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Impact of Drugs on the Environment: State of Play, Risks, Evaluation, Communication

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Abstract – The aim of this Round Table was to perform an initial assessment of the state of play of the impact of drugs on the environment. Demographic growth throughout the world and drug consumption which is constantly on the increase result in an ever increasing presence of medicinal substances in the various compartments (air, water, soil) with potential repercussions on the environment and on health. For the first time, the Giens pharmacology workshop have scheduled this topic outside the conventional sphere of action of Giens. A very high level of interest in this topic came forward both from the members of the round table and the listeners and it is certain that the round table opens the door to new initiatives for a subject about which there is still little knowledge. The following issues were therefore successively addressed: the fragmentation of the knowledge about the subject and its deficiencies concerning the impact on health, both of the wastes as a whole and that of specific drugs, the performances of the water treatment methods, the sources of pollution, the environmental impact, the lines of regulatory development, the impact on the environment and health and the training programmes to be set up among all protagonists, both professional and in the general public.

1. Introduction

The presence of drug residues in aquatic environments was detected during the 80's and led scientists to ask themselves about the consequences of these pollutants for the environment and human health.[1,2] Several thousands of tons of drugs for human or veterinary use are indeed consumed every year throughout the world and are discharged, in the original state or following metabolisation, into the environment. Environmental pollution by drug residues is clearly demonstrated today by a large number of field studies and renders drug wastes an emerging environmental problem.[2–6]

Drug residues have not only been found in surface waters, underground waters, residual waters and sewage treatment plant sludge, but also in some samples of drinking water.

In comparison to the many other environmental pollutants (pesticides, heavy metals and hydrocarbons...), the health risk feared is more specifically related to the specific nature of drugs, which are substances displaying a high level of biological activity at low concentrations. Although some effects on fauna and flora are fairly well known today[5,7] (bacterial resistance related to antibiotics? Endocrine disturbing effects of hormones and related molecules? Genotoxicity of many anticancer drugs?...), there are still may unknown factors in the health repercussions of environmental pollution by drug wastes[8–10] and the methods for demonstrating them are difficult, non-standardised and poorly developed.

The complexity of the problem is furthermore aggravated by the very wide diversity of molecules used, essentially excreted via the faecal or urinary route. There are a large number of sources of dispersal, which are both vague (general population treated at home) and specific (pharmaceutical industry, healthcare institutions).[11]

In the majority of cases, the drug wastes are discharged into the urban waste water networks where they reach the waste water treatment plants, which, by definition, are not designed to

⋆ For the list of participants, see end of article

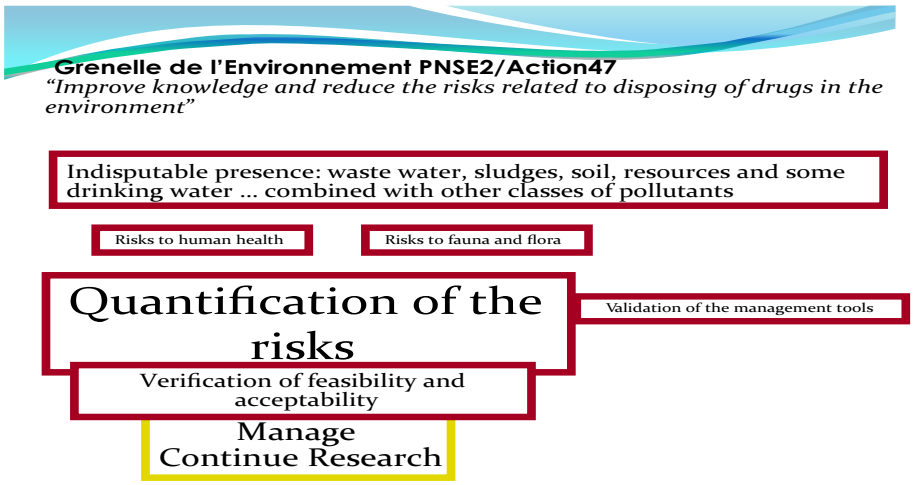

Fig. 1. Drug in "*Grenelle de l'environnement*".

eliminate drugs and therefore the efficacy is highly variable, between 0% for some compounds and more than 90% for other molecules.[12]

The organisational committee of Giens has become aware of these issues and has included this poorly known topic in the 2010 Giens workshops, a topic which we have the privilege of expanding with representatives of the Authorities, industrialists and experts.

This round table falls within the framework of both the *Grenelle de l'environnement* and the National plan for drug residues (PNRM).

The topic of drug residues is a subject which is both far-reaching and complex. This is why, within the context of the Giens workshops, it was chosen to restrict the scope of reflection to a number of aspects considered as having priority and/or more directly related to the competences of the participants in this round table.

Although the various different compartments of the environment may be affected by drug residues, the water compartment is the compartment in which pollution is to be feared the most and which has been the subject of the largest number of scientific studies. We have therefore restricted ourselves to the "water" compartment.

Furthermore, drugs for human use have been selected as the priority source of pollution, thereby taking account of the nature of the participants in Giens concentrated on human medicine (veterinary drugs must be subject to separate and additional studies given the massive quantities that these products represent). Furthermore, the specific problems related to radionuclides were not addressed.

It was our wish that these reflections on this subject should not be limited to the environmental risk to flora and fauna and should take consideration of the direct or indirect health impact of disposing of drugs in the environment.

Finally, all the participants considered that, as a preliminary to any reflection on the risks of environmental pollution by drug residues, it is important to reiterate the fact that the therapeutic value of drugs is their benefit/risk ratio.

Four questions were therefore asked:

- Which elements of knowledge must be improved and how?
- How can the sources be reduced?
- How can one increase consideration of the environmental risk in the marketing authorisation file and the transparency file?
- What form of communication is to be adopted? How can one create awareness among and educate citizens?

2. Which elements of knowledge must be improved and how?

At the beginning of this 21st century, one is obliged to admit that our knowledge in this field remains very patchy and limited. Although some datas are available concerning specific molecules and their repercussions on human health, it remains that the studies of the impact on the latter are still extremely limited and their methodology is worth developing. The effects of drug residues on humans are still to be demonstrated, even though it has already been possible to observe consequences for wildlife.

Among the points to be examined in depth, one may mention:

- The long-term effects of low concentrations on human health;
- The overall health impact of the media (first and foremost water) containing drugs (in drug and non-drug interaction with other pollutants) [it should not be forgotten that drugs are not isolated pollutants];

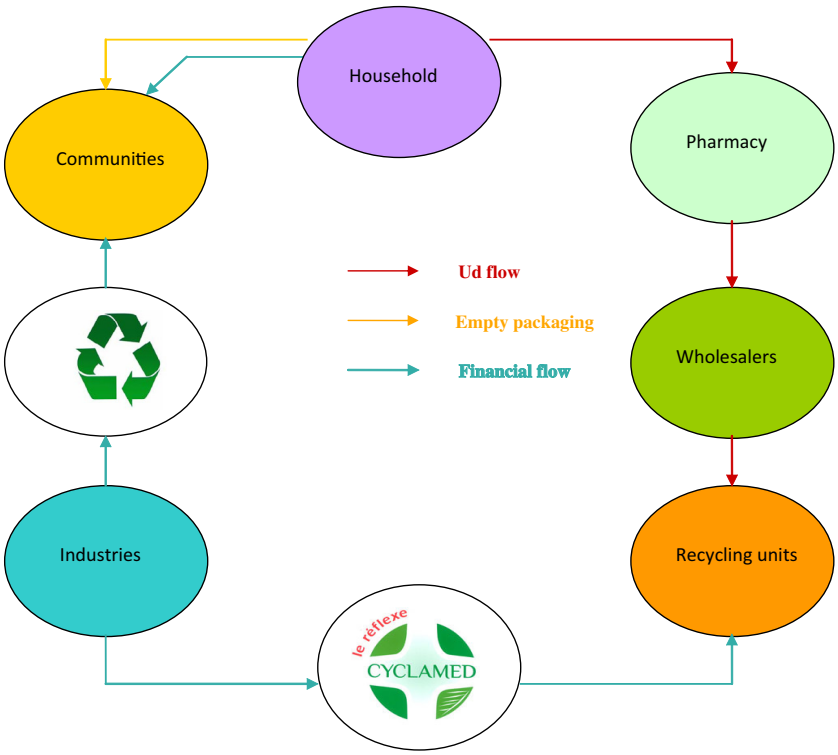

Fig. 2. Role of Cyclamed to reduce the environmental impact of durgs. (with kind authorization of Cyclamed).

- The effects of combinations of drugs or of drugs and other substances regularly ingested by humans;
- The effects on susceptible or specific populations (pregnant women, children, elderly persons, etc. ...);
- The role of the transformation products;
- Improvement of the domestic and hospital waste water treatment systems.

3. How can the sources be reduced?

Four main sources of disposal in the environment of drugs for use in humans have been identified:

- Excretion by patients in urine or faeces, either in the original active form or in the form of active or inactive metabolite;
- Unintentional or intentional industrial discharges, whether accidental or not, by chemical synthesis or production sites;
- Wastes from unused drugs (UD's) by patients who, instead of returning the latter to a pharmacy, either throw them in their dustbin or down their toilet, or dissolve them in tap water;
- Wastes from university, research or biology laboratories, or even by healthcare institutions (hospitals, clinics) or by outpatient healthcare personnel.

It is therefore necessary to apply adequate measures at each of these sources in order to limit pollution of our environment. Two areas have already been the subject of a very large-scale programme:

- Industrial wastes: the pharmaceutical and chemical industry has implemented drastic measures since the accidents of the 80's designed to minimise the risks of accidental discharges by setting up for example recovery tanks for the water used to extinguish a fire;
- Unused drugs: France was the first country in Europe to set up in 1993/1994 a system for recycling and energy recovery of UD's by households called Cyclamed. The pharmacist is obliged to collect them, which are then transported by the wholesalers to their distribution centre and subsequently to energy recovery units (figure 2). Thus, approximately 13 500 tons of UD's are recycled every year.[1]

4. How and why can one increase consideration of the environmental risk in the marketing authorisation file and the transparency file?

Faced with the increasing significance of the environmental risk, it appears necessary to achieve progress in the files allowing marketing authorisation of proprietary medicinal products and

likewise those submitted with a view to applying for eligibility for reimbursement.

In the same manner as assessment of efficacy and safety, the environmental impact and its health repercussions must be taken into account in the future by public decision-makers; it is therefore important for this purpose to provide them scientific enlightenment.

It is important to be aware of the ecotoxicity of the new drugs at the time of the marketing authorisation, not in order to prevent authorisation which is based on the benefit and risk to the patient, but in order to attempt if appropriate to limit or indeed antagonise this toxicity and a possible negative impact of the drug on the environment. The requirement for ecopharmacoepidemiological studies as part of the regulatory post-MA studies for example by an environmental constituent of the risk management plans represents an opportunity to improve the state of the knowledge on the subject.

Since 2006, account has been taken of the environmental impact in the MA file for new products, but the data remain confidential, which represents a limiting factor for some field studies. Furthermore, this assessment still comes up against various methodological difficulties. The KNAPPE programme (Knowledge and Need Assessment on Pharmaceuticals Products in Environment waters),[13] focused between 2005 and 2009 on identifying priority actions to be taken in order to limit the impact of pharmaceutical products in the environment. It noted the lack of standardised tests for assessment of certain effects, such as disturbing endocrine effects and the need for launching new European programmes concerning this subject of assessment of the effects.

Within the context of eligibility for reimbursement, if one may envisage the idea that an environmental impact may modify the medical service rendered to the community by the drug and that for similar medical efficiency, a more environment-friendly drug is liable to render a better service, no explicit criterion that takes account of the impact of the drug on the environment exists to date. The participants in the Round Table agreed on the need to provide scientific enlightenment of the public decision-makers concerning the anticipated environmental impact of the drug, but no consensus was achieved either on the structure involved in this assessment (multidisciplinary by necessity) or on the criterion to be used [integration in a modified public health interest (PHI)].

Did not one ought to incorporate new criteria, such as ecodesign of the drug or provision of antagonists or neutralisation systems for the drug wastes, in the price fixing decision?

A majority of protagonists now considers that the drug must be placed on a par with other products (biocides, etc.) and that consequently, the guidelines stipulating the rules for assessment of the environmental risk of all these compounds ought to be revised in the sense of harmonisation of the assessment criteria. For environmentalists, drugs for use in humans must fall within common law with regard to the environment. Although as a citizen one can only agree with this principle, one should nevertheless take account of the contribution that the drug makes to public health and of the fact that it must be subject to appropriate regulation.

5. How is one to communicate and create awareness?

Communication concerning the risk to the environment and health remains particularly complex and sensitive for populations. Information should be provided without panicking and "an appropriate balance between alarm and negligence" should be obtained. It therefore appears essential to distinguish between the types of communication according to category of citizens:

- For the general public, communication must be initially geared to the preventive measures that everyone can and should adopt, such as selective sorting, return of UD's to the pharmacy and observance of specific actions designed to limit pollution of natural environments;
- For healthcare professionals, improved information about the problem of drug wastes in the environment appears essential, whilst also calling on them to be intermediaries before their patients concerning the preventive measures that they can adopt.

Finally, the new organisation of our health system, through the hospitals, patients, health and territories law (HPST),[14] assigns a specific role to the Regional Health Agencies, the sphere of action of which also extensively covers health and environment problems. There is definitely a mainstay here for communication in the years to come.

6. Summary of the recommendations

There are a large number of protagonists in this complex area of disposal of drugs in the environment, ranging from the producer to the consumer and it must be acknowledged that efforts have been made by all for several years now. It remains that awareness of the problem is still recent and measures must be adopted in order to forestall the long-term repercussions on our environment, our health and the health of future generations.

In practice, for each of the questions raised, we propose the following few working topics:

6.1. Elements of knowledge to be improved

- Targeting specific actions in the basic research programmes concerning these more or less long-term risks to humans.

- Development and/or adaptation of the epidemiological measures in order to study the health impact of drugs on the environment.
- Acquisition of ecopharmacological and epidemiological data on exposure and effects.
- Encouragement of public/private partnerships in this sector.
- Assessment of the performances of the water processing systems on priority molecules.
- Focusing of research on classes of priority molecules (products with hormonal and cytotoxic activity and antibiotics...).
- Development of information about drugs derived from the new technologies (nanodrugs) and biotherapies.

6.2. Reduction of the sources

- Assessment of the relevance of pretreatment at source of the effluents from hospitals and medical and social institutions.
- Encouragement of research into neutralisation products for the most ecotoxic molecules.
- Create awareness among the research laboratories and their trusteeships.
- Optimisation of processing of the discharges from the chemical and pharmaceutical industry.

6.3. Progress in consideration of the environmental risk in scientific assessment (MA file, transparency file) and in public decisions (MA, application for reimbursement, prices)

- Request studies of impact on the environment and health for a priority list of "old" molecules not documented since introduced on to the market before 2006 (regulatory requirement date for performance of an assessment of the environmental risk in the MA file) but presenting a suspect risk (hormones, cytotoxic agents, antibiotics...) or being high-consumption molecules.
- Introduction of an environmental constituent in the risk management plan (RMP).
- Assessment of the direct or indirect impact on human health related to drug residues and those from other health products. Should this element be incorporated in a new public health debate? The debate is open.
- Setting up of an eco-onus and/or an eco-penalty.
- Introduction of the dimension of lasting development in the framework agreement between drug companies (LEEM) and the Economic Committee for Health Products (CEPS).

6.4. How is one to communicate?

- Continuation and intensification of the general public awareness campaigns for returning UD's to the pharmacy (Cyclamed).
- Creation of awareness among healthcare professionals and students in the medical and paramedical professions concerning the problem of drug substance residues in the environment.
- Development of the notion of selective sorting in citizens' minds.

7. Conclusion

Account must be taken of all these proposals as working approaches. Indeed, their cost and their practical realisation must be clearly understood with regard to the benefit that drugs provide to humans. Furthermore, this problem statement must also take into consideration veterinary medicine, which is a major consumer of drugs with substantial wastes (manures, etc. . . .) and be incorporated in a more global approach to environmental pollution in which drugs are only one of the factors in a multifactorial context in which many categories of chemical pollutants are involved (cleaning products, biocides, pesticides, etc.).

Drugs and the environment, a key work site for the 21st century.

Participants

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