STUDY ON THE ENVIRONMENTAL RISKS OF MEDICINAL PRODUCTS

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ABSTRACT:

The progress made by medical science during the last century and its positive impact on society are well known. Medicinal products are an important element of the medical practice and their beneficial effects (and side-effects) on human and veterinary health is widely acknowledged. However, the area where we lack a global view understands what happens when these medicinal products are discharged into the environment, either through consumption or as unused or expired products. Residues of various types of medicinal products (hormones, anti-cancer, antidepressants, antibiotics, etc.) have been detected in various environmental compartments, such as surface water, groundwater, soil, air, and biota. Such widespread occurrence obviously begs the question whether a concentration of medicinal products in the environment poses a risk for exposed biota or humans. In this context, we discussed about how the medicinal products enter the environment, behaviour of medicinal products, risks on the environment.

Keywords: *Medicinal products, Behaviour, Risks, Consumption, Environment*

INTRODUCTION:

Recent pharmacovigilance legislation in the EU acknowledges that the pollution of waters and soils with pharmaceutical residues is an emerging environmental issue. More recently, in the framework of the adoption of the Directive regarding priority substances in the field of water policy, the Commission has been asked to develop, instead of the report, a strategic approach to pollution of water by pharmaceutical substances by the end of 2015. This study, together with other relevant studies and reports, will provide the basis to develop that strategic approach. The study covers both human and veterinary medicinal products but personal care products are excluded.

The key steps (from an environmental perspective) in the life cycle of a medicinal product are manufacturing, consumption, and waste management. Contamination pathways along the life cycle depend upon the life-cycle step during which the emissions occur. In the contribution of manufacturing facilities to emissions of medicinal products and/or their residues is generally considered as negligible, even though pollution downstream of manufacturing plants has been sporadically observed while monitoring specific sites (e.g. the Rhine, Lake Leman in EU).

HOW DO MEDICINAL PRODUCTS ENTER THE ENVIRONMENT?

The consumption phase is considered to be the biggest contributor to the emissions of medicinal products into the environment, notably through excretions and incorrect disposal of unused medicines through sinks and toilets. Between 30 and 90% of the orally administered dose is generally excreted as active substance in the urine of animals and humans. However, the nature and number of medicinal residues mainly depend on the volumes and nature of the administered substances, their modes of administration, and metabolisation rates. Medicinal products can also directly enter the environment through feed surplus, notably in the case of aquaculture: a recent

survey measured up to 2.2 µg of teflubenzuron / kg of dry weight sediment coming from a marine fish farm in Scotland. Once in wastewater, treatment can partly eliminate or remove medicinal product residues, but some traces are still detectable in effluents as well as in the receiving surface and groundwater's. The residues remaining after wastewater treatment depend on the composition of the medicinal product, wastewater treatment process, and initial concentrations in the influent. For example, Ibuprofen, which is present in significant amounts in wastewater influents, is reduced by 60 to 96%, while Carbamazepine removal rates are much lower. As for landfills accepting medicinal products, sewage sludge can produce leachates containing concentrations like or even higher than those found in wastewater treatment plant influents.

BEHAVIOUR OF MEDICINAL PRODUCTS IN THE ENVIRONMENT

Once in the environment, medicinal products are transformed and transferred among different compartments, depending on the nature of the compounds and the characteristics of the host compartment. There exist voluntary initiatives for monitoring environmental concentrations of medicinal products in some Member States, particularly in the aquatic environment. These data suggest that several medicinal products are detectable in the environment, and their concentration depends on the geographical location, season, local administration practices, and specific environmental factors (humidity, etc.). The detected concentrations could be in the range of sub ng/L levels to more than several µg/L.

Medicinal products can degrade biotically or abiotically in soils and water, a process that in general reduces their potency, even if some degradation products might be persistent and thus of concern. According to a monitoring campaign performed in France, the molecules most frequently found in freshwaters are Carbamazepine (an anti-epileptic medicinal product) and its main metabolite, and Oxazepam (an anxiolytic) which is both a parent product and a metabolite of another pharmaceutical (Benzodiazepine). Highly lipid-soluble medicinal products may also have the ability to accumulate in the fat tissues of animals and can be thus introduced into the food chain (e.g. Ethynilestradiol could be a potential candidate for bioaccumulation in higher predators).

A KIND OF HAZARDS AND RISKS REPRESENT FOR ECOSYSTEMS

The mechanisms of transformations and transfer in the environment lead to the exposure of biota and constitute a potential risk for ecosystems. Although the scientific assessment of ecotoxicological effects of medicinal products on organisms is less developed compared to pesticides for example, it is becoming increasingly clear that some medicinal products, in particular anti-parasiticides, anti-mycotics, antibiotics and (xeno)estrogens, pose environmental risks in specific exposure scenarios. Examples of ecotoxicological effects of medicinal products include the contraceptive Ethinylestradiol, which impairs the reproduction of exposed fish populations; the effects of various antibiotics on environmental bacteria and algae; the impacts of the Benzodiazepine anxiolytic drug Oxazepam on European perch; and the effects of the antiparasiticide Ivermectin on dung fauna. The decline of vulture populations on the Indian subcontinent due to poisoning with Diclofenac, a non-steroidal painkiller, is a

good example of how unexpected exposure pathways feeding on carcasses can lead to severe ecotoxicological effects.

THE POTENTIAL IMPACTS ON HUMAN BEINGS

For humans, the possible impacts are less clear than for the environment, but there are concerns notably regarding certain type of molecules, even if to date there is no clear evidence of short-term health effects on humans. Antibiotics, anti-parasiticides, anti-mycotics and anti-cancer medicinal products are pharmaceutical groups that are especially intended to kill their target organism or target cells and might prove to be the most important pharmaceutical compounds affecting human health via environmental exposure. Chronic low-level exposure to medicinal products can occur through drinking water and through residues in leaf crops, root crops, fishery products, dairy products, and meat. The legislation in place for all veterinary medicinal products defines some Maximum Residue limits (MRL) for food of animal origin. However, to date no legal limit exists for human medicinal products potentially present in animal derived food (e.g. due to bioaccumulation from contaminated soil) since this pathway of exposure is assumed as negligible although the pathway is currently not well characterised.

HUMAN EXPOSURE THROUGH THE ENVIRONMENT

The detection of low levels of medicinal products in rivers and streams, drinking water, and groundwater has raised questions as to whether these levels may have consequences to human health. Humans are unintentionally exposed to very low concentrations of medicinal products via daily intakes of drinking water, leaf crops, root crops, fishes, dairy products, and meat [1]. Depending on the different use rates of organic fertilisers such as manure or sewage sludge and of treated surface water as drinking water, the potential exposure of humans to medicinal products may vary from countries to countries. Organic fertilisers transport medicinal products to food, and medicinal products in surface waters may end up in fish and drinking water.

Furthermore, the indirect environmental exposure of antibiotics and medicinal products having antibacterial, anti-viral or disinfectant properties may create antimicrobial or anti-viral resistance in human gut flora leading to less effective antibiotics or anti-viral medicinal products in the future. The biggest issue is the transport and spread of resistance around the globe from human to human. It is important to realise that incorrect application of antibiotics or anti-viral pharmaceuticals is a global problem that can affect vulnerable individuals many thousands of miles away. A minor exposure pathway might result from recreational activities (e.g. open water swimming, or children eating contaminated soil).

EXPOSURE THROUGH THE CONSUMPTION OF PLANT BASED PRODUCTS

Humans may be exposed to contaminants from sludge or manure through eating crops cultivated on soil where sludge or manure has been applied, if contaminants absorbed in the soil are transferred in plant roots, leaves, etc. The exposure of humans from plant-derived food materials has been estimated using consumption data from a national dietary survey [2] combined with estimated or measured plant concentrations of medicinal products for different model

plants [3]. Boxall and co-workers (2004) [4] studied the potential for a representative range of veterinary medicinal products to be taken up from soil by plants (lettuce and carrots) and to assess the potential significance of this route of exposure.

EXPOSURE THROUGH WATER CONSUMPTION

Humans may be exposed to contaminants dissolved in drinking water [5] or adsorbed to particles. As concentration levels of medicinal products in drinking water produced from surface water are generally higher than in drinking water produced from ground water [6][7], it can be discussed whether exposure is higher via the drinking water produced from surface sources. Higher levels of concentrations in surface water does not necessarily result in a higher level of human exposure to medicinal products in countries using predominantly surface water, since the actual exposure will mostly depend on the quality of drinking water treatment. The environmental occurrence of medicinal products in surface water have been evaluated and generally found to be low if the waste water is treated before release to the environment, as a large proportion of the contaminants may be removed during filtration processes in drinking water treatment plants. For example, Sanderson (2011) [8] collected data showing trace amounts of medicinal products in surface waters in the nano- to microgram per litre range, but only in the nanogram per litre range and in drinking water. No difference between surface and groundwater sources were reported in terms of human health risks.

The human health risks of trace amounts of medicinal products in drinking water have been evaluated in a report edited by the World Health Organisation (WHO, 2011) as well as in a few countries such as in the UK and the Netherlands [9] [10] [5] [11]. All reports conclude that, based on available evaluations, the majority of compounds a substantial margin of safety exists between the maximum concentration in drinking water and the concentrations likely to trigger adverse effects, and then that adverse health effects from targeted medicinal products occurring in European water are not expected to individually pose any appreciable risks to human health. However, although preliminary screening level assessments suggest the exposure to be low, they are often based on the use of proxy indicators such as the lowest therapeutic doses as points of departure for the risk assessment (e.g. in Boxall et al., 2011) [12], which does not reflect the specificities of pharmaceutical exposures through drinking water. Therefore, uncertainties remain, in particular with regards to the particularly active nature of the molecule, concerning mixture effects, chronic long-term effects at low doses and sensitive sub-populations. These aspects should be investigated further to verify whether the current exposure leads to a significant risk.

DIRECT SOIL INGESTION

The concentrations of contaminants (medicinal products) in soil or soil products after sludge or manure application are the basis for assessing the importance of the different routes for exposing medicinal products indirectly to humans in unanticipated ways. It is well known that children may ingest particles at playgrounds that were previously sludge amended. The highest concentrations of contaminants are found on the soil surface due to the use of sludge-containing soil mixtures for private gardens. In an epidemiologic study, 90% of the children

ingested less than 0.2 g soil per day [13]. This amount of soil has been used by several investigations e.g. SFT to establish quality classes for soil in kindergartens and playing grounds for children in Norway [14].

Halling-Sørensen and co-workers calculated the human health risk for intake of medicinal products via soil [15]. Calculations showed that humans would need to consume 200 g to 1 kg soil in order to be exposed to one adult Daily Defined Dose (DDD) of the medicinal product. The defined daily dose of a medicinal product is the assumed average maintenance dose per day for a pharmaceutical product used for its main indication in adults.

As stated by Alexander (2006) it was anticipated that it was not possible to eat more than 10 grams of soil per day. Thus, it is not possible for either children or adults to be exposed to a whole DDD in one day via soil. On the other hand, it is difficult to establish a "safe level" for medicinal products such as hormones, antibiotics and cancer medicinal products. Some groups (e.g. children) have for different reasons enhanced sensitivity towards medicinal products such as antibiotics. Humans developing allergies to antibacterial agents or other pharmaceutical products may suffer from being exposed to even very small doses of medicinal products. Contaminated soil ingestion in farmed animals can also be a potential exposure route, even if the current knowledge relates principally to metals [16] [17].

EXPOSURE THROUGH THE CONSUMPTION OF MEAT, DAIRY AND FISHERY PRODUCTS

Medicinal products can bioaccumulate in cattle and fish, either through direct exposure for therapeutic purposes or through the presence of pharmaceutical residues in the environment (e.g. in surface water for fish). Humans can then be exposed to the contaminants through the consumption of meat, dairy and fishery products. FAO, WHO, the International Office of Epizootics (OIE) and several national governments have lately raised the issue of irresponsible use of antibiotics in all production sectors, including fish industries, with particular concern for the potential risks to public health. Many governments around the world have introduced, changed, or tightened national regulations related to the use of veterinary medicines, and in particular of antibiotics. There is therefore a comprehensive control of residues of veterinary pharmaceuticals in products issued from farming and aquaculture, and most production is considered of high quality, not containing antibacterial agents, which are the most used in animals, over the MRL levels. While the level of antibiotic residue is low in most cases, this kind of low and constant exposure can lead to antibiotic resistance in both the animals fed the antibiotics and the humans who consume the food. In EU (Eudralex, 2005) [18], CVMP/VICH (EMA, 2013) [19] (EMA, 2011) [20] highlighted that consuming foods containing antibiotics could have a direct effect on an individual's own intestinal bacteria and could contribute directly to the bacteria in the bowel becoming resistant to later antibiotic treatment.

HAZARD POTENTIAL OF SOME CATEGORIES OF MEDICINAL PRODUCTS

The human medicinal products recognised as potential environmental and food

hazards are primarily medicinal products used in high volumes and medicinal product groups with special properties such as hormones, anticancer medicinal products, pain killers, and antibacterial medicinal products [1] [21]. High volumes of human medicinal products include groups such as non-steroid anti-inflammatory medicinal products, beta-blockers and lipid lowering agents. Hormones are substances involved in cell signalling in humans. They are effective at low concentrations (ng/l level) and as medicinal products; they are used as natural, nature identical and synthetic substances. As contaminants in the ecosystem, hormones have already been shown to disrupt biological signal pathways [22].

Anticancer medicinal products are optimally designed to kill/inhibit malignant tumour cells at doses that allow enough unaffected cells in critical tissues with high cell proliferation rates to survive so that recovery can occur. Different substance groups with specific mechanisms of actions are used in anticancer chemotherapy; however, most are generally genotoxic, mutagenic and reprotoxic already at relatively low concentrations. An unintended human exposure of anticancer medicinal products via drinking water or food could be problematic.

Antibacterial medicinal products are compounds that kill or inhibit the growth of bacteria. Antibacterial medicinal products comprise a fourth group of importance due to their potential for resistance development caused by selection for resistant bacteria. Several studies suggest a link between antibacterial use and antibacterial-resistant infections [23].

CONCLUSION

To effectively reduce the release of medicinal products into the environment and/or foster their elimination or removal. We can control the effects of medicinal products by developing the concept of green pharmacy and adapting packaging to influence consumption, developing and harmonising the implementation of collection schemes for unused medicinal products, developing source separation measures and wastewater treatments, actively involving public society and professionals through information and education, prioritising and monitoring molecules and/or environmental compartments of concern, consolidating existing knowledge, ensuring transparency and facilitating access to information, improving governance and building up an eco-pharmacovigilance network, implementing incentive economic instruments, developing the knowledge base through fostering of research activities. These actions were prioritised based on an internal brainstorming as well as stakeholders' inputs throughout the study. This prioritisation is however preliminary and would need further investigation before recommending certain options specifically.

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