Methodology to account for uncertainties and tradeoffs in pharmaceutical environmental hazard assessment

Sylvain Coutu[a,*], Luca Rossi[a], D. A. Barry[a], Nathalie Chèvre[b]

[a] *Laboratoire de technologie écologique, Institut d'ingénierie de l'environnement, Faculté de l'environnement naturel, architectural et construit (ENAC), Station 2, Ecole Polytechnique Fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland*
[b] *IMG, Faculté de Géosciences and Environnement, Université de Lausanne, 1015 Lausanne, Switzerland*

Abstract

Many pharmaceutical products find their way into receiving waters, giving rise to concerns regarding their environmental impact. A procedure was proposed that enables ranking of the hazard to aquatic species and human health due to such products. In the procedure, hazard assessment is based on five of the pharmaceutical product's individual physico-chemical properties. These properties are aggregated using the weighted Euclidian distance as the utility function. The weights and physico-chemical properties are considered as random variables. Physico-chemical property uncertainty criteria are obtained from a literature review. Weight uncertainty is based on a hazard ranking from a panel of experts, the histogram of which is converted into a continuous probability density function using statistical Kernel smoothing technique. The hazard-ranking procedure was applied to a list of common pharmaceuticals used in Switzerland. The procedure is target-specific. Two

*corresponding author. Tel: +41 (0)21-693-8024.
Email address: sylvain.coutu@epfl.ch (Sylvain Coutu)

rankings were presented: One giving priority to environmental protection and the other to human health. For most substances, the hazard rank depends on the target. For the Swiss case study, the ranking procedure led to the conclusion that the hormones ethinylestradiol and testosterone, along with the antibiotic erythromycin A, should be in all cases included in risk assessment methodologies, environmental concentration estimates and regular measurement campaigns. The methodology proposed is flexible and can be extrapolated to other substances and groups of experts.
Keywords: Pharmaceuticals, Environmental hazard, Micropollutants, Multi-criteria analysis, Expert judgment

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1. Introduction

Pharmaceuticals in the environment can have adverse effects on aquatic ecosystems (Kummerer, 2001) and on human health (Bruce et al., 2010), so it is beneficial to limit their presence in natural waters (European Commission, 1996; WHO, 2008). At the same time, human health mandates pharmaceutical usage, in which case they will be supplied continually to the environment. In order to avoid tradeoffs between human health and environmental protection, it is important to estimate the hazard of environmentally harmful pharmaceuticals so that their concentrations can be limited, if necessary, in the natural world. For example, with information on the relative hazard of pharmaceuticals, it is possible to substitute some substances with others less hazardous to the environment, whilst maintaining their therapeutic benefits.

A review of the literature shows that most studies deal with estimation of pharmaceutical risk to the environment (Camacho-Munõz et al., 2010; Cunningham et al., 2009; Enick and Moore, 2007, e.g.). Risk differs from hazard in that risk estimation involves integration of the occurrence of the substance in the environment, either directly using field campaigns or indirectly through the analysis of consumption data. There are several factors that can cause inaccuracies in pharmaceutical risk calculations can be subject to inaccuracy. First, there are many different patterns of pharmaceutical prescription and consumption around the world, and even within the same country, so transferring risk estimates from one place to another is not automatic (Ternes and Joss, 2006). Second, a common assumption is that drug sale volumes correlate with environmental concentrations. In consequence, many studies have used prescription amounts as a way to estimate environmental risk (Carlsson

et al., 2006; Cooper et al., 2008; Jones et al., 2002; Perazzolo et al., 2010; Valcárcel et al., 2011). However, Bisceglia and Roberts (2005) show that the total expenditure on pharmaceuticals does not correlate with either usage or environmental concentrations. Similarly, excretion factors are used to predict environmental concentrations and so to evaluate the risk of pharmaceutical substances (Besse and Garric, 2008; Perazzolo et al., 2010). Yet, compounds with low excretion rates can also be highly conservative in the environment, so estimates of concentrations based on excretion factors might also be poor predictors of environmental risk. For instance, Jjemba (2006) has shown that pharmaceutical concentrations in the environment correlate negatively with the amount of the parent compound excreted.

Unlike risk, hazard is specific neither to time nor space (Ternes and Joss, 2006). Rather, it refers to the physico-chemical characteristics of the substance. Hazard studies thus allow different substances to be compared with respect to their potential effects on the environment. In so doing, pharmaceutical hazard assessments are generic, and are a precursor to environmental risk assessments.

Relatively few studies focus on the hazard of chemical substances (Lithner et al., 2011; Logue et al., 2011), and even fewer aim to estimate the hazard of pharmaceuticals. Carlsson et al. (2006) estimated the hazard of chemicals in a list of pharmaceuticals based on European legislation (Directive 67/548/EEC1[1]). They allocated the substances investigated into the binary categories: "Dangerous for the environment" and "Not dangerous

[1]http://ec.europa.eu/environment/chemicals/, site last accessed on 12.09.2011

for the environment". Hazard evaluation is also emphasized in the REACH PBT approach (European Commission, 2006). This approach uses thresholds based on different parameters that are proxies for the capacity of the chemical to be persistent in (P), to bioaccumulate in (B), and to be toxic to (T) the environment. The thresholds are then compared to assess when the chemical should be classed as hazardous. Such concepts for drug hazard assessment fit under the rubric of EcoPharmacovigilance, a discipline that seeks to evaluate adverse events related to drugs in the ecosystem, taking into consideration all consequences to humans and other organisms (Kummerer and Velo, 2006).

The aforementioned existing hazard evaluation methods identify drug groups of similar hazard levels. There are several issues to note concerning their utility, however. First, they do not identify whether a given substance is more hazardous to human health than to the aquatic environment. Existing rankings are oriented towards protection of either the aquatic environment or human health, with no possibility to include tradeoffs between them. Second, they do not allow ranking the hazard of different substances. Third, uncertainties that can exist in the biochemical properties of individual chemical compounds are not accounted for, as demonstrated in various studies on the hazard of chemical substances (Tosato et al., 1991) and pesticides (Newman, 1995). In addition, environmental hazard studies necessarily introduce the concept of subjectivity (Alexander et al., 2010; Morse et al., 2001) in the form of expert judgment. However, no hazard identification method has included the quantification of this judgment. Consequently, the pharmaceuticals chosen for investigation in environmental studies are usually

not justified (Conley et al., 2008; Santos et al., 2009), except perhaps briefly (Carballa et al., 2008; Loffler et al., 2005).

Here, we propose a methodology to quantify and rank the relative hazard of pharmaceuticals. Hazard is calculated from an aggregation of different physico-chemical and toxicity criteria defining the drugs. Uncertainty in the criteria values is taken into account by considering them as uniform random variables within the range of values existing in the literature. Weights are assigned to quantify the subjectivity introduced by the relative influence of the different criteria used in the hazard assessment procedure. These weights are considered to be random variables extrapolated from an expert committee judgment. For this, the discrete choices of the decision makers (DMs) are converted into continuous probability density functions (PDFs) by kernel density estimation. This statistical technique enlarges the spectrum of weights that can be assigned to criteria, which is valuable when the number of experts is limited (Bowman and Azzalani, 1997).

The flexibility of the method makes possible adjustment of the classification depending on the priorities of decision makers. Two sets of weights are used: one giving priority to the protection of the aquatic environment and the other to human health. They are compared with the default ranking, defined as giving equal weight to each priority. The methodology is applied to a list of widely consumed pharmaceuticals in Switzerland. As a result, we propose an ordinal ranking of a list of pharmaceuticals whose consumption may lead to long term environmental impacts.

2. Materials and method

The general structure of the methodology is illustrated in Fig. 1. First, the choice of substances and relevant criteria used in this study is justified. Following this preliminary part, we present the different steps of the ranking methodology. Weights are used to reflect the relative subjective importance each criterion has in hazard quantification. Criteria and weights are expressed in terms of random variables, the PDFs of which characterize their uncertainty. A utility function is defined and later used to aggregate criteria based on their respective weights. Based on this utility function, a ranking of the hazard for the investigated substances is deduced.

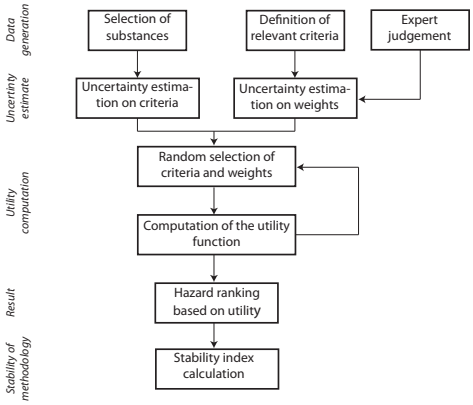

Figure 1: Schematic presentation of the distance ranking procedure. Expert judgment influences the definition of relevant criteria and their weights. The utility function is computed 10^5 times so that expected values are calculated from all weights and criteria combinations possible.

2.1. Choice of relevant parameters for hazard assessment

The hazard was evaluated for 58 pharmaceuticals. These were selected because they are either among the most consumed in Switzerland, or are usually considered as hazardous (Perazzolo et al., 2010). Five criteria are used to describe each chemical:

- PNEC (Predicted No Effect Concentration): The PNEC is a well-known parameter used in ecotoxicology to evaluate the hazard of a substance (Bound and Voulvoulis, 2004; Carlsson et al., 2006; Cooper et al., 2008). It is the concentration below which exposure to a substance is not expected to cause adverse effects;

- Log K_{ow}: This is the octanol/water partition coefficient. In ecotoxicology, it is usually used for estimating the bioaccumulation potential of a substance (Bound and Voulvoulis, 2004; Carlsson et al., 2006; Perazzolo et al., 2010);

- Solubility: Maximum solubility of the substance in water;

- SLTC (Specific Long Term Concern): The SLTC estimates long term effects of a substance, such as being carcinogenic, mutagenic, having embryotoxic properties or because they have a potential to foster bacterial resistance (typically antibiotics. These substances were listed by Kummerer (2001) and, in contrast to other criteria, are given as binary values (unity for substances with specific long term concerns and zero otherwise);

- TD (Therapeutic Dose): The dose that is estimated to produce the desired therapeutic effect. The TD is commonly used as an indicator for human toxicity, as proposed by Webb et al. (2003).

These five criteria lead to five parameters for each chemical, which are collected into five-element vectors, $\mathbf{P}(C_1, C_2, C_3, C_4, C_5)^T$, as presented in Fig. 2 The numerical values of all parameters were taken from Perazzolo et al. (2010).

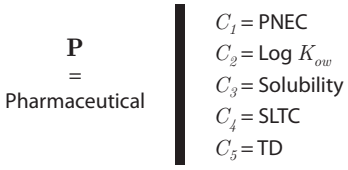

Figure 2: Vectorial representation of a pharmaceutical's physico-chemical characteristics. The five criteria C_1 to C_5 are described in the text

The parameters in $\mathbf{P}$ have different ranges and dimensions. Thus, each parameter is normalized according to:

$$C_{normalized} = \frac{C - C_{min}}{C_{max} - C_{min}}. \tag{1}$$

Here, C is the parameter to be normalized, and C_{min} and C_{max} are, respectively, the parameter-specific minimum and maximum values of C. In all cases, values of $C_{normalized}$ near zero indicate a low hazard, while high hazard is given by $C_{normalized}$ near unity.

2.2. Uncertainty estimation

2.2.1. Quantification of uncertainties in criteria

The parameters in **P** (Fig. 2) are subject to uncertainty (e.g., measurement error), i.e., C_i, $i = 1, \ldots, 5$, are considered as independent random variables, each with an associated PDF, f_i. Because the PDFs are unknown, here each f_i is defined as a uniform distribution in the interval $[0.8C_i, 1.2C_i]$. This corresponds to a 20% uncertainty in each criterion and thereby allows consideration of uncertainties that exist in toxicological parameter measurements. Note that it is also widespread to use a Gaussian PDF to describe measurement uncertainties (BIPM, 2008). However, here we here estimate the uncertainty not from direct measurements, but from values found in the literature. Thus, the uniform distribution was chosen because it keeps parameters within a reasonable range, without giving preference to one study or another. The methodology does not rely on the assumptions used at this step and, depending on the data used, different PDFs would be feasible.

2.2.2. Conversion of discrete preferences into continuous PDFs

Identification of criteria that contribute to hazard level evaluation, as well as quantifying relevant parameters, are not in themselves sufficient to define a ranking procedure (Alexander et al., 2010; Morse et al., 2001; Rashid, 2011). Hazard ranking varies depending on what the stakeholders are willing to protect and to trade-off. Ranking can be based on considerations of human health or aquatic ecosystems, for example. Each ranking will, however, be based on the same parameters, although the parameters will be weighted differently according to the target of the assessment.

Multi-criteria decision-making is performed with stakeholder involvement

(Sorvari and Seppälä, 2010) in order to determine the weighting applied to each parameter (Aragonés-Beltrán et al., 2009; Lithner et al., 2011). This step is thus part of our ranking procedure. A group of experts was asked, for each substance, to rank the proposed criteria according to their assessment of relevance to (i) environmental impact and (ii) human health. Multiple methodologies can be used to elicit judgments from each individual expert (Howell and Honey, 2010; Sorvari and Seppälä, 2010). For reasons of practicality, five experts were approached independently. Speaking more generally, however, definitive guidelines on the number of experts involved in the consultation are not available, particularly if the number depends upon the perceived level and variability of expertise per domain (Walls and Quigley, 2001). Indeed, the number of experts can range from 3 to more than 80 (Bolger and Wright, 1994). Again, our methodology does not rely on the number of experts consulted.

Each of the five experts consulted proposed an ordinal ranking for the elements of $\mathbf{P}$. The experts' ranks were binned to create histograms of the

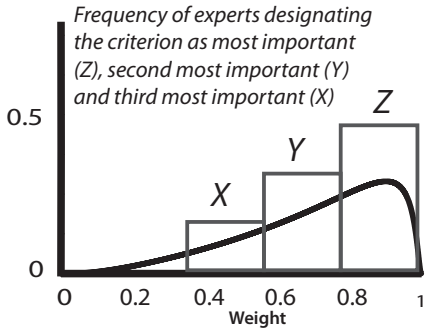

Figure 3: Illustration of extrapolation of discrete DM choice to continuous PDF using Kernel smoothing density estimate. A similar plot is obtained for each of the criteria.

rankings. These discrete distributions were converted to continuous PDFs to permit consideration of a larger spectrum of weighting possibilities, and thus to capture better the heterogeneity of experts' viewpoints. Moreover, this conversion allows extrapolation/smoothing of the weighting values to cases that may not be invoked due to the limited number of experts usually available. It should be noted that, if a large pool of experts were used, then the conversion to a continuous PDF has minimal impact.

The kernel density estimation method was used to convert the discrete histograms into continuous PDFs (Bowman and Azzalani, 1997). An application of the methodology to a synthetic histogram is illustrated in Fig. 3. Thus, we obtained five PDFs, one for each criterion's weight, which relate the diversity of the DMs' choices. We name these functions g_i, $i = 1, \ldots, 5$, each one being associated, respectively, with parameter C_i. The weight of each criterion is thus a random variable, ψ_i, defined by its associated PDF g_i. The five ψ_i values were grouped into the weight vector $\mathbf{W}$.

2.3. Utility score computation from criteria aggregation

For each chemical, the function $u(\mathbf{P}, \mathbf{W})$ is used to aggregate together criteria. The utility function used was based on the weighted Euclidian distance, defined as:

$$u(\mathbf{P}, \mathbf{W}) = \sqrt{\sum_{i=1}^{5} (C_i \psi_i)^2} \qquad \text{with } \sum_{i=1}^{5} \psi_i = 1. \tag{2}$$

By construction, $0 \leq u \leq 1$, with hazard increasing with increasing u. In Eq. (2), weights are selected randomly and independently in their respective

distribution. The sum of the weights must equal unity, so the individual weight values are normalized appropriately. Thus, each of the weights quantifies the relative contribution of its associated criterion to the multi-criteria hazard estimation.

The expected value of u is given by:

$$E(u(\mathbf{P},\mathbf{W})) = \int ... \int \sqrt{\sum_{i=1}^{5}(C_i\psi_i)^2} f_1(C_1)...f_5(C_5)g_1(\psi_1)...g_5(\psi_5) \; dC_1...dC_5 d\psi_1...d\psi_5. \tag{3}$$

Computation of Eq. (3) was performed using a Monte Carlo approach, in which the C_i and ψ_i values were selected randomly from their respective distributions, f_i and g_i, after which the utility, u, in Eq. (2) was calculated. By repeating this calculation many times (here, 10^5), we obtained the distribution for $u(\mathbf{P},\mathbf{W})$, the mean of which corresponds to the expected value. Thus, from Eq. (3) the expectation, denoted by $E(u(\mathbf{P},\mathbf{W}))$, was calculated for each of the 58 pharmaceuticals, with the hazard ranking determined by the values obtained.

As noted above, the experts ranked the pharmaceuticals according to three different perspectives. The computation of $E(u(\mathbf{P},\mathbf{W}))$ was repeated for the three different sets of weights, giving three ranked lists of pharmaceuticals. These results are compared in the following section to evaluate the stability of the methodology with respect to the different sets of weights considered.

2.4. Stability of the ranking

Three sets of weights were tested in our approach: one giving priority to protection of the aquatic environment, another assessing the hazard to human health, and finally, one assigning equal weight to each criteria. Here, we provide a means to compare the differences in the rankings obtained for the different sets of weights. For example, a substance that is safe for human health and highly hazardous for the environment will have very different rankings. This difference in rankings is quantified by the dispersion of ranks, which in this work was estimated using the *Gini* index, D. This coefficient can be formulated in many different ways and is here defined as:

$$D(R) = \frac{4}{(N-1)(n^2 - \mid \sin(n\pi/2) \mid)} \sum_{k=1}^{n-1} \sum_{l=k+1}^{n} d_{kl} \tag{4}$$

where N is the number of substances in the list, d_{kl} refers to the distance between the rank value R of one substance in one set of weights (set number k), to the other set of weights (set number l) ($1 \leq k \leq n-1$ and $k+1 \leq l \leq n$), n being the number of different perspectives considered (here, $n = 3$). Thus, d_{kl} can be expressed as:

$$\begin{aligned} d_{kl} &= \mid R_k - R_l \mid \\ &\text{with} \;\; 1 \leq k < n-1 \text{ and } k+1 \leq l \leq n. \end{aligned} \tag{5}$$

The *Gini* index given by Eq. (4) is by far the most frequently used index in data dispersion studies (Cressie, 1991). The expression used in this work presents the advantage that values are normalized so that highest dispersion index possible is unity (see Appendix A for details).

$D(R)$ was calculated for all 58 pharmaceuticals for the three different sets of weights investigated. This measure of statistical dispersion has a possible minimum of zero, a value that occurs when the compared rankings are identical. Thus, small values of the *Gini* index occur when the substance has a consistent ranking in each of the considered perspectives. In contrast, values closer to one indicate that the substance's rank is highly dependent on DMs' classification.

3. Results and discussion

3.1. Expert judgment evaluation

Expert judgment evaluation used only a limited number of DMs, but it serves here primarily to illustrate the methodology. Experts ranked the importance of the physico-chemical criteria to assess the hazard of pharmaceuticals to (i) the aquatic environment, and (ii) to human health. As explained previously, the discrete choices of the DMs were converted into a continuous weight functions. These functions are illustrated in Fig. 4 for (i) and in Fig. 5 for (ii).

If one seeks to assess hazard for the environment then, as can be seen in Fig. 4, PNEC and Log K_{ow} are the two parameters that have the highest probability of being heavily weighted. That is, among the proposed physico-chemical criteria, these were estimated as most important by the DMs in terms of environmental hazard. The spread of the curves convey the disagreement among the DMs for each criterion. The maximum solubility, in contrast, was not considered to be of major importance for environmental hazard. The PDFs for the SLTC and TD criteria have similar shapes in

Fig. 4. In contrast, as seen in Fig. 5, they were considered to be important by the DMs to assess the hazard for human health. Ideally, a human PNEC or an admissible daily intake (ADI) would be a better estimate of toxicity, but they are largely unknown for pharmaceuticals (Cunningham et al., 2009). For this reason, the TD and SLTC have been used in different studies as an indicator of pharmaceutical hazard for human beings (Cunningham et al., 2009; Webb et al., 2003).

Note that the goal of this study is not to give single values of the weights (and one could argue whether they exist) for the different criteria, but rather to provide a method that allows quantification of the variability that can exist among a group of DMs according to the target, and to evaluate how this variability impacts hazard assessment.

3.2. Pharmaceutical hazard ranking

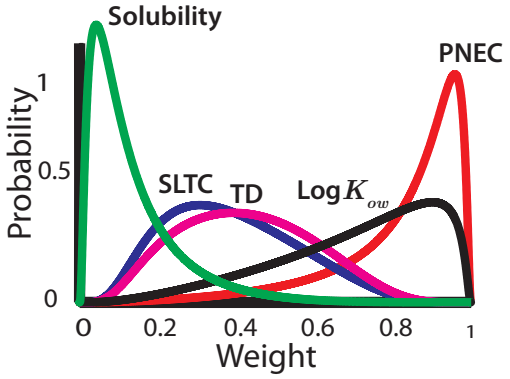

Figure 4: PDF of criteria weights when the target is the environment

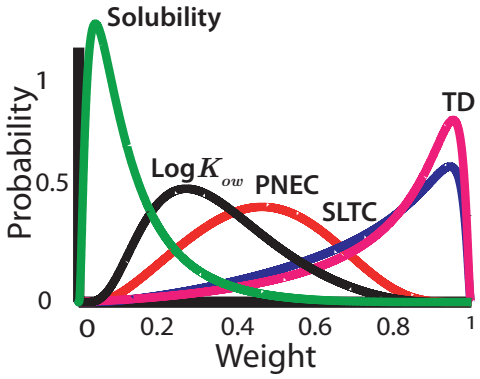

Figure 5: PDF of criteria weights when the target is human health

Table 1: Ranking of pharmaceutical hazard for the three priorities considered (only the highest 20 of the 58 substances are presented). The *Gini* index is given into brackets for each substance.

RANK	Environment	Human Health	No Priority
1	Ethinylestradiol (0.00)	Ethinylestradiol (0.00)	Ethinylestradiol (0.00)
2	Fenofibrate (0.23)	Testosterone (0.04)	Testosterone (0.04)
3	Tiagabine (0.23)	Erythromycin A (0.07)	Erythromycin A (0.07)
4	Testosterone (0.04)	Cortisone (0.18)	Norfloxacine (0.58)
5	Fluvastatin (0.21)	Sulfamethoxazole (0.33)	Cortisone (0.18)
6	Gemfibrozil (0.21)	Amoxicillin (0.33)	Sulfamethoxazole (0.33)
7	Erythromycin A (0.07)	Ciprofloxacin (0.40)	Amoxicillin (0.33)
8	Simvastatin (0.19)	Cyclophosphamid (0.40)	Ciprofloxacin (0.40)
9	Diclofenac (Voltaren) (0.21)	Norfloxacine (0.58)	Cyclophosphamid (0.40)
10	Irbesartan (0.18)	Mitomycine (0.42)	Mitomycine (0.42)
11	Ezetimibe (0.19)	Methotrexate (0.53)	Levetiracetam (28)
12	Bezafibrate (0.19)	Iopromide (0.54)	Methotrexate (0.53)
13	Fluoxetine (Prozac) (0.21)	Iopamidol (0.54)	Iopromide (0.54)
14	Cortisone (0.18)	Fenofibrate (0.23)	Iopamidol (0.54)
15	Ibuprofen (0.19)	Tiagabine (0.23)	Fenofibrate (0.23)
16	Ciprofibrate (0.19)	Fluvastatin (0.21)	Tiagabine (0.23)
17	Citalopram (0.19)	Gemfibrozil (0.21)	Fluvastatin (0.21)
18	Clofibrate (0.19)	Simvastatin (0.19)	Gemfibrozil (0.21)
19	Propranolol (0.19)	Irbesartan (0.18)	Simvastatin (0.19)
20	Celecoxib (0.19)	Diclofenac (Voltaren) (0.21)	Irbesartan (0.18)

Results for the different rankings obtained with the three different sets of weights (priorities) are presented for the 20 most hazardous substances in each ranking in Table 1. To evaluate in what proportion the priority influ-

ences the ranking, the *Gini* index is given for each of the substances, which we recall is a measure of consistency between the three priorities. The ranking for pharmaceuticals like ethinylestradiol, testosterone or erythromycin A is very stable, these substances being at the top of the three different rankings and thus presenting low *Gini* indexes (respectively 0, 0.04 and 0.07). On the other hand, substances like methotrexate, ciprofloxacin, cyclophosphamide, norfloxacin, mitomycine, iopromide and iopamidol show a very high dispersion in their ranking, with *Gini* indexes higher than 0.4. This means that whether these substances are considered hazardous (compared with others) depends strongly on what target is considered by DMs. We can observe in Table 2 that levetiracetam is the pharmaceutical that obtains the highest dispersion score, with a *Gini* index value of 0.58, as it is successively ranked 53, 46 and 11 with the three different sets of weights tested. Thus, the theoretical maximum dispersion index possible of 1 is not obtained in this study.

The experts consulted in this study are considered as representative of the DM population, so a study that would investigate the effects of pharmaceuticals on, for example, the aquatic environment would focus specifically on pharmaceuticals like fenofibrate, tiagabine, fluvastatine, simvastatine and diclofenac. This result is in agreement with those of Perazzolo et al. (2010) and Carlsson et al. (2006). Diclofenac has been found regularly in surface water (Carballa et al., 2007; Cunningham et al., 2009; Langford and Thomas, 2009; Santos et al., 2009), and as a consequence is expected to be considered as a tracer substance by authorities to indicate the occurrence of pharmaceuticals in the environment in Switzerland (OFEV, 2009). On the other hand, for

investigating the potential effects of drug residues in potable water on human health, effort should be directed towards different substances like cortisone, sulfamethoxazole, amoxiciline or ciprofloxacin. Moreover, due to their specific toxic characteristics (very low PNEC, very low therapeutic dose and potential long term effects), the hormones ethinylestradiol and testosterone, along with the antibiotic erythromycin A should be in all cases included in hazard assessment methodologies and regular measurement campaigns.

This hazard ranking methodology complements that of Carlsson et al. (2006). It is, to our knowledge, the only alternative methodology available for pharmaceutical hazard ranking. Carlsson et al. (2006) expressed the hazard for a list of pharmaceutical substances based on European legislation (European Commission, 2006), which as already mentioned assigns pharmaceuticals into two groups entitled "Dangerous for the environment" or "Not dangerous for the environment". This categorization lacks information on the relative hazard of any two substances belonging to the same group. Among the substances considered in the study of Carlsson et al. (2006) as dangerous to the environment, the one that gets the lowest rank in the methodology presented here is metoprolol, with a rank of 39 (Table 2). This suggests that all substances ranked higher than 39 in our ranking are potentially hazardous for natural ecosystems.

3.3. Limits and perspectives of the methodology

The hazard rankings proposed in this study were established from a limited number of criteria and DMs. These limited numbers (five criteria and

Table 2: Complete list of pharmaceuticals considered in this study. The table shows the hazard ranks for the three different priorities considered (Env - Environment, Hum - Humans, and no weighting). The *Gini* index provides information about the consistency of the hazard ranking across the three priorities. The *Gini* index varies between 0 and 1, with values close to 0 implying a consistent ranking across all possible ranks.

Name	Rank Env	Rank Hum	Rank no weight	*Gini*	Name	Rank Env	Rank Hum	Rank no weight	*Gini*
Acébutolol	42	44	46	0.07	Ibuprofene	15	24	26	0.19
Valproic acid	28	35	37	0.16	Iopamidol	44	13	14	0.54
Acipimox	54	50	24	0.53	Iopromide	43	12	13	0.54
Allopurinol	55	55	55	0.00	Irbesartan	10	19	20	0.18
Amoxicillin	25	6	7	0.33	Labetalol	26	33	35	0.16
Atenolol	52	54	54	0.04	Lamotrigine	31	36	38	0.12
Bezafibrate	12	22	23	0.19	Levetiracetam	53	46	11	0.74
Bisoprolol	40	43	45	0.09	Mesalazine	46	47	48	0.04
Carbamazepine	32	37	39	0.12	Metformin	58	58	58	0.00
Celecoxib	20	28	31	0.19	Methotrexate	41	11	12	0.53
Ciprofibrate	16	25	27	0.19	Metoprolol	39	42	44	0.09
Ciprofloxacin	29	7	8	0.40	Mitomycin	34	10	10	0.42
Citalopram	17	26	28	0.19	Morphine	48	49	50	0.04
Clofibrate	18	27	29	0.19	Nadolol	49	51	51	0.04
Clonazepam	33	38	40	0.12	Naproxen	23	32	34	0.19
Cortisone	14	4	5	0.18	Nebivolol	22	31	33	0.19
Cyclophosphamide	30	8	9	0.40	Norfloxacin	37	9	4	0.58
Diazepam (Valium)	27	34	36	0.16	Oxprenolol	38	41	43	0.09
Diclofenac (Voltaren)	9	20	21	0.21	Pravastatin	36	40	42	0.11
Erythromycin A	7	3	3	0.07	Pregabalin	45	45	47	0.04
Ethinylestradiol	1	1	1	0.00	Primidone	47	48	49	0.04
Etofibrate	21	30	32	0.19	Propranolol	19	29	30	0.19
Ezetimibe	11	21	22	0.19	Salicylic acid	35	39	41	0.11
Felbamate	50	52	52	0.04	Simvastatin	8	18	19	0.19
Fénofibrate	2	14	15	0.23	Sotalol	51	53	53	0.04
Fluoxetine (Prozac)	13	23	25	0.21	Sulfamethoxazole	24	5	6	0.33
Fluvastatine	5	16	17	0.21	Testosterone	4	2	2	0.04
Gabapentine	57	57	57	0.00	Tiagabine	3	15	16	0.23
Gemfibrozil	6	17	18	0.21	Topiramate	56	56	56	0.00

five DMs) were dictated by data availability on pharmaceutical properties, time, and DMs' availability. In this application, criteria values are identified for all substances. It is common to find ranking methodologies based on incomplete datasets but introduction of bias in this case is inevitable (Cooper et al., 2008; Kumar and Xagoraraki, 2010; Sanderson et al., 2004). In case more parameters are available for more pharmaceuticals, this work has the benefit that it can be easily and rapidly adapted while keeping the same computational framework.

In this work, the relative hazard for a list of drugs is estimated, but this does not give information about the absolute hazard of each substance. As a consequence, it cannot be used to affirm or refute any potential effect a substance can have on the environment. Instead, its goal is to compare the potential hazard of pharmaceuticals to different targets, in order to choose which ones require more detailed study in terms of the evaluation of their absolute hazard. If a given substance is defined as hazardous by numbers of toxicologists and ecotoxicologists, it is likely that all substances that have obtained a higher rank in the relative hazard evaluation of this study can be considered likewise.

4. Conclusion

Thousands of pharmaceuticals are produced and consumed each year. Many of them could reach the environment. But, only a restricted list of substances can be investigated in detail due to laboratory capacities, time available, legislation, and budgetary constraints. The selection of substances of interest can be greatly influenced by the goal of the study.

For a study that would investigate the effects of pharmaceuticals on the aquatic environment, specific substances of interest have been identified to be fenofibrate, tiagabine, fluvastatine, simvastatine and diclofenac. On the other hand, for a study concerning the potential effects of traces of drugs in potable water on human health, investigation efforts should be directed towards other substances like cortisone, sulfamethoxazole, amoxiciline or ciprofloxacin. In addition, because they possess specific toxic characteristics (very low PNEC, very low therapeutic dose and potential long term effects), the hormones ethinylestradiol and testosterone, along with the antibiotic erythromycin A should be in all cases included in risk-assessment methodologies, environmental concentration estimates and regular measurement campaigns.

As this study intends to define relative hazard for pharmaceutical substances and not risk, it can be generalized without consideration of time and space. It is so far the only ranking methodology of pharmaceuticals that allows the integration of the dispersion of stakeholders' diversity of point of views within one ranking.

Appendix A. Ranking table

In Eq. (4) consider only the sum:

$$D = \sum_{k=1}^{n-1} \sum_{l=k+1}^{n} d_{kl}, \tag{A.1}$$

where d_{kl} is the difference between rank values R for the different sets of weights, so:

$$d_{kl} =\mid R_k - R_l \mid \text{ with } 1 \leq k < n \text{ and } k < l \leq n. \tag{A.2}$$

Assume that the sets of weights have been ordered such that $R_l \geq R_k$, then $d_{kl} = R_l - R_k$.

After simplification we get:

$$D = \sum_{k=1}^{n-1} \sum_{l=k+1}^{n} d_{kl} = \sum_{k=1}^{n} R_k(2k - 1 - n) \tag{A.3}$$

In the sum $\sum_{k=1}^{n} R_k(2k-1-n)$, the factor of $2k-1-n$ is:

- negative for $k < (n+1)/2$ if n odd, $k < (n+2)/2$ if n even, and,
- positive for $k \geq (n+1)/2$ if n is odd, $k \geq (n+2)/2$ if n is even.

Thus, to find largest possible D, set $R_k = 0$ for $k \leq \frac{n+1+|\cos(n\pi/2)|}{2}$. Then the maximum of D is obtained by taking $R_k = N - 1$ for $k \geq \frac{n+1+|\cos(n\pi/2)|}{2}$.

So, the maximum possible D is:

$$\begin{aligned} D &= (N-1)\sum_{k=\frac{n+1+|\cos(n\pi/2)|}{2}}^{n}(2k-1-n) \\ &= (N-1)\frac{n^2-|\sin(n\pi/2)|}{4} \end{aligned} \tag{A.4}$$

If we wish to have $0 \leq D \leq 1$ in Eq. (4), then the leading coefficient should be $\frac{4}{(N-1)(n^2-|\sin(n\pi/2)|)}$.

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