Integrated Risk Index of Chemical Aquatic Pollution (IRICAP): Case studies in Iberian rivers

Francesc Fàbrega[a,b], Montse Marquès[a,b], Antoni Ginebreda[c], Maja Kuzmanovic[c], Damià Barceló[c,d], Marta Schuhmacher[a,b], José L. Domingo[a], Martí Nadal[a,*]

[a] *Laboratory of Toxicology and Environmental Health, School of Medicine, IISPV, Universitat Rovira i Virgili, Reus, Catalonia, Spain*

[b] *Environmental Engineering Laboratory, Departament d'Enginyeria Química, Universitat Rovira i Virgili, Tarragona, Catalonia, Spain*

[c] *Department of Environmental Chemistry, IDAEA-CSIC, Barcelona, Catalonia, Spain*

[d] *Catalan Institute for Water Research (ICRA), Emili Grahit 101, 17003 Girona, Catalonia, Spain*

***** Corresponding author at: Laboratory of Toxicology and Environmental Health, School of Medicine, IISPV, Universitat Rovira i Virgili, Reus, Catalonia, Spain. Tel.: +34977758930.

E-mail address: marti.nadal@urv.cat (M. Nadal).

ABSTRACT

The hazard of chemical compounds can be prioritized according to their PBT (persistence, bioaccumulation, toxicity) properties by using Self-Organizing Maps (SOM). The objective of the present study was to develop an Integrated Risk Index of Chemical Aquatic Pollution (IRICAP), useful to evaluate the risk associated to the exposure of chemical mixtures contained in river waters. Four Spanish river basins were considered as case-studies: Llobregat, Ebro, Jucar and Guadalquivir. A SOM-based hazard index (HI) was estimated for 205 organic compounds. IRICAP was calculated as the product of the HI by the concentration of each pollutant, and the results of all substances were aggregated. Finally, Pareto distribution was applied to the ranked lists of compounds in each site to prioritize those chemicals with the most significant incidence on the IRICAP. According to the HI outcomes, perfluoroalkyl substances, as well as specific illicit drugs and UV filters, were among the most hazardous compounds. Xylazine was identified as one of the chemicals with the highest contribution to the total IRICAP value in the different river basins, together with other pharmaceutical products such as loratadine and azaperol. These organic compounds should be proposed as target chemicals in the implementation of monitoring programs by regulatory organizations.

Keywords:

Risk index

Chemical mixtures

Aquatic pollution

Self-Organizing Maps (SOM)

Spanish river basin

1. Introduction

Due to the massive use of chemicals in industrial and agricultural activities, as well as their content in home products, water pollution in rivers has been growing in recent decades. Detectable and quantifiable amounts of chemicals can be found in rivers, sometimes at harmful concentrations for the environment and especially for the human health [1,2]. Furthermore, Mediterranean rivers are characterized by a strong rainfall and temperature seasonality, with periods of severe drought and floods [3,4]. Because of these special characteristics, climate change models conclude that Mediterranean regions will be among the most impacted regions in a near future [5]. Therefore, climate change and the anthropogenic manipulation of water resources in Mediterranean rivers may lead to enhance human health risks of river water exposure.

As humans are exposed to chemical mixtures rather than individual substances, new realistic approaches have been developed to assess the risks associated to combined exposure to sets of pollutants [6,7]. Classically, two main approaches have been used to evaluate the toxicity of chemical mixtures: concentration addition (CA) and independent action (IA), which assume a similar or different mode of action (MoA), respectively. Although these approaches have been successfully applied in the past [8], mixtures of compounds can interact, modifying therefore the final toxicity [9]. In 2004, the Agency of Toxic Substances and Disease Registry (ATSDR) elaborated a guide manual for the evaluation of join action of chemical mixtures [10], which contained flows charts to help toxicologists [11]. Nevertheless, proper schemes of the MoA considering possible interactions among pollutants, are clearly necessary [12].

Ranking systems allow the prioritization of chemicals according to their chemical, physical or toxicological properties. Ranking methods have become useful tools for stakeholders involved in water management. The European Union (EU) developed a combined monitoring-based and modeling-based priority settings (COMMPS) methodology [13]. COMMPS procedure is based on the exposure of pollutants in freshwater, as well as the effects of the pollutants on aquatic organisms and humans. Among ranking methods, an extended method to prioritize organic chemicals is the use of 3 basic properties: persistence, bioaccumulation and toxicity, commonly known as PBT [14, 15]. The main outcome of this exercise was the list of 33 priority substances identified under the Water Framework Directive (Directive 2000/60/EC) and its "daughter" specifically devoted to this issue (Directive 2008/105/EC). However, PBT models cannot be used to study interactions among compounds. Alternatively, Self-Organizing Maps (SOM) may be a good option. SOM are a kind of artificial neural network (ANN) extensively used in data analysis, which are able of friendly visualizing large amounts of information [16-18]. Data can be analyzed and the extracted results studied in a two-dimensional grid. In addition to information visualization, SOM has been also used for environmental modeling [19]. Due to the ability of the SOM algorithm to group data according to similar characteristics, it has been previously used to create PBT-based rankings pollutants [20,21]. Recently, SOM was also applied to elaborate an ecological hazard index of a series of pollutants found in Ebro River waters (Spain) [22].

In recent years, some statistical and mathematical tools have been used to detect the chemicals with a higher contribution. Some examples are *h*-index (Hirsch index) and Zipf's law, which were successfully applied in a recent study performed to prioritize pharmaceuticals in a wastewater treatment plant [23]. *H*-index is capable to identify the most relevant compounds in a list of ranked chemicals by means of a Pareto distribution, according to some specific parameters. In turn, Zipf's law, based on the inverse proportion between the frequency of one event and its ranking position, has been also widely applied in different domains [24].

The objective of the present study was to rank the hazard of 205 organic compounds analyzed in water samples from 4 river basins in Spain (Llobregat, Ebro, Júcar and Guadalquivir), according to the PBT properties of the pollutants. Firstly, a Hazard Index (HI) was developed and applied to each individual compound by using SOM. Secondly, an Integrated Risk Index of Chemical Aquatic Pollution (IRICAP) was elaborated to rank the human health risks depending on the HI and the concentration of each individual chemical. Finally, the compounds with the highest contribution were characterized using the *h* index and the power law exponent of the Zipf's law.

2. Materials and methods

2.1. Data and study area

As part of a large monitoring program [25], a total amount of 205 organic pollutants were analyzed in four Spanish rivers with different pressures and impacts: Llobregat, Ebro, Júcar and Guadalquivir. The former three are located in the Mediterranean catchment basin, while Guadalquivir waters discharge into the Atlantic Ocean (Fig. 1). A network of representative 77 sampling points was previously established to assess the main stressors of the river basins. The geographical distribution of the sampling sites is presented in Table S1 (Supporting Information).

The list of analyzed compounds included pharmaceutical products, illicit drugs, endocrine disruptors (ED), pesticides, perfluoroalkyl substances (PFAS), and UV filters. Eighty-one pharmaceutics, including analgesics such as ibuprofen and acetaminophen, antibiotics such as ofloxacin and amoxicilin, and antihypertensives such as enalapril and losartam, were determined. Pharmacy products, like psychiatric drugs, diuretic or veterinary pharmaceuticals, were also analyzed. Nineteen illicit drugs including cannabinoids, and recreational drugs such as cocaine, LSD or amphetamine, were also studied. Thirty-one endocrine disruptors were added to the set of target pollutants, including diethylstilbestrol and nonylphenol. Forty-two different pesticides (insecticides and herbicides) were analyzed, including ethion and propanil, among others. Finally, 21 perfluoroalkyl substances (PFASs) such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), and 11 UV filters, including benzophenone and octocrylene, were also determined. Full names and abbreviations are summarized in Table S2 (Supporting Information). Water samples were collected in Autumn of 2010 and 2011.

The Llobregat river basin is located in the north-east of Spain. It has a drainage basin of 1,948 km^2 and a total length of 170 km, being the main drinking water resource of Barcelona and surrounding cities. Because of its proximity to Barcelona, the lowest course of the river receives strong anthropogenic pressures. Urban and industrial waste water are discharged in the Llobregat river, in addition to the surface run off coming from agricultural and salt mining areas [26]. Furthermore, the Mediterranean climate of this area usually changes the water flow, and consequently the natural capacity of the river water dilution. The Ebro river basin is the largest in Spain in terms of water flow, with a drainage basin of 85,550 km^2 and a length of 928 km. Situated in the north of Spain, it is regulated by numerous dams and channels in all the river flow. At the end of the 20th century, approximately 30% of the river flow had decreased due to surface water extractions for irrigation, land use change (reforestation) and rainfall decrease as well as due to the impact of industrial activities, which are concentrated in the main cities along the river. An important “hot spot” of chemical pollution has been also identified in the Flix (Catalonia) reservoir, where thousands of tons of toxic substances (e.g., radionuclides, heavy metals, organochlorine compounds, etc.) have been accumulated [27-29]. These pressures have also altered the sediment regimes and the water quality. The Jucar river basin, located in the east of Spain, covers a drainage area of 21,632 km^2, and the main stream shows a length of 500 km. Agriculture pressures are located in the medium and lower parts of the river basin, where there is also a notable industrial activity. Since it flows in a semiarid zone, the most important problems of this basin are the hydrological modification of the river course, the aquifers overexploitation, and the river contamination. The Guadalquivir river basin is located in the south of Spain, with a drainage basin of 57,071 km^2 and a length on the main stream of 657 km. This area covers a population of approximately 7 million inhabitants, and the river consequently receives many anthropogenic pressures. The total agriculture area of the river basin is 700,000 ha (mainly rice, olives and fruit trees), with the consequent environmental effects. The regime of the river is highly modified by dams and reservoirs, especially in the lower course. Doñana National Park, a natural area severely affected by metal inputs after a mining accident [30], is located at the mouth of the river.

2.2. Hazard Index

Originally developed by Kohonen [31], Self-Organizing Maps (SOM) use an unsupervised learning algorithm that reduces large amounts of input data [32]. The results are generally visualized in two-dimension maps, allowing clustering the input information by grouping similar data. The final result is, on one hand, a Kohonen’s map showing the distribution of the input values on a two dimensional grid, and on the other hand, a set of component planes (*c*-planes) showing the clusters created by the algorithm in the Kohonen's grid. In previous studies, we successfully used SOM in order to create prioritization rankings of pollutants [20,21].

A Hazard Index (HI) was elaborated for the whole set of 205 compounds, using the PBT properties of each individual chemical. Data of persistence, bioaccumulation and toxicity were gathered using Estimation Program Interface (EPI) Suite™ for Microsoft® Windows, v 4.1 (EPI Suit™). EPI Suit™ is a set of tools developed by the US Environmental Protection Agency (US EPA) to estimate physical and chemical properties, environmental fate and aquatic toxicology of chemicals. It uses a database of more than 41,000 chemical compounds, coming from the PHYSPROP© database. The predictive methods and the equation used for each calculation parameter have been described elsewhere [33]. Half-lives were assessed by using Biowin™ tool. Based on a previously developed model [34], Biowin™ tool predicts the primary aerobic degradation of the organic compounds. The result is a semi-quantitative rate of times with the following units: 5-hours, 4-days, 3-weeks, 2-months and 1-years. Bioaccumulation was estimated by using BCFBAF™ tool. The method was initially developed by Meyland et al. [35,36], and subsequently improved by Arnot and Gobas [37], who added experimental values of bioconcentration factor (BCF). Finally, toxicity was estimated by applying the ECOSAR™ tool, which let assess the aquatic (fish) toxicology based on K_{ow} levels [38]. As low levels of persistence and toxicity derive in a higher hazard, inverse values obtained from the Biowin™ and ECOSAR™ tools, respectively, were considered in the HI building. Final data constituted a matrix of 205 compounds and 3 parameters (Supplementary data Table S2), which was run with the SOM toolbox for Matlab® [39]. Values were normalized using the same toolbox to obtain a variance equal to one for each parameter. A linear initialization was applied. The learning phase consisted on 10,000 steps, while the tuning phase added other 10,000 steps. HI was considered as the sum of the PBT values for each compound, after the SOM training. Default range (from 0 to 3) was re-scaled to 0-10.

2.3. Integrated Risk Index of Chemical Aquatic Pollution (IRICAP)

The Integrated Risk Index of Chemical Aquatic Pollution (IRICAP) was calculated by applying the following formula:

$$IRICAP = \frac{\sum (Hazard\,Index \times Chemical\,Concentration)}{Number\,of\,chemicals}$$

The HI of each individual compound was multiplied by the normalized water concentration found in each sampling point (unpublished data), being the final sum divided by the number of pollutants (205). Concentrations were normalized to avoid any overestimation. They were re-scaled from 0 to 10, being the same as the HI. The concentrations were normalized for each chemical by using the following formula:

$$C_{norm} = \frac{C_i - C_{\min}}{C_{\max} - C_{\min}}$$

2.4. H-index and Zipf's law

The list of 205 compounds was initially ordered according to their IRICAP. The percentage of the product of the normalized concentration by the HI was obtained for all the individual compounds studied in each sampling point. Afterwards, data were distributed following a Pareto distribution, using *h*-index and Zipf's law were used to study some of the characteristics of the distribution. The *h*-index was suggested by

Hirsch [40] in order to evaluate the quality of the scientific and academic publications. In the academic area, the number *h* is the number of papers published by an author that have the same number (*h*) of citations. However, this can be translated to other research areas. In the present study, all compounds were ranked according to the HI and the subsequent *h*-index was obtained. Furthermore, the *h*-content or percentage of IRICAP covered by *h*-compounds, was assessed. The *h*-compounds are defined as those located in the first *h* positions of the list of compounds, ordered according to the HI. Finally, the number of compounds representing the 90% of HI (referred to as P 90) was assessed by means of Pareto distributions.

The Zipf's law was formulated for the first time by the linguist Zipf, and it has been extensively used in experimental and social sciences [41]. It assumes that there is a relationship on the frequency of one event that varies depending of some attribute of the event. This mathematical relationship is called a power law. The power law usually follows this formula:

$$y(x) = c \cdot x^{-\alpha}$$

where y is the frequency of the event of rank x, c is a constant factor, and α is the power parameter. The α exponent is numerically determined by linear regression of the log-log transformed experimental data ($\log y = -\alpha \cdot \log x + \log c$). It may give a measure of the complexity of the distribution in the following sense: When $\alpha=0$, there is a situation of "minimum complexity", as $x^0=1$. In contrast, when $\alpha=\infty$ there is a situation of "maximum complexity", because $x^\infty=\infty$. Because α gives important information about the curve shape, this power parameter was assessed in each sampling point.

3. Results and discussion

3.1. Hazard Index

The final result for the HI was a two dimensional grid of 96 hexagons (12x8), where the compounds are spread around the cells according to PBT similarities. Moreover, three *c*-planes maps were obtained, one for each of the PBT parameters (Fig. 2). *C*-planes show the normalized values of half-lives, bioaccumulation and toxicity, obtained after the SOM training of the initial PBT data. The numerical values of the *c*-planes were extracted for the HI calculation developing specific commands using the SOM Toolbox for Matlab® (Table S3). HI outcomes are summarized in Table 1. Half-lives ranged from 0.04 to 2.48. A cluster of 16 PFASs was identified as the group of compounds with highest values of half-lives. The environmental persistence of some PFASs has been reported in previous studies [42]. Surprisingly, neither PFOS nor PFOA, two of the most known and well-studied PFASs, were among the perfluoroalkyl substances presenting a highest persistence. Half-life scores for other compounds were comparatively lower, being distributed in a list with no appreciable trends.

Bioaccumulation scores ranged from 0.29 to 2.70. In contrast to persistence, PFASs were not especially found to be bioaccumulative compounds, excepting PFOSA. In turn, 3 illicit drugs (THC, cannabidiol and canabinol) and 4 UV filters (4MBC, OD-PABA, EHMC, OC) presented the highest bioaccumulation factor (2.70). With regard to this, cannabinoids could present a high bioaccumulation potential due to their important lipophilicity [43]. Toxicity ranges were within 0.57 and 2.53. Two PFAS, PFDoA and PFUdA, seemed to be the most toxic compounds, with a toxicity score of 2.53. Moreover, some cannabinoids (e.g., THC, cannabidiol, and cannabinol) and UV filters (e.g., 4MBC, OD-PABA, EHMC and OC) were also among the most toxic chemicals among the 205 compounds analyzed (2.40). In general terms, most pesticides, such as pyriproxiphen, ethion and anazalil, also presented relatively high levels of toxicity. By contrast, and with the exception of irbesartan, pharmaceutical products mostly were in the lowest part of the list.

HI was obtained by summing the individual score of persistence, bioaccumulation, and toxicity, and re-scaling to 0-10. The final HI values ranged from 1.24 to 5.58. Some trends and clusters can be visually established by means of the SOM. Six PFASs (PFHxDA, PFODA, PFTeDA, PFTrDA, PFDoA, and PFUdA) were identified as the most hazardous pollutants, in terms of PBT parameters, reaching a HI value of 5.58. These perfluoroalkyl substances were characterized by a high environmental persistence and aquatic toxicity, but a relatively low bioaccumulation potential. However, PFOS and PFOA were not included in this set of hazardous pollutants, as their HI was lower (4.20 and 2.30, respectively). A group of cannabinoids (THC, cannabinol and cannabidiol) and UV filters (4 MBC, OD-PABA, EHMC, OC) showed also a high HI (5.45), given their high bioaccumulation and toxicity. Since pharmaceutical compounds generally have low half-lives and toxicity, most of them also showed a comparatively low HI. Bioaccumulation of each particular pharmaceutic determined its final position in the HI ranking. Thus, irbesartan, loratadine, and sertraline were identified as hazardous compounds (HI>5), which agree with previous results [44]. In turn, ciprofloxacin, enalaprilat, iopromide, metformin and ofloxacin, were selected as pharmaceutical compounds with a low hazard (HI=1.24). Illicit drugs did not show any special trend, being well distributed in the whole range of HI values. As above mentioned, cannabinoids were among the most hazardous compounds. In contrast, benzoilecgonine hazard was poor (HI=1.24). In the group of pesticides, hexythiazox was the most hazardous (HI=5.53), while Omethoate presented the lowest HI (1.53).

3.2. IRICAP: Case-studies

An IRICAP value was estimated in each one of the 77 sampling points of the four Spanish rivers above described. IRICAP was estimated by the HI and the water concentration of each one of the 205 compounds (unpublished data). Final IRICAP values are summarized in Table 2, and also depicted for all the four river basins in Fig. 3. A high value of IRICAP is an indicator of more hazard, while a small value of IRICAP indicates water hazardless in terms of risks.

In the Llobregat area, sampling was performed in 14 points across the river basin, including the main course and two tributaries: Anoia and Cardener. In general, the water hazard in Cardener was lower than that in the 2 remaining rivers, as expected owing to its location in the upper basin. The IRICAP score for Cardener ranged between 5.26 (CAR2) and 5.59 (CAR3). CAR1 is considered a reference station with no (or minimum) anthropogenic pressures. Water presented a low risk, with an IRICAP score of 5.58. CAR4, located after a wastewater treatment plant in Manresa, showed an IRICAP value of 5.88. In contrast, highest levels of IRICAP were found in the lowest part of the river basin. Specifically, ANO2, which receives agricultural pressures and the discharges of an industrial pole located in the town of Igualada, showed a high IRICAP value (10.29). ANO3, located at the mouth of the tributary river, is also impacted by the waste waters from a population living close to the river (IRICAP=7.09). Finally, the Llobregat river had an IRICAP ranging from 6.03 (LLO2) to 11.62 (LLO7). The IRICAP showed a logical tendency in Llobregat, as values increased downriver. The upriver area (LLO1 and LLO2) is a mountainous zone with no agricultural and industrial activities. In the mid part of the river course (from LLO3 to LLO6), there are urban and industrial areas, while the final point on the mainstream

(LLO7) is located near the mouth of the river close to the Barcelona town area, with high urban, industrial and agricultural activities in the surroundings. The IRICAP value in this last site was 11.62. It is the highest value of all the river basins, indicating a high degree of risk. The Ebro is the largest river of Spain and water was sampled in 24 points across the whole river basin. IRICAP ranged from 4.08 (GAL1) to 11.36 (ZAD). The Ebro river basin is constituted by several tributaries such as Arga, Cinca, Gallego and Matarranya, among others. GAL1 could be considered as a reference point (IRICAP=4.08), whereas GAL2 is much more affected by agricultural activities (IRICAP=5.93). The river mainstream, from EBR2 to EBR9, is severely affected by the anthropogenic activities of some cities located nearby: Miranda de Ebro (EBR2), Logroño (EBR4), Tudela (EBR5), and Tortosa (EBR8), all of them with a important populations. Furthermore, some sites also receive the impact of agricultural and industrial activities, such as EBR3 (Haro) and EBR7 (Flix), respectively. Despite Flix reservoir was previously identified as a “hot spot” of pollution due to accumulation of toxic sediments formerly discharged by an existing chloro-alkali industry, the sampling point presenting the highest risk was ZAD. It strongly receives the influence of the city of Vitoria, located a few kilometers upstream. It is important to highlight that the current IRICAP was exclusively developed taking into account the levels in the water compartment, while other environmental relevant compartments such as sediments or biota were disregarded. Pollutant levels of organic chemicals near Flix were not found to be of especial concern [28,29].

Fifteen points were sampled in the Jucar river basin: 8 in the mainstream, 5 in Cabriel tributary, and the remaining 2 in Magro tributary. IRICAP ranged from 4.41 (CAB2) to 7.80 (JUC8). Cabriel showed lower IRICAP values (range: 4.41-6.09), indicating the quality of its waters. Cabriel River is located in a semiarid area with a low industrial/agricultural pressure. In Magro River, MAG1 showed the highest IRICAP score (6.97). It corresponds to a point just located after a village with no wastewater treatment plant. Therefore, sewage is directly discharged to the river waters, influencing the environmental conditions of the river at that point. The Jucar has several scenarios in the mainstream with some agricultural and industrial areas. JUC1 should be considered as a reference point (IRICAP=6.52), although the risk score was somehow higher than that obtained in reference sites of other river basins. This value does not really differ from the IRICAP in JUC2 (6.47), which is affected by the Cuenca city, whose population exceeds 50,000 inhabitants. In JUC 3, the contamination from Cuenca city is diluted, resulting in a final IRICAP outcome of 5.79. From JUC4 to JUC 6, the IRICAP again increased (range: 7.07-7.63) as a consequence of the immediate affection of some small village and agricultural practices. Finally, JUC7 and JUC8 showed the highest IRICAP values (7.63 and 7.80, respectively) in the basin, which presents a high industrial activity in its mouth. In general terms, Guadalquivir was the river basin with the lowest IRICAP values, and consequently, with lower human health risks. The Guadalquivir river basin is constituted by other sub-river basins such as Yeguas, Bembézar, Guadaira or Genil, among others. Twenty-four sampling points were included. The IRICAP values ranged from 4.69 (YEG) to 6.32 (GUAA). Although notable high levels of metals were previously reported in Sanlúcar de Barrameda (GUA9) [45], a high degree of pollution is not reflected in our index, as only organic contaminants were considered in the development of the IRICAP. However, quantifiable amounts of some pharmaceutically active compounds have been recently reported in the waters of Doñana National Park [46,47]. The most polluted area of the basin was GUAA (IRICAP=6.32), a sampling point downstream a military area. On the other hand, the less polluted area corresponded to YEG (IRICAP=4.69).

The results obtained after application of *h*-index and Zipf's law are summarized in Table 3. The *h*-index ranged between 2 and 3 in all the sampling points, except for ZAD, whose *h*-index was 1. This means that 2-3 compounds are the most important contributors to the IRICAP score, being the determination of their levels in river water sufficient as indicators of the total risk in terms of both hazard and pollutant concentration. More specifically, the contribution percentage of the 2-3 compounds with respect to the total IRICAP, defined as the percentage of *h*-values content, would range from 1.74 % to 13.68% (ZAD and CAB2, respectively). Between 35 and 96 compounds (CAB2 and ZAD, respectively) summed up to 90% of the IRICAP (Table 3, P90). The current results denote that more than one-half of the 205 compounds here assessed play a minor role, since their aggregated contribution to the risk is less than 10%. Finally, the specific *h*-compounds for each sampling point are given in Table 4. In 3 of the river basins, xylazine was identified as one of the *h*-compounds. Xylazine is a veterinary drug used for sedation, anesthesia, muscle relaxation, and analgesia in animals. Loratadine, pyriproxyphen and azaperol were also catalogued as *h*-compounds (in Ebro, Jucar and Guadalquivir, respectively). In contrast, the *h*-compounds in Llobregat river basin were loratadine and azaparone. According to this, we strongly suggest that xylazine, firstly, as well as other major pharmaceutical products (loratadine, azaperol, loratadine, and azaperone) and pesticides (pyriproxyphen) should be definitively included in the set of pollutants that are routinely measured in river waters. As top contributors to health risks, their levels should be controlled when implementing water monitoring programs in rivers with typical Mediterranean regimes. Power-law equations generally fitted well to the ranked list of compounds in each sampling site (regression coefficient R^2 between 0.47 and 0.93). However, it must be also highlighted that ranges of the α exponent (from 0.99 to 2.44) were relatively small (Table 3). Values of α exponent obtained in all the sampling points denote relatively flat curves, thus indicating that there is a lack of compounds with a prominent dominating weight. Therefore, the IRICAP-based risk load is not clustered with a few compounds.

4. Conclusion

IRICAP means an important effort to elaborate methods for assessing human health risks associated to exposure to chemical mixtures, or the aggregated exposure to chemicals. Although interactions have not been considered in the current study, this tool was able to easily integrate a large amount of compounds to establish similar patterns, with the ultimate goal of prioritizing contaminants in terms of health risks. IRICAP showed logical and reliable results in most sampling points, taking into account the chemical characteristics of each site. Furthermore, IRICAP considers the joint effect of the chemical mixture, but not single groups of pollutants. Consequently, although some places (e.g., agricultural areas) are known to have high concentrations of pesticides, this effect is not reflected in IRICAP because of their low weight vs. other contaminants with a higher HI or concentration. An important limitation of the IRICAP is the use of theoretical values as HI parameters. Data on persistence, bioaccumulation and toxicity for each one of the 205 compounds were derived by applying the US EPA EPI Suit™ software, which is a very powerful tool to get estimative values when experimental information is not available. However, the process of modeling PBT data may be inherently associated to a high uncertainty. This is especially remarkable in the variable “toxicity”. In this case, only fish toxicity values were used to build the HI by means of the ECOSAR™ tool, which is in turn based on K_{ow} levels . This approach may lead to a significant bias, as the impact on aquatic species of other steps in the food web, or even on the human health, is not taken into account. In this framework, further improvements of the IRICAP, in general, and the Hazard Index, in particular, should be focused on incorporating as many species as possible. Species Sensitivity Distributions (SSDs) are distributions of species' responses to a given toxicant [48]. Using SSDs, instead of point toxicity values, could reduce the exclusion of key pollutants, for which fish toxicity is not significant, but the effects on other species may be notable. In order to solve other limitations of this index, as well as to improve the robustness of the model, further studies should include other groups of pollutants, such as heavy metals and POPs and include, if possible, other environmental compartments (sediments and biota). In addition, validation of the index should be considered in future studies by comparing IRICAP values with scores obtained by applying biological indices. Pareto distribution-based indices have been proven to be a useful complement for risk assessment. In the current study, the final results allowed estimating the distribution of the compounds in the curve. Furthermore, the *h*-compounds, this is, those with a highest contribution on the hazard/concentration-based risk, were identified. Xylazine, as well as loratadine, azaperol, loratadine, azaperone, and pyriproxyphen, should be selected as key pollutants when measuring the chemical pollution of fresh waters, at least in rivers of similar characteristics to those here evaluated. In conclusion, these chemicals must be priority pollutants in quality control monitoring networks of river basins. IRICAP may be a useful tool for stakeholders involved in water management, for its capabilities to evaluate and compare human risks in water river samples.

Acknowledgment

This study has been supported by the Spanish Ministry of Economy and Competitiveness, through the project Consolider-Ingenio 2010 CSD2009-00065. Maja Kuzmanovic acknowledges an AGAUR fellowship from the Generalitat de Catalunya.

6. References

[1] J.L. Fernández-Turiel, D. Gimeno, J.J. Rodriguez, M. Carnicero, F. Valero, Spatial and seasonal variations of water quality in a Mediterranean catchment: the Llobregat river (NE Spain), Environ. Geochem. Health 25 (2003) 453-474.

[2] R. Carafa, L. Faggiano, M. Real, A. Munné, A. Ginebreda, H. Guasch, M. Flo, L. Tirapu, P.C.v. der Ohe, Water toxicity assessment and spatial pollution patterns identification in a Mediterranean river basin district. tools for water management and risk analysis, Sci. Total Environ. 409 (2011) 4269-4279.

[3] M. Petrovic, A. Ginebreda, V. Acuña, R.J. Batalla, A. Elosegi, H. Guasch, M.L. de Alda, R. Marcé, I. Muñoz, A. Navarro-Ortega, E. Navarro, D. Vericat, S. Sabater, D. Barceló, Combined scenarios of chemical and ecological quality under water scarcity in Mediterranean rivers, TrAC Trend. Anal. Chem. 30 (2011) 1269-1278.

[4] J.C. López-Doval, N. De Castro-Català , I. Andrés-Doménech, J. Blasco, A. Ginebreda, I. Muñoz, Analysis of monitoring programmes and their suitability for ecotoxicological risk assessment in four Spanish basins, Sci. Total Environ. 440 (2012) 194-203.

[5] F. Giorgi, P. Lionello, Climate change projections for the Mediterranean region, Global Planet. Change 63 (2008) 90-104.

[6] J.P. Sumpter, A.C. Johnson, R.J. Williams, A. Kortenkamp, M. Scholze, Modeling effects of mixtures of endocrine disrupting chemicals at the river catchment scale, Environ. Sci. Technol. 40 (2006) 5478-5489.

[7] L.S. McCarty, C.J. Borgert, Review of the toxicity of chemical mixtures: Theory, policy, and regulatory practice, Regul. Toxicol. Pharmacol. 45 (2006) 119-143.

[8] T. Backhaus, M. Faust, Predictive environmental risk assessment of chemical mixtures: A conceptual framework, Environ. Sci. Technol. 46 (2012) 2564-2573.

[9] A. Boobis, R. Budinsky, S. Collie, K. Crofton, M. Embry, S. Felter, R. Hertzberg, D. Kopp, G. Mihlan, M. Mumtaz, P. Price, K. Solomon, L. Teuschler, R. Yang, R. Zaleski, Critical analysis of literature on low-dose synergy for use in screening chemical mixtures for risk assessment, Crit. Rev. Toxicol. 41 (2011) 369-383.

[10] ATSDR, The guidance manual for the assessment of joint toxic action of chemical mixtures, Agency for Toxic Substances and Disease Registry, US, 2004. Available at http://www.atsdr.cdc.gov/interactionprofiles/IP-ga/ipga.pdf (accessed March 25, 2013).

[11] S.B. Wilbur, H. Hansen, H. Pohl, J. Colman, P. McClure, Using the ATSDR guidance manual for the assessment of joint toxic action of chemical mixtures, Environ. Toxicol. Pharmacol. 18 (2004) 223-230.

[12] L.K. Teuschler, Deciding which chemical mixtures risk assessment methods work best for what mixtures, Toxicol. Appl. Pharmacol. 223 (2007) 139-147.

[13] EC, Revised proposal for a list of priority substances in the context of the Water Framework Directive (COMMPS Procedure), 98/788/3040/ DEB/E1, Fraunhofer-Institut Umweltchemie und Ökotoxicologie, 1999

[14] D.W. Pennington, J.C. Bare, Comparison of chemical screening and ranking approaches: The waste minimization prioritization tool versus toxic equivalency potentials, Risk Anal. 21 (2001) 897-912.

[15] J.A. Arnot, D. Mackay, Policies for chemical hazard and risk priority setting: can persistence, bioaccumulation, toxicity, and quantity Information be combined?, Environ. Sci. Technol. 42 (2008) 4648-4654.

[16] M. Mari, M. Nadal, M. Schuhmacher, J.L. Domingo, Application of self-organizing maps for PCDD/F pattern recognition of environmental and biological samples to evaluate the impact of a hazardous waste Incinerator, Environ. Sci. Technol. 44 (2008) 3162-3168.

[17] M. Alvarez-Guerra, C. González-Piñuela, A. Andrés, B. Galán, J.R. Viguri, Assessment of self-organizing map artificial neural networks for the classification of sediment quality, Environ. Int. 34 (2008) 782-790.

[18] R. Arias, A. Barona, G. Ibarra-Berastegi, I. Aranguiz, A. Elías, Assessment of metal contamination in dregded sediments using fractionation and Self-Organizing Maps, J. Hazard. Mater. 151 (2008) 78-85.

[19] A.M. Kalteh, P. Hjorth, R. Berndtsson, Review of the self-organizing map (SOM) approach in water resources: Analysis, modelling and application, Environ. Modell. Softw. 23 (2008) 835-845.

[20] M. Nadal, V. Kumar, M. Schuhmacher, J.L. Domingo, Definition and GIS-based characterization of an integral risk index applied to a chemical/petrochemical area, Chemosphere 64 (2006) 1526-1535.

[21] M. Nadal, V. Kumar, M. Schuhmacher, J.L. Domingo, Applicability of a neuroprobabilistic integral risk index for the environmental management of polluted areas: A case study, Risk Anal. 28 (2008) 271-286.

[22] W. Ocampo-Duque, R. Juraske, V. Kumar, M. Nadal, J.L. Domingo, M. Schuhmacher, A concurrent neuro-fuzzy inference system for screening the ecological risk in rivers, Environ. Sci. Pollut. Res. 19 (2012) 983-999.

[23] A. Ginebreda, A. Jelic, M. Petrovic, M.L. de Alda, D. Barceló, New indexes for compound prioritization and complexity quantification on environmental monitoring inventories, Environ. Sci. Pollut. Res. 19 (2011) 958-970.

[24] R. Hisano, D. Sornette, T. Mizuno, Predicted and verified deviations from Zipf's law in ecology of competing products, Phys. Rev. E. Stat. Nonlin. Soft. Matter. Phys. 84 (2011) 026117.

[25] A. Navarro-Ortega, V. Acuña, R.J. Batalla, J. Blasco, C. Conde, F.J. Elorza, A. Elosegi, F. Francés, F. La-Roca, I. Muñoz, M. Petrovic, Y. Picó, S. Sabater, X. Sanchez-Vila, M. Schuhmacher, D. Barceló, Assessing and forecasting the impacts of global change on

Mediterranean rivers. The SCARCE Consolider project on Iberian basins, Environ. Sci. Pollut. Res. 19 (2012) 918-933.

[26] Y. Cabeza, L. Candela, D. Ronen, G. Teijon, Monitoring the occurrence of emerging contaminants in treated wastewater and groundwater between 2008 and 2010. The Baix Llobregat (Barcelona, Spain), J. Hazard. Mater. 239–240 (2012) 32-39.

[27] M. Mola, M. Palomo, A. Peñalver, C. Aguilar, F. Borrull, Distribution of naturally occurring radioactive materials in sediments from the Ebro river reservoir in Flix (Southern Catalonia, Spain), J. Hazard. Mater. 198 (2011) 57-64.

[28] N. Ferré-Huguet, C. Bosch, C. Lourencetti, M. Nadal, M. Schuhmacher, J.O. Grimalt, J.L. Domingo, Human health risk assessment of environmental exposure to organochlorine compounds in the Catalan stretch of the Ebro River, Spain, Bull. Environ. Contam. Toxicol. 83 (2009) 662-667

[29] N. Ferré-Huguet, M. Nadal, M. Schuhmacher, J.L. Domingo, Human health risk assessment for environmental exposure to metals in the Catalan stretch of the Ebro River, Spain, Hum. Ecol. Risk Assess. 15 (2009) 604-623.

[30] G. Gómez, R. Baos, B. Gómara, B. Jiménez, V. Benito, R. Montoro, F. Hiraldo, M.J. González, Influence of a mine tailing accident near Doñana National Park (Spain) on heavy metals and arsenic accumulation in 14 species of waterfowl (1998 to 2000), Arch. Environ. Contam. Toxicol. 47 (2004) 521-529.

[31] T. Kohonen, Self-organized formation of topologically correct feature maps, Biol. Cybern. 43 (1982) 59-69.

[32] T. Kohonen, Essentials of the self-organizing map, Neural Netw. 37 (2013) 52-65.

[33] R.S. Boethling, P.H. Howard, W.M. Meylan, Finding and estimating chemical property data for environmental assessment, Environ. Toxicol. Chem. 23 (2004) 2290-2308.

[34] R.S. Boethling, P.H. Howard, W. Meylan, W. Stiteler, J. Beauman, N. Tirado, Group contribution method for predicting probability and rate of aerobic biodegradation, Environ. Sci. Technol. 28 (1994) 459-465.

[35] W.M. Meylan, P.H. Howard, D. Aronson, H. Printup, S. Gouchie, Improved method for estimating bioconcentration factor (BCF) from octanol-water partition coefficient, U.S. Environmental Protection Agency, SRC TR-97-006, 1997.

[36] W.M. Meylan, P.H. Howard, R.S. Boethling, D. Aronson, H. Printup, S. Gouchie, Improved method for estimating bioconcentration/bioaccumulation factor from octanol/water partition coefficient, Environ. Toxicol. Chem. 18 (1999) 664-672.

[37] J.A. Arnot, F. Gobas, A review of bioconcentration factor (BCF) and bioaccumulation factor (BAF) assessments for organic chemicals in aquatic organisms, Environ. Rev. 14 (2006) 257.

[38] H. Sanderson, D.J. Johnson, C.J. Wilson, R.A. Brain, K.R. Solomon, Probabilistic hazard assessment of environmentally occurring pharmaceuticals toxicity to fish, daphnids and algae by ECOSAR screening, Toxicol. Lett. 144 (2003) 383-395.

[39] E. Alhoniemi, J. Hollmén, O. Simula, J. Vesanto, Process monitoring and modeling using the Self-Organizing Map, Integr. Comput. Aid. E. 6 (1999) 3-14.

[40] J.E. Hirsch, An index to quantify an individual's scientific research output, Proceedings of the National Academy of Sciences of the United States of America 102 (2005) 16569-16572.

[41] M.E.J. Newman, Power laws, Pareto distributions and Zipf's law, Contemp. Phys. 46 (2005) 323-351.

[42] A.L. Myers, P.W. Crozier, P.A. Helm, C. Brimacombe, V.I. Furdui, E.J. Reiner, D. Burniston, C.H. Marvin, Fate, distribution, and contrasting temporal trends of perfluoroalkyl substances (PFASs) in Lake Ontario, Canada, Environ. Int. 44 (2012) 92-99.

[43] B.F. Thomas, D.R. Compton, B.R. Martin, Characterization of the lipophilicity of natural and synthetic analogs of delta-9-tetrahydrocannabinol and its relationship to pharmacological potency, J. Pharmacol. Exp. Ther. 255 (1990) 624-630.

[44] V. Roos, L. Gunnarsson, J. Fick, D.G.J. Larsson, C. Rudén, Prioritising pharmaceuticals for environmental risk assessment: Towards adequate and feasible first-tier selection, Sci. Total Environ. 421-422 (2012) 102-110.

[45] U. Kraus, J. Wiegand, Long-term effects of the Aznalcollar mine spill - heavy metal content and mobility in soils and sediments of the Guadiamar river valley (SW Spain), Sci. Total Environ. 367 (2006) 855-871.

[46] D. Camacho-Muñoz, J. Martín, J.L. Santos, I. Aparicio, E. Alonso, Occurrence, temporal evolution and risk assessment of pharmaceutically active compounds in Doñana Park (Spain), J. Hazard. Mater. 183 (2010) 602-608.

[47] M.D. Camacho-Muñoz, J.L. Santos, I. Aparicio, E. Alonso, Presence of pharmaceutically active compounds in Doñana Park (Spain) main watersheds, J. Hazard. Mater. 177 (2010) 1159-1162.

[48] R. Dowse, D. Tang, C.G. Palmer, B.J. Kefford, Risk assessment using the species sensitivity distribution method: Data quality versus data quantity, Environ. Toxicol. Chem. 32 (2013) 1360-1369.

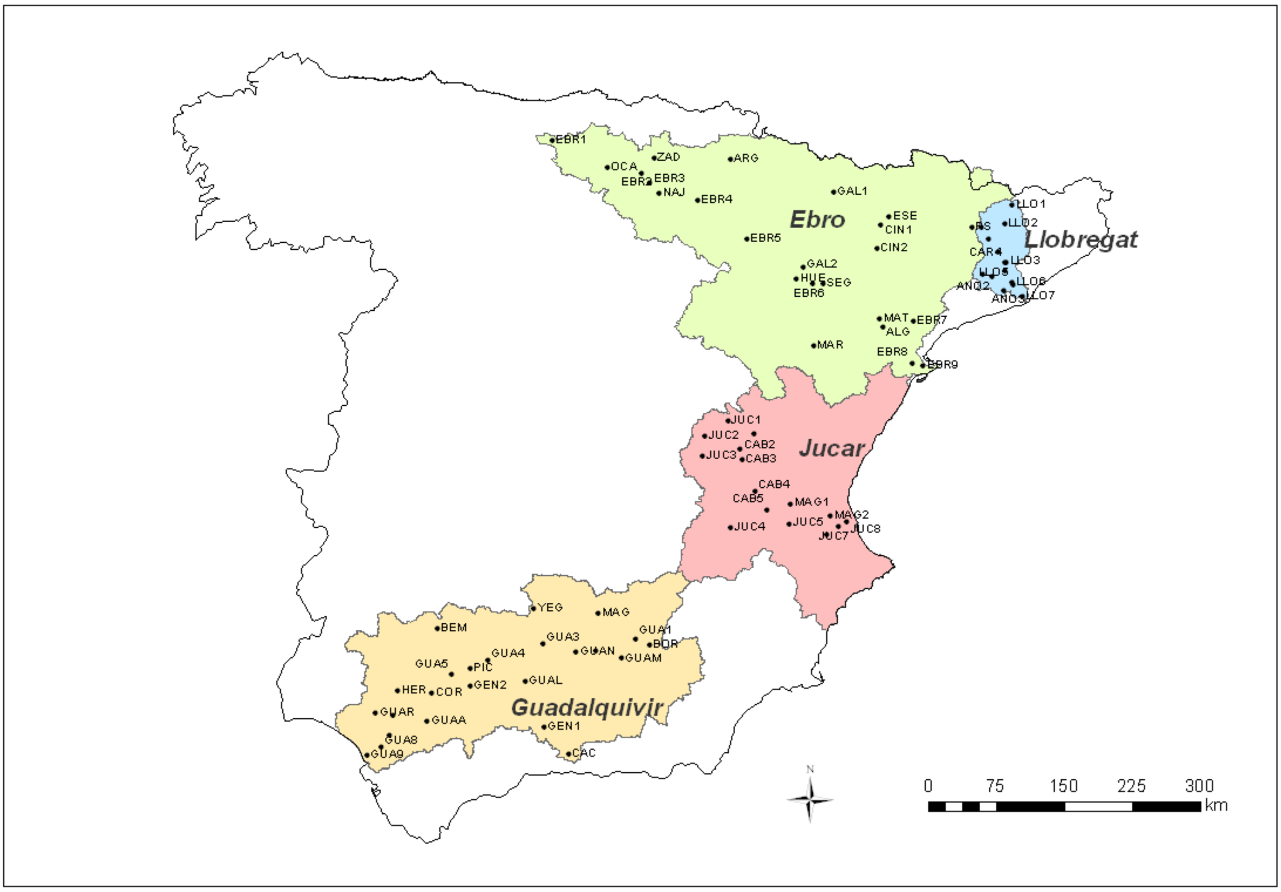

Fig. 1. Area of study.

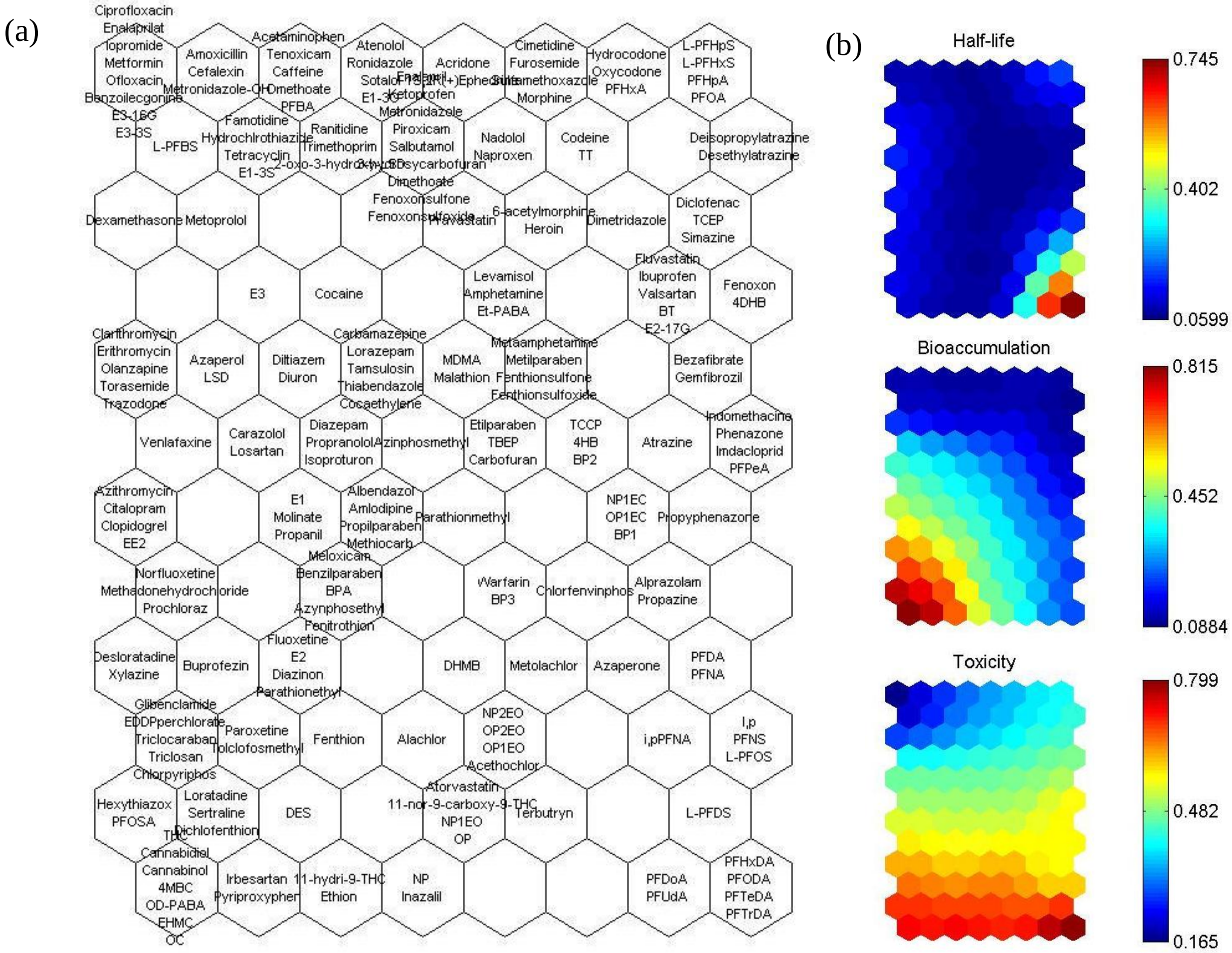

Fig. 2. Self-Organizing Map of the Hazard Index: a) Kohonen’s map, and b) c-planes of PBT.

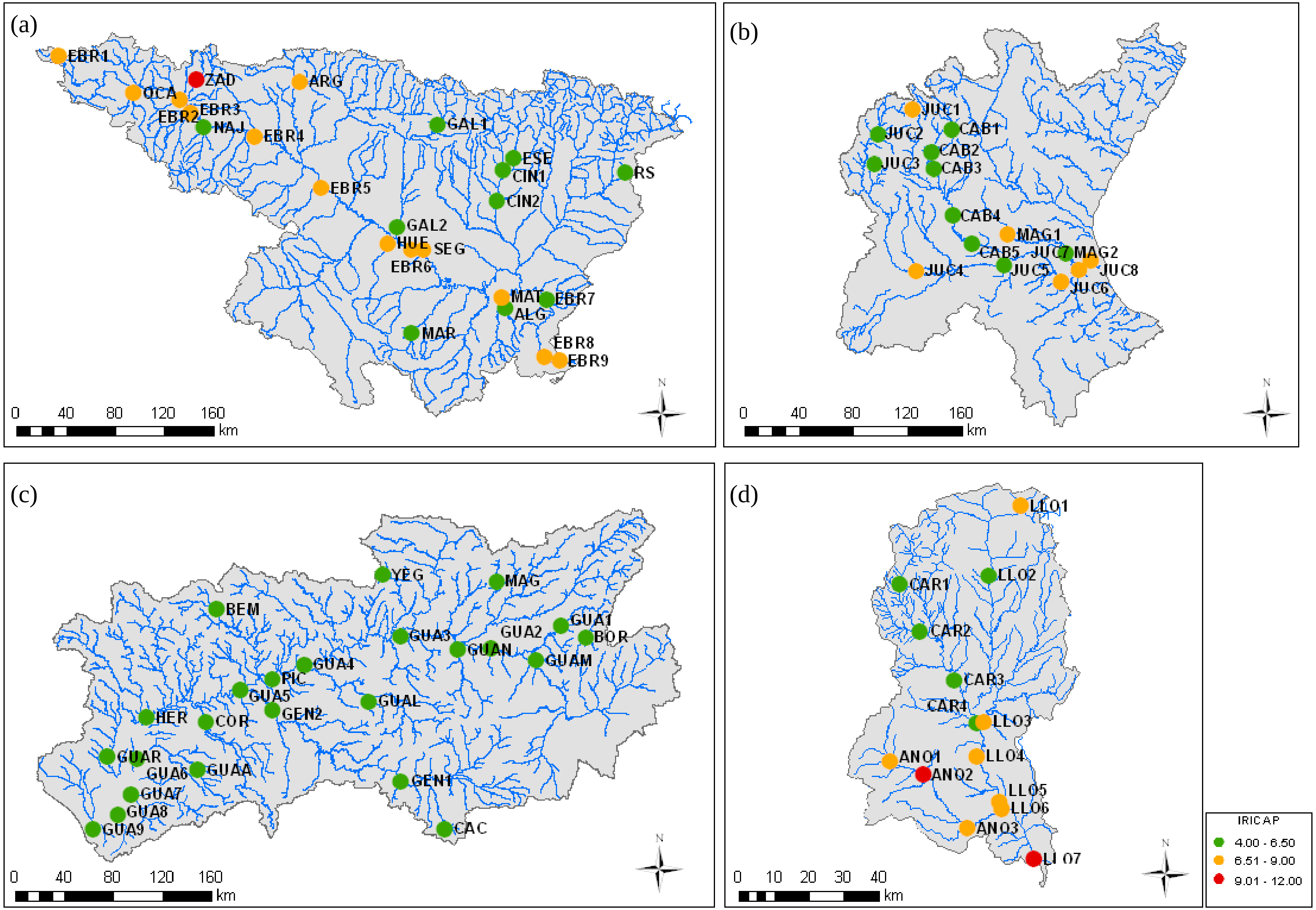

Fig. 3. IRICAP score of 4 Spanish river basins: (a) Ebro, (b) Jucar, (c) Guadalquivir, and (d) Llobregat.

Table 1

SOM- based Hazard Index (HI) developed for 205 organic compounds.

Compound	HI	Compound	HI	Compound	HI	Compound	HI	Compound	HI	Compound	HI
*PFHxDA	5.58	¶NP	4.34	*PFDA	3.52	#Cocaethylene	3.02	*PFOA	2.30	¥3-hydroxycarbofuran	1.76
*PFODA	5.58	¥Inazalil	4.34	*PFNA	3.52	¥Diuron	3.02	¥Fenoxon	2.29	¥Dimethoate	1.76
*PFTeDA	5.58	¥Fenthion	4.26	¥Metolachlor	3.46	¥Azinphos methyl	2.96	Δ4DHB	2.29	¥Fenoxon sulfone	1.76
*PFTrDA	5.58	*I,p-PFNS	4.20	¶E1	3.45	¶NP1EC	2.92	⊥Fluvastatin	2.21	¥Fenoxon sulfoxide	1.76
*PFDoA	5.58	*L-PFOS	4.20	¥Molinate	3.45	¶OP1EC	2.92	⊥Ibuprofen	2.21	⊥Acridone	1.75
*PFUdA	5.58	⊥Norfluoxetine	4.13	¥Propanil	3.45	ΔBP1	2.92	⊥Valsartan	2.21	#1S,2R(+)Ephedrine	1.75
#THC	5.45	#Methadonehydrochloride	4.13	⊥Azaperone	3.45	⊥Propyphenazone	2.90	¶BT	2.21	⊥Ranitidine	1.69
#Cannabidiol	5.45	¥Prochloraz	4.13	⊥Clarithromycin	3.40	¶Etilparaben	2.80	¶E2-17G	2.21	Trimethoprim	1.69
#Cannabinol	5.45	⊥Fluoxetine	4.06	⊥Erithromycin	3.40	¶TBEP	2.80	¥Deisopropylatrazine	2.21	#2-oxo-3-hydroxy-LSD	1.69
Δ4MBC	5.45	¶E2	4.06	⊥Olanzapine	3.40	¥Carbofuran	2.80	¥Desethylatrazine	2.21	⊥Metoprolol	1.64
ΔOD-PABA	5.45	¥Diazinon	4.06	⊥Torasemide	3.40	#Metaamphetamine	2.72	⊥Hydrocodone	2.15	⊥Atenolol	1.64
ΔEHMC	5.45	¥Paratión ethyl	4.06	⊥Trazodone	3.40	¶Metilparaben	2.72	⊥Oxycodone	2.15	⊥Ronidazole	1.64
ΔOC	5.45	*I,p-PFNA	3.99	⊥Carazolol	3.32	¶TCCP	2.72	*PFHxA	2.15	⊥Sotalol	1.64
¥Hexythiazox	5.32	⊥Atorvastatin	3.98	⊥Losartan	3.32	¥Fenthion sulfone	2.72	⊥Dimetridazole	2.14	¶E1-3G	1.64
*PFOSA	5.32	#11-nor-9-carboxy-9-THC	3.98	⊥Warfarin	3.28	¥Fenthion sulfoxide	2.72	⊥Diclofenac	2.12	⊥Famotidine	1.57
⊥Irbesartan	5.26	¶NP1EO	3.98	ΔBP3	3.28	Δ4HB	2.72	¶TCEP	2.12	⊥Hydrochlrothiazide	1.57
¥Pyriproxyphen	5.26	¶OP	3.98	⊥Albendazol	3.27	ΔBP2	2.72	¥Simazine	2.12	⊥Tetracyclin	1.57
⊥Loratadine	5.13	¥Terbutryn	3.94	⊥Amlodipine	3.27	¶E3	2.71	#6-acetylmorphine	2.10	¶E1-3S	1.57
⊥Sertraline	5.13	⊥Azithromycin	3.90	¶Propilparaben	3.27	#MDMA	2.68	#Heroin	2.10	⊥Acetaminophen	1.53
¥Dichlofenthion	5.13	⊥Citalopram	3.90	¥Methiocarb	3.27	¥Malathion	2.68	⊥Codeine	2.06	⊥Tenoxicam	1.53
*L-PFDS	5.06	⊥Clopidogrel	3.90	Azaperol	3.23	Indomethacine	2.66	¶TT	2.06	¶Caffeine	1.53
⊥Glibenclamide	4.91	¶EE2	3.90	#LSD	3.23	Phenazone	2.66	⊥Dexamethasone	2.02	¥Omethoate	1.53
#EDDPperchlorate	4.91	¥Alachlor	3.90	⊥Diazepam	3.17	¥Imdacloprid	2.66	⊥Pravastatin	1.99	*PFBA	1.53
¶Triclocaraban	4.91	¶NP2EO	3.74	⊥Propranolol	3.17	*PFPeA	2.66	⊥Cimetidine	1.91	*L-PFBS	1.46
¶Triclosan	4.91	¶OP2EO	3.74	¥Isoproturon	3.17	¥Atrazine	2.60	⊥Furosemide	1.91	⊥Amoxicillin	1.41
¥Chlorpyriphos	4.91	¶OP1EO	3.74	¥Chlorfenvinphos	3.17	#Cocaine	2.55	⊥Sulfamethoxazole	1.91	⊥Cefalexin	1.41
¶DES	4.86	¥Acethochlor	3.74	⊥Alprazolam	3.16	⊥Bezafibrate	2.42	#Morphine	1.91	⊥Metronidazole-OH	1.41
#11-hydri-9-THC	4.85	⊥Meloxicam	3.62	¥Propazine	3.16	⊥Gemfibrozil	2.42	⊥Nadolol	1.86	⊥Ciprofloxacin	1.24
¥Ethion	4.85	¶Benzilparaben	3.62	¥Paratión methyl	3.08	⊥Levamisol	2.35	⊥Naproxen	1.86	⊥Enalaprilat	1.24
⊥Paroxetine	4.64	¶BPA	3.62	⊥Carbamazepine	3.02	#Amphetamine	2.35	⊥Enalapril	1.76	⊥Iopromide	1.24
¥Tolclofos methyl	4.64	¥Azynphos ethyl	3.62	⊥Diltiazem	3.02	ΔEt-PABA	2.35	⊥Ketoprofen	1.76	⊥Metformin	1.24
⊥Desloratadine	4.57	¥Fenitrothion	3.62	⊥Lorazepam	3.02	*L-PFHpS	2.30	⊥Metronidazole	1.76	⊥Ofloxacin	1.24
⊥Xylazine	4.57	ΔDHMB	3.61	⊥Tamsulosin	3.02	*L-PFHxS	2.30	⊥Piroxicam	1.76	#Benzoilecgonine	1.24
¥Buprofezin	4.37	⊥Venlafaxine	3.58	⊥Thiabendazole	3.02	*PFHpA	2.30	⊥Salbutamol	1.76	¶E3-16G	1.24
										¶E3-3S	1.24

*PFCs, #Illicit drugs, ⊥Pharmaceutics, ¥Pesticides, ¶Endocrine disruptors, ΔUV filters

Table 2
Values for the IRICAP in the 77 sampling points studied.

Llobregat		Ebro		Júcar		Guadalquivir	
Site	IRICAP	Site	IRICAP	Site	IRICAP	Site	IRICAP
LLO7	11.62	ZAD	11.36	JUC8	7.80	GUAA	6.32
ANO2	10.29	HUE	8.47	JUC7	7.63	GUA3	5.93
LLO5	8.35	ARG	8.35	JUC4	7.07	GEN1	5.93
LLO6	7.75	EBR6	7.51	MAG1	6.97	GUA6	5.91
LLO1	7.60	EBR1	7.26	JUC6	6.79	GUA4	5.84
ANO3	7.09	EBR3	7.24	JUC1	6.52	HER	5.65
LLO4	6.92	EBR4	7.17	JUC2	6.47	GUA2	5.64
LLO3	6.88	EBR2	7.13	JUC5	6.43	GEN2	5.48
ANO1	6.76	OCA	7.10	CAB1	6.09	COR	5.41
LLO2	6.03	SEG	7.03	MAG2	6.04	GUAR	5.32
CAR4	5.88	EBR5	6.92	CAB3	6.01	GUAL	5.32
CAR3	5.59	EBR9	6.85	JUC3	5.79	CAC	5.26
CAR1	5.58	EBR8	6.59	CAB4	5.74	GUAN	5.16
CAR2	5.26	MAT	6.54	CAB5	5.64	GUA5	5.14
		MAR	6.40	CAB2	4.41	PIC	5.13
		EBR7	6.30			GUA8	5.11
		NAJ	6.25			GUA7	5.06
		CIN2	6.21			BOR	5.05
		ESE	6.01			GUA1	5.03
		GAL2	5.93			BEM	4.84
		RS	5.78			MAG	4.82
		ALG	5.53			GUAM	4.79
		CIN1	5.41			GUA9	4.71
		GAL1	4.08			YEG	4.69

Table 3
Results of *h*-index and Zipf's law applied on the IRICAP.

Sampling site	*h*-index	*h*-content (%)	P 90	α	Sampling site	*h*-index	*h*-content (%)	P 90	α
ANO1	3	9.98	62	1.74	CAB1	3	10.86	50	2.37
ANO2	2	4.66	90	1.25	CAB2	3	13.68	35	1.97
ANO3	2	6.41	84	1.45	CAB3	3	11.80	52	2.19
CAR1	2	6.48	56	1.87	CAB4	3	10.78	54	2.23
CAR2	2	6.87	53	1.95	CAB5	3	11.26	52	2.28
CAR3	2	6.46	57	1.88	JUC1	3	10.63	52	2.19
CAR4	2	6.14	68	1.54	JUC2	3	10.32	52	2.19
LLO1	3	10.36	60	2.00	JUC3	2	7.02	54	1.99
LLO2	3	10.43	52	1.87	JUC4	3	9.62	58	1.97
LLO3	2	6.72	63	1.67	JUC5	3	9.91	53	2.24
LLO4	2	6.32	63	1.65	JUC6	3	9.79	55	2.09
LLO5	2	6.52	76	1.38	JUC7	2	6.42	58	1.94
LLO6	2	5.38	79	1.36	JUC8	2	6.36	63	2.07
LLO7	2	4.36	95	1.11	MAG1	2	6.10	63	1.82
ALG	3	9.61	52	2.00	MAG2	2	6.73	58	2.08
ARG	2	4.13	83	1.34	BEM	3	11.10	50	2.20
CIN1	3	10.95	50	2.05	BOR	3	9.61	53	2.04
CIN2	2	6.69	56	1.88	CAC	2	8.18	48	2.40
EBR1	3	9.63	59	1.88	COR	2	7.07	52	2.11
EBR2	2	6.49	62	1.68	GEN1	2	6.70	61	1.84
EBR3	2	5.75	68	1.42	GEN2	2	7.20	59	1.93
EBR4	2	5.80	67	1.47	GUA1	3	10.68	50	2.22
EBR5	2	6.01	65	1.53	GUA2	2	7.39	59	1.88
EBR6	2	4.92	74	1.53	GUA3	2	7.09	60	2.02
EBR7	2	6.15	56	1.69	GUA4	2	7.46	58	1.79
EBR8	2	6.31	60	1.74	GUA5	3	10.42	55	1.99
EBR9	3	8.65	61	1.79	GUA6	2	7.12	63	1.85
ESE	3	9.87	51	1.96	GUA7	3	10.58	51	2.07
GAL1	3	13.44	36	1.95	GUA8	3	10.52	53	2.06
GAL2	2	6.19	59	1.86	GUA9	3	10.07	50	2.14
HUE	3	6.99	78	1.45	GUAA	2	6.48	64	1.81
NAJ	2	6.66	54	1.88	GUAL	2	9.18	53	2.13
MAR	2	6.50	52	1.92	GUAM	3	11.22	48	2.23
MAT	2	6.59	55	1.92	GUAN	3	10.41	59	1.89
OCA	2	5.86	63	1.75	GUAR	2	7.89	51	2.16
RS	3	10.26	49	2.14	HER	2	5.61	58	1.97
SEG	2	5.91	68	1.50	MAG	3	11.39	56	2.33
ZAD	1	1.74	96	0.99	PIC	3	10.49	52	2.03
					YEG	3	11.40	49	2.15

Table 4
List of *h*-compounds according to the IRICAP in 77 sampling sites in Spanish river basins.

Site	***h*-compounds**			**Site**	***h*-compounds**		
ANO1	Triclocaraban	Xylazine		CAB1	Pyriproxyphen	Xylazine	NP
ANO2	Triclosan	EDDPperchlorate		CAB2	Pyriproxyphen	NP	Dichlofenthion
ANO3	Loratadine	L-PFOS		CAB3	PFUdA	Xylazine	Pyriproxyphen
CAR1	Loratadine	Azaperone		CAB4	Xylazine	Pyriproxyphen	Hexythiazox
CAR2	Loratadine	Azaperone		CAB5	Xylazine	Pyriproxyphen	Buprofezin
CAR3	Loratadine	Azaperone		JUC1	Pyriproxyphen	Xylazine	Buprofezin
CAR4	Loratadine	Azaperone		JUC2	Pyriproxyphen	Xylazine	Desloratadine
LLO1	OC	EHMC	Hexythiazox	JUC3	NP	Hexythiazox	
LLO2	Xylazine	Paroxetine	Atorvastatin	JUC4	Dichlofenthion	Pyriproxyphen	Xylazine
LLO3	Triclocaraban	Xylazine		JUC5	Xylazine	Pyriproxyphen	Buprofezin
LLO4	Xylazine	Desloratadine		JUC6	Pyriproxyphen	Xylazine	Desloratadine
LLO5	PFTrDA	PFTeDA		JUC7	Dichlofenthion	Chlorpyriphos	
LLO6	Xylazine	Atorvastatin		JUC8	Hexythiazox	Ethion	
LLO7	Irbesartan	Sertraline		MAG1	Xylazine	Pyriproxyphen	
ALG	Triclocaraban	Xylazine	Paroxetine	MAG2	Xylazine	Pyriproxyphen	
ARG	Meloxicam	Azaperone		BEM	Xylazine	Azaperol	Desloratadine
CIN1	Xylazine	Loratadine	Meloxicam	BOR	Azaperone	Warfarin	Azaperol
CIN2	Xylazine	Loratadine		CAC	Xylazine	4MBC	
EBR1	Triclocaraban	Diethylstilbestrol	Xylazine	COR	Xylazine	Warfarin	
EBR2	Triclocaraban	Xylazine		GEN1	Xylazine	4MBC	
EBR3	Xylazine	Loratadine		GEN2	Xylazine	PFNA	
EBR4	Xylazine	Loratadine		GUA1	Xylazine	Azaperol	Desloratadine
EBR5	Xylazine	Loratadine		GUA2	Xylazine	11-nor-9-carboxy-9-THC	
EBR6	Loratadine	Meloxicam		GUA3	Xylazine	Estradiol (E2)	
EBR7	i,p-PFNA	Loratadine		GUA4	Xylazine	Desloratadine	
EBR8	Xylazine	Loratadine		GUA5	Xylazine	Azaperol	Diazepam
EBR9	Xylazine	Loratadine	Meloxicam	GUA6	Xylazine	Diazinon	
ESE	Xylazine	Loratadine	Meloxicam	GUA7	Xylazine	Azaperol	Diazepam
GAL1	Xylazine	Azaperone	Azaperol	GUA8	Xylazine	Azaperol	Desloratadine
GAL2	Loratadine	NP2EO		GUA9	terbutryn	Desloratadine	Alprazolam
HUE	Xylazine	Loratadine	Meloxicam	GUAA	Xylazine	NP	
NAJ	Xylazine	Loratadine	Meloxicam	GUAL	4MBC	Xylazine	
MAR	Xylazine	Loratadine		GUAM	Xylazine	Azaperol	Desloratadine
MAT	Xylazine	Fenthion		GUAN	Xylazine	Azaperol	Desloratadine
OCA	Xylazine	Loratadine		GUAR	Xylazine	NP	
RS	Xylazine	Loratadine	Meloxicam	HER	Propilparaben	Azaperol	
SEG	Xylazine	Loratadine		MAG	Xylazine	Estrone (E1)	Azaperol
ZAD	Fluoxetine			PIC	Xylazine	Azaperol	Desloratadine
				YEG	Xylazine	Desloratadine	Alprazolam