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Natural toxins: environmental contaminants calling for attention

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Abstract

Biosynthetic toxic compounds from plants and cyanobacteria constitute a chemically diverse family of at least 20,000 compounds. Recent work with natural toxin databases and toxin characterization shows that the majority of natural toxins are polar and mobile, with toxicity ranging from low to very high, while persistence is highly variable. Natural toxins may be produced in high quantities—some exceeding 10 g/m^2/year—resulting in high environmental loads. Recent phytotoxin monitoring indicates that one or more natural toxin is always present in a surface water sample, but that concentrations are highly variable often with pulses during rain events. Phytotoxins belong to many classes, but often with flavonoids and alkaloids dominating. Likewise, advanced monitoring discovers a wide spectrum of cyanobacterial metabolites that are released directly into surface waters during water blooms. Except of the few known cyanobacterial toxins, we have very limited info regarding their environmental fate and toxicity.

The 16 papers in this article collection present examples of natural toxin occurrence, properties, fate and toxicity. The overarching conclusion is that natural toxins should be monitored and characterized regarding their risk potential, and that natural toxins of greatest expected risk should be evaluated as thoroughly as industrial xenobiotics. Cyanotoxins are well known water contaminants that should be removed for producing drinking water, while for phytotoxins the current knowledge base is very limited. We advocate to intensify research on natural toxins, and to address the evident knowledge gaps on natural toxin analysis/monitoring, physical–chemical properties and degradation/pathways, transport modelling, and toxicity. The complex and dynamic interplays between biotic and site conditions such as vegetation, toxic plant densities, climate, soil types, nutrients and radiation, play decisive roles for both biotoxin formation and fate. Environmental and toxicological research in biosynthesized compounds extends beyond natural toxins, with important perspectives for risk assessment of biopesticides, growth regulators and biomedicine (or biologicals collectively) produced by plants and microorganisms.

Poisonous food

We are picky with what we eat and drink—for good reasons. We wisely avoid death cap mushroom, castor beans, and poison hemlock. Drinking water from a lake tainted green by cyanobacteria is a no-go. We will even be careful with green potatos, non-cooked chickpeas, beans and cassava due to their contents of glycoalkaloids, lectins and cyanogenic glycosides. These and many other organisms produce secondary metabolites that are strong poisons, also to humans. Ames et al. [1] estimated that 99.99% of dietary "pesticides" were of natural origin. There are more than 20,000 natural bioactive compounds that are toxic to humans covering a wide range of modes of action [2]. Some show low acute toxicity like the glycoalkaloids in potato or isoflavones in clover, medium toxicity as linamarin in cassava and coniin in poisonous hemlock, while some are very toxic like ricin in castor beans and the cyanotoxin saxitoxin produced by blue-green algae (Table 1). Many of these compounds may have or have had a function as natural defense chemicals in order for the toxin producing organism to compete with other species,

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Table 1 Examples of natural phyto- and phycotoxins, properties and toxicity

Toxin	Toxin class	Organism (example)	Max tissue conc.[a] mg/g DW	Log K_{ow}[b] L/L	Mode of toxicity	LD_{50}[c] mg/kg
Amanitin	Cyclo-peptide	*Amanita phylloides*	3	< 0	Hepatotoxin	0.3
Ricin	Protein (lectin)	*Ricinus communis*	32	–	Cytotoxin	0.02
Senecionine	Alkaloid	*Jacobaea vulgaris*	7	1.90	Hepatotoxic, potential carcinogen	50
Coniin	Alkaloid	*Conium maculatum*	4	2.6^{est}	Neurotoxin	8
Solanine	Glycoalkaloid	*Solanum tuberosum*	1	2.0^{est}	Cell membrane disruption	30
Formononetin	Isoflavone	*Trifolium pratense*	15	2.8^{est}	Estrogenic activity	–
Linamarin	Cyanogenic glycoside	*Manihot esculenta*	30	-1.4^{est}	Cyanide poisoning	1 (HCN)
Ptaquiloside	Terpenoide glycoside	*Pteridium aquilinum*	15	− 0.6	Carcinogen	–
Microcystin LR	Cyclo-peptide	*Microcystis aeruginosa*	13	− 1.2 (pH 7)	Hepatotoxin	0.06
Saxitoxin	Alkaloid	*Dolichospermum circinale*	4.5	-2.4^{est}	Neurotoxin	0.01

[a] Max tissue concentration in the producing species: amanitin [73], ricin [74], senecionine [6], coniin [75], solanin [76], formononetin [77], linamarin [78], ptaquiloside [79], microcystin LR [80], and saxitoxin equivalent [81]

[b] Estimated by EpiWin (^{est}) or literature data; senecionine [9], ptaquiloside [82], and microcystin LR [83]

[c] Acute toxicity, intraperitoneal (mice); from inchem.org if not otherwise stated or literature; ricin [84], coniin [85], not acute toxic; formononetin EC_{50} in µM range [86], ptaquiloside estimated threshold conc. for $1{:}10^6$ cancer incidence of arund 20 ng/L [82], saxitoxin [87], microcystin LR [88]; other microcystins [89]

and to protect itself against herbivoric and pathogenic attacks and other stressors [3, 4].

High loads

Many natural toxins are produced in remarkably high quantities with biomass contents up to several mass percent (Table 1). If plants occur as dense stands or in monocultures the production and hence the potential load per land area unit can be massive and much higher than seen for other land applied chemicals like pesticides. For instance a clover crop may produce isoflavones up to 220 kg per hectare annually [5], while quinolizidine alkaloids in lupin may reach annual production of 800 kg per hectare [6]. Bracken—a fern with invasive character—has been estimated to produce more than 20 kg of its carcinogenic illudane glycosides per hectare of land during a growing season [7]. The surface scums during massive cyanobacterial bloom events have been shown to reach maximum values over 100 mg/L of cyanotoxins microcystin [8].

Environmental contaminants

Natural toxins are biosynthesized and released within or in close proximity to surface water and groundwater reservoirs (Fig. 1). Thus, cyanobacterial blooms cause direct water contamination due to toxic secondary metabolites, while exudation from plants and rain wash off transfer toxins to soils from where they leach to surface waters and groundwater. A high fraction of natural toxins are polar and even charged, with octanol–water partition coefficients, log K_{ow}, typically in the range from − 5 to 3 [9, 10]. Hence, they are highly mobile in soils and sediments (Table 1). In a pioneering work, Günthardt et al. [11] created a database of plants and their toxins for Central Europe. Starting with a set of 844 plants and 1586 toxins, the authors found that about a third of the toxins would classify as persistent, mobile and toxic (PMT) based on QSAR estimated properties. This work also showed that alkaloids make up the dominating class of plant PMT compounds. The Janssen group compiled a database for secondary metabolites from cyanobacteria with more than 2000 entries classified into 13 classes [12]. Cyanotoxins are not only microcystins but can cover a high variation in chemical diversity and share similar PMT properties as plant toxins. Work with the databases has demonstrated an embarrassing lack of experimental data on physical chemical properties, environmental fate and toxicity for most natural toxins, and points to the need of reference materials and analytical methods.

They make it to the water

With the large masses of toxins being produced combined with their inherent PMT properties, natural toxins are expected to be frequently observed in streams, rivers and lakes. Some cyanotoxins have been widely monitored showing their frequent occurrence in waterbodies with cyanobacterial blooms. The most commonly studied and detected cyanotoxin microcystin occurs on average in up to tens of ug/L levels in pelagic water outside scums, but its concentrations can be up to several orders of magnitude higher in surface blooms and scums [8, 13]. Isoflavones originating from red clover or soybean dominated agricultural land occurred regularly in Swiss and US rivers in concentrations up to 217 ng/L [14, 15]. Mycotoxins,

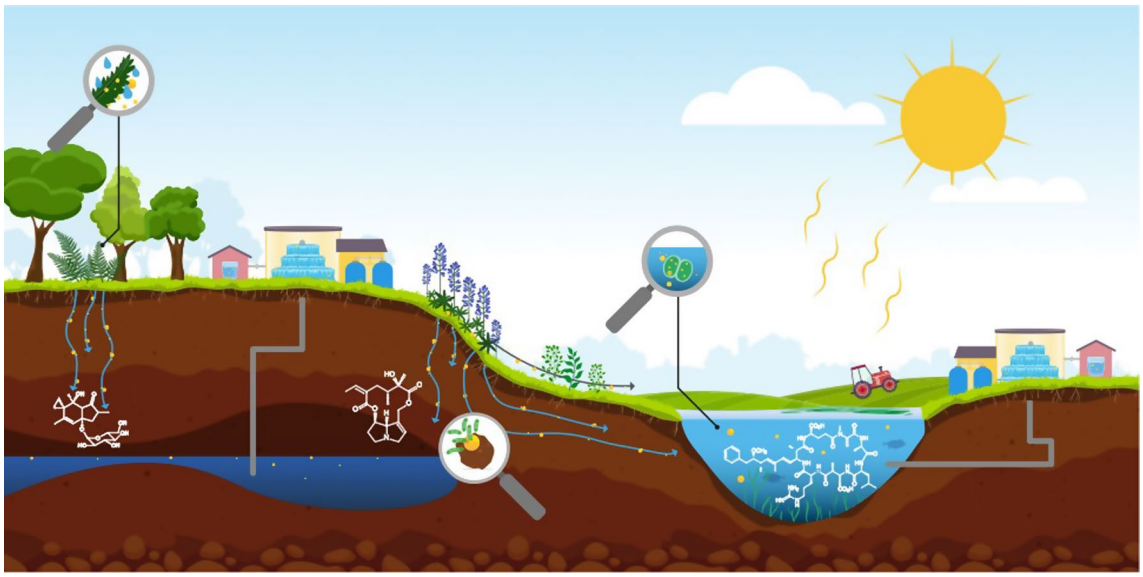

Fig. 1 Natural toxins from source to tap. Natural toxin (●) production by cyanobacteria and plants (cropland, forests, pasture, gardens), release and transfer to lake water and soils, transport via soils to groundwater and surface water reservoirs from which drinking water is abstracted. Molecular structures of ptaquiloside (left), senecionine (middle) and microcystin LR (right) illustrating the polar nature of natural toxins (cf Table 1)

produced by *Fusarium* spp. that attack small grain cereals during cultivation, were equally found in these surface waters [16–18]. More recently, a growing body of evidence for the presence of a larger number of phytotoxins from various classes of secondary plant metabolites in ground- and surface water was presented by various researchers in dedicated experimental field studies or surface water monitoring campaigns [6, 19–22]. Likewise, other types of natural compounds emitted primarily by the anthroposphere, such as food ingredients and personal care products, as well as human hormones are equally present in surface and groundwaters. Thus, caffeine, nicotine, estrogens, piperine, steroids and morphine occur frequently in screening studies of surface and groundwaters, e.g., [23–27].

Little is known on toxin transfer from plant to soil; passive and active release may take place both from above- and below-ground parts. Field studies indicate that fast and substantial release of toxins may occur during rain events generating pulses of toxins that propagates through soils to drainage and creek waters [5, 28, 29]. Hence, natural toxin concentrations and exposure in surface waters and in upper groundwater may be highly variable over time. This in turn calls for rain-event and flow-proportional sampling as random sampling may not lead to precise estimates of environmental loads. The multitude of toxin producing organisms predicts that natural toxins in freshwaters should be found as mixtures with likely fingerprints of the dominating toxin producers in the catchment or the water reservoir [19]. Climate-induced change in cropping patterns, fast migration of new (invasive) species, faster development of cyanobacterial blooms and appearance of new toxin varieties add to the complexity, e.g., [30].

Regulation, land management and water cleaning

Natural toxins are not currently part of general drinking water assessment and regulation; only the cyanotoxin microcystin LR has been considered for inclusion in the EU Drinking Water Regulative [31], while WHO recently has published guideline values for cyanotoxins in drinking water and recreational exposure scenarios [32]. This is in strong contrast to food and feed where more natural toxins are regulated and regularly monitored, for instance pyrrolizidine alkaloids in tea and honey and aflatoxins in nuts and seeds [33–35]. More monitoring, fate and toxicological data are needed for risk assessment of natural toxins in drinking water, and to lay the foundation of a regulation.

Many actions can be taken to control the production of natural toxins and their concentrations in water reservoirs. Reducing eutrophication and algal blooms in river, lake and coastal waters via control of nitrate and phosphorus discharges from agriculture and with wastewater has high priority for reduction of cyanobacterial blooms, and remains as one of the major global sustainability goals [36]. Crops can be bred to produce less toxic varieties as for alkaloids in lupin, cyanogenic glycosides in cassava, isoflavones in red clover, and glucosinolates in rape seed, e.g., [37–39], which however also could make plants more susceptible to pathogenic attacks. Toxin producing plants

in forests, grasslands and other non-cropped areas can be fought by burning, biological or chemical control or physically as practiced for bracken, ragwort, giant hogweed and Scotch broom, e.g., [40–42]. Finally, when natural toxins are already present in the water, they may be removed by water treatment at water works, e.g., by means of hydrolysis, microbial degradation in sand filters or advanced oxidation methods [43–45]. The major challenge is here for private and small scale water abstraction utilities that use water from smaller reservoirs and upper groundwaters, and employ no or very simple water treatment [46].

Focus on safe water supply—papers in this article collection

In 2020 an on-line conference "Natural Toxins—Environmental Fate and Safe Water Supply" was conducted to address knowledge gaps within the field of natural toxins and water quality (https://natoxaq.ku.dk/news/news-2016/final-conference/). The conference was organized as part of the EU Marie Curie ITN project "Natural toxins and drinking water quality—from source to tap" (NaToxAq) (see Box). The present ESEU article collection comprises 16 papers almost equally distributed between cyanotoxins and plant toxins. A short introduction to the papers is given below.

NaToxAq—fact box

- Marie Curie ITN consortium 2017—2021 comprising 22 public and private partners in 7 European countries addressing water contamination by phyto- and phycotoxins.
- 16 Early Stage Researchers (ESRs)
- Work content:
  - Analysis: target, non-target analysis, suspect screening, effect-directed analysis.
  - Monitoring: sampling, groundwater/surface water, source allocation, toxin fingerprints, invasive species.
  - Toxin phys-chem properties: sorption, degradation kinetics, metabolites, QSAR estimation, databases.
  - Risk assessment and reduction: human toxicity, environmental modelling, risk communication, water treatment.
- Outputs and further information: –>https://natoxaq.ku.dk/. "Toxin of the week", 45 research papers, databases of phyto and phycotoxins/metabolites, reports and outreach.

Cyanotoxins

The papers concerned with cyanobacterial metabolites focus on the characterization of their mixtures in surface water bodies, their fate and stability in the environment, toxicity and hazard characterization as well as strategies for their mitigation. They bring novel information on a wide spectrum of compounds, including many understudied cyanobacterial peptides or retinoids produced by cyanobacterial water blooms.

Li et al. [47] assessed cyanobacterial risk in 108 Swedish lakes based on long term monitoring data. They documented that nutrients are main drivers for the higher cyanobacterial occurrence and also multispecies dominated water blooms in the affected lakes. They suggest to set nutrient targets to protect safe water supply and recreation. The study of Filatova et al. [48] documents a wide diversity of cyanopeptides in three freshwater reservoirs serving as drinking water resources in the U.K. The 28 identified cyanopeptides included microcystins, anabaenopeptins, aeruginosins, cyanopeptolins, microginins, some of them reported in UK waters for the first time. Natumi et al. [49] characterized environmental stability and photochemical fate of these, and also other cyanopeptides (54 total) from common water-bloom forming cyanobacteria under environmental conditions. Some of them were shown to be relatively stable and thus could potentially pose risk in drinking water resources.

Two studies bring information relevant for hazard assessment of selected cyanobacterial metabolites. Lovin et al. [50] observed species-specific responses in two of the most common larval fish models (zebrafish and fathead minnow) after exposure to neurotoxin anatoxin-a, with more pronounced sublethal effects in fathead minnows at environmentally relevant concentrations. Kubickova et al. [51] conducted an extensive review focused on retinoid compounds that can be also produced by cyanobacterial blooms. They summarized their sources, modes of action and potential adverse effects and discussed their implication for risk assessment. This paper also introduces the concept of cyanobacterial metabolites as anthropo-natural compounds, since they are produced by natural organisms, but anthropogenic impact causes their high concentrations.

Keliri et al. [52] investigated a methodology for bloom control by comparing the treatment efficiency of collected cyanobacterial bloom samples with liquid hydrogen peroxide or metallic peroxide granules slowly releasing oxidants. They emphasize the importance of correct dosing and timing of the treatment to avoid undesirable side-effects, including potential release of cyanotoxins into the waterbody. A comprehensive

review by Schneider and Blaha [53] focuses on the applicability of advanced oxidation processes (AOP) during water treatment for removal of known cyanotoxins. It provides an overview of different AOP techniques that can be used for cyanotoxins degradation and the impact of technical parameters, toxin properties and water quality on its efficacy.

The cyanotoxin papers in this article collection bring novel information on some known cyanotoxins and mitigation of their presence, but also document that cyanobacterial metabolites comprise a much wider spectrum of compounds that can be released into surface waters during cyanobacterial water blooms. In contrast to relatively extensive literature on the few known cyanobacterial toxins, such as microcystins, we have only very limited information on many of the recently detected cyanobacterial metabolites. As documented by the included articles, some of them can be frequently present and highly relevant, but information on their occurrence, fate in the environment, stability and toxicity is largely missing.

Plant toxins

The papers presented in this issue on phytotoxins cover most of the well-established research domains in environmental chemistry. They range from investigations of specific environmental distribution and fate processes under laboratory conditions, over dedicated field experiments and monitoring campaigns in the real environment to effect studies and risk assessment.

Wu et al. [54] compared the stability of ptaquiloside in natural groundwater under environmentally relevant conditions with laboratory-based models and found a good agreement under slightly acid to neutral pH. Under such conditions, ptaquiloside was found to prevail for months. Schönsee et al. [55] quantified sorption coefficients to clays and found that for cationic phytotoxins, in particular, a high proportion in soils may be attributed to these minerals. Field studies on production and occurrence of quinolizidine alkaloids and indole alkaloids from lupin, and of ptaquiloside from bracken fern were conducted by Hama and Strobel [56], and Garcia-Jorgensen et al. [7], respectively. Both types of phytotoxins were produced in considerable amounts, and could be quantified in soil pore waters in concentrations up to 4.8 µg/L. Nanusha and co-workers screened German and Danish river waters for phytotoxins by both non-target and target analysis. They found thousands of overlapping peaks between water and plants from local vegetation [57], and detected 12 of 150 [58], and 27 out of 160 [59] targets (mostly for the secondary plant metabolite classes of alkaloids, coumarins and flavonoids), in concentrations up to 3 µg/L. Groundwater monitoring with a focus on illudane glycosides (including again ptaquiloside) was carried out by Skrbic et al. [60]. No residues were found in deep groundwater wells, but for the first time, these compounds were detected in some private shallow wells. The fact that some phytotoxins are produced in high amounts, can be stable for months, mobile, and are found in soil pore water, river waters and drinking water resources asks for effect studies and (eco-)toxicological risk assessment. Griffiths et al. [61] contribute to the hitherto still very limited data and report EC_{50} values of alkaloids lupin and ragwort on *Daphnia magna*. According to them, there is a potential risk for aquatic organisms in stagnant pond water in vicinity of corresponding vegetation.

In summary, the compilation of papers presented here on phytotoxins in the environment adds considerably to the currently still rather limited literature. Their authors convincingly show that the topic is relevant, and that we may expect surface water samples in many situations to contain one or more natural toxins. Natural toxins show a high and fascinating diversity in terms of origin, environmental chemistry and (eco-)toxicology that goes beyond our traditional notion of (anthropogenic) environmental micropollutants. As such, they finally have truly emerged!

The way forward

In our strive to supply safe drinking water, to provide healthy recreational space, and to ensure stability and functioning of both cropped and non-cropped ecosystems, we should look at all relevant contaminants. Anthropogenic contaminants monitored in water quality assessments often have been found to add little to explain the toxicity profiles of natural water samples [62, 63]. Obviously, natural toxins add to the toxicity profiles but they are seldomly included among the compounds analysed. Thus, future water quality monitoring should include selected natural toxins/classes [64, 65]. The fast development of high-throughput non-target analytical techniques as well as effect-directed screening may help to accelerate more comprehensive monitoring schemes. Monitoring for natural toxins calls for more work on development of analytical methods and sample pretreatment, availability of reference substances and mass spectra as well as databases for toxin prioritization.

A high abundance of natural toxins in natural water samples may call for revision of current regulative water quality criteria with more emphasis on the total spectrum of contaminants in the samples and their inherent toxicities (incl. mixture toxicity) rather than working with fixed cut-off criteria for a defined set of anthropogenic chemicals, e.g., as used in the EU Drinking Water Regulative.

Natural bioactive compounds have a long history as (bio)pesticides and (bio)medicine (traditional medicine) or as templates for synthetic compounds [66,

67]. Examples of biopesticides comprise pyrethrins extracted from chrysanthemum, the isoflavanoid rotenone from roots of certain legumes, and nicotine and strychnine alkaloids used as insecticide and molluscicide, respectively [68–71]. Plant-incorporated-protectants such as *Bacillus thuringiensis* (Bt) toxin in GMO crops have been successfully implemented but followed by numerous studies of environmental fate and effects of the Bt toxin on non-target organisms [72]. We are currently seeing a strong interest in use of natural bioactive compounds—or biologicals—as sustainable, low risk and climate-proof alternatives to synthetic chemicals. While biologicals are less regulated today, this is to come. This in turn will create a very strong push for further work on analysis, monitoring, fate, toxicity, and modelling of these myriads of bioactive natural compounds to ensure that proper risk assessments can be performed, but also to quantify the bioactivity, modes of actions and longevity of the biologicals in soils and other environmental compartments.

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