Journal of Hazardous Materials 279 (2014) 169–189

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

Review

Environmental side effects of pharmaceutical cocktails: What we know and what we should know

M.I. Vasquez[a], A. Lambrianides[b,1,2], M. Schneider[c], K. Kümmerer[c], D. Fatta-Kassinos[a,*]

[a] Department of Civil and Environmental Engineering and Nireas – International Water Research Center, University of Cyprus, P.O. Box 20537, 1678 Nicosia, Cyprus
[b] The Cyprus Institute of Neurology and Genetics, P.O. Box 23462, 1683 Nicosia, Cyprus
[c] Institute of Sustainable and Environmental Chemistry, Leuphana University Lüneburg, Scharnhorststraße 1/C13, 21335 Lüneburg, Germany

HIGHLIGHTS

- Designing strategies for pharmaceutical mixture testing.
- Mixtures of pharmaceuticals with emerging environmental concern.
- Methods of analysis of results relevant to mixtures of pharmaceuticals.
- Gaps of knowledge and future perspectives with regard to pharmaceutical mixtures effects.

ARTICLE INFO

Article history:
Received 10 March 2014
Received in revised form 3 June 2014
Accepted 20 June 2014
Available online 11 July 2014

Keywords:
Pharmaceutical
Mixture
Combined effects
Concentration addition
Independent action
Mode of action

ABSTRACT

Cocktails of pharmaceuticals are released in the environment after human consumption and due to the incomplete removal at the wastewater treatment plants. Pharmaceuticals are considered as contaminants of emerging concern and, a plethora of journal articles addressing their possible adverse effects have been published during the past 20 years. The emphasis during the early years of research within this field, was on the assessment of acute effects of pharmaceuticals applied singly, leading to results regarding their environmental risk, potentially not realistic or relevant to the actual environmental conditions. Only recently has the focus been shifted to chronic exposure and to the assessment of cocktail effects. To this end, this review provides an up-to-date compilation of 57 environmental and human toxicology studies published during 2000–2014 dealing with the adverse effects of pharmaceutical mixtures. The main challenges regarding the design of experiments and the analysis of the results regarding the effects of pharmaceutical mixtures to different biological systems are presented and discussed herein. The gaps of knowledge are critically reviewed highlighting specific future research needs and perspectives.

Contents

Abbreviations: CA, concentration addition; IA, independent action; CI, combination index; EC, effective concentration; TU, toxic unit; MIC, minimal inhibitory concentration; MoA, mode of action; LC, lethal concentration; NOEC, no observed effect concentration; PVL, Panton-Valentive leukocidin; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; NF, nuclear factor; AP, activator protein.

* Corresponding author. Tel.: +357 22893515; fax: +357 22895319.
E-mail address: dfatta@ucy.ac.cy (D. Fatta-Kassinos).

[1] Current affiliation.
[2] Former scientist of Nireas – IWRC.

http://dx.doi.org/10.1016/j.jhazmat.2014.06.069
0304-3894/

1. The importance of investigating the side effects of mixtures of pharmaceutical residues in the environment

The pollution of the environment with regard to the occurrence of pharmaceutical residues in mixtures is an area of increasing concern, with various open questions referring to their adverse effects towards non-target organisms [1]. The exposure of the latter to pharmaceuticals as multi-component mixtures (i.e. parent compounds, metabolites and transformation products) is a result of (i) the consumption of various medicinal products, (ii) their metabolism, which in some cases is very poor, (iii) their incomplete removal at the urban wastewater treatment plants and, (iv) their transformation either during transport in the sewage pipes, treatment or when in the natural environment. It is not an easy task to predict and fully characterize potential effects by modelling, as the effects can be altered, depending on the components of the mixtures, as well as the individual concentrations of the pharmaceutical residues (real-life scenarios are unlimited in number), but also due to a variety of natural stressors. The pharmaceutical compounds when in mixtures may interact biochemically in the same way with molecules such as, a protein receptor or an enzyme, hence activating the same specific target in an additive way. This is a mere assumption, which however cannot be neglected. Furthermore, many effects can result from mechanisms that are more complex than simply binding to a receptor. The various compounds may act through a combination of mechanisms, such as altering gene expression of cellular regulators, changing levels of intracellular concentrations of ions, or altering cellular metabolism. Each of these mechanisms can be affected at different levels depending on the mixtures involved. As a consequence, mixtures may have different effects on different tissues and organs [2] and, thus on different biological systems or organisms.

In a number of recent studies, it has been shown that pharmaceutical residues in the environment from a wide range of therapeutic groups such as, antibiotics, analgesics, anticancer drugs, contraceptives and anti-depressants have clear toxic effects [3–5]. Pharmaceuticals, unlike most other chemical compounds that enter the environment, are designed to alter physiological functions. More specifically, pharmaceuticals are designed to induce effects in humans and therefore there is a high probability of being biologically active towards wildlife species as well. The most frequently detected pharmaceutical compounds fall among others within the classes of analgesics, antibiotics, diuretics, beta-blockers, hormones, antidepressants, psychiatric, hormones, and lipid regulators. It has to be noted though that the results obtained from the various studies performed are biased by the capability of each laboratory's multi-residue method to analyze such compounds, and therefore the information provided on the type of the classes of pharmaceuticals present in mixtures in environmental matrices most often is not fully delineated.

When taken up by organisms, they may undergo metabolic detoxification, with the resultant metabolites excreted via the urine and/or faeces in the environment. The degree of metabolism varies, with some compounds not metabolized at all and excreted as parent compounds. Before excretion by organisms, pharmaceuticals, (besides the transformation that takes place during metabolism), are also susceptible to further biological transformation by microorganisms that live symbiotically in their intestinal tracks. Furthermore, biotic and abiotic transformation continues to take place during wastewater treatment, and also after the release of the pharmaceuticals in the environment. When in the environment, abiotic processes are usually the main route of degradation of pharmaceuticals, like photolysis and hydrolysis [6].

According to the scientific literature, most research on the effects of pharmaceuticals on biological systems is conducted so far using only one pharmaceutical compound at a time [7,8]. However, as mentioned above, pharmaceuticals do not only occur as isolated, pure substances in the environment. This is now acknowledged by current risk assessment and characterization strategies [9]. Despite this fact, the possible effects of pharmaceuticals to the environment are still evaluated individually according to the EMEA guidelines for the risk assessment of human pharmaceuticals [10], and of veterinary pharmaceuticals [11]. The exposure to mixtures of other chemical compounds e.g. pesticides, polycyclic aromatic hydrocarbon, trihalomethanes, are usually regulated by the summation of the concentration of individual compounds. The risk assessment of such mixtures, for example pesticides, is usually evaluated by the application of safety factors on the results obtained from assessing the effects of individual compounds [12]. This approach however, is of limited relevance to the mixtures of pharmaceuticals, mainly due to the fact that they do not have the same mode of action (MoA).

The assessment of the toxicity of pharmaceutical mixtures is both an urgent need and a great challenge to achieve more progressive and proactive risk assessment. Variation in the mixtures and the great number of potential adverse effects to human health and the environment makes it difficult though to design uniform guidelines. Regulation is a stringent necessity, since in environmental compartments only mixtures of compounds are present, and not isolated substances. At the European Commission level, there are some efforts to establish regulations for the risk assessment of chemical mixtures emitted in the environment [9]. Guidelines on mixtures by the WHO and US EPA, are already available, but they focus on the possible adverse effects on human health only [13]. In the publication "State of the Art Report on Mixture toxicity" [14] the