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Bibliometric analysis of emerging contaminants and cytostatic compounds: Understanding the current challenges

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ABSTRACT

Emerging contaminants (ECs) include a wide range of substances whose presence may pose a risk to the environment and human health. Research on cytostatic pollutants is increasing because the exponential growth of cancer treatments leads to higher discharge of cytostatic contaminants with wastewater treatment plant effluents. This systematic bibliometric review shows 4166 publications within the topic of ECs and cytostatic drugs in water bodies since 1996, mainly in the category of Environmental Science. China, Spain and USA are the most productive countries nowadays and Europe has 41,6 % of the publications. Research topics have shifted from identifying the presence of ECs, in the period 1996–2012, to understanding their fate, distribution, and long-term impacts as well as on developing removal technologies, in the period 2012–2023. 29 main keywords have been identified and classified into four thematic groups: contaminants, analytical techniques, water bodies and treatments. Principal component analysis has integrated them into two principal components (PC). PC1 includes keywords within the groups of water bodies and treatments, and it reflects 70 % of the original data variance; while PC2 represents the analytical topic, and it represents 20 % of the variance. The co-occurrence networks of keywords, analysed by VOSviewer, show four clusters in both periods, with "emerging contaminants", "pharmaceuticals", and "personal care products" as the most important. "Contaminants" that appear in the first period have been substituted by "treatment plants" in the last decade. The keyword "personal care products" shows the highest increase (14-fold), higher than "emerging contaminants" (13 times) and "cytostatic drugs" (10 times). In recent years, the research interest on the formation of transformation products during water treatments and their risks has increased as shown by the higher importance of keywords such as "transformation products", "risk assessment" and "toxicity", as consequence of the development of advanced oxidation treatments.

1. Introduction

As anthropogenic activities, industrialization, and technology have grown exponentially, the presence of emerging contaminants (ECs) has increasingly stressed ecosystems. ECs can be defined as materials or chemicals recently detected in aquatic environments, thanks to advancements in analytical chemistry in recent years. ECs are not necessarily new substances, but until now, they could not be detected, even though they have been used in several applications. Their presence may pose a risk to the environment and human health, presenting significant challenges for ecosystems and public health. However, these compounds are still rarely included in European regulations or monitoring programmes, although they may be regulated in the future if they are found to pose significant risks to the aquatic environment. Some of these ECs have already been officially recognised as harmful to public health. Consequently, they are included in the list of Priority Substances, whose control is regulated at the European level under the Water Framework Directive (WFD, European Parliament, 2000). On the other hand, in April 2024, the European Parliament revised the Urban Wastewater Treatment Directive (UWWTD, Council Directive, 1991) to better

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protect public health and the environment. The modification requires an additional quaternary treatment for removing at least 80 % of a broad spectrum of micro-pollutants that will be mandatory for all plants over 150,000 p.e. (and over 10,000 p.e. based on a risk assessment) by 2045. An initial list of 12 ECs has been considered to determine the efficiency of this treatment. However, cytostatic pharmaceutical residues are not included in either of these lists. These chemicals act by targeting DNA alteration through various mechanisms, making their effects on aquatic organisms intrinsic. This study aims to emphasize the importance of considering these pollutants in relation to environmental and, indirectly, human health.

According to the NORMAN Substance Database, ECs can be classified into 21 categories (Norman-Network, 2023), including pharmaceuticals, personal care products (PCPP), pesticides (agriculture), surfactants, disinfection by-products, flame retardants, and industrial chemicals, among others. Currently, more than 700 emerging pollutants, their metabolites, and transformation products, are listed as being present in the European aquatic environment (Norman-Network, 2023). Pharmaceuticals belong to one of the prominent classes, characterized by extensive chemical diversity (Geissen et al., 2015), and are linked to both human and veterinary treatments. Among the most prescribed and consumed medicines are antibiotics, anti-inflammatories, antidepressants, and hypolipidemic agents . Antibiotics have been widely studied due to their high concentration in hospital wastewater and because conventional biological processes create favourable conditions for the development of antibiotic resistance genes and horizontal gene transfer under sub-inhibitory antibiotic concentrations (Zheng et al. 2018).

Pharmaceuticals are found in aquatic ecosystems influenced by different sources (Gómez-Canela et al. 2014). Their presence in the environment is partly due to the fact that some of them can be excreted in unmetabolized forms at rates of up to 95 %, thereby discharging into domestic wastewater systems (Baranowska and Kowalski 2010). Once ingested or injected, pharmaceuticals are typically metabolized in the human body into more polar and soluble forms (Gracia-Lor et al. 2014). However, most of these compounds and their active metabolites are not routinely monitored, and many studies have shown that they may be resistant to water treatment processes, meaning their presence in natural water bodies is expected. These ECs have been detected in wastewater treatment plants (Isidori et al. 2016), surface water (Azuma et al. 2015), groundwater (López-Serna et al. 2013), and even drinking water (Mendoza et al. 2016).

Some pharmaceuticals and PCPP, among other substances, could interfere with the hormonal systems of living organisms. According to the European Union framework on endocrine disruptors (EDCs), these natural or human-made chemicals should be monitored to avoid disturbing the natural environment and affecting human health. Consequently, ECs began to be incorporated into water policy legislation (European Parliament, 2000). Since then, some of these substances have been included in monitoring programs aimed at complying with the Directive 2013/39/EU. It was not until nearly 20 years later that the European Union published a strategic approach to pharmaceuticals in the environment, which responded to legislative requirements to assess the magnitude of the problem of water and soil contamination by pharmaceutical residues (European Commission 2019).

Regarding pharmaceutical pollution, cytostatic compounds, commonly used in chemotherapy treatments, have gained particular attention (Santana-Viera et al. 2016). These compounds are also referred to as antineoplastic agents (Guichard et al. 2017), chemotherapy drugs, or anticancer drugs (Besse et al. 2012). Designed to inhibit cell growth and proliferation, these compounds, have beneficial therapeutic uses but also present potential risks when released into the environment (Gouveia et al. 2019). The use of cancer treatments is rapidly increasing, and it is expected to rise further over the next 15–20 years, according to the Global Cancer Observatory (https://gco.iarc.fr/en). Consequently, the presence of cytostatic compounds in various aquatic environments has drawn the attention of researchers and policymakers (Booker et al., 2014; Olalla et al., 2018). The main sources of these contaminants include pharmaceutical manufacturing, hospitals, and urban wastewater. Once released into the environment, cytostatic compounds can persist in water bodies, soil, and sediments, potentially leading to bioaccumulation and adverse effects on aquatic and terrestrial organisms (Azuma et al. 2015).

Managing ECs, especially cytostatic compounds, is a complex challenge. It requires a multidisciplinary approach, which often contributes to fragmented knowledge. Studies must focus on their detection and monitoring, which is complicated due to their extremely low concentrations and the diversity of substances involved (Kümmerer et al. 2016). Advanced specific water treatments are required, since traditional treatments are not highly effective in removing these compounds (Zhang et al. 2013a; Ganesh Kumar et al. 2023). Furthermore, the ecological and health impacts of long-term exposure to low levels of cytostatic compounds remain poorly understood, complicating risk assessment and regulatory efforts (Wormington et al. 2020). Policymakers, researchers, industry, and hospital stakeholders must collaborate to develop effective strategies to mitigate the release of cytostatic compounds into the environment and protect public health and ecosystems from potential harm. Several review papers have been published recently, but they focus primarily on defining the problem (Castellano-Hinojosa et al. 2023) or specific aspects such as environmental fate (Wormington et al. 2020), distribution (Mukherjee et al. 2021), identification (Santana-Viera et al. 2016), degradation (García et al. 2019), toxicity, or risks (Yadav et al. 2021). Therefore, although much research has been carried out in the last decades on emerging contaminants and cytostatic compounds, the knowledge is still fragmented.

This review presents a systematic bibliometric analysis of the papers published up to 2024, as the base first, to understand the evolution of research hotspots along the years and, second, to identify the current challenges and future research trends. Emerging contaminants include a broad number of contaminants, but this paper is focused on the presence of cytostatic drugs in water bodies. The first review on cytostatic drugs was published in 2013 (Zhang et al. 2013). Since then, the number of publications has increased exponentially. Therefore, two main periods have been analysed: before 2013, and from 2013 to 2023. The study includes the keyword classification, co-occurrence, country/region distribution of publications and cooperation network within the two periods. Furthermore, a timeline view of research topics has been carried out to understand the evolution of research and to identify gaps and future research topics. Thus, this paper represents a state-of-the-art advancement by providing a holistic approach to analyse the research trends on cytostatic drugs over the past decades worldwide, with the aim of identifying remaining challenges. Since the keyword “cytostatic drugs” in the context of water contamination has started to be used in the last decade, a more general term of “emerging contaminants” had to be included in this study.

2. Materials and methods

To explore the research findings regarding the evolution of ECs and cytostatic compounds in aquatic environments, the steps indicated in Fig. 1. have been followed.

2.1. Data source and search strategy

The literature for this study was sourced from the Web of Science Core Collection (WoSCC) database, specifically the Science Citation Index Expanded (SCI-E) edition, on December 31, 2023. This database was selected due to its comprehensiveness and authority, rigorous quality control, prestigious metrics such as the Journal Impact Factor, and comprehensive citation analysis tools. To ensure that the retrieved literature is closely related to this study, the search terms were TS= (“emerging contaminants” OR “cytostatic” OR “cytostatic drugs” OR

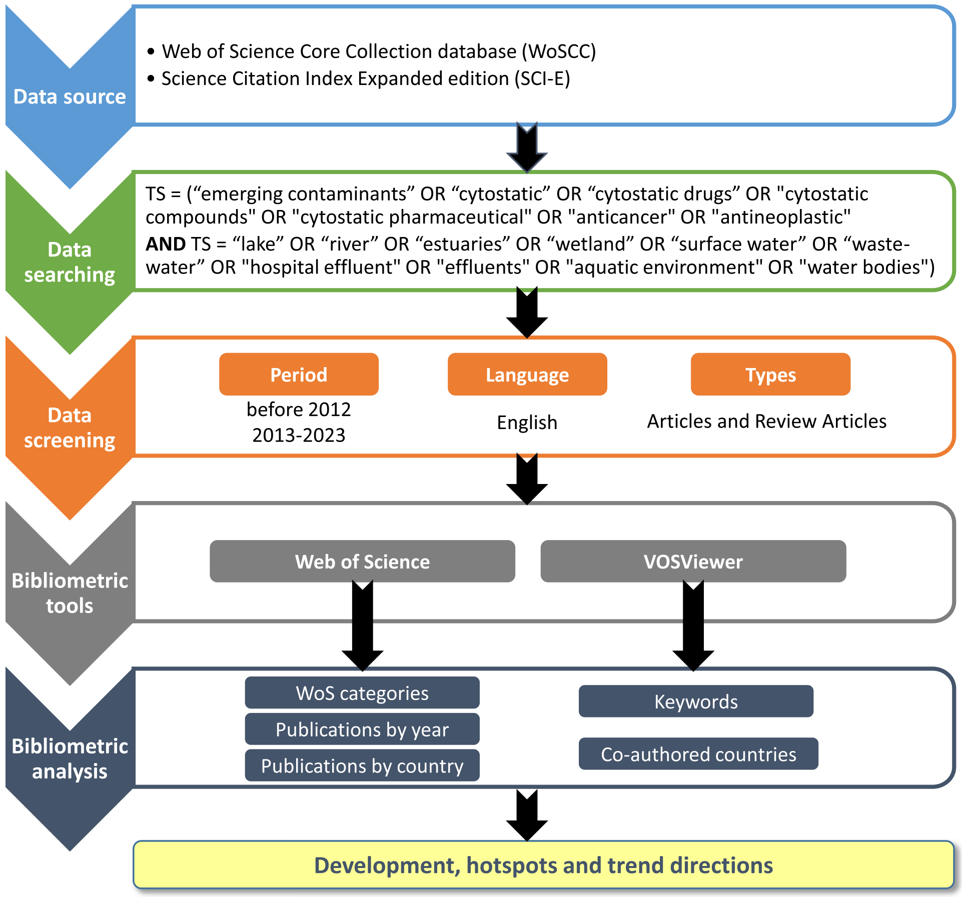

Fig. 1. Research workflow chart.

"cytostatic compounds" OR "cytostatic pharmaceutical" OR "anticancer" OR "antineoplastic") AND TS=("lake" OR "river" OR "estuaries" OR "wetland" OR "surface water" OR "waste-water" OR "hospital effluent" OR "effluents" OR "aquatic environment" OR "water bodies").

In the search settings, the publication date range included two periods: before 2012, which marks the date of the first review published on cytostatic drugs in the aquatic environment (Zhang et al. 2013), and from 2013 to 2023. The language was set to "English", and the publication types were selected as "Articles" and "Review Articles".

Finally, the information from all publications was exported annually in the Tab Delimited File format from the WoSCC database, including the title, author, abstract, keywords, and citation information, to conduct a bibliometric analysis using VOSviewer.

2.2. Bibliometric analysis

The number of publications, the categories, and the number of publications per country for both periods were analysed in WoSCC using the filter and statistics functions.

VOSviewer was used to visualize co-occurrence networks of keywords to determine the current status and research trends in the field across different periods, as well as the country/region networks to illustrate the distribution of research output and collaborations among countries/regions (Van Eck and Waltman, 2010). Fractional counting was applied to ensure that each reference cited in a publication has equal influence in the bibliographic coupling analysis. This approach implies that each reference is considered equally representative of the content of the publication (Perianes-Rodriguez et al. 2016). Before conducting the network analysis, the keywords were reviewed to account for variations in expression that conveyed the same meaning. The following keywords were standardized to ensure consistency across the dataset: "advanced oxidation" and "advanced oxidation process" were standardized to "advanced oxidation processes"; "cytostatic", "cytostatics", "cytostatic pharmaceuticals" and "anticancer drugs" were standardized to "cytostatic drugs"; "emerging contaminant" and "emerging pollutants" were standardized to "emerging contaminants"; "endocrine-disrupting chemical" and "endocrine-disrupting compounds" were standardized to "endocrine disruptors"; "pharmaceutical compounds" was standardized to "pharmaceuticals"; "pollutants" was standardized to "contaminants"; "surface-water" and "surface water" were standardized to "surface waters"; and "wastewater" and "waste water" were standardized to "waste-water".

2.3. Keyword classification

First, the classification of keywords was performed based on the analysis of occurrences obtained from VOSviewer data analysis and Principal Component Analysis (PCA) conducted using Python. After standardizing keywords expressed in different forms but with identical meanings, a co-occurrence analysis of all keywords, including author keywords and keywords Plus, was carried out using VOSviewer. This analysis was conducted for two periods, 1996–2012 and 2013–2023, and subsequently on a yearly basis from 2013 to 2023, considering a minimum occurrence threshold of five for each keyword.

2.4. Principal component analysis

Principal Component Analysis was performed using Python (Jupyter Notebook 6.3.0 version) on the occurrence data of the various keywords. PCA was applied as a statistical tool for dimensionality reduction, simplifying the 29 datasets into fewer variables while retaining as much information as possible. The principal components (PC) are the new variables generated by PCA. Each PC represents a linear combination of the original variables, and they are orthogonal (uncorrelated) to one another. This approach facilitates the visualization and interpretation of research trends over time.

2.5. Article keyword analysis

VOSviewer was employed to analyse the co-occurrence of keywords for the studied periods (Van Eck and Waltman, 2010). This analysis provides insight into research trends and popular topics related to cytostatic drugs. Python was also used to analyse trends and relationships between the main keywords throughout the studied period.

3. Results and discussion

3.1. Publication outputs

The analysis of the categories to which the research belongs over time provides insight into the evolving scope of research directions and fosters multi-category synergy. Prior to 2012, 321 relevant articles (271 articles + 50 review articles) on this subject were published, classified in 45 categories. The earliest article retrieved was *"Trace analysis of the antineoplastics ifosfamide and cyclophosphamide in sewage water by two-step solid-phase extraction and gas chromatography mass spectrometry"*, published in 1996 by Steger-Hartmann et al. (Steger-Hartmann et al., 1996). This publication developed a highly sensitive, specific and reproducible method for the analysis of two antineoplastics in sewage water, classified under the categories "Biochemical Research Methods" and "Chemistry, Analytical".

In contrast, from 2013 to 2023, a total of 3845 relevant articles (3230 articles + 615 review articles) spanning 66 categories, were published. This reflects a nearly twelvefold increase in publications related to the ECs in wastewater in this period, and a significant increase in categories from 45 to 66. The top 10 WoSCC categories with the highest number of publications for both periods are displayed in Fig. 2. Categories are ranked in descending order of the number of publications for the period 1996–2012.

The broad number of categories underscores the multidisciplinary

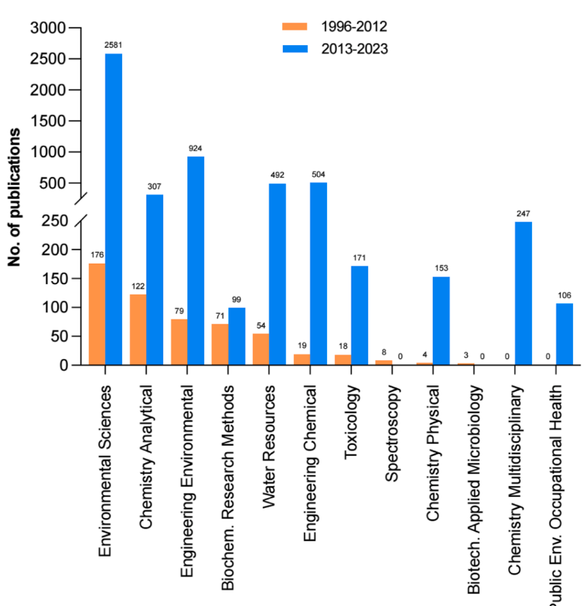

Fig. 2. Top 10 WoSCC categories with the most significant number of publications for periods 1996–2012 and 2013–2023.

nature of research required to tackle challenges posed by ECs. Addressing these issues requires collaboration among engineers, chemists, toxicologists, ecologists, public health professionals and regulatory experts. shows that addressing the challenges posed by ECs requires interdisciplinary research involving engineers, chemists, toxicologists, ecologists, public health experts, and regulatory experts among others. These joint efforts are crucial for developing and validating new methodologies to detect, assess, and mitigate the risks associated with these compounds.

As shown in Fig. 2**,** Environmental Sciences was the most productive category in both periods accounting for 176 (54.7 %) and 2581 (69.5 %) publications, respectively. This highlights the increasing recognition of the ecological impacts of cytostatic drugs on the environment. During the period 1996–2012, Chemistry Analytical was the second most represented category, emphasizing the development of techniques for the detection and quantification of these contaminants (122 publications, 38 %). Analytical advancements such as solid-phase extraction followed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) were pivotal due to their high sensitivity and specificity. Publications in the categories of Chemistry Multidisciplinary and Public Environmental Occupational Health were absent during the period 1996–2012 but showed a significant rise in the last decade. This reflects an increased focus on both the chemical characterization of cytostatic compounds and the growing concerns about their potential impacts on human health.

Between 2013 and 2023, the second most prominent category was Engineering Environmental, followed by Engineering Chemical and Water Resources with 924, 504 and 492 publications, respectively. This trend suggests heightened recent attention to the environmental effects of ECs, particularly in aquatic systems, and highlights the role of chemical engineering in developing new treatments for their removal from water bodies.

The total number of published papers serves as an indicator of the growing interest in cytostatic compounds in water. Fig. 3 shows that before 2013, 321 documents on this subject were published (averaging 20 publications per year since 1996). However, post-2013, a marked increase in annual publication volume was observed, rising from 116 in 2013 to nearly 600 in the last three years. Despite the exponential growth in publications, this trend has stabilized since 2022.

3.2. Keyword analysis

Table S.1 highlights the most frequent keywords associated with "cytostatic drugs" for both periods. The total number of keywords increased sevenfold from 1688 during 1996–2012, to 12,520 in 2013–2023. Although "cytostatic drugs" ranked 20th and 22nd, respectively, its occurrence surged more than tenfold, from 27 to 281 mentions.

Notably, some keywords were absent from the top ranks in both periods. For example, terms related to analytical techniques, such as "liquid chromatography", "mass-spectrometry" or "tandem mass-spectrometry" appeared only in the 1996-2012 period. In contrast, keywords related to water treatment for the removal of these compounds became prominent, such as "waste-water treatment", "degradation", "advanced oxidation processes" or "adsorption". Terms linked to the risk of these substances, such as "risk-assessment", "toxicity" or "transformation products" were not widely represented in the 1996-2012 period but gained substantial relevance in the last decade, as shown in Table S.2.

To deeply understand of temporal trends, 29 distinct keywords from Table S1 (excluding "Metabolites" and "Pesticides" due to their low ranking) were classified into four thematic categories: "Contaminants", "Analytical techniques", "Water bodies", and "Treatments" (Table 1).

The PCA showed that these 29 keywords could be integrated into only two mathematical independent variables called PC that capture 90 % of the original data variance, with PC1 accounting for 70 % and PC2 for 20 %, as shown in Fig. 4.

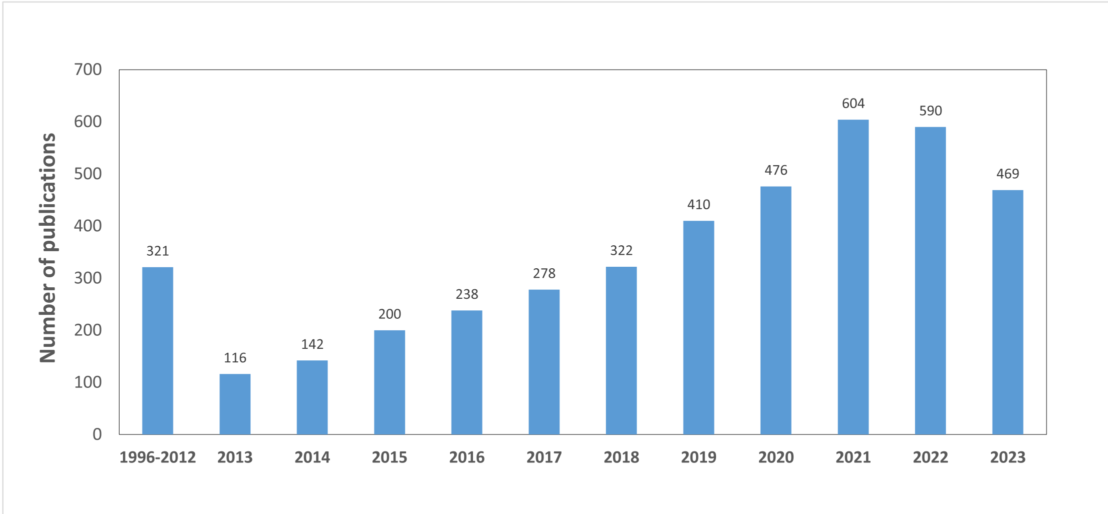

Fig. 3. Number of publications on cytostatic drugs presented in water bodies.

Table 1
Classification of the main keywords from 1996 to 2023.

Thematic groups	Keywords
Contaminants	emerging contaminants (KW 1) pharmaceuticals (KW 3) personal care products (KW 5) endocrine disruptors (KW 6) drugs (KW 23) contaminants (KW 15) antibiotics (KW 27) cytostatic drugs (KW 29) toxicity (KW 28) risk-assessment (KW 20)
Analytical techniques	solid-phase extraction (KW 4) liquid-chromatography (KW 9) mass-spectrometry (KW 13) tandem mass-spectrometry (KW 24)
Water bodies	waste-water (KW 2) surface waters (KW 7) aquatic environment (KW 8) drinking-water (KW 11) environment (KW 17) aqueous-solution (KW 25)
Treatments	removal (KW 10) fate (KW 12) sewage-treatment plants (KW 14) waste-water treatment (KW 16) degradation (KW 18) treatment plants (KW 19) advanced oxidation processes (KW 21) adsorption (KW 22) transformation products (KW 26)

The rest of the data variance collected in the following PCs, represent less than 3 % each, so they were considered residual. Consequently, the data packed in the first two variables can be plotted to give an easy visual representation of the tendency through the studied period, as shown in Fig. 5. Each dot of the representation belongs to a keyword.

Fig. 5 shows the presence of three main clouds (represented by different colours), which means that each keyword (KW) that belongs to a cloud shares a trend (positive correlation) with the rest of the dots in the group. Keywords in red belong to analytical fields such as "solid-phase extraction" (KW 4) or "liquid chromatography" (KW 9); keywords in green are related to water bodies and contaminants topics like "drinking water" (KW 11), "aquatic environment" (KW 8), "pharmaceuticals" (KW 3) or "cytostatic drugs" (KW 29), and keywords in blue are related to contaminants and treatments such as "emerging contaminants" (KW 1), "personal care products" (KW 5), "adsorption" (KW 22), "waste-water treatment" (KW 16) or "advanced oxidation processes" (KW 21). This positive correlation means that if the number of publications of one of the keywords increases, the rest of the same cloud are likely to increase as well, and vice versa.

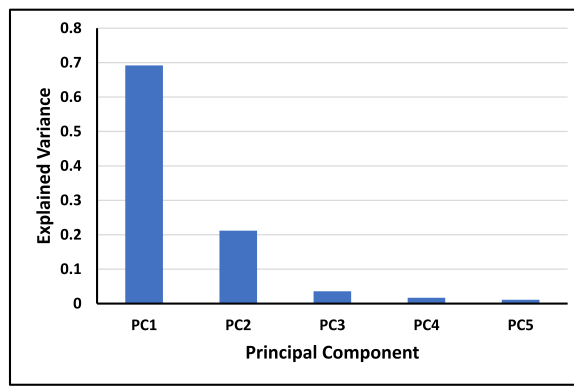

Fig. 4. Explained variance of the data for the first 5 PCs.

It is important to understand that the visual representation of the data gives a statistical explanation of a logical correlation over time between the keywords belonging to each group. It simplifies the study of a huge amount of data over a long period in just one scatter plot, showing clear connections between different kinds of papers that could be missed in a preliminary study.

In addition, the positioning of keywords along the principal components reflects their relative importance. Red dots (analytical methodologies) dominate PC2, representing the 20 % of the variance. Meanwhile, green and blue dots (contaminants, water bodies and treatments) capture the bulk of PC1, reflecting 70 % of the dataset's variability.

The relationship between the keywords within a cloud is related to the timeline. The behaviour of these clouds shows the relevance and evolution of the topic along the years. The value of this information is that it statistically correlates the behaviour over time of common topics.

3.2.2. *Co-occurrence analysis*

The examination of keyword co-occurrence serves as a crucial methodological tool, revealing research directions and prevalent topics (Ghorbani and Sabour 2021). Therefore, this approach is essential for extracting valuable insights into current research trends on cytostatic

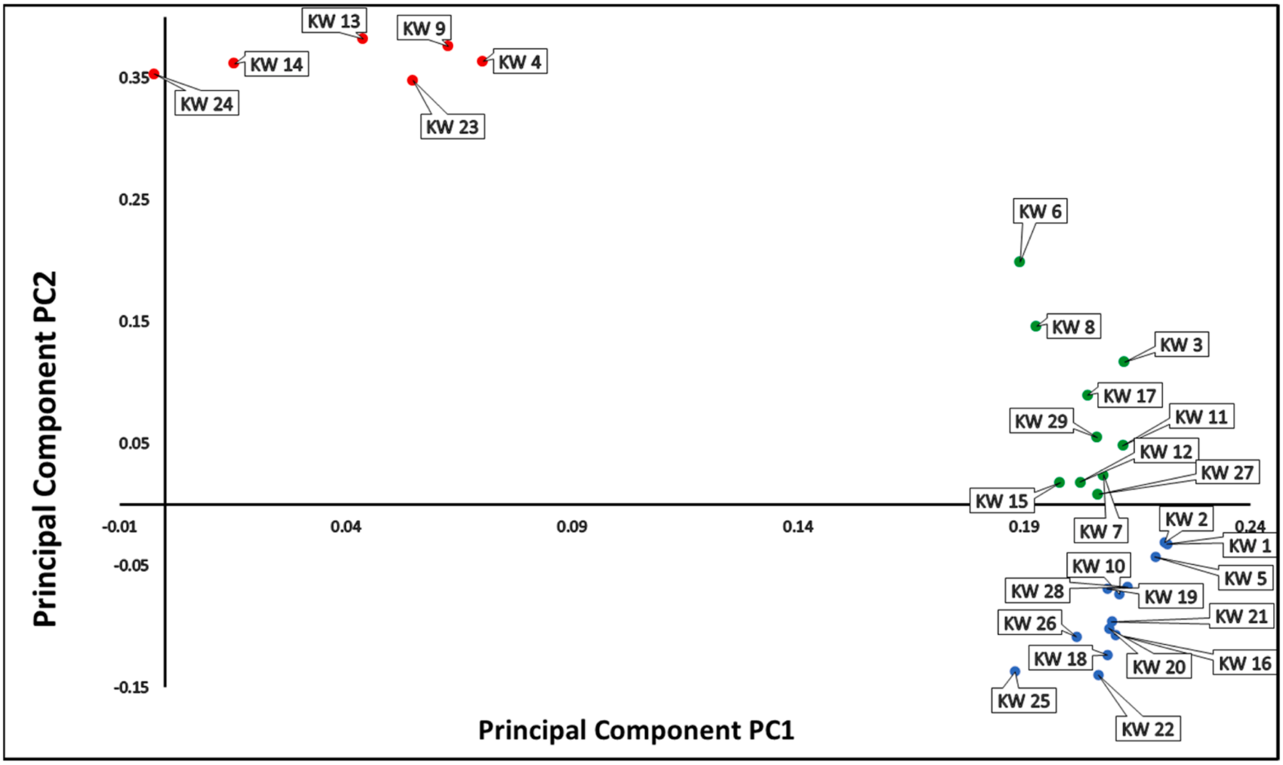

Fig. 5. PC2 vs PC1 (2012–2023).

drugs in aquatic environments. The generated co-occurrence maps of the top 40 keywords with the highest frequency are shown in Fig. 6 spanning the periods 1996 to 2012 (A) and 2013 to 2023 (B). Each node symbolizes an individual keyword, while each curve illustrates the co-occurrence relationship between the connected pair of keywords. The minimum keyword occurrence is set at 15 and 139 in cases A and B, respectively.

Throughout both specified year-periods, the main terms "emerging contaminants," "pharmaceuticals" and “personal care products” consistently stood out as the most frequently appearing keywords in the titles and summaries of the publications. In both periods, keywords are divided into 4 clusters (with colors red, blue, green and yellow), representing the major research directions on this topic. To provide a more in-depth perspective and accessible analysis of keywords, each cluster will be discussed individually.

Upon analyzing the red-colored cluster, in both periods, "emerging contaminants" is the most frequently used keyword, with 184 occurrences in 1996 to 2012 and 2360 occurrences in 2013 to 2023. This cluster has 12 and 13 keywords in each period respectively. During the first period, keywords such as “performance liquid-chromatography”, “tandem mass-spectroscopy”, “solid-phase extraction”, and “liquid-chromatography”, were associated with the main keyword, "emerging contaminants", but vanish as keywords from 2013 to 2023 in this cluster. As previously mentioned, these keywords are directly related to the analytical techniques required to quantify ECs which constituted the primary research focus before 2013.

Advancements in analytical chemistry have enabled the detection of contaminants at trace levels (ng/L). Techniques such as LC-MS/MS and high-resolution mass spectrometry (HRMS) can identify and quantify ECs and their transformation products with high sensitivity and specificity. However, these keywords related to the analysis methods that were part of this cluster before 2013 have now been included in the green cluster (“personal care products”), since new analytical protocols are being developed for this type of contaminants. This indicates the growing interest in residues from personal care products in recent years. Additionally, in the 2013–2023 period, new keywords related to degradation treatments are included, such as “biodegradation”, “photocatalytic degradation”, “oxidation”, “transformation products”, “activated carbon”, and "adsorption". This shift illustrates that current research trends are increasingly focused on the removal of these contaminants. With established analytical protocols, the efficiency of advanced treatments has become a major research focus, as conventional treatments in urban wastewater treatment plants are insufficient for removing ECs.

The blue-colored cluster contains 12 and 9 keywords in the respective periods, with "pharmaceuticals" being the keyword with the highest occurrence. The keyword “cytostatic drugs” is within this group in the first period, with a link strength value of 2,4. However, in the second period, it has a link strength of 25.3 with “pharmaceuticals” although it is classified in the cluster of “personal care products”. The link strength value indicates the number of publications in which two keywords occur together.

The green-colored cluster is centered around "personal care products". This keyword has gained substantial importance in recent years, with occurrences rising from 73, in the 1996–2012 period, to 1006 in the last decade, a 14-fold increase. This growth surpasses that observed with other keywords such as "cytostatic drugs" and "emerging contaminants", which have experienced increases of 10 and 13 times respectively between the periods studied. This trend aligns with the significant increase in the use of personal care products, including a broad range of items such as cosmetics, shampoos, soaps, lotions, sunscreens or fragrances. The market holds a prominent position, contributing an estimated U$ 60.7 billion to the European market volume in 2023. The main additional keywords in this cluster (“surface waters”, “aquatic environment”, “drinking-water”, and “risk assessment”) suggest that researchers are increasingly focusing on the fate and distribution of these contaminants in the environment. Further research is necessary to assess the environmental impact of personal care products particularly on aquatic systems. In this case, analytical specific studies have also increased as already mentioned. The study of wastewater treatment and treatment

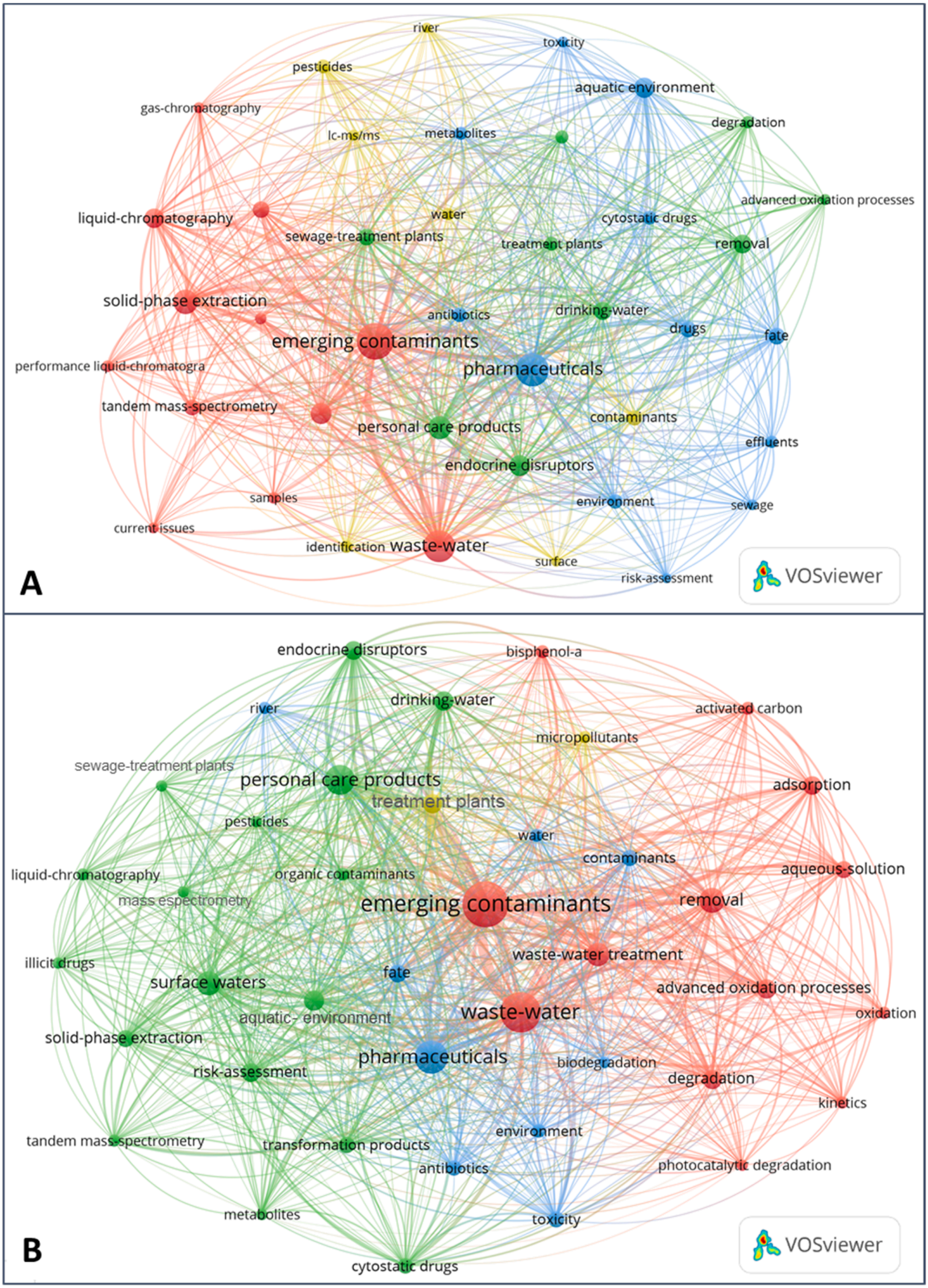

Fig. 6. Co-occurrence network of top 40 keywords with the most frequent co-occurrence.
A: 1996–2012 and B: 2013–2023

plants continues to be a key research focus in this domain.

The yellow-colored cluster is centered around “contaminants” in the first period, with 7 items mainly related with identification and water bodies. However, in the second period this cluster only contains two items: “treatment plants” and “micropollutants”, with a high link strength with “emerging contaminants” (68.1), “personal care products” (37.1) and “pharmaceuticals” (29.1).

It is important to note that some keywords such as "transformation products", "risk assessment" and "toxicity,” have gained greater importance over the past decade, with occurrences increasing from 14, 15, and 17 to 297, 379, and 285, respectively. This highlights new research trends in this area. When ECs are released into the environment, they can undergo chemical, biological, and physical transformations, leading to the formation of transformation products. These products can sometimes be more toxic, persistent, and bioaccumulated than their parent compounds (Česen et al. 2016). Understanding their formation and behavior is crucial for comprehensive risk assessments. Toxicity is also a key factor since cytostatic contaminants and their transformation products exhibit complex toxicity profiles, affecting biological systems and species (Maculewicz et al. 2022). Traditional toxicity tests may not represent the full spectrum of adverse effects, so more sophisticated and comprehensive assessment methods are necessary, including bioassays and in vitro studies, as well as methods to identify long-term consequences. This trend reflects the evolving understanding of environmental science, public health concerns, and regulatory frameworks. Clearly, the potential risks associated with ECs are not fully understood, which increases the challenges for regulatory agencies and public health authorities. It is expected that research in the next years will be focused on improved risk assessments and risk mitigation to assure freshwater safety in the long term (Isidori et al. 2016). New knowledge needs to be developed to help regulatory bodies prioritize their decisions. This public pressure is driving more research and policy initiatives aimed at understanding and mitigating these risks.

3.2.3. Timeline view analysis

The analysis of the evolution of research on cytostatic compounds in wastewater over the last decades reveals significant advances in several key areas from basic detection and initial impact assessments to sophisticated monitoring techniques and advanced treatment technologies. The focus has expanded from identifying the presence of these compounds to understanding their fate, distribution, and long-term ecological impacts, as well as developing effective and sustainable methods for their removal. Fig. 7 illustrates that quantification and removal of the ECs from water bodies are the two main areas of research.

Regarding anticancer drugs, one of the earliest reviews to compile relevant information on analysis and removal efficiencies was conducted by Zhang et al. (2013), where a limited number of compounds were considered. However, this review marked the starting point for addressing new challenges, such as improving removal processes and advancing knowledge about the risks these compounds pose to ecosystems.

Traditionally, one of the main drawbacks in the analysis of ECs has been the lack of multi-residue methods capable of quantifying compounds at low concentrations with adequate accuracy and precision. However, improvements in sample treatment methodologies and instrumental analysis techniques have enabled the separation, identification, and quantification of active ingredients and degradation products at concentrations as low as parts per billion, and even parts per trillion, which have significant environmental impact (López-Serna et al. 2013).

In summary, significant efforts were made in the 1990s to develop quantification protocols (Ternes 1998). Early techniques were relatively rudimentary, relying on high-performance liquid chromatography and gas chromatography-mass spectrometry (GC–MS). Studies were limited and focused on large hospitals and industrial sources. By the 2000s, the introduction of LC-MS/MS significantly improved the sensitivity and specificity of detecting low concentrations of contaminants, broadening the scope of studies (Petrovic 2003). In the 2010s, HRMS enabled the detection of an even wider range of compounds at trace levels, and research expanded to systematically monitor wastewater from various sources, including residential areas, highlighting the ubiquity of these compounds. The increasing number of compounds analysed and the complexity of the matrices have been major challenges to overcome (Martín et al. 2011; Ferrando-Climent et al. 2013; Gómez-Canela et al. 2014; Azuma et al. 2015; Santana-Viera et al. 2016). In the 2020s, research has focused on understanding the fate and transformation of cytostatic compounds in wastewater environments (Maculewicz et al. 2022). This trend is shown in Fig. 7 and Fig. 8**A**, which track the evolution of publications with keywords related to the development of analytical methods (liquid-chromatography, mass spectrometry, and solid-phase extraction). These publications decreased significantly from 2013 onwards, while keywords related to the removal of these

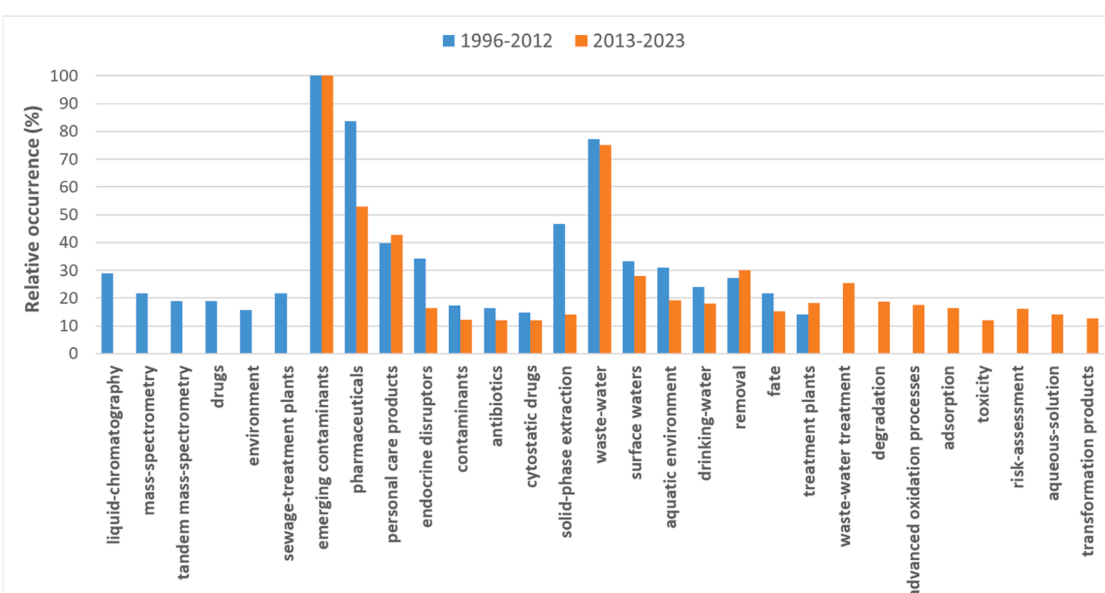

Fig. 7. Keywords with the most significant occurrences in 1996–2012 and 2013–2023.

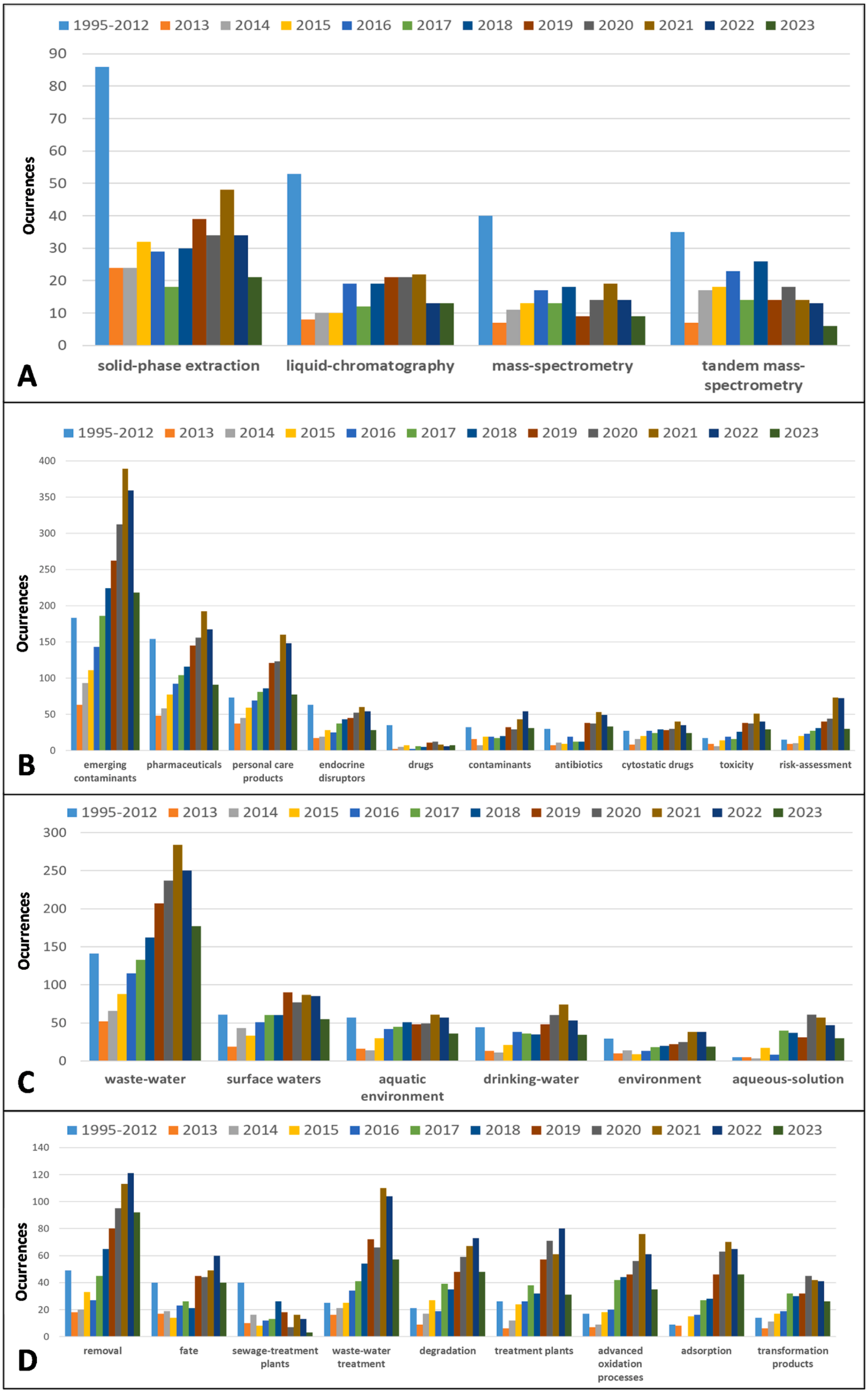

Fig. 8. Evolution of keywords of thematic groups.
A: "Analytical Techniques"; B: "Contaminants"; C: "Water bodies"; D: "Treatments"

compounds from wastewater (removal, advance oxidation processes, and adsorption) have gained special interest. In other words, as a greater number of compounds can now be quantified at lower concentrations with higher reliability, subsequent publications have shifted their focus towards removal methods.

Sample treatment is essential for obtaining clean and concentrated extracts. This is made possible by the solid phase extraction technique, which relies on sorption and desorption phenomena driven by chemical affinity. The optimization process begins with selecting the appropriate adsorbent and solvents, which can be challenging, especially when the analytes exhibit a wide range of properties. Common solid phase extraction adsorbent materials include octadecyl silica, polymeric, and hydrophilic-lipophilic materials, typically used with either disks or, more frequently, cartridges. The Oasis HLB cartridge from Waters is the most widely used due to its balanced combination of lipophilic and hydrophilic monomers. Additionally, low pH is generally preferable for molecule polarization (Baranowska and Kowalski 2010; Zhou et al. 2023).

Unquestionably, the main separation techniques are gas chromatography (GC) and liquid chromatography (LC), while mass spectrometry (MS) is the most widely used detection technique. However, GC–MS analysis often requires derivatization—an additional sample preparation step necessary to increase the volatility of most pharmaceutical compounds — which limits its application (Farré et al. 2001). Consequently, LC-MS and LC-MS/MS have gained special interest for the analysis of ECs and their metabolites in aqueous environmental samples (Ternes 2001). The use of tandem MS (MS^2) coupled with LC analysis has substantially increased the selectivity and the sensitivity of the analyses, achieving lower detection limits compared to single-quadrupole LC-MS. Precursor ions for quantification and product ions as qualifiers for target compound identification are extracted from reference materials and then applied to real samples using selected ion monitoring or multiple reaction monitoring modes. Pharmaceuticals are typically detected using an electrospray ionization (ESI) interface under positive or negative ionization conditions, with protonated or deprotonated molecules commonly selected as precursor ions. As a result, LC-MS/MS enables the separation and detection of compounds with the same molecular mass but different product ions, even when they share the same elution time. Furthermore, this analytical technique is preferred for its enhanced sensitivity and selectivity, particularly in complex matrices.

Fig. 8**B** illustrates the evolution of publications within the thematic group on "Contaminants". Initially, ECs and pharmaceuticals showed similar publication numbers**.** However, since 2013, the number of publications on ECs has increased exponentially as research has expanded to cover a broader range of contaminants. Pharmaceuticals continue to account for the highest percentage of publications, which is justified by the existence of over 3000 active pharmaceutical ingredients currently on the market (European Commission 2019). Among these, antibiotics and cytostatic keywords have higher relevance due to their potential effects on the environment (Kümmerer 2009). Additionally, personal care products and endocrine disruptors have gained increasing attention in recent years.

In general, there is a clear upward trend in the number of publications included in the contaminants thematic group.

When focusing on the subgroup of keywords related to pharmaceuticals, the largest number of keywords are associated with antibiotics and cytostatic drugs. This growing number of publications reflects the increasing efforts to address the gaps in knowledge regarding the occurrence, impact, and remediation of contamination caused by these pharmaceuticals, highlighting their importance in the field of water quality.

The subgroup of the terms related to contaminants, micropollutants, and drugs can lead to disagreement. However, in this paper, the differentiation made by many authors between these concepts is considered important. Contaminants and micropollutants can include both emerging and non-emerging chemicals, while drugs may refer to both licit and illicit substances. In the toxicity subgroup, it is important to emphasize the difference between toxicity and risk assessment, as toxicity represents only one stage of a risk assessment. Toxicity identifies hazards, whereas risk assessment evaluates the actual risks (Chapman 2000).

In terms of trends, 2021 shows a higher rate of publications including these keywords related to "Contaminants". It is likely that the Covid isolation period influenced the increase in publications. Before 2012, only the number of publications featuring "endocrine disruptor" as a keyword exceeded this count. This suggests, as mentioned above, that this is a type of contamination that endocrine disruptors have been studied for over thirty years, highlighting both the complexity of the issue and the ongoing development of new techniques to expand the boundaries of knowledge.

Fig. 8**C** illustrates the evolution of the keywords within the thematic group "Water bodies". The occurrence of the keywords is linked not only to their relevance but also to the availability of measurement methods. Most publications focus on wastewater analysis, which is understandable given its significance in researching various treatments aimed at improving the efficiency of wastewater treatment plants. Consequently, it is the most relevant category. Surface water ranks second in occurrence, which is expected, as many studies are focused on identifying contaminants resulting from effluent discharges. Furthermore, surface water is directly related to aquatic services and environmental health, encompassing rivers, lakes, reservoirs, and coastal waters, among others (Galindo-Miranda et al. 2019). Studies on drinking water are also important due to their direct connection to human health. However, the greatest challenge in these analyses lies in the concentration levels, which can be less than a nanogram per litre, up to three orders of magnitude lower than those typically found in wastewaters (Valcárcel et al. 2018).

Fig. 8**D** illustrates the evolution of the keywords within the thematic group of "Treatments". The primary trend is a shift toward advanced tertiary treatments, such as advanced oxidation processes and adsorption. It is well known that goal of the wastewater treatment plants is to remove solids and mineralize organic molecules to relatively harmless by-products and inactivation of microbes. However, low and non-biodegradable compounds, as ECs, limit its efficiency and are responsible of the presence of recalcitrant compounds that need to be removed by advanced treatments (Kumar et al. 2023). Double membrane processes are effective, but fouling is a challenge as well as the high costs (Jamil et al. 2019). Advanced oxidation processes (ozone (O_3), hydrogen peroxide (H_2O_2), UV irradiation, and combinations of these, such as O_3/UV, H_2O_2/UV, and photocatalysis) are a promising option because they can degrade and mineralize the contaminants, they usually present fast reaction kinetics and are effective for various types of EC. However, it has been reported that they also enhance the toxic by-product formation through its side reactions, in the presence of bromine, chloride or nitrogen (Rayaroth et al. 2022). This justified that, recently, there has been an increasing interest in identifying transformation products and their associated toxicity. Another promising option is adsorption which is cost effective, particularly with activated carbons, easy to operate and there is no-byproduct formation. However, this technology has the disadvantages of limited capacity, selective removal of contaminants, it does not degrade them, and it requires the regeneration and disposal of spent adsorbents (Saravanan et al. 2023).

As traditional wastewater treatment plants only remove a portion of ECs, they require the implementation of extended treatments. However, there is no consensus among experts regarding the most efficient technologies, since this often depends on the specific contaminants being studied. Future research is likely to emphasize integrated approaches, as the combination of advanced oxidation with adsorption to tackle the challenges posed by cytostatic compounds in wastewater and address the issue of the presence of complex mixtures.

3.3. Key countries/territories contributors and collaboration analysis

Geographic productivity in the field of cytostatic drug pollution in water was assessed based on the number of articles published per country/territory from 2013 to 2023. According to the dates available in WoSCC, these publications are distributed across 109 countries/regions. Table 2 presents the top 15 countries/territories on this topic, accounting for 69 % of the total number of publications. China is the most prolific country, representing 13.2 % of the total, with 738 publications. Spain ranks second, accounting for 10.3 % of the total with 576 articles. As one of the most water-stressed industrialized nations worldwide, Spain is proactively addressing the imperative of ensuring long-term water security. Through robust research in the field of water, the country leverages its expertise to tackle water-related challenges, focusing on technological advancements, policy frameworks, and innovative solutions to comprehensively understand, conserve, and utilize water resources efficiently. The USA ranks third, with 446 publications (8.0 %) followed by Brazil (328 publications, 5.9 %), India (290 publications, 5.2 %), Italy, Germany, Portugal, Canada, France, England, Australia, Mexico, Poland, and South Korea.

Additionally, an analysis of international academic collaboration among the most productive countries was conducted over two-year periods, spanning from 1996 to 2012 (Fig. 9**A**) and from 2013 to 2023 (Fig. 9**B**). Each data point represents a specific country, and the size of the point indicates the number of publications from that country. The interconnecting lines between points illustrate collaborative relationships among countries, with the thickness of these lines being proportional to the number of collaborative publications, serving as a measure of the depth of the relationship. Cooperation between each pair of countries was assessed on the affiliations of co-authors and a minimum publication threshold of five collaborative publications. The different colors on the network map represent the various clusters that indicate close collaboration between countries or institutions.

During the 1996–2012 period, authors from 55 different countries published a total of 321 papers on the topic. Spain, the USA, and Germany were the top three productive countries, publishing 96, 69, and 43 articles, respectively. Together, they accounted for 49.4 % of the total publications. As shown in Fig. 8A, the co-authorship collaboration was divided into five collaborative clusters. Spain led the ranking not only in the number of published articles (96), but also in the number of cooperative relationships (9) with other countries/regions, including the USA, Brazil, Canada, and six European countries/territories: Germany, Switzerland, Italy, Belgium, England, and the Netherlands. However, the most significant collaboration during this period occurred between the USA and China. This close collaborative partnership has also been reported in numerous other research fields (Zhu et al. 2021).

In the last decade (Fig. 8B), European countries accounted for 41.6 % of author affiliations, Asia for 26.1 %, North America for 10.8 %, South and Central America for 10.4 %, Africa for 3.8 % and Australia for 2.5 %. During this period, the number of countries/territories significantly increased to 109, and the international collaboration network became more intricate and interwoven, resulting in seven clusters of collaborative networks. In addition to Spain and the USA, identified as key contributors from 1996 to 2012, China and Brazil have emerged as the top four productive countries in the most recent decade. Despite Germany's, continued significant contribution with 190 articles, its ranking has dropped to seventh position. Other countries, such as India, Italy, Portugal, and Canada, also play a significant role as contributors to this topic. In terms of international research collaboration, Spain continues to lead in cooperation with other countries/territories. The top five research collaborators with Spain over the last ten years are Portugal, Italy, Brazil, Mexico, and the USA, with link strength values of 32.5, 27.82, 22.00, 20.34, and 16.34, respectively.

Table 2
Countries/territories in Top 15 WoSCC from 2013 to 2023.

Row	Country/territories	Number of articles[1]
1	CHINA	771
2	SPAIN	591
3	USA	457
4	BRAZIL	334
5	INDIA	305
6	ITALY	241
7	GERMANY	190
8	PORTUGAL	190
9	CANADA	156
10	FRANCE	137
11	ENGLAND	136
12	AUSTRALIA	131
13	MEXICO	110
14	POLAND	110
15	SOUTH KOREA	97

[1] Full counting of each article for every country represented by the authors. According to WoSCC, an article may be counted multiple times, once for each country represented by its author.

4. Conclusions

From 1996 to 2023 the number of papers published in the field of ECs and cytostatic contaminants in water bodies has been increasing year by year, especially after 2012. This shows the increased awareness and concern in this field. Most papers are published in the category of Environmental Science. The research leader in this field is in Europe with a 41,6 % of the publications. The most productive countries are China (13,2 %), Spain (10,3 %) and USA (7,8 %). 29 main keywords have been identified and classified into four thematic groups: contaminants, analytical techniques, water bodies and treatments. Two PCs represent 90 % of the original data. PC1 (70 %) includes keywords within the groups of water bodies and treatments, while PC2 (29 %) represents the analytical topic.

In the first period (1996–2012), studies were focused on identifying the presence of pharmaceutical residues (mainly antibiotics and hormones) while in the last decade more specific contaminants, including cytostatic compounds, are being studied, highlighting their persistence in the environment and potential risks to aquatic ecosystems and human health. The advancement of analytical techniques has enabled the quantification of traces levels of ECs (ng/L). Specific protocols must be developed for each new compound to comprehensively monitor and identify a broad range of ECs. Since the water matrix may influence the results, the optimization of the solid-phase extraction step is extremely important.

The co-occurrence networks of keywords, analysed by VOSviewer, show four clusters in both periods, the most important ones being emerging contaminants, pharmaceuticals, personal care products. The cluster contaminants that appear in the first period has been substituted by treatment plants in the last decade. Most studies focus on evaluating the efficiency of water treatment methods for removing these contaminants. The results show varying degrees of success depending on each specific case. Advanced treatments, including ozonation, photocatalysis, adsorption, and membrane filtration, are promising but all of them presents some disadvantages. Therefore, combined treatments are being studied nowadays.

The keyword "personal care products" shows the highest increase (14-fold), higher than "emerging contaminants" (13 times) and cytostatic drugs" (10 times). During the last few years, the research interest on the formation of transformation products during water treatments and their risks has increased, as shown by the higher importance of keywords such as "transformation products", "risk assessment" and "toxicity", and as a consequence of the development of advanced oxidation treatments which form by-products when contaminants are not totally mineralized or by side reactions. Long-term studies are required to assess the chronic impacts of low-level exposure on ecosystems and human health, with the aim of contributing to a greater

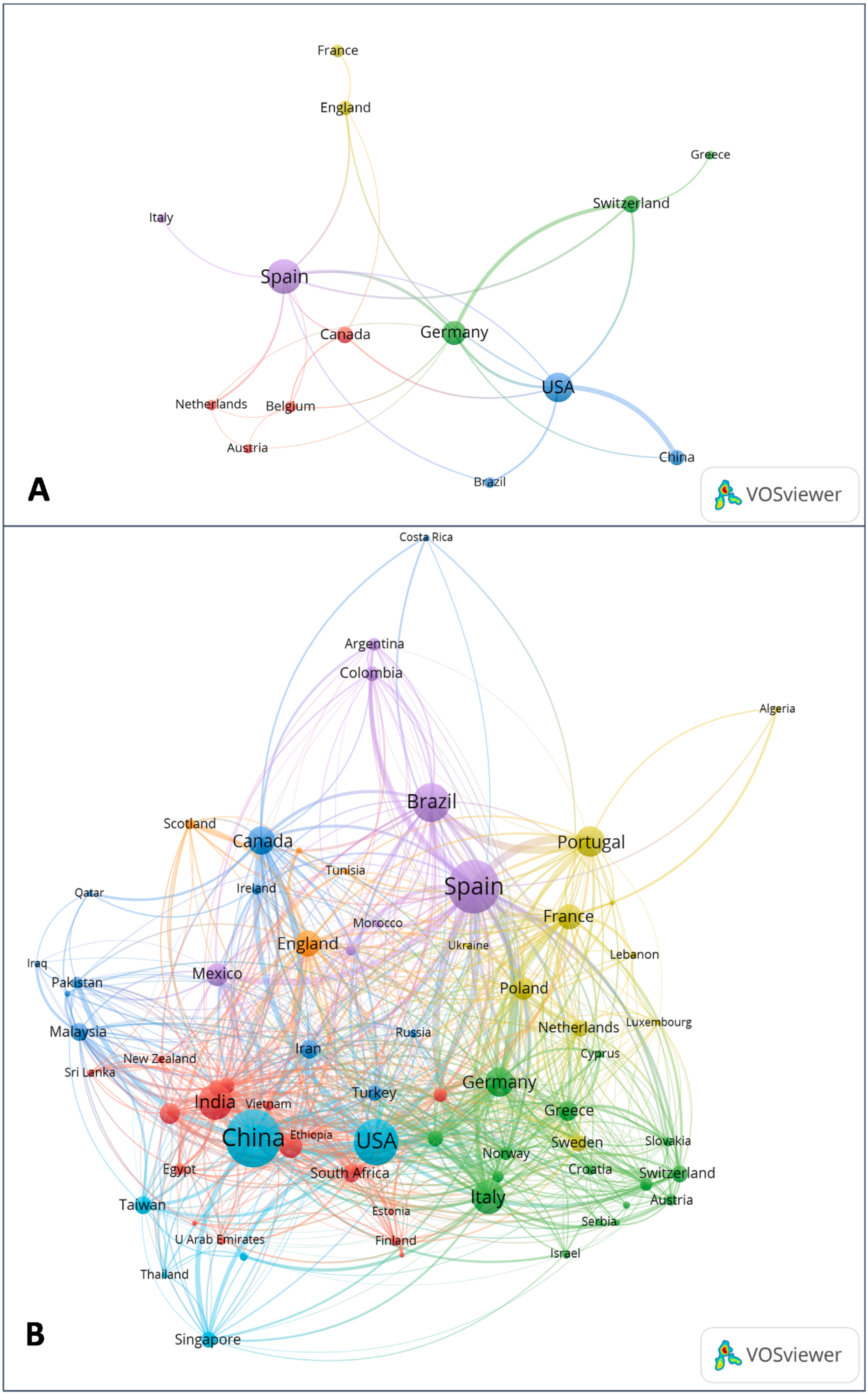

Fig. 9. Collaboration network among countries and institutions in the field of cytostatic drug pollution in water, with minimum publication threshold of five collaborative publications.
A: 1996–2012 and B: 2013–2023

understanding of the risks to ecosystems and their services, with a particular emphasis on drinking water.

The intensity and focus of research have varied globally, with developed countries leading in both the number and scope of studies. Results show the high increase of interdisciplinary and collaborative manuscripts.

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CRediT authorship contribution statement

Cristina Corpa: Writing – review & editing, Writing – original draft, Methodology. **Ana Balea:** Writing – original draft, Formal analysis, Conceptualization. **Guillermo Nieto:** Writing – original draft, Methodology. **Yelizaveta Chernysh:** Writing – review & editing, Funding acquisition. **Lada Stejskalová:** Writing – review & editing, Supervision. **Angeles Blanco:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **M. Concepcion Monte:** Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hazadv.2024.100538.

Data availability

No data was used for the research described in the article.

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