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Screening level mixture risk assessment of pharmaceuticals in STP effluents

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ARTICLE INFO

Article history:
Received 2 May 2013
Received in revised form
29 October 2013
Accepted 4 November 2013
Available online 15 November 2013

Keywords:
Pharmaceuticals in the environment
Mixture risks
Concentration Addition

ABSTRACT

We modeled the ecotoxicological risks of the pharmaceutical mixtures emitted from STP effluents into the environment. The classic mixture toxicity concept of Concentration Addition was used to calculate the total expected risk of the analytically determined mixtures, compare the expected impact of seven effluent streams and pinpoint the most sensitive group of species. The risk quotient of a single, randomly selected pharmaceutical is often more than a factor of 1000 lower than the mixture risk, clearly indicating the need to systematically analyse the overall risk of all pharmaceuticals present. The MCR, which is the ratio between the most risky compound and the total mixture risk, varies between 1.2 and 4.2, depending on the actual scenario and species group under consideration. The mixture risk quotients, based on acute data and an assessment factor of 1000, regularly exceed 1, indicating a potential risk for the environment, depending on the dilution in the recipient stream. The top 10 mixture components explain more than 95% of the mixture risk in all cases.

A mixture toxicity assessment cannot go beyond the underlying single substance data. The lack of data on the chronic toxicity of most pharmaceuticals as well as the very few data available for *in vivo* fish toxicity has to be regarded as a major knowledge gap in this context. On the other hand, ignoring Independent Action or even using the sum of individual risk quotients as a rough approximation of Concentration Addition does not have a major impact on the final risk estimate.

1. Introduction

Pharmaceuticals are detected in an ever increasing number of drinking water supplies, effluents and aquatic ecosystems, e.g. (Segura et al., 2009; Heberer, 2002; Lopéz-Serna et al., 2012). Consequently, a range of experimental investigations has been undertaken during the last years with the aim to describe the hazards and risks of pharmaceuticals for the aquatic environment (recently reviewed e.g. by Brausch et al., 2012). Several studies came to the conclusion that clear ecotoxic effects are only to be expected at concentrations well above environmentally realistic levels. Hence the risk of pharmaceuticals to the environment has repeatedly been assessed as negligible, e.g. (Han et al., 2006; Miege et al., 2006; Wilson et al., 2004), or limited to specific cases, e.g. (Brain et al., 2006; Lienert et al., 2007).

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0043-1354/$ – see front matter
http://dx.doi.org/10.1016/j.watres.2013.11.005

Table 1 – Analytical fingerprints used for the presented risk assessment. S1-F: Châtillon-sur-Chalaronne, Lyon, France, L1-F: south of Lyon, France; L2-Gr: Iraklio, Crete, Greece; M1-I: Latina, Italy; L4-I: Naples, Italy; L5-S: Göteborg, Sweden. For further details see (Andreozzi et al., 2003). All values were converted to μmol/L from the original publication. n.d. = not determined.

Compound	CAS	S1-F	L1-F	L2-Gr	M1-I	L3-I	L4-I	L5-S
Acebutolol	37517-30-9	3.86E-04	2.38E-04	2.97E-05	1.19E-04	5.94E-05	3.27E-04	n.d.
Aminopyrine	58-15-1	1.86E-03	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Betaxolol	63659-18-7	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bezafibrate	41859-67-0	n.d.	2.96E-03	n.d.	n.d.	n.d.	2.52E-03	n.d.
Carbamazepine	298-46-4	4.15E-03	5.08E-03	4.36E-03	1.27E-03	1.44E-03	2.12E-03	3.68E-03
Ciprofloxacin	85721-33-1	1.81E-04	1.81E-04	2.11E-04	2.11E-04	1.81E-04	1.21E-04	9.05E-05
Clofibrate	637-07-0	n.d.	n.d.	3.30E-03	n.d.	n.d.	n.d.	n.d.
Clofibric Acid	882-09-7	n.d.	n.d.	n.d.	3.17E-03	n.d.	1.07E-03	2.14E-03
Diclofenac	15307-86-5	1.38E-03	8.44E-04	3.01E-03	1.59E-03	5.00E-03	1.84E-02	n.d.
Enoxacin	74011-58-8	9.37E-05	3.12E-05	9.37E-05	9.37E-05	3.12E-05	9.37E-05	3.12E-05
Fenofibrate	49562-28-9	3.33E-04	5.54E-05	4.43E-04	4.43E-04	2.77E-04	4.43E-04	n.d.
Fenoprofen	31879-05-7	1.16E-03	7.84E-04	n.d.	n.d.	n.d.	n.d.	n.d.
Flurbiprofen	5104-49-4	8.60E-04	n.d.	n.d.	n.d.	n.d.	1.39E-03	n.d.
Gemfibrozil	25812-30-0	5.35E-03	2.40E-04	2.84E-03	3.24E-03	3.36E-03	1.90E-02	8.27E-03
Ibuprofen	15687-27-1	8.82E-03	9.70E-05	2.42E-04	8.73E-04	9.70E-05	9.70E-05	3.45E-02
Ketoprofen	22071-15-4	n.d.	6.37E-03	n.d.	n.d.	n.d.	n.d.	n.d.
Lomefloxacin	98079-51-7	5.12E-04	5.41E-04	8.25E-04	9.11E-04	5.12E-04	6.26E-04	3.70E-04
Metoprolol	37350-58-6	2.99E-04	2.99E-04	3.74E-04	3.74E-05	3.74E-05	3.74E-04	1.46E-03
Naproxen	22204-53-1	7.51E-03	2.21E-03	n.d.	1.26E-03	1.78E-03	2.27E-02	9.34E-03
Norfloxacin	70458-96-7	1.57E-04	2.51E-04	2.19E-04	2.19E-04	1.88E-04	1.88E-04	9.39E-05
Ofloxacin	82419-36-1	9.13E-04	1.41E-03	1.27E-03	1.61E-03	8.03E-04	8.58E-04	3.32E-04
Oxprenolol	6452-71-7	1.88E-04	7.54E-05	3.77E-05	3.77E-05	n.d.	1.13E-04	n.d.
Phenazone	60-80-0	n.d.	n.d.	n.d.	n.d.	1.97E-03	n.d.	n.d.
Propranolol	525-66-6	3.86E-05	1.54E-04	3.86E-05	3.86E-05	3.86E-05	3.47E-04	3.86E-05
Sulfamethoxazole	723-46-6	3.55E-04	2.76E-04	3.55E-04	3.95E-05	n.d.	1.18E-04	7.90E-05
Trimethoprim	738-70-5	1.38E-04	6.89E-05	2.76E-04	1.38E-04	1.03E-04	4.48E-04	1.72E-04

However, pharmaceuticals do not occur as isolated, pure substances in an environmental compartment. A broad range of different substances is used simultaneously in human and veterinary medicine in any given area, hence pharmaceuticals often occur in the environment as multi-component mixtures (e.g. Vulliet and Cren-Olivé, 2011; Kasprzyk-Hordern et al., 2008; Moldovan, 2006; Loos et al., 2009; Gómez et al., 2007; Kolpin et al., 2002; Lopéz-Serna et al., 2012).

The joint ecotoxicity of such chemical cocktails is typically higher than the toxicity of each individual compound (Kortenkamp et al., 2009). In particular, even if the compounds of a mixture are present only below their respective toxicity threshold, a joint toxic effect cannot be ruled out *a priori*. Such a pattern was observed for example in multi-component mixtures of quinolone antibiotics (Backhaus et al., 2000), a set of 14 dissimilarly acting pharmaceuticals (Backhaus et al., 2000), or a mixture of cimetidine, fenofibrate, furosemide and phenazone (Fent et al., 2006). Even mixtures of only comparatively few compounds often show a similar pattern. A mixture of fluoxetine and clofibric acid killed more than 50% of a daphnia population after an exposure of 6 days, although the components were present at concentrations that did not provoke significant effects individually (Flaherty and Dodson, 2005). In the same study, a significant shift in sex ratio was observed after an exposure to a three-component mixture of erythromycin, triclosan and trimethoprim – again at a mixture concentration at which all components were present at concentrations that did not provoke significant individual effects. Binary combinations of clofibric acid and carbamazepine as well as diclofenac and ibuprofen show clear mixture effects in acute Daphnia tests, although each individual component was present in a concentration below its individual no observed effect concentration (NOEC) (Cleuvers, 2003). Eguchi and colleagues demonstrated that trimethoprim, even if present only at its NOEC concentration, shifts the concentration–response curve of sulfamethoxazole and sulfadiazine in algae towards 4–5 times higher toxicities (Eguchi et al., 2004).

Hence, ignoring possible mixture effects might run the risk of underestimating the actual impact of pharmaceuticals in the environment, depending on the number of compounds involved, their concentrations and ecotoxicological profiles.

We have recently outlined a strategy for the compound-based environmental risk assessment of chemical mixtures (Backhaus and Faust, 2012), which is primarily based on the classical mixture toxicity concept of Concentration Addition (CA). Two possible approaches for assessing the risk of a chemical mixture were outlined:

I. The risk quotient of a given mixture is estimated as the sum of the individual EnvConc/PNEC ratios of each mixture component. EnvConc = Environmental Concentration, which can be modeled (Predicted Environmental Concentration, PEC), measured (Measured Environmental Concentration, MEC), or which can represent the concentration near an effluent outlet (Environmental Introductory Concentration, EIC). PNEC represents the Predicted No Effect Concentration, calculated e.g. according to the corresponding guideline of the European Chemicals Agency (ECHA, 2008). As the scenario listed in Table 1 is based on a