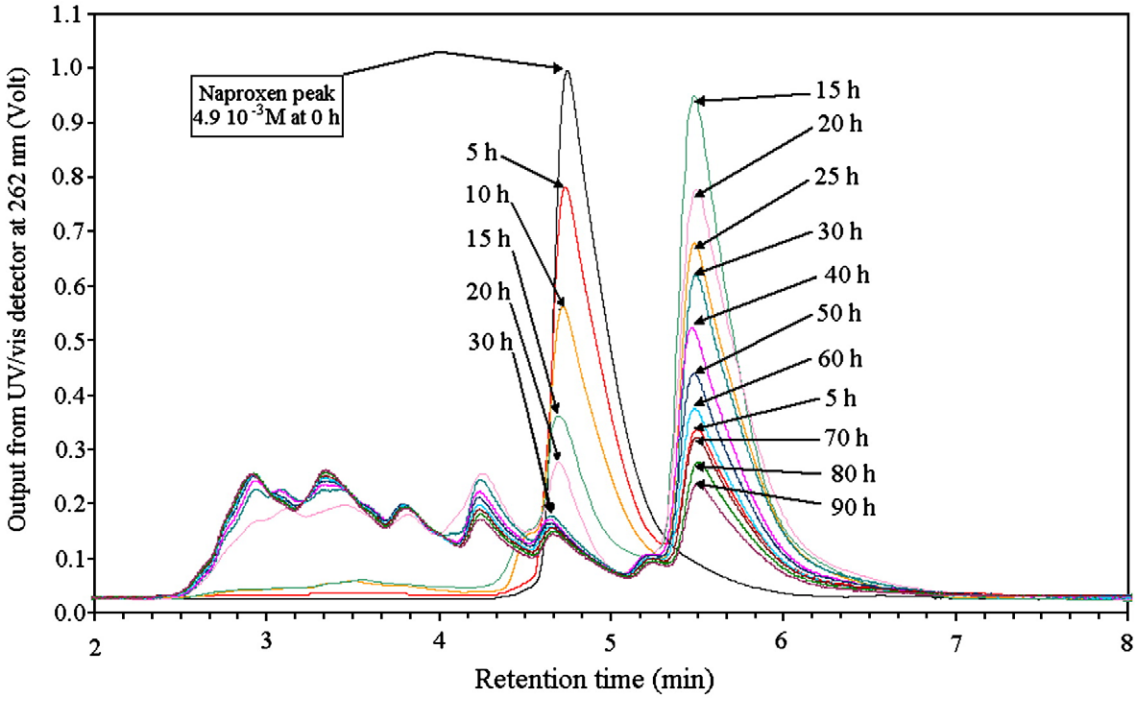

Fig. 3. Trend of a simulated daylight photodegradation of Naproxen. HPLC chromatograms refer to different irradiation time by a simulating solar lamp (D65 spectrum, 600 W/m^2). Source: running thesis of one of the authors.

Naproxen active principle corresponds an increase of residues that in turn degrade to different residues that persist after 90 h of continuous irradiation by a simulating solar lamp.

Aquatic habitat suffers from direct and indirect effect of pharmaceutics, phytosanitary, personal health care and gross domestic products [12]. The indirect effect is mainly due to the presence, and consequent surface-active effect, of detergents as well as of hydrophobic compounds in the products that, layering in both the cases on the water surface, prevent the solar penetration and the needed exchange of gaseous compounds, first of all provoking a BOD decrease. The real noxious or toxic effect depends on the particular desired action of the single product.

The capability of pharmaceuticals to exert toxic effects towards living organisms is generally tested by using algae, fish and mollusc.

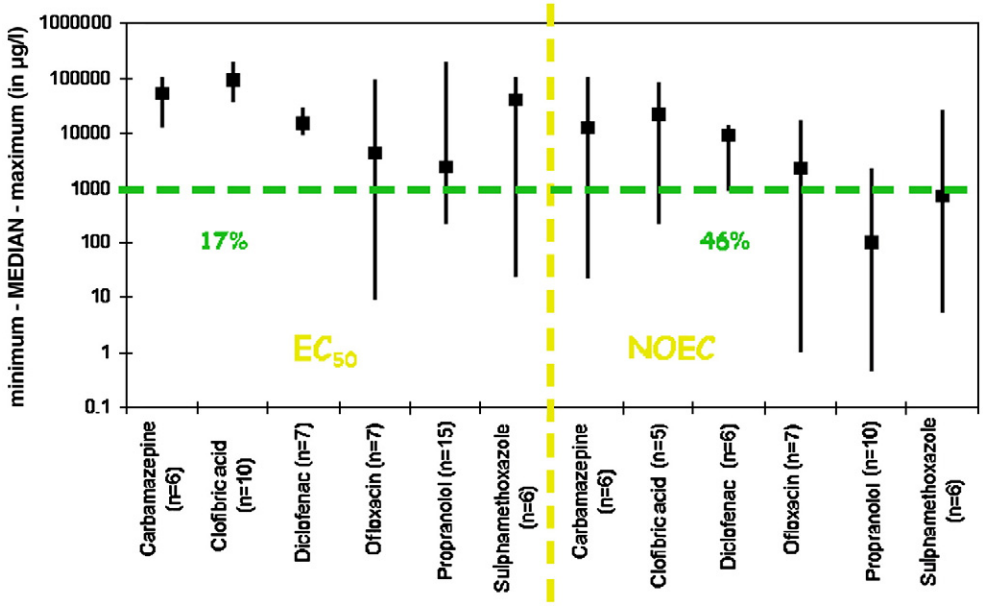

Fig. 4. Median and range of acute LD_{50} and chronic NOEC for different drug tested on different aquatic species. Source: REMPHARMAWATER European Project.

In Fig. 4, acute (LD_{50}) and chronic (NOEC) effects of 6 widely used drugs on 15 different species (algae, fishes, crustaceans, rotifers) are compared. Both the effective concentration causing effect (LD_{50}) and the no observed effect concentration (NOEC), even if have relative high median value, in some case range from value of the microlitre for litre order.

6. Classical and innovative treatment of drugs waste

The common treatment adopted in STPs (oxidation, ozonization, UV disaffection, membrane processes...) results almost ineffective in the abatement of drugs; from researchers performed in Netherlands, the removal rates results an efficiency lower than 10% for X-ray contrast media and lower than 25% for antibiotics; removal of antiepileptics, betablockers and lipid-lowering agents ranges from 10 to 80% and a 95% removal can be obtained for household analgesics.

Among the innovative technologies, heterogeneous photocatalysis can be considered promising. It bases on the intrinsic electronic properties of some semiconducting solids that are so suitable to act as photocatalysts. They can be used either suspended in the polluted aqueous effluent (so needing a filtration for their recovery) or supported on various rigid supports. The technology of membrane processes has already been demonstrated to be competitive with respect to other separation processes, so, a coupling of a photocatalytic reaction with a membrane separation process can exploit the synergy of both the technologies as the membrane plays both the role of confining the photocatalyst and of separation barrier selective at molecular level.

7. Analytical methods for drugs determination

Due to the complexity of the matrices containing drugs (wastewaters) and to the generally very low level at the STPs exit and overall in surface water, a separative or extraction technique and an enrichment of the samples is needed [12,13]. Chromatographic techniques such as GC–MS and LC–MS are the most suitable for both the control of the purifying plants and determination of the drug content in surface waters. A preconcentration can be obtained using suitable adsorbents materials, they must be inert toward the analytes of interest in order to avoid their transformation and consequent invalidation of the analysis, highly selective to avoid possible interferences and must ensure an easy re-extraction of all the compounds of interest.

8. Guidelines and laws

The USA Food and Drug Administration (FDA) have regulated pharmaceuticals in the environment since 1977 under the auspices of the National Environmental Policy act of 1969. Regulation occurs through the environmental review process for New Drug Applications submitted to the FDA. In Europe, draft guidelines for environmental risk assessments (ERAs) that accompany Marketing Authorisation Approval Applications have been available; the most recent guidelines were issued on January 2005 and are expected to be approved and implemented on 2006. A key change in these guidelines is the requirement for chronic rather than acute ecotoxicity testing, recognising that most pharmaceutical active ingredients are not acutely toxic but may have longer-term chronic effects on aquatic organisms at low levels. In Canada a requirement for environmental assessment is in place and a specific ERA process for pharmaceuticals is under development. In Sweden, a classification scheme based on environmental characteristics of active pharmaceutical ingredients (APIs) is being implemented.

9. Ecopharmacology projects

Even if not exhaustive and very simplified, the exposition of the problematic bound to the consumption of pharmaceuticals, health care and gross domestic products, evidences the complexity of an Ecopharmacology research even when involves only one product. Since the late 1980s GlaxoSmithKline (GSK) actively worked with various regulatory agencies to ensure the knowledge of the potential environmental impact of pharmaceuticals and to minimise the related risks. 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 [1,14]. The industry task force developed a state-of-the-art geographically explicit model to facilitate a deeper understanding of the potential environmental distribution of pharmaceuticals at a local or regional level. The PhATE™ (Pharmaceutical Assessment and Transport Evaluation) model is a watershed-based approach and was developed as a tool to more realistically estimate concentrations of active pharmaceutical ingredients (APIs) discharged to US surface waters through consumption of medicines. Monitoring data generated by the United States Geological Survey were used to corroborate the model [14].

PhATE™ 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.

Calculated PEC take into account the consumed amount of product, the number of inhabitants, the daily effluent volume, the percentage removal in the worst case (i.e. no metabolism and no STP removal) and an estimated dilution factor.

Such indicator is also used by European researchers; in Fig. 5 values of the Maximal Environmental Concentration (MEC) found in German STP effluents and surface waters are compared with the corresponding PEC values using 5 widely used medicinals. It can be seen that MEC and PEC are of the same order but can noticeably differ.

US Industries also anticipated Europe in the set up a model to carry out human health risk assessments for 26 active pharmaceutical ingredients (APIs) with the Project PhRMA PhATE™ (Pharmaceutical Assessment and Transport Evaluation) and, always under PhRMA, are working on potential impact of APIs on aquatic life.

Can Europe improve Ecopharmacology? The European Community already funded some projects on the subject (see

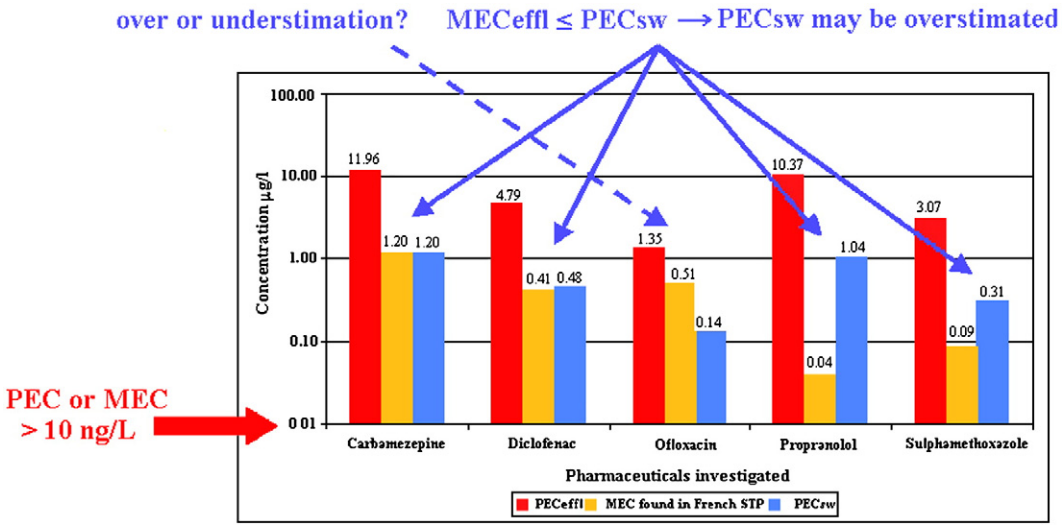

Fig. 5. Comparison of PEC and MEC for 5 widely used drugs in effluents and surface waters. Source: REMPHARMAWATER European Project.

the next dedicated paragraph) but data coming from them, surely need not only to be increased but also to be analysed at the best. In our opinion, using expert systems and a chemometrics data treatment this goal can be reached.

10. Help by chemometry, multivariate analysis and expert systems

Even if already said, the complexity of Ecopharmacology must be stressed in order to understand the real need for an help by advanced data management. Starting from the drug production and ending with their environmental impact we can shortly list the main supports obtainable through chemometry, multivariate analysis and expert systems (see the next paragraph)

a) model design: the implementation of multivariate analysis in drug design is not a news. Through this approach the pharma companies obtain a solid result in design and a consistent reduction in times. The Quantitative Structure–Activity Relationship (QSAR) chemometrics methods [15] must be cited, the process by which chemical structure is quantitatively correlated with a well defined pharmacological/chemical reactivity/activity.
b) sampling: one of the most important step in the measurement iter; error in this stage cannot be corrected. Citing the famous book of D.L. Massart the sampling have main roles in the knowledge system with: measurability and controllability, estimators of system states, choice of an optimal measuring system: cost considerations, multivariate statistical process control, sampling for spatial description, sampling for prediction, etc. [16].
c) data collection: by the modern data acquisition systems, it is easy to obtain large amount of data which fill the computer memory and the mass storage but without chemometrics they constitute only “a collection” of numbers!
d) data treatment: scaling, outliers detection, missing data fill, leverage point discovery, pattern recognition, cluster analysis are only a few examples of the possible data treatments, surely necessary, to obtain valid data able to be inserted into databases or expert systems.
e) decision: the large amount of data, coming from the information on drug production and regional sale, from the analyses of water bodies (including wastewaters) looking for the active principles and their metabolites and taking into account the type and number of remediation processes, can be finally inserted, we hope, in a European (government) expert system for their management letting to suggestions for the environment protection.

11. Expert systems (ES)

Expert systems are computer programs that are derived from a branch of computer science research called artificial intelligence (AI). AI’s scientific goal is to understand intelligence by building computer programs that exhibit intelligent behaviour.

These computer programs was developed by researchers in AI first in the early of 1960s up to 1970s and finally commercialized in the 1980s. Today is “embedded” in many control softwares to monitor and guide industrial productions.

An expert system generally consists of three levels: a graphical user interface (GUI) to interact with users in a friendly manner, an inference engine which drives the knowledge base through reasoning processes, and a knowledge base, database and model base which are used to store data, knowledge, information and rules.

Often the GUI works interactively through a system of questions–answers. The questions are submitted to human (or sensor) and the software elaborates them, through a suitable algorithm, basing on the knowledge base; the last is continuously enriched by the new data and, overall, from the correspondence between its own solution and the real solution. Just as an example: if from meteoclimatic data the ES foreseen that it will rain but this don’t occur, the system store its solution as wrong. So, ES not only have to make calculations but act as a

human, i.e. solve problems through learning, reasoning, understand language and so on.

The primary goal of expert systems research is to make expertise available to decision makers and technicians who need answers quickly. There is never enough expertise to go around (certainly it is not always available at the right place and the right time). The same systems can assist supervisors and managers with situation assessment and long-range planning.

These knowledge-based applications of artificial intelligence have enhanced productivity in business, science, engineering, and the military. With advances in the last decade, today's expert systems' clients can choose from dozens of commercial software packages with easy-to-use interfaces.

The most famous examples of early expert systems, in medical field, are:

1. MYCIN, one of the first useful expert systems for diagnosing and recommending treatment of bacterial infections of the blood, developed by Shortliffe and associates at Stanford University at the beginning of eighties [17].
2. deDombal's Leeds Abdominal Pain System, an expert system for acute abdominal pain, developed by F.T. deDombal at the University of Leeds.
3. Help System, a hospital-based system, developed at LDS Hospital in Salt Lake City.

In the field of prediction of environmental pollution, one of the more recent expert systems used in U.S.A. is the PhATE™ (Pharmaceutical Assessment and Transport Evaluation).

Today, we found several recent examples of expert systems used (for example) in the development and production of pharmaceutical formulations [18]. Also we find example of "modelling" for two pharmaceutical molecules in rural environment [19].

We hope for a large expert system that can maintain ANY information obtained in Europe about: productions, sale, distribution, import–export, discovering in water plan, academy of government measure, of pharmaceutical in surface water. With those mass of input data the E.S. can, probably, answer to many queries from researchers and from law-writers as:

- Why the most sold drug is not the most widely dispersed?
- Why this drug reach the bearing stratum?
- Why two drugs of the same toxicity have different environmental impacts?
- How many times must we wait to see an environment impact of new drugs?
- …

12. European Projects

Even if the products considered in this paper could be included in ERA-based European Projects (http://www.cordis.lu), we here furnish a list of only those specific on the treated subject.

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.

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.

Rempharmawater (Ecotoxicological Assessments and Removal Technologies for Pharmaceuticals in Wastewater): the 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 ecotoxicological, physical and chemical data, properties, etc. on the drugs studied.

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.

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.

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 enduser 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).

Reclaim Water (water reclamation technologies for safe artificial groundwater recharge): from project web page "Solutions to global water stress problems are urgently needed yet must be sustainable, economical and safe" and also "Major concerns about the safety of this exploitation route of an alternative water source are connected to microbial and chemical contaminants occurring in wastewater, among which

are emerging trace organics like endocrine disrupters and pharmaceuticals". The project started in October 2005 and live for 36 months.

13. Conclusions

Problems related to use and abuse of pharmaceuticals, plant protection, health care and gross domestic products are actually worldwide considered. Governments, first in time the United States, acknowledged the solicitation started from researches that evidenced their presence in the environment and overall, even if at very low concentration, in drinking water [14]. The achievement of a high quality drinking water is not only a problem in USA or EU [20]. As a consequence Ecopharmacology-based projects were funded and ERA guidelines and laws become stricter for these compounds.

As the subject is relatively new and both the number of the products and the consumed quantities are very high, actually available literature is limited and in most of the cases, for a single product, incomplete.

In conclusion, this paper aims to promote an international interdisciplinary cooperation in the Ecopharmacology field and, possibly, in the submission of an European Project concerning the setup of an Expert System starting from a treated by Advanced Statistical Methods database, containing all the actually available data and going on with new data.

Really a decision support systems for the selection of the most efficient management options to prevent effects on biodiversity and to prioritise contamination sources and contaminated sites is mentioned in the MODELKEY (Models for Assessing and Forecasting the Impact of Environmental Key Pollutants on Marine and Freshwater Ecosystems and Biodiversity) European Project that started with the sixth Framework program and will end on 2010, but a reading of the full program could reveal any lack.

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