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Comprehensive Toxic Plants−Phytotoxins Database and Its Application in Assessing Aquatic Micropollution Potential

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Supporting Information

ABSTRACT: The production of toxic plant secondary metabolites (phytotoxins) for defense is a widespread phenomenon in the plant kingdom and is even present in agricultural crops. These phytotoxins may have similar characteristics to anthropogenic micropollutants in terms of persistence and toxicity. However, they are only rarely included in environmental risk assessments, partly because a systematic overview of phytotoxins is missing. Here, we present a newly developed, freely available database, Toxic Plants−PhytoToxins (TPPT), containing 1586 phytotoxins of potential ecotoxicological relevance in Central Europe linked to 844 plant species. Our database summarizes phytotoxin patterns in plant species and provides detailed biological and chemical information as well as in silico estimated properties. Using the database, we evaluated phytotoxins regarding occurrence, approximated from the frequencies of Swiss plant species; environmental behavior based on aquatic persistence and mobility; and toxicity. The assessment showed that over 34% of all phytotoxins are potential aquatic micropollutants and should be included in environmental investigations.

KEYWORDS: *natural toxins, poisonous plants, invasive species, aquatic pollution, risk assessment*

INTRODUCTION

Today, many anthropogenic chemicals are recognized as environmentally relevant micropollutants because of their persistence and toxicity. Of special concern are anthropogenic chemicals that are directly applied to the environment (e.g., pesticides)[1] or released through wastewater treatment plants (WWTP, e.g., pharmaceuticals and the ingredients of personal-care products).[2,3] Consequently, monitoring programs have emerged to systematically investigate the appearance of these chemicals. Among all released chemicals, persistent, bioaccumulative, and toxic (PBT) substances are of particular importance because they can concentrate in the food chain and cause long-term effects.[4,5] Recently, persistent, mobile, and toxic (PMT) substances have also increasingly come into focus as a result of the threat they pose to water quality.[6,7] These relatively polar PMT substances are not bioaccumulative and were often neglected in traditional screenings until concerns arose related to them being much less effectively removed in WWTPs and thus being highly problematic for the aquatic environment.[8]

In contrast to anthropogenic PBT and PMT compounds, plant-produced compounds with similar properties have received little attention as potential micropollutants, although the production of toxic plant secondary metabolites (PSMs) is common in the plant kingdom and even takes place in agricultural crops. These so-called phytotoxins, including allelochemicals, allergens, hallucinogens, fatal toxins, and biopesticides, constitute a category of natural compounds with various toxic effects and diverse molecular structures (e.g., alkaloids, terpenes, phenylpropanoids, and polyketides).[9,10] Phytotoxins might contribute to mixture toxicities and locally even outcompete anthropogenic chemicals in their overall risk because of constant production and comparatively high concentrations in plants.[11] Particularly, plants with high local abundance often induced by human activity, such as crops, invasive neophytes, or foreign ornamental garden plants, might be of concern.

The environmental behavior of phytotoxins has been investigated only for a limited number of compounds. Indeed, case studies on single phytotoxins have demonstrated relevant exposure, for instance in the case of strongly toxic glycoalkaloids produced from potato (*Solanum tuberosum*),[12] estrogenic isoflavones from red clover grasslands (*Trifolium pratense*),[13] or the carcinogenic ptaquiloside from the non-agricultural bracken fern (*Pteridium aquilinum*).[14]

Environmental investigations including a larger number of phytotoxins are often hindered by the high number of structurally diverse phytotoxins and a lack of analytical standards and validated methodologies.[11,15] Another prerequisite for a systematic investigation of a wide range of phytotoxins is the availability of a comprehensive database

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including both plants and their toxins. The importance of phytotoxins and PSMs in general in specific domains such as pest management, the culinary industry, the perfume industry, and medicinal research has led to the development of several excellent databases. Because they are often optimized for the specific needs of certain communities (e.g., SuperToxic[16] and Super Natural II[17] in medicinal research), they are of limited use in other fields. For environmental chemists and regulators, the Aggregated Computational Toxicology Online Resource (ACToR)[18] from the U.S. Environmental Protection Agency (EPA) is a specialized chemical database, but like most of them, it does not provide connections between PSMs and plant species. In this respect, the KNApSAcK database[19] is useful because it contains chemical information and especially plant-species−metabolite relationships. Databases on toxic plants can also be useful, such as the compendium from the European Food Safety Authority (EFSA)[20] or the Clinical Toxicology (CliniTox) database, but they generally contain limited chemical information.[21] Indeed, textbooks[22−25] are often the most detailed data sources regarding the combination of plant species, phytotoxins, and toxicity information, but printed information is of limited use for efficient and systematic computer-based data analysis. Overall, an environmental risk assessment remains challenging (if not impossible) because of the lack of databases containing phytotoxins, plant species, toxicities, and environmentally relevant chemical properties.

Here, we describe the compilation of potentially relevant toxic plants in Central Europe together with their corresponding phytotoxins in a newly developed and freely available database: Toxic Plants−PhytoToxins (TPPT, available for download from https://www.agroscope.admin.ch/agroscope/en/home/publications/apps/tppt.html). The established database contains 844 plant species with biological information, including, among others, plant names, distribution, human toxicity, and vegetation type, and 1586 phytotoxins with chemical information covering compound identification, structural characterization, in silico estimated physicochemical and toxicological properties, and corresponding references. To the best of our knowledge, the TPPT database is unique in summarizing phytotoxin patterns in individual plant species while at the same time providing detailed information about both plants and toxins. The TPPT database was then used for a preliminary aquatic risk assessment, in which the phytotoxins were evaluated on the basis of (1) their occurrence, approximated from the plant species' frequencies in Switzerland, (2) their environmental behavior, including aquatic persistence and mobility according to Arp et al.,[6] and (3) their acute rodent and aquatic toxicity. The applied prioritization procedure is a first important step to differentiating phytotoxins on the basis of their properties and identifying critical PSM classes that should be included in surface-water screenings.

■ MATERIALS AND METHODS

TPPT-Database Purpose and Range Definition. The TPPT database was designed to facilitate environmental risk assessments of phytotoxins, such as their prioritization according to their relevance for the aquatic environment, and therefore covers plant species and phytotoxins together with exposure- and effect-related information. Although we acknowledged the existence of several good databases, it was not feasible to start from an existing database, and we preferred to start ab initio. In the first step, all higher plant species that (i) occur in Switzerland as naturally growing plants, invasive neophytes, agricultural plants, or ornamental garden plants and (ii) have possible negative effects due to their produced PSMs affecting humans, animals (including husbandry animals), the aquatic ecosystem, or other plants (allelopathy) were included in the TPPT database. Agricultural plants that do not grow in Switzerland but still have global importance were also included, such as the cacao tree, cotton, and the most important coffee plant (*Coffea arabica*).[23] The vegetation of Switzerland was chosen because it covers several altitudinal zones from foothill to alpine, is species-rich (over 3600 different higher plant species), and is largely representative for Central Europe.[26−28] The southern part of the country is further influenced by the Mediterranean climate. We focus on higher plant species, and therefore, other natural toxin sources, such as algae or cyanobacteria, are not covered by the TPPT database, although they also produce relevant natural toxins.[29,30] In a second step, the major toxic PSMs present in the previously selected plants were identified, added to the database, and if the data were available, complemented with minor toxic PSMs. The emphasis was placed on PSMs with known adverse effects. Although primary metabolites could also cause toxicity, in contrast to PSMs they do not act as defense compounds but serve in essential plant physiological functions, notably photosynthesis and carbon, nitrogen, and fatty acid metabolism.[9,31] This second step was often vague, because plants mostly produce several different PSM classes composed of high numbers of compounds that mostly have not yet fully been resolved and identified and of which several might be toxic. Moreover, the phytotoxin−plant-species relationship regularly varies between different regions, plant chemotypes, and seasons. Aside from this natural complexity, the term "toxin" is not clearly defined, because toxicity depends on dosage, and there are other forms of negative effects apart from acute toxicity, such as allergenic or mutagenic activity. Clearly, many PSMs also have beneficial effects on other organisms or humans or are not phytotoxic at all.[23,32] Finally, the research knowledge on toxic substances is frequently limited, and the available literature is partially inconsistent. The degree of toxicity and the plant abundance are two major factors that lead to research into a plant species, and often only a few plant species are investigated within a genus. As a consequence of these uncertainties, no concentrations, either in the plant species or in the environment, are included in the TPPT database, and PSMs with uncertain occurrence, either due to missing data or due to extreme natural variations, are marked accordingly.

Data Sources. Table 1 summarizes data sources that were combined from various scientific fields to compile first the toxic plant species together with their biological information, followed by the corresponding phytotoxin−toxic-plant-species relationships and phytotoxin structures. Besides these main data sources, a literature search was conducted to find journal articles specific for a plant species or PSM class and complement the phytotoxin−plant-species relationships. The data compilation is further detailed in the Supporting Information (SI), and individual references for each phytotoxin are provided in the databases. For the chemical information, we used PubChem[33] and ChemSpider,[34] and the molecular structures, including, if available, the stereochemistry, were compared between the two databases to avoid errors in the structure identification. The identifiers of these two chemical databases were also included, because they contain complementary information, as well as references to other databases. In cases where the possible structures or their stereochemistry were different, the structure from PubChem was preferred. Experimentally determined toxicity end points were also collected (for details, see the SI), resulting in a total of 318 measurements for 184 phytotoxins. All information was manually assembled from the mentioned sources. In a final step, all data fields were quality-controlled regarding the plausibility of the content and possible spelling mistakes.

TPPT-Database Setup. The setup of the TPPT database is visualized in Figure 1. The TPPT database is structured around two main data tables, the toxic-plant-species table and the phytotoxin table, which are indexed by internal numbers, and a superior table that relates the phytotoxins to the plant species. The toxic-plant table contains 17 data fields with biological information covering plant-

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Table 1. Data Sources Used to Compile the Information in the Toxic-Plants−Phytotoxins (TPPT) Database[a]

information	data sources
plant species and biological information (all naturally growing plant species in Switzerland)	compendium from Lauber et al.[43]
plant species and biological information (plant species toxic to humans)	textbook from Teuscher and Lindequist[23]
	textbook from Roth et al.[24]
plant species and biological information (plant species toxic to humans)	Clinical Toxicology (CliniTox) database[21]
plant species (invasive plant species)	National Data and Information Center on the Swiss Flora (info flora)[28]
	Swiss Ordinance on the Handling of Organisms in the Environment (Annex 2, list with prohibited invasive alien organisms)[49]
	EU Regulation No. 1143/2014 (list of invasive alien species of Union concern)[50]
phytotoxin−toxic-plant-species relationships	textbook from Teuscher and Lindequist[23]
	textbook from Roth et al.[24]
	KNApSAcK database[51]
	compendium from the European Food Safety Authority (EFSA)[20]
	CliniTox database[21]
	Web of Science literature search (individual scientific journals)

[a]For data-compilation details, see the SI.

species name and systematics as well as plant distribution, habitat, toxicity, and categorization (i.e., ornamental garden plant, agricultural plant, invasive neophyte, or naturally growing plant). The phytotoxin table contains 14 data fields for phytotoxin identification and chemical information and also the literature references for the phytotoxin−toxic-plant-species relationships. The phytotoxin−toxic-plant-species-relationships table defines the phytotoxin patterns, including the composition data field, which gives more information on the major toxin, uncertainty, and natural variations, as far as they are known (see Table 2). Additionally, a remarks table contains extra notes in a comment field and an approximate score describing the available scientific knowledge for a given plant genus. Table 2 gives a detailed content description and illustrative examples for each data field in the main database tables. Additional information, including experimental toxicity data, in silico property estimations, aquatic micropollution potential analysis, and corresponding literature references, are organized in subtables in the phytotoxin table.

The TPPT database was built with the common and fast open-source database software SQLite.[35] This SQL-based software supports most of standard SQL and, together with the file-based setup, allows individual adaptation of the TPPT database for a given purpose, the creation of different searches, or the exporting of single parts of the TPPT database. SQLite can be used with different interfaces, some of which are also free, and the database can also be accessed from different programming languages, such as R.[36,37] Additionally, we converted the database into the simpler, user-friendly Excel spreadsheet. The TPPT database can be downloaded from the following homepage: https://www.agroscope.admin.ch/agroscope/en/home/publications/apps/tppt.html.

In Silico Estimations of Physicochemical Properties and Toxicities. In environmental risk assessments, several properties of a substance are needed to estimate its exposure and effects. Because experimentally measured data are often not available for phytotoxins, we included outputs from four different estimations tools: The often applied software Estimation Program Interface (EPI) Suite from the U.S. EPA was used to predict most physicochemical properties, including several distribution and degradation parameters.[38] Although EPI Suite is often criticized for being inaccurate, it also has major advantages: it requires only the SMILES structure as input, it can be run in batch mode, and it is freely available.[6,39] Additional physicochemical parameters not available through EPI Suite, in particular the pK_a, were predicted with ACD/Percepta, ACD/Lab's Percepta Predictor software (Advanced Chemistry Development Inc.).[40] To characterize mammalian toxicity, ProTox was used, which predicts the rodent oral toxicity as the median lethal dose (LD_{50}) in milligrams per kilogram of body weight.[41] The ecotoxicity was predicted using the U.S. EPA's ecological structure−activity relationships (ECOSAR) predictive model (version 2.0), which estimates acute and chronic toxicity at the lethal median concentrations (LC_{50}) and chronic values for three model organisms: fish, daphnia, and green algae.[42] For all these tools, the applicability is limited, covering mostly only organic, uncharged, low-molecular weight (often <1000 g/mol) substances, and thus do not apply for all phytotoxins. Consequently, an applicability specification is given for each phytotoxin, but it should be noted that all predictions are fraught with some uncertainty. However, they fulfill the purpose of primary prioritization because there are also other uncertainties (e.g. those related to plants, see above). More details on the prediction tools, the included information, and descriptions of the data fields are provided in the SI.

Aquatic Micropollution Potential Assessment. We developed a prioritization system to evaluate the phytotoxins on the basis of their aquatic micropollution potentials, including (i) the phytotoxin occurrence, (ii) the environmental behavior based on aquatic

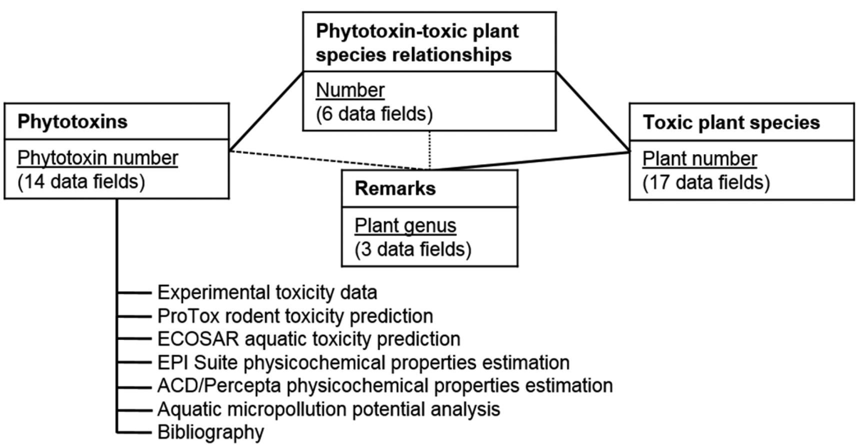

Figure 1. Visualization of the toxic-plant−phytotoxin (TPPT)-database setup with all the included tables. The four main tables are given together with the underlined primary keys and the numbers of included data fields in brackets. Individual fields are described in Table 2. Tables with additional information (i.e., experimental toxicity data, in silico property estimations, aquatic micropollution potential analysis, and bibliography) are subtables in the phytotoxin table and are described further in Tables S1−S6.

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Table 2. Description of the Individual Data Fields of the Main Tables in the Toxic-Plants–Phytotoxins (TPPT) Database Exemplified by the Phytotoxin Ptaquiloside

table	data field	content description	example
phytotoxins	phytotoxin number	continuous numbering of the phytotoxins, labeled with a T for toxins	T1433
phytotoxins	phytotoxin name	most common English name, important alternative names in brackets	ptaquiloside (braxin C)
phytotoxins	CASRN	Chemical Abstract Service Registry Number[a]	87625-62-5
phytotoxins	major plant genus	all plant genera that are included in the database and contain the phytotoxin	*Pteridium*
phytotoxins	additional plant genus	plant genera that produce the phytotoxin but are not included in the database because of low toxicity	—
phytotoxins	PSM class	plant-secondary-metabolite (PSM) classes to which the phytotoxin belongs[b]	terpene, sesquiterpene, norsesquiterpene
phytotoxins	InChIKey	short version of the IUPAC Chemical Identifier (InChI)	GPHSJPVUEZFIDE-YVPLJZHISA-N
phytotoxins	stereo SMILES	SMILES with stereoinformation[a]	C[C@@H]1C[C@]2(C=C(C3(CC3)[C@@]([C@H]2C1=O)(C)O)C)O[C@H]4[C@@H]([C@H]([C@@H]([C@H](O4)CO)O)O)O
phytotoxins	canonical SMILES	SMILES without stereoinformation[c]	—
phytotoxins	molecular formula	molecular formula including charge	$C_{20}H_{30}O_8$
phytotoxins	molecular weight	molecular weight (g/mol)	398.5
phytotoxins	ChemSpider_ID	ChemSpider identification number	10312775
phytotoxins	PubChem_CID	PubChem compound identification number	13962857
phytotoxins	references	all references used for the phytotoxin–plant-species-relationship assembly	Rasmussen et al. (2003),[52] Rasmussen et al. (2005),[14] Hoerger et al. (2009),[53] Teuscher and Lindequist (2010),[23] KNApSAcK database[51]
phytotoxin–toxic-plant-species relationships	number	continuous numbering	4183
phytotoxin–toxic-plant-species relationships	composition	additional information about the composition (e.g., major, minor, mix, possible) or the role (e.g., precursor, metabolite, aglycone)[a]	major toxin
toxic plant species	plant number	continuous numbering of the plant species, labeled with a P for plant species	P14
toxic plant species	Latin plant name	plant species name in Latin	*Pteridium aquilinum* (L.) Kuhn
toxic plant species	German plant name	plant species name in German[a]	Adlerfarn
toxic plant species	English plant name	plant species name in English[a]	bracken fern
toxic plant species	plant genus	genus of the plant species	*Pteridium*
toxic plant species	plant family	family of the plant species	Dennstaedtiaceae
toxic plant species	global spatial distribution	distribution of the plant within the world[d]	global
toxic plant species	Swiss frequency	percent of 10 km^2 areas in which the plant species is found (for Switzerland)	52
toxic plant species	Swiss appearance	distinction between alien and domestic plants in Switzerland	domestic
toxic plant species	vegetation type	type of vegetation in which the plant species grows[e]	forest plant
toxic plant species	blooming period	time period in which the plant species is blooming	July–Sept
toxic plant species	toxic plant part	definition of the toxic plant part[a,f]	whole plant
toxic plant species	human toxicity	approximate characterization of the toxic effect on humans[g]	toxic
toxic plant species	animal toxicity	approximate strength of the animal toxicity[h]	very strongly toxic
toxic plant species	invasive foreign	specification of whether a plant species is invasive[i]	—
toxic plant species	garden plant	information on whether a plant species is used as a garden plant (yes/—)	—
toxic plant species	agricultural plant	information on whether a plant species is used as an agricultural plant (yes/—)	—
remarks	plant genus	remarks are combined for the plant genus[j]	*Pteridium*
remarks	comment	data field for all kind of comments and additional information or specifications	Norsesquiterpenoids are toxic (carcinogenic); the major one is ptaquiloside. Further, the cyanogenic glycoside prunasin and the enzyme thiaminase are present.
remarks	scientific-knowledge-availability score	description of the knowledge found in the literature of the phytotoxin–plant-species relationships[k]	2.5

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Table 2. continued

[a]As available. [b]Different hierarchical degrees of nomenclature are given. [c]Only included if the phytotoxin has no stereocenters or if no stereoinformation is available. [d]Largely with continental resolution. [e]Options include meadow plant, forest plant, weed and ruderal plant, shore and marsh plant, fresh water plant, mountain plant, pioneer plant, xerophyte, and agricultural and ornamental garden plant. [f]For example, aerial part, bark, bulb, capsule, flower, fruit, herb, latex, leaf, pollen, rhizome, root, seed, tuber, whole plant, wood, or some more specific definitions. [g]For acute toxicity, the strength is given as weakly toxic, toxic, strongly toxic, very strongly toxic, or toxic (unknown strength); for all other impacts, the toxic effect is described: nontoxic, unknown, allergenic, skin-irritating, cytotoxic, estrogenic, phototoxic, stimulating, carcinogenic, or liver toxic. [h]Option include weakly toxic, toxic, strongly toxic, or very strongly toxic; for very specific toxins, the animal is also added. [i]Also includes law regulations for Switzerland and the European Union. [j]Additional plant genera that do not contain plant species in the database are remarked with a star. [k]Based on personal expert opinion. 0: The toxic plant is perceived as such, but no information or only indications about phytotoxins are available. 1: Some plant secondary metabolites (PSMs) are described; however, there is no information as to toxicity, total number of PSMs, or concentrations. 2: There is knowledge of the major phytotoxins regarding concentration or toxicity. 3: Perfect knowledge (not possible in reality). Also included are 1.5 and 2.5 for if the knowledge is somewhere in between.

persistence (P) and mobility (M), and (iii) the acute rodent and the acute aquatic toxicity. A similar prioritization method was implemented for regulatory purposes by the German Environment Agency.[7] Prior to the analysis, we removed ionic species and high MW substances (>1000 g/mol), because they are not in the applicability domains of the predictions tools. Furthermore, substances were removed if no predictions were possible for a needed parameter. This resulted in 1506 substances included in the prioritization.

First, minimal phytotoxin occurrence is required as a prerequisite for their environmental importance. It was semiquantitatively approximated via the occurrence of the corresponding phytotoxin-producing plants. To this end, the Swiss-frequency parameter included in the TPPT database from Lauber et al.,[43] which encodes the distribution of a plant species in Switzerland, was used to define an occurrence factor and derive more general occurrence categories: no, very low, low, medium, and high occurrence (for technical details, see the SI).

Second, the environmental behavior was assessed by adapting the PM scoring procedure from Arp et al. in a simplified manner.[6] The PM scoring uses the D_{oc}, the pH-dependent soil-organic-carbon−water partition coefficient (K_{oc}), as a measure of mobility, and the degradation half-life ($t_{1/2}$) as a measure of the aquatic persistence (including biodegradation and hydrolysis). In this prioritization, we only used estimated properties because of a lack of experimental data. Furthermore, phototransformation was omitted because no good quantitative structure−activity relationships (QSARs) were available, and volatilization was excluded because it is not a true persistence parameter.[6] The final classification distinguishes (i) the unproblematic compounds, including immobile compounds, unstable compounds, and transient compounds (immobile and unstable), from (ii) potentially relevant compounds, which are further classified in groups 1 to 5 with increasing importance (for technical details, see the SI).

Third, for the effect on mammalian species, the predicted and measured acute rodent toxicity (LD_{50}) was included, and for the effect on aquatic organisms, the predicted acute aquatic toxicity (LC_{50} or the half-maximal effective concentration, EC_{50}) was considered for the most sensitive species of fish, daphnia, and green algae. The substances were classified using the official system from the globally harmonized system of classification and labeling of chemicals (GHS; for details, see the SI).

All the phytotoxin information used in the prioritization is summarized in a combined table in the TPPT database, as defined in Table S6 in the SI. After performing the assessment for the individual phytotoxins, the phytotoxins were combined such that entire PSM classes were ranked according to the number of priority phytotoxins. Additionally, for all five parameters (i.e., phytotoxin occurrence, degradation half-life, log K_{oc} or log D_{oc}, acute rodent toxicity, and acute aquatic toxicity), sensitivity and uncertainty analyses were performed. The sensitivity analysis was completed by individually varying the parameters by a factor of 2 and assessing the changes in the prioritization. For the uncertainty analysis, the derived uncertainty factors from Strempel et al. were adapted,[5] and the minimum and maximum numbers of prioritized phytotoxins were determined.

RESULTS AND DISCUSSION

The TPPT database is a manually compiled and freely available database (downloadable from https://www.agroscope.admin.ch/agroscope/en/home/publications/apps/tppt.html) providing information about toxic plants in Central Europe and their phytotoxins. In total, 1586 phytotoxins produced by 844 plant species are included, which results in 6268 relationships between plant species and phytotoxins with a maximum of 30 phytotoxins per plant species. The strength of the TPPT database lies in the combination of the phytotoxin−plant-species relationships with detailed biological and chemical information.

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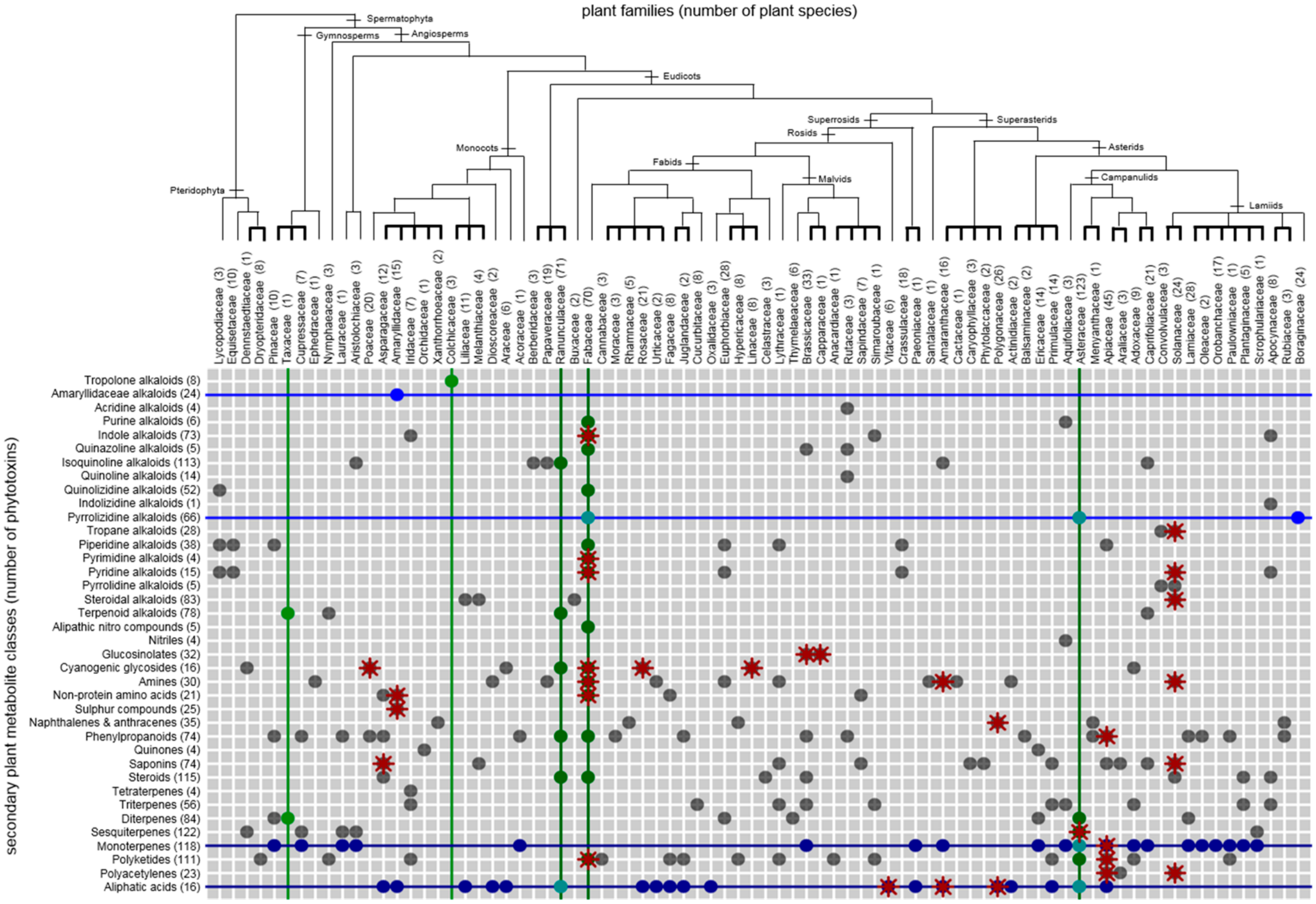

Figure 2. Distribution of the plant-secondary-metabolite (PSM) classes (*y*-axis) in the different plant families (*x*-axis). The brackets contain the number of phytotoxins for a PSM class and the number of plant species per plant family. In the genealogical tree, the thick branches combine the plant families into the systematic orders, for which the interrelationships are shown.[48] The gray dots show all combinations; the blue, green, and turquoise dots and lines indicate the examples discussed in the main text; and the red stars indicate agricultural plant species.

TPPT Database: Toxic Plant Species. Of the total 844 plant species, 69 are agricultural plants, 176 are garden plants (ornamental garden plants and herbs), 689 occur naturally in Switzerland (105 are also garden plants), and 13 do not grow in Switzerland but were included because of their global agricultural importance. These numbers suggest that roughly 20% of the naturally growing plant species (over 3600) in Switzerland produce some PSMs with adverse effects. Among all plants, 241 are alien species in Switzerland, and of these, 70 plant species are invasive: 14 are of priority importance in the European Union, and 15 are prohibited in Switzerland (3 are on both concern lists). Interestingly, of the 26 most concerning plants, only 14 are ornamental garden plants that evaded into the environment, whereas 4 are weed and ruderal plants, and even more concerning in the present context, 8 are invasive water plants. Most of the invasive species are generally assumed to be nontoxic to humans, but their aquatic toxicity is still unknown, and for some of the invasive species their toxicity is entirely unknown. Overall, according to the categorization in Lauber et al.,[43] only 5.2% of the plants in the TPPT database are very strongly toxic, and 9.0% are strongly toxic, but considerably more plants, namely 37%, are classified as medium toxic. The rest of the plant species are classified as weakly toxic (17%), allergenic (12%), toxic but not further classified (5.9%), nontoxic (4.5%), phototoxic (4.1%), carcinogenic (1.3%), unknown (1.2%), liver toxic (0.6%), estrogenic (0.4%), stimulating (0.4%), or cytotoxic (0.1%). The classification according to specific modes of action, such as carcinogenicity or liver toxicity, is not complete because many plants have not been tested systematically for them. Of all included toxic plant species, 46% occur in less than 10% of the area of Switzerland and only 15% occur in more than 50%, which is a consequence of the highly diverse vegetation zones in this country. The TPPT database contains additional biological information, such as the vegetation type, the blooming period, and the toxic plant part, which can be used to set up dedicated environmental-monitoring networks.

TPPT Database: Phytotoxins. For all plant species, 1586 phytotoxins were identified and classified into the different PSM classes, as indicated in Figure 2. The highest number of toxins is found for alkaloids and terpenes, which prevail among all PSMs, making up between 60 and 70%.[9] PSM classes with intermediate phytotoxin numbers are the steroids, saponins, phenylpropanoids, and polyketides. Steroids and saponins are glycosylated structures with mostly higher molecular weights, and parts of the structures are also synthesized from isoprene units such as the terpenes. Phenylpropanoids and polyketides are more diverse classes, including, among others, coumarins and lignans in the former and flavones, cannabinoids, and catechins in the latter. Several PSM classes only contain small numbers of individual substances, such as the glucosinolates or the cyanogenic compounds. Although the physicochemical

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properties within a PSM class are often similar, these properties cover a broad range across all classes: the molecular weights range between 31 and 1968 g/mol and are most often between 300 and 400 g/mol, the in silico estimated log K_{ow} values range between −10.45 and 13.59 (which goes beyond the applicability domain of KOWWIN[38]) with an average of 1.89, and the numbers of functional groups also vary with up to 26 hydrogen-bond donors and up to 49 hydrogen-bond acceptors. The corresponding distribution curves are shown in Figure S1. Finally, it should be noted that the absolute number of phytotoxins in a PSM class is no indicator of their overall environmental risk, but rather the physicochemical and toxicological properties of the different PSM classes are relevant, as discussed in the case study below.

TPPT Database: Phytotoxin−Toxic-Plant-Species Relationships. Figure 2 assigns the different PSM classes to the taxonomic plant families, showing that the prevalences within plant families vary strongly for different PSM classes. Whereas some PSM classes have broad distributions, such as those of the aliphatic acids or monoterpenes (Figure 2, dark blue lines), other classes are limited to a small number of plant families, as it is the case for most alkaloids (e.g., Amaryllidaceae alkaloids or pyrrolizidine alkaloids; Figure 2, light blue lines). A broad distribution might be attributed to either an early phylogenetic development, or to a convergence in plant evolution. Detailed discussions of the evolution of PSMs and their distribution in different plants are given elsewhere, for example, by Wink.[9]

Asteraceae, Ranunculaceae, and Fabaceae are plant families with very high numbers of toxic plant species (over 50 species per plant family; Figure 2, dark green lines). However, whereas the Fabaceae have a large variability of PSM classes (Figure 2), the Asteraceae and Ranunculaceae contain only small numbers of PSM classes. For instance, the Asteraceae produce mostly pyrrolizidine alkaloids and terpenes. The other extreme includes the plant families with only a few toxic plant species, but several of them are very important due to their high toxicity. For example, the English yew (*Taxus baccata*, Taxaceae; Figure 2, light green) is often grown in gardens, and the autumn crocus (*Colchicum autumnale*, Colchicaceae; Figure 2, light green) is problematic because of confusion with wild garlic (*Allium ursinum*, Amaryllidaceae). Overall, for only approximately 10% of the plants, no data on the occurrence of toxic PSMs are available. For the majority of the PSM classes with adverse effects, some phytotoxins are known, although the number of known phytotoxins may still vary. Figure 2 also demonstrates the high PSM-class variability in agricultural plants (Figure 2, red stars): there are steroidal alkaloids in potato; pyridine alkaloids in tobacco; monoterpenes and phenylpropanoids in many herbs, including dill, coriander, and parsley; glucosinolates in cabbages; and cyanogenic glycosides in many fruits, including apple and peach.

TPPT Database: Limitations. We compiled the TPPT database to the best of our knowledge; however, it is practically impossible to generate a complete database, and expert judgements were needed in case of contradictory data. Regarding the phytotoxin−toxic-plant-species relationships, a false-positive uncertainty exists because of the possible inclusion of less relevant phytotoxins, and a false-negative uncertainty exists as a result of the absence of information about not-yet-recognized but relevant phytotoxins. Several causes add to these uncertainties, including limited data availability, conflicting literature data, and biological variations such as spatial differences or subspecies. To account for these uncertainties, we included a comment field and a scientific-knowledge-availability score, reflecting the number of references for a certain plant genus, and some data fields were even left blank. Finally, the TPPT database can be updated and extended whenever new research data are available.

Although much information is included in the TPPT database, a remarkable part of it, in particular the phytotoxins' physicochemical properties and toxicity, is in silico estimations and not (yet) experimentally measured data. These estimations provide the first approximations of the properties and some rather good calculations (e.g., ptaquiloside has a predicted log K_{ow} of −0.95 and a measured log K_{ow} of −0.68),[14] but they need to be evaluated critically. Compared with typical anthropogenic substances, phytotoxins often have higher molecular weights and are more ionizable with more functional groups, which also indicates that they are underrepresented in QSAR-calibration data sets. Therefore, two prerequisites are required before QSAR estimations can reliably be performed for phytotoxins: first, measurements need to be performed to generate experimental data, and second, the QSAR applicability domain needs to be expanded and validated using the experimental data. For now, the implementation of these prerequisites would exceed the scope of this paper, but they are necessary for more in-depth environmental risk assessments.

Assessment of Phytotoxins with Respect to Their PMT Characteristics. For the assessment of the phytotoxins' PMT characteristics, four primary properties were taken into consideration: the shortest degradation half-life, the pH-dependent K_{oc}, the acute rodent toxicity, and the acute aquatic toxicity. The distributions of these properties, shown in Figure 3, largely follow those of anthropogenic chemicals, as presented, for example, by Strempel et al.[5] Differences exist for the pH-dependent K_{oc} (Figure 3b), which tends to be higher, and the half-life (Figure 3a), where it becomes visible that the phytotoxins generally have higher degradability. Most probably, the persistence would even further decrease if a more appropriate QSAR for hydrolysis half-life estimations were available. The half-life is also the most sensitive property, as indicated by the dark shaded area in Figure 3a, but the toxicity predictions are much more uncertain despite low sensitivities (Figure 3c,d).

For the assessment of the environmental behavior, the phytotoxins were classified according to the PM characteristics from Arp et al.,[6] and the resulting classification of the phytotoxins in terms of aquatic persistence and mobility is shown in Figure 4a,b, respectively. The classified aquatic persistence is either relatively high (P4) or low (P1), for which the major degradation mechanism is biodegradation, accounting for over 98% of the shortest half-lives. Regarding the mobility, the classification provides evidence that most phytotoxins are mobile in the environment, with over 1000 compounds in the most mobile (M5) category. This reflects the generally high polarity of PSMs and the corresponding low number of nonionizable compounds (39%). Even several terpene classes with a generally low water solubility are mobile in the environment because of the high number of oxygen atoms. The classification in the combined PM score is shown in Figure 4c. The environmentally less relevant categories (transient, unstable, and immobile) make up almost 37% as a result of the high number of rapidly degradable phytotoxins. Including the uncertainty analysis, the values range between 17 and 65%, which is a broad range and the result of a very sensitive degradation half-life, as indicated in Figure 3b.

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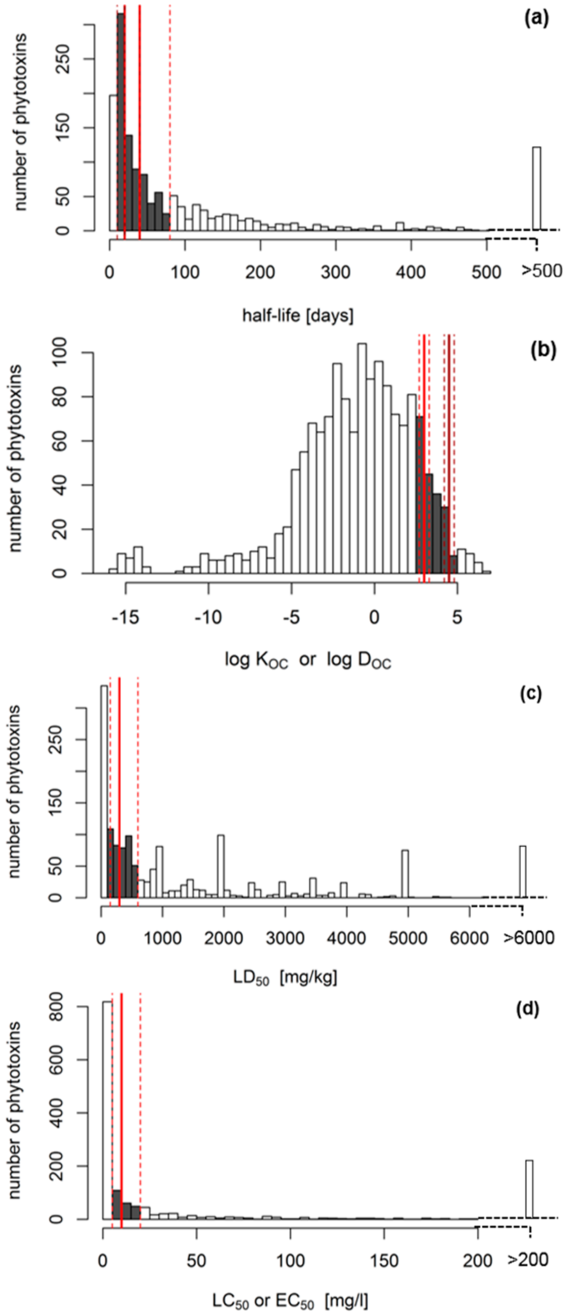

Figure 3. Distribution and sensitivities of the included phytotoxins within the four primary PMT properties: (a) degradation half-life, (b) soil-organic-carbon−water-partition coefficient (K_{oc}) or pH-dependent soil-organic-carbon−water-partition coefficient (D_{oc}), (c) acute rodent toxicity (median lethal dose, LD_{50}), and (d) acute aquatic toxicity (lethal median concentration, LC_{50}, or half-maximal effective concentration, EC_{50}). In each panel, the red line indicates the threshold in the prioritization procedure, the dashed lines indicate the sensitivity range defined by a factor of 2 around the threshold, and the filled columns point out the affected range of the data. For (a,b), two thresholds are included, a more cautious dark-red one and a less cautious brighter-red one.

However, phytotoxins with high production and release might still accumulate and as such maintain relatively high steady-state concentrations. Consistently, the most critical score, PM5, accounts for 40%, ranging between 15 and 68%, including the uncertainties. The classification largely reflects the P score, whereas the M score has a minor influence because most of the compounds are mobile. The estimation of degradation half-lives should therefore be evaluated even more critically. This classification is also in accordance with the results from Arp et al. in the analysis of anthropogenic compounds.[6] Although this is a preliminary analysis with high uncertainties, the high fraction of prioritized phytotoxins should raise concerns about their impact on the aquatic environment. The most critical PSM classes in terms of environmental behavior include several alkaloid classes, steroids, and saponins (see Table S9). Other PSM classes have more varying properties, but diterpenes, triterpenes, sesquiterpenes, polyketides, and naphthalene- and anthracene-derivatives might also be potentially relevant. Generally, of less importance are aliphatic acids, cyanogenic glycosides, polyacetylenes, nonprotein amino acids and amines, glucosinolates, phenylpropanoids, sulfur compounds, monoterpenes, and other small-molecular-weight alkaloids, which mostly degrade fast.

To assess the impacts on organisms, the toxicities of the phytotoxins were assessed. The rodent and aquatic toxicities were evaluated on the basis of the classes of the GHS and were shown to be uncorrelated to each other (see Figure S3). The acute rodent toxicity, based on measured and predicted ProTox data, showed the following classification according to GHS for acute toxicity to humans: 18, 41, 18, 12, and 5% in GHS classes 5, 4, 3, 2, and 1 (with increasing toxicity) respectively; 6% were nontoxic according GHS categorization (Figure S2a). This classification is also reflected by the ProTox training set.[41] Interestingly, only a small fraction of the toxins are strongly toxic, but over 40% are only in category 4. By far the most toxic PSM class seems to be steroids, followed by certain alkaloids and saponins (see Table S9). For the aquatic toxicity, a different distribution into the GHS classes for substances with acute hazard to the aquatic environment was found: 20% were in the least toxic GHS class, 3; 22% were in GHS class 2; 39% were in the most toxic GHS class, 1; and 20% were predicted to be non-ecotoxic (Figure S2b). Here, a major portion of the phytotoxins are classified in the worst category and are therefore highly relevant. Overall, green algae were predicted to be most sensitive, accounting for 53% of the lowest toxicities, followed by daphnia (26%) and fish (21%). The most ecotoxic classes are again alkaloids but also several terpenes, polyacetylenes, phenylpropanoids, and polyketides, whereas the steroids and saponins seem to be less critical compared with the acute rodent toxicity (see Table S9).

Prioritization of Phytotoxins According to Their Aquatic Micropollution Potentials and Identification of the Most Critical PSM Classes. Finally, we combined the prerequisite of a general phytotoxin occurrence with the PM scoring and toxicity in a simple qualitative risk assessment to identify the most critical PSM classes for the aquatic environment. A prioritization procedure was performed by setting a limit for each of the three characteristics, as shown in Figure 5. The phytotoxin occurrence was taken as the first prioritization step, because the general occurrence is a prerequisite for any micropollution potential, and phytotoxins with medium or high occurrence (65% in total) were regarded as potentially the most relevant (more details are found in the SI). Therefore, 526 phytotoxins were removed in this step. For now, we used the plant distribution in Switzerland to derive the phytotoxins' occurrence, but for a more in-depth assessment the plant abundance and phytotoxin concentrations

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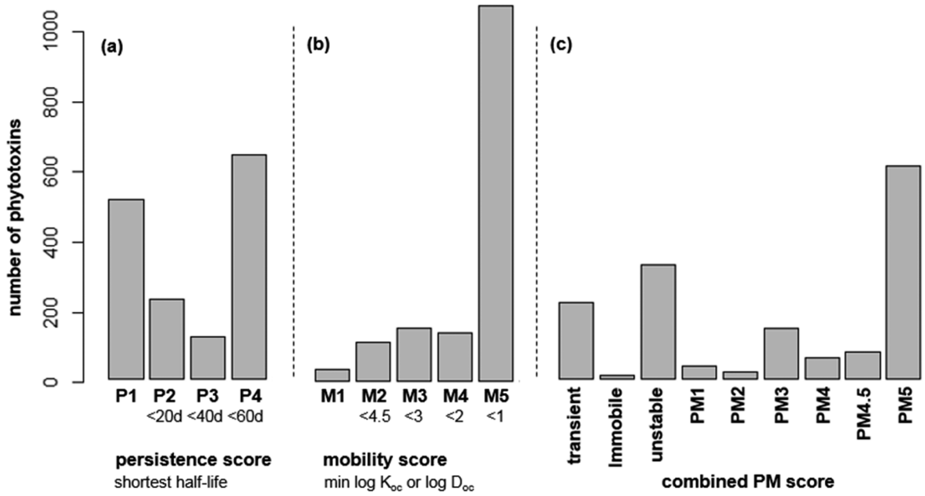

Figure 4. Classification of phytotoxins according to (a) aquatic persistence (P) score, (b) mobility (M) score, and (c) combined PM score based on Arp et al.[6] The phytotoxins are categorized with increasing importance according to the shortest half-life (given in days) for aquatic persistence and to the minimal logarithmic soil-organic-carbon—water-partition coefficient (log K_{oc}) or the pH-dependent soil-organic-carbon—water-partition coefficient (log D_{oc}) for the mobility. The combined PM scores differentiate transient, immobile, unstable, and potential aquatic micropollutants with increasing importance (from 1 to 5).

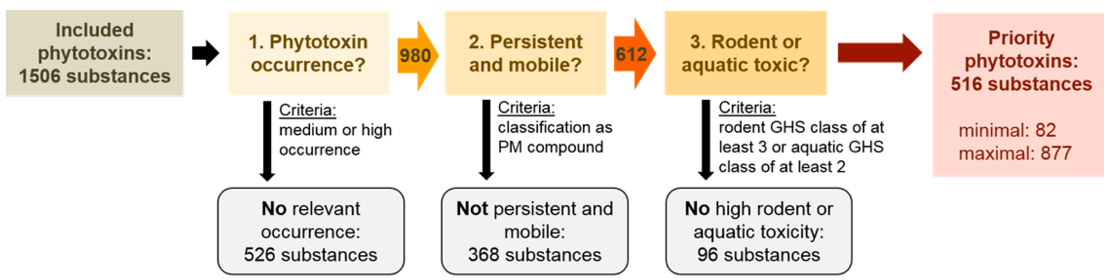

Figure 5. Scheme of the prioritization procedure combining phytotoxin occurrence, environmental behavior, and toxicity to identify phytotoxins of possible relevance for the safety of the aquatic environment in Central Europe. The number of excluded phytotoxins in each step is stated together with the starting number and the prioritized number. For details, see the text.

in the plants would be necessary. Furthermore, rarely occurring phytotoxins might also pose a local risk in plant hot-spots and catchment areas without much dilution and should not be fully ignored in more extensive assessments. In the second prioritization step, all phytotoxins were removed that were either not persistent or not mobile (i.e., were not classified into a PM category), which included 368 phytotoxins. And in the last step, 96 phytotoxins were removed, because they were neither harmful in terms of acute rodent toxicity (GHS category 4 or less) nor ecotoxic (GHS category 3 or less). On this basis, 516 phytotoxins of priority remained; taking the uncertainty into account resulted in a minimum of 82 phytotoxins and a maximum of 877 phytotoxins. This high uncertainty is caused by the very sensitive half-life estimations and the uncertain toxicity estimations (see above). The average number of prioritized phytotoxins corresponds to over 34% of all phytotoxins in the TPPT database and is a remarkably high number. It should be kept in mind that the prioritization is mainly based on predicted properties, and only a subset of all worldwide produced phytotoxins is included. However, even if only a small fraction of the potentially relevant phytotoxins are actually present in the aquatic environment, they might sum up and pose a risk.

Table 3 ranks PSM classes according to the percentage of individual plant toxins prioritized in the above procedure (a complete list is presented in Table S10). It clearly shows that alkaloids; terpenes, including steroids and saponins; and partially polyketides are potentially the most relevant for the aquatic environment. These PSM classes contain high numbers of toxic, frequently produced, mobile, and persistent phytotoxins, which are important to consider in monitoring programs and risk assessments. Several PSM classes are supposed to be unproblematic, either because of low production by local plants or fast degradation in the environment, which applies, for instance, to cyanogenic glycosides and glucosinolates that are often produced by agricultural plants.

To evaluate the prioritization, we analyzed the classification of some phytotoxins for which one or several environmental case studies were found in the literature. Rasmussen et al. analyzed the environmental behavior of the carcinogenic ptaquiloside and concluded that this norsesquiterpene could possibly leach into the aquatic environment depending on soil type, temperature, and most crucially the pH.[44] Correctly, this phytotoxin was prioritized in the present risk assessment. Artemisinin is another prioritized sesquiterpene which is further used as an antimalaria drug and for which the detected soil concentrations were found to be in the range of toxic-effect concentrations.[45] Also prioritized were estrogenic isoflavones; for example, formononetin was regularly detected in the drainage water of a red clover field and even in river waters.[13] An example of an unprioritized phytotoxin is juglone, which is

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Table 3. Ranking of the Potentially Relevant Plant-Secondary-Metabolite (PSM) Classes According to the Number of Priority Phytotoxins That Were Identified by the Procedure Described in the Text[a]

PSM class	total phytotoxins included	prioritized phytotoxins	examples
steroids	115	56	digitoxigenin, strophanthidin
terpenoid alkaloids	77	52	aconitine, taxine B
pyrrolizidine alkaloids	65	48	lycopsamine, heliosupine
steroidal alkaloids	81	45	protoveratrine A, cyclobuxine D
isoquinoline alkaloids	89	45	protopine
quinolizidine alkaloids	52	34	lupanine, sparteine
sesquiterpenes	122	31	ptaquiloside, artabsin
polyketides	110	30	formononetin, lupulone
indole alkaloids	72	27	vincamine
triterpenes	56	26	cucurbitacin B, elaterinide
diterpenes	83	26	baccatin III, mezerein
Amaryllidaceae alkaloids	23	19	galanthamine, lycorine

[a]Examples of specific phytotoxins are also given. A table with all PSM classes and a figure of all exemplified chemical structures are given in Table S10 and Figure S5, respectively.

a toxic napthoquinone (phenylpropanoid) produced by walnut trees. Von Kiparski et al. found that juglone is microbially and abiotically degradable and actually quite short-lived in soils with microbial activity, which is consistent with the estimated biodegradation half-life of 12 h.[46] However, juglone was found in soils beneath walnut trees and von Kiparski et al. concluded that juglone can still accumulate in soils with low microbial activity because of the high amounts released.[46] Correctly, juglone is not prioritized here because the degradation in water is usually even faster and no accumulation is possible. The two major potato plant glycoalkaloids, α-solanine and α-chaconine (steroidal alkaloids), were also not prioritized, which is in accordance with the results found by Jensen et al.[12] Their results indicated low leaching potential because no glycoalkaloids were detected in the groundwater despite concentrations of up to 25 kg/ha in the plants themselves. However, these two glycoalkaloids were excluded in the prioritization procedure because of low occurrence, but they were classified in the highest PM category (PM 5), which indicates an erroneous PM classification. In fact, in silico estimations for higher-molecular-weight compounds with several sugar units are generally not very precise and are probably outside the application domain. However, for many PSM classes, no environmental-behavior studies were found, particularly for many important PSM classes, such as most alkaloids.

Although the above examples illustrate the general plausibility of the proposed prioritization procedure and also its limitations, its actual predictive power remains to be evaluated with monitoring campaigns that include plant toxins. For the time being, several PSM classes could be identified for which further investigations should be done, and this work provides a starting point for this endeavor. Overall, the TPPT database was shown to be useful for preliminary risk assessments. Furthermore, the TPPT database is expected to be of value in other fields dealing with toxic plants and their toxins and might be applied by environmental scientists, food scientists, veterinary scientists, biologists, or toxicologists. For example, in the Marie Skłodowska-Curie Innovative Training Network NaToxAq, which focuses on natural toxins in the aquatic environment, the TPPT database is applied in the phytotoxin investigations.[47] To conclude, we would like to emphasize the necessity for further research on phytotoxins in the environment because we found over 34% to be potential aquatic micropollutants. There is a need for, on the one hand, better estimations and more measured property data to enable more precise estimations and, on the other hand, monitoring programs actually including phytotoxins as target or suspect analytes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jafc.8b01639.

Methodological details on data compilation, measured toxicity data, in silico physicochemical-property estimations (EPI Suite and ACD/Percepta), in silico rodent-toxicity prediction (ProTox), in silico aquatic toxicity predictions (ECOSAR), occurrence analysis, PMT analysis, sensitivity and uncertainty analysis, and descriptions of all data fields in the TPPT database; further results including distributions of different physicochemical properties among all phytotoxins, distributions of phytotoxins in the occurrence and toxicity categories, comparison of the acute rodent toxicity and the acute aquatic toxicity, details on the sensitivity and uncertainty analyses, characterization of PSM classes and resulting prioritization, and chemical structures of phytotoxins discussed in the main text (PDF)

TPPT database (XLSX)

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