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# Spatial and thematic distribution of research on cyanotoxins

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ABSTRACT

Cyanobacteria in surface water are well known for their ability to form toxic blooms responsible for animal mortality and human poisoning. Accompanying major progress in science and technology, the state of knowledge of cyanotoxins has dramatically increased over the last two decades. The bibliometric approach applied in this study shows the evolution of research and identifies major gaps to be filled by future work. Although the publication rate has gradually increased from one hundred to three hundred articles per year since the 1990s, half of the literature available focuses on microcystins and another quarter on saxitoxins. Other cyanotoxins such as beta-N-methylamino-L-alanine or cylindrospermopsin remain vastly disregarded. Moreover, most of the publications deal with toxicity and ecology while other research areas, such as environmental and public health, require additional investigation. The analysis of the literature highlights the main journals for the communication of knowledge on cyanotoxins but also reveals that 90% of the research is originated from only ten countries. These countries are also those with the highest H-index and average number of citation per article. Nonetheless, the ranking of these countries is significantly altered when the amount of publications is normalized based on the population, the number of universities, the national gross domestic product or the government revenue. However, the lower amount of publications from Eastern Europe, Africa and South America could also reflect the lack of monitoring campaigns in these regions. This lack could potentially lead to the underestimation of the prevalence of toxic cyanobacterial blooms and the diversity of toxins worldwide.

## 1. Introduction

Cyanobacteria are ubiquitous microorganisms that exist mainly in marine and freshwater environments, but are able to subsist in infertile areas and extreme temperatures (Mur et al., 1999). These photosynthetic prokaryotes and potential precursors of the ozone layer are primarily known for their frequently occurring blooms in surface water worldwide (Merel et al., 2010a, 2013; Svrcek and Smith, 2004). This phenomenon, often consisting of the accumulation of cells and the formation of a green layer at the surface, typically arises in eutrophic water with a high concentration but a specific ratio of nutrients (Downing et al., 2001; Heisler et al., 2008). Beyond their anti-aesthetic characteristics, cyanobacterial blooms are also a significant health concern due to their ability to perform the biosynthesis of harmful metabolites called cyanotoxins, which can be responsible for animal deaths as well as human poisonings (Briand et al., 2003; Chorus et al., 2000; Kuiper-Goodman et al., 1999; Merel et al., 2013).

Cyanotoxins encompass a wide range of molecules often classified in three categories, according to their target

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organ (Merel et al., 2013; van Apeldoorn et al., 2007). Hepatotoxins affecting the liver are probably the most common cyanotoxins and refer to a group of structurally different compounds (Codd et al., 2005) including over 90 variants of microcystin (MC), 9 variants of nodularin (NOD) and 3 variants of cylindrospermopsin (CYL). Similarly, neurotoxins affecting the nervous system consist of multiple metabolites, among which 20 variants of saxitoxin (STX), 3 variants of beta-N-methylamino-L-alanine (BMAA), 5 variants of anatoxin-a (ANTX-a) and a single variant of anatoxin-a(s) (ANTX-a(s)) are included. Dermatotoxins, which induce skin irritation, mainly include multiple but poorly characterized lipopolysaccharides (LPS), constituents of the cyanobacteria membrane that exhibit toxicity only once released in the surrounding water as a result of cell breakdown. Other dermatotoxins such as 3 variants of lyngbyatoxin (LTX) and 2 variants of aplysiatoxin (APTX) have also been identified in marine environments but have not been reported in freshwater (van Apeldoorn et al., 2007). However, the list of cyanotoxins is expected to keep increasing in the coming decades due to the perpetual progress in analytical science allowing the detection and identification of new compounds.

Humans are typically exposed to cyanotoxins through the ingestion of contaminated food, the ingestion of contaminated drinking water, and the accidental ingestion/inhalation or dermal adsorption of toxin during recreational activities in waters affected by a toxic bloom (Merel et al., 2013). For instance, STX, also known as paralytic shellfish poison, has been associated with multiple human intoxications through seafood, resulting in numbness, paralysis and death (Kuiper-Goodman et al., 1999). CYL was also shown to be responsible for the Palm Island mystery disease in Australia, when the toxin occurring in the drinking water supply induced severe gastroenteritis in the local population and resulted in over 100 hospitalizations (Bourke et al., 1983; Byth, 1980; Griffiths and Saker, 2003). Similarly, the occurrence of MC variants in water was reported as the cause of epidemic gastroenteritis and lethal human poisonings (Jochimsen et al., 1998; Pouria et al., 1998; Teixeira et al., 1993) leading the world health organization to release a guideline of 1 μg/L of the common variant MC–LR as the maximum concentration in drinking water (WHO, 1998). Consequently, several studies have investigated the early detection of cyanobacteria in surface water (Bastien et al., 2011; Brient et al., 2008) and the fate of cyanotoxins during several drinking water treatment processes such as membrane filtration (Teixeira and Rosa, 2006, 2005), adsorption on activated carbon (Hnatukova et al., 2011; Ho et al., 2011), ozonation (Brooke et al., 2006; Rodríguez et al., 2007; Shawwa and Smith, 2001) or chlorination (Ho et al., 2010; Merel et al., 2010b, 2009).

The health concerns related to toxic cyanobacterial blooms as well as the constant progress in science over the last two decades have dramatically increased the number of studies on the topic. While several recent review papers provide a scientific state of the art (Merel et al., 2013; Sharma et al., 2012; Westrick et al., 2010), this article aims to provide a world overview of research on cyanotoxins from a different perspective by focussing on spatial and thematic distribution. The study also intends to evaluate the scientific knowledge available using bibliometric tools in order to identify research gaps and highlight efficient vectors of communication.

## 2. Methodology

### 2.1. Selection of cyanotoxins

Cyanotoxins are comprised of a wide number of compounds. This study aims to be as exhaustive as possible by considering all the toxins usually described in key references and illustrated in Fig. 1. However, no variant-specific data was collected since such level of detail was not considered relevant. Moreover, since variants are named after their toxin family, it was assumed that the lack of variant-specific searches would not impair the data set. For instance, any article obtained when searching for the variant “microcystin-LR” would be included among those obtained when searching for “microcystin”.

### 2.2. Data collection

The publications related to cyanotoxins were retrieved through the Thomson Reuters Web of Science database. Preliminary statistics were obtained when searching by “topic” for publications regarding any of the toxins in Fig. 1 between the year 1900 and the year 2012. The articles retrieved were subsequently filtered by publication year, country, journal title, funding agency, research area, document type and language. More details were also obtained by combining these different filters and searching for each toxin individually. In this paper the results regarding ANTX-a and ANTX-a(s) were combined under ANTX.

Data regarding the number of universities per country were obtained through the International Association of Universities (URL available in the web references section) in December 2012. In this study, the term university refers to higher education institutions offering at least a postgraduate diploma/degree.

Demographic plus economic data such as National Gross Domestic Product (NGDP) and General Government Revenue (GGR) were obtained through the International Monetary Fund (URL available in the web references section). For all countries, NGDP and GGR were considered in US dollar equivalent in order to ensure a comparison as homogeneous as possible.

### 2.3. Data handling

Research on cyanotoxins was preliminary assessed by plotting directly the amount of publications per toxin or per country on graphics, tables or maps. Then, demographic factors were also considered and the annual amount of publications was normalized based on the population of each country and the number of universities. Similarly, economic factors were also incorporated in order to assess the investment of each country in research, and the annual amount of publications was normalized based on NGDP and GGR (both expressed in billion US dollars). However, assigning on average one year for data collection plus six

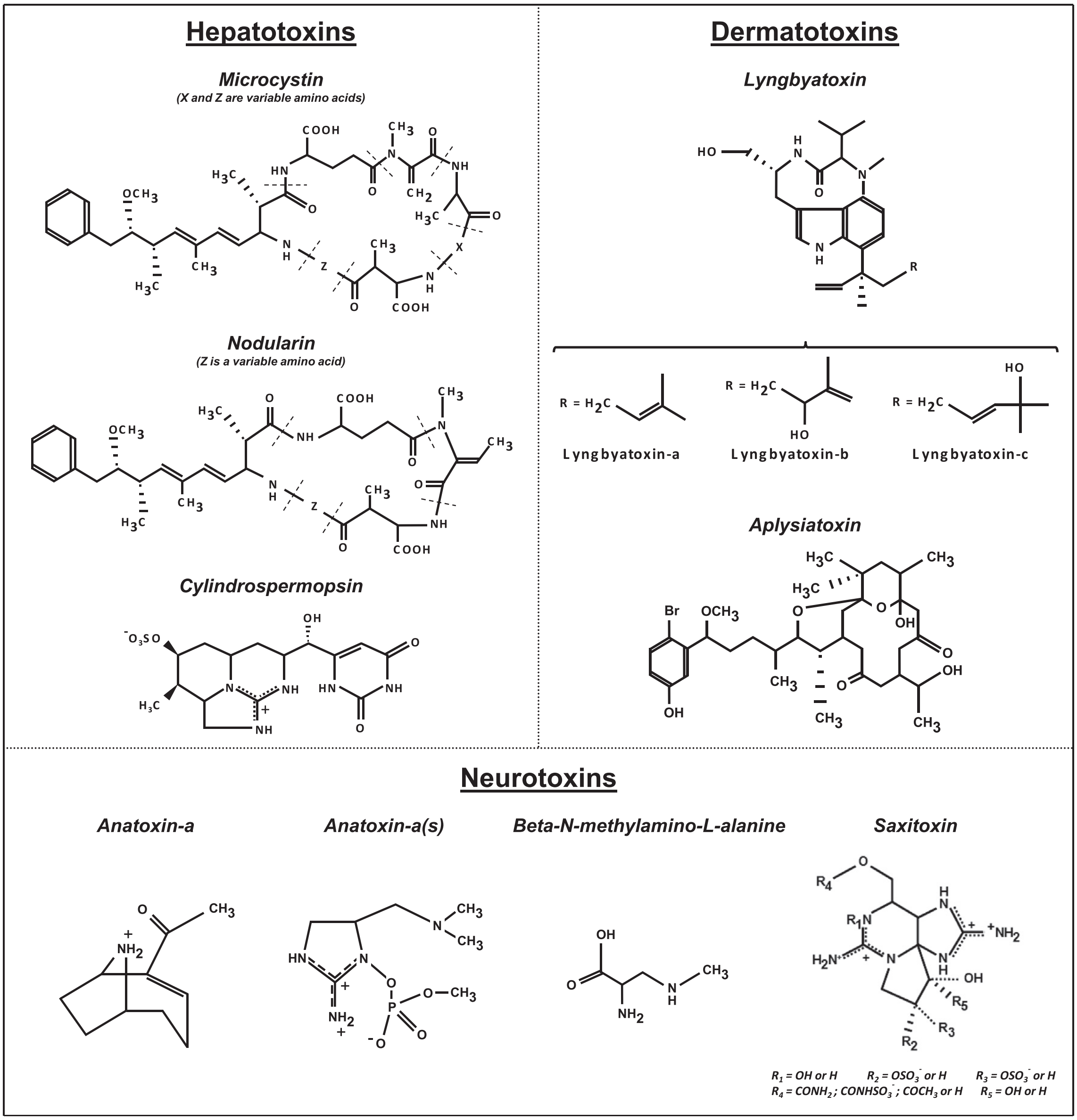


**Fig. 1.** Structure of cyanotoxins.

months for writing and peer-review process, it was considered that an article would be published approximately two years after the allocation of funding. Therefore, in this study, the amount of publications of year "*n*" was normalized based on NGDP and GGR of year "*n* − 2".

## 3. Results

### 3.1. Overview of literature available on cyanotoxins

Accompanying the constant progress in different fields of science and the growing awareness of the health risk associated with potentially toxic cyanobacterial blooms, the annual number of articles published on cyanotoxins dramatically increased over the last two decades. Indeed, as shown in Fig. 2, the cumulative number of publications increased exponentially since 1980 to reach a total of 5293 items in 2012. While these were primarily research articles (4366), the remaining were mostly proceedings (467), abstracts (214), and review articles (198). Other document types such as corrections of published papers (18), letters (15), editorials (9) or books (2) were negligible.

The wide majority of publications on cyanotoxins were published in English (98.2%). Other publications retrieved in this study were written in Chinese (0.5%), Japanese (0.5%), German (0.2%), French (0.2%), Portuguese (0.1%), Spanish (0.1%), Polish (<0.1%), Italian (<0.1%), Serbian (<0.1%) and Turkish (<0.1%). However, more publications

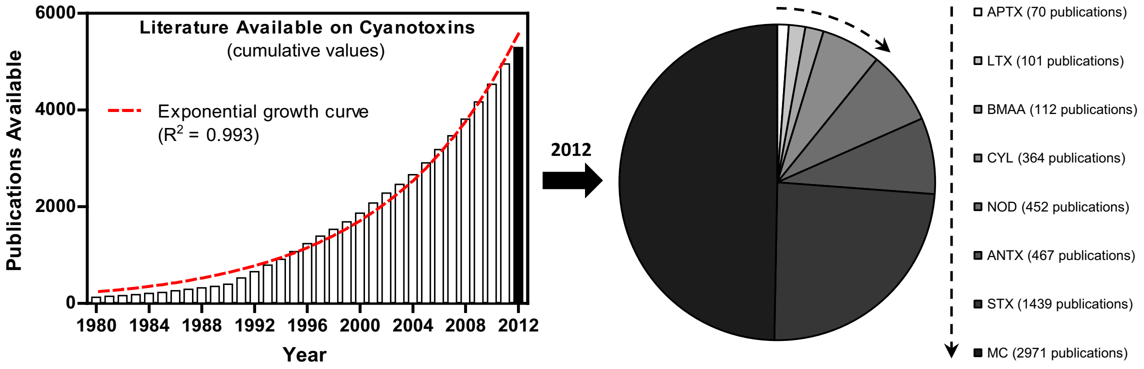


**Fig. 2.** Abundance and thematic distribution of the literature available on cyanotoxins.

in these languages or others are likely to exist but they were not accessible through the current bibliographic search method.

The total number of authors of publications on cyanotoxins was not determined in this study. However, the author with the highest amount of publications was associated with 108 documents or 2% of the literature available. Similarly, the dozen authors publishing the most appear to account for 592 documents or 11% of the overall literature. The affiliation of these authors also revealed that the expertise on cyanotoxins was spread over at least seven countries and covered multiple research areas.

## 3.2. *Thematic distribution of research on cyanotoxins*

The thematic distribution of research on cyanotoxins considered the amount of knowledge available per toxin but also per research area. The quantification of publications available for each toxin and research area aims to reveal research needs in order to support the orientation of future studies.

### 3.2.1. *Distribution of publications based on toxins*

The chronological survey indicates the oldest publications available from the early 1960s were focused almost exclusively on STX and ANTX later on. While the annual amount of publications for these toxins has been regularly increasing, the first articles related to NODs as well as MCs appeared in the late 1980s and quickly became predominant, as shown in Fig. S1. Similarly, the articles related to CYL appeared in early 1990s and strongly increased over the last decade. However, while some articles on APTX, LTX and BMAA have been published since the 1980s, the annual amount of publications for these toxins remains low and almost constantly below 10 items per year.

The cumulative amount of publications on cyanotoxins in 2012 reveals a current state of knowledge and research essentially focused on MCs, as shown in Fig. 2. Indeed, MCs (all variants included) are associated with 2971 publications, which represent more than 56% of the overall literature. With over 1400 publications, STXs come in second position representing 27% of the literature available. Although NODs are often associated with MCs due to their structural similarities, they represent only less than 9% of the publications on cyanotoxins. Similarly, ANTX and CYL represent respectively 9% and 7% of the literature available. However, with an individual contribution lower than 2%, the other toxins BMAA, LTX and APTX remain poorly considered.

### 3.2.2. *Distribution of publications based on research areas*

The publications available on cyanotoxins were split between more than 100 research areas. However, as indicated in Table 1, most of the studies available focus on toxicology (24%), ecology (19%), chemistry (18%) and pharmacology (17%). While water biology as well as biochemistry and molecular biology still account for 13% of the articles published on cyanotoxins, engineering and water resources only represent 7% of the literature. Other research areas including economy, public health or epidemiology are even less considered since they represent only 5% or less of the literature.

## 3.3. *Spatial distribution of research on cyanotoxins*

The spatial distribution of research on cyanotoxins was determined based on the affiliation of the authors. The research activity of each country was considered quantitatively as well as qualitatively. Quantitative assessment was performed according to the total number of publications (period 1900–2012) and the annual amount of publications (averaged over the period 2004–2012). Moreover, for a fair comparison of the countries, the annual amount of publications was subsequently normalized based on the population, the number of universities, the NGDP and the GGR. Qualitative assessment was performed according to the average amount of citation per publication as well as the H-index.

### 3.3.1. *Overall spatial distribution*

The overall amount of publications on cyanotoxins reveals that most of the research is originated from a dozen countries. As presented in Fig. 3, these countries account for more than 90% of the literature available. Among them, USA is by far the leader with 31% of the articles, while China and Japan come next with 10% each. The ten countries with the most publications also include Germany (8%), UK and

**Table 1**
Distribution of publications on cyanotoxins per research area.

| Research area | Publications | Percentage of literature | Research area | Publications | Percentage of literature |
|---|---|---|---|---|---|
| Toxicology | 1248 | 24% | Biotechnology Applied Microbiology | 270 | 5% |
| Environmental Sciences Ecology | 1009 | 19% | Biophysics | 221 | 4% |
| Chemistry | 934 | 18% | Cell Biology | 208 | 4% |
| Pharmacology Pharmacy | 920 | 17% | Plant Sciences | 183 | 3% |
| Marine Freshwater Biology | 714 | 13% | Physiology | 168 | 3% |
| Biochemistry Molecular Biology | 689 | 13% | Food Science Technology | 147 | 3% |
| Water Resources | 394 | 7% | Science Technology | 130 | 2% |
| Engineering | 385 | 7% | Oceanography | 128 | 2% |
| Microbiology | 313 | 6% | Life Sciences Biomedicine | 124 | 2% |
| Neurosciences Neurology | 277 | 5% | Fisheries | 116 | 2% |

Australia (7% each), Canada (6%) then Finland, France and Spain (4% each).

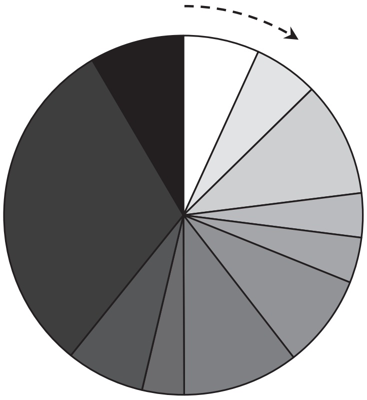
The world view of the overall number of publications (Fig. 4) also localizes most of the research efforts in Australia, China, North America and Western Europe (detailed spatial distribution of publications for individual toxins in Fig. S2a–S2h). Cyanotoxins have also been studied in Latin America, but to a lower extent, and mostly in Brazil, which accounts for 176 publications. Indeed, while each of Argentina, Chile and Mexico represent 25–50 articles, other Latin American countries are usually limited to 5 items or less. Similarly, research on cyanotoxins also appears to be limited in Africa and Asia with only a few countries such as South Africa, Egypt, Russia or India, associated with more than 10 publications.

### *3.3.2. Spatial distribution over the period 2004–2012*

The average annual amount of publications over the period 2004–2012 offers a more contemporary view of research on cyanotoxins by disregarding the older articles. The limitation to recent papers further confirms the uneven spatial distribution of research through the accentuation of disparities (Fig. 4). USA and China remain the countries with the most publications, with more than 25 articles per year on average, followed by Australia, Canada, France, Germany, Japan, Spain and UK with 15–25 articles per year on average. Latin America appears as a growing source of publications, particularly with 5–15 articles per year from Brazil as well as 2–5 articles per year from Argentina, Chile and Mexico. However, research activities in Africa (except for South Africa), Asia (except for India) and Western Europe remain mostly non-existent or limited with less than two publications per year on average.

### *3.3.3. Spatial distribution normalized for population*

The annual amount of publications over the period 2004–2012 was normalized for population in order to minimize any bias due to the size of each country. As a result, the ranking of the most publishing countries is significantly impaired (Table 2) and the world overview changes respectively (Fig. S3). The main consequence is the strengthening of Western Europe along with the important downgrading of the three countries with the most overall publications (USA, Japan and China now ranked 26th, 28th and 53rd). Indeed, normalizing the amount of publications for population mostly restores the balance in favour of smaller countries with fewer inhabitants such as Slovenia, Denmark or Portugal, and countries with low population density like Australia or Scandinavia. For instance, Finland's ranking improved from 9th to 1st and Australia remained ranked 6th. A similar trend is also observed in Latin America where Brazil, largely ahead in terms of overall amount of publications, now appears preceded by Chile and Uruguay. While homogenising the data for a better interpretation, normalization might also induce a new bias when comparing countries with a strong and regular research activity to those publishing irregularly. Therefore, a second examination of the normalized data was



| ***Country*** | ***Main National Funding Agencies*** |
|---|---|
| □ Australia (7%) | Australian Research Council |
| □ Canada (6%) | Natural Sciences and Engineering Research Council |
| □ China (10%) | NSF, Academy of Sciences |
| □ Finland (4%) | Academy of Finland |
| □ France (4%) | National Research Agency |
| ■ Germany (8%) | NSF, Ministry of Education and Research |
| ■ Japan (10%) | JSPS, Ministries of Science and Environment |
| ■ Spain (4%) | Ministry of Science, Autonomous Communities (Galicia, Andalusia) |
| ■ UK (7%) | Local Governments and Research Councils |
| ■ USA (31%) | NSF, NIH, NIEHS, EPA, NOAA |
| ■ Others (9%) | European Union, Brazil (CNPQ, FAPESP) |

**Fig. 3.** Origin of publications on cyanotoxins and associated funding agencies.

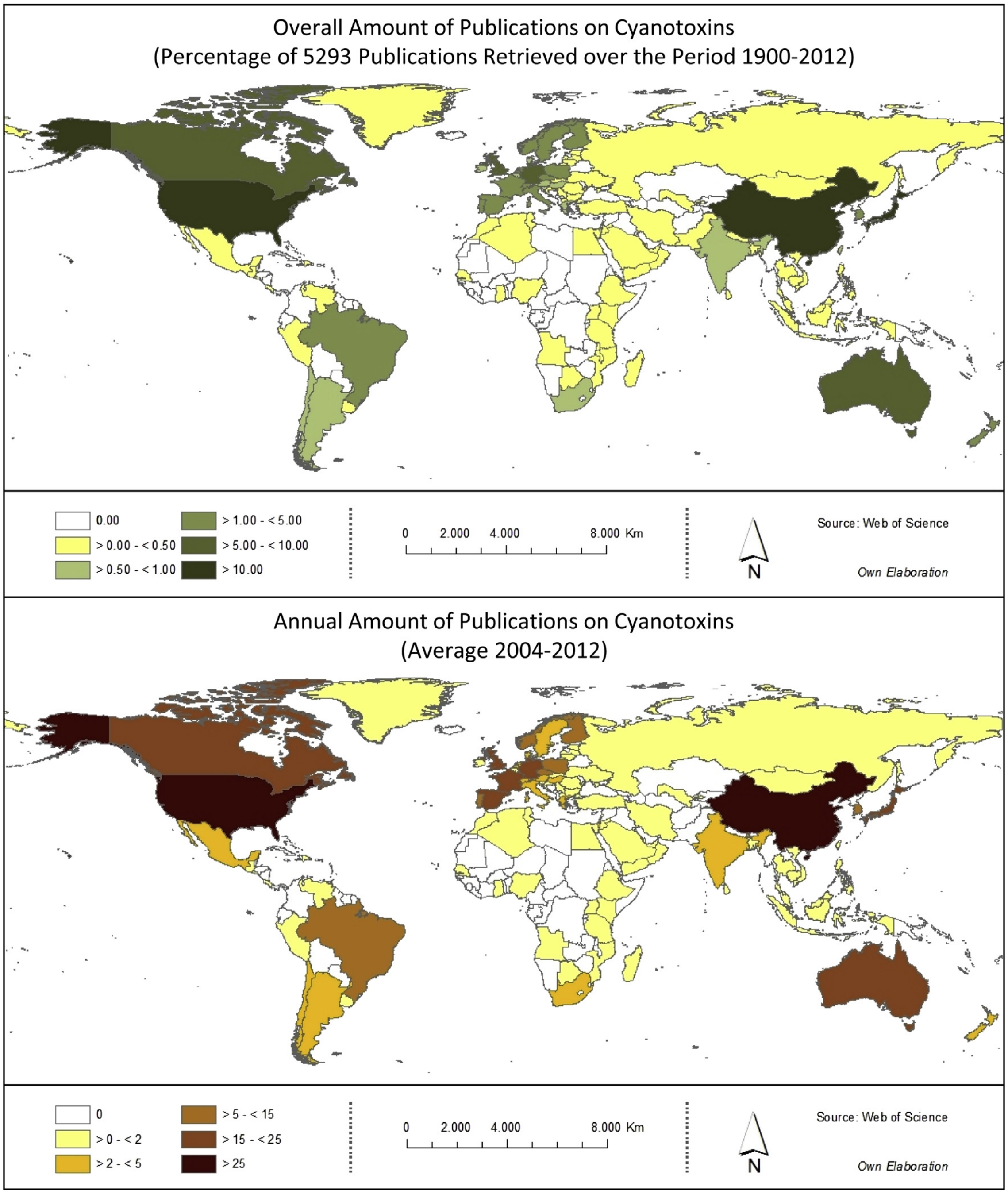


**Fig. 4.** World overview of publications on cyanotoxins.

performed excluding the countries with less than two publications per year on average over the period 2004–2012. As a result, the world overview changes again (Fig. S3) since only 34 countries could still be considered. This mainly results in excluding several countries from Africa, along with a few others from Eastern Europe and South America. However, such exclusion does not significantly affect the ranking of the countries (Table 2), except for China that was initially heavily disadvantaged by its population size.

### *3.3.4. Spatial distribution normalized for universities*

The annual amount of publications over the period 2004–2012 was normalized based on the number of universities to assess and compare the average research productivity of higher educational institutions in each country. Consequently, the ranking of the countries is strongly altered (Table 2) and the world overview of research changes accordingly (Figure S4). Australia and Finland appear as the two countries with the highest publication rate with more than 25 articles per year for

**Table 2**
Ranking of countries based on the amount of publications and scientific impact.

| Ranking criteria | Period | USA | Japan | China | Germany | UK | Australia | Canada | France | Finland | Spain |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Global number of publications | 1900–2012 | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th | 9th | 10th |
| Annual amount of publications | 2004–2012 | 1st | 4th | 2nd | 3rd | 8th | 5th | 9th | 7th | 12th | 6th |
| Publications/inhabitant | 2004–2012 | 26th (23rd) | 28th (25th) | 51st (32nd) | 19th (17th) | 24th (22nd) | 6th (5th) | 12th (11th) | 23rd (21st) | 1st (1st) | 14th (13th) |
| Publications/university | 2004–2012 | 40th (29th) | 35th (27th) | 17th (12th) | 22nd (16th) | 19th (14th) | 1st (1st) | 15th (10th) | 29th (22nd) | 2nd (2nd) | 7th (5th) |
| Publications/$ of NGDP | 2004–2012 | 62nd (30th) | 63rd (31st) | 26th (13th) | 45th (23rd) | 54th (27th) | 11th (7th) | 34th (18th) | 53rd (26th) | 2nd (1st) | 28th (14th) |
| Publications/$ of GGR | 2004–2012 | 62nd (28th) | 61st (27th) | 18th (9th) | 58th (25th) | 59th (26th) | 19th (10th) | 44th (19th) | 66th (32nd) | 13th (7th) | 38th (15th) |
| Citations/publication | 1900–2012 | 7th | 11th | 48th | 5th | 3rd | 8th | 14th | 19th | 10th | 40th |
| H-index | 1900–2012 | 1st | 5th | 9th | 2nd | 3rd | 4th | 6th | 8th | 7th | 10th |

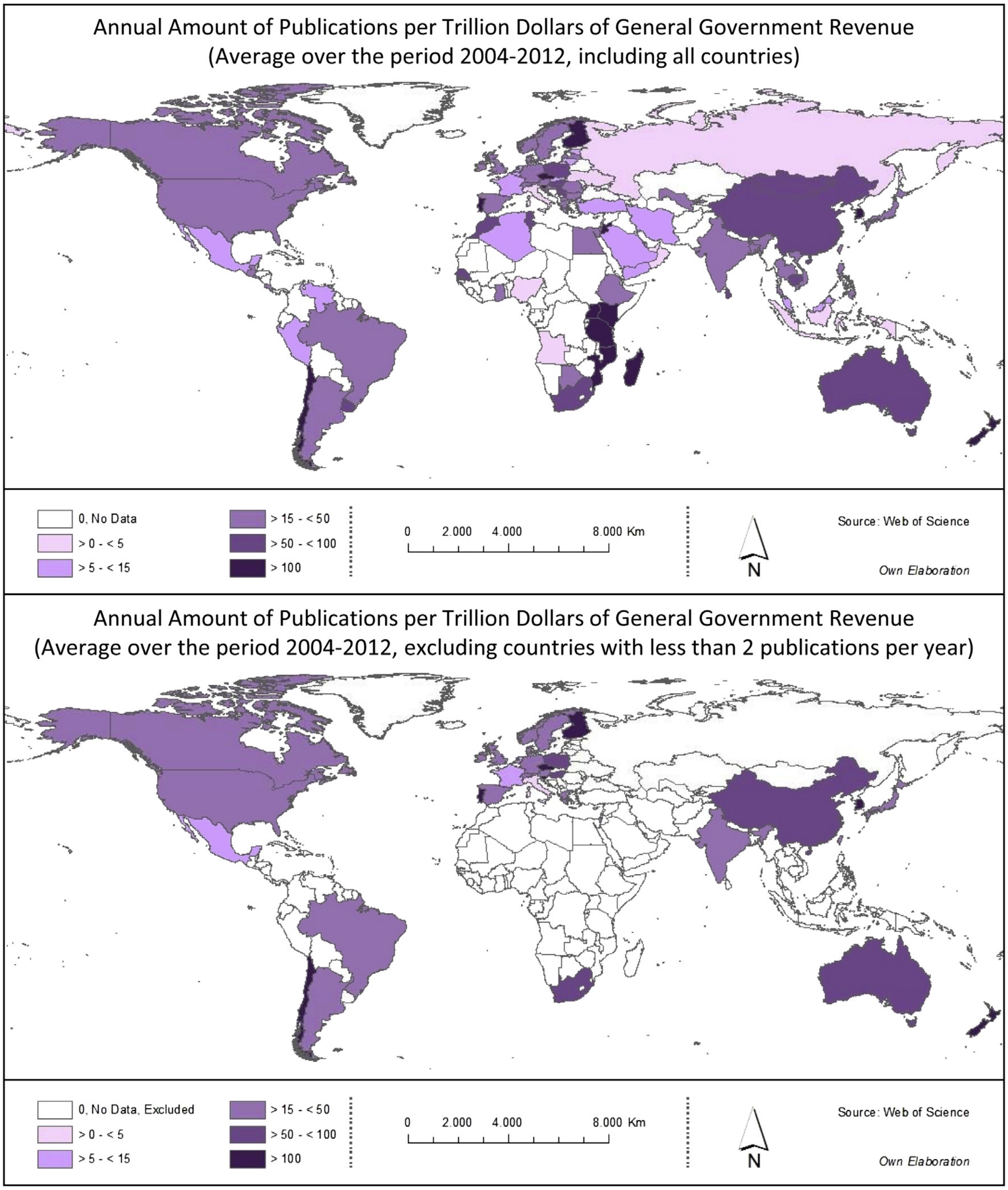
() Indicates the ranking when considering only the 34 countries with at least an average of 2 publications per year over the period 2004–2012.

100 universities. Spain also improves its ranking from 10th to 7th when considering the amount of publications per university. However, with similar considerations, USA and Japan, ranked 1st and 2nd based on the overall amount of publications, are now respectively ranked 40th and 35th, while China only decreases from 3rd to 17th. Similarly, Brazil, by far the most publishing country in Latin America, falls behind Argentina, Chile and Uruguay when normalizing for universities. Examining again the data after excluding the countries with less than two publications per year on average over the period 2004–2012 does not significantly alter the ranking even though the world overview dramatically changes (Fig. S4). Indeed, most of the countries from Africa and Asia are excluded.

### 3.3.5. *Spatial distribution normalized for economic indicators*

The annual amount of publications over the period 2004–2012 was normalized based on NGDP and GGR to account for the economic level of each country. Consequently, the ranking of countries is strongly modified (Table 2) and the world view changes dramatically (Fig. 5 and Fig. S5). For instance, while very few publications on cyanotoxins are originated from Africa, after normalization for economic criteria, Uganda, Kenya, Madagascar and Mozambique appear to generate approximately 10 times more publications than USA or other European countries. In fact, as shown in Table 2, the most publishing countries tend to be relegated to the bottom of the rankings and appear less research productive relative to their economy. Only Australia and Finland remain among the most productive countries after considering NGDP and GGR. While excluding the countries with less than two publications per year on average over the period 2004–2012 changes again the world overview (Fig. 5 and Fig. S5), it also significantly improves the ranking (Table 2). Nevertheless, even with such consideration, USA, Japan, Germany, UK and France remain the less productive countries from the 34 still considered. China, Canada and Spain however reach the first half of the ranking while Australia and Finland remain among the most productive countries.

The chronological study over 30 years mostly indicates that the amount of publications, both normalized and non-normalized for NGDP, generally results in two curves with a similar pattern (Fig. 6). However, the amount of publications per billion dollars NGDP can be used as an indicator of the relative investment in research on cyanotoxins made by each country. Therefore, while the normalized value allows a theoretically unbiased comparison between two countries for a specific year, it also allows a consistent assessment of the research activity of a country year after year. For instance, while Canada and France have a similar number of annual publications, the normalized value is two fold higher for Canada, which therefore seems to invest twice as much of its NGDP in research (Fig. 6). Moreover, the annual amount of publications from the USA dramatically increased over the last decade, but the normalized value remained roughly constant, which indicates that a similar percentage of the NGDP was invested in research.



Annual Amount of Publications per Trillion Dollars of General Government Revenue (Average over the period 2004-2012, including all countries)

Annual Amount of Publications per Trillion Dollars of General Government Revenue (Average over the period 2004-2012, excluding countries with less than 2 publications per year)

**Fig. 5.** World overview of publications on cyanotoxins normalized for general government revenue (GGR).

### *3.3.6. Spatial distribution of scientific impact*

The assessment of research activity for each country cannot be limited to the number of articles published every year, even though it is an important criterion, but it should also consider the impact of the research on the scientific community. While there are multiple ways to estimate the research impact, such assessment is rarely performed at the level of a country. The current study successively considered the average amount of citations per publication and the H-index, both well-known and global indicators but usually applied to assess the significance of individuals in their own field of expertise.

The average number of citation per publication leads to a more homogeneous world overview (Fig. 7) than the raw number of publications itself (Fig. 4.). USA, Germany, UK, Finland and Australia appear to have more than 30 citations per article on average, as expected due to the number of world experts on cyanotoxins associated with these

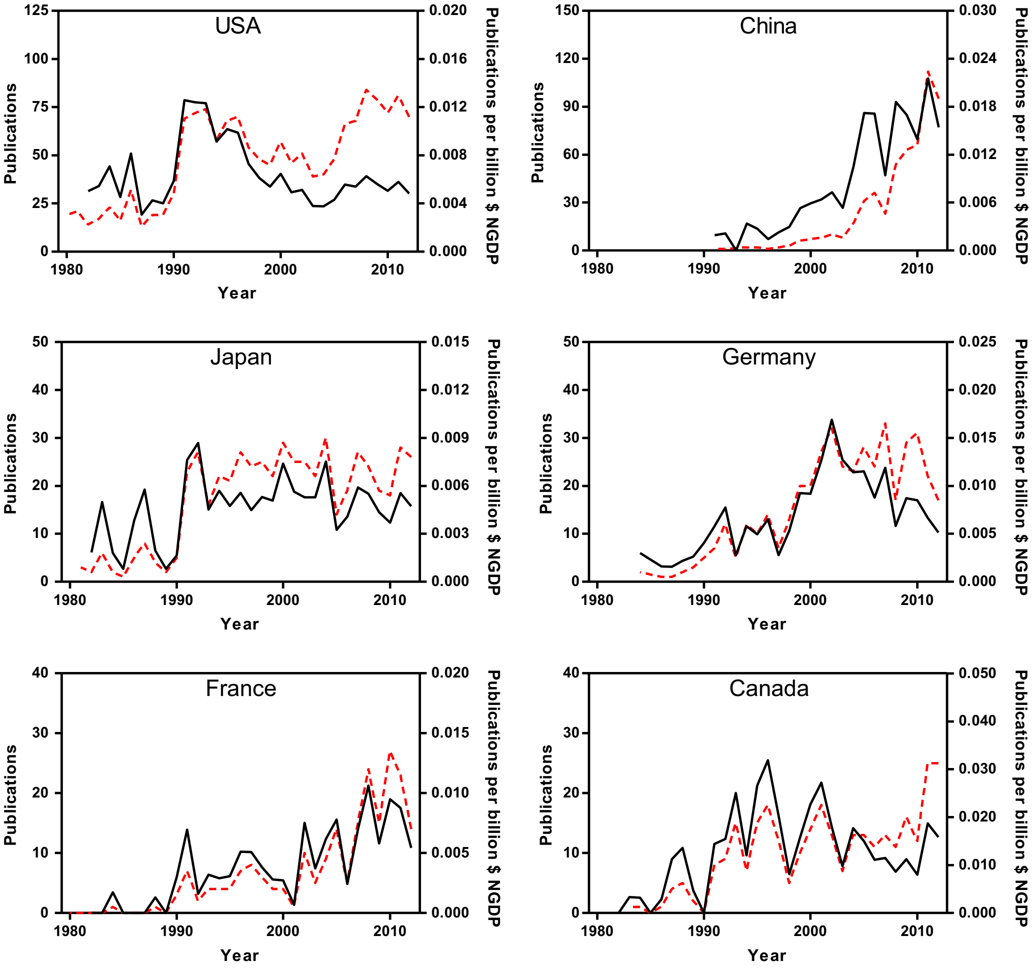
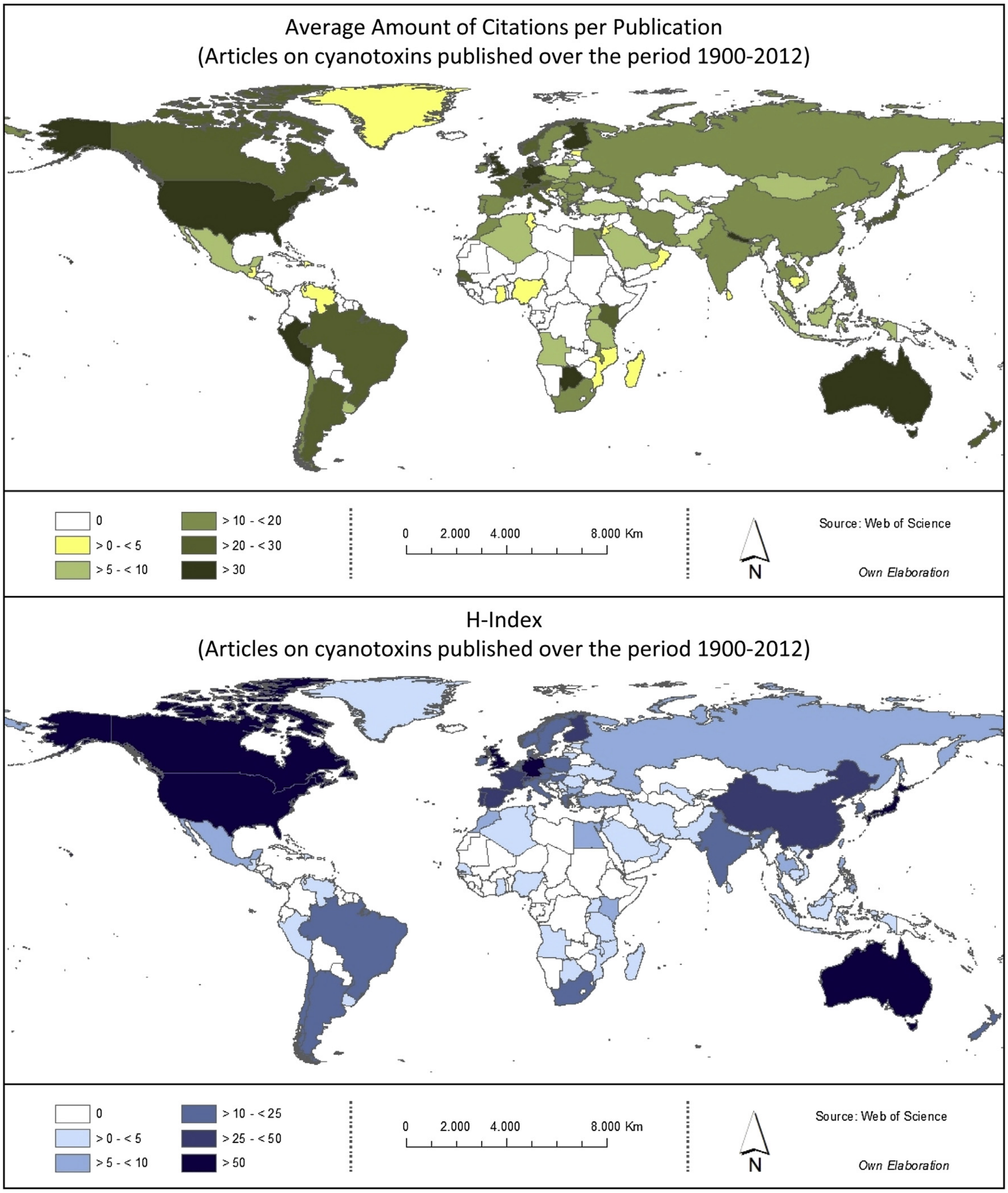


**Fig. 6.** Evolution of the annual amount of publications, with (whole line) and without (dashed line) normalization for NGDP.

countries. However, smaller countries with lower incomes such as Peru, Nepal or Botswana also achieve an average greater than 30 citations per article. While Western Europe forms a cluster of countries with more than 20 citations per article on average, along with Canada in North America as well as Brazil and Argentina in South America, most of Eastern Europe and Asia still achieve an average greater than 10 citations per publication. However, citations appear as non-existent for most of the countries in Africa along with a few others in South America, but it is important to notice that a comparison with the world overview of the amount of publications (Fig. 4) explains such lack of citation by the lack of research activity in these countries rather than a lower scientific impact. Overall, the amount of citation per publication does not really affect the ranking of the countries and the most publishing countries still appear as the most impactful. Only the ranking of China (now 48th) and Spain (now 40th) is significantly altered (Table 2), which mostly reflects the more recent increase of their research activity (significant increase over the last decade) compare to the other countries.

The H-index applied to countries rather than individuals shows a world overview (Fig. 7) closer to that obtained when considering the global amount of publications (Fig. 4), as expected since this indicator incorporates the number of citations as well as the number of publications. Four areas of dominant countries clearly appear. The first area covers North America with USA and Canada having an H-index above 50. The second area is Australia itself, isolated but also with an H-index above 50. The third area, in Asia, includes Japan and China with an H-index respectively above 50 and above 25. Western Europe forms the fourth area of dominant countries, mostly through Germany and UK with an H-index above 50 as well as France, Spain, Portugal and Finland with an H-index above 25. Most of the countries from Africa along with a few others from South America show a nil H-index value but a comparison with the research activity (Fig. 4) explains this observation by a lack of publication rather than a low research impact. The H-index barely affects the ranking of the countries. In fact, even though the order slightly changes (Table 2), the ten countries with the highest amount of publications are also the ten countries with the highest H-index.



Average Amount of Citations per Publication
(Articles on cyanotoxins published over the period 1900-2012)

Source: Web of Science

Own Elaboration

H-Index
(Articles on cyanotoxins published over the period 1900-2012)

Source: Web of Science

Own Elaboration

**Fig. 7.** World overview of the scientific impact of research on cyanotoxins.

### 3.4. *Funding of research on cyanotoxins*

The main sources of funding were retrieved through Web of Science, which identifies and indexes the sources from the acknowledgement section of each publication. As expected, most of the funding comes from national agencies located in the ten countries with the highest number of publications listed in Fig. 3. While some private sources of funding were also identified, they were in minority in comparison to foundations (NSF), institutes (NIH), ministries or other public entities. This observation is consistent with the lack of potential commercial applications derived from cyanotoxins.

Public but non-local agencies also provide funding for research on cyanotoxins. The European Union finances several research programs developed in or across several European countries, such as the program CYANOCOST (URL available in the web references section). In addition, some grants might be attributed with the objective of strengthening international partnership between research teams. Therefore, some publications may have a dual source of funding and should be associated with different countries through the respective affiliations of the co-authors. However, in some rare cases, national funding agencies may also open the call for projects to foreign research teams. Consequently, in a limited number of publications, the funding source may not necessarily match the affiliation of co-authors.

### 3.5. Journals for communication of research on cyanotoxins

Publications related to cyanotoxins were retrieved from more than one hundred journals, the ten most significant of which are presented in Table 3, along with some bibliometric considerations. As expected, these journals mostly have a large scope around toxins or water related issues in general. For instance, the journal Toxicon, dedicated to research on all aspects of natural toxins, gathers by itself 10% of the publications while other journals focussing on a specific research area or on a wider range of environmental contaminants only reach 1% or less. In addition, Table 3 shows that the impact factor is not associated with the H-index and therefore publishing in a high impact factor journal does not necessarily imply more citations for an article. For example, the most cited article on cyanotoxins was published in a 3.5 impact factor journal while the fifth most cited paper was published in a 53.3 impact factor journal. Consequently, Table 3 provides a list of journals likely to publish articles on cyanotoxins, but not necessarily the most suitable, depending on the research topic.

## 4. Discussion

### 4.1. Literature retrieved and limitations

The substantial amount of publications on cyanotoxins considered in this study has been retrieved using Web of Science, supposedly widely accessible and covering an extensive range of journals across multiple disciplines. Therefore, it can be considered that the amount of items published in peer reviewed journal (articles, abstracts, proceedings or editorial) and retrieved in this study is representative of the total number available. However, it should be mentioned that the number of books is clearly underestimated. Indeed, while Web of Science retrieves only 2 books related to all cyanotoxins, Science Direct retrieves more than 20 books related to the single cyanotoxin microcystin.

The discrepancy between databases has already been reported (Coatrieux et al., 2004) and it is well known that the same search could lead to different results. For instance, when searching for the word microcystin in the title of articles between 2000 and 2012, Medline retrieves 776 publications while Web of Science retrieves 1108. However, a complete overlap of the results is not certain and despite the greater number reported by Web of Science it is likely that some publications might be retrieved only with Medline. Therefore, in order to avoid omitting any

**Table 3**
Statistics on journals with the highest amount of publications on cyanotoxins.

| Journal | Publications related to cyanotoxins | | Citations of publications related to cyanotoxins | | | | Indicators of influence | |
|---|---|---|---|---|---|---|---|---|
| | Amount[a] | Fraction of literature | Total[a] | Maximum[a] | Average per year[a] | Average per Paper[a] | H-index[a] | Impact factor 2011[a] |
| Toxicon | 516 (1) | 9.7% | 13,688 (1) | 418 (12th most cited paper) | 291.23 (2) | 26 (45) | 58 (1) | 2.508 (59) |
| Environmental Toxicology | 187 (2) | 3.5% | 5036 (3) | 166 (81st most cited paper) | 335.73 (1) | 27 (43) | 39 (4) | 2.407 (62) |
| Harmful Algae | 111 (3) | 2.1% | 1218 (19) | 60 (573rd most cited paper) | 121.8 (6) | 11 (87) | 20 (18) | 3.083 (48) |
| Water Research | 100 (4) | 1.9% | 3305 (6) | 215 (49th most cited paper) | 165.25 (4) | 33 (25) | 35 (6) | 4.865 (14) |
| Journal of Biological Chemistry | 87 (5) | 1.6% | 5396 (2) | 404 (15th most cited paper) | 163.52 (5) | 62 (6) | 43 (2) | 4.773 (15) |
| Applied and Environmental Microbiology | 85 (6) | 1.6% | 4164 (4) | 154 (96th most cited paper) | 181.04 (3) | 49 (12) | 40 (3) | 3.829 (28) |
| Aquatic Toxicology | 64 (7) | 1.2% | 1949 (10) | 141 (117th most cited paper) | 92.81 (8) | 30 (34) | 27 (8) | 3.761 (33) |
| Environmental Science & Technology | 61 (8) | 1.1% | 1401 (17) | 119 (160th most cited paper) | 70.05 (9) | 23 (53) | 23 (12) | 5.228 (11) |
| Biophysical Journal | 60 (9) | 1.1% | 1452 (15) | 230 (42nd most cited paper) | 37.23 (29) | 24 (51) | 21 (16) | 3.653 (36) |
| Journal of the American Chemical Society | 53 (10) | 1.0% | 3259 (7) | 344 (22nd most cited paper) | 65.18 (11) | 61 (7) | 36 (5) | 9.907 (3) |

[a] The value between parentheses indicates the ranking of the journal with respect to the parameter reported in the column.

publication from any type, an absolutely accurate study would require performing the same search with all the databases available. Conversely, beyond being a time consuming and nearly impossible task, searching all databases would also lead to multiple replicates problematic to manage that might induce a bigger bias than a single search in an exhaustive database like Web of Science.

The present study does not consider the “grey literature”. This term refers to any typed or printed document meant to reach a limited audience outside of the commercial publishing channels and outside of the conventional bibliographic control utilities (AFNOR, 1987). According to this definition, the grey literature encloses patent documents, theses, scientific reports… The term grey literature also includes journals published internally in some universities, a frequent practice in South America. Consequently, it should be noted that the limited access to this kind of literature might slightly alter the world overview of research on cyanotoxins.

The current study was performed looking for the different cyanotoxins, not in “title”, “abstract” or “keywords” but as “topic”. However, it is not clear how Web of Science groups the articles by topics. Therefore, it cannot be excluded that some publications were retrieved and associated with “anatoxin” while the toxin was only mentioned in the list of references. Due to the amount of publications retrieved in this study, the legitimacy of each article could not be verified individually. Consequently, even though “false positives” are possible, it is expected that they would occur in minor and similar proportion for each cyanotoxin and therefore would not affect the overall results presented in this study.

### 4.2. Thematic distribution of research on cyanotoxins

The thematic distribution reveals that more than 50% of the research focuses on MCs. This tendency could be easily explained by the fact that MCs are known as the most widespread cyanotoxins. However, one could also argue that the deadly human intoxications associated with MCs in Brazil are causing them to be more frequently monitored and consequently more frequently detected than other cyanotoxins. Moreover, the short term health risks due to acute intoxication may also favour studies on MCs in comparison to other cyanotoxin like BMAA, the potential long term health effects of which include an increase of Alzheimer’s and other neurodegenerative diseases (Cox et al., 2003; Pablo et al., 2009).

The thematic distribution also indicates that STXs are the second most studied cyanotoxins after MCs. However, one should consider that the number of publications retrieved may be biased since these toxins are not only produced by cyanobacteria in freshwater, but also by dinoflagellates in sea water. In fact, when searching simultaneously for the words saxitoxin and cyanobacteria in Web of Science, only 10% of the original publications are still retrieved. Nevertheless, regardless of the microorganism studied, the knowledge available on STXs remains accurate, with perhaps the exception of the biosynthesis pathway and regulation.

Among the research areas, toxicology, environmental sciences and chemistry were found widely predominant. However, more research in these fields, as well as in biochemistry, is still necessary in order to improve the knowledge of toxin biosynthesis, particularly pathways and regulation mechanisms. In addition, many studies report the occasional occurrence of cyanotoxins in a limited area, but more global monitoring studies are required in order to assess the prevalence of toxic cyanobacterial blooms and decide on the necessity for a regulation. Moreover, monitoring campaigns should also include countries from Africa, Asia and South America where less data is available. Economic studies should also be undertaken in order to assess the cost/benefit of preventive or remedial measure against toxic cyanobacterial blooms.

### 4.3. Quantitative spatial distribution of research on cyanotoxins

The analysis of the overall amount of publications revealed an uneven distribution of research centred on the ten countries with the highest NGDP. However, this overview is based on the affiliation of co-authors but it does not necessarily reflect the area where the research was conducted. Moreover, while grey literature is not included in this study, this might significantly alter the real world overview of research on cyanotoxins.

The concentration of research activities in the richest countries could be explained by the significant cost of facilities, equipment and supplies necessary for the investigation on cyanotoxins. Indeed, mass spectrometers for the quantification of toxins generally cost several hundred thousand dollars while procuring a few micrograms (μg) of standards still cost several hundred dollars. However, some countries of Africa with very few publications were also shown to be much more productive than the richest countries relatively to their NGDP. This could be partially explained considering that some of the studies published by low income countries were undertaken and co-funded with some partner institutions in Europe or USA. Consequently, studies co-funded between several countries indicate that the amount of publications per billion dollars NGDP may not be a truly reliable indicator of the investment made in research.

Normalizing the amount of publications for the population, the universities or the economy theoretically allows a better and more accurate comparison of several countries. However, normalizing the values can also induce other biases. For example, the amount of universities in each country is determined by the institutions of higher education offering at least a post-graduate diploma/degree. Nonetheless, the fraction of institutions also engaged in research activities is not considered. Therefore, a country with a predominance of private universities focussing mainly on the enrollment of students will likely be penalized compared to a country with a predominance of public institutions expected to develop more research programs. Moreover, in order to objectively assess the investment of a country in cyanotoxin research, one should also consider normalizing the amount of publications according to other parameters, such as the volume of surface water or the length of the coastal shore. Indeed, a country with less surface water will less likely be vulnerable to toxic blooms and consequently invest less in cyanotoxin research. However, such a country should not be penalized for this when assessing its research activity.

### 4.4. Qualitative spatial distribution of research on cyanotoxins

The research activity was also assessed qualitatively through the average number of citation per publication and the H-index. Although these indicators are global, easily understandable and well known by most scientists, each of them comes with its own limitations and potential bias. On the one hand, the average amount of citation per article may appear as a fair indicator to compare the significance of research, as one might think that each article stands the same chance of being cited depending on its scientific merit. However, this indicator might favour countries with a lower amount of citations but spread over a small number of publications. For example, with 81 citations per article, Peru appears as the country with the highest scientific impact while it has only two publications. Moreover, the average number of citation per article would disadvantage countries with a large but recent research activity against countries with a smaller but more ancient research history (older articles have more time to gather citations). On the other hand, the H-index considers the number of citation as well as the number of publications. However, this indicator would tend to place on the same level countries with few but high impact publications and countries with many but usually lower impact publications. While the intrinsic limitations of each indicator prevents an unbiased assessment of research quality, the average number of citation per publication as well as the H-index are complementary and shouldn't be considered alone.

### 4.5. Scientific journals

Publications on cyanotoxins were retrieved from more than one hundred journals. The most publishing journals listed in Table 3 are only the most likely to publish research on cyanotoxins, but not necessarily the most suitable. The statistical values such as the H-index or the impact factor are provided as indicators of journal performance and article significance in December 2012. However, these do not consider the age of the journal and should not be directly considered as a type of ranking. Selecting the most suitable journal for an article always remains a balance between several parameters, including the research field of the author and the expected audience.

### 4.6. General significance and limitations of bibliometry

The first articles on bibliometry retrieved through Web of Science were published in 1976. With a maximum of 3 publications per year, bibliometry was poorly considered until 1997 when it started receiving more interest up to reaching 20 publications in 2012.

Overall, bibliometry allows assessing the research activity of institutions and individuals, not only from the amount of articles published but also in terms of scientific impact of those publications. While even the scientific impact is quantified through specific indicators such as the impact factor or the H-index, bibliometry contributes to lower the subjectivity when evaluating and comparing the research activity of two institutions or two individuals. In addition, it also provides results that can be interpreted by a general audience unaware of the ranking of the journals in different fields.

The bibliometric approach of the research activity also has its own intrinsic limitations. Indeed, while everything (including the scientific impact) can be quantified through specific indicators, these numbers are generated from the publications retrieved in data bases. Therefore, depending on the data base used, some documents may not be retrieved and induce a bias in the analysis. However, although it might be less obvious, the opposite can also occur. Indeed, when using several data bases in order to recover more documents, duplicates or triplicates may also occur causing another challenge and another type of bias. Overall, bibliometry will tend to favor individuals or institutions generating mostly publications in widely indexed journal compared to those equally productive but generating mostly "grey literature". Moreover, while bibliometry is expected to allow an accurate and objective comparison of researchers or institutions, this is only true within the same research field. For example, the highest impact factor for a journal in the category "Toxicology" is 21 while the highest impact factor in the category "limnology" is 3. Hence, from two institutions conducting research on cyanobacterial blooms and publishing the same amount of papers in the best journal of their respective field, a bibliometric study focusing on journal impact factor might present the institution performing toxicological studies as more significant than the other institution performing limnological studies. Consequently, the respective limitations of each bibliometric indicator must be understood and considered carefully in order to avoid any over-interpretation of the data. While new indicators should be developed to limit the bias and to provide a more global assessment of research activity, the final interpretation and conclusion should always rely on multiple indicators.

## 5. Conclusion

The overview of research on cyanotoxins at the end of 2012 indicates that MCs are the most studied compounds followed by STXs, as they represent respectively 56% and 27% of the articles published. While ANTX, NODs and CYL have been passably investigated, other cyanotoxins such as the neurotoxin BMAA, as well as the dermatotoxins LTX and APTX, have been poorly considered. Moreover, the amount of publications indicates that research activities mainly emerge from USA, Canada, Europe and Australia. Emerging countries in South America also appear to be a growing source of publications before Asia and Africa. However, despite their low overall amount of publications, some low income countries were shown to be more productive than the richest countries with respect to their economic conditions.

The overview of investigation on cyanotoxins also reveals some research needs besides global studies on BMAA, LTX and APTX. Indeed, most of the research has been focussing on toxicology and chemistry but further studies are still needed to understand the production of cyanotoxins and the regulation factors. Moreover, a wide monitoring campaign including countries from Africa, Asia and South America would also be required in order to assess the prevalence of cyanobacterial blooms worldwide and the diversity of toxins.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.toxicon.2013.09.008.

## Conflict of interest statement

The authors declare that there are no conflicts of interest.

## References

AFNOR, 1987. Vocabulaire de la documentation. Paris.

Bastien, C., Cardin, R., Veilleux, E., Deblois, C., Warren, A., Laurion, I., 2011. Performance evaluation of phycocyanin probes for the monitoring of cyanobacteria. J. Environ. Monit. 13, 110–118.

Bourke, A.T.C., Hawes, R.B., Neilson, A., Stallman, N.D., 1983. An outbreak of hepato-enteritis (the Palm Island mystery disease) possibly caused by algal intoxication. Toxicon 21, 45–48.

Briand, J.F., Jacquet, S., Bernard, C., Humbert, J.F., 2003. Health hazards for terrestrial vertebrates from toxic cyanobacteria in surface water ecosystems. Vet. Res. 34, 361–377.

Brient, L., Lengronne, M., Bertrand, E., Rolland, D., Sipel, A., Steinmann, D., Baudin, I., Legeas, M., Le Rouzic, B., Bormans, M., 2008. A phycocyanin probe as a tool for monitoring cyanobacteria in freshwater bodies. J. Environ. Monit. 10, 248–255.

Brooke, S., Newcombe, G., Nicholson, B., Klass, G., 2006. Decrease in toxicity of microcystins LA and LR in drinking water by ozonation. Toxicon 48, 1054–1059.

Byth, S., 1980. Palm Island mystery disease. Med. J. Aust. 2, 40–42.

Chorus, I., Falconer, I., Salas, H., Bartram, J., 2000. Health risks caused by freshwater cyanobacteria in recreational waters. J. Toxicol. Environ. Health Part B 3, 323–347.

Coatrieux, J.L., Bansard, J.Y., Kerbaol, M., 2004. About the use of bibliometry for evaluation, or how to devaluate disciplines? ITBM–RBM 25, 61–66.

Codd, G.A., lindsay, J., Young, F.M., Morrison, L.F., Metcalf, J.S., 2005. Harmful cyanobacteria: from mass mortalities to management measures. In: Huisman, J., Matthijs, H.C.P., Visser, P.M. (Eds.), Harmful Cyanobacteria. Springer Netherlands, Dordrecht (Netherlands), pp. 1–23.

Cox, P.A., Banack, S.A., Murch, S.J., 2003. Biomagnification of cyanobacterial neurotoxins and neurodegenerative disease among the Chamorro people of Guam. Proc. Natl. Acad. Sci. U. S. A. 100, 13380–13383.

Downing, J.A., Watson, S.B., McCauley, E., 2001. Predicting cyanobacteria dominance in lakes. Can. J. Fish. Aquat. Sci. 58, 1905–1908.

Griffiths, D.J., Saker, M.L., 2003. The Palm Island mystery disease 20 years on: a review of research on the cyanotoxin cylindrospermopsin. Environ. Toxicol. 18, 78–93.

Heisler, J., Glibert, P.M., Burkholder, J.M., Anderson, D.M., Cochlan, W., Dennison, W.C., Dortch, Q., Gobler, C.J., Heil, C.A., Humphries, E., Lewitus, A., Magnien, R., Marshall, H.G., Sellner, K., Stockwell, D.A., Stoecker, D.K., Suddleson, M., 2008. Eutrophication and harmful algal blooms: a scientific consensus. Harmful Algae 8, 3–13.

Hnatukova, P., Kopecka, I., Pivokonsky, M., 2011. Adsorption of cellular peptides of *Microcystis aeruginosa* and two herbicides onto activated carbon: effect of surface charge and interactions. Water Res. 45, 3359–3368.

Ho, L., Kayal, N., Trolio, R., Newcombe, G., 2010. Determining the fate of *Microcystis aeruginosa* cells and microcystin toxins following chloramination. Water Sci. Technol. 62, 442–450.

Ho, L., Lambling, P., Bustamante, H., Duker, P., Newcombe, G., 2011. Application of powdered activated carbon for the adsorption of cylindrospermopsin and microcystin toxins from drinking water supplies. Water Res. 45, 2954–2964.

Jochimsen, E.M., Carmichael, W.W., An, J.S., Cardo, D.M., Cookson, S.T., Holmes, C.E.M., Antunes, M.B.D., de Melo, D.A., Lyra, T.M., Barreto, V.S.T., Azevedo, S., Jarvis, W.R., 1998. Liver failure and death after exposure to microcystins at a hemodialysis center in Brazil. New Engl. J. Med. 338, 873–878.

Kuiper-Goodman, T., Falconer, I., Fitzgerald, J., 1999. Human health aspects. In: Chorus, I., Bartram, J. (Eds.), Toxic Cyanobacteria in Water: a Guide to Their Public Health Consequences, Monitoring and Management. E & FN Spon, London, pp. 113–153.

Merel, S., LeBot, B., Clément, M., Seux, R., Thomas, O., 2009. MS identification of microcystin-LR chlorination by-products. Chemosphere 74, 832–839.

Merel, S., Clément, M., Thomas, O., 2010a. State of the art on cyanotoxins in water and their behaviour towards chlorine. Toxicon 55, 677–691.

Merel, S., Clément, M., Mourot, A., Fessard, V., Thomas, O., 2010b. Characterization of cylindrospermopsin chlorination. Sci. Total Environ. 408, 3433–3442.

Merel, S., Walker, D., Chicana, R., Snyder, S., Baurès, E., Thomas, O., 2013. State of knowledge and concerns on cyanobacterial blooms and cyanotoxins. Environ. Int. 59, 303–327.

Mur, L.R., Skulberg, M.O., Utkilen, H., 1999. Cyanobacteria in the environment. In: Chorus, I., Bartram, J. (Eds.), Toxic Cyanobacteria in Water: a Guide to Their Public Health Consequences, Monitoring and Management. E & FN Spon, London, pp. 15–40.

Pablo, J., Banack, S.A., Cox, P.A., Johnson, T.E., Papapetropoulos, S., Bradley, W.G., Buck, A., Mash, D.C., 2009. Cyanobacterial neurotoxin BMAA in ALS and Alzheimer's disease. Acta Neurol. Scand. 120, 216–225.

Pouria, S., de Andrade, A., Barbosa, J., Cavalcanti, R.L., Barreto, V.T.S., Ward, C.J., Preiser, W., Poon, G.K., Neild, G.H., Codd, G.A., 1998. Fatal microcystin intoxication in haemodialysis unit in Caruaru, Brazil. Lancet 352, 21–26.

Rodríguez, E., Onstad, G.D., Kull, T.P.J., Metcalf, J.S., Acero, J.L., Von Gunten, U., 2007. Oxidative elimination of cyanotoxins: comparison of ozone, chlorine, chlorine dioxide and permanganate. Water Res. 41, 3381–3393.

Sharma, V.K., Triantis, T.M., Antoniou, M.G., He, X., Pelaez, M., Han, C., Song, W., O'Shea, K.E., de la Cruz, A.A., Kaloudis, T., Hiskia, A., Dionysiou, D.D., 2012. Destruction of microcystins by conventional and advanced oxidation processes: a review. Separ. Purif. Technol. 91, 3–17.

Shawwa, A.R., Smith, D.W., 2001. Kinetics of microcystin-LR oxidation by ozone. Ozone-Sci. Eng. 23, 161–170.

Svrcek, C., Smith, D.W., 2004. Cyanobacteria toxins and the current state of knowledge on water treatment options: a review. J. Environ. Eng. Sci. 3, 155–185.

Teixeira, M.d.G., Costa, M.d.C., de Carvalho, V.L., Pereira, M.d.S., Hage, E., 1993. Gastroenteritis epidemic in the area of the Itaparica Dam, Bahia, Brazil. Bull. Pan Am. Health Organ. 27, 244–253.

Teixeira, M.R., Rosa, M.J., 2005. Microcystins removal by nanofiltration membranes. Separ. Purif. Technol. 46, 192–201.

Teixeira, M., Rosa, M.J., 2006. Neurotoxic and hepatotoxic cyanotoxins removal by nanofiltration. Water Res. 40, 2837–2846.

van Apeldoorn, M.E., van Egmond, H.P., Speijers, G.J.A., Bakker, G.J.I., 2007. Toxins of cyanobacteria. Mol. Nutr. Food Res. 51, 7–60.

Westrick, J.A., Szlag, D.C., Southwell, B.J., Sinclair, J., 2010. A review of cyanobacteria and cyanotoxins removal/inactivation in drinking water treatment. Anal. Bioanal. Chem. 397, 1705–1714.

WHO, 1998. Guidelines for Drinking-water Quality, second ed.. In: Addendum to Volume 2, Health Criteria and Other Supporting Information World Health Organization, Geneva.

## Web references

CYANOCOST. http://cyanocost.com/ (last accessed 29.06.13.).

International Association of Universities. http://www.iau-aiu.net/content/list-heis (last accessed 19.02.13.).

International Monetary Fund. http://www.imf.org/external/pubs/ft/weo/2012/02/weodata/download.aspx (last accessed 19.02.13.).