

This is the **accepted version** of the journal article:

Agathokleous, Evgenios; Peñuelas, Josep. «Monitoring, regulation, and mitigation of cyanotoxins in the environment to protect human health and wildlife». *Environmental Science & Technology*, Vol. 56, issue 20 (October 2022), p. 14225-14227. DOI 10.1021/acs.est.2c06618

This version is available at <https://ddd.uab.cat/record/299862>

under the terms of the  ^{IN} COPYRIGHT license

26 Cyanotoxin environmental concentrations vary considerably, e.g. smaller than 0.1 to 150 000 µg/L
27 for microcystins, the most common cyanotoxins [1]. Contamination with cyanotoxins presents a
28 growing challenge to human health and agendas of environmental protection worldwide due to the
29 associated adverse health outcomes of exposure to cyanotoxins [2]. Human metabolism can be
30 disrupted and renal system affected at daily intakes smaller than the tolerable daily intakes (2.4 µg
31 microcystin-LR for a 60-kg adult) recommended by the World Health Organization (WHO) [2].
32 Cyanotoxins also negatively affect animals at exposures lower than the toxicological threshold below
33 which exposures are considered safe [2]. Unregulated cyanotoxins can lead to widespread deaths of
34 wildlife [3].

35 Toxic cyanobacteria are dominant organisms in harmful algal blooms. Harmful algal blooms
36 have intensified worldwide since the 1980s due to anthropogenic (e.g. fertilizer use, population
37 growth, gross domestic product) and climatic (e.g. temperature, wind speed, atmospheric pressure,
38 and rainfall) factors, and blooms are often more intense in less developed regions, such as in Asia,
39 South America, and Africa [4]. These factors suggest an enhanced risk for increased exposure to
40 cyanotoxins, which differs among regions. Anthropogenic contaminants in the environment can also
41 stimulate the synthesis of cyanotoxins and their release in the environment [4], but recent studies
42 indicated that the ingestion of anthropogenic chemicals by cyanobacteria can lead to the synthesis
43 and release of novel cyanotoxins with the potential to lead to massive deaths of wild animals [3].

44 Worldwide authorities should routinely monitor cyanotoxin concentrations in the environment
45 while accounting for novel harmful toxins that may be produced by chemical reactions upon
46 contaminant ingestion by cyanobacteria. Continuous active monitoring of cyanotoxin-releasing
47 organisms is also needed to keep their population at low levels, especially during harmful algal
48 blooms when their population and cyanotoxin release can increase considerably. Various sensors
49 have been developed, permitting rapid cyanotoxins detection in real-world water samples. For
50 example, a nanoprobe-based quantum-dot haptens senses MC-LR ≥ 0.03 µg/L [5]. More advanced

51 fluorescent sensors now also exist, permitting quick detection (within 5 min) and discrimination of
52 multiple common cyanotoxins with smartphones, by integrating aptamers and single-stranded DNA
53 dyes [6]. Such sensors accurately identify and measure widely-occurring cyanotoxins, including
54 anatoxin-*a*, cylindrospermopsin, nodularin and MC-LR, with a low detection limit (<3 nM) close to
55 the WHO's guideline for maximum permissible concentration in drinking water [6]. These recent
56 advances offer an opportunity to address risks from trace concentrations of individual cyanotoxins as
57 well as cyanotoxins mixtures. The use of novel DNA-based nanosensors may facilitate a more
58 effective and faster identification and sensing of cyanotoxins in the future [7]. These could also be
59 coupled with proteomic and transcriptomic analyses of cyanobacteria to characterize potentially new
60 toxins, especially since the current scientific literature lacks such studies at low doses of stress [4].
61 The active engagement of the public in the monitoring activities of local environmental institutions
62 within a citizen-science approach could help in such programs to expand the coverage of waters
63 regularly observed for harmful algal blooms. Local institutions and citizen scientists could also make
64 observations for potential unusual behavior or death of animals and other organisms, and if known
65 cyanotoxins or other known causes are not identified, chemical research should consider the
66 possibility of newly-formed cyanotoxins [3].

67 Regulations are urgently needed to limit cyanotoxins in the environment. Some provisional
68 guidelines of exposure exist. For example, the provisional daily limit of ingestion is 1 µg/L, whereas
69 in 2015 the USA EPA issued an advisory guideline for a 10-day ingestion of 1.6 µg/L for all ages
70 except for infants and young children (0.3 µg/L) [1]. To prevent adverse effects on human health and
71 the environment as well as deaths of wildlife that are often hard to identify [3], policies are urgently
72 needed to regulate cyanotoxins in the environment, increase water quality, and minimize associated
73 risks. However, to achieve this, a multi-dimensional approach is required. Policies are needed to set
74 critical levels of cyanotoxins in the environment –at least the most abundant like microcystins- for

75 the protection of human health and wildlife, considering the available science on the effects of
76 cyanotoxins on various organisms.

77 Developed countries have technologies to treat water for cyanotoxins, but such treatments are
78 expensive and produce waste byproducts that need further treatment for mitigation. Mitigation efforts
79 that should be implemented include the application of existing algaecides at early stages of harmful
80 algal bloom formation, to prevent expansion of cyanobacteria and restrict the synthesis and release of
81 cyanotoxins. There are various effective algaecides, such as CuSO_4 , H_2O_2 , UV, and KMnO_4 , but
82 careful selection of the most ideal doses is needed to avoid undesired stimulation of cyanobacteria
83 due to insufficiently high doses [4]. This complicates the mitigation efforts because high doses of
84 algaecides might severely affect organisms other than target algal, and thus the selection of doses
85 should be done case-specifically and considering effects on local non-target organisms. To avoid
86 adaptation of cyanobacteria to algaecides [4], combinations of different algaecides should be
87 considered. New algaecides need to be developed within a green chemistry perspective to mitigate
88 harmful algae while minimizing potentially hazardous substances. New technologies with decreased
89 treatment costs, e.g. cyanotoxin-degrading bacteria, should also be developed for the control of
90 harmful cyanobacteria. In addition, intergovernmental cooperation is needed to account for regional
91 differences.

92 Many drivers of global change such as climate change, eutrophication and anthropogenic
93 chemical contamination may also enhance harmful cyanobacteria, enrich their toxins, further degrade
94 water quality, and enlarge the risk for increased exposure to cyanotoxins [4]. They all decrease the
95 availability and/or quality of water, increasing the dependence on reclaimed water for multiple
96 purposes, and should be taken into account to tackle the issue of cyanotoxin contamination.

97 Cyanotoxin contamination, regulation and mitigation thus require a multi-dimensional
98 approach from numerous disciplines across physical sciences, engineering, and technology (Fig. 1).
99 Satisfying this requirement adequately will offer an opportunity to improve water quality, protect

100 human and environmental health, and facilitate the achievement of many of the Sustainable
101 Development Goals (SDGs), including the urgent need to provide safely-managed drinking water
102 services to the 2.1 billion people that have not, e.g. >50% of India's population.

103
104 **Acknowledgements:** E.A. acknowledges multi-year support from The Startup Foundation for
105 Introducing Talent (No. 003080) of Nanjing University of Information Science & Technology
106 (NUIST), Nanjing, China, and the Jiangsu Distinguished Professor program of the People's
107 Government of Jiangsu Province. J.P. acknowledges funding support from the Spanish Government
108 project PID2019-110521GB-I00, the Fundación Ramón Areces project CIVP20A6621, and the
109 Catalan government project SGR2017-1005.

110
111 **Conflict of Interest Disclosure:** The authors declare no competing financial interest.

112
113 **Supporting Information:** References supporting this exposition.

114 **Biography**

115 **Evgenios Agathokleous**



117
118 Evgenios Agathokleous studied crop science (Diploma, February 2013) at the Agricultural University
119 of Athens, Greece. As a scholar of the Japanese government, he continued his studies in Japan, where
120 he received a PhD in Environmental Resources (March 2017) from Hokkaido University. Upon

121 completion of the PhD course he was awarded a fellowship for postdoc research by the Japan Society
122 for the Promotion of Science (JSPS) and continued research at the Forestry and Forest Products
123 Research Institute (FFPRI) and Hokkaido University (April 2017 to March 2019). Then, he moved to
124 Nanjing University of Information Science & Technology (NUIST), China, where he is now a
125 professor of ecology at the School of Applied Meteorology. He teaches various subjects of ecology
126 and general academic matters to students at all levels. He is the principal investigator of a series of
127 research programs and focuses mainly on plant stress and species interactions under various
128 environmental stressors as well as methods for mediating stress effects.

130 **References**

- 131 [1] EPA, Drinking Water Health Advisory for the Cyanobacterial Microcystin Toxins, Washington, DC,
132 2015.
- 133 [2] J. He, J. Chen, F. Chen, L. Chen, J.P. Giesy, Y. Guo, G. Liang, X. Deng, W. Wang, P. Xie, Health
134 Risks of Chronic Exposure to Small Doses of Microcystins: An Integrative Metabolomic and
135 Biochemical Study of Human Serum, *Environ. Sci. Technol.* 56 (2022) 6548–6559.
136 <https://doi.org/10.1021/acs.est.2c00973>.
- 137 [3] S. Breinlinger, T.J. Phillips, B.N. Haram, J. Mareš, J.A. Martínez Yerena, P. Hrouzek, R. Sobotka,
138 W.M. Henderson, P. Schmieder, S.M. Williams, J.D. Lauderdale, H.D. Wilde, W. Gerrin, A. Kust,
139 J.W. Washington, C. Wagner, B. Geier, M. Liebeke, H. Enke, T.H.J. Niedermeyer, S.B. Wilde,
140 Hunting the eagle killer: A cyanobacterial neurotoxin causes vacuolar myelinopathy, *Science*. 371
141 (2021) 6536. <https://doi.org/10.1126/science.aax9050>.
- 142 [4] E. Agathokleous, J. Peñuelas, R.A. Azevedo, M.C. Rillig, H. Sun, E.J. Calabrese, Low levels of
143 contaminants stimulate harmful algal organisms and enrich their toxins, *Environ. Sci. Technol.* 56
144 (2022) 11991–12002. <https://doi.org/10.1021/acs.est.2c02763>.
- 145 [5] L. Feng, A. Zhu, H. Wang, H. Shi, A nanosensor based on quantum-dot haptens for rapid, on-site
146 immunoassay of cyanotoxin in environmental water, *Biosens. Bioelectron.* 53 (2014) 1–4.
147 <https://doi.org/10.1016/j.bios.2013.09.018>.

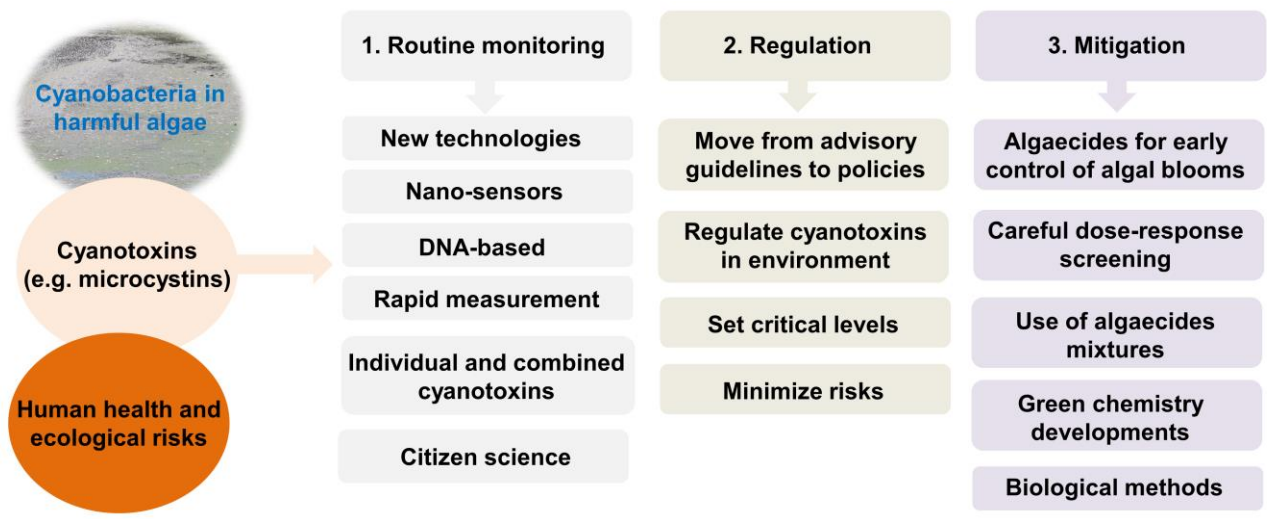
148 [6] M. Kim, S.M. Ko, C. Lee, J. Son, J. Kim, J.M. Kim, J.M. Nam, Aptamer-based fluorescent sensor
 149 array for multiplexed detection of cyanotoxins on a smartphone, *Anal. Chem.* 91 (2019) 10448–10457.
 150 <https://doi.org/10.1021/acs.analchem.9b00750>.

151 [7] T. Suo, M. Sohail, S. Xie, B. Li, Y. Chen, L. Zhang, X. Zhang, DNA nanotechnology: A recent
 152 advancement in the monitoring of microcystin-LR, *J. Hazard. Mater.* 403 (2021) 123418.
 153 <https://doi.org/10.1016/j.jhazmat.2020.123418>.

154

155

156 **Figure & caption**
 157 **Figure 1.** A path to reduce cyanotoxin risk.



158