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Pim de Voogt *Editor*

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Reviews of Environmental Contamination and Toxicology Volume 253

Editor
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Foreword

International concern in scientific, industrial, and governmental communities over traces of xenobiotics in foods and in both abiotic and biotic environments has justified the present triumvirate of specialized publications in this field: comprehensive reviews, rapidly published research papers and progress reports, and archival documentations These three international publications are integrated and scheduled to provide the coherency essential for nonduplicative and current progress in a field as dynamic and complex as environmental contamination and toxicology. This series is reserved exclusively for the diversified literature on "toxic" chemicals in our food, our feeds, our homes, recreational and working surroundings, our domestic animals, our wildlife, and ourselves. Tremendous efforts worldwide have been mobilized to evaluate the nature, presence, magnitude, fate, and toxicology of the chemicals loosed upon the Earth. Among the sequelae of this broad new emphasis is an undeniable need for an articulated set of authoritative publications, where one can find the latest important world literature produced by these emerging areas of science together with documentation of pertinent ancillary legislation.

Research directors and legislative or administrative advisers do not have the time to scan the escalating number of technical publications that may contain articles important to current responsibility. Rather, these individuals need the background provided by detailed reviews and the assurance that the latest information is made available to them, all with minimal literature searching. Similarly, the scientist assigned or attracted to a new problem is required to glean all literature pertinent to the task, to publish new developments or important new experimental details quickly, to inform others of findings that might alter their own efforts, and eventually to publish all his/her supporting data and conclusions for archival purposes.

In the fields of environmental contamination and toxicology, the sum of these concerns and responsibilities is decisively addressed by the uniform, encompassing, and timely publication format of the Springer triumvirate:

Reviews of Environmental Contamination and Toxicology [Vol. 1 through 97 (1962–1986) as Residue Reviews] for detailed review articles concerned with any aspects of chemical contaminants, including pesticides, in the total environment with toxicological considerations and consequences.

Bulletin of Environmental Contamination and Toxicology (Vol. 1 in 1966) for rapid publication of short reports of significant advances and discoveries in the fields of air, soil, water, and food contamination and pollution as well as methodology and other disciplines concerned with the introduction, presence, and effects of toxicants in the total environment.

Archives of Environmental Contamination and Toxicology (Vol. 1 in 1973) for important complete articles emphasizing and describing original experimental or theoretical research work pertaining to the scientific aspects of chemical contaminants in the environment.

The individual editors of these three publications comprise the joint Coordinating Board of Editors with referral within the board of manuscripts submitted to one publication but deemed by major emphasis or length more suitable for one of the others.

Coordinating Board of Editors

Preface

The role of *Reviews* is to publish detailed scientific review articles on all aspects of environmental contamination and associated (eco)toxicological consequences. Such articles facilitate the often complex task of accessing and interpreting cogent scientific data within the confines of one or more closely related research fields.

In the 50+ years since *Reviews of Environmental Contamination and Toxicology* (formerly *Residue Reviews)* was first published, the number, scope, and complexity of environmental pollution incidents have grown unabated. During this entire period, the emphasis has been on publishing articles that address the presence and toxicity of environmental contaminants. New research is published each year on a myriad of environmental pollution issues facing people worldwide. This fact, and the routine discovery and reporting of emerging contaminants and new environmental contamination cases, creates an increasingly important function for *Reviews.* The staggering volume of scientific literature demands remedy by which data can be synthesized and made available to readers in an abridged form. *Reviews* addresses this need and provides detailed reviews worldwide to key scientists and science or policy administrators, whether employed by government, universities, nongovernmental organizations, or the private sector.

There is a panoply of environmental issues and concerns on which many scientists have focused their research in past years. The scope of this list is quite broad, encompassing environmental events globally that affect marine and terrestrial ecosystems; biotic and abiotic environments; impacts on plants, humans, and wildlife; and pollutants, both chemical and radioactive; as well as the ravages of environmental disease in virtually all environmental media (soil, water, air). New or enhanced safety and environmental concerns have emerged in the last decade to be added to incidents covered by the media, studied by scientists, and addressed by governmental and private institutions. Among these are events so striking that they are creating a paradigm shift. Two in particular are at the center of ever increasing media as well as scientific attention: bioterrorism and global warming. Unfortunately, these very worrisome issues are now superimposed on the already extensive list of ongoing environmental challenges.

The ultimate role of publishing scientific environmental research is to enhance understanding of the environment in ways that allow the public to be better informed or, in other words, to enable the public to have access to sufficient information. Because the public gets most of its information on science and technology from internet, TV news, and reports, the role for scientists as interpreters and brokers of scientific information to the public will grow rather than diminish. Environmentalism is an important global political force, resulting in the emergence of multinational consortia to control pollution and the evolution of the environmental ethic. Will the new politics of the twenty-first century involve a consortium of technologists and environmentalists, or a progressive confrontation? These matters are of genuine concern to governmental agencies and legislative bodies around the world.

For those who make the decisions about how our planet is managed, there is an ongoing need for continual surveillance and intelligent controls to avoid endangering the environment, public health, and wildlife. Ensuring safety-in-use of the many chemicals involved in our highly industrialized culture is a dynamic challenge, because the old, established materials are continually being displaced by newly developed molecules more acceptable to federal and state regulatory agencies, public health officials, and environmentalists. New legislation that will deal in an appropriate manner with this challenge is currently in the making or has been implemented recently, such as the REACH legislation in Europe. These regulations demand scientifically sound and documented dossiers on new chemicals.

Reviews publishes synoptic articles designed to treat the presence, fate, and, if possible, the safety of xenobiotics in any segment of the environment. These reviews can be either general or specific, but properly lie in the domains of analytical chemistry and its methodology, biochemistry, human and animal medicine, legislation, pharmacology, physiology, (eco)toxicology, and regulation. Certain affairs in food technology concerned specifically with pesticide and other food-additive problems may also be appropriate.

Because manuscripts are published in the order in which they are received in final form, it may seem that some important aspects have been neglected at times. However, these apparent omissions are recognized, and pertinent manuscripts are likely in preparation or planned. The field is so very large and the interests in it are so varied that the editor and the editorial board earnestly solicit authors and suggestions of underrepresented topics to make this international book series yet more useful and worthwhile.

Justification for the preparation of any review for this book series is that it deals with some aspect of the many real problems arising from the presence of anthropogenic chemicals in our surroundings. Thus, manuscripts may encompass case studies from any country. Additionally, chemical contamination in any manner of air, water, soil, or plant or animal life is within these objectives and their scope.

Manuscripts are often contributed by invitation. However, nominations for new topics or topics in areas that are rapidly advancing are welcome. Preliminary communication with the Editor-in-Chief is recommended before volunteered review manuscripts are submitted. *Reviews* is registered in WebofScience™.

Inclusion in the Science Citation Index serves to encourage scientists in academia to contribute to the series. The impact factor in recent years has increased from 2.5 in 2009 to 7.0 in 2017. The Editor-in-Chief and the Editorial Board strive for a further increase of the journal impact factor by actively inviting authors to submit manuscripts.

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Feeding Behavioural Studies with Freshwater *Gammarus* spp.: The Importance of a Standardised Methodology

Giulia Consolandi, Alex T. Ford, and Michelle C. Bloor

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Abbreviation

AFDW Ash-free dry weight

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1 Introduction

Freshwater Gammarids are common leaf-shredding detritivores, and they usually feed on naturally conditioned organic material, in other words leaf litter that is characterised by an increased palatability, due to the action and presence of micro-organisms (Chaumot et al. 2015; Cummins 1974: Maltby et al. 2002). *Gammarus* spp. are biologically omnivorous organisms, so they are involved in shredding leaf litter and are also prone to cannibalism, predation behaviour (Kelly et al. 2002) and coprophagy when juveniles (McCahon and Pascoe 1988). *Gammarus* spp. is a keystone species (Woodward et al. 2008), and it plays an important role in the decomposition of organic matter (Alonso et al. 2009; Bundschuh et al. 2013) and is also a noteworthy prey for fish and birds (Andrén and Eriksson Wiklund 2013; Blarer and Burkhardt-Holm 2016). Gammarids are considered to be fairly sensitive to different contaminants (Ashauer et al. 2010; Bloor et al. 2005; Felten et al. 2008a; Lahive et al. 2015; Kunz et al. 2010); in fact Amphipods have been reported to be one of the most sensitive orders to metals and organic compounds (Wogram and Liess 2001), which makes them representative test organisms for ecotoxicological studies and valid sentinel species for assessing water quality status (Garcia-Galan et al. 2017).

Since Gammarids play an important role in the breakdown of organic matter in freshwater environments, it is understandable that their feeding behaviour is often used as a sublethal endpoint, to investigate water quality status and the effects of different contaminant types (Crane and Maltby 1991). Gammarid feeding activity could be altered by the presence of contaminants in the water, which could potentially alter their food source, influence the organism's biological function and cause abnormal behavioural responses. These types of feeding investigation have been carried out as in situ (i.e. directly in the environment) and ex situ (i.e. in the laboratory) studies (Bundschuh et al. 2011b; Dedourge-Geffard et al. 2009; Maltby et al. 2002; Zubrod et al. 2015). It has been demonstrated that feeding assays using Gammarids are representative of natural leaf decomposition in the environment (Maltby et al. 2002) and could be used to assess the effects of chemical contaminants and also understand the consequences of new-generation contaminants, such as plastic debris in freshwater environments (Blarer and Burkhardt-Holm 2016; Weber et al. 2018). Even though feeding behaviour studies have been carried out for almost half a century, there is a lack of standardisation for both ex situ and in situ methods. Without standardisation, there is a risk that the effects of a test substance could be under- or overestimated during in situ and ex situ approaches, which could reduce their usefulness in environmental biomonitoring programs. This paper aims to review the literature on feeding as an endpoint for amphipod ecotoxicology, by highlighting disparities in the published methodologies, and to help develop standardised protocols. Peer-reviewed literature was accessed through search engines, databases and library archives. In general, most feeding studies have reported four main stages: (1) acclimation period, (2) food preparation, (3) exposure and (4) end of the experiment and feeding rate calculation. The aforementioned four

stages have been reviewed separately, and the variability of the published methodologies has been considered, in order to draw attention to the current discrepancies in the literature.

2 Acclimation Conditions

The first stage of an experiment (both in situ and ex situ) is the acclimation period that should be used to acclimate the organisms to the experimental conditions. However, the acclimation conditions are not always fully disclosed, and when they are, they sometimes contradict the experimental conditions. The reproducibility of an experiment is also highly dependent on many abiotic and biotic factors, which are rarely taken into consideration for Gammarid feeding studies (Coulaud et al. 2011). In the following sections, different variables (duration, temperature, light/dark cycles, type of water and organisms) that could impact the outcome of an experiment have been reviewed separately and summarised in Table 1, in order to emphasise the full range of variability within the literature. In some studies, Gammarids are sourced from laboratory breeding programs (e.g. Blockwell et al. 1996; Bloor and Banks 2006a, b; McCahon and Pascoe 1988).

2.1 Duration

Acclimation periods vary depending on the study (see Table 1), for example, Agatz et al. (2014) kept specimens of *Gammarus pulex* in the laboratory for 3 days prior to the start of the experiment, whereas another study left *Gammarus fossarum* organisms to acclimate for 21 days (Garcia-Galan et al. 2017). Typically the acclimation period used for Gammarids appears to be between 5 and 7 days, but some studies have selected longer intervals up to 35 days (see Table 1). Agatz and Brown (2014) stated that a 1-day acclimation period helped to reduce the variability of their results by just 1.6%, suggesting that a longer acclimation period could potentially have an even greater impact on reducing the intraspecific variability and consequently strengthen the statistics. Although experimental controls are incorporated into the majority of experimental designs, it becomes difficult to compare published peer-reviewed research when the test organisms have experienced anything between 3 and 35 days acclimation to laboratory conditions (Agatz et al. 2014; Garcia-Galan et al. 2017) (see Table 1), even more so when the organisms are used as water quality biomonitors for in situ experiments (see Table 1).

Table 1 Existing differences in the literature regarding *Gammarus* spp. acclimation conditions

Test organism	Age/sex/size organism	Duration	Temperature	Light/dark cycle	Type of water Aeration pH	Type of study	References
Gammarus fossarum	Free from parasites No gravid females	7 days	16°C	12:12	Mixed water Aerated	Feeding and assimilation study	Blarer and Burkhardt-Holm (2016)
Gammarus fossarum	Adults with a cephalothorax length between 1.2 and 1.6 mm	7 days	15°C		River water	Feeding preferences study	Bundschuh et al. (2009)
Gammarus fossarum	Conducted as described by Bundschuh et al. (2009)					Feeding rate study	Bundschuh et al. (2011a)
Gammarus fossarum	Free from parasites Adults with a cephalothorax length between 1.2 and 1.6 mm	7 days	15°C		River water	Feeding rate study	Bundschuh et al. (2011b)
Gammarus fossarum	Free from parasites No gravid females Adults with a cephalothorax length between 1.2 and 1.6 mm	7 days	15°C		River water	Feeding rate study	Bundschuh et al. (2013)
Gammarus fossarum	Adults with a cephalothorax length between 1.2 and 1.6 mm	7 days	15°C	Total darkness	River and tap water mixture	Feeding behavioural study	Bundschuh et al. (2017)
Gammarus fossarum	Juveniles and adult males	15 days	12°C	10:14	Groundwater mixed with osmosed water Aerated	Ex situ and in situ feeding assay	Coulaud et al. (2011)
Gammarus fossarum	Dry mass = 6.8 ± 0.7 mg	7 days	10°C			Decomposition and feeding rate study	Danger et al. (2012)

Gammarus fossarum		20–25 days	12°C	10:14	Drilled groundwater Aerated	In situ feeding experiment	Dedourge-Geffard et al. (2009)
Gammarus fossarum	Adult males	21 days	12°C	10:14	Groundwater Aerated	Bioaccumulation study	Garcia-Galan et al. (2017)
Gammarus fossarum	Adult females	30–35 days	12°C	16:08	Drilled groundwater Aerated	Reproductive cycle and feeding study	Geffard et al. (2010)
Gammarus fossarum	Adult males with diameter from 1.6 to 2.0 mm	7 days	16°C	Total darkness	SAM-5S medium	Feeding rate study	Newton et al. (2018)
Gammarus fossarum		10 days	12°C	8:16	Drilled groundwater Aerated	Feeding behaviour and biomarkers analysis	Xuereb et al. (2009)
Gammarus fossarum	Free from parasites Adults with a cephalothorax length between 1.2 and 1.6 mm	7 days	15°C		River water Aerated	Feeding, accumulation and growth study	Zubrod et al. (2010)
Gammarus fossarum	Free from parasites Adult males (6–8 mm)	7 days	20°C	Total darkness	Aerated medium	Feeding and survival study	Zubrod et al. (2014)
Gammarus fossarum	Free from parasites Adult males (6–8 mm)	7 days	16°C	Total darkness	SAM-5S medium Aerated	Toxicity and feeding study	Zubrod et al. (2015)
Gammarus fossarum	Free from parasites Different sizes	3 days	16°C		SAM-5S medium Aerated	Feeding behavioural and physiological responses	Zubrod et al. (2017)
Gammarus pseudolimnaeus	Juveniles and adults					Feeding behavioural study	Bärlocher and Kendrick (1973b)
Gammarus pulex	Free from parasites Dry body mass 3.8–15 mg	3 days	13°C	12:12	Artificial pond water	Feeding rate study	Agatz et al. (2014)

(continued)

Table 1 (continued)

Test organism	Age/sex/size organism	Duration	Temperature	Light/dark cycle	Type of water Aeration pH	Type of study	References
Gammarus pulex	Organisms with parasites Both sexes Juveniles and adults	1 day	13°C	12:12	Artificial pond water Aerated pH = 7.4–7.9	Feeding rate studies	Agatz and Brown (2014)
Gammarus pulex	Free from parasites Adults (mean size 9.7 ± 1.4 mm) No gravid females	1. 4 days 2. 4 days	1. 15°C 2. 20°C		River water Artificial water Aerated	Feeding rate study with the Multispecies Freshwater Biomonitor	Alonso et al. (2009)
Gammarus pulex	3–7 mm		13°C	12:12	Dechlorinated tap water pH = 7.7	Feeding behavioural study	Blockwell et al. (1998)
Gammarus pulex	Adult males	7 days	15°C	12:12		In situ feeding assay	Crane and Maltby (1991)
Gammarus pulex	Males with first thoracic segment of 0.7–1.2 mm in size	7 days	15°C	12:12	River water	Feeding behavioural study	De Castro-Català et al. (2017)
Gammarus pulex	Adults (7–9 mm)	10 days	12°C		Well water pH = 7.19 ± 0.02	Physiological and behavioural responses	Felten et al. (2008a)
Gammarus pulex	Free from parasites Adult males (dry weight 6.5–12.0 mg)		15°C	12:12	Artificial pond water	In situ and laboratory feeding studies	Forrow and Maltby (2000)
Gammarus pulex	Adults (dry weight 8–10 mg)					Feeding behavioural study	Graça et al. (1993a)
Gammarus pulex	Adults (9–10 mm) Juveniles (2.5–3.5 mm)		15°C	12:12	Artificial pond water	Feeding behavioural study	Graça et al. (1993b)
Gammarus pulex	Adults		13°C			Feeding behavioural study	Hahn and Schulz (2007)

Gammarus pulex	Wet weight = 1.5–2.5 mg	10 days			Dechlorinated city tap water	Growth and feeding rate study	Hargeby and Petersen (1988)
Gammarus pulex	Both sexes		14°C	12:12	River water	Energetic state study	Iltis et al. (2017)
Gammarus pulex	Males (13–16 mm)		12°C	14:10	Aerated	Predation behaviour study	Kelly et al. (2002)
Gammarus pulex	Adults	7–14 days	19–22°C		Dechlorinated tap water Aerated pH = 8.28 ± 0.06	Feeding and bioaccumulation study	Lahive et al. (2015)
Gammarus pulex	Adult males (mean dry weight = 8.24 mg)	5–10 days	15°C	12:12	Artificial pond water	In situ feeding assay	Maltby et al. (2002)
Gammarus pulex	Adult males (dry weight = 7–10 mg)	7 days	15°C	12:12	Artificial pond water	Scope for growth assay	Naylor et al. (1989)
Gammarus pulex		1 day	14°C	16:8		Feeding behavioural study	Taylor et al. (1993)
Gammarus pulex	Adults Juveniles	7 days	16°C	16:8	ISO medium Aerated	Feeding activity and physiological responses	Weber et al. (2018)
Gammarus roeselii	Both sexes		15°C	12:12	Lake water	Feeding, assimilation and growth study	Gergs and Rothhaupt (2008)
Gammarus spp.		7 days			River water Aerated	Selective feeding study	Arsuffi and Suberkropp (1989)
Gammarus spp.		5 days	10°C		River water pH = 7.2	Physiological and behavioural responses	Maul et al. (2006)

2.2 Temperature

During the acclimation period, organisms need to be kept at a constant temperature and with a precise light/dark cycle. Gammarids from temperate countries are usually maintained at a temperature between 10 and 22°C (see Table 1). The temperature adopted in an experimental design is often selected to reproduce seasonal conditions, but unfortunately the literature does not always specify the selection criteria. Temperature can have a significant impact on Gammarids and on amphipods in general (Labaude et al. 2017). Foucreau et al. (2014) discovered that temperatures higher than 15°C altered various physiological parameters in *Gammarus pulex* populations in North France. Southern specimens consumed more oxygen at higher temperatures and had a higher glycogen content, which means they have a higher energy supply. Cold-acclimated organisms consumed more energy and oxygen when they are exposed to higher temperatures, and they presented a lower heat tolerance (Semsar-kazerouni and Verberk 2018). Interestingly, Alonso et al. (2009) acclimated their organisms at 15°C for 4 days, after which time the organisms were transferred to a 20°C room to acclimate for a further 4 days. Moving organisms from a low to a high temperature could have potentially affected the experimental results (Alonso et al. 2009). Furthermore, temperature plays an important role in the immune system of crustaceans (Le Moullac and Haffner 2000). Therefore, it is difficult to compare studies where the test animals have been acclimated at different temperatures, as this could have influenced their energy stores or their immune systems, for example. These differences could also be reflected in the organisms' behavioural reactions, which could be incorrectly interpreted as a result of exposure to specific contaminants. In fact, both Nilsson (1974) and Coulaud et al. (2011) reported an increased feeding rate with an increased temperature. The extent of the feeding rate increase was also dependent on leaf species (i.e. *Alnus glutinosa* or *Fagus sylvatica*) (Nilsson 1974). Acclimation temperature plays an even greater role in in situ experiments where the chosen temperature should be as close as possible to real-life environmental conditions. Interestingly, Coulaud et al. (2011) linked temperature and feeding rate through a linear regression, in order to better understand the impact of temperature on the Gammarids feeding. It was found that a small increase in mean temperature (from 12 to 13°C) could enhance the feeding rate by 7.3%.

2.3 Light and Dark Cycles

The same principle could be applied to the different light/dark cycles used during the acclimation period. The most commonly adopted light/dark cycle is 12:12 h (see Table 1) that reflects typical equinox conditions. However, some studies acclimate their organisms in total darkness, and in other studies, the adopted cycle is not specified (see Table 1). Sometimes a seasonal cycle is selected, in order to replicate the time of year when the organisms are collected from the wild, such as summer

with a light/dark cycle of 16:8 h (Weber et al. 2018) or autumn with a cycle of 10:14 h (Garcia-Galan et al. 2017) (see Table 1). Adopting different light/dark cycles could make the comparison between studies challenging, since light could influence the organisms' physiological processes and behaviour (Perrot-Minnot et al. 2013).

2.4 Media Selection

The type of media selected for an experiment is another factor that could have an impact on the outcome of a study. Some researchers prefer to use an artificial medium (see Table 1) that guarantees standardisation (Agatz et al. 2014; Maltby et al. 2002), and in other studies, river water is sometimes used as a medium. However, river water might be contaminated, and this could therefore interfere with the organisms' cleansing process during their acclimation period, which makes it a peculiar choice of test media. Numerous studies have also used river water or a mixture (Alonso et al. 2009; Blarer and Burkhardt-Holm 2016; Bundschuh et al. 2009, 2017; De Castro-Català et al. 2017; Dedourge-Geffard et al. 2009; Gergs and Rothhaupt 2008; Iltis et al. 2017; Maul et al. 2006; Zubrod et al. 2015) (see Table 1). For example, Bundschuh et al. (2017) combined river water with tap water, which also has limitations as the tap water could be contaminated (Magi et al. 2018). Potentially, any type of water could be contaminated, which is why the authors recommend that researchers should report the chemical breakdown (i.e. presence of contaminants) of their chosen water media along with their study findings so that any contamination is transparent.

Gammarus pulex allocates up to 11% of its energy supply to osmotic regulation (Sutcliffe 1984), and Gammarids have been proven to be acid-sensitive (*Gammarus fossarum*; Felten and Guerold 2001; *Gammarus pulex*, Sutcliffe and Carrick 1973). In fact, acidic conditions induce a range of physiological and behavioural alterations, such as a reduction in the ventilation activity of *Gammarus pulex* (Felten et al. 2008b). These findings highlight the importance of measuring pH, as a shift in pH might influence the outcome of an experiment and prevent comparisons between studies. pH is rarely reported and presumably not measured in the environment during the collection process, the acclimation period or the experiment. Along with the chemical parameters of the acclimation media, the authors also recommend that pH is another factor that should be measured during the acclimation period, to ensure that accurate baseline data is recorded.

2.5 Characteristics of the Test Organism

Another important factor that plays a fundamental role in the reproducibility of a feeding experiment is the organism itself. Organisms of different age and sex may behave or respond differently to contaminants. For example, juveniles are more

sensitive to contaminants than adult organisms (Adam et al. 2010), and their feeding rate varies over time, making them more suitable for short-term feeding studies (Agatz and Brown 2014). Agatz and Brown (2014) and Nilsson (1974) identified that smaller specimens of *Gammarus pulex* have a higher feeding rate but higher variability over time, in comparison to larger organisms.

However, other studies have reported that the feeding rate increases with organism size (Coulaud et al. 2011), but the adoption of different units of measurement and a small size range might be contributing factors for those findings. It has been suggested that using organisms with a specific body mass (given in dry weight) could reduce experimental variability. For feeding studies, up to a 57% reduction in variability has been documented for specific body mass studies compared to mixed body mass studies (Agatz and Brown 2014). There is also a recommendation that body length should be used as an indicator of dry weight and the correlation for organisms between 2 and 16 mm (Graça et al. 1993b).

Alternatively, organisms might be divided into size groupings by applying passive underwater separation techniques (Bundschuh et al. 2009, 2017; Zubrod et al. 2017), by measuring the dorsal length of the Gammarids' first thoracic segment after the organisms are photographed (De Castro-Català et al. 2017), by considering their wet weight (Blockwell et al. 1996; Danger et al. 2012; Weber et al. 2018) or by using their dry weight at the end of an experiment (Agatz et al. 2014). There is no agreed standard method on how to separate or select specimens of Gammarids for this experimental technique, but the chosen method will ultimately determine the unit of measurement for calculating the feeding rate, e.g. if wet weight is used, the unit of measurement will be wet weight. The use of either dry or wet weight seems straightforward, but it is only an estimate, and it lacks accuracy, as the dry weight range is only known at the end of the study. Furthermore, wet weight does not provide an accurate measurement due to the unknown volume of liquid in each sample. Blotting the sample dry before weighing could help to remove a proportion of the moisture, but it could potentially stress the organisms and consequently affect the results; therefore, the authors recommend the use of dorsal length as the authors believe it to be a more accurate way to measure the organisms. In in situ experiments, the organisms are often divided by size before the start, but the weight is not taken into consideration. This means that the amount of consumed food is usually related to the number of living organisms at the end of the experiment (e.g. Coulaud et al. 2011; Dedourge-Geffard et al. 2009) (see Table 3).

Same-sex tests with organisms (female-only, Geffard et al. 2010, or male-only, Crane and Maltby 1991; De Castro-Català et al. 2017; Forrow and Maltby 2000; Kelly et al. 2002; Maltby et al. 2002; Naylor et al. 1989; Zubrod et al. 2015) (see Table 1) of a specific size are often undertaken, although sex is not always specified, which leads to female and male organisms being used indiscriminately (Agatz et al. 2014; Agatz and Brown 2014; Alonso et al. 2009; Arsuffi and Suberkropp 1989; Bärlocher and Kendrick 1973a; Blarer and Burkhardt-Holm 2016; Blockwell et al. 1998; Bundschuh et al. 2009, 2011b, 2013, 2017; Dedourge-Geffard et al. 2009;

Gergs and Rothhaupt 2008; Graça et al. 1993a, b; Hahn and Schulz 2007; Lahive et al. 2015; Taylor et al. 1993; Weber et al. 2018; Xuereb et al. 2009; Zubrod et al. 2017) (see Table 1).

As a rule, and not only in feeding studies, gravid females and organisms affected by the acanthocephalan parasite are usually excluded from experiments (Agatz et al. 2014; Alonso et al. 2009; Blarer and Burkhardt-Holm 2016; Bundschuh et al. 2011b, 2013; Forrow and Maltby 2000; Zubrod et al. 2015, 2017) unless they are specifically chosen for the purpose of the study (Agatz and Brown 2014; Pascoe et al. 1995). Alonso et al. (2009) developed a feeding study using the Multispecies Freshwater Biomonitor, and neither length nor sex influenced the feeding activity of either sex of *Gammarus pulex*. However, it is debatable whether these results might only be applicable to the type of contaminant used in the investigation, as some contaminants might affect male and female Gammarid feeding behaviour in different ways.

3 Food Preparation

The food source selected for an experiment using Gammarids is important, but especially so for feeding studies, both in the acclimation period and in the experiment itself. Gammarids are shredder detritivores, and they usually feed on conditioned organic material, in other words material that has been colonised by microorganisms, such as leaf litter. In the natural environment, freshly abscised leaves are colonised by fungi and then by bacteria (Baldy et al. 1995), which facilitate the decomposition process and transform the material, making it more palatable and accessible to the organisms (Bärlocher and Kendrick 1975; Cummins 1974; Gessner et al. 1999).

Gammarus spp. have displayed selective behaviour towards leaf species and their conditioning level (Agatz and Brown 2014; Graça et al. 1993a, b, 2001) and the type of fungi (Arsuffi and Suberkropp 1989). Interestingly, Graça et al. (2001) compared food preferences of shredders from temperate (*Gammarus pulex* and *Sericostoma vittatum*) and tropical (*Nectopsyche argentata* and *Phylloicus priapulus*) streams. When provided with conditioned and/or unconditioned leaves from either a temperate (*Alnus glutinosa*) or tropical (*Hura crepitans*) country, *Gammarus pulex* showed a significant preference for the conditioned leaves compared to unconditioned leaves of the same species. Leaves are characterised by different hardness, texture and more importantly by dissimilar C:N ratios, which means the various leaf species provide the organisms with differing energy supplies. A lower C:N ratio signifies a better quality food, and conditioned material is usually characterised by a lower C:N ratio compared to unconditioned material (Graça et al. 1993b). Some species such as alder (*Alnus* spp.) are characterised by a lower C:N ratio and higher palatability compared to others, such as horse chestnut (*Aesculus* spp.) (Agatz and Brown 2014), which could lead to the organisms growing larger (Bärlocher and Kendrick 1973b).

In feeding assays, there are several options when considering a food source. The most common choice is to provide the Gammarids with conditioned organic material. Depending on the study, the adopted leaf species may be different. The most commonly used leaves are alder (*Alnus* spp.), elm (*Ulmus* spp.), horse chestnut (*Aesculus* spp.), maple (*Acer* spp.), poplar (*Populus* spp.) and oak (*Quercus* spp.) (see Table 2). In some cases, the Gammarids' diet is enriched with *Tubifex* worms (Coulaud et al. 2011; Dedourge-Geffard et al. 2009; Geffard et al. 2010; Xuereb et al. 2009). Occasionally, they are provided with other types of food, such as alimentary chips (Novo Crabs®, JBL GmbH & Co., Germany) (Foucreau et al. 2014), Chironomidae (Gergs and Rothhaupt 2008), *Artemia salina*'s eggs (Blockwell et al. 1998; Pascoe et al. 1995; Taylor et al. 1993), industrial shrimp food (Henry et al. 2017), fish food (Semsar-kazerouni and Verberk 2018) or ground and tropical fish food mix (Blockwell et al. 1996).

During the acclimation period, organisms are normally fed ad libitum with pre-prepared conditioned leaves (Blarer and Burkhardt-Holm 2016; Blockwell et al. 1998; Bloor 2010; Bundschuh et al. 2011b; Crane and Maltby 1991; Dedourge-Geffard et al. 2009; Geffard et al. 2010; Naylor et al. 1989; Newton et al. 2018; Xuereb et al. 2009; Zubrod et al. 2015). The conditioning process can vary, and the differences between the techniques can be found in Table 2.

In behavioural studies, food is supplied to the organism during the testing regime and is usually the same food type as provided during the acclimation period. The type of food used in a study could influence the feeding activity, especially if the organisms are fed on leaves that are not palatable or with leaves that have dissimilar energy budgets (e.g. Agatz and Brown 2014).

Sometimes leaves are collected at the beginning or during fall, specifically handpicked senescent *Alnus glutinosa* leaves that are not decomposed (Bundschuh et al. 2009, 2017), whereas in other studies, the leaves are specifically collected after they had abscised (Hargeby and Petersen 1988). After collection the leaves are either used straight away or stored for later use (see Table 2). Storage methods vary throughout the literature, for example, Bundschuh et al. (2009, 2011a, b, 2013, 2017) froze their leaves at −20°C, but this methodology ultimately alters the structure of the leaves (Burke et al. 1976). More commonly, the leaves are dried at room temperature and stored in the dark until needed (e.g. Naylor et al. 1989) (see Table 2). However, Gessner et al. (1999) highlighted that drying leaves in an oven or at room temperature ultimately ruins the leaf tissue. In the natural environment, leaves usually reach water bodies soon after abscission (Fisher 1977). Consequently, storing leaves for later use does not mimic the natural chain of events, and storing will ultimately disrupt their structure. Gessner and Schwoerbel (1989) demonstrated that freezing or drying leaves increases mass loss in the first few days when in water, and this accelerates the conditioning process, which is usually statistically delayed in fresh leaves (Bärlocher 1992).

The conditioning process involves soaking the leaves in water and mixing them with an unknown fungi species (Nilsson 1974) or by inoculating the leaves with a specific fungi species (Naylor et al. 1989). In the first instance, river water might be used in the laboratory to condition the leaves, and it is usually inoculated with

Table 2 Existing differences in the literature regarding the conditioning process

Leaf species	Leaf storage	Conditioning water	Fungi species	Conditioning period	Conditioning time	Amount of leaves during acclimation	Type of study	Reference
Acer saccharum *Ulmus* spp.	Cut in discs of 9 mm in diameter, leached in tap water for 4 days at 12°C, and dried at 40°C for 2 days Stored at room temperature	*Experiment food:* nutrient-enriched river water	*Alternaria* sp. *Fusarium* sp. *Cladosporium* sp. *Humicola grisea* *Aspergillus niger* *Tricladium angulatum* *Tetracladium marchalianum* *Anguillospora longissima* *Clavariopsis aquatica* *Flagellospora curvula*				Feeding study	Bärlocher and Kendrick (1973b)
Acer saccharum	Air-dried and stored in plastic bags until use	*Experiment food*: river water		4 days	After being cut in leaf discs of 1.1 cm in diameter and being dried for 3 days at 60°C		Physiological and behavioural responses	Maul et al. (2006)
Aesculus hippocastanum	*Acclimation food:* stored in tap water for 3 months *Experiment food:* dried at room temperature	*Acclimation food:* tap water *Experiment food:* enriched water	*Cladosporium* spp.	10 days	*Experiment food:* before re-drying at 60°C	Ad libitum	Feeding study	Agatz et al. (2014)
1. *Aesculus hippocastanum* 2. *Alnus glutinosa*	*Acclimation food:* whole horse chestnut leaves stored in tap water *Experiment food*:	*Acclimation food:* tap water *Experiment food:* 1. Enriched water or tap water	*Acclimation food:* *Cladosporium* spp. *Experiment food:*	*Acclimation food:* 3 months *Experiment food:*	*Experiment food:* 2. After being cut in discs of 2.0 cm in diameter, but before re-drying at 60°C		Feeding study	Agatz and Brown (2014)

(continued)

Table 2 (continued)

Leaf species	Leaf storage	Conditioning water	Fungi species	Conditioning period	Conditioning time	Amount of leaves during acclimation	Type of study	Reference
	1. Air-dried in the dark at room temperature (20°C)	2. Nutrient medium	1. *Cladosporium* spp.	1. 2 weeks or 3 months 2. 10 days				
Aesculus hippocastanum		*Acclimation food:* conditioned in organically enriched dechlorinated water (Bird and Kaushik 1985)		10 days		Ad libitum	Feeding study	Blockwell et al. (1998)
Aesculus hippocastanum		Organically enriched water, following method of Bird and Kaushik (1985)		10 days			Feeding study	Taylor et al. (1993)
Alnus glutinosa	Air-dried for 1 h and then stored at −20°C	*Acclimation food:* decaying leaves collected in a pond *Experiment food:* cut in leaf discs of 2 cm in diameter and conditioned directly in the river		21 days	After being cut in leaf discs of 2 cm in diameter, but before been dried at 60°C for 24 h Soaked for 24 h in water before being used in the experiment	*Acclimation food*: ad libitum	Feeding and assimilation study	Blarer and Burkhardt-Holm (2016)
Alnus glutinosa	Froze at −20°C until use	*Experiment food:* soaked in tap water for 24 h and then conditioned in a nutrient medium with added leaf litter from the river		From 19 to 22 days	After being cut in leaf discs of 1.5 cm in diameter and been dried at 60°C for 24 h		Feeding preferences study	Bundschuh et al. (2009)

Alnus glutinosa	Frozen at −20°C and stored until use. Following the method described by Bundschuh et al. (2009)	*Acclimation food:* preconditioned leaves *Experiment food:* conditioning medium (Dang et al. 2005) inoculated with leaves previously conditioned directly in the river		12 days	After being cut in leaf discs of 1.6 cm in diameter and dried		Feeding preferences study	Bundschuh et al. (2011a)
Alnus glutinosa	Froze at −20°C until use	*Acclimation food:* preconditioned alder leaves *Experiment food:* conditioned in a nutrient medium with added leaves that were previously conditioned directly in the river		10 days	After being cut in leaf discs of 2 cm in diameter, but before been dried at 60°C for 24 h	Preconditioned alder leaves fed ad libitum	Feeding study	Bundschuh et al. (2011b)
Alnus glutinosa	Froze at −20°C until use	*Acclimation food:* preconditioned alder leaves *Experiment food:* conditioned in a nutrient medium with added leaves that were previously conditioned directly in the river		10 days	After being cut in leaf discs of 2 cm in diameter, but before been dried at 60°C for 24 h		Feeding study	Bundschuh et al. (2013)

(continued)

Table 2 (continued)

Leaf species	Leaf storage	Conditioning water	Fungi species	Conditioning period	Conditioning time	Amount of leaves during acclimation	Type of study	Reference
Alnus glutinosa	Froze at −20°C until use	*Acclimation food:* preconditioned Alder leaves *Experiment food:* conditioned in a mixture of tap water and stream water with preconditioned leaves coming from the river		18 days	Before being cut in leaf discs of 2 cm in diameter and been dried at 60°C for 24 h Soaked for 24 h in tap water before being used in the experiment		Feeding study	Bundschuh et al. (2017)
Alnus glutinosa		*Acclimation and experiment food:* groundwater Freeze-dried *Tubifex* worms added to the food twice a week		6 days		Ad libitum	Laboratory and in situ feeding study	Coulaud et al. (2011)
Alnus glutinosa			*Cladosporium*			Ad libitum	In situ feeding study	Crane and Maltby (1991)
Alnus glutinosa		*Experiment food:* conditioned in a river water		14 days			Feeding study	De Castro-Català et al. (2017)
Alnus glutinosa		*Acclimation and experiment food:* conditioned in water Freeze-dried *Tubifex* worms added to the food twice a week		6 days		*Acclimation food*: *Ad* libitum	In situ feeding study	Dedourge-Geffard et al. (2009)

Alnus glutinosa	Air-dried and stored at room temperature until use	*Acclimation food:* fungally conditioned leaves *Experiment food:* two different types depending on the experiment 1. Leaves were naturally conditioned in the river 2. Method described by Naylor et al. (1989)	2. *Cladosporium*		Before being cut in leaf discs of 1 cm in diameter and been blotted dry and weighed Used immediately afterwards		In situ and laboratory feeding studies	Forrow and Maltby (2000)
Alnus glutinosa		*Acclimation food:* conditioned in water Freeze-dried *Tubifex* worms added to the food twice a week		6 days		*Acclimation food*: ad libitum	Reproductive cycle and feeding study	Geffard et al. (2010)
Alnus glutinosa		*Experiment food:* naturally conditioned in the lake		21 days			Feeding, assimilation and growth study	Gergs and Rothhaupt (2008)
Alnus glutinosa *Hura crepitans*	Air-dried and stored until use	*Experiment food*: different types. Depending on the experiment 1. Conditioned directly into the river 2. Leaves soaked in tap water		1. 14 days 2. 24 h	Before being cut in leaf discs of 1.4 cm in diameter		Feeding study	Graça et al. (2001)
Alnus glutinosa	Frozen at −20°C until use	*Experiment food:* river water		14 days	After being cut in leaf discs of 2 cm in diameter		Feeding study	Hahn and Schulz (2007)
Alnus glutinosa		*Acclimation and experiment food:* method described by Naylor et al. (1989)					In situ feeding study	Maltby et al. (2002)

(continued)

Table 2 (continued)

Leaf species	Leaf storage	Conditioning water	Fungi species	Conditioning period	Conditioning time	Amount of leaves during acclimation	Type of study	Reference
Alnus glutinosa	Dried and stored	*Acclimation and experiment food:* enriched water	*Cladosporium* spp.	10 days	After being rehydrated, cut in leaf discs of 1.6 cm in diameter and autoclaved, but before being dried for 2 days at 60°C Rehydrated again before being fed	*Acclimation food*: ad libitum	Scope for growth assay	Naylor et al. (1989)
Alnus glutinosa	Froze at −20°C	*Acclimation food:* preconditioned leaves *Experiment food:* 1. Conditioning medium as Dang et al. (2005) inoculated with alder leaves conditioned in the river for 14 days 2. Conditioning medium		1. 13 days 2. 14 days	1. After being cut in leaf discs of 1.6 cm in diameter, being froze for 24 and subsequently weighed Unconditioned leaves either submerged for 2 min or 48 h in SAM-5S medium 2. Before being cut in leaf discs of 2.0 cm in diameter and being directly fed to the organisms	*Acclimation food:* ad libitum	Feeding study	Newton et al. (2018)
Alnus glutinosa Fagus sylvatica	Dried at 20°C	*Experiment food:* river water		10 days			Feeding, assimilation and respiration study	Nilsson (1974)
Alnus glutinosa		*Acclimation and experiment food:* conditioned in water Freeze-dried *Tubifex* worms added to the food twice a week		6 days		*Acclimation food*: ad libitum	Feeding behaviour and biomarkers analysis	Xuereb et al. (2009)

Alnus glutinosa	Frozen at −20°C and stored until use. Following the method described by Bundschuh et al. (2011b)	*Acclimation food:* preconditioned leaves *Experiment food:* conditioning medium (Dang et al. 2005) inoculated with leaves previously conditioned directly in the river		10 days	After being cut in leaf discs of 2.0 cm in diameter, but before being dried at 60°C for 24 h and weighed Soaked for 24 h in tap water before being used in the experiment	*Acclimation food*: ad libitum	Feeding, accumulation and growth study	Zubrod et al. (2010)
Alnus glutinosa	Frozen at −20°C and stored until use. Following the method described by Zubrod et al. (2010)	*Acclimation food*: preconditioned leaves *Experiment food*: conditioning medium (Dang et al. 2005) inoculated with leaves previously conditioned directly in the river		10 days	After being cut in leaf discs of 2.0 cm in diameter, but before being dried at 60°C for 24 h and weighed. Soaked for 48 h in tap water before being used in the experiment	*Acclimation food*: ad libitum	Feeding an survival study	Zubrod et al. (2014)
Alnus glutinosa	Frozen at −20°C and stored until use	Conditioned in medium with leaves that were previously conditioned directly in the river for 14 days		12 days		*Acclimation food*: ad libitum	Toxicity and feeding study	Zubrod et al. (2015)
Alnus glutinosa	Frozen at −20°C and stored until use	Conditioned in stream water with leaves that were previously conditioned directly in the river for 14 days and for 14 days in the lab		13 days			Feeding behaviour and physiological responses	Zubrod et al. (2017)
Alnus spp.	Air-dried and stored	River water with detritus		At least 10 days	After being air-dried	Ad libitum	Laboratory breeding program	Bloor (2010)

(continued)

Table 2 (continued)

Leaf species	Leaf storage	Conditioning water	Fungi species	Conditioning period	Conditioning time	Amount of leaves during acclimation	Type of study	Reference
Fraxinus pennsylvanica *Acer saccharum* *Quercus velutina*	Cut in discs of 1–2 cm in diameter, leached in tap water for 4 days at 12°C, and dried at 40°C for 2 days Stored at room temperature in polyethylene bags		*Alternaria* spp. *Fusarium* spp. *Cladosporium* spp. *Aspergillus niger* *Humicola grisea* *Tricladium angulatum* *Tetracladium marchalianum* *Anguillospora longissima* *Clavariopsis aquatica* *Flagellospora curvula*	14 days	After drying			Bärlocher and Kendrick (1973a)
Populus sp.		*Acclimation food:* conditioned naturally in the river *Experiment food*: mixture of stream water and Dutch Standard Water (DSW)		*Acclimation food*: *Experiment food:* 4 days			Feeding rate study with the Multispecies Freshwater Biomonitor	Alonso et al. (2009)
Populus tremuloides		*Experiment food:* incubation medium Stream water	*Flagellospora curvula* *Alatospora acuminata* *Clavariopsis aquatic*	Either 10 or 15 days depending on the fungi and then 72 h in stream water	*Experiment food*: before drying at 45°C		Selective feeding study	Arsuffi and Suberkropp (1989)

			Tetracladium marchalianum *Lemonniera aquatica* *Heliscus lugdunensis* *Articulospora inflata* *Filosporella annelidica*					
Quercus petraea		*Experiment food:* conditioned directly into the stream		35, 56 or 82 days	Before being cut in leaf discs of 1.2 cm in diameter and being frozen at −18°C	*Acclimation food:* ad libitum with plant detritus from the stream	Decomposition and feeding study	Danger et al. (2012)
Ulmus carpinifolia	Air-dried and leached for 96 h in distilled water and air-dried again	*Acclimation food:* decaying leaves *Experiment food:* incubated in soft water		*Experiment food:* 2–3 weeks	Before being given to the organisms	*Acclimation food*: ad libitum	Growth study	Hargeby and Petersen (1988)
Ulmus procera		*Experiment food*: different types. Depending on the experiment 1. Conditioned in stream water where leaf material from the river was added 2. Leaves soaked in tap water 3. Artificial pond water 4. Artificial pond water	*3.* *Anguillospora longissima* *Articulospora tetracladia* *Fusarium cavispermum* *Fusarium* spp. *Cylindrocarpon* spp. *Heliscus lugdunensis* *Lemonniera aquatica* *Tetracladium*	1. 14 days 2. 4 days 3. 15 days 4. 14 days	3. After being cut in leaf discs of 1.6 cm in diameter, but before drying at 60°C for 4 days 4. After being cut in leaf discs of 1.6 cm in diameter and after being dried at 60°C for 4 days		Feeding study	Graça et al. (1993a)

(continued)

Table 2 (continued)

Leaf species	Leaf storage	Conditioning water	Fungi species	Conditioning period	Conditioning time	Amount of leaves during acclimation	Type of study	Reference
			marchalianum *Tetracladium setigerum* *Triclodium angulatum* *4. Anguillospora longissimi*					
Ulmus procera		*Experiment food:* different types. Depending on the experiment 1. Conditioned in artificial pond water where leaf material from the river was added 2. Leaves soaked in tap water		1. 21 days 2. 4 days	After being cut in leaf discs of 1.6 cm in diameter and after being dried at 60°C for 4 days		Feeding study	Graça et al. (1993b)

organic material taken directly from the river as a natural source of fungi and bacteria (e.g. Zubrod et al. 2015, 2017) (see Table 2). Leaves can also be directly conditioned in situ by placing them in small nets/bags that are suspended in a river and retrieved after a specific number of days (Alonso et al. 2009; De Castro-Català et al. 2017; Forrow and Maltby 2000; Graça et al. 2001; Zubrod et al. 2015) (see Table 2).

Although river water might reproduce natural environmental conditions, it is sometimes contaminated, and this might have an impact. When river water is used, a chemical breakdown of the water should be undertaken and reported along with the study findings, so that any contamination is transparent. It is especially important to disclose if the river water is contaminated with the substance(s) under investigation in the study. If the test substances are present in the river water, the organism could be exposed to that concentration and also the experimental dose. Therefore, the organisms' response would not be a true reflection of the test concentration(s) but instead the reported dose combined with the concentration found in the river water. For example, contaminants might be absorbed onto the leaf surface and passed onto the organisms, or they could be released into the media, which might happen during the acclimation period and/or during the experiment itself, resulting in a compromised feeding activity. Therefore, the observed findings might be an indirect effect, due to the leaf quality and not as a direct result of the contaminant being tested.

The conditioning process usually takes around 2 weeks, but there are clear differences in the literature about this stage (see Table 2). The process ranges from a few days (Alonso et al. 2009), to several weeks (Blarer and Burkhardt-Holm 2016), and up to months (Danger et al. 2012) (see Table 2). When *Gammarus* spp. are offered a choice between leaves that have been conditioned for different periods of time, they prefer those that have been conditioned for the longest (Agatz and Brown 2014; Bird and Kaushik 1985). Consequently, experiments (in situ or ex situ) that provide the organisms with leaves that have been conditioned for a short or longer time period could potentially underestimate or overestimate the actual feeding activity of *Gammarus* spp.

It has been demonstrated that conditioned leaf material is more palatable (Agatz and Brown 2014; Graça et al. 1993b) and that different species of leaves (i.e. *Acer* spp. and *Ulmus* spp.), depending on the conditioning stage, might be more or less palatable compared to the others (Bird and Kaushik 1985). Consequently, it could be argued that it is impossible to compare experiments where organisms have been fed with organic material that has been conditioned for different periods of time. Organisms fed on leaves that have been conditioned for 1 week will probably eat less than those fed with the same leaves conditioned for 3 weeks, and leaf unpalatability might be mistakenly attributed to contaminant exposure. It has also been identified that *Gammarus pulex* fed with unconditioned leaves have a considerably lower respiration rate (Graça et al. 1993b).

Depending on the methodology used, the conditioning process might take place in different phases. There are studies where the leaves are provided to the organisms directly after the conditioning process (Bärlocher and Kendrick 1973a; Bloor 2010; Bundschuh et al. 2009; Forrow and Maltby 2000; Newton et al. 2018), whereas in

some cases the leaves are redried and soaked in water before feeding them to the organisms (Agatz et al. 2014; Blarer and Burkhardt-Holm 2016; Bundschuh et al. 2011b, 2013, 2017; Naylor et al. 1989), in order to prevent them from floating on the surface. In this case, the drying process requires the use of an oven, but unsurprisingly the time and temperature used vary between research groups. Bear in mind that the same food might be provided during the acclimation period and also during the experiment itself, unless the feeding experiment aims to study the feeding variation when a food source is either contaminated or compromised. In these studies, a specific contaminant or mixture of contaminants are usually incorporated during the conditioning process (Bundschuh et al. 2009; Hahn and Schulz 2007). When the conditioned leaves are oven-dried, they need to be resoaked in water before being provided to the organisms, in order to avoid floatation (e.g. Bundschuh et al. 2017; Zubrod et al. 2010). The water used to soften the leaves varies between research groups, and the water could act as a new source of contamination, especially if it differs from the one used during the original conditioning process.

4 Exposure and Feeding Rate Calculation

After the conditioning process and the acclimation period, the next step in a feeding study is the exposure itself. During this time, the Gammarids are exposed directly (i.e. the contaminant is in the water with the *Gammarus* spp.) (Zubrod et al. 2010) or indirectly (i.e. the contaminant is added during the conditioning process) (Bundschuh et al. 2009) to a contaminant, and their feeding behaviour is studied and estimated (see Table 3). These experiments might have different goals: they might be undertaken to either measure the changes in Gammarid feeding activity, Gammarid feeding preferences, or to study the effects on their growth. Consequently, the period of exposure could vary dramatically from a few hours (Bundschuh et al. 2011a) to a week (Felten et al. 2008a) or even several weeks (Weber et al. 2018), and sometimes fungal biomass analysis (estimated as ergosterol) and assimilation are incorporated, to strengthen the findings obtained from the feeding rate (Bundschuh et al. 2009; Newton et al. 2018).

Occasionally in feeding studies, the organisms undergo a period of starvation before the experiment is undertaken (De Castro-Català et al. 2017) (see Table 3). The main purpose of this starvation phase is to ensure that the organisms are at the same hunger state, but the duration of this phase varies in the literature. Once the experiment starts, the Gammarids are commonly provided with a precise amount of food, in other words the leaves provided have usually been dried, weighed and conditioned. This latter step, as previously mentioned, could have been carried out before the drying process or afterwards, so the final product could have different characteristics depending on the study. In order to provide the organisms with the same amount of food, the leaves are cut in small discs that range from a diameter of 0.7 to 4 cm depending on the research group (see Table 3). Before or after the conditioning process, the leaf discs are oven-dried for a specific period of time,

Table 3 Existing differences in the literature regarding feeding behavioural experiments

Leaf species	Contaminant	Water used for the experiment	Light/dark cycle	Leaf disc size (diameter)	Length of the feeding study	Drying temperature and time (before and after exposure)	Starvation	Equation used	References
Aesculus hippocastanum	Imidacloprid	Artificial pond water	12:12	1.6 cm 3 at the time and exchanged every 24 h	7 days (4 days exposure +3 days recovery phase)	*Leaves*: Before: 60°C for 48 h After: *Organisms*: After: 65°C for 48 h		$FR = \frac{F[t-1]-\frac{F[t]}{M}}{G \times t}$ FR = feeding rate $F[t-1]$ = initial leaf dry weight (mg) $F[t]$ = final leaf dry weight (mg) G = dry weight of Gammarus (mg) ld = leaching decomposition factor t = time (days)	Agatz et al. (2014)
1. *Aesculus hippocastanum* 2. *Alnus glutinosa*		Artificial pond water	12:12	1. 1.6 cm 2. 2.0 cm	*Experiment 1*: 96 h *Experiment 2*: 9 days *Experiment 3*: 15 days	*Leaves*: 1. 2. Before: 60°C to constant weight After: *Organisms*: After: 90°C for 24 h Wet weight transform in dry weight using a linear regression		$FR = \frac{F[t-1]-\frac{F[t]}{M}}{G \times t}$ FR = feeding rate $F[t-1]$ = initial leaf dry weight (mg) $F[t]$ = final leaf dry weight (mg) G = dry weight of Gammarus (mg) ld = leaching decomposition factor t = time (days)	Agatz and Brown (2014)
Alnus glutinosa	Microplastic debris	Mixed water (municipal water and softened water)		2.0 cm 2 discs at the time every 7 days	28 days	*Leaves*: Before: 60°C for 24 h After: 60°C for 24 h		$FR = \frac{L_i \times (CF) - L_f}{w \times t}$ FR = feeding rate L_i = initial leaf dry weight (mg) L_f = final leaf dry weight (mg) w = animal's average wet weight (mg) t = feeding time (days) CF = leaf change correction factor $CF = \frac{\left[\sum\left(\frac{C_f}{C_i}\right)\right]}{n}$ C_f= final dry weight of control leaf discs (mg) C_i= initial dry weight of control leaf discs (mg) n = number of replicates	Blarer and Burkhardt-Holm (2016)

(continued)

Table 3 (continued)

Leaf species	Contaminant	Water used for the experiment	Light/dark cycle	Leaf disc size (diameter)	Length of the feeding study	Drying temperature and time (before and after exposure)	Starvation	Equation used	References
Alnus glutinosa	In situ and ex situ feeding assays	In situ: river water Ex situ: river water		In situ: 5 leaf discs per cage of 1.6 cm in diameter Ex situ: 5 leaf discs per pot of 1.6 cm in diameter	6 days	*Leaves*: Before: After: 60°C for 4 days *Organisms*: After: 60°C for 4 days	24 h	$C = \frac{(L_1 \times C_L) - L_2}{W \times 6}$ C = feeding rate L_1 = initial leaves dry weight (mg) L_2 = final leaves dry weight (mg) W = organisms dry weight (mg) C_L = leaf weight change correction factor $C_L = \frac{\Sigma\left(\frac{C_2}{C_1}\right)}{N}$ C_1 = control leaf discs initial dry weight (mg) C_2 = control leaf discs final dry weight (mg) N = number of control replicates	Bloor and Banks (2006b)
Alnus glutinosa	Antibiotics (added during the conditioning process)	River water	Total darkness	1.5 cm 4 leaves at the time to assess food choice	58 h	*Leaves*: Before: 60°C for 24 h After: 60°C for 24 h *Organisms*: After: 60°C for 24 h	96 h	$C = \frac{\{[(f_b - f_a) - (n_b - n_a)] \times 24\}}{g \times t}$ C = leaf mass consumed f_b = initial dry mass of the leaf disc exposed to feeding (before conditioning) (mg) f_a = final dry mass of the leaf disc exposed to feeding (mg) n_b = initial dry mass of the leaf disc protected from feeding (mg) n_a = final dry mass of the leaf disc protected from feeding (mg) g = animal's dry weight (mg) t = feeding time (hours)	Bundschuh et al. (2009)
Alnus glutinosa	Fungicide tebuconazole			1.6 cm 4 leaf discs at the time, but only 2 discs were accessible to the organism	12 h	*Leaves*: Before: After: *Organisms*: After:			Bundschuh et al. (2011a)

Alnus glutinosa	Secondary treated wastewater	River water or secondary treated wastewater		2.1 cm 2 leaves at the time every 7 days	4 weeks	*Leaves*: Before: 60°C for 24 h After: 60°C for 24 h *Organisms*: After: 60°C for 24 h		$C = \frac{[L_b \times (k) - L_e]}{g \times t}$ C = leaf mass consumed L_b = initial dry mass of the leaf disc (mg) L_e = final dry mass of the leaf disc (mg) g = animal′s dry mass (mg) t = feeding time (days) k = leaf change correction factor $k = \frac{\sum \left[\frac{L_{ob} - L_{oe}}{L_{ob}}\right]}{n}$ L_{ob} = initial dry mass of control discs (mg) L_{oe} = final dry mass of control leaf discs (mg) n = number of replicates	Bundschuh et al. (2011b)
Alnus glutinosa	Antibiotics (added during the conditioning process and in the water with the Gammarids)	River and tap water mixture		1.1 cm 2 leaves at the time	24 days	*Leaves*: Before: 60°C for 24 h After: 60°C for 24 h *Organisms*: After: 60°C for 24 h		$C = \frac{[L_a \times (1-k) - L_b]}{g \times t}$ C = leaf mass consumed L_a = initial dry mass of the leaf disc (mg) L_b = final dry mass of the leaf disc (mg) g = animal's dry mass (mg) t = feeding time (days) $k = \frac{\sum \left[\frac{L_c - L_d}{L_c}\right]}{n}$ L_c = initial dry mass of control discs (mg) L_d = final dry mass of control leaf discs (mg) n = number of replicates	Bundschuh et al. (2017)
Alnus glutinosa	In situ feeding assay	River water		1.7 cm 4 leaf discs per cage	6 days	*Leaves*: Before: After: 60°C for 48 h *Organisms*: After: 60°C for 48 h		$C = \frac{(L_1 \times C_1) - L_2}{W \times T}$ C = feeding rate L_1 = initial leaves dry weight (mg) L_2 = final leaves dry weight (mg) W = organisms dry weight (mg) C_1 = leaf weight change correction factor T = feeding time (days)	Crane and Maltby (1991)

(continued)

Table 3 (continued)

Leaf species	Contaminant	Water used for the experiment	Light/dark cycle	Leaf disc size (diameter)	Length of the feeding study	Drying temperature and time (before and after exposure)	Starvation	Equation used	References
Alnus glutinosa	Ex situ and in situ feeding assay	Ex situ *experiment*: In situ *experiment*: River water	Ex situ *experiment*: 10:14 In situ *experiment*:	2.0 cm Ex situ*:* 20 discs per 20 gammarids In situ: 20 discs for 20 gammarids	Ex situ: 14 days In situ: 7 days	*Leaves*: *Before and after:* photo scanned		$FR_i = \frac{(S_{control} - S_i)}{\left(\frac{l_{i,0}+l_{i,t}}{2}\right)\times t}$ FR_i = feeding rate of replicate i $S_{control}$= total surface of the control leaf discs at the end S_i= total surface of the leaf disc at the end of replicate i t = feeding time (days) $l_{i,\,0}$ = number of living gammarids at the start $l_{i,\,t}$ = number of living gamamrids at the end	Coulaud et al. (2011)
Alnus glutinosa Quercus petraea		Filtered river water		1.0 cm 2 leaf discs at the time, with just one accessible to the organism	68–72 h	*Leaves*: Before: wet weight was used After: 65°C *Organisms*: After: 65°C			Danger et al. (2012)
Alnus glutinosa	Antidepressant and fungicide (added to the leaves during the conditioning or in the water)	Filtered river water	12:12	1.3 cm	14 days	*Leaves*: Difference between initial and final ash-free dry mass (AFDW)	24 h		De Castro-Català et al. (2017)
Alnus glutinosa	Metals: in situ experiment			2.1 cm 20 leaf discs at the time for each cage	14 days	*Leaves*: Before and after: photo scanned		$FR = \frac{\sum_{i=1}^{4} \frac{\left(S_{i,0} - S_{i,t}\right)}{\frac{l_{i,0}+l_{i,t}}{2}}}{7}$ FR = feeding rate $i = (i = 1 - 4)$ is the ith replicate S= total surface of leaf discs in each container (mm^2) l = number of living gammarids	Dedourge-Geffard et al. (2009)
Alnus glutinosa	Cadmium	Well water		2.0 cm	7 days	*Leaves*: Before: 105°C for 24 h After: 105°C for 24 h *Organisms*: After: 105°C for 24 h		$FR = \frac{(L_f \times C) - L_i}{Wf}$ FR = feeding rate L_f = leaf final dry weight (mg) L_i = leaf initial dry weight (mg)	Felten et al. (2008a)

								W = organisms dry weight (mg) T = exposure time (days) C = leaching correction factor $C = \frac{\Sigma\left(\frac{L_b}{L_a}\right)}{8}$ L_b = final dry weight of control leaves (mg) L_a = initial dry weight of control leaves (mg)	
Alnus glutinosa		In situ: river water *Lab experiments*: artificial pond water			In situ: 6 days or 12 days *Lab experiments*: 6 days	*Leaves*: Before: (just wet weight) After: 60°C for 48 h *Organisms*: After: 60°C for 48 h		$C = \frac{(L_b \times C_L) - L_a}{W \times T}$ C = consumption of leaf material L_b = leaf discs initial dry weight (mg) L_a = leaf discs final dry weight (mg) W = organisms dry weight (mg) T = exposure time (days) C_L= correction factor of autogenic changes in leaf weight $C_L = \frac{\Sigma\left(\frac{Lc_a}{Lc_b}\right)}{N}$ Lc_a = control leaf discs final dry weight (mg) Lc_b=control leaf discs initial dry weight (mg) N = number of control replicates	Forrow and Maltby (2000)
Alnus glutinosa		Natural drilled groundwater		2.0 cm	21 days	*Leaves*: Photo scanned at the beginning and after 7 days when replaced		$FR = \frac{\Sigma_{i=1}^{N} \frac{(S_i - S_{i-1})}{n_t + n_{t-1}}}{T}$ FR = feeding rate T = total experiment duration (days) S_t=total surface of leaf discs in each container (mm^2) n_t = number of living gammarids	Geffard et al. (2010)
Alnus glutinosa	Antibiotics (added in the water during the conditioning process)	Pure natural water	Total darkness	2.0 cm	3 h	*Leaves*: Before and after: photo scanned *Organisms*: After: lyophilized for 18 h and stored in an exsiccator		Leaf area was calculated by counting the pixel numbers of each single leaf disc.	Hahn and Schulz (2007)
Alnus glutinosa		In situ: river water		Naylor et al. (1989)	6 days	*Leaves*: Before: (Naylor et al. 1989) After: 60°C for 4 days		$FR = \frac{(L_1 \times C_L) - L_2}{W \times 6}$ FR = feeding rate L_1 = initial leaves dry weight (mg) L_2 = final leaves dry weight (mg)	Maltby et al. (2002)

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Table 3 (continued)

Leaf species	Contaminant	Water used for the experiment	Light/dark cycle	Leaf disc size (diameter)	Length of the feeding study	Drying temperature and time (before and after exposure)	Starvation	Equation used	References
						Organisms: After: 60°C for 4 days		W = organisms dry weight (mg) C_L = leaf weight change correction factor	
Alnus glutinosa	Fungicides	SAM-5S	Darkness	1.6–2.0 cm	24 h 24 days	*Leaves*: Before: After: 60°C for 24 h *Organisms*: After: 60°C for 24 h		Calculated following the method of Zubrod et al. (2015)	Newton et al. (2018)
Alnus glutinosa	Anti-cholinesterase compounds			2.0 cm 5 for each tested concentration. Each beaker containing 20 organisms.		*Leaves*: Before: photo scanned and every 24 h		$FR_t = \frac{\Sigma_{i=1}^{5}\Sigma_{t=1}^{D}\left[\frac{S_{i,t}-S_{i,t-1}}{\frac{l_{i,t}+l_{i,t-1}}{2}}\right]/5}{D}$ FR_t = Feeding rate $i = (i = 1-5)$ is the ith replicate D = is the Dth day during the experiment period S = total surface of leaf discs in each beaker (mm^2) l = number of living gammarids	Xuereb et al. (2009)
Alnus glutinosa	Fungicides tebuconazole	River water		Prepared following the method of Bundschuh et al. (2011b) 2 leaf discs at the time	7 days	*Leaves*: Before: After: 60°C *Organisms*: After: 60°C		$C = \frac{L_b \times k - L_e}{g \times t}$ C = feeding rate L_b = initial dry mass of the leaf discs (mg) L_e = final dry mass of the leaf discs (mg) g = dry weight of Gammarus fossarum (mg) t = feeding time (days) k = leaf change correction factor $k = \frac{\Sigma((L_{ob}-L_{oe})/L_{ob})}{n}$ L_{ob} = initial dry mass of the leaf discs (mg) L_{oe} = final dry mass of the leaf discs (mg) n = number of replicates	Zubrod et al. (2010)

Alnus glutinosa	Fungicides	SAM-5S		3.0 cm 2 leaf discs at the time	7 days	*Leaves*: Before: 60°C for 24 h After: 60°C for 24 h *Organisms*: After: 60°C for 24 h		Calculate as described in Zubrod et al. (2010)	Zubrod et al. (2014)
Alnus glutinosa	Fungicides	Bioassay medium		2.0 cm	6 days	*Leaves*: Before: After: 60°C for 24 h *Organisms*: After: wet weight		$C = \frac{L_n - L_f}{t}$ C = consumption of leaf material L_n= dry weight of leaf discs prevented from feeding (mg) L_f= dry weight of leaf discs available for feeding (mg) t = exposure time (days)	Zubrod et al. (2015)
Populus sp.	Cadmium	Dutch standard water	Total darkness	Half a disc 3.0 cm in diameter	2 days	*Leaves*: Before conditioning: 60°C for 48 h After conditioning: 60°C for 48 h After experiment: 60°C for 48 h *Organisms*: After: 60°C for 48 h	4 days	$\mathrm{FA} = \frac{F_i - F_f}{G}$ FA = feeding activity F_i = initial leaf dry weight (mg) F_f = final leaf dry weight (mg) G = dry weight of Gammarus (mg)	Alonso et al. (2009)
Populus tremuloides		River water	12:12	Whole leaves 48 leaves each	3 days	*Leaves*: Before: 45°C After: 45°C *Organisms*: After: 45°C		$\mathrm{RCR} = \frac{\left[\frac{\text{mg food ingested}}{\text{d}}\right]}{\text{mg}}$ mean animal weight × 100 = %body weight weight consumed /day RCR = relative consumption rate	Arsuffi and Suberkropp (1989)
Quercus petraea	Microplastics	ISO medium		4 cm 1 disc every 8 days	48 days	*Leaves*: Before: 40°C After: 40°C *Organisms*: After: wet weight		Relative feeding rate calculate as mg leaf material consumed per mg body mass per day	Weber et al. (2018)
Ulmus procera		Artificial pond water		1.6 cm	1 day	*Leaves*: Before: 60°C for 4 days After: 60°C for 4 days *Organisms*: After: 60°C for 4 days		$\mathrm{FR} = \frac{W_i - W_t}{t}$ FR = feeding rate W_i = mean weight of control discs (mg) W_t = final weight of leaf discs offered as food (mg) t = feeding period (days)	Graça et al. (1993a)

which is usually at the same temperature and for the same time period as used after the exposure (see Table 3). Once the leaf discs have been weighed, they are usually resoaked in water or conditioned, if that is still to be done, and provided to the Gammarids during the experiment, after sometimes rinsing with water.

During and after the exposure, data are collected to calculate the feeding rate of the organisms. The feeding rate equation is similar throughout the literature, but variations can still be found. For example, the data might not have been collected in the same way, even though the same equation might have been used. The most common way to estimate the feeding rate is to compare leaf dry weight before and after exposure to the amphipods, in relation to the duration of the experiment and the weight of the organisms. Commonly, the dry weight of the leaves is adjusted with a constant. This constant takes the loss in weight due to leaching and microbial decomposition into consideration. It is often calculated as the ratio of the control leaves final dry weight and their initial dry weight (e.g. Blarer and Burkhardt-Holm 2016) (see Table 3), but sometimes the equation might vary (e.g. Bundschuh et al. 2011b) (see Table 3). The control leaves are leaf discs that went through the same conditioning process, and through the same experimental conditions as those fed to the organisms, but they themselves were not.

The constant is not always positioned in the same place within the feeding rate equation. Most commonly, it multiplies with the initial dry weight of the leaves (e.g. Maltby et al. 2002) (see Table 3) as the initial dry weight might not be exact. A small amount of leaf might have been lost due to leaching and microbial decomposition during the conditioning process, for example. Sometimes it divides the final dry weight of the leaves (Agatz et al. 2014) (see Table 3). A proportion of the leaf might have been lost through leaching and the decomposition process, and not through Gammarids consumption. Both constant positions are trying to adjust the equation by compensating for the same problem, leaching and decomposition, but mathematically the equations are dissimilar and the results might be different.

Weight is sometimes considered as wet weight (Danger et al. 2012) or as ash-free dry weight (AFDW) (De Castro-Català et al. 2017) rather the normal dry weight (see Table 3). Once the exposure is complete, the leaf discs are collected and dried. The drying process is normally carried out in an oven and/or furnace (i.e. AFDW) at a specific temperature for a specific duration, which was also used for leaf disc preparation. As shown in Table 3, the temperature at which the leaves are dried can be very different and so can the duration of the process.

On rare occasions, the feeding rate is calculated by measuring differences in the leaf disc's surface area, which instead of being weighed are photographed and later analysed with a specific software (Coulaud et al. 2011; Hahn and Schulz 2007) (see Table 3). Scanning the leaf surface might result in very accurate data when it is calculated by pixel size or in mm^2, for example. This calculation does not incorporate a leaching constant (leaf change correction factor), which takes into account the loss of leaf weight due to the conditioning process. Differences in leaf surface could potentially occur as it happens with the loss in weight method. The authors acknowledge that it is still unclear if the choice of feeding equation and the different ways of calculating the feeding rate are actually comparable and equivalent. Interestingly

Coulaud et al. (2011) reported a relationship between the surface and the dry mass of their leaf discs, in order to facilitate possible comparisons between studies with different methodologies. Consequently, it is recommended that a leaf change correction factor should be calculated based on leaf surface loss, to take leaf conditioning changes into consideration and to make data from these different techniques more comparable.

5 Conclusions

Feeding behaviour has been used to investigate the sublethal effects of a wide range of contaminants over the years. As well as providing information on an organism level, feeding studies could also be adapted to understand the possible effects on entire populations, and therefore potential threats to a population could be transposed, to understand the prospective repercussions on the ecosystem.

Throughout this review, it is noticeable that there are variations within the adopted methodologies for the acclimation conditions, the leaf conditioning process and the leaf species used. This review has also highlighted that several different equations are used in the literature to quantify the feeding rate of Gammarids.

During the acclimation period, the organisms are kept at temperatures ranging from 10 to 22°C, even though all of the species considered in this review are from temperate countries. Temperature has been proven to have a significant impact on Gammarids by affecting their physiological parameters and their immune system. Temperature could ultimately have an impact on their feeding rate, which increases when the temperature is raised. The authors recommend that a constant temperature is maintained during the acclimation period and the experiment itself, in order to have a reliable estimation of the feeding rate, independent of a temperature difference. Moreover, the acclimation and experimental temperature should reflect the average conditions for the country where the experiment is being undertaken. In fact, both Maltby et al. (2002) and Coulaud et al. (2011) demonstrated that temperature has a major impact on feeding rate variability during in situ experiments. Consequently, when an in situ experiment includes several different deployments in different geographical areas, temperature should be measured in each location, so that the impact of temperature on the feeding rate can be estimated. Furthermore, the media in which the organisms are acclimated should always be aerated.

Similarly, the authors recommend that light/dark cycles aiming to reproduce seasonal conditions should be avoided, in order to allow the reproducibility of a study regardless of the time of the year. However, this is not the case for in situ studies. The temperature and light/dark cycles during acclimation for in situ experiments should best replicate the natural environment. Consequently natural light/dark conditions and the air and water temperature should be measured, reported and replicated.

Ex situ experiments should be standardised (e.g. using an artificial medium if possible), meaning that the medium's parameters (i.e. pH, conductivity, total

hardness) should be measured and reported, and the medium should be screened beforehand for contamination. If contamination is present, it is important to record the concentrations of the specific contaminant to identify the background level, to have a better understanding of the possible effects. This is especially noteworthy when river water is used to acclimate the organisms, in particular for in situ experiments where river water mimics natural environmental conditions for the acclimation period. It is difficult to say how long the acclimation should last. The authors recommend that further research is required to determine the impact of time frame on acclimation periods and to determine if a longer acclimation period results in stronger data with a lower level of variability.

Several different food types have been highlighted during this review, including different leaf species and conditioning methods. Even though Gammarids are biologically omnivorous organisms, a leaf-based diet is recommended in feeding studies, both during the acclimation period and the exposure, and the same food should be used for both (i.e. same leaf species and same preparation). *Alnus* spp. are the most commonly used leaf material for freshwater Gammarid feeding studies. The authors therefore recommend *Alnus* spp. as a standardised food source for ecotoxicological assays. However, the distribution of *Alnus* spp. is not ubiquitous around the world, and therefore it might be challenging for some researchers to source them for their experiments. In such situations, industrial feed might be a better solution to overcome the problem of non-standardisation. If leaf material is used, applying a conditioning process is recommended, since conditioned material has been proven to be more palatable and have a lower C:N, which translates to a better energy supply. Moreover, it has also been demonstrated how leaf palatability increases when they are conditioned for longer time periods. Consequently, a short conditioning period (i.e. a few days) should be avoided, and organisms should be fed on leaves conditioned for at least 10 days. However, this time period should be prolonged if using fresh leaf material, since it has been reported that conditioning takes longer. In ex situ experiments, conditioning should be conducted using an artificial media inoculated with *Cladosporium* spp., which is the most common fungi species used in the literature to condition leaves. This will ultimately reduce the likelihood of contamination that might result from using river detritus as a source of fungi inoculum for conditioning leaves.

On the other hand, for in situ studies, the conditioning process should ultimately replicate, as accurately as possible, real-life environmental conditions and processes, which means using river water, inoculum and Gammarids from the study site. As previously mentioned, the composition of the water needs to be identified and also the chemical parameters; the latter could then be replicated during the conditioning process. For in situ experiments, the authors recommend conditioning the leaf material directly in the river. For example, placing leaves in small net bags that are submerged and secured in the river where the experiment would take place. This would provide the Gammarids with the same type of food during the acclimation period and exposure. However, conditioning takes time, so it should be undertaken well in advance of the experiment.

It is still unclear if conditioning should take place before or after the leaves are cut into discs, dried in the oven and weighed. Consequently, the authors recommend that further investigations need to be undertaken to compare if drying the leaf discs in the oven should be undertaken before or after the conditioning process and if either of these methodologies alter the feeding rate of Gammarids. Organisms are usually fed ad libitum during the acclimation period. To further reduce the inner variability and strengthen the data, the authors recommend incorporating a starvation period in the experimental design. This starvation period should take place before the feeding experiment, and its purpose is to synchronise the organisms' hunger levels. The authors also recommend that organisms of a comparable size range should be used in experiments as it has been proven that Gammarids of different sizes have a different feeding rate. Juveniles are more sensitive to contaminants, but their feeding rate is characterised by a higher variability over time, which makes them more suitable for short-term studies. On the other hand, because of their greater sensitivity, juveniles are better for ecotoxicological studies by providing ecologically relevant risk assessments for contaminants. *Gammarus* spp. has been widely adopted for ecotoxicological studies, but the genus contains many different species, and even though very similar, there are still differences in their sensitivities, meaning that the choice of one species over the other should be carefully considered, depending on the contaminant tested.

This is of particular interest for in situ experiments since the adopted species would be dependent on the site, but also dependent on the season, which could determine the availability of particular organism sizes. So in order to further reduce inner variability and allow better estimation of the feeding rate, organisms should be measured at the start of an experiment, possibly by photography and length measurements, in order to have a pool of organisms of the same size and potentially the same life stage. This is particularly noteworthy when growth is measured alongside the organisms feeding rate.

The source of the organisms might also have an impact on the results. Organisms collected in the wild could be better suited for in situ studies, as they could provide a more realistic site-specific response. However, local site-related species may be characterised by previous exposure histories that could ultimately influence their feeding rate (e.g. they could potentially be acclimated to a certain level of pollution). This is a problem that has to be taken into consideration both for in situ and ex situ experiments. Perhaps laboratory-bred organisms should be used to reduce variability even further, and it would provide a constant stock of Gammarids (Blockwell et al. 1996; Bloor and Banks 2006a, b; McCahon and Pascoe 1988). However, breeding Gammarids is not always possible and it is highly species dependent. Long-term culturing could also potentially lead to a higher or lower contaminant sensitivity and a reduced genetic variability.

The last step of a feeding study involves the quantification of the feeding rate by using an equation. As highlighted in this review (see Table 3), there are various equations in the literature that are indiscriminately used to calculate the feeding rate. However, some of these equations are mathematically different, and it raises the question, are the equations and the feeding rates generated by them equal?

The feeding rate can be estimated by using the leaf weight or surface area. The equation that is most commonly adopted estimates the feeding rate by comparing leaf dry weight before and after being provided to the Gammarids, divided by the time (expressed in days) and the weight of the organisms. Usually the dry weight of the leaf discs is adjusted with a constant. The authors recommend that the position of the constant is dependent on when the leaves are conditioned and dried. If the leaves are conditioned after being dried and weighed, the constant should multiply with the initial dry weight, so that it takes into consideration that the leaf disc might have lost more weight through being submerged in water during the experiment. However, if the leaf discs are dried and weighed after being conditioned, the final dry weight should be divided by the constant, because some of the leaf material might have been lost through leaching and not through Gammarid feeding.

Another consideration is that the constant is not always calculated in the same way, and this could ultimately alter the experimental results. Again, the authors recommend that further research is required to understand the impact of the various constant positions on the outcome of a study. Until then, the authors recommend that the equation provided by Maltby et al. (2002) is adopted, as it is representative of real-life environmental feeding.

When leaf area is used to calculate the feeding rate, the constant is not often included in the equation. This means that the possible loss of leaf material due to the leaching process is not taken into consideration. Leaf area is often used to calculate the feeding rate for in situ experiments, so the authors recommend that if this method is going to be used, a set of control leaves should also be established, in order to calculate a leaching constant based on the difference in surface area.

It is clear that a standardised protocol is required, which would benefit the scientific community and regulatory authorities and allow them to interpret and compare published literature to understand the impact of various contaminants (and mixtures) on the environment. This could be achieved by undertaking serial experiments to clarify what impact these heterogeneities have on the final results. There are methodologies such as Naylor et al. (1989) and Nilsson (1974) that have been used many times, but unfortunately, there are still others that are the result of a mixed methodology. The variability within feeding studies has already been acknowledged, and the first steps towards standardisation have evolved (Agatz and Brown 2014).

A standardised ex situ methodology would greatly benefit this field of research, by not only allowing a more meaningful comparison between the peer-reviewed literature, but also to better understand the impact that specific contaminants could have on Gammarid populations and ecosystems. This could be enhanced further if ex situ experiments are placed side by side with biomarker analysis and in situ studies. In theory, in situ tests could provide a realistic and integrated understanding of real environmental pollution. If standardised, in situ tests could be used by regulators to critically evaluate the state of an ecosystem and the potential impact that a certain contaminant or mixture could have on the environment. This is of particular interest since the establishment of the Water Framework Directive (European Union 2000), which outlines that all European water bodies should reach ‘good quality status’ by

2015 and has since been extended. The establishment of a standardised suite of in situ and ex situ feeding assays would provide a realistic monitoring tool and environmental risk assessment, which would be of benefit to the scientific community, and also decision makers.

6 Summary

Feeding behaviour of freshwater Gammarids has been used for several decades as a sublethal toxicity endpoint. Feeding behaviour has been demonstrated to be an effective endpoint, but there is not a standardised assay. This paper aims to review the existing published literature to highlight the methodological discrepancies in feeding behavioural studies (both in situ and ex situ). Key discrepancies in the acclimation period are temperature, duration, media, light/dark cycles and the characteristics of the test organisms. Interestingly, the food preparation method and the choice of feeding rate equation are also diverse. Non-standardisation of any of these factors could influence the outcome of the experiment and render a comparison between studies difficult. There is an undeniable need for scientific discussion and agreement on a standardised protocol for feeding behavioural studies, to ensure that all future studies are directly comparable and to enhance the usefulness of feeding assays as a biomonitoring tool to assess water quality.

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Environmental Sorption Behavior of Ionic and Ionizable Organic Chemicals

Luise Henneberger and Kai-Uwe Goss

Contents

Keywords Ionizable organic chemicals · Speciation · Sorption · Modelling · Bioaccumulation · Intermolecular interactions

1 Introduction

Many chemicals of environmental concern are ionic or ionizable organic chemicals (IOCs), including various pharmaceuticals, pesticides, surfactants, and ingredients of personal care products, as well as metabolites and degradation products of the above-named classes of chemicals (Franco et al. 2010). In principle, two different

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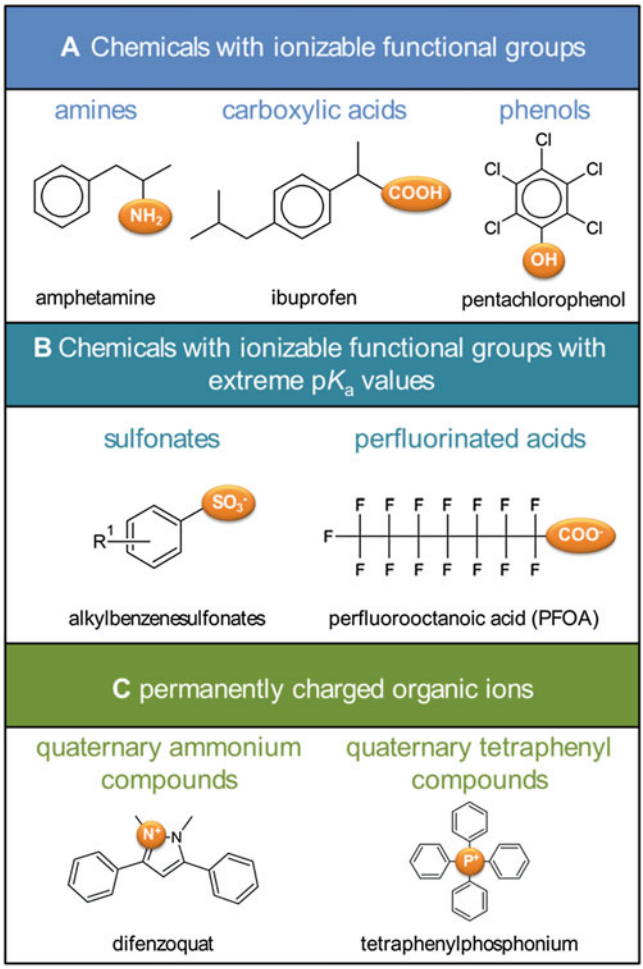

Fig. 1 Examples of ionic and ionizable organic chemicals that differ in their degree of ionization

types of IOCs can be distinguished: permanently charged chemicals and ionizable structures, for which speciation is pH-dependent (see also Fig. 1a–c). Examples for chemicals with ionizable functional groups are carboxylic acids, primary, secondary, and tertiary amines, and phenols (Fig. 1a). Sulfonates and perfluorinated acids are a special type of ionizable chemicals, because their pK_a values are extremely low and the neutral species of these chemicals may be negligible (Fig. 1b). Typical examples of permanently charged structures are quaternary ammonium and phosphonium compounds and ionic liquids (Fig. 1c) (Ranke et al. 2007, 2009). Recently, the focus has turned on quaternary phosphonium compounds as they were identified as emerging environmental contaminants (Schlüsener et al. 2015). However, currently used methods for the assessment of chemical persistence, bioaccumulation, toxicity, and sorption in soil are not applicable to IOCs (Claßen et al. 2016; Tolls 2001),

because their sorption behavior is far more complex than the partitioning of neutral organic chemicals. In general, relevant sorption of IOCs can be expected, if the sorption phase exhibits charged functional groups, as many environmental sorbents do. Possible environmental sorption phases of concern include soil components with high ion exchange capacity (e.g., clay minerals and organic matter) and biological matrices such as proteins and zwitterionic head groups of phospholipids. This manuscript outlines physicochemical principles of ion sorption and reviews the current scientific knowledge regarding bioaccumulation and toxicity of IOCs. Furthermore, examples of experimental studies on ion sorption are presented and existing modeling approaches for the sorption of IOCs are discussed.

2 Physicochemical Principles of Ion Sorption

For IOCs at least four different types of sorption processes are possible that are not mutually exclusive (Fig. 2). Organic ions can bind to charged binding sites by ion exchange (Vlachy et al. 2009). This sorption process is utilized for technical ion exchangers and for solid phase extraction of charged analytes (Bäuerlein et al. 2011, 2012). Examples of natural ion exchange materials include soil organic matter, which acts as a cation exchanger, as well as clay minerals and proteins (Jafvert 1990; Sassman and Lee 2005; Wilting et al. 1980). Another very important sorption process for IOCs is sorption at neutral interfaces between two phases of very different polarity. If the chemical has a charged hydrophilic head group and a large hydrophobic moiety, the neutral part of the molecule can sorb to a nonpolar phase, while the head group stays in the more polar phase (e.g., surfactants at the interface of an oil–water mixture). IOCs can also partition as free ions into a bulk organic phase but stay in the vicinity of the interface, while the (inorganic) counter ions reside in the water phase (Westall et al. 1985). This process is limited by the

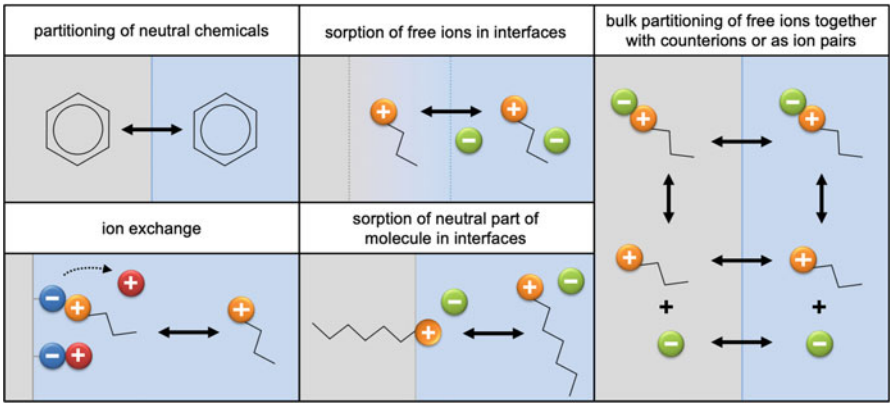

Fig. 2 Sorption processes of neutral and ionic chemicals

involved charge separation and is dependent on the concentration of the ions present in the solution, the distance, and the dielectric constant of the surrounding medium. In principle, the flux of free ions and their steady-state at and across interfaces can be calculated based on chemical and electrostatic gradients using the Nernst equation. A special case is the sorption of IOCs into biological membranes that possess a positive dipole potential which favors the sorption of anions (Benz 1988). Free ions can also partition between uncharged bulk phases together with their counter ions (as free separate ions) and as ion pairs, e.g., partitioning between water and an organic solvent like octanol (Ingram et al. 2011; Jafvert et al. 1990; Zhao and Abraham 2005). In this case the free separate ions and the ion pairs (both will be in equilibrium with each other) can distribute throughout the complete bulk phases because there is no charge separation and therefore no electrostatic force that keeps them in the vicinity of the interface. Significant partitioning of ion pairs is only expected if the stability constant of the ion pair is already high in water, which is typically the case if both ions are relatively hydrophobic (e.g., an alkylamine cation combined with an alkylacid anion) (Schunk and Maurer 2005). In the environment, the formation of ion pairs is probably of minor importance, because it is unlikely that a hydrophobic counter ion is available at sufficiently high concentration for relevant ion-pair formation (Hallén et al. 1985). The partitioning of free organic ions together with inorganic counter ions from water to an organic phase is also expected to be rather insignificant, because the counter ions are often small ions with a high surface charge density (Ingram et al. 2011). These ions tend to stay in water rather than to form ion pairs, because of favorable dipole–charge interactions with the water molecules (Westall et al. 1990).

The partitioning of neutral organic chemicals is dominated by van der Waals interactions and H-bond formations. In contrast, sorption of IOCs is often driven by interactions of their charge with complementary charges in the environment (e.g., with ion exchangers and in electric fields) followed by H-bond interaction and interactions with strong dipoles like water (Collins et al. 2007). The relative importance of charge–charge and charge–dipole interactions decreases, as the hydrophobicity of an ion increases (Lund et al. 2008). Whereas small inorganic ions usually have high surface charge densities, the charge density of organic ions can vary widely. In fact, hydrophobic ions that show strong sorption from water to an uncharged organic phase typically have low charge densities at their surface (Lund et al. 2008). Low surface charge densities of ions are either a result of delocalization of the charge (see bis(fluorosulfonyl)imid, Fig. 3b) or the charge is hidden in the center of a bulky molecule (e.g., tetraphenyl and quaternary ammonium ions, Fig. 3a). Another factor that has to be considered is the hydration shell that forms around a charged molecule and that may also alter the effective surface charge density if it stays in place when the molecule interacts with charged sorption sites (Hammer et al. 2018; Hühnerfuss 1989).

Another difference between neutral organic chemicals and IOCs in terms of sorption behavior is that the sorption of ions can be highly influenced by pH value and salt concentration of the surrounding medium (Sassman and Lee 2005; ter Laak et al. 2006). The pH value can affect the sorption of ions by two different

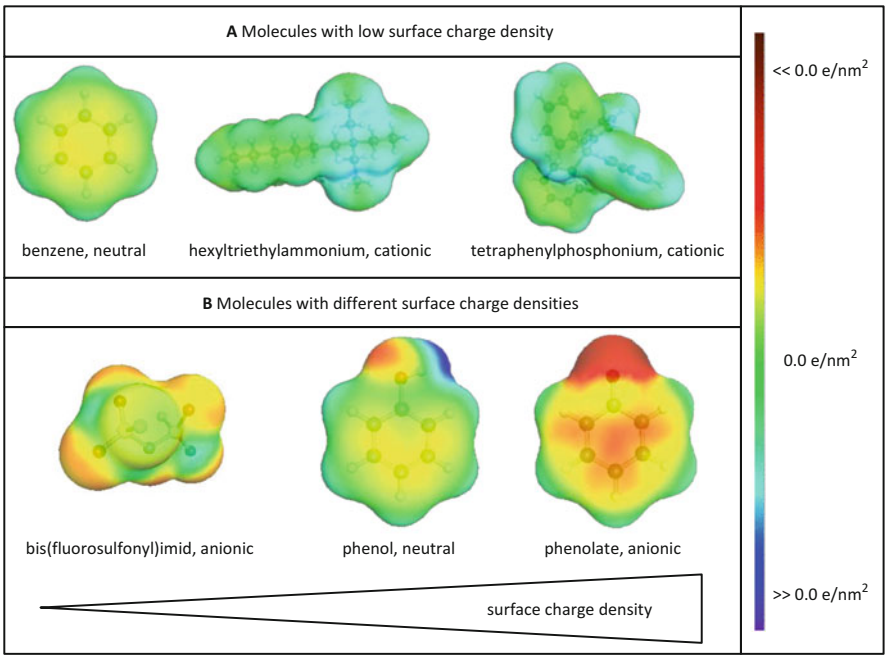

Fig. 3 Surface charge densities of different neutral and ionic chemicals (calculated with TURBOMOLE V6.5 2013)

mechanisms: (1) the speciation of ionizable chemicals is pH-dependent and (2) the conformation and charge status of the sorption phase can change when changing the pH, e.g., the conformation and charge of proteins like human serum albumin is highly pH-dependent (Peters 1995). The salt concentration can also influence sorption either by competing for the same sorption sites at an ion exchange sorbent (Droge and Goss 2013b) or by their impact on ion-pair formation. Westall and coworkers report that the partition constants of neutral ion pairs correlate well with the partition constants of the corresponding neutral organic acids (Jafvert et al. 1990) and for high pH and ionic strength, partitioning between water and octanol is dominated by ion-pair partitioning rather than the partitioning of free ions (Strathmann and Jafvert 1998; Westall et al. 1985). As a result, the octanol–water partitioning of IOCs increases with salinity because of the increasing amount of available partners for ion-pair formation (mass action law). Consequently, there cannot be a single log K_{ow} value for an IOC. Instead, the log K_{ow} of an IOC must always be an operationally defined value for a concrete concentration and composition of counter ions (typically the inorganic ions will prevail) present in the aqueous phase. Yet another sorption mechanism that depends on the presence of inorganic ions in the aqueous solution is “ion bridging” by which a multivalent (inorganic) ion such as Ca^{2+} could connect an organic anion to a negatively charged surface site (Chen et al. 2012; Figueroa et al. 2004; Haftka et al. 2015).

Sorption processes of ions are often nonlinear (i.e., concentration dependent). Nonlinear binding isotherms of IOCs have been observed for the sorption to technical ion exchangers (Liu et al. 2007; Wu et al. 2008) and to soil organic matter (Droge and Goss 2012b). Nonlinear isotherms must occur, according to the mass action law, for ion-pair sorption (Escher and Sigg 2004). However, they can also be a result of the heterogenicity of the sorbent offering sorption sites with different sorption energies and they will occur close to saturation for any sorbent (homogeneous or heterogeneous) with a limited amount of sorption sites (e.g., ion exchange sorbent).

In context of the various conceivable sorption processes at charged interfaces it is also instructive to discuss possible parallels to the sorption of metal ions. The well-established Nica–Donnan concept (Benedetti et al. 1996; Milne et al. 2003) describes sorption of metal ions to charged surfaces as the combination of partitioning to an electrical double layer adjacent to the charged surface and sorption to specific ion exchange sites. In principle this should also hold for IOCs at charged surfaces. A quantitative description of these processes will, however, be much more complex for IOCs than for metal ions. Metal ions are spherical and their charge will equally distribute about their complete spherical surface. The resulting charge density which is relevant for the interaction strength can thus be calculated rather easily and it will have just one distinct value for the complete metal ion. In addition, the interactions of a metal ion are dominated by the ionic interactions and the cavity effect. Van der Waals and H-bond interactions are probably negligible in most cases. This is completely different for IOCs. The charge is located at the functional group of the molecule and in most cases not evenly distributed about the surface of the whole molecule. However, the local charge densities on all parts of the molecule need to be known (which in turn requires knowledge of the 3D structure of the molecule) if a quantitative understanding of the sorption behavior is required. Next to the cavity energy and the ionic interactions, van der Waals and H-bond interactions play an important or even dominant role for IOCs. The Nica–Donnan model may, however, readily be employed to explain differences in the competition of a given organic cation with various metal cations for ion exchange sites and the influence of pH (Chen et al. 2013; Iglesias et al. 2009).

3 Bioaccumulation and Biosorption of IOCs

Bioaccumulation of neutral organic chemicals is mainly driven by the total lipid fraction of an organism and for some neutral chemicals (H-bond donor chemicals) the protein fraction can also contribute to bioaccumulation (Endo et al. 2013). For IOC, instead, several sorption phases may be relevant (Figs. 2 and 4).

Figure 4 shows the average composition of the human body (Goss et al. 2018). Storage lipids (i.e., nonpolar lipids) that are typically the major sink for nonpolar chemicals are assumed to be negligible as sorbing matrix for IOCs (Schmitt 2008). Although it appears that the sorption of IOCs to storage lipids was never investigated by experiment, this assumption is inferred from the weak sorption in octanol for

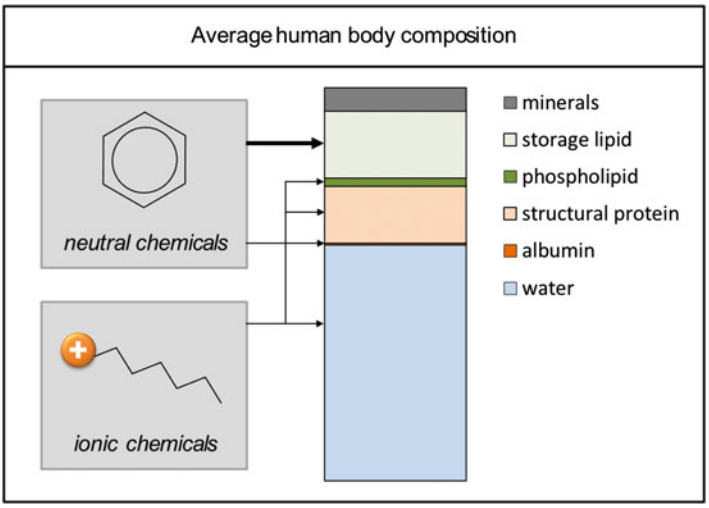

Fig. 4 Sorption phases for neutral and ionic chemicals in vivo. The fractions of the different phases are true to scale and based on the average human body composition published by (Goss et al. 2018)

ionized organic acids and bases as compared to their corresponding neutral form (Escher and Schwarzenbach 1996; Jafvert et al. 1990; Johnson and Westall 1990). However, phospholipids (i.e., polar lipids), the major constituent of cellular membranes, can have high sorption capacities for IOCs (Austin et al. 1995; Avdeef et al. 1998; Escher et al. 2002; Escher and Schwarzenbach 1996; Escher et al. 2000; Ottiger and Wunderli-Allenspach 1997; Smejtek et al. 1996; Thomae et al. 2007). Experimental liposome–water partition constants up to 10^5 ($L_{water}/L_{membrane}$) and higher can be found in the literature (Bittermann et al. 2014). High affinity to biological membranes has also implications on the toxicity of IOCs, as it is directly linked to baseline toxicity (for further discussion see below). However, phospholipids constitute only about 0.7% of the total body weight (Goss et al. 2018). Hence, they may not be dominating for the bioaccumulation of IOCs.

Another possible sorption phase for IOCs is the protein fraction of an organism. The most relevant proteins for the in vivo distribution of IOCs are probably serum proteins and structural proteins. Binding data to serum albumin, the main protein in blood plasma, is often available from the literature, especially for pharmaceuticals (Henneberger et al. 2016a; Kragh-Hansen 1981; Peters 1995). Hydrophobic acids are well known to have high affinities for serum albumin (Bischel et al. 2011; Fanali et al. 2012; Fasano et al. 2005), while cationic chemicals show strong binding to other serum proteins like α_1-acid glycoprotein (Kremer et al. 1988). Again, the amount of serum proteins (0.4%) is small compared to the high quantities of structural proteins (11%) (Goss et al. 2018). Structural proteins form the cytoskeleton of all cells and are present in high amounts in muscle tissue (mainly actin and myosin), connective tissue (collagen), and skin, hair, and nails (keratin). For neutral organic chemicals the partition constants to structural proteins are usually more than one order of magnitude lower than partition constants to serum albumin (Endo et al.

2012). For anionic chemicals the binding to structural proteins is much weaker compared to serum albumin (partition constants can differ by more than three order of magnitude), while cations seem to show similar sorption to serum albumin and structural protein (Henneberger et al. 2016b). Because binding to proteins can be very specific, other protein classes might be important for some IOCs. For example, perfluorinated acids show high affinities for serum albumin and the fatty-acid-binding protein in the liver, explaining the preferential accumulation of perfluorinated chemicals in blood and liver (Luebker et al. 2002; Ng and Hungerbühler 2014; Woodcroft et al. 2010; Zhang et al. 2013).

Even hydrophilic IOCs that mainly reside in the water phase of the body may still be enriched within organisms due to an ion trap effect when internal and external pH differ (see also Sect. 6).

Bioaccumulation is defined as a steady-state distribution. Hence, not only the equilibrium sorption is important, but also the kinetics of uptake, metabolism, and excretion of IOCs. Uptake and excretion are influenced by the membrane permeability of the various chemical species (see below) but also the local pH (e.g., in the gastrointestinal tract or of the gills) is important (Erickson et al. 2006). Hepatic metabolism in fish has been investigated systematically for more than 50 ionic species with an in vitro assay (Chen et al. 2016). For neutral chemicals such information can be scaled up to the total organism and combined with physicochemical properties for an assessment of the bioconcentration potential of a chemical (Nichols et al. 2013). However, it is not yet clear how the necessary quantitative in vitro to in vivo extrapolation (QIVIVE) would work for ionic species because their sorption must be understood for the QIVIVE procedure.

In general, we can expect bioaccumulation in fish to be less of a concern for IOCs than for neutral chemicals but a case by case assessment remains necessary. Biomagnification in fish and trophic magnification in aquatic food webs have already been reported for perfluorinated acids which are almost completely ionized at environmental pH values (Kelly et al. 2009; Martin et al. 2003; Ng and Hungerbühler 2014). The available literature on the bioaccumulation potential of IOCs in fish has been reviewed by Armitage et al. (2017). In two more recent papers from our own group the tissue specific sorption of anions in fish and terrestrial organisms was assessed (Goss et al. 2018) and a screening of the bioaccumulation potential of almost 2000 IOCs was performed (Bittermann et al. 2018). For air breathing animals a general statement in terms of biomagnification is not possible. In this case neither neutral nor ionic chemicals are efficiently excreted via an aqueous phase and much will depend on the chemicals metabolism (Goss et al. 2018).

4 Sorption of IOCs in Soil/Sediment and to Polymers

Soils are known to have a distinct cation exchange capacity which should be relevant for the sorption of organic cations. And indeed, there are a number of studies revealing that the cation exchange capacity of both, clay and humic substances in

soil, and complexation with metal oxides contributes significantly to the overall sorption capacity. These studies have systematically investigated the influence of competing inorganic cations that are naturally available in soils as well as the influence of pH, different types of minerals, and the structure of the considered cations (Droge and Goss 2012a, b, 2013b; Jolin et al. 2017; MacKay and Seremet 2008; MacKay and Vasudevan 2012; Pils and Laird 2007; Sassman and Lee 2005; Tolls 2001). It was found that the ionic species contributes significantly to the total sorption of ionizable organic bases, even if the fraction of the ionic species is not dominating (Droge and Goss 2012b). For anionic organic species, sorption in soils is less pronounced due to the rather small anion exchange capacity, but still not negligible (Higgins and Luthy 2006; Rodriguez-Cruz et al. 2005; Tülp et al. 2009). For zwitterions it was shown that both charged functions of the molecule can matter so that the sorption process becomes even more complex (Carrasquillo et al. 2008; Figueroa and MacKay 2005; MacKay and Seremet 2008).

The sorption of IOCs to different types of polymers has also been studied. Finding a polymer that has a reasonably high sorption capacity for charged chemicals is challenging, but it is the prerequisite for successful solid phase microextraction (SPME) and passive sampling of IOCs (Bäuerlein et al. 2011). Polyacrylate (PA) has been used for SPME of weak organic acids and bases (Broeders et al. 2011; Escher et al. 2002; Haftka et al. 2013; Ohlenbusch et al. 2000). However, only the neutral species of these chemicals partitions to PA and permanently charged IOCs can only be sampled, if the molecule has a large hydrophobic tail (e.g., surfactants) (Chen et al. 2012; Rico-Rico et al. 2009). Recently, C18 based materials have been reported to be suitable sorption materials for IOCs (Henneberger et al. 2019; Peltenburg et al. 2015b; Vuckovic et al. 2009). Peltenburg et al. have successfully used the so-called mixed-mode SPME fibers that combine hydrophobic C18 and cation exchange groups for sampling of organic bases (Peltenburg et al. 2013, 2015a, b, 2016). Ion exchange polymers were also used as sorption materials for IOCs (Bäuerlein et al. 2011). In fact, ions of opposite charge show high affinities for ion exchange polymers, but the material has to be thoroughly calibrated, because sorption is nonlinear (i.e., concentration dependent) and highly influenced by the concentration of other ions present in the solution (Bäuerlein et al. 2012; Oemisch et al. 2014).

5 Modeling of Ion Sorption

In contrast to neutral chemicals, the modeling of organic ions´ sorption is still limited to several specific modeling approaches mostly with small domains of applicability. For neutral chemicals the octanol–water partition constant (K_{ow}) is often used to model sorption to biological phases. This approach has been extended to ionizable chemicals as well. The simplest sorption model for ionizable chemicals is shown in Eq. 1. In this equation, the pH-dependent distribution ratio between octanol and water (D_{ow} (pH)) for an ionizable chemical is calculated from the octanol–water

partition constant of the neutral species ($K_{ow,neutral}$), assuming that the neutral fraction of the chemical ($f_{neutral}$) is dominating the sorption, because the ionized fraction does not partition from water to the organic phase (Schmitt 2008).

$$D_{ow}\,(\mathrm{pH}) = f_{neutral} \cdot K_{ow,\,neutral} \tag{1}$$

This model works for ionizable chemicals, if the fraction of the ionic species is small and if the ionic species is not very hydrophobic. If the ionic fraction of the chemical (f_{ion}) is contributing to the sorption, Eq. 2 is used to calculate D_{ow} (pH). For this calculation the octanol–water partition constant of the ionic species ($K_{ow,ion}$) is required in addition.

$$D_{ow}\,(\mathrm{pH}) = f_{neutral} \cdot K_{ow,\,neutral} + f_{ion} \cdot K_{ow,\,ion} \tag{2}$$

In principle, Eq. 1 is not applicable to permanently charged ions (e.g., quaternary ammonium compounds and ionic liquids, Fig. 1c) and compounds that show strong dissociation (e.g., perfluorinated acids, Fig. 1b). Furthermore, for the calculation of D_{ow} (pH), it has to be considered that there is not a single value for $K_{ow,ion}$. To keep charge neutrality, the ionic species of the chemical is always sorbing to octanol together with a counter ion (either as free ions or as ion pairs). Hence, $K_{ow,ion}$ must be dependent on the concentration of the available counter ions (Johnson and Westall 1990; Westall et al. 1985). Given the complexity of the sorption processes (see Fig. 2 and corresponding discussion) to natural matrices like proteins, phospholipids, humic matter, minerals, and others, it comes as no surprise that octanol, and consequently D_{ow} (pH), has little value as a surrogate for predicting sorption to natural sorbents (Bittermann et al. 2016; Droge and Goss 2012b; Henneberger et al. 2016a).

As stated above, for charged environmental and biological phases, like soil organic matter and proteins, ion sorption definitely needs to be taken into account. Several models that explicitly consider the sorption of ions have been developed. However, these models are often either lacking sufficient mechanistic background or have a very limited domain of applicability. Polyparameter linear free energy relationships (PP-LFERs) have been successfully used to model various sorption processes of neutral organic chemicals (Endo and Goss 2014), including biological phases such as proteins and lipids (Endo et al. 2011, 2012; Endo and Goss 2011; Geisler et al. 2012). Abraham and coworkers have extended the original PP-LFER approach by adding two new descriptors for ionic interactions (J^+ and J^-, Eq. 3) (Abraham 2011; Abraham and Acree 2010a, b, c, d, 2015, 2016).

$$\log K_{1/2} = \mathrm{c} + \mathrm{e} \cdot E_i + \mathrm{s} \cdot S_i + \mathrm{a} \cdot A_i + \mathrm{b} \cdot B_i + \mathrm{v} \cdot V_i + j^+ \cdot J_i^+ + j^- \cdot J_i^- \tag{3}$$

In this equation the logarithmic partition constant of an ion between phase 1 and 2 ($\log K_{1/2}$) is calculated using two different sets of descriptors. The small letters (e, s, a, b, v, j+, j^-) represent the properties of the sorption system. The properties of

the chemical are defined by the capital letters: E is the excess molar refraction, S represents polar interactions, A the H-bond donor properties, B the H-bond acceptor properties, and V is the molar volume of the chemical. J^+ and J^- characterize the interactions that are connected to the positive or negative charge of the ion. The equation was originally developed for solvents, but has been demonstrated to give reasonable predictions for structural proteins as well (Henneberger et al. 2016b). Unfortunately, for ions this modeling approach appears rather empirical with no clear mechanistic background. Furthermore, the required chemical descriptors are not available for many ions and the influence of pH, competing ions, or ion pairing cannot be considered. Various other attempts have been made to predict sorption of ionic species in soils. These models appear to cover some aspects quite well such as the relative influence of competing ions, the cation exchange capacity, or some molecular structural entities within a class of compounds (Droge and Goss 2013a; Figueroa et al. 2004; Higgins and Luthy 2007; Jones et al. 2005; MacKay and Vasudevan 2012; Sassman and Lee 2005). However, none of these models is able to predict soil or sediments sorption coefficients for some standardized conditions (pH, ionic strength, and composition) from molecular structure across a large number of chemical classes. Sorption of ions to albumin was shown to depend on the 3D geometry of the ions (Henneberger et al. 2016a). A 3D QSAR model was able to cover and explain these effects (Linden et al. 2017), but this model is neither user friendly nor able to cover a wider chemical domain. Much more successful was the attempt to predict the sorption of both anions and cations to phospholipid membranes (Bittermann et al. 2014, 2016; Timmer and Droge 2017). This can be done with a commercial software, COSMOmic, that is based on quantum chemical calculations and has a wide application domain due to its fundamental nature. For 235 molecules (among them 24 cations and 51 anions) the predictive error was 0.65 log units (Bittermann et al. 2014) and for 19 cationic amine surfactants in a separate work the predictive error was even smaller (Timmer and Droge 2017).

6 Toxicity and Toxicokinetics of IOCs

6.1 Membrane Sorption and Narcosis

As stated above, the membrane sorption of ionic species from water is usually smaller than that of their corresponding neutral species, but it is by no means negligible. In general, anions show a stronger distribution to membranes than cations because of the positive dipole potential in the interior of the membrane (Flewelling and Hubbell 1986a, b). This is nicely illustrated by tetraphenylborate and tetraphenylphosphonium which are almost identical with practically the same 3D geometry and the same charge density but with opposite signs. However, their membrane–water partition constants ($K_{mem/water}$) differ by several orders of magnitude with log $K_{mem/water} = 5.2$ [L_{water}/L_{mem}] for the tetraphenylborate anion and log $K_{mem/water} = 1.2$ for the tetraphenylphosphonium cation (Flewelling and Hubbell 1986a).

Recent publications suggest that baseline toxicity or narcosis for organic ions occurs at about the same critical membrane concentration of 100 mmol/L_{mem} as for neutral chemicals (Baumer et al. 2017; Bittermann and Goss 2017; Bittner et al. 2018; Escher et al. 2017). Hence, narcotic effects can be predicted from the fraction of the ionic and neutral species freely dissolved in water and their respective liposome–water partition constants, which can be calculated (see above) in case of lacking experimental values.

6.2 Membrane Permeability

The very hydrophobic inner part of biological membranes constitutes the major energy barrier for the permeation of ions. This is even more pronounced for cations than for anions due to the positive dipole potential in the membrane (Flewelling and Hubbell 1986b). As a result, the membrane permeability of ionic species is orders of magnitude smaller than that of the corresponding neutral species (Ebert et al. 2018). This has a number of consequences for the toxicokinetics of permanent ions and ionizable compounds.

If the membrane permeability of an ionic species is much smaller than that of its corresponding neutral species, then the so-called ion trap effect will occur between compartments that are separated by a membrane and possess different pH values. In this case, equilibrium sorption between both compartments is reached, when the neutral species has attained equal concentrations on both sides of the membrane. However, if the pH is different this directly infers that the concentrations of the ionic species on both sides of the membrane are different, due to the dissociation equilibrium. In the extreme case of an impermeable ionic species the effect can be calculated by Eq. 4.

$$\frac{\text{total internal conc.of chemical } i}{\text{total external conc.of chemical } i} = \frac{\text{fraction of neutral species at external pH}}{\text{fraction of neutral species at internal pH}} \quad (4)$$

This can lead to an increased accumulation of acids in aquatic organisms if the aquatic pH is acidic while the organisms maintain an internal pH around 7.4 as can be exemplified as follows: the pesticide 2,4-D has a pK_a of about 3.4 which means that only 1% of the chemical is in its neutral form at an aqueous pH of 5.4. If the freely dissolved concentration of the neutral species of 2,4-D in an exposure medium at pH 5.4 is 1 mmol/l (i.e., the total freely dissolved 2,4-D concentration is 100 mmol/l), then the freely dissolved neutral concentration in an organism exposed to this solution also is 1 mmol/l if equilibrium between organism and exposure medium is obtained. If the internal pH of this organism is 7.4, then the neutral fraction is only 0.01% of the total concentration which means that in this case the total freely dissolved internal concentration must be 10,000 mmol/l which is 100 times higher than the total external freely dissolved concentration. Within an organism this effect can lead to a preferred trapping of bases in acidic intracellular vesicles such as

lysosomes (Gulde et al. 2018; Heikkinen et al. 2009). Such an increased freely dissolved concentration in some parts of an organism can, of course, also result in increased membrane concentration in adjacent membranes and thus an increased toxic effect as compared to the aqueous exposure concentration (Neuwoehner and Escher 2011). This might explain observed pH effects on toxicity that cannot be explained otherwise (e.g., (Bittner et al. 2018; Boström and Berglund 2015; Neuwoehner and Escher 2011)).

Some hydrophobic anions possess a membrane permeability that – although still much smaller than that of their neutral corresponding species – can still be important. At mitochondrial membranes that keep up a proton gradient for the generation of ATP, acids with relatively permeable anionic species will act as proton shuttles and destroy the natural proton gradient – an effect known as uncoupling (LeBlanc 1971; McLaughlin and Dilger 1980). This toxic effect is observed for many chloro- and nitrophenols, for example, and it is pH-dependent (Escher et al. 1999). In a recent paper, a series of systematic measurements for the membrane permeability of a diverse set of organic anions ranging over 10 orders of magnitude is presented which is the first data set of that kind (Ebert et al. 2018). These anionic permeabilities nicely correlate with the predicted hexadecane–water partition coefficient of the respective anions which should provide a promising opportunity for predicting toxic effects by uncoupling (Ebert et al. 2018).

Besides these effects on equilibrium sorption and toxicity there are also direct kinetic effects: The total membrane permeability of an acid or base results from the parallel transport of neutral and ionic species. Neutral species are usually limited in their permeability by the aqueous boundary layer, which is always present adjacent to both sides of a membrane. Ionic species are usually limited by the membrane itself and not by the aqueous boundary layer (ABL). Thus, if both species travel in parallel (i.e., speciation is about 50/50) and are quickly interchangeable by acid–base reactions, then they can readily pass any combination of ABL and membrane. If one species prevails, then the respective dominating permeability barrier becomes more and more important (Avdeef 2012). The latter situation becomes extreme for permanent ions. This means that cells (either in a cellular toxicity assay or as part of an organism) may have to be exposed for quite a long time to some ions and ionizable chemicals before they reach a steady-state internal concentration, provided that the chemical is not taken up by active transport. In this case a toxicity assay that is run for only 24 h might not show any effect (because the steady-state concentration is not yet reached within the cells) although the compound might eventually turn out to be toxic if enough time for equilibration is provided. Fischer et al. (2018) studied this situation for 7 ionizable chemicals and one permanently charged cation and found delayed but still substantial cellular uptake after 24 h. This could be explained by the high intrinsic permeability of the remaining neutral species of the ionizable chemicals. For the permanently charged cation the authors concluded that permeation as an ion pair or via ion channels or active transport must be responsible for this finding. More experimental work in this direction is needed.

Organic ions may also pass membranes by active transport through transporter proteins (König et al. 2013). While this is a well-studied topic in pharmaceutical

sciences, there appears to be no generalizable quantitative information available on these transport pathways. Active transport across membranes always competes with passive (diffusive) transport. Hence it appears likely that active transport will generally be more important for ionic species than for neutral ones because neutral species have a much higher diffusive membrane permeability than ionic species. The most likely effect of active transport is as a barrier against the uptake of ionized chemicals. Efflux transporters imbedded in the apical membrane of epithelial cell layers can effectively reduce the uptake of substrate chemicals. This has been demonstrated in Fischer et al. (2013). Increased uptake of ionized chemicals by influx transporters is rather unlikely to occur because these transporters would have to be located in all membranes of the epithelial cell layers and the energy demand for such a transport cascade would be high.

7 Conclusions

Much more experimental data for ionic sorption in well-defined environmentally relevant scenarios are needed. "Well defined" means that not only the pH is controlled in such experiments but also the availability of competing ions and/or corresponding ions for ion-pair formation is reported and possible concentration dependencies are investigated. In general, we are lacking experimental data for zwitterions (glyphosate as a prominent example) and polyvalent ions. We are also lacking systematically determined sorption data for all kinds of organic ions to α-glycoprotein, a transport protein in blood that is known to be important for cations. Existing sorption data for albumin have been measured for fatty-acid free albumin which might not be representative for the albumin in vivo. Hence, additional data for fatty-acid-loaded albumin would be of interest. Sorption experiments to soil have so far focused on amine-cations and pharmaceuticals and need to be diversified. Whenever new experimental data become available, they should be used to evaluate/recalibrate existing predictive models and possibly develop new models. In any case, it is clear that IOCs will demand sorption models that are much more complex than anything that may have been useful for neutral organic chemicals in the past. While empirical log K_{ow} models have brought us a long way for neutral chemicals, a good mechanistic concept will be required for any IOC sorption model with a satisfying predictive power. Further investigation into the parallels with the sorption of metal ions may be helpful.

8 Summary

This review first gives an overview on the principles that govern ionic sorption in environmental systems which are more complex than the simple partition processes of neutral chemicals. Our current knowledge on various topics such as

bioaccumulation, sorption in soils, and nonspecific-toxicity reveals that ionic species can actually be quite hydrophobic contrary to commonly held beliefs. Existing models for the quantitative prediction of organic ions´ sorption in soils and biota are quite restricted in their application range compared to neutral chemicals which is due to the higher complexity of the various ionic sorption processes. In order to further advance our understanding more high-quality sorption data are needed with a focus on multivalent and zwitterionic ions in all partition systems as well as cations in biological matrices.

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Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Ecotoxicology of Heavy Metal(loid)-Enriched Particulate Matter: Foliar Accumulation by Plants and Health Impacts

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Abbreviations

ATSDR	Agency for Toxic Substances and Disease Registry
EDI	Estimated daily intake
EPA	Environmental Protection Agency
ESEM	Environmental scanning electron microscopy
GIS	Geographic information system
GPS	Global positioning system
GSH	Glutathione
HI	Hazard index
HQ	Hazard quotient
ILTCR	Lifetime cancer risk
MDI	Maximum daily intake
Metal-PM	Heavy metal-enriched particulate matter
PN	Particulate matter
ROS	Reactive oxygen species
SH	Thiol
THQ	Total hazard quotient
USEPA	United States Environmental Protection Agency
WHO	World Health Organization
XRD	X-ray diffraction

1 Introduction

The atmosphere plays a major role in contaminant cycle at the global scale. Atmospheric contamination by particulate matter (PM)-bound metals is a great issue for the public and for government agencies worldwide owing to their highly toxic nature (Popoola et al. 2018; Zhang et al. 2017). Heavy metal(loid)s constitute an important class of atmospheric pollutants primarily because of their toxic effects on living beings with high persistence, specific gravities, densities, atomic weights, and tendency to bioaccumulate (Murtaza et al. 2019; Natasha et al. 2018a; Shahid et al. 2014, 2017a; Shakoor et al. 2015). Therefore, several previous studies emphasized the need of understanding the fate, behavior, chemistry, biochemistry, ecology,

biology, and cellular and molecular biology of these heavy metal(loid)s in soil-plant-human interaction (Rafiq et al. 2018; Shahid 2017; Shahid et al. 2018a, b; Shakoor et al. 2019; Xiong et al. 2017).

Particulate matter has a high potential for adsorbing toxic heavy metal(loid)s and making metal-PM complexes of various composition and sizes (Zhang et al. 2018a). The presence of high levels of these metal-PMs in the atmosphere is confronting the environmental quality and human/animal health worldwide (Uzu et al. 2011b; Xiong et al. 2016a). Emission and presence of metal-PM in the atmosphere have gained considerable attention as it has the capability to deteriorate atmospheric quality and impacts human health (Ercilla-Montserrat et al. 2018; Jimoda 2012; Xiong et al. 2014b). Atmospheric contamination with these metal-PMs has increased considerably during the last two decades due to rapid urbanization, economic development, and industrialization. The situation is highly worsening in regions with intense industrial activity (Douay et al. 2008; Pruvot et al. 2006; Schreck et al. 2014; Uzu et al. 2011b).

These metal-PMs involve substantial contamination of different ecosystem compartments: soils, plants, surface waters, and animals including humans (Donisa et al. 2000; Li et al. 2017b; Wu et al. 2017; Xiong et al. 2014a). The potential of these metal-PMs to transport over long range along with high persistency has made the situation more complex and worsened. It is reported that metal-PM can remain in the atmosphere for up to 30 days after their release from the source (Tian et al. 2015). These metal-PMs can induce antagonistic effects on ecosystems and human health many miles away from the source of origin (Dai et al. 2018; Shahid et al. 2013).

Metal-PM can negatively affect human health via two major pathways including the inhalation of atmospheric PM (Goix et al. 2014; Huang et al. 2018; Uzu et al. 2011b) or ingestion of the contaminated soil, dusts, or vegetables (Chuang et al. 2018; Guney et al. 2010; Xiong et al. 2014a). Especially in industrial areas, the heavy metal(loid) concentrations in the atmosphere, soil, dust, water, and crop plant tissues have been reported to be several times higher than their threshold levels (Arshad et al. 2008; Ye et al. 2017). The size, composition, and shape of the PM strongly affect their impact on both ecosystems (Schreck et al. 2012b; Uzu et al. 2011a, b) and human health (Schwartz and Neas 2000).

In the last decade, many studies focused on atmospheric contamination by heavy metal(loid)s and associated health risks. A better understanding of sources, emissions, fate, and associated health hazards can be a useful contribution to the scientific literature. This review highlights the atmospheric contamination due to metal-PM, their sources, speciation and transportation in the atmosphere, dry and wet deposition on soil and plant, foliar uptake by plants, human inhalation, possible human diseases, and the management strategies to control atmospheric contamination.

2 Atmospheric Contamination by PM-Bound Metal(loid)s

Heavy metal(loid)s in the environment are released both by natural processes and anthropogenic activities (Foucault et al. 2013; Khalid et al. 2017a; Pierart et al. 2015; Pourrut et al. 2011; Shahid et al. 2015). The major sources of metal-PM are smelters, power plants, mining operations, and automobiles. Some studies categorized these sources as stationary (petroleum refineries, industrial boilers, smelters, and manufacturing facilities) and mobile (automobiles) sources (Chan et al. 2016; Morawska et al. 1998, 2008; Shamshad et al. 2018). Open burning is also considered a major source of heavy metal(loid) emission to the atmosphere (Wang et al. 2017; Ye et al. 2017).

2.1 Sources of PM-Bound Metal(loid)s

The recent advancements in industrial processes resulted in a release of a large amount of fine and ultrafine metal-PM into the air due to the use of thinner filters (Hu et al. 2018; Uzu et al. 2011a; Viswanath and Kim 2016; Xiao et al. 2018). Cecchi et al. (2008b) reported that metal recycling processes in factories involve several stages such as crushing, fusion, reduction, and refining. They reported that each stage of metal recycling generates considerable amounts of undesirable by-products such as PMs of Cu, Zn, As, Sb, Sn, Bi, and Ag. Uzu et al. (2011a) reported that refining and furnaces are main sources of metal-PM production during industrial processes. Indeed, during the recycling of Pb, Pb-acid batteries are melted at very high temperature, thus releasing several metals such as Cu, As, Sn, and Sb.

The metal type and concentration attached with PM vary with the size of PM. For example, it was reported that As, Cd, Pb, and V mainly attach with fine PM having a diameter of less than 2.1 μm, whereas Ni, Co, Cr, and Ce occur mainly in coarse PM with a diameter greater than 2.1 μm, while Sb, Mn, Cu, Zn, Pd, Pt, and Rh occur at high levels in the medium range PM of 1.1–4.7 μm (Zereini et al. 2005). Similarly, Uzu et al. (2011a) reported that Al and Na were mainly attached with $PM_{1–2.5}$ while As with $PM_{2.5–10}$.

The release of metal-PM is more pronounced in developed countries with significant industrial development (Türtscher et al. 2017). For example, in Europe and France, 4,800 and 108 tons of Pb, respectively, were released into the atmosphere in 2007 (Schreck et al. 2012a). The Pb was mainly released into the atmosphere as PM from Pb production and acid battery recycling (Ettler et al. 2005; Uzu et al. 2011a). Therefore, the fallouts of atmospheric PM represent the main source of Pb contamination in the environment at the global scale (atmosphere and soil) (Donisa et al. 2000). Regardless of the strong decrease in vehicle and industrial Pb emissions in the recent past (Glorennec et al. 2007), Pb-enriched PM is still released into the environment, especially by Pb recycling facilities (Batonneau et al. 2004; Ohmsen 2001; Sobanska et al. 2000). Similarly, the release of other heavy metal(loid)s such as As, Cd, and Cu into the atmosphere has also been reported.

The emission of heavy metal(loid)s and their attachment with PM vary with metal type and size/composition of PM, as well as with the type of industry and industrial

processes. For example, Uzu et al. (2011a) compared PM emission from three different working places from a lead smelter: refining, furnace, and emission. They reported that PM < 2.5 was mainly emitted from emission area, while $PM_{2.5–100}$ was mainly emitted from both refining and furnace areas. Using X-ray diffraction (XRD), they also reported that different types of minerals of metal are emitted from different working place origins (refining, furnace, and emission).

Goix et al. (2014) carried out the environmental scanning electron microscopy (ESEM-EDX) analysis of atmospheric fallouts of a Pb recycling factory to understand the variation in the attachment of heavy metal(loid)s with two size fractions of PM ($PM_{2.5}$ and PM_{10}). They reported that numerous Pb-rich nanoballs were observed in $PM_{2.5}$ compared to the PM_{10}.

Vehicle emission is considered as the main source of heavy metal(loid) introduction into the atmosphere (Duong and Lee 2011; Zheng et al. 2010). A study conducted by Park and Kim (2005) showed that major contributors of the ambient atmospheric contamination of the urban atmosphere are soil dust (13%), vehicle exhaust (26%), and field burning (4%). Automobile emissions release toxic metals into the atmosphere like Pb, Zn, and Cd (Viard et al. 2004). Similarly, the highest airborne heavy metal(loid)s concentration was found in streets with heavy traffic in Germany. Road traffic emissions are usually classified as exhaust and non-exhaust emissions. The brake and asphalt wears are considered among the most important sources of some metal(loid)s. Significant amounts of heavy metal(loid) particles such as Zn, Cd, Co, Cr, Cu, Hg, Mo, Ni, and Pb are also associated with dust from tire wear (Adamiec et al. 2016). Lough et al. (2005) calculated fine (2.5 μm) and coarse (10 μm) PM contributions from vehicle emissions at tunnel entrances and exits.

2.2 Concentration Range of PM-Bound Metal(loid)s

Atmospheric contamination by fine metal-PM is considered a serious health risk for people living in industrial areas and megalopolises (Goix et al. 2014; Juda-Rezler et al. 2011; Xiong et al. 2014a; Zhang et al. 2018b). Several national, regional, and international environmental and health organizations have reported threshold levels of different heavy metal(loid)s in the atmosphere (Table 1). For example, the quality

Table 1 WHO guideline values of heavy metal(loid)s in the atmosphere (ng/m^3)

Element	WHO[a]	EU[b]	Average timing
Cadmium	5	5	Annual
Lead	500	500	Annual
Manganese	150	–	Annual
Mercury	1,000	–	Annual
Arsenic	–	6	Annual
Ni	–	20	Annual
$PM_{2.5}$	–	25,000	Annual
PM_{10}	–	40,000	Annual

[a](WHO 2000a)
[b]The European Union (Directive 1999/30/CE)

standards for ambient atmosphere levels of Pb have been defined in Europe (Directive 1999/30/CE). More recently, this Directive has been integrated into 2008/50/CE which recommends the annual limit values for Pb at 500 ng/m^3. The heavy metal(loids) such as As, Cd, Ni, and Hg are included in Directive 2004/107/CE, which recommends the annual target values for Ni, Cd, and As at 20, 5, and 6 ng/m^3, respectively, in the atmosphere.

However, numerous studies have reported high levels of metal-PM in the atmosphere of urban areas characterized by high population densities, several folds higher than the threshold levels (Lanzerstorfer 2018; Weerasundara et al. 2017). A summary of atmospheric heavy metal(loid) level (ng/m^3) associated with particulate matter of different fractions (PM_{10}, $PM_{7.5}$, $PM_{2.5}$, PM_1) is shown on Table 2. A study conducted in Cantabria region, Spain (Fernández-Olmo et al. 2016), reported high concentrations of metal-PM in the atmosphere: 9.24, 0.25, 354, 3.38, 0.55, 17.5, 20.2, and 4.86 ng/m^3, respectively, for PMs of Pb, Cd, Zn, Ni, As, Mn, Cu, and Cr. The mean value of PM of As was reported to be 0.534 ng/m^3 in Łódź, Poland (Krzemińska-Flowers et al. 2006); 230–2,230 ng/m^3 in Islamabad, Pakistan (Shigeta 2000); 0.91 ng/m^3 in the UK (Directive 2005); 7.77 ng/m^3 in Tehran, Iran (Hassanvand et al. 2015); and 5–20 ng/m^3 in Cologne, Germany (Iffland et al. 1994). The reported atmospheric heavy metal(loid) concentrations in La Plata City, Argentina, are Zn 273 ± 227, Cd 0.41 ± 0.42, Ni 3.2 ± 3.5, Mg 1,472 ± 967, Pb 64 ± 62, Ca 5,343 ± 3,614, Cu 30 ± 27, Fe 1,183 ± 838, Mn 26 ± 20, and Cr 4.3 ± 2.4 ng/m^3 (Bilos et al. 2001).

The concentration of Cd-PM ranges between 0.05 and 0.2 ng/m^3 in Northern Europe, 0.06 and 0.12 ng/m^3 in Southern Europe, and 0.2 and 0.5 ng/m^3 in Central Europe (Aas and Breivik 2005). Similarly, Cd atmospheric concentration ranged from 6–360 ng/m^3 in the USA and 10–53 ng/m^3 in Japan (WHO 1987b). Momani et al. (2000) showed the Zn, Cu, Pb, and Cd levels of 344, 170, 291, and 3.8 ng/m^3, respectively, in the atmosphere of Amman, Jordan.

The concentration of metal-PM in the atmosphere varies among different areas such as urban, rural, and industrial areas. For example, the mean concentration of Cu-PM in atmosphere ranges between 5 and 200 ng/m^3 in rural and urban areas (ATSDR 2002). The average concentration of Pb-PM in global urban and industrial atmosphere is 0.2–0.6 μg/m^3 and 0.5–1.0 μg/m^3 (Shigeta 2000), respectively, while global industrial, urban, and rural levels of As-PM in atmosphere are >1,000 ng/m^3, 3–200 ng/m^3, and 0.02–4 ng/m^3 (Facts 2008), respectively. The varying atmospheric concentration of Cd-PM has been reported between 1 and 3 ng/m^3 in rural and urban areas (Seemayer and Hadnagy 1992). The mean Cd-PM concentrations in industrial, rural, and urban atmosphere are 15–150 ng/m^3, 0.1–5 ng/m^3, and 2–15 ng/m^3 (Friberg et al. 1992).

In the city of Irbid, Jordan, the measured concentrations of metal-PM were 986 ng/m^3 Fe, 111 ng/m^3 Pb, 117 ng/m^3 Cu, 23 ng/m^3 Mn, 8 ng/m^3 Ni, and 283 ng/m^3 Zn in urban area, while the reported values for the metal-PM were 682 ng/m^3, 21 ng/m^3, 55 ng/m^3, 17 ng/m^3, 5 ng/m^3, and 213 ng/m^3 for Fe, Pb, Cu, Mn, Ni, and Zn in rural areas (Gharaibeh et al. 2010). The highest level of Pb-PM, 2,147 ng/m^3, was recorded at an industrial station in Coimbatore, India

Table 2 Concentration of heavy metal(loid)s (ng/m^3) associated with particulate matter of different fractions (PM_{10}, $PM_{7.5}$, $PM_{2.5}$, PM_1)

Country	PM	Heavy metals										References
		As	Cd	Pb	Cr	Hg	Ni	Cu	Mn	Zn	Fe	
Spain[a]	PM_{10}	3.4	–	14	–	0.07	2.9	–	–	–	–	(Alvarez et al. 2004)
Greece[a]	$PM_{7.5}$	–	0.4–2.9	30–135	–	–	1.4–21	26–420	3–89	4–432	–	(Voutsa and Samara 2002)
Greece[b]	$PM_{7.5}$	–	0.6–0.7	10–111	–	–	2.7–45	22–222	11–395	340–1,200	–	(Voutsa and Samara 2002)
China[b]	PM_{10}	–	–	–	0.6 ± 0.02	–	–	1.8 ± 0.13	0.8 ± 0.03	7 ± 0.2	–	(Wang et al. 2007)
China[b]	$PM_{2.5}$	–	–	–	0.8 ± 0.02	–	–	2.2 ± 0.13	1.2 ± 0.1	10 ± 0.1	–	(Wang et al. 2007)
Kolkata, India[b]	PM_{10}	–	5.2 ± 3.8	118 ± 94	6.3 ± 4.2	–	8.3 ± 4.2	–	2.1 ± 1.5	534 ± 302	123 ± 90	(Gupta et al. 2007)
Jharkhand, India[c]	PM_{10}	–	0.00004–0.00007	0.00004–0.0003	0.0002–0.0004	–	0.00001–0.0002	0.00006–0.006	0.00008–0.000178	0.0002–0.0002	0.001–0.003	(Dubey et al. 2012)
Northeastern China[b]	–	0.06 ± 0.0039	0.009 ± 0.001	0.58 ± 0.007	0.206 ± 0.05	–	0.069 ± 0.013	–	0.462 ± 0.05	–	–	(Piao et al. 2008)
Ispra, Italy[b]	–	0.9 ± 0.4	0.5 ± 0.2	98 ± 40	6.5 ± 3.5	–	12.2 ± 3.8	10.5 ± 3.7	14 ± 5	119 ± 33	511 ± 201	(Rizzio et al. 2001)
Saclay Paris, France[a]	–	0.7 ± 0.5	0.39 ± 0.2	15.4 ± 6.5	4.1 ± 1.9	–	2.1 ± 0.6	18.4 ± 6.7	6.9 ± 2.4	45.8 ± 24	483 ± 221	(Ayrault et al. 2010)
Rio de Janeiro [b]	–	–	0.9	101	421	–	0.5	335	1,216	2,120	38,903	(Quiterio et al. 2004)
Frankfurt, Germany[d]	–	1	0.3	32.6	16.3	–	7.3	101.5	35.3	105.6	–	(Zereini et al. 2005)
Dhaka, Bangladesh[e]	–	–	–	121 ± 137	5.01 ± 3.7	–	–	9.20 ± 7.7	19.7 ± 27	827 ± 1,071	338 ± 304	(Begum et al. 2013)
Islamabad, Pakistan[a]	–	–	3.4 ± 2.7	63 ± 56	7.2 ± 5.2	–	–	38 ± 15	38.8 ± 14	3,325 ± 2001	1,343 ± 554	(Shah et al. 2012)
Jeddah, Saudi Arabia[b]	PM_{10}	2.4	49.8	8.0	4.4	–	5.6	8.4	55.4	20.7	2,040	(Alghamdi 2016)
Lahore, Pakistan[a]	PM_{10}	22	77	4,400	30	–	18	73	300	11,000	8,200	(von Schneidemesser et al. 2010)

(continued)

Table 2 (continued)

Country	PM	Heavy metals										References
		As	Cd	Pb	Cr	Hg	Ni	Cu	Mn	Zn	Fe	
Vienna, Austria[d]	PM_{10}	0.9 ± 1.1	0.5 ± 0.4	11 ± 7.7	5.5 ± 6.8	–	5.7 ± 5.7	21 ± 15	13 ± 6.8	40 ± 19	780 ± 360	(Limbeck et al. 2009)
Taipei, Taiwan[b]	PM_{10}	1.2	0.4	21.6	5.4	–	8.4	15	17	55	540	(Gugamsetty et al. 2012)
Taipei, Taiwan[b]	$PM_{2.5}$	3.2	0.4	7.3	0.8	–	5.1	3.7	9.8	14.3	199	(Gugamsetty et al. 2012)
Algiers, Algeria[a]	PM_1	54.7	–	204	19.8	–	–	1,231	2,061	–	3,294	(Talbi et al. 2017)
Algiers, Algeria[a]	$PM_{2.5}$	93	–	371	45	–	–	2,662	3,299	–	7,203	(Talbi et al. 2017)
Algiers, Algeria[a]	PM_{10}	79	–	119	42.3	–	–	861	3,805	–	5,215	(Talbi et al. 2017)
La Plata, Argentina [b]	–	–	0.4 ± 0.4	64 ± 62	4.3 ± 2.4	–	3.2 ± 3.5	30 ± 27	26 ± 20	273 ± 227	1,183 ± 838	(Bilos et al. 2001)
Amman, Jordan[f]	–	–	3.8	291	–	–	–	170	–	344	–	(Momani et al. 2000)
Cantabria region, Spain[b]	–	0.6	0.3	9.2	–	–	3.4	–	–	354	–	(Fernández-Olmo et al. 2016)
Coimbatore, India[a,b,e]	–	–	2.8	14.4	14.2	–	31.4	389	–	520	–	(Mohanraj et al. 2004)
Tamil Nadu, India [b]	–	–	BDL	210–620	5–800	–	BDL-300	300–920	–	10,550–24,960	1,800–6,000	(Vijayanand et al. 2008)
Washington, USA[f]	–	0.8–15.7	1.5–30	2.9–137	17–112	–	–	–	–	–	–	(Melaku et al. 2008)

"BDL" Below detection limit
[a]Urban site
[b]Industrial site
[c]Mining areas
[d]High traffic area
[e]Residential area
[f]Size not mentioned

(Mohanraj et al. 2004). The atmospheric concentration of metal-PM may vary over different seasons (Li et al. 2017b; Zhang et al. 2016). For example, WHO (1987a) reported airborne As concentration 450 ng/m^3 in winter and 70 ng/m^3 in summer for the same geographic location.

The abovementioned studies showed that the atmospheric concentration of metal-PM may rise beyond the toxic/threshold levels (reported by EU regulated levels, WHO guidelines, or EPA's RfCs) in different regions of the world. However, their levels greatly vary in rural, urban, and industrial areas. In contrast to soil heavy metal(loid) contamination, atmospheric contamination does not remain constant and varies greatly with their intensity of emission from the source. Moreover, the climatic conditions (wind, temperature, rainfall, etc.) also affect atmospheric level of metal-PM. Therefore, it is of great importance to identify their possible sources of emission from different natural and anthropogenic sources. Moreover, the atmospheric contamination of metal-PM by different sources requires constant monitoring compared to soil contamination.

2.3 Speciation of PM-Bound Metal(loid)s

Nowadays, metal speciation is highly topical, because the biogeochemical behavior of a metal is highly dependent on its speciation in addition to total metal content (Rafiq et al. 2017; Shahid et al. 2012a, b). Fine and coarse PMs are also reported to contain different chemical forms of a metal (Anake et al. 2017; Helali et al. 2016; Osán et al. 2010). Heavy metal(loid)s attached with atmospheric PM have different species or fractions which show different bioavailability and potential risk to living beings (Feng et al. 2009; Huang et al. 2018). Heavy metal(loid)s associated with PM varies with the type of metal and particulate (Helali et al. 2016; Kang et al. 2017). Various studies have been conducted for the assessment of heavy metal(loid) speciation and their spatial and temporal variation with PM (Jia et al. 2018; Kang et al. 2017; Pattanaik et al. 2016). Most of the heavy metal(loid)s are associated with PM_{10} and $PM_{2.5}$, which can penetrate the respiratory tract and pulmonary region causing adverse health effects (Krzemińska-Flowers et al. 2006).

Donnelly (1993) reported that incineration of solid waste emits toxic heavy metal(loid)s into the atmosphere like As, Pb, Cr, Cd, Hg, Ag, and Be. These heavy metal(loid)s upon incineration are generally converted into their respective oxides and chlorides and are therefore released into the atmosphere in oxide or chloride forms along with fine PM. Goix et al. (2014) carried out Raman microspectrometry of atmospheric fallouts of a Pb recycling factory. They reported that $xPbO.PbSO_4$, $PbCO_3$, α-PbO, Na_2SO_4, $PbSO_4$, and $ZnSO_4$ were identified in both $PM_{2.5}$ and PM_{10} samples as major species. Similarly, Uzu et al. (2011a) reported Pb, PbS, PbO, $PbSO_4$, and $PbO{\cdot}PbSO_4$ as the major species of Pb from a lead recycling factory. They reported that the differences observed in chemical composition and

Table 3 Heavy metal(loid) species in atmosphere associated with PM

Metals	Species in atmosphere	Association with PM	References
Ni	NiS, $NiFeO_4$, $NiSO_4.H_2O$	PM_{10}	(GALBREATH et al. 2003)
Pb	PbO, $PbCO_3$, PbS, $PbSO_4$, PbO. $PbSO_4$	PM_{10}, $PM_{2.5}$	(Uzu et al. 2011a)
As	As(III), As(V)	PM_{10}, $PM_{2.5}$	(Gonzalez-Castanedo et al. 2015)
Cd	$CdSO_4$, CdS,	PM_{10}, $PM_{2.5}$	(Uzu et al. 2011a)
Hg	Hg(II)S	$PM_{2.5}$	(Kolker et al. 2013)
Zn	ZnS, $ZnSO_4$, $ZnCO_3$, $Zn(NO_3)_2$	$PM_{2.5}$	(Osán et al. 2010)
Cr	Cr(III), Cr(VI)	PM_{10}	(Catrambone et al. 2013)
Cu	$CuSO_4$, CuO	PM_{10}	(Roy et al. 2015)

speciation can be due to industrial processes. In another study, using Raman spectroscopy and XRD, Uzu et al. (2009) revealed minor variation in the speciation in decreasing order of their abundance: PbS, $PbSO_4$, $PbSO_4$-PbO, a-PbO, and PbO. Recently Liu et al. (2018b) showed source-specific speciation profiles of different heavy metal(loid)s (Mn, Cr, V, Co, Cu, Ni, As, Zn, Sn, Cd, Ba, Sb, and Pb) from ten anthropogenic sources in China.

Table 3 shows the speciation of heavy metal(loid)s associated with PM. Sanchez-Rodas et al. (2017) showed that the percentage of Sb(V) in PM_{10} was 64–69% near a traffic station in Granada, 73–77% at traffic stations of Cordoba, 85–86% from the industrial station of Cordoba, and 84–88% for the fugitive emissions of the brass industries. Uzu et al. (2011a) reported that $CaCl_2$-exchangeable Pb ratio was relatively low (<0.02%) compared to Cd (up to 18%) emitted from a Pb recycling factory. It is well known that the metal speciation governs the biogeochemical behavior of a metal. In fact, different metal species vary with respect to their bioaccessibility and bioavailability. Voutsa and Samara (2002) reported the high bioaccessible concentration of Cd (20%), Cu (42%), Ni (46%), Zn (41%), and Mn (52%) in industrial and urban atmosphere of Greece. Similarly, study conducted by Feng et al. (2009) indicated that about 91% of Cd, 85% of Pb, and 74% of As were in bioavailable form and cause severe toxicity to exposed organisms. These findings suggest that it is of great importance to assess the soluble fractions of all metals in relation to their associated health risks. Moreover, the metal bioaccessibility and associated health risks may be correlated with PM size. In fact, it is proposed that metal extractability/bioaccessibility increases with decreasing size of PM (Uzu et al. 2011a). They identified three sources of PM directly affecting the workers near a secondary Pb smelter for battery recycling: (1) ambient air from rotary furnaces; (2) ambient air from refinery; and (3) channeled emissions which vacate gases and fumes from the furnace to outside of the factory. They reported that Pb exchangeability and extractability were the highest for channeled emissions.

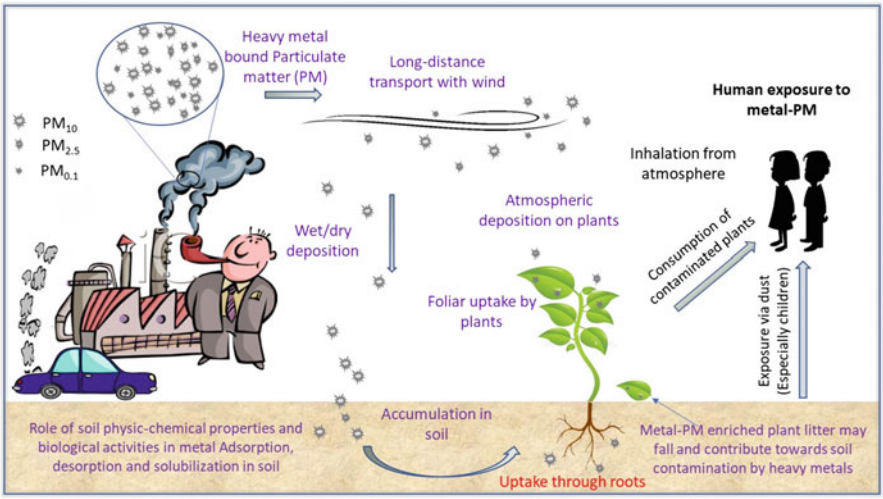

Fig. 1 Heavy metal(loid)-enriched particulate matter (metal-PM) released from various sources into the atmosphere and deposition on different terrestrial ecosystems (soil, water, plant, and animals/human)

2.4 Atmospheric Deposition of PM-Bound Metal(loid)s

Heavy metal(loid)-enriched PM can accumulate in different compartments of the environment. Some of these metal-PMs distribute on a local scale within the range of 10 km. However, some metal-PMs are more persistent and can be distributed over long distance up to a regional scale over hundreds of kilometers away from the source (National Research Council 2000; Ouyang et al. 2018; Xu et al. 2017) (Fig. 1). Transport of PM and metal-PM varies on a temporal and spatial scale (Grantz et al. 2003b; Lü et al. 2018; Markus et al. 2016; Wang et al. 2018; Weerasundara et al. 2017). The fine metal-PMs having low falling velocity are easily transferred to different areas by the wind and possibly deposited at long distances far away from the point of their emission through precipitation (Hoodaji et al. 2012). These metal-PM then accumulate in different compartments of the environment.

3 Soil Contamination Due to Atmospheric Deposition of Metal-PM

The final removal of atmospheric contaminants is their deposition on the surface of the earth. Due to increasing atmospheric contamination, numerous sites/soils around the globe have been reported contaminated by heavy metal(loid)s (Nadal et al. 2004; Rachwał et al. 2017b; Shahid et al. 2012c; Sharma et al. 2018; Weerasundara et al.

2018). Atmospheric contaminants are one of the major sources of heavy metal(loid) deposition and accumulation in soil (Ahmed and Ishiga 2006). The deposition of metal-PM on soil has become a global issue due to the rapid increase in industrialization and urbanization.

Soil deposition of metal-PM is higher near industrial and mining areas. The average concentration of heavy metal(loid)s in soils may exceed their background levels due to the deposition of metal-PMs from the atmosphere (Hu et al. 2018; Liang et al. 2017b; Pratte et al. 2018). Different authors reported heavy metal(loid) concentrations in soil after atmospheric deposition of metal-PM (Table 4).

Deposition of metal-PM on soil can be wet or dry deposition (Gunawardena et al. 2013; Lynam et al. 2015). Wet and dry depositions are considered important phenomena of atmosphere cleaning. Wet deposition represents the absorption into droplets followed by precipitation of these droplets by rain (Lynam et al. 2015; Zhu et al. 2016b). Wet deposition also takes places via impaction on the earth's surface (dew formation, fog, and mists) (Amodio et al. 2014). Wet deposition results in the washout of both PM-bound metal(loid)s and vapor phase. Dry deposition represents the uptake at the earth's surface (water, soil, or vegetation) (Amodio et al. 2014). Dry deposition of PM-bound metal(loid)s involves the removal of all the particles suspended in the air. Dry deposition occurs with several mechanisms like interception, sedimentation, turbulent diffusion, Brownian diffusion, diffusiophoresis, inertial forces, thermophoresis, and electrical migration (Amodio et al. 2014; Zufall et al. 1999). Deposition rates of atmospheric pollutants (including PM-bound metal(loid)s) are governed by PM characteristics (size and shape), surface properties (microscale roughness, friction velocity, and temperature), and meteorological dynamics (relative humidity, wind velocity) (Amodio et al. 2014; Zufall et al. 1999). Several previous studies have evaluated wet and dry deposition of PM-bound metal(loid)s at global scale. For example, Pan and Wang (2015) evaluated dry and wet depositions of PM-bound metal(loid)s at ten sites in Northern China. They reported that atmospheric deposition of Cu, Pb, Zn, Cd, As, and Se represents the same intensity as their accumulations/increases in the topsoil.

The flux of dry and wet depositions may vary with particle size, season, and area. Pan and Wang (2015) reported that the dry deposition was more consistent with spatial distribution of the total (dry plus wet) deposition flux compared to wet deposition. They also reported that dry deposition dominated the total flux for the majority of heavy metal(loid)s that exist as coarse particles (Pan and Wang 2015). Azimi et al. (2003) carried out sampling and analysis of atmospheric deposition of heavy metals (Al, Cd, Cr, Cu, Fe, Na, Pb, and Zn) at the University of Paris XII. They reported that the prevalent deposition type was dry deposition which represents 80%, 60%, and 40% for Pb, Cu, and Cd, respectively. Ye et al. (2018) evaluated atmospheric deposition based on insoluble/soluble fractions of five heavy metals (Cr, Pb, Cu, Cd, and Zn) at Dinghushan (suburban) and Guangzhou (urban) sites. They reported that the ratios of wet/dry deposition fluxes showed that wet deposition mainly governed the heavy metal deposition compared to dry deposition. They also reported that wet deposition fluxes significantly vary with seasonal variation between winter and summer monsoon seasons in this region. Previously, Sakata and

Table 4 Heavy metal(loid) concentration in soil (mg/kg) due to atmospheric deposition of metal-enriched particulate matter

Heavy metal(loid)s concentration in soil										References
As	Cd	Pb	Cr	Fe	Zn	Cu	Ni	Hg	Mn	
14.96	0.59	37.82	93.03	34.39	21.13	33.26	–	178.19	552.50	(Liang et al. 2017b)
13.4[a]	0.07	30	68	28.5	96	25	–	0.07	777	
–	–	119	72.1	27.3	408	98	37.6	–	–	(Tang and Han 2017)
–[a]	–	22.3	59.8	37.8	69.9	43.6	24.9	–	–	
16	32	–	14	–	–	29	3	1	25	(Djebbi et al. 2017)
7[a]	0.2	–	74	–	–	14	22	0.02	272	
40.46	7.56	45.43	32.3	–	512.09	17.86	18.77	–	399.98	(Li et al. 2017a)
14[a]	0.11	38	54	–	101	18	32	–	601	
–	0.1–0.90	5.7–46	–	–	56–130	13.4–54	–	–	–	(Zaborska et al. 2017)
–[a]	0.06	11	–	–	90–110	15	–	–	–	
17.54	0.49	61.48	–	20,458	83.47	19.88	18.93	–	688.90	(Rachwał et al. 2017a)
21.4[a]	0.40	47.4	–	22,441	69.7	16.4	21.6	–	511	
–	0.2	25.4	27.7	–	125.9	32.9	25.3	–	–	(Yan et al. 2016)
–[a]	–	–	–	–	–	–	–	–	–	
–	–	314.2	135.7	–	1294.6	189.9	60.0	–	–	(Li et al. 2014)
–[a]	–	29.2	66.9	–	71.8	23.4	31.5	–	–	

[a]Background concentration of heavy metal(loid)s in soil of the study area

Asakura (2011) also revealed wet deposition as the dominant deposition mechanism for atmospheric pollutants, especially in monsoon areas of Asia. This shows that the ratios of wet/dry deposition fluxes may vary at different locations around the globe. The possible reason of variation in the ratios of wet/dry deposition fluxes can be due to differences in climatic conditions at different locations or the type/size of metal-PM. However, the phenomenon needs more clarity/research for conclusive elucidation.

The average deposition of Cr, Cd, and Pb on soil was 0.96 ± 0.48, 0.28 ± 0.25, and 1.90 ± 1.54 mg/m^2/year in China (Zhu et al. 2016a). The reported values of heavy metal(loid)s in agricultural topsoil after atmospheric deposition of metal-PM are 20,458, 688.90, 18.93, 19.88, 83.47, 0.49, 61.48, and 17.54 mg/kg for Fe, Mn, Ni, Cu, Zn, Cd, Pb, and As, respectively (Rachwał et al. 2017a). Zaborska et al. (2017) studied the spatial variation in metal concentration and their deposition rate in sediments of Svalbard. The study indicated the concentration of heavy metal(loid)s as 5.7–45.8 for Pb, 13.4–54.4 for Cu, 0.1–0.90 for Cd, and 55.6–130.4 mg/kg for Zn. It was then indicated that the area received these pollutants from North American sources through different possible transfer mechanism of metal-PM.

Different types of conventional devices are used for wet, dry, and bulk deposition sampling. The devices used for atmospheric deposition sampling can be distinguished into different categories based on deposition type: (1) dry deposition sampling when there is no precipitation, (2) wet deposition sampling only during rain, and (3) bulk deposition sampling for both the dry and wet depositions (Amodio et al. 2014). Recently, Wu et al. (2018) used Dustmate for collecting the dry deposition PM concentration and rain collectors for the assessment of wet depositions. Different types of devices used in atmospheric deposition sampling of PM-bound metal(loid)s include wet-dry deposimeter sampler, HDPE bucket sampler, HDPE funnel-bottle sampler, HDPE automatic wet-dry sampler, HDPE automatic wet-only sampler, water surface sampler, PVC dry deposition sampler, high- and low-volume samplers, etc. (Amodio et al. 2014). Previously, Aas et al. (2009) investigated the field intercomparison of three types of samplers to determine the atmospheric deposition at different locations in Europe. The study revealed that the samplers used showed efficient performance at different locations. They proposed that at industrial, rural, and urban locations, Bergerhoff samplers are necessary to use.

Owing to the deposition of metal-PM, high concentrations of heavy metal(loid)s were detected in the soil and sediments of mining area of Xikuangshan, China: 32.3, 399.98, 18.77, 17.86, 512.09, 40.46, 7.56, 45.43, and 273.67 mg/kg for Cr, Mn, Ni, Cu, Zn, As, Cd, Pb, and Sb, respectively (Li et al. 2017a). They further reported that windborne transport plays a significant role in the dispersal of the metal-PM. A significant increase in annual dust (metal-PM) fall rate was measured in some areas of India (Tiwari et al. 2008). Among heavy metals, the annual atmospheric deposition rate was Mn (387.3), Zn (336.6), Cr (124.4), Pb (71.0), Ni (51.2), Cu (39.8), and Cd (6.93) g/h/year. The deposition of metal-PM was correlated with some meteorological factors such as wind velocity, humidity, and temperature (Tiwari et al. 2008).

The deposition rate of metal-PM varies with the type of metal. For example, Sharma et al. (2008) reported that the deposition rates of PM_S of Cu, Zn, and Cd were significantly higher during winter and summer seasons, while deposition rate of Pb was higher in summer and rainy seasons. Pandey et al. (2008) investigated the deposition of dust, Pb, Cd, Ni, Zn, Mn, and Cu at selected urban and suburban sites of Varanasi, India, using a dust collector. Average fluxes of 2.88, 0.34, 2.96, 12.22, 22.27, and 2.89 g/h/year were measured for Pb, Cd, Cr, Ni, Zn, Mn, and Cu, respectively. The result showed that the dust load was significantly higher in summer and winter as compared to rainy season. Rohbock (1982) evaluated mass balances of dry and wet deposition rates separately at 13 sites in Germany. They reported that metals bound to large PM are deposited mainly via dry deposition, whereas metals bound to submicron PM are deposited by wet deposition.

After falling on soil surface, the metal-PMs can have different fates in the soil. This fate of metal-PM is controlled both by soil physicochemical properties as well as the type, size, and composition of metal-PM. In most cases, the metal-PM is sorbed on the upper soil surface. For example, Cecchi et al. (2008b) reported that the soil in the vicinity of a Pb recycling plant was contaminated by Pb, Cu, As, Zn, Sb, and Sn in the upper horizons.

Inside the soil, heavy metal(loid)s deposited by atmospheric deposition may occur in different chemical forms. Speciation of atmospheric deposited metal may vary with the type of metal and the soil characteristics (Jung 2008; Olaniran et al. 2013; Shahid et al. 2013). Cecchi et al. (2008b) reported that 40–60% Pb was mainly found in the acid-soluble fraction (carbonates and phosphates) between 0 and 50 cm, while 20–50% Pb was contained mainly in the form of iron oxides. Similarly, Clemente et al. (2006) found 42% Pb in the same acid-soluble fraction near a Pb-Zn mine area. It is reported that the heavy metal(loid) fraction deposited on soil from the atmosphere is generally present in the soil solution (Shahid et al. 2013). These metals deposited from atmosphere do not become the structural part of soil constituents. Therefore, it is believed that the heavy metal(loid) contents introduced to soil via atmospheric deposition or other human activities are more bioavailable than those present in parent materials or minerals (Cecchi et al. 2008a). However, this bioavailable/exchangeable fraction of atmospheric deposited metal may vary with the type of soil and metal as well as the size of PM.

It is also observed that the size of PM attached to metal affects metal bioavailability in soil. Uzu et al. (2009) carried out a microculture experiment with numerous calcareous soils spiked with micronic and submicronic PM containing 1,650 $\pm$ 20 mg/kg Pb. They reported a higher soil-plant transfer with the finest PM. This shows that size and composition of PM emitted from industrial units must be monitored for their possible environmental pollution and associated health risks.

In addition to direct atmospheric deposition of metal-PM on soil, these metal-PMs may get attached on plant canopy and then fall on soil with plant litter. In this case the speciation and fate of metal may vary greatly compared to direct fall of metal-PM on soil. A study conducted by Shahid et al. (2013) indicated high metal contamination of topsoil from the decaying of industrially contaminated popular leaves (litter containing metal-PM). It was demonstrated that organic matter

produced from the decomposition of plant litter could induce progressively a transformation of inorganic metal components into more available organic metal components. In this way, there can be a greater risk of soil-plant metal transfer. However, there exists comparatively less data about the deposition of metal-PM-contaminated plant litter on soil and its subsequent fate in soil. Further studies are required to investigate the speciation, bioavailability, and uptake of metals released from the decomposition of contaminated leaves.

4 Plant Contamination Due to Atmospheric Deposition of Metal-PM

Besides the deposition on soil, metal-PM also falls on foliar organs of plants (Martin et al. 2018; Pratte et al. 2018). Urban vegetation is considered an excellent biological filter as they are efficient in adsorbing and reducing harmful UV rays, noise, and atmospheric contamination (metal-PM) (Bottalico et al. 2016; Safari et al. 2018). Dust deposition on a plant's canopy is a continuous process that is controlled by wind and gravity, which allows atmospheric dust back to the ground (González et al. 2014; Grantz et al. 2003a). Dust deposition and retention on leaf surface particularly depend on the roughness of the surface and size of the PM (Fowler 2002; Liu et al. 2018a; Shahid et al. 2017b).

The forest canopy/ecosystem is highly sensitive to atmospheric PM due to the large interaction surface area (leaf area index = 3–10 m^2/m^2) (Bytnerowicz et al. 2007; Paoletti et al. 2010; Serengil et al. 2011; Sicard et al. 2016; Ulrich et al. 1995). This interaction between plant canopy and metal-PM includes adsorption of PM, assimilation, or release of PM by the canopy (Balestrini et al. 1998; Gandois et al. 2010). Several studies have evaluated the composition of atmospheric deposition on plant canopy as well as the interaction (adsorption, assimilation, etc.) processes occurring in the phyllosphere (Gandois et al. 2010; Hou et al. 2005). It is reported that these interaction processes between metal-PM and forest canopy depend on element-specific dynamics and the morphology of forest canopy. For example, the speciation, composition, and size of metal-PM govern their environmental pathways, availability, and transport or immobilization in the ecosystem compartments (Gandois et al. 2010).

Yang et al. (2005) investigated that most of the atmospheric pollutants are removed by vegetative cover. They estimated that trees remove about 1,261 tons of pollutants in 2002 from the atmosphere of central part of Beijing, China. In a city of China, Chen et al. (2015) indicated that vegetation on greenbelts improved atmospheric quality near footpaths by 7–15% and remarkably removed PM_{10}. A case study in Strasbourg, France, indicated that during 1 year of the study, trees in the city removed almost 88 tons of total atmospheric pollutants from which 12 tons of PM_{10} and 5 tons of $PM_{2.5}$ were removed (Selmi et al. 2016). A study suggested that trees can trap atmospheric pollutants up to about 7% of total air pollutant concentration at Marylebone, London (Jeanjean et al. 2017).

Bottalico et al. (2016) examined the potential of green urban forests to remove atmospheric PM_{10} in the city of Florence. Annual removal of PM_{10} was estimated to be 0.0204 t/ha by conifers, 0.0176 t/ha by evergreen broadleaves, 0.0152 t/ha by deciduous broadleaves, and 0.0247 t/ha by remaining mixed forests. Nowak (1994) concluded that plants in urban areas removed approximately 215,000 tons of PM_{10}/y in the USA.

Plants are commonly used as bioindicator to detect the presence of metals/heavy metals in the atmosphere and soil (García-Florentino et al. 2018; Kłos et al. 2018; Naderizadeh et al. 2016; Sawidis et al. 2011). Generally, most of the heavy metal (loid)s present in the soil system are taken up by plants through their root system, but plants are also capable to absorb heavy metal(loid)s through aerial organs directly from the atmosphere (Shahid et al. 2017b). Less data is available on the absorption of heavy metal(loid)s except for some essential metals like Fe, Cu, Mg, Zn, Ni, and Si (Al-Khlaifat and Al-Khashman 2007; Hong et al. 2016; Kumar et al. 2016; Wang et al. 2016). Moreover, majority of the studies on foliar heavy metal(loid) uptake are not recent, and the atmosphere-plant transfer pathways and mechanisms reported remained unclear (Little 1978; Salim et al. 1993a).

It is proposed that metal-PM deposits on adaxial and abaxial surfaces of the leaves and is trapped in cuticle of the leaves (Mo et al. 2015; Shahid et al. 2017b). It is also reported that the foliar entrance of metal-PM mainly depends on the size of PM. Uzu et al. (2011b) used micro-X-ray fluorescence mappings and reported that coarse Pb-rich spots were located in necrotic zones of lettuce leaves. These spots were mainly concentrated at the base of the central nervure. Using scanning electron microscopy coupled with energy dispersive X-ray, it was shown that fine particles were mainly found beneath the leaf surface. Xiong et al. (2014a) carried out SEM-EDX analysis of Pb-PM-exposed spinach and cabbage leaves and reported that metals were found all over the leaf surfaces and the coverage rate for Pb-PM on the leaf surface was about 2%.

In addition, fine PMs were found inside stomatal openings. Similarly, Schreck et al. (2012b) reported that highest Pb concentration attached with fine PM (<1 μm) was present on the surface and in necrotic zones of lettuce leaves. In ryegrass leaves, they reported that highest Pb concentrations were found on the leaf surface as well as plain tissue. This shows that foliar uptake and accumulation also vary with plant type and PM size. Fewer studies have focused on the intra- and intercellular pathway of heavy metal(loid) and PM movement after foliar uptake.

Studies have shown that plants growing near industries/smelters have high concentrations of heavy metal(loid)s in their foliar tissues (Celik et al. 2005; Gajbhiye et al. 2016b; Tomašević et al. 2004; Uzu et al. 2010) (Table 5). Birbaum et al. (2010) reported that smaller particles can enter the leaves, while large particles make aggregates and are trapped in the waxy cuticle layer (Fig. 2). Bondada et al. (2004) reported that metals can pass through the waxy layer and eventually are absorbed by the underlying cells of the leaves. Leaf structure plays the main role in the adsorption of heavy metal(loid)s from the atmosphere. Uptake of heavy metal(loid)s can occur through foliar surfaces of leaves such as stomata, aqueous pores, ectodesmata, lenticels, and cuticular cracks (Fernández and Brown 2013; Winner and Atkinson 1986).

Table 5 Heavy metal(loid) concentration (mg/kg) in plants growing in natural conditions, after foliar uptake of heavy metals

Metals	Plant species	Study area	Conc.	References
Pb	*Pongamia pinnata*	Power plant	11.9	(Gajbhiye et al. 2016a)
	Kigelia pinnata	Power plant	12.6	(Gajbhiye et al. 2016a)
	Alstonia scholaris	Power plant	11.9	(Gajbhiye et al. 2016a)
	Cassia siamea	Industrial area	3.34–16	(Gajbhiye et al. 2016b)
	Fagus sylvatica	Forest area	9.2	(Türtscher et al. 2017)
	Cedrus deodara	Industrial area	2.8	(Liang et al. 2017a)
	Nerium indicum	Industrial area	1.97	(Liang et al. 2017a)
	Alstonia scholaris	Highway, India	0.467	(Parekh et al. 2016)
	Ficus benghalensis	Highway, India	0.539	(Parekh et al. 2016)
	Polyalthia longifolia	Highway, India	3.259	(Parekh et al. 2016)
	Azadirachta indica	Highway, India	3.389	(Parekh et al. 2016)
	Inula viscosa	Highway, Palestine	7.25	(Swaileh et al. 2004)
Fe	*Kigelia pinnata*	Thermal power plant	1,294	(Gajbhiye et al. 2016a)
	Butea monosperma	Thermal power plant	1,669	(Gajbhiye et al. 2016a)
	Cassia siamea	Industrial area	648–2,911	(Gajbhiye et al. 2016b)
	Fagus sylvatica	Forest area	115.8	(Türtscher et al. 2017)
	Inula viscosa	Highway, Palestine	730	(Swaileh et al. 2004)
Mn	*Butea monosperma*	Thermal power plant	159	(Gajbhiye et al. 2016a)
	Mangifera indica	Thermal power plant	158	(Gajbhiye et al. 2016a)
	Fagus sylvatica	Forest area	828	(Türtscher et al. 2017)
	Inula viscosa	Highway, Palestine	140	(Swaileh et al. 2004)
Cr	*Mangifera indica*	Thermal power plant	27.9	(Gajbhiye et al. 2016a)
	Alstonia scholaris	Highway, India	2.746	(Parekh et al. 2016)
	Ficus benghalensis	Highway, India	2.305	(Parekh et al. 2016)
	Polyalthia longifolia	Highway, India	0.504	(Parekh et al. 2016)
	Azadirachta indica	Highway, India	1.799	(Parekh et al. 2016)
	Inula viscosa	Highway, Palestine	7.03	(Swaileh et al. 2004)
Cu	*Mangifera indica*	Thermal power plant	27.5	(Gajbhiye et al. 2016a)
	Fagus sylvatica	Forest area	11	(Türtscher et al. 2017)
	Platanus acerifolia	Industrial area	6.37	(Liang et al. 2017a)
	Nerium indicum	Industrial area	6.86	(Liang et al. 2017a)
	Inula viscosa	Highway, Palestine	10.6	(Swaileh et al. 2004)
Cd	*Pongamia pinnata*	Thermal power plant	14.5	(Gajbhiye et al. 2016a)
	Cassia siamea	Industrial area	6.5–12.1	(Gajbhiye et al. 2016b)
	Cedrus deodara	Industrial area	0.105	(Liang et al. 2017a)
	Pittosporum tobira	Industrial area	0.109	(Liang et al. 2017a)
	Alstonia scholaris	Highway, India	0.065	(Parekh et al. 2016)
	Ficus benghalensis	Highway, India	0.008	(Parekh et al. 2016)
	Polyalthia longifolia	Highway, India	0.987	(Parekh et al. 2016)
	Azadirachta indica	Highway, India	0.768	(Parekh et al. 2016)
	Inula viscosa	Highway, Palestine	0.1	(Swaileh et al. 2004)
Zn	*Fagus sylvatica*	Forest area	35.2	(Türtscher et al. 2017)
	Pittosporum tobira	Industrial area	38.6	(Liang et al. 2017a)
	Osmanthus fragrans	Industrial area	28.8	(Liang et al. 2017a)
	Inula viscosa	Highway, Palestine	47.6	(Swaileh et al. 2004)
Ni	*Fagus sylvatica*	Forest area	7.4	(Türtscher et al. 2017)
	Inula viscosa	Highway, Palestine	4.87	(Swaileh et al. 2004)

Xiong et al. (2014a) showed that adsorption of heavy metal(loid)s is highly dependent on the morphology and physiology of the leaves as well as on the species of metals. Metals can penetrate through the cuticle layer of foliar organs and adopt symplastic or apoplastic pathway to move between cells and thus can be released into the phloem and are distributed throughout the plant (Shahid et al. 2017b; Xiong et al. 2014a). It is anticipated that metals after foliar application can penetrate through the cuticle into the intracellular spaces of the leaves from where they can undergo phloem loading (Geiger 1975) and translocated throughout the plant. Previous studies indicate the transport of foliar-applied metals into the roots. Leaves absorb maximum metal and a little is transported to the roots <1% (Colle et al. 2009). Dollard (1986) reported the 0.1%, 0.1–0.3%, and <1% transfer of foliar-applied lead to the root tissues, in radish, carrot, and broad beans. So far, less data is reported on shoot to roots to transfer of metals.

Like root uptake, foliar metal uptake could also be in a dose- and time-dependent manner. For example, Bondada et al. (2004) reported the linear relation between As content in plant and the foliar-applied doses of arsenic over time. Likewise, a linear relation was reported between the foliar Zn levels and the concentration inside the plant (Deshpande et al. 2017). Hong et al. (2016) reported a significant increase of the metal concentration inside the plant with higher levels of foliar-applied concentration. Hence, it can be concluded that metal uptake by foliar organs and translocation inside the plant can be through the following possible pathways: (1) deposition on the foliar surface; (2) penetration into the plant through different leaf structures such as cuticle, stomata, pores, etc.; (3) apoplastic or symplastic movement; (4) phloem loading; and (5) translocation in the plant (Fig. 2). However, more studies are needed to fully elaborate the uptake mechanisms and accumulation patterns of heavy metal(loid)s through foliar surfaces.

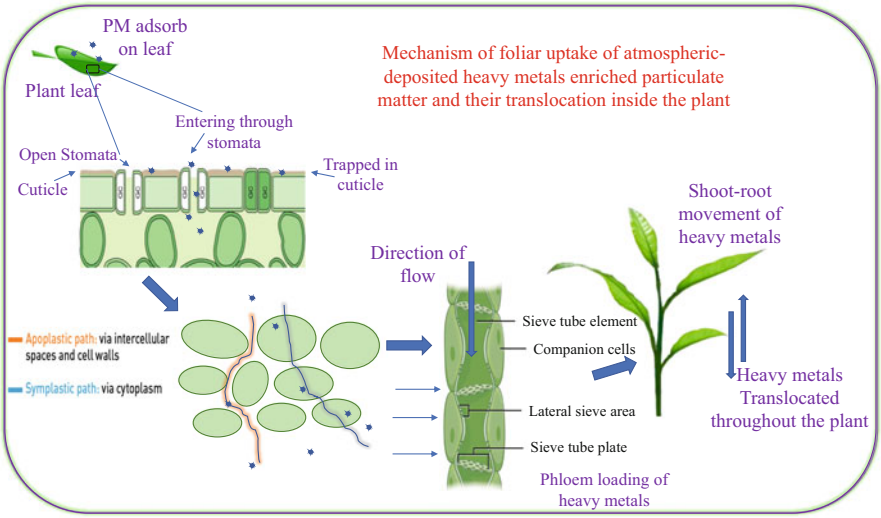

Fig. 2 Mechanism of foliar uptake of heavy metal(loid)s and their translocation inside the plant

5 Health Risks Associated with Metal(loid) Accumulation by Vegetables via Foliar Deposition

Urban agriculture (gardening) is developing globally due to its perceived health benefits and economic conditions. However, urban agriculture may sometimes increase human exposure to metal(loid)s through ingestion of metal contaminated vegetables, when grown on polluted urban sites (Bi et al. 2018; Szolnoki et al. 2013; Xiong et al. 2014a). Recently, several studies have focused on the human health risks associated with the use of contaminated vegetables/crops (Mombo et al. 2015; Xiong et al. 2016b; Yang et al. 2016b).

After foliar deposition of metal-enriched PM, vegetables may absorb and accumulate high levels of metals (Edelstein and Ben-Hur 2018; Li et al. 2018; Mombo et al. 2016) (Tables 5 and 6). During the past recent years, some studies evaluated the accumulation of heavy metal(loid)s in vegetables cultivated in areas with high atmospheric deposition of metal-rich PM. For example, Schreck et al. (2012b) reported 108, 107, 99, 122, and 171 mg/kg of Pb accumulation in lettuce shoot after exposure to industrial atmospheric fallouts of a secondary lead recycling plant, respectively for 1, 2, 3, 4, and 6 weeks. In another study, Schreck et al. (2012b) evaluated the concentration of Pb, As, Sn, Sb, Cu, Zn, and Cd in three vegetables (lettuce, ryegrass, and parsley) after exposure to atmospheric fallouts resulting from the emissions of a battery recycling factory. They reported that the Pb content reached about 100, 300, and 100 mg/kg DW in lettuce, ryegrass, and parsley, respectively.

In another study (Schreck et al. 2014), these authors reported 700 mg/kg of Pb in shot tissues of ryegrass, which was several times higher than the maximum allowable level set by the European Commission Regulation for leafy vegetables (0.3 mg/kg FW). Similarly, Cd concentrations of 1.7, 0.8, and 1.6 mg/kg DW were found for lettuce, parsley, and ryegrass, respectively, compared to limit values of 0.2 mg/kg of fresh weight, which is about 4 mg/kg dry weight (Kabelitz and Sievers 2004). Under foliar application of Pb-PM, 485 and 214 mg/kg of Pb were reported, respectively, in spinach and cabbage (Xiong et al. 2014a). Similarly, Uzu et al. (2010) reported that after 43 days of Pb-PM exposure, the thoroughly washed leaves of lettuce contained 335 ± 50 mg/kg of Pb in shoot tissues.

Nevertheless, there exist rare data about health risk assessment due to the foliar uptake of heavy metals. Xiong et al. (2014a) measured the gastric bioaccessibility of metal(loid)s (Sb, Cd, Zn, and Pb) in spinach and cabbage after metal-PM atmospheric/foliar application. They reported that the gastric bioaccessibility ranged from 13.9 to 98% of these metal(loid)s. Similarly, Schreck et al. (2012b) reported that Pb bioaccessibility is 45% for lettuce exposed for 1 month to foliar application of Pb-PM. Therefore, it is proposed that the leaf morphology controls both the metal(loid) uptake by plants and metal gastric bioaccessibility once exposed to human digestion fluids (Uzu et al. 2011b).

During the recent past, health risk assessment has emerged as a key factor to monitor environmental pollutants and their associated health risks (Khalid et al. 2018;

Table 6 Heavy metal(loid) concentration (mg/kg) after foliar uptake in plants grown in soil/hydroponic medium

Metals	Plant specie	Concentration	Plant part	Experiment type	Time duration	References
As	*Lactuca sativa*	0.6–1.1	Edible part	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
	Spinacia oleracea	0.73	Edible part	Brush application (50 mg/plant)	4 weeks	(Natasha et al. 2018b)
	Petroselinum crispum	0.3–0.4	Edible part	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
	Lolium perenne	0.5–0.8	Edible part	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
Pb	*Lactuca sativa*	107.4–122	Edible part	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
	Lactuca sativa	335	Edible part	Industrial fallouts	43 days	(Uzu et al. 2010)
	Petroselinum crispum	96–298.7	Edible part	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
	Raphnus sativus	0.188	Edible part	0.0, 3.1, 9.0, 18.8 (50 ml spray)	12 weeks	(Salim et al. 1993b)
	Lolium perenne	320–700	–	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
Cd	*Brassica oleracea*	59.20	Edible part	Brush application (300 mg PM)	3 weeks	(Xiong et al. 2014a)
	Lactuca sativa	1.7	Edible part	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
	Petroselinum crispum	0.6–0.8	Edible part	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
	Raphnus sativus L.	0.021–10.892	Edible part	0.4, 1.1, 3.6, 10.9 (50 ml spray)	12 weeks	(Salim et al. 1993b)
	Lolium perenne L.	0.8–1.6	–	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
	Spinacia oleracea	317.30	Edible part	Brush application (300 mg PM)	3 weeks	(Xiong et al. 2014a)
Cu	*Raphnus sativus* L.	0.131–24.695	Edible part	0.0, 2.5, 3.8, 5.0, 7.5 (50 ml spray)	12 weeks	(Salim et al. 1993b)
	Rosa damascena	1.05–1.33	–	spray (1, 2%)	–	(Kumar et al. 2016)
	Lactuca sativa	6.3–6.8	Edible part	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
	Petroselinum crispum	2.4–4.4	Edible part	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
	Lolium perenne L.	5.9–7.0	–	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
Zn	*Spinacia oleracea*	144.20	Edible part	Brush application (300 mg PM)	3 weeks	(Xiong et al. 2014a)
	Lactuca sativa	29.1–31.6	Edible part	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
	Petroselinum crispum	23.4–25.4	Edible part	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
	Lolium perenne L.	26.5–32.1	–	Industrial fallouts	2–4 weeks	(Schreck et al. 2012b)
	Rosa damascena	4.46–5.3	–	spray (1, 2%)	–	(Kumar et al. 2016)
	Brassica oleracea	73.30	Edible part	Brush application (300 mg PM)	3 weeks	(Xiong et al. 2014a)
Sb	*Spinacia oleracea*	5.50	Edible part	Brush application (300 mg PM)	3 weeks	(Xiong et al. 2014a)
	Brassica oleracea	199.50	Edible part	Brush application (300 mg PM)	3 weeks	(Xiong et al. 2014a)
Fe	*Spinacia oleracea*	975.0	NM	Spray 100 ppm	50 days	(El-Aila et al. 2015)

Tabassum et al. 2018). Risk assessment traces the pathway of exposure and also estimates the probability and nature of possible toxic effects of a pollutant to humans when exposed to that pollutant (Arslan et al. 2016; Diepens et al. 2016). Recently, several research reports and studies used different kinds of risk assessment parameters/tools to estimate the possible associated health risks (Antoniadis et al. 2019; Khalid et al. 2018). In this study, we used the previously reported heavy metal(loid) concentrations in edible plant parts due to foliar deposition and uptake and estimated the values of different risk assessment parameters such as hazard quotient (HQ), estimated daily intake (EDI), maximum daily intake (MDI), lifetime cancer risk (ILTCR), total hazard quotient (THQ), and hazard index (HI) both in adults and children (Tables 7, 8, 9, 10, and 11). The parameters used to calculate these risk assessment factors are described in detail in Tables 12 and 13.

The values of estimated daily intake (EDI) were determined using total heavy metal(loid) concentration in edible parts of plants after foliar uptake (Khalid et al. 2017b).

$$\mathrm{EDI} = \frac{C_{\mathrm{ep}} \times \mathrm{IR} \times C_{\mathrm{f}} \times \mathrm{EF} \times \mathrm{ED}}{\mathrm{BW} \times \mathrm{AT}}$$

The hazard quotient (HQ) was estimated using the ratio of average EDI to the oral reference doses (RfD) of metals (Rehman et al. 2016).

$$\mathrm{HQ} = \frac{\mathrm{EDI}}{\mathrm{RfD}}$$

The incremental lifetime cancer risk (ILTCR) through ingestion of edible plant parts contaminated with heavy metal(loid)s after foliar uptake was calculated as described by Shahid et al. (2018b).

$$\mathrm{ILTCR} = \mathrm{EDI} \times \mathrm{CSF}$$

The target hazard quotient (THQ) was calculated as follows.

$$\mathrm{THQ} = 10^{-3} \times \frac{\mathrm{EF} \times \mathrm{ED} \times \mathrm{IR} \times C_{\mathrm{f}}}{\mathrm{RfD} \times \mathrm{BW} \times \mathrm{AT}}$$

To assess the overall potential for non-carcinogenic effects posed by more than one heavy metal, a hazard index (HI) approach has been developed based on EPA's Guidelines for Health Risk Assessment of Chemical Mixtures (USEPA 1986). The hazard index is equal to the sum of the THQs of all metals.

$$\mathrm{HI} = \sum_{n=1}^{n} (\mathrm{THQ})n$$

Table 7 Health risk assessment in adults due to foliar deposition and uptake of heavy metal(loids)

Plants	HQ	EDI	ILTCR	THQ	References
As					
Lactuca sativa	0.58	0.0002	0.00026	0.0068	(Schreck et al. 2012b)
Petroselinum crispum	0.21	0.0001	0.00009	0.0025	(Schreck et al. 2012b)
Pb					
Lactuca sativa	4.78	0.019	0.00016	0.056	(Schreck et al. 2012b)
Lactuca sativa	13.14	0.053	0.00045	0.155	(Uzu et al. 2010)
Petroselinum crispum	11.71	0.047	0.00040	0.138	(Schreck et al. 2012b)
Raphnus sativus	0.01	0.000	0.00000	0.000	(Salim et al. 1993b)
Pongamia pinnata	0.47	0.002	0.00002	0.005	(Gajbhiye et al. 2016a)
Fagus sylvatica	0.36	0.001	0.00001	0.004	(Türtscher et al. 2017)
Ficus benghalensis	0.02	0.000	0.00000	0.000	(Parekh et al. 2016)
Cd					
Azadirachta indica	0.13	0.001	0.0567	0.1093	(Parekh et al. 2016)
Brassica oleracea	9.29	0.009	0.0016	0.0031	(Xiong et al. 2014a)
Lactuca sativa	0.27	0.000	0.0008	0.0015	(Schreck et al. 2012b)
Petroselinum crispum	0.13	0.000	0.0104	0.0201	(Schreck et al. 2012b)
Raphnus sativus L.	1.71	0.002	0.3036	0.5856	(Salim et al. 1993b)
Spinacia oleracea	49.78	0.050	0.0139	0.0268	(Xiong et al. 2014a)
Pongamia pinnata	2.27	0.002	0.0000	0.0000	(Gajbhiye et al. 2016a)
Ficus benghalensis	0.00	0.000	0.0007	0.0014	(Parekh et al. 2016)
Ni					
Fagus sylvatica	0.06	0.001	0.00098	0.000683	(Türtscher et al. 2017)
Cu					
Raphnus sativus L.	0.10	0.004	0.0000	0.001139	(Salim et al. 1993b)
Lactuca sativa	0.03	0.001	0.0000	0.000314	(Schreck et al. 2012b)
Petroselinum crispum	0.02	0.001	0.0000	0.000203	(Schreck et al. 2012b)
Mangifera indica	0.11	0.004	0.0000	0.001269	(Gajbhiye et al. 2016a)
Fagus sylvatica	0.04	0.002	0.0000	0.000508	(Türtscher et al. 2017)
Cr					
Mangifera indica	0.003	0.004	2.188	0.0000343	(Gajbhiye et al. 2016a)
Ficus benghalensis	0.000	0.000	0.181	0.0000028	(Türtscher et al. 2017)
Azadirachta indica	0.000	0.000	0.141	0.0000022	(Parekh et al. 2016)
Mn					
Mangifera indica	0.05	0.025	0.000	0.000583	(Gajbhiye et al. 2016a)
Fagus sylvatica	0.26	0.130	0.000	0.003056	(Türtscher et al. 2017)
Zn					
Spinacia oleracea	0.08	0.023	0.000	0.000887	(Xiong et al. 2014a)
Lactuca sativa	0.02	0.005	0.000	0.000194	(Schreck et al. 2012b)
Petroselinum crispum	0.01	0.004	0.000	0.000156	(Schreck et al. 2012b)
Brassica oleracea	0.04	0.011	0.000	0.000451	(Xiong et al. 2014a)
Fagus sylvatica	0.02	0.006	0.000	0.000217	(Türtscher et al. 2017)

(continued)

Table 7 (continued)

Plants	HQ	EDI	ILTCR	THQ	References
Fe					
Spinacia oleracea	0.02	0.153	0.000	0.00018	(El-Aila et al. 2015)
Butea monosperma	0.03	0.262	0.000	0.000308	(Gajbhiye et al. 2016a)
Fagus sylvatica	0.00	0.018	0.000	2.14E-05	(Türtscher et al. 2017)
Sb					
Spinacia oleracea	2.16	0.001	0.000	0.025377	(Xiong et al. 2014a)
Brassica oleracea	78	0.031	0.000	0.920487	(Xiong et al. 2014a)

Table 8 Range (minimum and maximum values) of HQ, EDI, ILTCR, and THQ for adults presented in Table 7

Metal	Range	HQ	EDI	ILTCR	THQ
As	Minimum	0.2	0.0001	0.000	0.002
	Maximum	0.6	0.0002	0.000	0.007
Pb	Minimum	0.0	0.000	0.000	0.0001
	Maximum	10	0.041	0.000	0.120
Cd	Minimum	0.0	0.000	0.000	0.0000
	Maximum	39	0.039	0.236	0.455
Ni	Minimum	0.0	0.001	0.001	0.0005
	Maximum	0.0	0.001	0.001	0.0005
Cu	Minimum	0.0	0.001	0.000	0.0002
	Maximum	0.1	0.003	0.000	0.0010
Cr	Minimum	0.0	0.000	0.000	0.0000
	Maximum	0.0	0.003	0.002	0.0000
Mn	Minimum	0.4	0.019	0.000	0.000
	Maximum	0.2	0.101	0.000	0.002
Zn	Minimum	0.3	0.003	0.000	0.0001
	Maximum	0.3	0.018	0.000	0.0007
Fe	Minimum	0.0	0.014	0.000	0.000
	Maximum	0.0	0.203	0.000	0.000
Sb	Minimum	1.7	0.001	0.000	0.020
	Maximum	61	0.024	0.000	0.715

The limit values of HQ, THQ, and HI are 1, while that of ILTCR is 10^{-4} (Briki et al. 2017; Mansouri et al. 2015). Values below these limits represent that the exposed population is unlikely to endure any toxic effect.

It is observed that the HQ, THQ, and ILTCR values for several heavy metal(loid)s and vegetables exceeded their respective limit values (Tables 7 and 9). Tables 8 and 10 show the range (minimum and maximum values) of these risk assessment parameters, respectively, in adults and children. It can be seen that the maximum values of HQ were higher than limit value (10, 39, and 61, respectively for Pb, Cd, and Sb in adults) (Table 8). Similarly, high ILTCR values have also been observed

Table 9 Health risk assessment in children due to foliar deposition and uptake of heavy metal(loids)

Plants	HQ	EDI	ILTCR	THQ	References
As					
Lactuca sativa	1.12	0.0003	0.00050	0.013188	(Schreck et al. 2012b)
Petroselinum crispum	0.41	0.0001	0.00018	0.004796	(Schreck et al. 2012b)
Pb					
Lactuca sativa	9.32	0.037	0.00032	0.109702	(Schreck et al. 2012b)
Lactuca sativa	25.60	0.102	0.00087	0.30123	(Uzu et al. 2010)
Petroselinum crispum	22.83	0.091	0.00078	0.268589	(Schreck et al. 2012b)
Raphnus sativus	0.01	0.000	0.00000	0.000169	(Salim et al. 1993b)
Pongamia pinnata	0.91	0.004	0.00003	0.0107	(Gajbhiye et al. 2016a)
Fagus sylvatica	0.70	0.003	0.00002	0.008273	(Türtscher et al. 2017)
Ficus benghalensis	0.04	0.000	0.00000	0.000485	(Parekh et al. 2016)
Azadirachta indica	0.26	0.001	0.00001	0.003047	(Parekh et al. 2016)
Cd					
Brassica oleracea	18.10	0.018	0.1104	0.212929	(Xiong et al. 2014a)
Lactuca sativa	0.52	0.001	0.0032	0.006115	(Schreck et al. 2012b)
Petroselinum crispum	0.24	0.000	0.0015	0.002877	(Schreck et al. 2012b)
Raphnus sativus L.	3.33	0.003	0.0203	0.039176	(Salim et al. 1993b)
Spinacia oleracea	97.01	0.097	0.5917	1.141256	(Xiong et al. 2014a)
Pongamia pinnata	4.43	0.004	0.0270	0.052153	(Gajbhiye et al. 2016a)
Ficus benghalensis	0.00	0.000	0.0000	2.88E-05	(Parekh et al. 2016)
Azadirachta indica	0.23	0.000	0.0014	0.002762	(Parekh et al. 2016)
Ni					
Fagus sylvatica	0.11	0.002	0.00190	0.001331	(Türtscher et al. 2017)
Cu					
Raphnus sativus L.	0.19	0.008	0.0000	0.002221	(Salim et al. 1993b)
Lactuca sativa	0.05	0.002	0.0000	0.000611	(Schreck et al. 2012b)
Petroselinum crispum	0.03	0.001	0.0000	0.000396	(Schreck et al. 2012b)
Mangifera indica	0.21	0.008	0.0000	0.002473	(Gajbhiye et al. 2016a)
Fagus sylvatica	0.08	0.003	0.0000	0.000989	(Türtscher et al. 2017)
Cr					
Mangifera indica	0.006	0.009	0.00426	0.000067	(Gajbhiye et al. 2016a)
Ficus benghalensis	0.000	0.001	0.00035	0.000006	(Türtscher et al. 2017)
Azadirachta indica	0.000	0.001	0.00028	0.000004	(Parekh et al. 2016)
Mn					
Mangifera indica	0.10	0.048	0.000	0.001137	(Gajbhiye et al. 2016a)
Fagus sylvatica	0.51	0.253	0.000	0.005956	(Türtscher et al. 2017)
Zn					
Spinacia oleracea	0.15	0.044	0.000	0.001729	(Xiong et al. 2014a)
Lactuca sativa	0.03	0.010	0.000	0.000379	(Schreck et al. 2012b)
Petroselinum crispum	0.03	0.008	0.000	0.000305	(Schreck et al. 2012b)
Brassica oleracea	0.07	0.022	0.000	0.000879	(Xiong et al. 2014a)
Fagus sylvatica	0.04	0.011	0.000	0.000422	(Türtscher et al. 2017)

(continued)

Table 9 (continued)

Plants	HQ	EDI	ILTCR	THQ	References
Fe					
Spinacia oleracea	0.03	0.298	0.000	0.00035	(El-Aila et al. 2015)
Butea monosperma	0.05	0.510	0.000	0.00060	(Gajbhiye et al. 2016a)
Fagus sylvatica	0.00	0.035	0.000	0.00004	(Türtscher et al. 2017)
Sb					
Spinacia oleracea	4.20	0.002	0.000	0.049456	(Xiong et al. 2014a)
Brassica oleracea	152	0.061	0.000	1.793891	(Xiong et al. 2014a)

Table 10 Range (minimum and maximum values) of HQ, EDI, ILTCR, and THQ for children presented in Table 9

Metal	Range	HQ	EDI	ILTCR	THQ
As	Minimum	0.4	0.000	0.000	0.005
	Maximum	1.1	0.000	0.001	0.013
Pb	Minimum	0.0	0.000	0.000	0.000
	Maximum	25.6	0.102	0.001	0.301
Cd	Minimum	0.0	0.000	0.000	0.000
	Maximum	97.0	0.097	0.592	1.141
Ni	Minimum	0.1	0.002	0.002	0.001
	Maximum	0.1	0.002	0.002	0.001
Cu	Minimum	0.0	0.001	0.000	0.000
	Maximum	0.2	0.008	0.000	0.002
Cr	Minimum	0.0	0.001	0.000	0.000
	Maximum	0.0	0.009	0.004	0.000
Mn	Minimum	0.1	0.048	0.000	0.001
	Maximum	0.5	0.253	0.000	0.006
Zn	Minimum	0.0	0.008	0.000	0.000
	Maximum	0.1	0.044	0.000	0.002
Fe	Minimum	0.0	0.035	0.000	0.000
	Maximum	0.1	0.510	0.000	0.001
Sb	Minimum	4.2	0.002	0.000	0.049
	Maximum	152.5	0.061	0.000	1.794

for Cd and Cr. The values of THQ and integrated risk (HI) were not higher than limit values (1) for all metal(loid)s (Table 7, 9, and 11). The trends of HQ, ILTCR, and THQ were almost the same for children, even with higher values (Table 10). This shows that there can be high chances of heavy metal(loid) exposure and associated toxicity in humans via the foliar transfer pathway. It is highly necessary to continuously monitor the atmospheric contamination by heavy metal(loid)-enriched PM, especially in areas of extensive industrial and mining activities as well as near metropolises.

Table 11 Hazard index (HI) of more than one metal(loid) for adult and children presented in Tables 7 and 9

Plants	Metals	Adult	Child	Reference
Lactuca sativa	As, Pb, Cd, Cu, Zn	0.065	0.127	(Schreck et al. 2012b)
Pongamia pinnata	As, Cd	0.005	0.011	(Gajbhiye et al. 2016a)
Fagus sylvatica	Pb, Ni, Cu, Cr, Zn	0.008	0.017	(Türtscher et al. 2017)
Ficus benghalensis	Pb, Cd	0.001	0.003	(Parekh et al. 2016)
Petroselinum crispum	As, Pb, Cd, Cu, Zn	0.161	0.313	(Schreck et al. 2012b)
Raphnus sativus	Pb, Cd, Cu	0.587	1.144	(Salim et al. 1993b)
Mangifera indica	Cu, Cr, Mn	0.002	0.004	(Gajbhiye et al. 2016a)
Brassica oleracea	Cd, Zn, Sb	0.924	1.801	(Xiong et al. 2014a)
Spinacia oleracea	Cd, Zn, Sb	0.053	0.103	(Xiong et al. 2014a)

Table 12 Oral reference doses (RfD) and upper tolerable daily intake limit (UL) for metals (USEPA 2009)

Metals	UL (mg/day)	RfD (mg/kg/day)	CSF (mg/kg/day)
Fe	0.45×10^{2}	7×10^{-1}	1.5
Zn	0.4×10^{2}	3×10^{-1}	0.0085
Cu	0.10×10^{2}	4×10^{-2}	6.1
Pb	2.40×10^{-1}	4×10^{-3}	–
Cd	6.40×10^{-2}	1×10^{-3}	0.5
Mn	0.11×10^{2}	33×10^{-3}	0.84
Cr	1.05×10^{-2}	0.015×10^{2}	–
Ni	0.01×10^{2}	2×10^{-2}	–
As	–	3×10^{-4}	–

Table 13 Different parameters and their values used to calculate the risk assessment factors

Abbreviation	Parameters	Value	Reference
C_{metal} (mg/kg)	Concentration of metal in plant edible part	–	–
IR (g/day)	Average ingestion rate of vegetable/crop	100.4	(USEPA 1997)
C*f*	Conversion factor	0.085	(Rehman et al. 2016)
EF (days/year)	Exposure frequency	365	–
ED (years)	Exposure duration (average life expectancy)	64.4	(WHO 2015)
AT (days)	Average time of exposure	23,506	(Shahid et al. 2017c)
BW (kg)	Average body weight	70	(WHO 2016)

6 Human Diseases Associated with Direct Inhalation of Metal-PM from the Atmosphere

Ambient air pollution is considered an important source of human diseases (Brauer et al. 2015; Mukherjee and Agrawal 2017). Although metal-PM ingestion is considered as a secondary exposure pathway in adults, it is the main route by which

Table 14 Human diseases associated with direct inhalation of heavy metal(loid)s from the atmosphere

Metal	Health risks	Lifetime risk (at air conc. 1 μg/m^3)
As	Lung, bladder, liver, kidney, skin, and colon cancer; neurological, vascular, and hematological lesions; cardiovascular diseases; abdominal cramps; weight loss; decrease in peripheral nerve conduction velocities; hyperkeratosis; warts; and melanosis	1.5×10^{-3}
Cd	Kidney disorders, lung cancer, increased mortality rate, genotoxic effects	1.8×10^{-3}
Cr	Chrome ulcers; acute irritative dermatitis and allergic eczematous dermatitis; corrosive reactions on the nasal septum; toxic effects on the liver, skin, kidneys, and blood-forming organ; cardiovascular diseases; necrosis; respiratory organ and gastrointestinal tract cancer	4×10^{-2}
Pb	Nervous disorders, renal carcinogenicity, cell hyperplasia, cytomegaly and cellular dysplasia, gene mutations, blood pressure and cardiovascular effects, inhibits the activity of the cytoplasmic enzyme δ-ALA, effects on heme biosynthesis	–
Ni	Renal disorders, mucosal irritation, asthma, allergic dermatitis, nasal carcinoma, laryngeal cancer, kidney cancer, prostate cancer, lung cancer	3.8×10^{-4}
Mn	Neurotoxicity, respiratory tract illnesses rather, sexual dysfunction	–
Hg	Nervous system disorders, cognitive decrements and emotional alterations, kidney failure, pink disease, toxic effect to the fetus during pregnancy	–

Source (WHO 2000b)

children are exposed to metals via ingestion of contaminated dust (Dimitriou and Kassomenos 2017). After ingestion, metal-PM can induce a range of toxic effects in humans depending on its characteristics (type, size, and composition) (Table 14; Fig. 3). Various cardiovascular diseases are associated with direct inhalation of airborne metal-PM (Croft et al. 2017; Kastury et al. 2017; Lawal 2017; McGuinn et al. 2017; Yin et al. 2017).

Evidence indicated that metal-PM is directly related to cardiovascular diseases, chronic diseases, and mortality such as chronic obstructive pulmonary disease, pulmonary hypertension, myocardial infarction, asthma, and cancers (Delfino et al. 2004; Dominici et al. 2006; Peng et al. 2008; Pope et al. 2004). The World Health Organization in 2012 has established that atmospheric pollution causes cardiovascular diseases and respiratory and lung cancer eventually leading to premature death at the rate of 72%, 14%, and 14%, respectively (WHO 2014). Yang et al. (2016a) found that $PM_{2.5}$ is significantly correlated with the number of daily outpatient visits for cardiovascular diseases during high atmospheric pollution events in Taiwan. In China, the estimated national burden of diseases due to ambient $PM_{2.5}$ was about 1.1 million deaths in 2015 (Liu et al. 2018b).

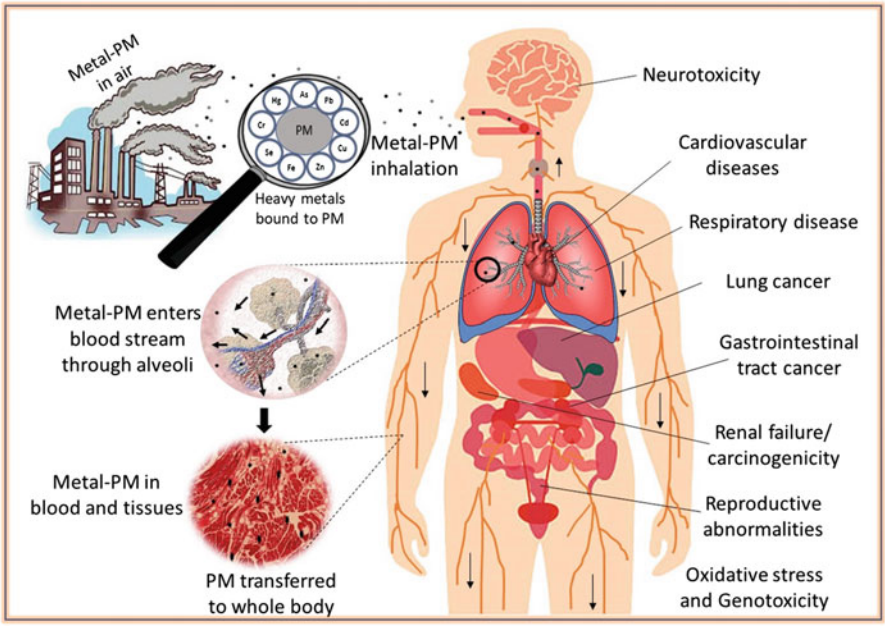

Fig. 3 Human diseases due to ingestion of heavy metal(loid)-enriched particulate matter

Metal-rich PM is classified as carcinogenic by the International Agency for Research on Cancer (IARC 2013) as these metal-PMs are linked to lung cancer (Møller and Loft 2010; Quezada-Maldonado et al. 2018; Raaschou-Nielsen et al. 2016; Santibáñez-Andrade et al. 2017) and ultimately lead toward mortality (Chang and Xu 2017). Similarly, a high mortality rate due to $PM_{2.5}$ was reported by Badaloni et al. (2017). The WHO has estimated that more than two million premature deaths per year worldwide can be due to the toxic effects of outdoor/indoor atmospheric pollution (WHO 2006).

After inhalation, metal-PM has been reported to deposit in different parts of the body. The metal-PM deposition rates in the lungs are estimated to be 50%, with an alveolar absorption rate of >90% of the deposited amount (Löndahl et al. 2014). The most important mechanisms for deposition of inhalable PM < 10 in the respiratory system are inertial impaction, gravitational settling, and diffusion. Coarse particles (PM > 3 μm) mainly deposit by impaction due to abrupt changes in the direction of the air flow that occur in the mouth (or nose) and the upper respiratory tract (Darquenne and Prisk 2004). The PM less than 10 nm has high diffusion velocity and deposit mainly in the head airways and tracheobronchial region (Schulz and Brand 2000). For particles with diameters in the range 20–40 nm, the majority (up to about 50%) deposit in the alveolar region during exercise (Löndahl et al. 2014).

Goix et al. (2014) assessed the toxicity and threat score of fine and ultrafine metallic PM (emitted into the atmosphere) by performing complementary in vitro

tests (cytotoxicity, human bioaccessibility, and oxidative potential). They classified the toxicity of particles as $CdCl_2 > CdO > CuO > PbO > ZnO > PbSO_4 > Sb_2O_3$. Several studies revealed elevated levels of heavy metal(loid)s in blood upon human exposure to airborne dust/PM (Acton 2012; Li et al. 2015). Uzu et al. (2011a, b) evaluated human Pb toxicity and bioaccessibility after its emissions from a Pb recycling plant. They reported that the process Pb-PM displayed differences in granulometry, metal content, and percentage of inhalable fraction depending on their origin (refining, furnace, and emissions) and PM size (PM_{10}, $PM_{2.5}$, PM_1, and $PM_{0.1}$). They reported that the finest Pb-PM_1 induced the most significant pro-inflammatory effect in human bronchial epithelial cells.

Heavy metal(loid)s are considered as highly harmful to the human even at low levels of exposure. This is because of the fact that humans do not have an effective tolerance or excretion mechanism for these metal(loid)s. Metal-PM generates ROS (reactive oxygen species) in human beings and induces different associated diseases (Valavanidis et al. 2005). When human beings are exposed to metal-PM, oxidative stress rises pulmonary pathology through airway inflammation (Ghio et al. 2012). Squadrito et al. (2001) found the induction of ROS when heavy metal(loid)-enriched PM is deposited in the lungs after inhalation from the atmosphere. These ROS, overproduced due to heavy metal(loid) toxicity, cause oxidative stress and deleterious effects at the deposition site (Fryzova et al. 2018). Apart from direct ROS generation by the airborne PM, ROS can also be generated by interacting with the cells on which PM is deposited such as epithelial cells of lungs and pulmonary macrophages (Santibáñez-Andrade et al. 2017; Valavanidis et al. 2013).

One of the main toxic effects of heavy metal(loid)s deposition inside the human body is induced by their ability to bind to biomembrane structures, modifying their function. For example, Pb has been reported to react with thiol (SH) groups, resulting in damage to glutathione (GSH) (Gurer-Orhan et al. 2004). Glutathione is a cellular antioxidant and plays a key role to scavenge ROS by taking part in bio-reductive reactions (Shahid et al. 2017a). In this way, GSH protects cells from oxidative stress. Thus, metal-PM ingestion into the human body is linked with oxidative stress, which is generally considered a secondary mechanism of metal-PM toxicity (Cho et al. 2005; Uzu et al. 2011b). Numerous studies have confirmed the association of metal-PM ingestion with oxidative stress by using both in vitro biological assays (respiratory epithelial or macrophages cells) (Baulig et al. 2004) and cellular assays (Dithiothreitol test) (Cho et al. 2005).

7 Management Strategies to Reduce Air Contamination by Metal-PM

Keeping in view the health risks associated with the atmospheric contamination and deposition of metal-PM on terrestrial ecosystem, it is highly necessary to control and manage the atmospheric environment. The management of atmospheric

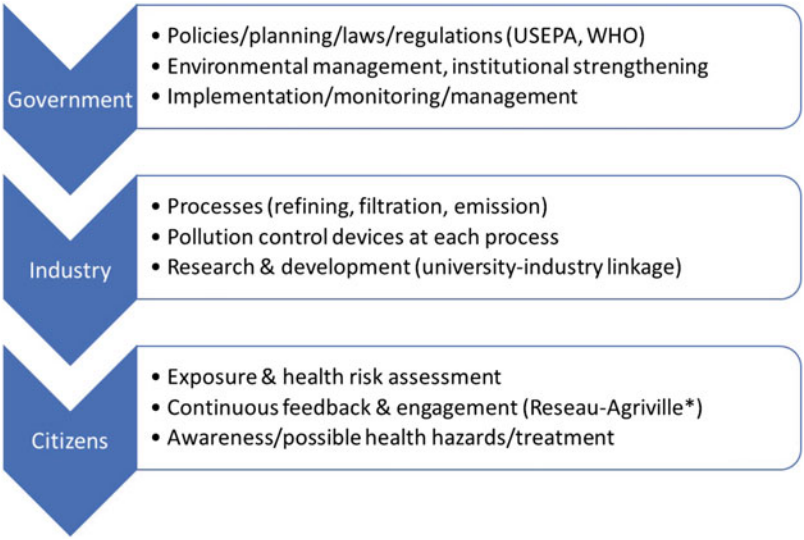

Fig. 4 Socio-scientific management and remediation practices required at local, national, and global level. ∗Reseau-Agriville: https://reseau-agriville.com/

environmental contamination requires a global as well as local approach due to its small and global scale effects (Fig. 4).

In the USA, the Environmental Protection Agency has established many regulatory steps to reduce the emission of toxic pollutants into the atmosphere. These include reducing toxic pollutant emission from industries, vehicles, and engines through new stringent emission standards and cleaner burning of fuel and tending to reduce indoor atmospheric contamination (USEPA 2017). The EPA forces industries to reduce the emissions of toxic pollutants and gases. According to EPA, industries must install filters in their smokestacks to remove particles and scrubber to remove oxides of different gases with water channels. Similarly, several developed countries and regions such as the European Union, Australia, Japan, and Canada have established their guideline values for different types of atmospheric pollutants (including metal-PM). The regulatory guidelines established by these countries can be adopted, after necessary modifications if required, in other countries throughout the globe to reduce the atmospheric emission of heavy metals. This practice can be highly effective to reduce atmospheric contaminations by different types of pollutants, especially in less-developed countries.

At the regional scale, national and local government agencies must strictly implement the environmental protection and management rules and practices. Industries, especially in less-developed areas, should install pollution control devices to remove toxic gaseous/solid pollutants by absorption, dispersing, filtering, and diluting them. Government laws, regulation, and licensing are effective ways to reduce emissions from industry. The pollution control devices may include cyclones, precipitators, fabric filter bags, wet scrubbers, and gravity settlers.

Similarly, automobile emission is also a major source of atmospheric contamination. Many technology-based innovations to decrease atmospheric contamination from automobiles include utilization of lead-free fuel and the use of hybrid and electric vehicles. Use of electricity-powered buses in metropolitan of big cities (e.g., London, UK) is a step toward environmentally sustainable development.

In order to control the atmospheric metal-PM contamination, the monitoring and environmental risk assessment/management tools/models can be used (Dore et al. 2014). For example, geographic information system (GIS) and global positioning system (GPS) can be used for risk assessment/management tools/models related to atmospheric metal-PM pollution. Similarly, the remote sensing, as well as the meteorological and air pollution dispersion models (Regional heavy metal transport model, Weather Research and Forecasting, The Air Pollution Model, Regional Atmospheric Modeling System, and MM5 modeling system software), can also be used for various aspects of atmospheric pollution (Cheng et al. 2007; Hurley et al. 2005; Stein et al. 2015). In addition, statistical models have also been used for heavy metal(loid)s modeling (Peng et al. 2016).

Moreover, awareness among the community is always a key factor in controlling the atmospheric contamination and remediating/minimizing the toxic health hazards. Similarly, the education and publicity of controlling atmospheric contamination are also very important. Public awareness activities such as pollution remediation and awareness seminars at school/college/university and community level (farmers, small-scale industrialists) can be highly effective. In addition, mass media, as well as the government and nongovernment organizations (NGOs, social society), might play their part in this facet.

8 Future Perspectives

- The majority of the studies describing the characterization and toxicity of metal-PM in the ambient atmosphere provide information about quantitative levels for PM_{10} fractions. There is very little data available for the submicronic fraction ($PM < 2.5$). Therefore, more studies may be conducted for submicronic highly reactive and toxic fractions of metal-PM. Moreover, the reference or threshold levels for atmospheric heavy metal(loid)s (Cd, Pb, Ni, As, and Cr) are currently based on coarse PM (the European Union, the World Health Organization, and the Chinese “Ambient Air Quality Standards”).
- The natural background concentration of heavy metal(loid)s in energy sources (coal, petrol, etc.) used in industry/vehicles is one of the major sources of metal-PM emission to the atmosphere. It has been reported that the metal-PM concentration in the atmosphere is closely related to energy consumption source. Therefore, energy sources used in the industry/vehicles need further investigation in relation to the atmospheric release of metal-PM.

- The attachment of heavy metal(loid)s to PM occurs during their release from the source (primary metal-PM), or they may get attached to PM in the atmosphere after their release (secondary metal-PM). The interaction or the type of binding between heavy metal(loid)s and PM (primary and secondary metal-PM) has not yet been described in the literature. Moreover, the type of industrial processes, source of energy used in these processes, as well as the meteorological factors may also affect the interaction between heavy metal(loid)s and PM and thereby their composition, speciation, and associated health risks. Attention may, therefore, be given to these factors and interactions of metals and PM.
- The long-distance travel, as well as the deposition and fate (adsorption/desorption in the soil, uptake by plants, and deposition in lungs) of metal-PM in the environment, is associated with composition and the size of metal-PM, meteorological conditions, physicochemical properties of soil/phyllosphere. Therefore, the temporal and spatial distributions, as well as the effects of different factors, need to be studied in detail.
- Total heavy metal(loid) or metal-PM concentrations in the environment (air, soil, water) are commonly used as the main criteria for assessing the pollution conditions and associated hazards. However, recent data show that the biogeochemical behavior of metals in the environment is mainly governed by their chemical speciation. The scarcity of data about metal speciation in the industrially emitted PM is mainly due to the lack of analytical tools, both sensitive and specific to the size of the particles. Therefore, more attention is required to establish tools to assess chemical speciation of metal-PM as well as the relationship of chemical speciation of heavy metal(loid)s in PM with their biogeochemical behavior in the atmosphere-soil-plant-human system.
- Some studies also highlight that comparatively less attention is given to metal-PM emitted from the industries compared to traffic emissions (urban areas). The chemical speciation, composition, and the biogeochemical behavior of metal-PM emitted from different sources (industry, automobiles, mining, etc.) may vary greatly. Therefore, metal-PM emitted from different sources and the associated health risks may be categorized accordingly.
- Contrary to European countries where human health is nowadays protected thanks to European Commission Regulation (EC) No. 221/2002 and REACH regulation (EU n°1907/2006) promoting a more secure use and release of chemical substances in the atmosphere/environment, the less developed countries such as subcontinent need to reinforce the global information and the restrictions for (eco)toxic chemical substance release into the atmosphere in order to avoid and reduce human exposure and sanitary impacts. Moreover, on the global scale, available socio-scientific publications illustrate that ecological transitions are necessary in various sectors in order to preserve human and environmental/atmospheric health.
- There is also limited data regarding metal-PM uptake by vegetables and crops, accumulation in edible plant parts, and the associated human health hazards. Moreover, elicitor molecules such as silicon, salicylic acid, and methyl salicylate have been well-reported to affect plant growth and defense mechanisms under

different types of stress (Benhamou 1996; Tierranegra-García et al. 2011; Zia et al. 2017). However, the role of these elicitor molecules toward metal foliar uptake, toxicity, and detoxification is not yet well-established. Therefore, studies may be performed to evaluate the effect of different elicitors toward foliar metal uptake, its toxicity, and detoxification.

9 Summary

This review highlighted the fate and behavior of metal-PM in the ecosystems as well as their associated health risks. Metal-PM is emitted to the atmosphere by various natural and anthropogenic activities, the latter being the major source. During their processing in factories, different chemical forms of heavy metal(loid)s may attach to PM of varying sizes. The chemical form of a metal and the size of PM depend on the source. The concentration of metal-PM in the atmosphere may vary among different areas such as urban, rural, and industrial areas. In industrial areas, the concentration of metal-PM in the atmosphere may reach up to several folds higher than the permissible levels set by WHO as reported in various countries of Europe, Asia, and America.

After release into the atmosphere, metal-PM can travel over a long distance depending on their composition and size, in addition to meteorological and climatic factors. Transport of metal-PM varies on a temporal and spatial scale. Atmospheric metal-PM finally deposit to terrestrial ecosystems such as soil, water, buildings, and plant canopy. In this way, these metal-PMs contaminate different parts of the ecosystem by heavy metals.

In soil, metal-PM becomes the part of soil depending on the nature of soil or is being uptake by plants. Heavy metal(loid)s deposited from the atmospheric are considered relatively more available for plant uptake compared to those present/adsorbed in the soil.

Deposition of metal-PM on aerial plant parts is considered an important source of plant contamination. Although rarely discussed and explained, foliar heavy metal(loid) deposition and uptake can be a major source of heavy metal(loid) accumulation in plants (shoots). In addition, metal-PM can be inhaled directly by humans and get deposited in different organs inside the body. After inhalation, metal-PM can induce several toxic effects to humans. At cellular level, heavy metal(loid)s can overproduce reactive oxygen species inside the human body, thus leading to oxidative stress and toxicity to various micro- and macromolecules.

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Role of Biofilms in Contaminant Bioaccumulation and Trophic Transfer in Aquatic Ecosystems: Current State of Knowledge and Future Challenges

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Contents

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Abbreviations

AAS	Atomic absorption spectrometry
BCF	Bioconcentration factor
BMF	Biomagnification factor
CLSM	Confocal laser scanning microscopy
DDT	Dichlorodiphenyltrichloroethane
DNA	Deoxyribonucleic acid
DOM	Dissolved organic matter
EDTA	Ethylenediaminetetraacetic acid
EPS	Extracellular polymeric substances
GC-MS	Gas chromatography-mass spectrometry
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-OES	Inductively coupled plasma optical emission spectrometry
K_{ow}	Octanol-water partition coefficient
LC-MS	Liquid chromatography-mass spectrometry
LOQ	Limit of quantification
PAHs	Polycyclic aromatic hydrocarbons
PCBs	Polychlorinated biphenyls
STXM	Scanning transmission X-ray microscopy
TBEP	Tris(2-butoxyethyl) phosphate
TEM	Transmission electron microscopy

1 Introduction

Freshwater environments host microbial biomass that can aggregate and attach to submerged inorganic (like rock, gravel, sediment) or organic (like leaf litter, macrophytes) substrates. These microbial assemblages, called “biofilms” (Watnick and Kolter 2000), are composed of eukaryotic (e.g., microalgae, fungi, protozoa) and

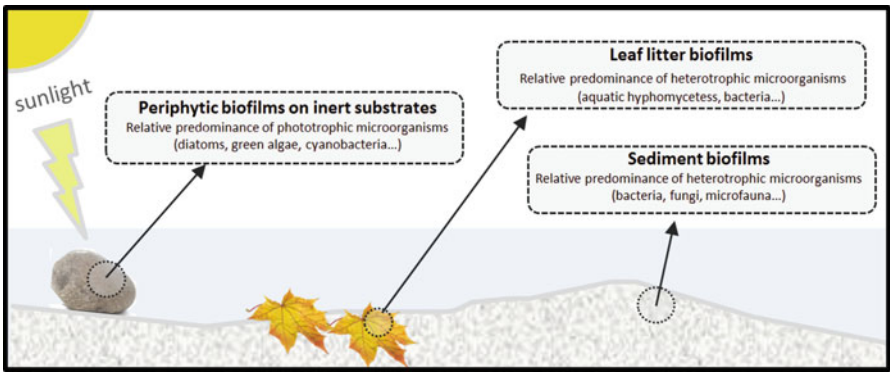

Fig. 1 Schematic representation of the theoretical distribution of aquatic microbial biofilm communities according to the kind of immersed substrates under light conditions (adapted from Pesce et al. 2017)

prokaryotic (e.g., bacteria, cyanobacteria) microorganisms (Battin et al. 2016) whose form, distribution, and metabolism (i.e., autotrophy, heterotrophy, mixotrophy) are highly dependent, among other factors, on nature of the substrate (Fig. 1), light intensity, and availability of dissolved organic and inorganic nutrients (Sabater et al. 2006; Ylla et al. 2009). Autotrophic biofilms (or periphyton), which grow on inert surfaces like cobbles exposed to light, are generally dominated by diatoms, cyanobacteria, and green algae, whereas heterotrophic biofilms can be found attached to sediments or organic substrates like leaf litter and are dominated by bacteria and fungi. Biofilms are embedded within a self-produced matrix of extracellular polymeric substances (EPS) that is made up of (exo)polysaccharides and a variety of proteins, glycoproteins, and glycolipids together with high amounts of extracellular DNA (Flemming et al. 2007) and even suspended particulate matter and detritus from the surrounding environment (Flemming 1995). Biofilms are thus characterized by high structural complexity allowing multiple interactions with contaminants (Battin et al. 2003). In addition, due to their high metabolic activity and their role in aquatic food webs, microbial biofilms are likely to influence contaminant fate in aquatic ecosystems.

Here we review the distribution of contaminants within aquatic biofilms and the role of these benthic microbial communities in contaminant fate. The contaminants we cover are metals (e.g., copper, mercury, cadmium, etc.) and organic micropollutants (e.g., pesticides, pharmaceuticals, and other man-made substances).

Diverse and ubiquitous contamination of lakes and rivers (e.g., Fent et al. 2006; Pal et al. 2010; Murray et al. 2010) exposes aquatic microbial biofilms to a potential accumulation of substances transported by the water flow (in a dissolved form or bound to suspended organic and inorganic matter) and/or adsorbed onto benthic substrates (sediment, leaf litter). Therefore, the kind of substrate where biofilms develop has a huge influence on their mode of exposure to contaminants (in terms of nature, quantity, bioavailability) as well as their role in subsequent contaminant

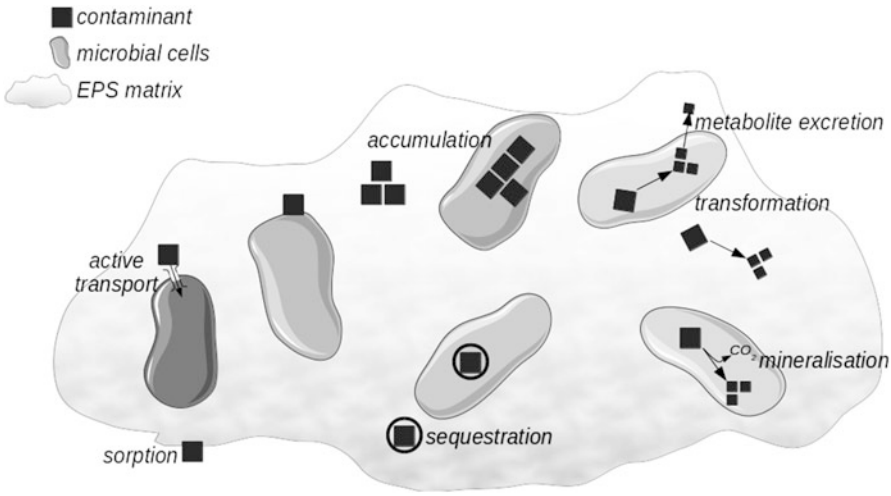

Fig. 2 Schematic representation of the interactions between contaminants and microbial biofilms

transfers through aquatic food webs. However, investigations on this topic are fragmentary (i.e., one substrate/one contaminant) and difficult to unify in a common framework since they lack real representativeness for contaminant mixtures in complex systems harboring diverse substrates and/or microbial communities.

By their complexity, microbial biofilms can have multiple interactions with contaminants (Fig. 2) and therefore influence its fate in the environment. All microbial biofilms have the ability to neutralize contaminants by sorption (i.e., passive sequestration through interaction with biological matter), accumulation (i.e., increased active internalization in cells), and sequestration for metals (i.e., formation of insoluble precipitates through interaction with microbial metabolites) (Barkay and Schaefer 2001) or microbial transformation for organic substances (Edwards and Kjellerup 2013; Carles et al. 2017). All these interactions are susceptible to occur either within the cells or extracellularly within the EPS matrix. Microbial biofilms offer a diverse range of sorption sites including cationic and anionic sites as well as lipophilic/hydrophobic regions, as contaminants can bind to EPS, cellular membranes, cell walls, and more. In addition, enzymatic machinery required for contaminant transformation can either be present intracellularly or be excreted in the extracellular matrix. Metal distribution within microbial biofilms has been investigated for the last 25 years, and work continues with ongoing analytical developments. However, investigations into the sorption and/or accumulation of organic contaminants in microbial biofilms still run into technical limits, such as the large amount of biofilm needed to ensure reliable quantification of accumulated contaminants according to analytical level of detection.

Biofilm matrix features a high degree of microheterogeneity, which enables microbial biofilms to concurrently harbor a high diversity of contaminants (Flemming 1995). For instance, the presence of uronic acids (such as

D-glucuronic, D-galacturonic, and mannuronic acids) was found to facilitate the sorption of various cationic metals (e.g., Pb^{2+}, Cu^{2+}) (Flemming 1995). Sorption of organic contaminants is partly driven by hydrophobic interactions, and so octanol-water partition coefficient (K_{ow}) is often used to estimate the sorption capacity of organic contaminants in microbial biofilms. However, other types of interactions also occur (e.g., ionic, electrostatic, etc.) and thus need to be considered.

Microbial biofilms influence contaminant fate in aquatic ecosystems through their contribution to biotransformation processes and trophic transfers. Indeed, both phototrophic and heterotrophic biofilms are foundational to aquatic food webs. Phototrophic biofilms generate biomass from light energy and carbon dioxide, thus providing organic substrates and oxygen (Roeselers et al. 2008), while heterotrophic biofilms are able to decompose various organic materials and thus play a key role in nutrient fluxes in aquatic ecosystems (Romani and Sabater 2001; Battin et al. 2003). Accordingly, while periphytic biofilms are at the base of "green" food webs supported by primary production (Danger et al. 2008; Zou et al. 2016), biofilms formed on organic substrates play a functionally pivotal role in "brown" food webs based on allochthonous organic matter decomposition (Hall and Meyer 1998). The spatial proximity between autotrophic and heterotrophic microorganisms also drives carbon and nutrient cycling within periphytic biofilms where autotrophic biomass and activity can stimulate the development and activity of heterotrophic microbial communities (Romani et al. 2004). This same pattern has been observed in detritus-based food webs where primary production can stimulate leaf litter decomposition by microbial heterotrophs (Danger et al. 2013). In aquatic environments, "green" and "brown" food webs thus tend to connect through complex interactions (Zou et al. 2016). Biofilm assemblages play a key role in interconnecting between these "green" and "brown" food webs that are foundational to ecosystem functioning (Krumins et al. 2013; Zou et al. 2016) (Fig. 3). Whatever the substrate and food web involved, these biofilm assemblages are consumed by various microbial predators (e.g., amoeba, ciliate, rotifers; Neury-Ormanni et al. 2016) and meso-/macrofauna (Alvarez and Peckarsky 2005; Guasch et al. 2016) or fish (Schneck et al. 2013), which means that contaminants bioaccumulated in microbial biofilms are likely to be transferred to higher trophic levels in the food web (Singh et al. 2006).

During the last decade, research on the role of microbial biofilms in contaminant fate and transfer has mainly focused on metal accumulation in periphytic biofilms (e.g., Ancion et al. 2010; Fabure et al. 2015; Pesce et al. 2018) and on the degradation of organic contaminants in sediments (e.g., Pesce et al. 2009, 2013; Trinh et al. 2012). Nevertheless, recent studies have highlighted the potential role of periphytic and leaf litter biofilms in organic contaminant accumulation and trophic transfer (e.g., Kohušová et al. 2011; Ruhí et al. 2016). Furthermore, the daughter directive 2008/105/EU of the Water Framework Directive and Guidance Document No. 25 both recognize the importance of monitoring and preserving the sediment compartment to preserve aquatic ecosystems (European Commission 2010). However, scarce few studies have focused on contaminant accumulation in sediment microbial communities.

Scientific literature on contaminant bioaccumulation in microbial biofilms remain dispersed, insofar as most of the studies available are focusing on one type of

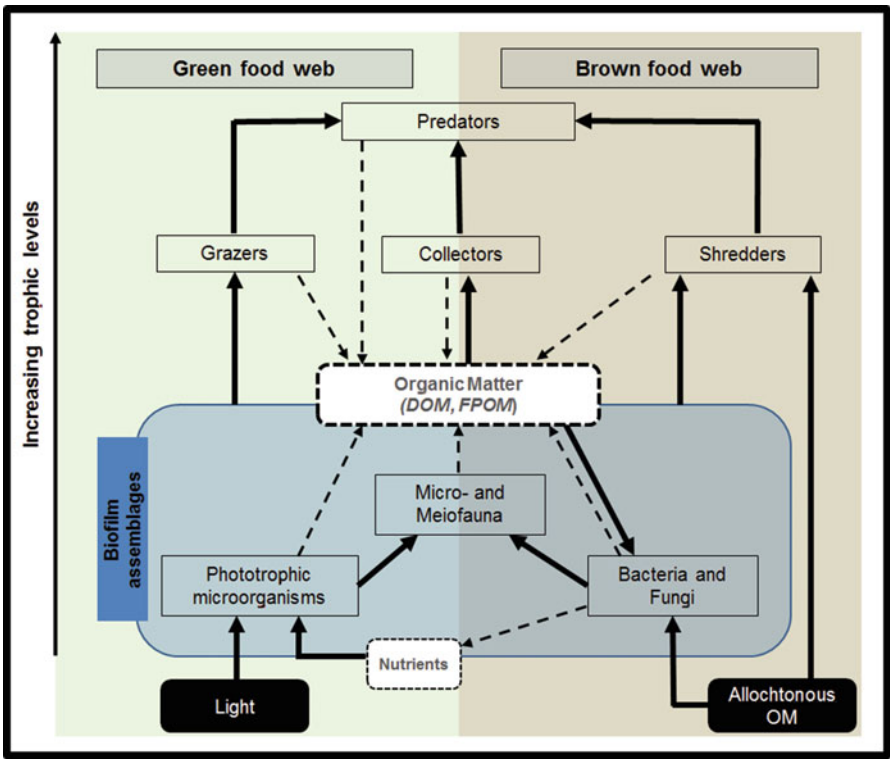

Fig. 3 Schematic representation of the role of biofilm communities in aquatic "green" and "brown" food webs. Solid arrows indicate consumption, and dotted arrows indicate production (*OM* organic matter, *DOM* dissolved organic matter, *FPOM* fine particle organic matter)

contaminants (e.g., metals, pesticides, or pharmaceuticals) or on biofilm growing on one type of substratum (either cobbles, sediments, or leaf litter). An overview of the methods available to detect, identify, quantify, and localize contaminants accumulated in biofilms growing on different types of substrata is clearly missing. Such a methodological review is nevertheless helpful to identify conceptual and technological limitations as well as to guide method development effort. Since analytical methods are the first essential step to measure contaminant bioaccumulation in microbial biofilms, an overview of those methods and its specificities is essential to facilitate the accurate interpretation of bioaccumulation results.

In this context, the present review aims to provide a critical report of:

- The analytical methods currently on use for detecting and quantifying contaminants in microbial biofilms developing in different benthic substrata (Sect. 2)
- The current state of knowledge and the future challenges concerning the role of biofilms in contaminant accumulation (Sects. 3 and 5) as well as in trophic transfers in the aquatic food web (Sects. 4 and 5)

2 Analytical Methods for Quantification of Contaminants in Microbial Biofilms

A short overview of the current analytical methods used for quantification of metals and organic micropollutants in microbial biofilms is available in Table 1.

2.1 Metals

Concurrent to analytical developments, studies dealing with bioaccumulation in microbial biofilms have applied mainly to metal contaminants. Thus, in the early 1990s, methods such as atomic absorption spectrometry (AAS; Avery and Tobin 1993) or radiotracers (White and Gadd 1987; Avery et al. 1993) were developed in order to quantify metal (e.g., Zn, Fe, Cu, or Cs) concentrations in microorganisms

Table 1 Current methods to estimate contaminant accumulation in microbial biofilms

		Approaches to detect, identify, and quantify contaminants in:			
		Sediments/ leaf material colonized by microbial biofilms	Periphytic biofilms	The intracellular compartment of periphytic biofilm or bound to EPS	Approaches for identifying where contaminants are located within biofilms
Metals	Sample preparation	Aqua regia digestion	Nitric digestion	Chemical method (water, EDTA washing) + physical separation (centrifugation)	Incubation with fluorescent probes for CLSM
	Analysis	AAS, ICP-OES, ICP-MS			Imaging techniques TEM-EDX, STXM, CLSM
Organics	Sample preparation	Solvent extraction		Physical extraction (sonication and centrifugation) + solvent extraction	Incubation with fluorescent probes for CLSM
	Analysis	GC-MS, LC-MS-MS			Imaging techniques STXM, CLSM

AAS atomic absorption spectrometry, *ICP* inductively coupled plasma, *OES* optical emission spectrometry, *MS* mass spectrometry, *GC* gas chromatography, *LC* liquid chromatography, *EPS* extracellular polymeric substances, *EDTA* ethylenediaminetetraacetic acid, *STXM* scanning transmission X-ray microscopy, *TEM-EDX* transmission electron microscopy coupled with energy-dispersive X-ray spectroscopy, *CLSM* confocal laser scanning microscopy

(typically cyanobacteria, algae, or fungi). The appropriate method was selected according to different criteria, such as accuracy, sensitivity, amount of sample available, and the need or not to identify the location of the contaminant in the microorganism structure (White and Gadd 1995). The democratization of inductively coupled plasma optical emission and inductively coupled plasma mass spectrometry (ICP-OES and ICP-MS) allowing high-sensitivity analysis of several elements at the same time led to a large number of studies on Cu, Zn, Pb, and Cd bioaccumulation in microbial biofilms (e.g., Meylan et al. 2003; Farag et al. 2007; Bradac et al. 2009, 2010). The bulk of research on metal bioaccumulation in microbial biofilms was conducted on periphytic biofilms collected in situ on rock and/or gravel (e.g., Ancion et al. 2010) or on artificial substrates (low-density polyethylene membranes (Fechner et al. 2012); glass discs (Ivorra et al. 1999); glass slides (Morin et al. 2008)) beforehand immersed in the water column to allow biofilm colonization. These artificial substrates were also used in microcosm experiments to obtain enough biological material to combine metal analysis and toxicity tests under controlled exposure conditions (Fechner et al. 2011; Kim et al. 2012; Lambert et al. 2012).

To assess total metal concentration in the microbial biomass, hot (100°C) concentrated nitric acid digestion (by using a heating plate or a microwave oven) is commonly used to extract total metal content from samples that had previously been oven-dried at 50°C or freeze-dried (e.g., Morin et al. 2008; Fechner et al. 2012). To better discriminate between intracellular and extracellular metal bioaccumulation in microbial assemblage, biofilms are first flushed with a solution of ethylenediaminetetraacetic acid (EDTA) at 4 mM during 10 min (e.g., Meylan et al. 2004; Bradac et al. 2009; Arini et al. 2012; Fabure et al. 2015). This step removes the metals adsorbed to cell membranes and a fraction of the inorganic complexes in the biofilm structure (Meylan et al. 2003). The amount of intracellular metal content in the microbial assemblage is then deduced by analyzing the two fractions (raw and EDTA-washed) of a sample. To better identify metal (Al, Cu, Zn, and Pb) site within the EPS matrix and better characterize the exposure of microbial cells to metals, Aguilera et al. (2008) proposed subsequent extractions and centrifugation steps to separate first the "colloidal fraction" (extracted with distilled water), then the "capsular fraction" (extracted with NaCl at 80°C, ultrapure water at 30°C, Dowex at 4°C, or crown ether at 4°C), and finally the cellular debris from microbial biofilms. Metal content can then be quantified independently in each of the three collected fractions to determine the amount of intracellular metal (in the cellular debris) as well as the metal concentration in the EPS matrix (in the colloidal and capsular fractions). The colloidal fraction includes carbohydrates and proteins that are loosely bound to microorganisms, whereas the capsular fraction contains tightly bound compounds. However, Aguilera et al. (2008) showed that no single extraction method was able to extract all the potential EPS components with the same efficiency.

There have been several developments to assess metal accumulation and distribution in freshwater periphytic communities, but none in microbial communities from sediment or from leaf litter. Indeed, studies dealing with metal contamination

and microbial communities associated to these substrates are only based on total analysis of the metal in the whole sediment (e.g., Farag et al. 2007; Kohušová et al. 2011) or leaf litter (e.g., Sridhar et al. 2008; Schaller et al. 2011), including attached biofilms. The analytical procedures commonly used include a first step of extraction with aqua region or nitric acid, for instance, on fresh or dried sediment/leaf litter. Then, metal concentrations in the extracts are measured by conventional analytical methods (ICP-OES, ICP-MS, or AAS). To date, and to the best of our knowledge, no study has been conducted to separate and specifically assess metal concentrations in microbial communities from sediment or leaf litter.

Besides traditional fractionation and extraction methods, imaging techniques have been developed to investigate interactions between metals and biofilms and to visualize metals within the biofilm structure. Analytical electron microscopy techniques such as transmission electron microscopy (TEM), often coupled with energy-dispersive X-ray spectrometry, have been used to identify metal bioaccumulation in microbial biofilms, in particular in bioremediation studies in which biofilms are used as a sink to accumulate metals from contaminated waters (Mattila et al. 1997; Miller et al. 2012). For example, this technique allowed Vilchez et al. (2011) to show that Cr(III) bioaccumulated in the EPS matrix of microbial biofilms, while Pb(II) was detected in both the EPS matrix and the microbial biofilm cells. In order to determine macromolecules and metals composition in EPS from microbial biofilms, TEM can also be coupled to electron energy loss spectrometry, which is a complex technique for measuring atomic composition and chemical binding and speciation, even for lower elements (C, O). The main drawback of TEM is that sample preparation often requires dehydration, creating artifacts such as particle shrinkage or aggregation (Dynes et al. 2006a). Furthermore, the high energy of TEM causes radiation damage in biological samples, which leads to spectral distortions, making high-resolution mapping difficult (Hitchcock et al. 2008).

Other imaging techniques such as confocal laser scanning microscopy (CLSM) and scanning transmission X-ray microscopy (STXM) are especially well suited for biofilm studies as they can be applied to fully hydrated biological materials and reduce radiation damage (see Neu et al. 2010 for a comparative review on those techniques applied to biofilms). In CLSM, metal binding to specific fluorescent probes allows detection and localization of those contaminants within biofilms (for a description of the different probes available, see the review by Hao et al. 2013). In particular, the metal-sensitive probe Newport Green has been successfully used to investigate Ni and Zn bioaccumulation in river biofilm (Wuertz et al. 2000; Lawrence et al. 2019). The combination of different probes can be particularly useful to compare localization of various metals on microbial aggregates (Hao et al. 2016). STXM, which uses near-edge X-ray absorption fine structure as the contrast mechanism, provides spatially resolved quantitative information on the distribution of elements, macromolecules, and redox states in the biofilm matrix (Lawrence et al. 2003; Behrens et al. 2012). According to Lawrence et al. (2016), STXM is "capable of mapping the biochemical composition of bacteria and biofilms at the subcellular scale [...] as well as speciation of metals." Comprehensive reviews on STXM applied to biofilms have found that it holds relevancy for investigating

metal (Cu, Fe, Mn, Ni) speciation in biofilm matrices (Neu et al. 2010; Behrens et al. 2012). Dynes et al. (2006a) used STXM to highlight the close association of Ni with Mn-oxides and the role of EPS in the sequestration of metals in aquatic microbial biofilms. This technique also allowed Lawrence et al. (2012, 2016) to follow the dissolution and fate of Cu nanoparticles (Lawrence et al. 2012) and the fate and speciation of Ce, TiO_2, and Cu in river biofilms (Lawrence et al. 2016). Yang et al. (2016) characterized the biotransformation of selenium oxyanions by biofilms using STXM and X-ray fluorescence imaging (at higher energies than STXM). Finally, STXM image sequences revealed that Fe localization (on the cell surface or within the EPS matrix) was speciation-dependent in a monospecific biofilm of *Pseudomonas aeruginosa* (Hunter et al. 2008). The main limitations of the STXM techniques are their low sensitivity and limit of resolution (25–50 nm against 4 nm for TEM techniques). Indeed, to our knowledge, very few STXM studies have been conducted at environmentally relevant concentrations: one study reports results on Mn, Fe, and Ni with water concentrations ranging from 0.01 to 0.02 mg Mn L^{-1}, 0.02 to 0.06 mg Fe L^{-1}, and 1 to 10 mg Ni L^{-1}, respectively (Hitchcock et al. 2009).

The combination of different imaging techniques remains essential to determine metal distribution in biofilms and better understand the interactions between metals, cellular components, and extracellular material (van Hullebusch et al. 2003). In a recent study, Lawrence et al. (2019) combined CLSM with different fluorescent probes, scanning electron microscopy, and X-ray microprobe analyses to show that Ni was mainly associated to EPS in biofilm and was four times more concentrated around specific microcolonies than in the rest of the microbial community.

2.2 *Organic Contaminants*

In contrast to the substantial research on metal distributions within periphytic biofilms, there is a dearth of studies dealing with the accumulation in microbial assemblages of organic contaminants. These studies mainly focus on pesticides, polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), and more recently pharmaceuticals, hormones, and parabens. And the few studies published fail to detail analytical methods for the quantification of organic contaminants in the biofilm following both laboratory and in situ exposure (Schorer and Eisele 1997; Headley et al. 1998; Lawrence et al. 2001; Writer et al. 2011; Kohušová et al. 2011; Ruhí et al. 2016). Due to the high complexity of the biofilm matrix, nonselective solvent extraction methods generate analytical interferences; therefore biofilm contamination by organic contaminants is preferably estimated indirectly from contamination in water (Wang et al. 2002; Proia et al. 2013a, b). To directly measure the concentration of organic contaminants in periphytic biofilms, samples are first collected from the surfaces of stones or artificial substrates and then freeze-dried before analysis (Wang et al. 1999; Huerta et al. 2016). Organic contaminants are commonly extracted from the whole biofilm matrix without fractionation to avoid matrix destruction and cell lysis. However, Chaumet et al. (2019a) recently

proposed a physical extraction method to separate the diffusible from the cell-bound EPS and microorganism fractions to further measure pesticide concentrations accumulated in each of these two fractions. Solvent extraction of organic contaminants from dried biofilm is then performed by pressurized liquid extraction (Writer et al. 2011; Huerta et al. 2016), ultrasonic extraction (Headley et al. 2001), shaking extraction (Wang et al. 1999; Du et al. 2015), or Soxhlet extraction (Schorer and Eisele 1997). Organic extracts are sometimes purified by solid-phase extraction (Coat et al. 2011; Writer et al. 2011; Du et al. 2012, 2015) or directly analyzed by chromatographic techniques (Headley et al. 2001). Liquid or gas chromatography coupled to mass spectrometry (LC-MS or GC-MS, depending on the compounds) is preferred to achieve the requisite selectivity and sensitivity (Coat et al. 2011; Dobor et al. 2012; Du et al. 2012; Huerta et al. 2016; Ruhí et al. 2016). As an example, liquid chromatography with UV detection was not sufficiently sensitive for analysis of *N*-methyl pyrrolidinone in biofilm extracts with a limit of quantification (LOQ) at 100 ng g^{-1}, whereas LC-MS was able to reach a LOQ of 2 ng g^{-1} (Headley et al. 2001; Huerta et al. 2016). While current identification and quantification methods generally include extraction and purification steps, Headley et al. (1995) proposed in the 1990s a method based on the direct injection of a small biofilm sample using an insertion probe. Subsequent detection and identification of contaminants and metabolites were performed by tandem mass spectrometry (MS-MS) (Headley et al. 1995). Unfortunately, the absence of separation of biofilm components prior to sample introduction in the ion source induced interferences that limit the detection of a wide range of contaminants at low-level concentration.

As for metal detection (Sect. 2.1), imaging techniques, such as CLSM and STXM (Neu et al. 2010), have been successfully used to investigate organic contaminant bioaccumulation in biofilms (Lawrence et al. 2001, 2016; Dynes et al. 2006b). These nondestructive imaging techniques were applied on hydrated biofilm samples and allowed direct observation of contaminants localization in the complex structure of preserved biofilms. Fluorescence was usually used to detect contaminant with CLSM, either by investigating fluorescent contaminants (Wolfaardt et al. 1994) or by using specific probes targeting the contaminant investigated (Lawrence et al. 2001). Contaminant identification by STXM was probe-independent and based on comparison with suitable reference spectra (Neu et al. 2010). Thus, coupling CLSM with monoclonal antibodies specific to atrazine, Lawrence et al. (2001) showed that bioaccumulation of this pesticide in river biofilms resulted from atrazine sorption to specific microcolonies. Using STXM, Dynes et al. (2006b) revealed differences in bioaccumulation patterns of the antimicrobial chlorhexidine between pennate and centric diatoms within a complex microbial biofilm. To our knowledge, STXM has not been used for quantification of organic contaminant accumulation in biofilms; however the optical density obtained by STXM reflected the amount of contaminant and could therefore be used for relative comparison between samples (Dynes et al. 2006b). Up to now, these techniques have only been applied on complex microbial biofilms exposed in laboratory at relatively higher concentrations of organic contaminants than those found in the aquatic environments.

Only a few studies have reported on the evaluation of analytical method performances such as recoveries and LOQ (Coogan et al. 2007; Huerta et al. 2016) or matrix effects (Headley et al. 2001; Ruhí et al. 2016). The relatively low amounts of contaminants sorbed on biofilms (trace levels) and the limited biomass collected (often <200 mg) mean that LOQ values are generally in the same order of magnitude as the measured concentrations. As an example, Huerta et al. (2016) reported LOQs from 0.07 to 6.7 ng g^{-1} for pharmaceuticals (in 200 mg of phototrophic biofilms), whereas most of the values measured in biofilm samples were between 1.8 and 22 ng g^{-1}. Matrix effects due to the specificity of the analyzed biofilm are also under-addressed. To illustrate, when Huerta et al. (2016) compared analyses of biofilm extracts against the initial solvent mixture spiked with different contaminants at the same concentration level, they observed either ion suppression or ion enhancement depending on organic contaminant, thus demonstrating that concentrations values in biofilm extracts can be biased (i.e., over- or underestimated) due to matrix effects. For quantification purposes, matrix-matched calibration together with added internal surrogates (ideally labeled compounds) is thus advocated to compensate for these matrix effects (Huerta et al. 2016; Ruhí et al. 2016).

3 Contaminant Bioaccumulation in Microbial Biofilms from Freshwater Ecosystems

Microbial biofilms can adsorb and accumulate both metals and organic contaminants. The nature of the contaminant, the surrounding environmental conditions, and the type of biofilm have all been found to influence contaminant bioaccumulation patterns. Note that bioaccumulation cannot be apprehended in the same way in periphytic biofilms, which are easily detached from their growth substrate, nor in biofilms strongly attached to leaf litter or fine detritus in sediments, which makes it difficult to specifically quantify the contaminants accumulated in the microbial biomass.

3.1 Contaminant Bioaccumulation in Periphytic Biofilms

Natural periphytic biofilms have been found to host a large variety of contaminants. Current knowledge on bioaccumulation in periphyton is illustrated and discussed here based on a meta-analysis of 24 published studies (Table S1). The data collected gather field and laboratory experiments including simultaneous quantification of contaminants in water and periphyton (Fig. 4) with biofilms sampled at various stages of maturity. Most of this data comes from chronic exposures, but some pulsed exposures are also included. To estimate uptake efficiency, bioconcentration factors (BCFs) were used as a proxy and were calculated as the ratio between the concentration measured in the biofilm and the dissolved concentration in the medium

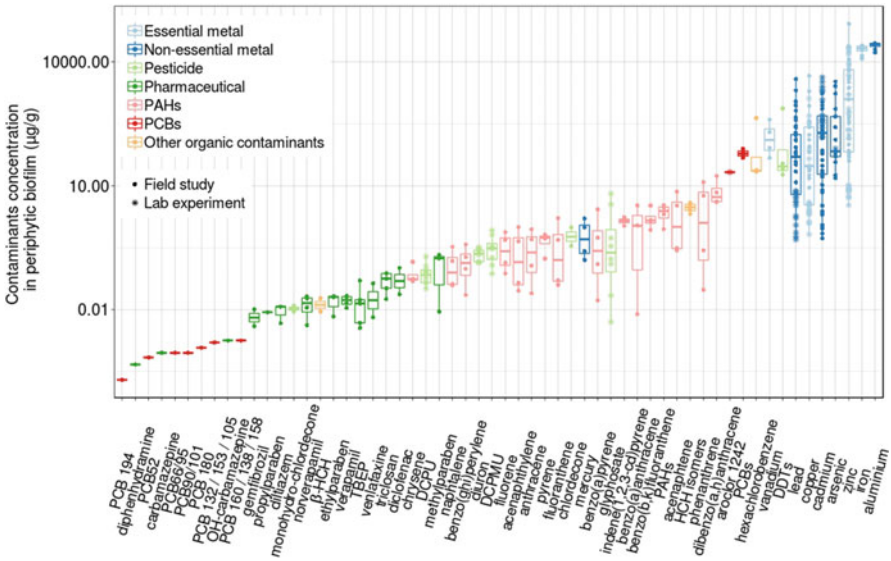

Fig. 4 Concentration of contaminants in periphytic biofilms in µg g^{-1} of biofilms (dry weight) ($n = 400$), data from 24 published studies. Plain circles stand for observations from the field, stars for observations from laboratory experiments. *PAHs* polycyclic aromatic hydrocarbons, *PCBs* polychlorinated biphenyls, *HCH* hexachlorocyclohexane, *TBEP* tris(butoxyethyl)phosphate, *DCPU* *N*-(3,4-dichlorophenyl) urea, *DCPMU* *N*-(3,4-dichlorophenyl)-*N*-(methyl) urea, *DDTs* dichlorodiphenyltrichloroethane

(Wang et al. 1999) (see Fig. 5 and Table S1 for details). BCF calculations rely on accurate estimation of chemical concentrations in both surface water and biofilm and are thus strongly influenced by LOQs – for instance, high LOQs in water could lead to an overestimated BCF (Arnot and Gobas 2006).

In periphyton, the bioaccumulation of any type of contaminant results from a dynamic process (Chaumet et al. 2019a, b). The concentration of a contaminant within periphyton tends to an equilibrium between uptake, elimination, and biotransformation and is also influenced by growth-related dilution effects. Contaminant uptake in biofilm depends strongly on the nature of the chemical (metal vs. organic) and on the 3D architecture and composition of the biofilm. First, contaminants enter EPS via passive diffusion and can then either be accumulated/transformed in this extracellular matrix or taken up within the cells (by passive diffusion and facilitated or active transport). The complex composition of the EPS matrix of biofilms offers many adsorption sites for both polar and hydrophobic contaminants (Schorer and Eisele 1997; Flemming and Wingender 2001). Biofilms take up both metals and organic contaminants that can then be stored (extra- or intracellularly) and/or transformed by the community. Periphytic biofilms can accumulate very high concentrations of metals, particularly aluminum, iron, and zinc, which can be found at up to 24–28 mg g^{-1} of dry biofilm (Fig. 4, Table S1). Advanced analytical methods, including imaging techniques (see Sect. 2), have

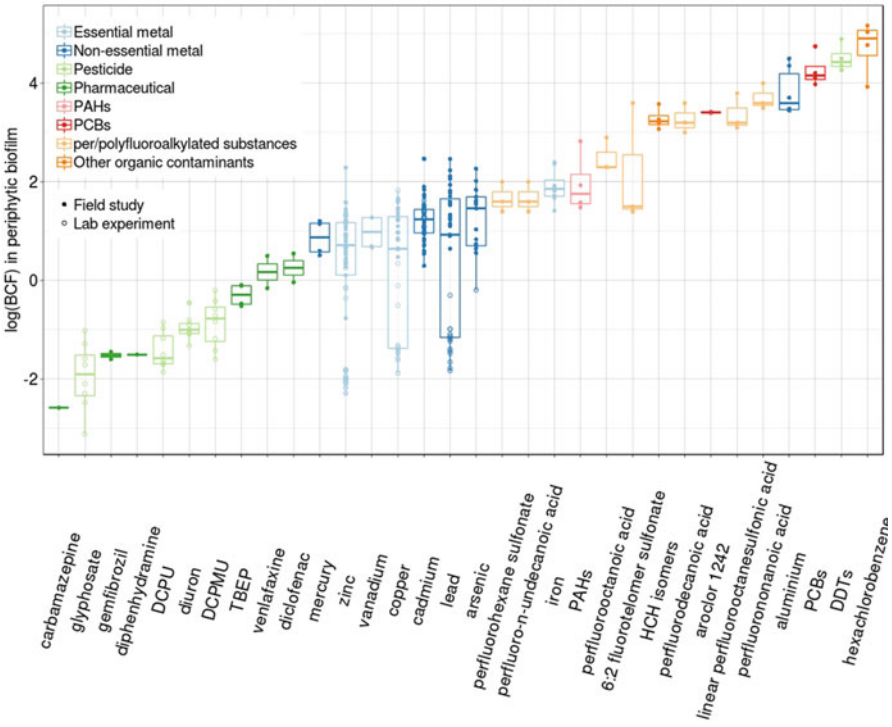

Fig. 5 Bioconcentration factor, expressed as log(BCF), for periphytic biofilms ($n = 304$), data from 22 published studies. Plain circles stand for observations from the field, stars for observations from laboratory experiments. *PAHs* polycyclic aromatic hydrocarbons, *PCBs* polychlorinated biphenyls, *HCH* hexachlorocyclohexane, *TBEP* tris(butoxyethyl)phosphate, *DCPU* *N*-(3,4-dichlorophenyl) urea, *DCPMU* *N*-(3,4-dichlorophenyl)-*N*-(methyl) urea, *DDTs* dichlorodiphenyltrichloroethane

afforded a relatively precise mapping of metals in periphyton, which can be found in different microenvironments of periphytic biofilms depending on the metal form/speciation and the characteristics of the microenvironment. Precipitates can be found in the biofilm matrix at the cell surfaces (Brown et al. 1998), while positively charged metal ions can accumulate in negatively charged cell walls and EPS. Metal speciation is also reported to influence the site of metal bioaccumulation (bound to membrane vs. EPS; Hunter et al. 2008). Biofilms have also evolved enzymatic mechanisms of metals reduction (Lloyd 2003) or metal sequestration via thiol-rich polypeptides known as phytochelatins able to sequester excess intracellular metals in a stable, detoxified form (e.g., Lavoie et al. 2012). Depending on the metal and environmental conditions, they are able to store and concentrate large amounts of metals that are potentially transferable to higher trophic levels.

As stated earlier, there is less data available on the bioaccumulation of organic contaminants in periphytic biofilms. However, the pattern seems to be that these contaminants tend to accumulate at lower final concentrations (Fig. 4), but some more efficiently (i.e., with higher BCFs), than metals (Fig. 5, Table S1). These

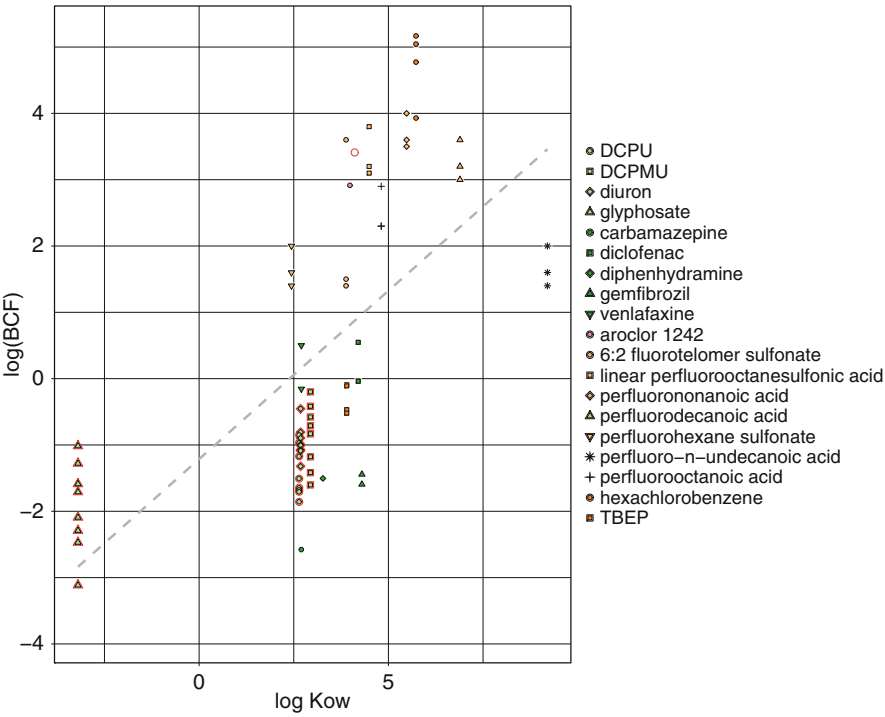

Fig. 6 Bioconcentration factor, expressed as log(BCF) of organic contaminants in periphytic biofilms vs. log K_{ow} of the accumulated contaminants ($n = 70$). Linear regression: log(BCF) = 0.51 ∗ log K_{ow} − 1.21 ($r^2 = 0.42$, $p < 0.01$). Data from nine published studies. Data points circled in red are observations from laboratory experiments; all other points are observations from field studies. *DCPU N*-(3,4-dichlorophenyl) urea, *DCPMU N*-(3,4-dichlorophenyl)-*N*-(methyl) urea, *TBEP* tris(butoxyethyl) phosphate

differences could be driven by differences in exposure concentrations; although concentrations of organic contaminants in surface water were not often reported, they were generally found at lower levels than for metals. Thus, in studies for which concentrations in both biofilms and surface water were reported, all median dissolved concentrations of metals were superior to 1 μg L^{-1} (except for mercury), while the median dissolved concentrations for all the organic contaminants studied were below 1 μg L^{-1}. Organic contaminants tend to get adsorbed to the organic matter trapped in the biofilm, EPS, and cell membrane due to their specific chemical properties and high lipid content (Wolfaardt et al. 1998; DeLorenzo et al. 2001; Métivier et al. 2013). The bioaccumulation of organic contaminants in biofilms is driven by their hydrophobicity, which can be estimated by their partition coefficient between octanol and water, called log K_{ow} (Fig. 6). Log K_{ow} correlates positively with the log BCFs of organic contaminants (Pearson correlation coefficient; $n = 70$; $r^2 = 0.42$, $p < 0.05$), and models have been developed to predict contaminant bioaccumulation in biofilms based on physical-chemical properties (Ruhí et al.

2016). Besides their hydrophobicity, organic contaminants possess other specific characteristics than can also help them bioaccumulate. For instance, the highest BCF values were observed for halogenated contaminants such as hexachlorobenzenes (BCF up to 147,000 L g^{-1}), PCBs (BCF up to 56,000 L g^{-1}), or per- and polyfluoroalkylated substances (BCF up to 10,000 L g^{-1}) (Fig. 5, Table S1), suggesting that the compounds' high electron affinity with living cells is also strongly involved in its accumulation. Nevertheless, validation of this hypothesis remains bottlenecked by technical limitations, as the quantification of intracellular organic contaminants in microbial biofilms is not yet possible (Sect. 2.2). Non-organochlorine pesticides and pharmaceuticals measured in periphytic biofilms generally show lower BCFs (BCF $<$ 3.6 L g^{-1}) than metals and fluorinated or organochlorine contaminants (e.g., DDT, dichlorodiphenyltrichloroethane; BCF up to 78,550 L g^{-1}). The lower concentration of these contaminants in periphytic biofilms could also be explained by different biodegradation processes for different substances. For instance, studies have shown that periphytic microbial communities can partially transform and/or mineralize pesticides (e.g., the phenylurea herbicide diuron (Pesce et al. 2009) and glyphosate (Carles et al. 2019)) and antibiotics (e.g., the sulfonamide antibiotics sulfamethazine and sulfamethoxazole (Vila-Costa et al. 2017)). Metabolites are thus sometimes found in biofilms (e.g., atrazine metabolites (Lawrence et al. 2001) or glyphosate metabolites such as aminomethylphosphonic acid (Carles et al. 2019)), but it is not always possible to discriminate those produced through biodegradation by the biofilm itself from those that were already present in the water column before being bioaccumulated. Additionally, the lower BCFs observed for the non-organochlorine pesticides (i.e., glyphosate, diuron, and its metabolites) could also be explained by higher exposure concentrations since those values were applied in laboratory experiments (contrary to BCF values for pharmaceuticals obtained in the field); further field study investigating pesticides bioaccumulation in natural periphytic biofilms is therefore required to confirm those first observations.

Each step of the bioaccumulation process is influenced by a number of factors such as exposure duration and concentration, physical-chemical conditions, and biofilm composition. Hydrology and geomorphology are also likely to influence bioaccumulation especially by driving contaminants repartition between aquatic compartments (surface water, particulate matter, sediment, periphytic biofilm).

In the dataset analyzed, exposure duration was not significantly correlated with metal BCFs, which argues for fast adsorption of metals in the biofilm matrix. Among the metals considered, aluminum had the highest uptake efficiency even at low exposure concentrations (BCF up to 31,800 L g^{-1}), irrespective of exposure duration (1–35 days). Corcoll et al. (2012) hypothesized that the amount of Al accumulated was thus "background" content for the biofilms studied. In contrast, Pb accumulation above a certain exposure concentration (exceeding more than ten times the criteria for chronic exposure concentration as defined by the US Environmental Protection Agency) dropped strongly with log BCF < -1. Exposure concentrations influence metal bioaccumulation; thus a positive correlation (Pearson correlation coefficient; $n = 238$; $r^2 = 0.28$, $p < 0.05$) was found between metal concentration in biofilm and

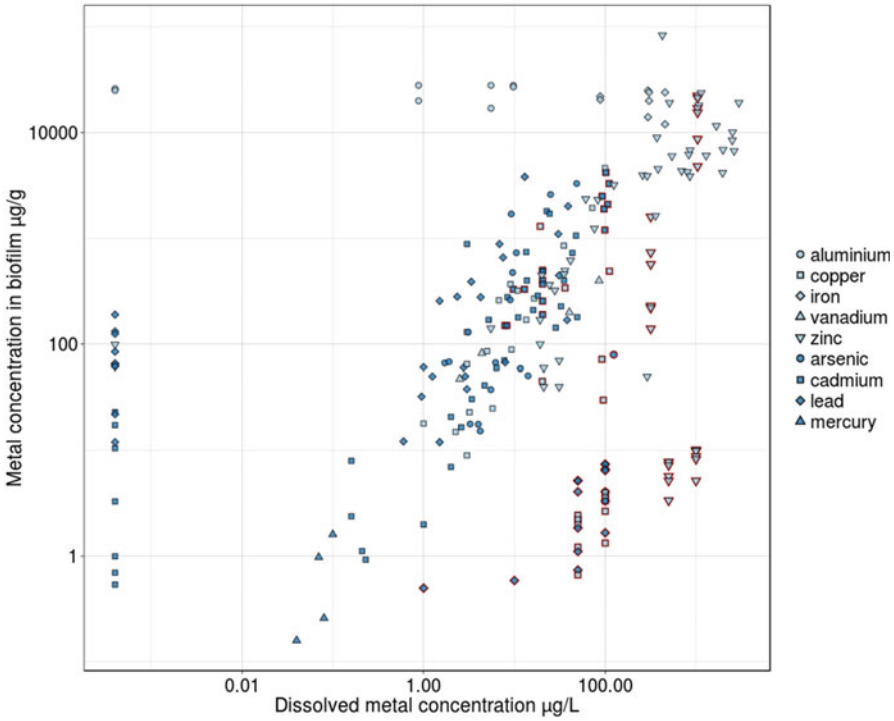

Fig. 7 Metal concentration in biofilm (µg g^{-1}) vs. dissolved concentrations of metals in surface water (µg L^{-1}). Data points circled in red are observations from laboratory experiments; all other points are observations from field studies ($n = 238$; data from 14 published studies)

dissolved metal concentrations (Fig. 7). Nevertheless, our database, in line with several studies, also highlighted that BCF in biofilms is not always positively correlated with exposure concentrations. Indeed, logBCFs tend to decrease with increasing dissolved metal concentration in particular in laboratory experiments (Fig. S1) questioning the pertinence of using this parameter as a proxy of exposure. Indeed, metal speciation, including complexation, in the dissolved fraction can influence bioaccumulation (Meylan et al. 2004; Bradac et al. 2009, 2010; Dranguet et al. 2017). Thus, Meylan et al. (2004) showed that Zn accumulation in periphytic biofilm was mainly driven by dissolved Zn concentrations, while weakly complexed Cu controlled its bioaccumulation in microbial biofilms. High amounts of suspended metal-contaminated particulate matter can also get entrapped directly by the biofilm matrix, thus driving further accumulation of large additional amounts of metals (Morin et al. 2008). Therefore, metal BCF calculations based on dissolved concentrations only may underestimate the correlation between exposure and bioaccumulation values (intracellular content and BCF).

Discrepancies between exposure, measured as dissolved concentrations, and bioaccumulation, measured as BCF, were also found for some organic contaminants. A study on per- and polyfluoroalkylated substances by Munoz et al. (2016) found

inverse correlations between exposure concentrations and BCFs along a gradient of contamination concentrations in the Seine River. This divergence could also be the consequence of a saturation of cellular binding sites at high exposure concentrations, with a possible influence of competition between contaminants in mixtures. Indeed, competitive sorption is likely to occur in the environment due to the co-occurrence of multiple contaminants in surface waters. For instance, the accumulation rate of the organosulfur fungicide isoprothiolane in two microalgae (*Scenedesmus quadricauda*, *Aulacoseira granulata*) and one cyanobacterium (*Microcystis aeruginosa*) decreased in presence of other pesticides (the herbicide p-nitrophenyl 2,4,6-trichlorophenyl ether and the insecticide O,O-dimethyl O-(3-methyl-4-nitrophenyl) phosphorothioate) in the mixture (Guanzon et al. 1996). This phenomenon is more likely to occur in laboratory experiments in which biofilms are usually exposed to higher concentrations than those found in the environment. Indeed, in our dataset BCF calculated from laboratory experiments were generally lower than those from field experiment (Figs. 5, 6 and S1).

The influence of environmental factors on metal accumulation in periphytic biofilm has been reviewed by Guasch et al. (2010). In particular, metal speciation is influenced by a range of physicochemical factors (including pH, salinity, and nutrients), affecting their bioavailability (Meylan et al. 2003) and subsequent accumulation and toxicity for microbes. Biofilm characteristics (community composition, biomass, organic matter content, EPS content) can also influence the bioavailability and therefore the accumulation and toxicity of contaminants (Berglund 2003; Berglund et al. 2005; Lambert et al. 2016; Pesce et al. 2018). In river biofilms, the sorption of certain contaminants such as triazines or metals has been attributed to specific bacterial colonies producing an EPS matrix with a unique composition (Lünsdorf et al. 1997; Lawrence et al. 2001). A change in community composition can modify lipid content and therefore influence the accumulation of organic compounds such as PCBs according to their high log K_{ow} value (Wang et al. 1999). Finally, toluene accumulation in a bacterial biofilm has been shown to increase negatively charged carboxyl groups in EPS and might thus enhance biofilm ability to accumulate cations such as metal ions (Schmitt et al. 1995).

Through their capacity to uptake contaminants from the surface water, periphytic biofilms can also be viewed as passive samplers of contaminants in surface waters. This has prompted the idea that identifying and quantifying the contaminants accumulated within the biofilm could be a monitoring strategy for surveillance of aquatic ecosystem contamination by both organic contaminants (e.g., PAHs; Froehner et al. 2012) and metals (Leguay et al. 2016). However, following equilibrium partitioning theory, contaminants accumulated in biofilms are also likely to diffuse back in the water when their dissolved concentration has dropped. Sorption and desorption kinetics have been studied for some contaminants such as PCBs and PAHs (Bertini 2016) and for a handful of pesticides (Headley et al. 1998) and antibiotics (Wunder et al. 2011). Therefore, due to the dynamic processes involved in contaminant accumulation in biofilms and the potential influence of many abiotic and biological parameters, the use of bioaccumulation in biofilms as an indicator of contamination has been challenged, in particular for organics (Bertini 2016).

Further investigations are needed to better determine the timeframe integrated by contaminant accumulation in biofilms as a function of chemical, biological, and environmental properties.

3.2 Contaminant Bioaccumulation in Sediment or Leaf Litter Microbial Communities

Up to now, data on in situ bioaccumulation of metals and organic contaminants in submerged microbial communities associated with sediments, leaves, or drift particulate matter has always included both biotic accumulation and abiotic sorption on the substratum. As stated earlier, this is partly due to the fact that microbial communities cannot be easily detached from these substrates and that the microbial biomass obtained is still very limited (and not sufficient for chemical analyses).

The distribution of organic contaminants in the different river compartments (water, sediment, and leaf litter) is influenced by the hydrology and geomorphology of the system as well as by the physical and chemical properties of the contaminant. For instance, suspended and bed sediments in the San Joaquin River and its tributaries (in one of the most productive agricultural regions of the USA) serve as a sink for hydrophobic contaminants (e.g., PAHs, DDT), whereas water-soluble herbicides (e.g., atrazine, simazine, dimethyl tetrachloroterephthalate) are mostly present in the dissolved phase of the water column (Pereira et al. 1996). A similar pattern of pesticide distribution has been observed in rivers in Europe (e.g., Fernandez et al. 1999) and Asia (e.g., Chen et al. 2006). Pesticide dissipation in water can be enhanced or reduced by the presence of sediments and according to the properties of pesticide molecules (Laabs et al. 2007). Sediments can also accumulate pharmaceuticals. An extensive study in four Spanish rivers (Ebro, Llobregat, Júcar, and Guadalquivir) highlighted the presence of endocrine disruptors accumulated in sediments at concentrations up to 7 ng g^{-1} (Gorga et al. 2015). Similar levels of the hormone β-estradiol were also quantified in sediments of the River Ouse (UK) (Labadie and Hill 2007), whereas lower levels were reported in three rivers in the Tianjin area (China) (Lei et al. 2009). Several antibiotics from urban sources and aquaculture activities (e.g., sulfamethazine, sulfamethoxazole, norfloxacin, among others) have been detected in the sediments of the Pearl River Estuary (South China) at concentrations ranging from 1 to 8 ng g^{-1} (Liang et al. 2013). While contaminant accumulation in sediments contributes to the removal of toxic substances from the surface, this apparent remediation is only temporary since those contaminants can later be remobilized following changes in redox conditions leading to the redissolution from sediment and diffusion from pore water and/or during intense hydrological events, as shown by Domagalski et al. (2010) for pyrethroid insecticides in different rivers. Flash-flood events in the Ebro river basin were also found to mobilize huge amounts of hexachlorobenzene, DDT, and PCBs largely exceeding existing regulatory reference values established for sediments (Quesada et al. 2014).

Sediments are also recognized as an important sink of metals in freshwater environments. Indeed, numerous studies have reported the accumulation of metal contaminants in sediments from various kinds of ecosystems including streams (e.g., Rodrigues and Formoso 2006), estuaries, and large rivers (e.g., Hamzeh et al. 2016), artificial reservoirs (e.g., García-Ordiales et al. 2016), and natural lakes (e.g., Gascón Díez et al. 2017) all over the world, from Europe (e.g., Thevenon et al. 2011) to the USA (e.g., Garvin et al. 2017), South America (e.g., Smolders et al. 2003), Asia (e.g., Liao et al. 2017), and Africa (e.g., Kilunga et al. 2017). While anthropogenic activities can explain part of this contamination, metals are also naturally present in sediments as geogenic particulate components (Ho et al. 2013). The ubiquity of metal contamination in freshwater sediments is illustrated in a report summarizing the results of an extensive chemical survey (567 sampling stations) designed to measure metal concentrations in sediments from various fluvial ecosystems dotted across France (INERIS 2010). The reported median, average, and maximum concentrations (in mg kg^{-1} dry weight sediment) were, respectively, 7.3, 12.4, and 1,005 for As; 0.7, 10.2, and 7,285 for Cd; 36.0, 52.1, and 5,300 for Cr; 21.7, 48.5, and 4,330 for Cu; 0.1, 1.2, and 200 for Hg; 19.0, 26.8, and 2,380 for Ni; 32.6, 122.0, and 50,420 for Pb; and 130.0, 446.0, and 142,500 for Zn (INERIS 2010).

Comparatively, there has been less effort to investigate organic and inorganic contaminant accumulation in submerged leaf litter. This could be explained by the ephemeral presence of the substratum in the ecosystem but also by the fact that studies addressing contamination gradients are mostly focused on downstream contaminated sections where riparian vegetation is often poor. However, leaf litter has been proven to adsorb metals (Sridhar et al. 2001) and a range of herbicide and fungicide molecules (Passeport et al. 2013; Vallée et al. 2014; Rossi et al. 2018). The sorption potential of these contaminants on leaf substrates may depend on their stage of decomposition (e.g., Dimitrov et al. 2014 for the fungicide tebuconazole). Leaf litter accumulated in rivers has comparatively similar (and/or greater) pesticide adsorption capacities to sediments (Margoum et al. 2006; Passeport et al. 2011). Vallée et al. (2014) revealed that straw has greater retention potential than sediments and soils for three herbicides and three fungicides in constructed wetlands. These results show the importance of organic carbon content and nature in the pesticides sorption process. A tracer injection experiment was conducted in the field in a "wet" forest buffer zone to test its potential for reducing loads of glyphosate, isoproturon, metazachlor, azoxystrobin, epoxiconazole, and cyproconazole (Passeport et al. 2014). Results confirmed that leaf litter layer thickness was a key parameter that influences the potential for delaying and reducing pesticide transfers and increasing their degradation.

As observed for periphytic biofilms and discussed above, bioaccumulation of organic contaminants in sediments, leaves, or drift particulate matter can be influenced by substratum characteristics and/or environmental factors. A field study in the Pearl River Estuary (South China) found that sediment total organic carbon and water pH were the most important factors influencing the dynamics of distribution of the antibiotics norfloxacin and erythromycin between water and sediments, respectively (Liang et al. 2013). Different environmental parameters,

including pH and temperature, were also shown to be important drivers of metal accumulation in sediments (Lin and Chen 1998; Saeedi et al. 2011; Li et al. 2013), in which the sorption, release, and transport of metals are important processes influencing the chemical quality of water bodies (Tao et al. 2005; Fan et al. 2007).

After sorption to sediments and leaf litter material, organic contaminants can be partially or totally biodegraded by the attached microbial communities. Thus, two species of aquatic hyphomycetes (*Heliscus lugdunensis*, *Clavariopsis aquatica*) typically associated with submerged leaf litter were found to biotransform 1-naphthol (Augustin et al. 2006) or technical nonylphenol (Sole et al. 2008). Recently, leaf-associated communities from sites downstream of agricultural areas were shown to exhibit a greater potential to degrade the maize herbicide nicosulfuron compared to those from upstream communities, and this was partly explained by the pre-exposure history of these communities to the contaminant (Carles et al. 2017). In these microbial communities, Carles et al. (2018) isolated an ascomycete fungus (*Plectosphaerella cucumerina* AR1) capable of transforming nicosulfuron into its two major metabolites (2-amino-4,6-dimethoxypyrimidine and 2-(aminosulfonyl)-*N*,*N*-dimethyl-3-pyridinecarboxamide) in the presence of glucose. Microbial biofilms from river sediments have also been shown to degrade nonylphenol (Wang et al. 2014) and the herbicides diuron (Pesce et al. 2009) and isoproturon (Trinh et al. 2012), among others.

3.3 *Contaminant Distribution in Different Kinds of Biofilms and Potential Contribution to Trophic Transfer in Aquatic Ecosystems*

Periphytic, sediment, and leaf litter biofilms can all act as both sink and source of contaminants for the aquatic ecosystem. Only a few studies have set out to investigate in situ the relationship between contaminant concentrations in periphytic biofilms and in sediments in contaminated rivers, and the focus has been exclusively on metals (Farag et al. 1998, 2007; Holding et al. 2003; Kohušová et al. 2011; Ancion et al. 2013). Conceptually, any sound assessment of contaminant bioaccumulation in microbial biofilms and its consequences on trophic transfers of contaminants in aquatic ecosystems needs to account for the ecological dynamics affecting each type of aquatic biofilm. Periphytic biofilms follow a several-stage life cycle from colonization and co-adhesion to final detachment (due to biological mechanisms and/or physical constraints), and so contaminant bioaccumulation in these microbial communities can be viewed as transient. Bioaccumulation of contaminants on leaf litter is also transient (according to the leaf litter decay rates) and seasonally specific as it depends on the availability of plant litter (e.g., litter fall peaks in autumn in temperate rivers). In sediments, contaminants are accumulated in microbial biofilms attached to sediment but also complexed with inert material. The specific bioaccumulation of microbial biofilms in this accumulation cannot be,

however, distinguished from the total accumulation in sediments because of methodological difficulties in discriminating the biotic from the abiotic fraction of sediments. Nevertheless, due to both physicochemical and biological characteristics, sediments can store contaminants for much longer, and can thus be viewed as a more stable compartment, even if disruptions (flood events, changes in pH or redox potential, etc.) can trigger releases.

By taking up contaminants from the surface water, microbial biofilms help to "clean" the water. But they can only completely degrade a few organic contaminants (the in situ efficiency of this kind of process being still unknown), and so the remaining bulk of accumulated contaminants (and/or their metabolites) will be either resuspended in the water column in a dissolved or complexed form (e.g., following biofilm detachment or sediment mobilization) or get transferred to higher trophic levels.

4 Contaminant Transfer from Microbial Biofilms Through Food Webs

In freshwater ecosystems, microbial biofilms are an important food resource (in both the green and brown food webs; Fig. 3), even if potentially contaminated by metals or organic contaminants. Microcosm and field studies conducted to investigate the role and importance of these biofilm communities in contaminant trophic transfer have revealed important differences in terms of contaminant fate through food webs.

4.1 Current Approaches Used to Follow Contaminants Through Food Webs

Microcosm experiments are commonly used to reproduce simple food webs under controlled conditions in order to limit any confounding factors likely to influence the bioaccumulation process (e.g., temperature, nutrients, pH, ionic composition) and explore the fate of the contaminants. These microcosm experiments typically consist in exposing animals to a food source, namely, a single (often algal) microorganism species or natural biofilms, spiked with a contaminant. For instance, simplified food chains, i.e., from primary producers to consumers such as crustaceans, insects, bivalves, and more rarely fish, have been reproduced in microcosm experiments to determine the trophic transfer of metals or metallic nanoparticles (Croteau et al. 2005; Conley et al. 2009; Komjarova and Blust 2009; Prokes et al. 2012; Golding et al. 2013; Kim et al. 2016). These microcosm studies usually contaminate the food resource in an independent spiking process before introducing it into the microcosm.

For instance, algae spiked with metals have been used to demonstrate trophic transfers of a variety of metals to bivalves or crustaceans (Croteau et al. 2005; Goulet et al. 2007; Komjarova and Blust 2009). Experimental studies can more precisely gauge contaminant fates by spiking with labeled contaminants. Radioisotopes of metals have been used to label food sources and thus trace species-specific bioaccumulation dynamics by monitoring the radioactivity in consumers after pulse-chase feeding (Conley et al. 2009; Golding et al. 2013). Food-resource enrichment by stable isotopes of metals makes an interesting alternative approach to determine the relative contributions of food and water to metal contamination in grazers (Komjarova and Blust 2009). Indeed, isotopic ratio measurements can be used in microcosm experiments to characterize and model the physiological mechanisms involved in the assimilation of metals by the consumers from the biofilm they ingested (Croteau et al. 2005). To our knowledge, the trophic transfer of organic contaminants from biofilms to higher-level organisms has not yet been studied in microcosm experiments.

Microcosm experiments do provide accurate information on the dietary dynamics of contaminants in simplified food chains, but they are often specific to a prey/consumer pair, and consequently only partially reflect the environmental complexity governing trophic transfers (e.g., multiple food sources, biofilm structure, nutrient loads, and more). In addition, the choice of the microorganism(s) used as a contaminated food source and the spiking method remain challenging tasks. Indeed, metals assimilation by consumers has been reported to be closely related to microbial species and their respective ability to bioaccumulate metals, to metal distribution in the microbial cells, and obviously to community structure (Goulet et al. 2007; Conley et al. 2009; Komjarova and Blust 2009; Golding et al. 2013). On one hand, the influence of community complexity is omitted when monospecific biofilms are used as a food source. On the other hand, the acclimatization and exposure of a field-collected biofilm to laboratory conditions are likely to provoke structural and morphological changes in this complex food source (Fechner et al. 2011; Barral-Fraga et al. 2016). In most food web experiments, microbial biofilms are contaminated prior to introduction in the microcosm (e.g., Conley et al. 2009; Komjarova and Blust 2009; Xie et al. 2010; Kim et al. 2012; Li et al. 2012; Perrier et al. 2018; Hudson et al. 2019); nevertheless a few studies, usually in complex mesocosms, have also investigated the effect on trophic transfer of concomitant contamination of food resource and media, thus mimicking field conditions (e.g., Pinder et al. 2011; Cleveland et al. 2012; Kim et al. 2016; Friesen et al. 2017; Park et al. 2018).

One way to go beyond the limitations of microcosm experiments is to follow contaminant fate directly in the field. Indeed, various studies have investigated the bioaccumulation of metals or organic compounds in natural environments by collecting a variety of organisms including – but not limited to – microbial biofilms (Croteau et al. 2005; Vinot and Pihan 2005; Walters et al. 2008, 2015; Coat et al. 2011; Jardine et al. 2013; Ruhí et al. 2016). Understanding trophic enrichment with a contaminant in the field first requires an accurate description of local food web structures. Hence, stable carbon and nitrogen isotopes in biological tissues and microbial biofilms are usually analyzed (Croteau et al. 2005; Walters et al.

2008, 2015). Besides isotopic ratio measurements, lipid content assessment is recommended for studies focused on hydrophobic contaminants such as PCBs (Walters et al. 2008; Coat et al. 2011). Although using stable isotopes of C and N offers interesting perspectives to learn prey and consumer trophic positions and thus demonstrate trophic transfer through food webs, the technique does require sophisticated and expensive equipment (Burns and Ryder 2001). Moreover, the results of stable isotope measurements in microbial biofilms represent a "mean" of different signatures (bacteria, algae), which could be a limiting factor for determining accurate relationships between selective grazers and their specific food source within biofilm communities.

4.2 *Role of Microbial Biofilms in Contaminant Transfers Through Aquatic Food Webs*

The food web interactions of microbial biofilms concern insects, gastropods, fish, and shrimps. Some of these grazers may exhibit food preferences and thus preferentially consume specific microbial groups or taxa. For instance, the shrimp *Paratya australiensis* was shown to specifically reduce diatom biomass in grazed biofilms, indirectly enhancing the green algal growth (Burns 1997). Besides affecting the composition of biofilms, grazers can also impact their 3D architecture (Robson and Barmuta 1998). However, in return, grazers can be influenced by the nutritional quality of the biofilm as well as its contaminant content. It is well known that microbial biofilms are a primary food resource in aquatic ecosystems, yet few studies have investigated contaminants transfers from microbial biofilms through aquatic food webs and the resulting bioaccumulation through trophic transfer (e.g., Jardine et al. 2013; Walters et al. 2015), or feedback-loop control of other ecosystem components on contaminant concentrations in periphytic communities (Roessink et al. 2010). In addition, most of these studies focused on the trophic transfer of contaminants from periphytic biofilms to primary consumers and, more rarely, to predators, which limits the assessment of biomagnification processes (i.e., increasing contaminant concentrations with increasing trophic levels) through food webs involving contaminated biofilms. The biomagnification factor (BMF), which is calculated based on the assumption that contaminant concentration in a consumer depends on contaminant concentration in its prey (sometimes corrected for trophic-level difference between the consumer and its prey; Fisk et al. 2001), serves to convey this process. A BMF > 1 corresponds to a magnification of contaminant concentrations in consumers/predators. BMFs adjusted to trophic positions can be calculated using the following equation:

$$\mathrm{BMFconsumer(i)} = \left[\left(\mathrm{Cconsumer(i)}/\mathrm{Cdiet(i)}\right)/\left(\delta^{15}\mathrm{Nconsumer(i)}/\delta^{15}\mathrm{Ndiet(i)}\right)\right]$$

where Cconsumer(i) is concentration of contaminant in the consumer, Cdiet(i) is concentration of contaminant in the diet, δ^{15}Nconsumer(i) is trophic level of consumer, and δ^{15}Ndiet(i) is trophic level of diet.

Both essential (e.g., Cu, Zn, Se) and nonessential (e.g., Hg, Cd, As) metals are readily absorbed by primary producers and can be transferred from microbial biofilms to higher trophic levels (i.e., macroinvertebrates and predators) where they could exert adverse effects (Croteau et al. 2005; Magellan et al. 2014; Walters et al. 2015; Hepp et al. 2017). For instance, the consumption of spiked biofilms was reported to be a significant route of exposure to Cd for the amphipod *Hyalella azteca* (Conley et al. 2009) and to Se for the insect *Centroptilum triangulifer* (Golding et al. 2013). However, biomagnification was only observed for Hg, Zn, and sometimes Se (Farag et al. 2007; Conley et al. 2009; Jardine et al. 2012, 2013). Biomagnification of methylmercury (MeHg) from microbial biofilms to primary consumers (Jardine et al. 2013) and to fish (Walters et al. 2015) is a relatively well-studied phenomenon, and resulting MeHg BMFs ranging from 1 to 31 have been reported in different sites (Jardine et al. 2013). Various studies have also highlighted the influence of environmental parameters on Hg biomagnification throughout the food web (Jardine et al. 2012, 2013). In particular, low pH led to an increase in Hg supply for primary producers, which then also increased biomagnification at higher trophic levels (fish). Due to biomagnification processes, even low levels of water contamination can lead to high concentrations of toxic metals in wildlife. Walters et al. (2015) found that Se and Hg concentrations in top-level organisms from a large food web (including organic matter, benthic biofilm, invertebrates, and fish) regularly exceeded the exposure risk thresholds for wildlife, thus revealing the ecosystem risks due to trophic transfers of Hg and Se in aquatic food webs.

Organisms have evolved internal mechanisms for metals regulation that can complicate efforts to map these trophic transfers. As essential metals are actively regulated by freshwater organisms in order to maintain internal concentrations, gauging the enrichment of essential metals between trophic levels is far from straightforward and linked to species-specific biological needs. During exposure to labeled algae in microcosms, Cu was found to mainly accumulate by dietary route in the bivalve *Corbicula fluminea*, whereas it was preferentially absorbed by aqueous route in the crustacean *Daphnia magna* (Croteau et al. 2005; Komjarova and Blust 2009). Species-specific differences in biomagnification were also found for Se, which was biomagnified from contaminated periphytic biofilms to a primary consumer: the mayfly *Centroptilum triangulifer* (Conley et al. 2009). In addition, after assimilation of Se from contaminated biofilms, mayflies transferred about 46% of their Se body burdens into their eggs, resulting in a reduction of fecundity at environmentally relevant concentrations (Conley et al. 2009). Conversely, although primary producers were found to be potential sources of Se contamination for their direct consumers (i.e., mussels, shrimps, or macroinvertebrates), Se enrichment through trophic levels was not significant in various field studies in the Mirgenbach reservoir (France; Vinot and Pihan 2005), in the San Joaquin River (USA; Croteau et al. 2005), or in the Colorado River (USA; Walters et al. 2015). These differences may be at least partially explained by the high variability in Se concentrations among

macroinvertebrate species, as observed in a field study by Walters et al. (2015). Zn is another essential metal with toxicity at high concentrations that was also found to transfer through the food web (Farag et al. 2007) and biomagnify in the mayfly *Centroptilum triangulifer* (Kim et al. 2012). While Zn concentration in mayfly larvae was 16–19-fold higher than in the labeled contaminated periphyton used as a food resource, Zn concentration in adults was only threefold to eightfold higher than in diet (Kim et al. 2012). Therefore, dietary bioaccumulation dynamics in biofilm consumers depend on the species, its growth stage, and its subsequent physiological abilities to assimilate and/or eliminate metals.

Moreover, there may be only very limited trophic transfer for metals or metallic nanoparticles. For example, titanium nanoparticles were fairly highly accumulated in sediment biofilm but barely transferred from biofilms to river snails and Chinese muddy loaches, with BMFs of just 0.01–0.02 and 0.04–0.05, respectively (Kim et al. 2016), highlighting the low degree of bioaccumulation of TiO_2 in these consumers.

Organic contaminants, and in particular persistent chemicals, are likely to be transferred and/or biomagnified from microbial biofilms to higher trophic levels. Concentrations of tris(2-butoxyethyl) phosphate (TBEP), a flame retardant quantified consistently across all food web compartments, were found to increase with trophic levels (Ruhí et al. 2016). Indeed, in a Mediterranean river food web, microbial biofilms accumulated the lowest amount of TBEP, whereas intermediate concentrations of TBEP were found in the primary consumer *Ancylus*, and the highest concentrations were found in the omnivore filter-feeding *Hydropsyche* and the macroinvertebrate predator *Phagocata* (Ruhí et al. 2016). Similarly, concentrations of the drug carbamazepine in a stream food web including biofilms, invertebrates, and vertebrates were correlated with trophic position (Du et al. 2014). PCB concentrations were also significantly correlated with trophic level, as described in Walters et al. (2008, 2011), with an average BMF close to 1.6. The hydrophobicity of PCBs (i.e., their K_{ow} value) strongly modulates their trophic transfer and biomagnification (Walters et al. 2008, 2011). Whereas the influence of K_{ow} on biomagnification varies substantially across food webs, model predictions of standardized K_{ow}-based BMFs remain consistent with field observations (Walters et al. 2011). Like metals, some organic contaminants were also found to be biomagnified slightly (e.g., low increase of chlorpyrifos concentrations from biofilm to snail; Lundqvist et al. 2012) or not (e.g., diclofenac, gemfibrozil (Ruhí et al. 2016); diphenhydramine (Du et al. 2015)) through the food web.

Exposure scenarios and environmental conditions are also likely to influence contaminant fate through food webs. For instance, TiO_2 nanoparticles accumulated much more in biofilm after sequential low-dose exposures than after a single high-dose exposure (Kim et al. 2016). On one hand, environmental conditions may influence contaminant uptake and dynamics in microbial biofilms and thus modulate the amount available for further trophic transfer. On the other hand, microbial biofilm quality as a food resource (e.g., C/N) is also likely to influence trophic transfers of nutrients and contaminants. In addition, C/N ratio can also be modulated by environmental factors (e.g., flow velocity; Coat et al. 2011), while dissolved organic matter (DOM) concentrations in surrounding water can modify contaminant

bioavailability for primary consumers and thus trophic transfers within the food web. Lundqvist et al. (2012) showed that increasing DOM concentrations in water led to increasing sorption of chlorpyrifos in biofilms. However, despite the resulting high concentrations in biofilms, dietary uptake of chlorpyrifos by snails remained relatively low, and the results showed that the combined presence of biofilms and of medium- and high-DOM concentrations reduced the share of chlorpyrifos bioavailable for snails. Testing two other insecticides (carbofuran and lindane) exhibiting lower hydrophobicity levels than chlorpyrifos on a low-to-high-DOM concentration gradient, Lundqvist et al. (2012) also demonstrated that the accumulation of pesticides by the snails was influenced by both DOM concentrations and pesticide hydrophobicity.

Microbial biofilms are an important food resource in freshwater ecosystems, and our literature analysis highlights their potential to accumulate contaminants and modify their bioavailability, thus influencing their transfers through food webs. However, the role of biofilms in dietary contaminant exposure has been neglected for a long time, and the importance of biofilms in trophic transfers of those potentially toxic substances is still understudied, leaving a critical lack of knowledge, especially but not exclusively concerning biofilms attached to sediments or organic substrates such as leaf litter.

5 Conclusions and Future Challenges

This literature review, which illustrates the dynamic interactions between contaminants and biofilms in aquatic ecosystems, underscores widely different levels of knowledge according to the kind of substrate where the biofilm grows and the food web pathway(s) to which it contributes. Accordingly, while studies on periphyton show that biofilms are able to accumulate a wide range of metals and organic contaminants, the role of biofilms in the distribution of contaminants among different aquatic compartments (surface water, periphyton, sediments, leaf litter) and the associated biota remains unclear and has not, to our knowledge, been quantified. This is mainly due to the fact that we still lack methods to specifically assess and measure contaminants in microbial communities of complex solid matrices such as sediment or leaf litter. Moreover, even though several studies have attempted to investigate chemical concentrations simultaneously in different aquatic compartments (sediment, surface water, and biofilm; Kohušová et al. 2011), there is still a lack of data on the role of microbial communities in contaminant accumulation (or release) processes in sediments and organic substrates. This issue remains a bottleneck, given the abovementioned methodological limitations. Field or microcosm surveys including systematic characterization of the contamination in these different aquatic compartments combined with laboratory experiments quantifying sorption/desorption rates under various controlled conditions are now needed to better estimate the role played by biofilms in contaminant fluxes within the aquatic ecosystem and their food webs.

Contaminant adsorption, storage or sequestration, transformation, and, finally, release in the environment are still mainly investigated in periphyton studies using metals and a few organics as model compounds. However, there is a gap of knowledge on the transfer kinetics of contaminants in periphytic assemblages and their resulting toxic effects (Chaumet et al. 2019a, b). To better understand the fate of organic contaminants in periphyton, the development and validation of sensitive and specific high-performance analytical methods combined with the measurement of intracellular concentrations of organic contaminants, using novel partitioning methods (Chaumet et al. 2019a), are the first technical challenges to overcome.

Microcosm experiments have brought valuable insights into contaminant transfer from biofilms to consumers, but future research should now aim to push beyond these relatively simple models and attempt to address the real-world complexity, i.e., both contaminant transfer from biofilm to upper trophic levels and ecological interactions with other ecosystem components (Roessink et al. 2010), as well as the influence of environmental factors such as temperature, organic matter, and so on.

Future studies need to consider the potential effects of global change and specifically how (1) shifts in water contamination patterns (i.e., land-use change, evolving agricultural practices, antibiotic resistances), (2) climate change (i.e., global warming, droughts, floods), and (3) the presence of invasive species (i.e. top-down versus bottom-up effects) can affect contaminant bioaccumulation by biofilms and consequences on trophic transfer – a challenge that also raises new questions requiring further interdisciplinary research bridging environmental chemistry, ecotoxicology, and ecology.

6 Summary

Freshwater environments host microbial biomass that can aggregate and attach to different kinds of submerged substrates (rock, sediment, leaf litter). These microbial assemblages, which are called biofilms, can accumulate the contaminants transported by the water flow and/or adsorbed onto the substrates where they develop. Furthermore, due to their high metabolic activity and their role in aquatic food webs, microbial biofilms are also likely to influence contaminant fate in aquatic ecosystems.

Here, by focusing on metals and organic micropollutants, we provide a critical overview of the analytical methods currently in use for detecting and quantifying these contaminants in microbial biofilms developing in different benthic substrata, together with a look at the state of current knowledge and future challenges concerning the role of biofilms in contaminant accumulation and trophic transfers in the aquatic food web.

From this literature review emerge the following issues:

- Concurrent to analytical developments, studies dealing with bioaccumulation in microbial biofilms have been applied mainly to metal contaminants, and there is still only limited knowledge on the accumulation of organic contaminants in these microbial assemblages.
- A large variety of metals and organic contaminants has been found in natural periphytic biofilms, which grow on inert surfaces like cobbles exposed to light. In contrast, due to technical limitations, data on the bioaccumulation of contaminants in submerged microbial communities associated with sediments, leaves, or drift particulate matter has always included both biotic accumulation and abiotic sorption on the substratum.
- Microbial biofilms represent an important food resource in freshwater ecosystems, yet their role in dietary contaminant exposure has been neglected for a long time, and the importance of biofilms in trophic transfer of contaminants is still understudied, leaving a critical lack of knowledge especially but not exclusively concerning biofilms attached to sediments or organic substrates such as leaf litter.

These issues pose a set of challenges that need to be overcome in order to better:

- Characterize the accumulation of contaminants in sediment and organic-substrate biofilms
- Evaluate the role played by biofilms in contaminants fluxes within aquatic ecosystems and aquatic food webs
- Assess how different environmental pressures such as shifts in water contamination, climate change, or the presence of invasive species (i.e., top-down versus bottom-up effects) may affect contaminant bioaccumulation in biofilms and the resulting consequences in food webs

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Surface Properties and Environmental Transformations Controlling the Bioaccumulation and Toxicity of Cerium Oxide Nanoparticles: A Critical Review

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Abstract Increasing production and utilization of cerium oxide nanoparticles (CNPs) in recent years have raised wide concerns about their toxicity. Numerous studies have been conducted to reveal the toxicity of CNPs, but the results are sometimes contradictory. In this review, the most important factors in mediating CNPs toxicity are discussed, including (1) the roles of physicochemical properties (size, morphology, agglomeration condition, surface charge, coating and surface valence state) on CNPs toxicity; (2) the phase transfer and transformation process of CNPs in various aqueous, terrestrial, and airborne environments; and (3) reductive dissolution of CNPs core and their chemical reactions with phosphate, sulfate/S^{2-}, and ferrous ions. The physicochemical properties play key roles in the interactions of CNPs with organisms and consequently their environmental transformations, reactivity and toxicity assessment. Also, the speciation transformations of CNPs caused by reactions with (in)organic ligands in both environmental and biological systems would further alter their fate, transport, and toxicity potential. Thus, the toxicity mechanisms are proposed based on the physical damage of direct adsorption of CNPs onto the cell membrane and chemical inhibition (including oxidative stress and interaction of CNPs with biomacromolecules). Finally, the current knowledge gaps and further research needs in identifying the toxicological risk factors of CNPs under realistic environmental conditions are highlighted, which might improve predictions about their potential environmental influences. This review aims to provide new insights into cost-effectiveness of control options and management practices to prevent environmental risks from CNPs exposure.

Keywords Cerium oxide nanoparticles · Environmental transformation · Redox reactions · Surface properties · Toxicity

Abbreviations

AA	Acrylic acid
Alg	Alginate
AS	Artificial soil solution
ATP	Adenosine triphosphate
CA	Citric acid
C-CNPs	Cubic cerium oxide nanoparticles
CEC	Cation exchange capacity
CNPs	Cerium oxide nanoparticles

E	Redox reactions
EDTA	Ethylenediaminetetraacetic acid
EELS	Electron energy loss spectroscopy
E_H	Redox potential
E_V	Valence band
FA	Fulvic acid
GA	Gum arabic
GSH	Glutathione
HA	Humic acid
HAADF-STEM	High-angle annular dark-field scanning transmission electron microscopy
HMT	Hexamethylenetetramine
I-CNPs	Irregularly shaped cerium oxide nanoparticles
IS	Ionic strength
K_d	Partitioning value
K_r	Relating retention value
K_{sp}	Solubility product
LB	Luria broth
NOM	Natural organic matter
$O_2^{\cdot-}$	Superoxo species
O_2^{2-}	Peroxo species
O-CNPs	Octahedral cerium oxide nanoparticles
$^{\cdot}OH$	Hydroxy
P	Phosphate
P-CNPs	Polygonal cerium oxide nanoparticles
pe	Electrochemical potential
PVP	Polyvinylpyrrolidone
R-CNPs	Rod cerium oxide nanoparticles
ROS	Reactive oxygen species
S-CNPs	Spherical cerium oxide nanoparticles
STXM	X-ray scanning transmission microscopy
$V_o^{\cdot\cdot}$	Oxygen vacancy
WWTPs	Wastewater treatment plants
XANES	X-ray absorption near-edge structure spectrum
XPS	X-ray photoelectron spectrum

1 Introduction

Cerium, the most abundant of the rare earth elements, has attracted considerable attention in the field of materials science and biological applications with its unique electronic configuration of $[Xe]4f^15d^16s^2$ (Montini et al. 2016). In combination with oxygen in a nanoscale formulation, cerium oxide nanoparticles (CNPs) adopt a

crystalline structure with an oxygen vacancy being created upon the loss of lattice oxygen atoms (Esch et al. 2005; Fronzi et al. 2009; Tsai et al. 2008). The unique excellent ability of cerium oxides to shuttle between Ce(III) (Ce_2O_3) and Ce (IV) (CeO_2) makes CNPs of particular interest to microelectronics or semiconductor industries (Conesa 1995), mechanical polishers (Hoshino et al. 2001; Stanek et al. 2008), pharmacological agents (Pelletier et al. 2010), and fuel additives in diesel (Johnson and Park 2012; Sajith et al. 2010). The wide production and application of CNPs will inevitably lead to increasing concentrations in many natural and engineered compartments such as surface waters (Conway et al. 2014; Zhao et al. 2017), soils (Layet et al. 2017; Liu and Cohen 2015), wastewater (Lazareva and Keller 2014; Wang et al. 2018b), sewage sludge (Lazareva and Keller 2014; You et al. 2017), and air (Hong et al. 2014; Johnson and Park 2012). However, there is concern that CNPs may present hazards to ecological receptor species, due to their small particle size and intensified reactivity by design (Antoine Thill et al. 2006a; Nel et al. 2006). As early as 2001, a report about human health risks of cerium oxides from diesel fuels warrants immediate attention to fully assess the ecological and environmental effects of CNPs (Antoine Thill et al. 2006a; Liu et al. 2015). Thereafter, extensive investigations into the toxicity of CNPs have been conducted (Heckert et al. 2008; Pešić et al. 2015), which is a serious issue requiring high precaution.

Thill et al. (2006) found that CNPs injured the outer membrane of *E. coli* cells and posed a lethal effect. Moreover, CNPs could be one of the prooxidants changing the intracellular redox status of cells (Miao et al. 2017; Pešić et al. 2015; Xu et al. 2018; You et al. 2015), which provokes the loss of survival ability. Garcia et al. reported the strong inhibitory action of CNPs on the anaerobic activated sludge from wastewater treatment plants (WWTPs) and consequently a substantial inhibition in biogas production (García et al. 2012). However, the study of Limbach et al. showed that CNPs posed no effects on the heterotrophic microbial agglomerations from a municipal WWTP (Limbach et al. 2008). Lethal toxicities of CNPs in *Daphnia magna* and *Cophixalus riparius* have been demonstrated at 1 mg/L after exposure for 96 h (Lee et al. 2009), while in other researches no acute toxicity was observed in *Daphnia magna* at 10 mg/L after the same duration exposure (Gaiser et al. 2011) or even up to 1,000 mg/L after a 48 h exposure (van Hoecke et al. 2009). The list of studies revealing the effects of CNPs on the environment and potentially on humans is long and has been extensively reviewed over the past years (Batley et al. 2013; Collin et al. 2017; Ganguly et al. 2018; Milani et al. 2017; Petosa et al. 2010). However, few papers have well identified and systematically summarized the critical factors in relation to the physicochemical properties of CNPs leading to the existed contradictory results.

Because of the susceptibility of CNPs to environmental transformation, factors such as pH, redox potential (E_H), as well as the quantity and composition of natural organic matter (NOM) are likely to influence the transport and simultaneously transformations of CNPs (Auffan et al. 2009; Collin et al. 2014; Liu et al. 2011). Interactions and transformations of CNPs under different environmental scenarios and toxicological media are well known to occur (Louie et al. 2014; Merrifield et al.

2017; Römer et al. 2013). In the case of CNPs, the chemical transformations such as Ce(IV) to Ce(III) cycling and associated soluble species are likely to be vital for understanding their biological and environmental behaviors (Graham et al. 2014; Li et al. 2012; Lópezmoreno et al. 2010; Thill et al. 2006). In particular, the redox reactions between CNPs and redox-active ions or (in)organic ligands will strongly impact their surface properties and consequently their transport, reactivity, and toxicity in terrestrial and aquatic environments (Barton et al. 2014; Liu et al. 2015; Rollin-Genetet et al. 2015; Safi et al. 2010). Furthermore, transformations mediated by microorganisms and exposure media may alter the core of CNPs and their surface functional groups, leading to altered surface composition, agglomeration state, and toxicity potential (Barton et al. 2014; Dowding et al. 2013; Louie et al. 2014; Römer et al. 2013). Therefore, it is necessary to systematically shed light on the distribution, transformation and speciation of CNPs under different environmental exposure conditions as well as the related ecosystem impacts.

Since mounting growth of commercial CNPs production will result in potentially negative influences on ecosystems, the underlying mechanisms are urgently required. In several reports on the toxicity of CNPs (Fang et al. 2010; Heckert et al. 2008; Kuang et al. 2011; Pešić et al. 2015), the biological impact of CNPs has been investigated at the cellular and molecular levels. At the cellular level, CNPs were generally considered to be a prooxidant, resulting in the induction of oxidative stress and cytotoxicity after cell internalization (Ma et al. 2016; Park et al. 2008b; Pešić et al. 2015). At the molecular level, when CNPs enter the cytoplasm, they tend to interact with biological components like protein and nucleates, which lead to key enzyme inactivation and DNA damage (Collin et al. 2014; Liu et al. 2013; Marie et al. 2014; Milani et al. 2012). Furthermore, considering the chemical process, the redox property of ceria with transition between Ce(III) and Ce(IV) is of critical importance to understand its potential toxicity mechanisms, for the transformation between Ce(IV) and Ce(III) makes CNPs acting as quenchers or producers of reactive oxygen species (ROS) (Thill et al. 2006; Zhang et al. 2011). Nevertheless, the intrinsic physicochemical properties and further transformations of CNPs in the exposure systems are ignored in drawing the general conclusions and perspectives for the potential mechanisms on CNPs toxicity.

Accordingly, the aims of this review are to (1) highlight and discuss types of physicochemical properties relating to the bioaccumulation and toxicity of CNPs; (2) illustrate the distribution, translocation, and speciation of CNPs under different environmental scenarios, with an emphasis on the bioaccumulation and toxicity outcomes; (3) discuss the phase transformation of CNPs core during interacting with environmental components as well as the results of such transformations on toxicity; and (4) underline the potential physiological and biochemical impacts of CNPs and propose the related mechanisms. Finally, important knowledge gaps that need to be addressed to better understand the potential risk, safe production, and handling of CNPs are raised.

2 Physicochemical Properties of CNPs: Impact on Biosorption and Toxicity

The toxicity of CNPs reported in the literatures is in conflict with either being lower (Collin et al. 2017) or higher (Merrifield et al. 2017; Thill et al. 2006) even with the same exposure scenarios. Differences are possibly linked to the various physicochemical properties (size, morphology, agglomeration, surface charge, coating, and surface oxidation state) of CNPs, as schematically illustrated in Fig. 1, which can be obtained by appropriate selection of synthesis methods and precursors. Physicochemical properties may mediate the colloidal dispersion and stability of CNPs, transformation in the biological system, and pathway of cellular internalization (Ganguly et al. 2018; Rogers et al. 2010; van Hoecke et al. 2009). In this connection, the relationships between physicochemical properties and environmental effects of CNPs are summarized in this section and listed in Table 1.

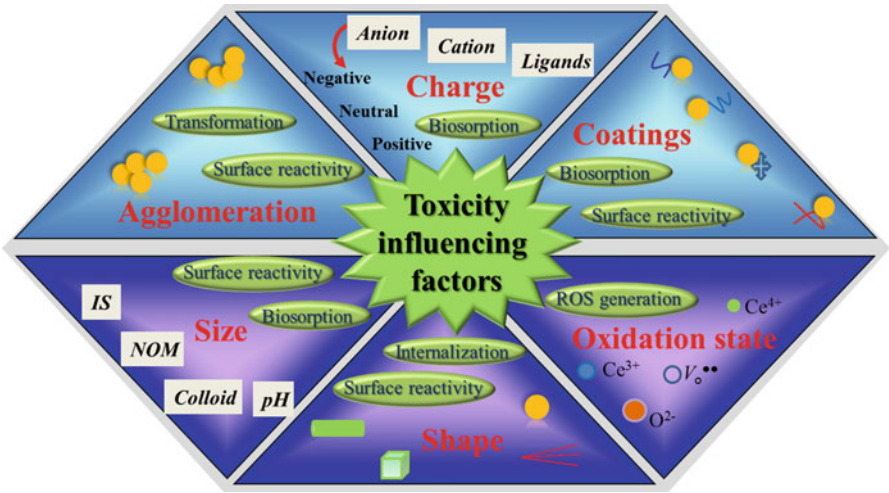

Fig. 1 Schematic diagram illustrating the physicochemical properties affecting the toxicity of CNPs. In the charge section, CNPs with the intrinsic characteristic of positive, negative, and neutral charge might be influenced by cations, anions, and also ligands under various environmental conditions, which would result in the altered surface charge outcomes and biosorption (in green ellipse) of CNPs. In the size section, the pH, ionic strength (IS), natural organic matter (NOM), and even inorganic colloids or clays would impact the surface properties of CNPs, leading to the variations of size, biosorption, and also surface reactivity of CNPs. In the coating part, the diverse coatings () would influence the biosorption and surface reactivity of CNPs. The illustrations in green ellipses are characteristics influenced by the respective physicochemical properties and lead to the different toxic effects of CNPs

Table 1 A list of studies assessing the influences of physicochemical properties of CNPs on their toxicity to organisms

Influencing factors		Testing organism	Variables	Exposure media	Zeta potential in media (mV)	Exposure length	Measured endpoints	Toxicity effects with various concentrations	Potential mechanism	Ref.
Size	7 nm	*Escherichia coli*	The point of zero charge is at pH 10.5 Uncoated Aggregated	Luria Bertani (LB) media	Positive charge	Over night	Growth	No influence of CNPs	The impacts of LB medium on the oxidation of CNPs is limited	Thill et al. (2006)
				KNO_3 washed E. coli suspension	Positive charge	3 h	Survival (counting colony forming (CFU))	More than 90% survival <0.9 mg/L 50% survival for 5 mg/L 100% mortality at 230 mg/L	The highly adsorption and reduction of CNPs linked to a strong cytotoxicity	
	14 nm	*Daphnia magna*	Specific surface area: 61 m^2/g	Elendt M4 medium	−6.6 ± 1.9	21 days	Reproduction	Effect concentration (EC)10: 8.8 mg/L EC20: 11.8 mg/L EC50: 20.5 mg/L	The difference in toxicity could be explained by the different surface area and the clustering of NPs around the cells	van Hoecke et al. (2009)
	20 nm	*Daphnia magna*	42 m^2/g	Elendt M4 medium	−9.1 ± 2.6	21 days	Reproduction	EC10: 12.8 mg/L EC20: 17.2 mg/L EC50: 25.4 mg/L		
	29 nm	*Daphnia magna*	29 m^2/g	Elendt M4 medium	−3.9 ± 0.8	21 days	Reproduction	EC10:20.0 mg/L EC20: 26.5 mg/L EC50: 42.7 mg/L		
	7 nm	*P. subcapitata*	Polydispersity index: 0.455; Sphere; $\%Ce^{3+}$: 28	OECD medium	−12.2 ± 0.64	72 h	Growth inhibition	No influence of CNPs within 50 mg/L	The main driver of toxicity of CNPs is the surface content of Ce^{3+} rather than size	Pulidoreyes et al. (2015)
	50 nm	*P. subcapitata*	Polydispersity index: 0.503 Cube $\%Ce^{3+}$: 26	OECD medium	−24.4 ± 1.03	72 h	Growth inhibition	No influence of CNPs within 50 mg/L		
	3.5 nm	Soil microbiota	Pristine/citric acid-coated	Clay loam calcareous soil	26.4 (pH 5) −40 (citric acid coated, pH 3 to 10)	30 days	Bacterial community structure	1.0 mg/kg dry soil lowered the microbial enzymatic activities Citric acid coating decreased the effects of CNPs on	Particle agglomeration and the catalase mimetic activity of CNPs are key parameters in modulating CNPs effects on	Hamidat et al. (2017)

(continued)

Table 1 (continued)

Influencing factors		Testing organism	Variables	Exposure media	Zeta potential in media (mV)	Exposure length	Measured endpoints	Toxicity effects with various concentrations	Potential mechanism	Ref.
								enzymes activities and bacterial community structure	microbial community and also functions	
	31 nm	Soil microbiota	Pristine	Clay loam calcareous soil	15 (pH 5)	30 days	Bacterial community structure	1.0 mg/kg dry soil promoted the selection of genera resistance to oxidative stress		
	3–5 nm	Endothelial cells	Specific surface area: 92 m^2/g Prepared by H_2O_2 Surface Ce^{3+}/Ce^{4+} ration: 1.28	Endothelial basal medium	-10.07 ± 1.72	48 h	Cell viability	No influence: 0.86 mg/L EC20: 17 mg/L	The differences in catalytic (ATPase) activity, morphology, and oxygen extraction energy may underlie the biomechanism of the toxicity	Dowding et al. (2013)
	5–8 nm	Endothelial cells	102 m^2/g Prepared by NH_4OH Ce^{3+}/Ce^{4+} ration: 0.37	Endothelial basal medium	-9.89 ± 1.27	48 h	Cell viability	No influence: 0.86 mg/L EC20: 17 mg/L		
Morphology	Octahedral	*Cucumber*	Size: 25.2 ± 2.3 nm	Hoagland solution	-8 ± 3.2	21 days	Biomass of *cucumber* Adsorption and transformation of CNPs in *cucumber*	2,000 mg/L CNPs showed no adverse effects on shoot and root biomass	The differently shaped CNPs resulted in their different transformation and translocation capacities in plants, which may further influence the interactions between CNPs and plants, leading to the different nano-bio effects	Zhang et al. (2017)
	Cubic	*Cucumber*	Size:30.9 ± 12.4 nm	Hoagland solution	-10 ± 0.3	21 days	Biomass of *cucumber* Adsorption and transformation of CNPs in *cucumber*	2,000 mg/L CNPs showed no adverse effects on *cucumber* biomass		
	Rod	*Cucumber*	Size: 8.9 ± 0.9 nm Length: 106 ± 9 nm	Hoagland solution	-40 ± 0.2	21 days	Biomass of *cucumber* Adsorption and transformation of CNPs in *cucumber*	2,000 mg/L CNPs showed no adverse effects on shoot and root biomass,but showed the		

								highest chemical reactivity		
	Irregular-shaped	*Cucumber*	Size: 26 ± 18 nm	Hoagland solution	−0.7 ± 0.1	21 days	Biomass of *cucumber* Adsorption and transformation of CNPs in *cucumber*	2,000 mg/L CNPs showed no adverse effects on *cucumber* biomass		
	Rods	Macrophage from RAW264.7	Size: 6.8–8.3 nm Specific surface area: 37 m^2/g	Dulbecco's Modified Eagle Medium	−31 ± 7 (pH 7)	24 h	Lactate dehydrogenase (LDH) release Tumor necrosis factor alpha (TNFα) production	15 mg/L and 30 mg/L CNPs induced significant LDH release and TNFα production	Morphology influences CNPs toxicity by governing how CNPs particles align at the biological cell surface and also the chemical reactivity of CNPs	Forest et al. (2016)
	Octahedron	Macrophage from RAW264.7	Size: 10.0–12.0 nm Specific surface area: 60 m^2/g	Dulbecco's Modified Eagle Medium	−17 ± 5 (pH 7)	24 h	Lactate dehydrogenase release Tumor necrosis factor alpha production	No influence of CNPs within 120 mg/L		
	Cubes	Macrophage from RAW264.7	Size:12.6–15.0 nm Specific surface area: 61 m^2/g	Dulbecco's Modified Eagle Medium	9 ± 6 (pH 7)	24 h	Lactate dehydrogenase release Tumor necrosis factor alpha production	No influence of CNPs within 120 mg/L		
	Rods	Human myeloid cell line	Diameter: 7–9.5 nm Length: 33.2–310.4 nm Aspect ratio (R): 1–31	RPMI 1640 medium	N.a.	24 h	Cellular viability Lysosomal damage Cathepsin B release	No effect on cell viability with doses as high as 100 mg/L with R up to 31	Nanowire bundles and nanocubes with sharp edges and corners in their crystal structure may induce more mechanical damage to cell membrane	Ji et al. (2012)
	Wires	Human myeloid cell line	Diameter:9.5 nm Length:>495.7 nm Aspect ratio (R): > 52	RPMI 1640 medium	N.a.	24 h	Cellular viability Lysosomal damage Cathepsin B release	A significantly higher cell death rate was seen with the R higher than 52		
	Rod	*P. subcapitata*	Polydispersity index: 0.809 Size: >50 nm %Ce^{3+}: 36	OECD medium	−21.2 ± 0.78	72 h	Growth inhibition	No influence of CNPs within 50 mg/L	The main driver of toxicity of CNPs is the surface content of Ce^{3+} and zeta	Pulidoreyes et al. (2015)
	Cube	*P. subcapitata*			−24.4 ± 1.03	72 h				

(continued)

Table 1 (continued)

Influencing factors		Testing organism	Variables	Exposure media	Zeta potential in media (mV)	Exposure length	Measured endpoints	Toxicity effects with various concentrations	Potential mechanism	Ref.
			Polydispersity index: 0.503 Size: 50 nm %Ce^{3+}: 26	OECD medium			Growth inhibition	No influence of CNPs within 50 mg/L	potential, rather than the morphology	
	Spheres	*P. subcapitata*	Polydispersity index: 0.589 Size: 7 nm %Ce^{3+}: 28	OECD medium	−25.6 ± 2.54	72 h	Growth inhibition	No influence of CNPs within 50 mg/L		
Aggregation		Human lung fibroblasts cell culture	Four different size fractions ranging from 25–50 up to 250–500 nm	RPMI 1640 medium	Around −18	240 min	Time-dependent uptake of CNPs in cells	At low concentration of 100 ng/g, the biological uptake processes in the cell surface are faster than the physical transport to cell	The agglomerates influenced diffusion and sedimentation which contribute to a lower CNPs uptake and thus ecotoxicity	Limbach et al. (2005)
Agglomeration		*Pseudokirchneriella subcapitata*	Size: 14 nm	OECD medium Synthetic waters containing NOM	N.a.	48 h	Algal growth inhibition experiment	In synthetic waters containing NOM, the observed EC20 value was a factor 3 higher as compared to the value obtained in OECD medium	The aggregation of CNPs could explain the reduction in toxicity through a decrease in bioavailability of the CNPs	van Hoecke et al. (2011)
Coating	Citric acid	NIH/3T3 cell culture	Size: 15 nm	Dulbecco's Modified Eagle's Medium	N.a.	24 h	Cell mortality	21% mortality was observed for citric acid-CNPs at 10 mM	For citric acid-CNPs, the enhanced interactions resulted in a net toxicity	Ould-Moussa et al. (2014)
	Acrylic acid	NIH/3T3 cell culture	Size: 15 nm	Dulbecco's Modified Eagle's Medium	N.a.	24 h	Cell mortality	With acrylic acid-CNPs the cell viability remained high at 10 mM		
	Citric acid	Snail and planorbarius corneus	Size: around 8 nm	Volvic water	−40 ± 5	4 weeks	Oxidative stress assessment	Citric acid enhanced the defense capacity of cells toward the oxidative stress	Citric acid can not only reduce the potential reactivity of NPs but also enhance the effects	Marie et al. (2014)

								induced by 1 mg/L CNPs	of other antioxidants	
	Humic acid (HA)	*Caenorhabditis elegans*	Size: 18.2 nm	Moderately hard reconsituted water	+21.9	48 h	Cell intensity	200 mg Ce/L induced no significant mortality, while 1 mg/L noncoated CNPs influence the growth of *Caenorhabditis elegans*	HA decreased the bioaccumulation of CNPs in cells and reduced the toxicity	Collin et al. (2014)
	Citric acid (CA)	*Raphanus sativus*	Size: around 8 nm	Deionized water	−57 ± 0.6	5 days	Seed germination	200 mg/L CA coated CNPs increased root biomass compared to bare CNPs	CA coating plays significant roles in reducing the Ce uptake	Trujillo-Reyes et al. (2013)
	Citric acid (CA)	*Dreissena polymorpha*	Size: 3–4 nm Point of zero charge: pH 7–7.5	OECD sediments and spring water (Volvic)	Around −20	21 days	mRNA, catalase activity, and lysosomal system	1 mg/L CA-CNPs posed stress effects on the mussels, and its bioaccumulation is three times more than bare CNPs	CA coating enhanced CNPs colloidal stability and led to different bioaccumulation patterns	Garaud et al. (2016)
	Citric acid (CA)	Tomato and fescue	Size: 3.9 ± 1.8 nm	Sandy soil and clay soil rich in organic matter	−40 ± 5 (pH 3–10)	16 h day and 8 h night	Phytoavailability of CNPs	Organic matter and citric acid could be related to increased mobility	The organic matter and citric acid coating enhanced the phytoavailability of Ce	Layet et al. (2017)
	Citric acid (CA)	*Planorbarius corneus* *Eudiaptomus vulgaris*	Size: 3.9 ± 1.8 nm	Spring water of Volvic	−40 ± 5 (pH 3–10)	28 days	Fate and transport of CNPs in aquatic mesocosms	Both the accumulation and dissolution of CA-CNPs are higher than bare CNPs	CA-CNPs were stable as collodial suspension, resulting in the release of Ce into water	Tella et al. (2015)
Surface charge	+	*Caenorhabditis elegans*	Size: 15.3 nm	Moderately hard reconsituted water	+28.5	48 h	Cell mortality	50 mg Ce/L induced about 76% mortality	Surface charge affected the uptake of CNPs in cells and also the oxidation state of Ce in tissues after uptake	Collin et al. (2014)
	0	*Caenorhabditis elegans*	Size: 17.8 nm	Moderately hard	−9.3	48 h	Cell mortality			

(continued)

Table 1 (continued)

Influencing factors		Testing organism	Variables	Exposure media	Zeta potential in media (mV)	Exposure length	Measured endpoints	Toxicity effects with various concentrations	Potential mechanism	Ref.
				reconsituted water				1,000 mg Ce/L induced about 16.7% mortality		
	–	*Caenorhabditis elegans*	Size:13.9 nm	Moderately hard reconsituted water	−31.5	48 h	Cell mortality	1,000 mg Ce/L induced about 3.3% mortality		
	+	Normal and cancer cell lines	Size: 5 nm Zeta potential: ~ +30 mV	Modified Ham, s F12 medium	N.a	3 h	Cell viability	1.0 mM was toxic to most of the cell lines studied	Polymer-coated CNPs display different levels of toxicity depending upon cellular uptake and subsequent subcellular localization	Asati et al. (2010)
	0	Cancer cell lines	Size: 14 nm Zeta potential: ~ 0 mV	Modified Ham, s F12 medium	N.a	3 h	Cell viability	1.0 mM exhibit minimal toxicity		
	–	Normal and cancer cell lines	Size: 5 nm Zeta potential: ~ −48 mV	Modified Ham, s F12 medium	N.a	3 h	Cell viability	1.0 mM induced significant cytotoxicity		
	+	*Triticum aestivum*	Size: 12.0 ± 3.4 nm Electrophoretic mobility (EM):1.15 ± 0.3 μm·cm·V^{-1}·s^{-1}	Hoagland's medium	+22 ± 0.61	34 h	Uptake and translocation of CNPs in the plants	CNPs (+) adhered to the plant roots the strongest	The electrostatic interactions between charged particles and plant tissues play important roles in distribution of CNPs in plants and also the toxicity effects	Spielman-Sun et al. (2017)
	0	*Triticum aestivum*	Size: 19.4 ± 5.7 nm EM: −0.02 ± 0.21 μm·cm·V^{-1}·s^{-1}	Hoagland's medium	−0.5 ± 3.9	34 h	Uptake and translocation of CNPs in the plants	CNPs (0) had higher concentration in the nonvascular leaf tissue		
	–	*Triticum aestivum*	Size: 14.5 ± 3.3 nm EM:-1.59 ± 0.41 μm·cm·V^{-1}·s^{-1}	Hoagland's medium	−30.3 ± 6.6	34 h	Uptake and translocation of CNPs in the plants	CNPs (−)was mostly in the leaf veins		
	+	Bone cancer cell lines	pH 9 Size: 50 nm 0.1 M dextran coated	Dulbecco's Modified Eagle's Medium	+6.32 ± 1.59	24 h	Cytotoxicity assay and reactive oxygen species generation	EC50: >250 mg/L	The surface charge of CNPs control the cellular uptake, localization, and also the "oxidase-	Alpaslan et al. (2015)
	+				+0.58 ± 2.2	24 h		EC50: >250 mg/L		

		Bone cancer cell lines	pH 7 Size: 45 nm 0.1 M dextran coated	Dulbecco's Modified Eagle's Medium			Cytotoxicity assay and reactive oxygen species generation		like" activity of CNPs	
	+	Bone cancer cell lines	pH 6 Size: 29 nm 0.1 M dextran coated	Dulbecco's Modified Eagle's Medium	+16.68 ± 3.98	24 h	Cytotoxicity assay and reactive oxygen species generation	EC50: 100 mg/L		
Surface oxidation state	$\%Ce^{3+}$: 21	Leukocyte cell line	Size: 6 nm Specific surface area:57 m^2/g	RPMI 1640 medium	−27.6 eV (pH 7)	72 h	Cell viability, intracellular reactive oxygen species, superoxide, and glutathione	200 mg/L protection in vitro: 73% Protection in cells: 45% Anti-apoptotic: 46%	Ce^{3+}/Ce^{4+} redox reactions are responsible for the outstanding biological properties of CNPs	Celardo et al. (2011)
	$\%Ce^{3+}$: 18	Leukocyte cell line	Size: 10 nm Specific surface area:58 m^2/g	RPMI 1640 medium	−27.2 eV (pH 7)	72 h	Cell viability, intracellular reactive oxygen species, superoxide, and glutathione	200 mg/L protection in vitro: 71% Protection in cells: 32% Anti-apoptotic: 41%		
	$\%Ce^{3+}$: 10	Leukocyte cell line	Size: 11 nm Specific surface area:63 m^2/g	RPMI 1640 medium	−26.5 eV (pH 7)	72 h	Cell viability, intracellular reactive oxygen species, superoxide and glutathione	200 mg/L protection in vitro: 61% Protection in cells: 13% Anti-apoptotic: 22%		
	$\%Ce^{3+}$: 6	Leukocyte cell line	Size: 13 nm Specific surface area:47 m^2/g	RPMI 1640 medium	−25.9 eV (pH 7)	72 h	Cell viability, intracellular reactive oxygen species, superoxide, and glutathione	200 mg/L protection in vitro: 37% Protection in cells: 5% Anti-apoptotic: 12%		
	$\%Ce^{3+}$: 58	*P. subcapitata*	Polydispersity index: 0.455 Sphere Size: 5 nm	OECD medium	−12.2 ± 0.64	72 h	Growth inhibition	1 mg/L CNPs significantly inhibited cell growth	CNPs with higher Ce^{3+} can efficiently scavenge radicals and produce H_2O_2 which becomes toxic to cells	Pulidoreyes et al. (2015)
	$\%Ce^{3+}$: 40	*P. subcapitata*	Polydispersity index: 0.589 Sphere Size: 18 nm	OECD medium	−21.1 ± 1.01	72 h	Growth inhibition	5 mg/L CNPs significantly inhibited cell growth		

(continued)

Table 1 (continued)

Influencing factors		Testing organism	Variables	Exposure media	Zeta potential in media (mV)	Exposure length	Measured endpoints	Toxicity effects with various concentrations	Potential mechanism	Ref.
	$\%Ce^{3+}$: 26	*P. subcapitata*	Polydispersity index: 0.503 Sphere Size: 50 nm	OECD medium	−24.4 ± 1.03	72 h	Growth inhibition	50 mg/L induced no inhibition effects		
	$\%Ce^{3+}$: 44	Human dermal fibroblasts cell lines	Size: 3.8 nm Coating: oleic acid	DMEM medium (Lonza)	N.a.	24 h	Intracellular reactive oxygen species (ROS) generation	50 mg/L CNPs resulted in 75% decrease in ROS generation	CNPs with smaller size containing more Ce^{3+} were more reactive toward H_2O_2	Lee et al. (2013)
	$\%Ce^{3+}$: 30	Human dermal fibroblasts cell lines	Size: 8.2 nm Coating: oleic acid	DMEM medium (Lonza)	N.a.	24 h	Intracellular reactive oxygen species generation	50 mg/L CNPs resulted in 30% decrease in ROS generation		

To understand the toxicity effects of CNPs, the physicochemical properties, exposure environment, and tested organisms require to be taken into consideration. N.a means not available

2.1 Size

The various sizes of CNPs can be achieved by specific synthesis methods. For example, wet chemical and microemulsion methods provide satisfactory control over CNPs size, with the former yielding CNPs of small particle size (Das et al. 2012; Tarnuzzer et al. 2005). The latter one may produce dense and crystalline CNPs with large particle size (>25 nm) (Zhang et al. 2011). However, the change of particle size would affect the interactions at CNPs-biological interface. As exhibited in Table 1, there exist numerous toxicity studies suggesting the significance of size in toxicity and verifying that nanoscale is the prime cause in toxicity induction, since smaller CNPs were found to be more toxic against algae (Rogers et al. 2010), *Caenorhabditis elegans* (Roh et al. 2010), *Brassica rapa* (Ma et al. 2016), *Cucurbita pepo* L. (Hawthorne et al. 2014), *E. coli*, and *B. subtilis* (Pelletier et al. 2010) than the larger ones. Due to comparable size with the biomacromolecules (Hassan et al. 2016; Limbach et al. 2005; van Hoecke et al. 2009), the intake of smaller CNPs occurs easily, thus inducing the oxidative stress as well as physiological damage inside the cellular environment (Ma et al. 2016; Park et al. 2008b; Pešić et al. 2015). On the contrary, it was demonstrated that the size of CNPs did not show any measurable correlation with algae and kidney bean plants' (*Phaseolus vulgaris*) growth inhibition (Majumdar et al. 2016a, b; Pulidoreyes et al. 2015). Surprisingly, larger CNPs were reported to show higher toxicity to eukaryotic cells than smaller ones (Schubert et al. 2006), as reported by Dahle (2013). Similarly, Park et al. observed that 30 nm CNPs displayed toxic effects toward BEAS-2B cells (Park et al. 2008b), while at the same concentration, Fang et al. illustrated that 13 nm CNPs induced no cytotoxicity in the same cell line (Fang et al. 2010). This phenomenon could be attributed to the greater agglomeration tendency of the smaller-sized CNPs than the larger ones, which sequestrated their reactions reactivity and thus toxicity in the individual exposure medium (Dahle 2013; Hamidat et al. 2017; Kumar et al. 2014).

In another analysis, authors explored the effects of size on the conversion between antioxidant and prooxidant activity of CNPs. The study found that at the same concentration of 10 μM, 15–20 nm CNPs had excellent antioxidant ability and thus an obvious protection effect, whereas CNPs (5–10 nm) behaved in the opposite manner (Lu et al. 2016). In contrast, Auffan et al. detected that 7 nm CNPs induced DNA damage in human dermal fibroblasts (Auffan et al. 2017a) and the formation of ROS in human dermal fibroblasts was confirmed by Culcasi et al. under the same conditions (Culcasi et al. 2012). Nevertheless, Karakoti et al. demonstrated the antioxidant activity of 4 nm CNPs in human dermal fibroblasts (Karakoti et al. 2009). These conflicting findings illustrate that CNPs with only different sizes perform differently, even at the same dosage in the same system.

Generally, to estimate the size effects of CNPs and to draw general conclusions, different susceptibility, varying feeding habits, and metabolism among tested species are vital factors that need to be taken into account. Importantly, when concluding the size effects of CNPs, factors including CNPs internalization, agglomeration, and surface property need to be comprehensively considered. Also, subcellular location and surface reactivity of CNPs controlled by their particle size can be detrimental to cells, which are still less understood.

2.2 Morphology

Recent developments in synthesizing NPs can enable preparation of CNPs with kinds of morphologies including spheres, rods, cubes, wires, octahedrons, and polygon (Chen and Stephen Inbaraj 2018; Dowding et al. 2013). More specifically, by adopting hydrothermal synthesis methods, [$Ce(NO_3)_3{\cdot}4H_2O$] as a precursor yielded coarse particles, whereas cerium(IV) salts [$Ce(SO_4)_2{\cdot}4H_2O$ and $Ce(NH_4)_4(SO_4)_2{\cdot}2H_2O$] produced fine powders (Hirano and Kato 1996). Commonly, nanoparticle size and morphology are responsible for their transformation and translocation in biological system, which is highly related to their toxicity and the biological response (Gatoo et al. 2014; Tong et al. 2013; Zhang et al. 2017). It has been widely accepted that CNPs with higher aspect ratios (including tube, belt, rod, and wire vs polyhedron) lead to more severe cytotoxicity to cells (Forest et al. 2016; Li et al. 2014; Lu et al. 2016). Forest et al. (2016) reported that rodlike CNPs could increase the toxicity in macrophages from RAW264.7 cell line, while the cubic and octahedral CNPs exhibited no such effects. Moreover, in cellular environment, CNPs were reported to transform from sphere into urchin-shaped structures and set in motion a series of events triggering cell lysis (Li et al. 2014). Nevertheless, another study suggested that compared with nanorods, nanowire bundles and nanocubes with sharp edges and corners in their crystal structure may induce more mechanical damage to cell membrane (Ji et al. 2012). They could lead to misbalance of the ionic concentration as well as redox state inside and outside the cell. Thereby, it is speculated that the morphological biotransformation of CNPs is of key significance and more difficult to depict in their toxicological effects.

The important role of morphology in the intrinsic chemical reactivity of CNPs is an additional factor that must be considered. Zhang et al. compared the uptake and transformation of octahedral (O-CNPs), cubic (C-CNPs), rod (R-CNPs), and irregularly shaped CNPs (I-CNPs) in cucumber plants. They found that the reactivity of CNPs decreased in the order of R-CNPs > I-CNPs > C-CNPs > O-CNPs, which brought the efficient accumulation, translocation, and transformation of R-CNPs in the plants (Zhang et al. 2017). Dowding et al. also proposed that CNPs with morphologies of spherical (S-CNPs, 5–8 nm) and polygonal (P-CNPs, 8–10 nm) did not take part in the decreased cell viability in 48 h, whereas S-CNPs are more active than P-CNPs toward surface oxygen release (Dowding et al. 2013). Taken together, the shape of CNPs determines their surface reactivity, thus impacting their environmental behavior and also the organisms-CNPs interaction, which is believed to underlie their toxicity effects in the chronic exposure environment (Thill et al. 2006; van Hoecke et al. 2009).

As a general rule, the smaller the size and the larger the aspect ratio of CNPs would result in the greater chance for the cells to uptake. Additionally, CNPs with specific morphology can mechanically damage cells because of their sharp edges and redox reaction activity. Thus, the effect of size and morphology of CNPs on toxicity does not seem to provide uniform results, since the agglomeration characteristics, the properties of CNPs, the cell type, and also culture environment may lead to prominent variation in the outcome of size- and morphology-dependent studies. The observed inconsistency requires more systematic and in-depth investigation.

2.3 Agglomeration

Nanoparticles properties in natural environments are expected to be altered by complex factors, including pH, ionic strength (IS) or NOM and one of the critical changes is agglomeration (Petosa et al. 2010). The formation of aggregates in the solution is greatly favored for small NPs because of a high number of primary particles at the same mass concentration, while larger ones maintained unagglomerated or settled to the bottom (Ludwig et al. 2005). Detailed reviews about agglomeration mechanisms can be found elsewhere (Batley et al. 2013; Collin et al. 2017; Petosa et al. 2010). The deep understandings on agglomeration enable a better assessment of NPs transport and ecological consequences through environmental compartments.

There is growing evidence that notable agglomeration yields higher rates of sedimentation and less mobility and surface area. It is also clear that NPs surface area is predictably related to the surface reactivity and this relationship transfers well to the most toxicity studies (Pelletier et al. 2010; Rogers et al. 2010; van Hoecke et al. 2009). Therefore, in many past studies, CNPs with a greater agglomeration state during the exposure experiment have a less inhibitory effect on the tested organism (Limbach et al. 2005; Petosa et al. 2010; Xu et al. 2018; Zeyons et al. 2009). As a function of agglomeration state, the direct transport through the cell wall of aquatic organisms and the phagocytosis process by membrane of human lung fibroblasts may be prevented and the individual CNPs diffusion across the cell membrane might also be reduced (Auffan et al. 2010; Ludwig et al. 2005). Additionally, heteroaggregation between CNPs and NOM or inorganic colloids in the environment could hinder the direct contact between CNPs and bacteria (Thill et al. 2006; Collin et al. 2014; Zeyons et al. 2009), which mitigates the toxicity of CNPs. In addition to the natural compositions, the biomacromolecule like polymeric or humic substances secreted by both microorganisms and plants as a defense response plays key roles in CNPs agglomeration, which is an exciting outcome to reduce the ecological risk (Ma et al. 2015; Wang et al. 2018a; You et al. 2017). On the other hand, heteroaggregation between CNPs and soft biogenic particles may increase their bioavailability for filter feeders, which need further attention to provide clear mechanisms.

Currently, agglomeration is demonstrated to reduce CNPs toxicity when the toxic response is resulted from a surface area-mediated reaction. However, there still exist challenges and limitations in delineating the influence of agglomeration on uptake and subsequent toxicity, because it is a dynamic process influenced by chemical, hydrodynamic, and biological conditions. Also, agglomeration may serve to promote the persistence of CNPs as it decreases the rate of dissolution and transformation, which may shift the exposure pathway to a different location compared to the dispersed CNPs.

2.4 Surface Charge

The surface charge contains significant information on the colloidal stability, transport, and importantly the NPs interactions with biological system in the environment. In the previous in vitro studies, the surface charge of CNPs has been reported to dictate CNPs cellular uptake and to control their cytotoxicity (Alpaslan et al. 2015; Asati et al. 2010; Nel et al. 2009). The toxicity of cationic CNPs in general exhibited more toxic than their neutral or anionic counterparts. The overall charge of the cell membrane is negative, and hence CNPs (positively charged or neutral in nature) can be easily uptaken and get simply bound to the cell membrane through electrostatic interaction, leading to the damage of cell membrane integrity and resulting in the lysis of cells (Asati et al. 2010; Collin et al. 2014; He et al. 2012; Spielman-Sun et al. 2017).

In addition to the cellular uptake, the subsequent subcellular localization of surface-charged CNPs takes a key part in the cytotoxicity profile of CNPs. Asati et al. found that CNPs (+) displayed significant toxicity as they entered the lysosomes of the cells, while minimal toxicity is observed when the CNPs (0) and CNPs (−) localized in the cytoplasm or did not enter the cells (Asati et al. 2010). Similarly, Spielman-Sun et al. concluded that the tissue localization and transformation of CNPs within *Triticum aestivum* were significantly affected by their different surface charge (Spielman-Sun et al. 2017). Further, risks associated with CNPs exposure will be determined partially by the environmental processes. Collin et al. (Collin et al. 2014) and He et al. (2012) proposed respectively to add humic acid (HA) and phosphate (P) in the exposure media to attenuate the toxicity. Both HA and P could adjust the positive surface charge density by conferring a net negative surface charge and thus decrease CNPs accumulation and toxicity.

Overall, it is clear from the few studies that the roles of surface charge on CNPs interactions with cell surface and subsequent toxicity must be considered. However, to gain a deeper understanding, the key components mediating surface charge of CNPs in environmental systems and their consequent localization in biological substructure require more precise control of variables, which will contribute to eliminate possible associated toxic effects.

2.5 Coating

The surface of any material is the prominent route of interaction with the cellular environment. Therefore, studies have been conducted to develop coatings around NPs with the aims of providing steric, electrostatic, or electrosteric repulsive forces among particles to resist agglomeration and dissolution (Collin et al. 2017; Ganguly et al. 2018; Levard et al. 2012). Various types of compounds including NOM, carboxylic acid, polysaccharides, and polymers have been applied to functionalize CNPs surface. Fulvic acid (FA) and HA are ubiquitous component of water and

soils, which favor to stabilize dispersed NPs (Collin et al. 2014; Schwabe et al. 2013). Citric acid (CA) and acrylic acid (AA) are prevalent carboxylic acid serving as capping or reducing agents (Barton et al. 2014; Ould-Moussa et al. 2014). Polysaccharides are common coatings including gum arabic (GA), dextran, and alginate (Alg) (Schwabe et al. 2013; Spielman-Sun et al. 2017; Zhao et al. 2012a, b). Polymer such as polyvinylpyrrolidone (PVP) has also been introduced to functionalize CNPs surface (Taylor et al. 2016).

The nature of the coating plays an important part in various levels of toxicity, as listed in Table 1. For instance, surface modification of CNPs with HA, CA, and AA constitute a protection against toxic cellular effects by decreasing the potential surface reactivity (Barton et al. 2015; Heckert et al. 2008) and reducing the ROS generation (Marie et al. 2014), which both mitigated the toxicity (Barton et al. 2014; Marie et al. 2014; Trujillo-Reyes et al. 2013). In respect to the surface functionalization with FA and GA, though the plant growth and translocation factor of CNPs exhibited no difference, the content of CNPs associated with root (bare $>$ FA $>$ GA) was influenced (Schwabe et al. 2013). On the contrary, other studies indicated that CA coating promoted the internalization of CNPs in cells and the concentrations of dissolved Ce ions in water column, leading to greater toxicity than the uncoated ones (Garaud et al. 2016; Ould-Moussa et al. 2014; Tella et al. 2015). The conflicting results might be deemed from the different exposure system as well as the inspected endpoints in the individual studies. Similar conclusions with higher toxicity were drawn by Zhao et al. (2012a, b), Booth et al. (2015), and Dowding et al. (2013) when CNPs were stabilized by Alg, poly-AA, and hexamethylenetetramine (HMT), respectively. The different effects of various coatings have been generally concluded as the hydrophobic coating imposed high levels of toxicity and vice versa for hydrophilic coatings (Yin et al. 2005).

Several CNPs were synthesized by coating with biocompatible polymers such as dextran (Alili et al. 2011; Barkam et al. 2015), oleic acid (Lee et al. 2013), 2-ethylhexanoic acid (Dowding et al. 2013), sodium bis(2-ethylhexyl)sulfosuccinate (Chaudhury et al. 2013), and polyethylene glycol (PEG) (Cimini et al. 2012; Vincent et al. 2009). As a result, the surface stability of CNPs can be greatly improved, which is a vital aspect to be considered for biological applications and cytotoxicity. The surface functionalization of CNPs for biocompatibility can protect CNPs from interacting with ions and create more effective means in the presence of biological environment. Alili et al. (2011) found that concentrations of dextran-coated CNPs being nontoxic for normal (stromal) cells show a cytotoxic effect on squamous tumor cells. Similarly, Cimini et al. (2012) reported that PEG-coated and anti-Aβ antibody-conjugated antioxidant nanoparticles (Aβ-CNPs-PEG) specifically target the Aβ aggregates, and concomitant rescue neuronal survival better than Aβ-CNPs, by modulating the brain-derived neurotrophic factor signaling pathway.

Consequently, such hermetic coatings may define the surface of CNPs and in part or significantly affect their behavior in the environment. But it is important to consider that the various molecular weight and chemical structure of coating compounds will change how well they stabilize the CNPs against agglomeration, interaction, and ultimately toxicity in the environment.

2.6 Surface Oxidation State and Oxygen Vacancy ($V_o^{\cdot\cdot}$)

The surface oxidation state of CNPs can vary depending on synthesis methods and conditions. Accordingly, the synthesis process conducted at high temperatures yields CNPs with lower Ce^{3+}/Ce^{4+} ratio and larger particle size (Chen and Stephen Inbaraj 2018). Different chemicals such as sodium hydroxide, ammonium hydroxide, and hexamethylenetetramine used during synthesis could produce CNPs with lower Ce^{3+}/Ce^{4+} ratio (Dowding et al. 2013). Besides, the reaction of CNPs with elements such as zirconium (Zr) and platinum (Pt) was shown to lead to an increase in surface Ce^{3+}/Ce^{4+} ratio (Zhang et al. 2006). Several trivalent metal ions such as lanthanum, samarium, gadolinium, yttrium, and neodymium have been used as dopants to increase oxygen vacancy concentration (Babu et al. 2009; Grulke et al. 2014; Patil et al. 2006; Shehata et al. 2014). With transforming between Ce(IV) and Ce(III) and leaving $V_o^{\cdot\cdot}$ in the lattice (shown in Fig. 1), CNPs easily form nonstoichiometric compositions of CeO_{2-x}, which makes CNPs acting as quenchers or producers of ROS (Lu et al. 2016; Pulidoreyes et al. 2015). A correlation between the size and lattice parameter of CNPs was established by Deshpande et al. (2005) who claimed that the smaller the CNPs particle size, the higher the surface Ce(III)/Ce (IV) ratio. In this regard, the ratio of Ce(III)/Ce(IV) at CNPs surface is the key to understand their potential toxicity (Collin et al. 2017), as exhibited in Table 1.

As reported, the CNPs' antioxidant and prooxidant properties are closely related to the % surface Ce(III) values (Deshpande et al. 2005; Lu et al. 2016; Wu et al. 2018a, b). Lu et al. (2016) reported that at the same concentration of 10 μM, CNPs (15–20 nm, 27.55% of Ce(III)) displayed an excellent antioxidant ability and thus an obvious protection effect, whereas CNPs (5–10 nm, 30.74% of Ce(III)) behaved in the opposite manner. Similarly, Pulidoreyes et al. (Pulidoreyes et al. 2015) found that the % surface Ce(III) is the main driver of CNPs toxicity in the case of where CNPs did not internalize in the alga. Through oxidative reactions, CNPs could abiotically generate H_2O_2 (Xia et al. 2008; Zhao et al. 2012a, 2012b), while Ce (III) was reported to be able to redox-cycle with H_2O_2 to form ROS such as hydroxyl ($^{\cdot}OH$) (Seal 2008). A step forward understanding demonstrates that $^{\cdot}OH$ and CNPs can create a high amount of Ce(III), which could scavenge additional $^{\cdot}OH$, ultimately strengthening the antioxidant activity of CNPs (Deshpande et al. 2005; Lee et al. 2013). However, when the quantity of Ce(III) reaches a certain level, CNPs convert their antioxidant activity to oxidant activity (Lu et al. 2016), which can partially explain the contradictory results in medicinal applications and toxicological research. $^{\cdot}$Detailed information about the ROS generation is reviewed in Sect. 5.

As to the $V_o^{\cdot\cdot}$, they are thought to make CNPs more effective at generating Ce(III) than the equivalent bulk material and act as "active center" of various redox reactions exhibited by CNPs (Lee et al. 2013). On the other side, $V_o^{\cdot\cdot}$ can significantly alter biological interactions and allocate oxygen moieties from biological molecules, inhibiting a set of biological antioxidant effects and inducing toxicity response (Gupta et al. 2016). Celardo et al. (2011) demonstrated that $V_o^{\cdot\cdot}$ did not

contribute to the biological properties of CNPs, but its effects on Ce(III) /Ce (IV) redox reactions need to be further clarified.

Collectively, the various physicochemical properties tailored by synthesis methods and tested organism types reflect the different environmental effects of CNPs. Nevertheless, there is no consensus on which CNPs characteristic is primarily responsible for the observed effects. Perhaps the dynamic and stochastic transformation of CNPs under environmental scenarios is more realistic in controlling CNPs' ecological processes and effects, as discussed next.

3 Phase Transformation of CNPs in Different Environmental Scenarios: Impact on Bioaccumulation and Toxicity

In the case of CNPs to readily chemically transform between Ce(IV) and Ce(III), the physicochemical transformations that accompany engineered and/or incidental colloids/coatings, as well as pursuant reactions in different environmental scenarios, strongly complicate the understanding and evaluating on risks in relation to the release of CNPs in the environment (Barton et al. 2014; Dahle et al. 2015; Merrifield et al. 2013, 2017). To correctly forecast the environmental and ecological risks, it is necessary to increase the knowledge of the transformations of CNPs in various environmental scenarios.

The Hard/Soft Acid/Base theory predicts the tendency of Ce to strongly bond with hard base ligands like hydroxyl ions and P over hard acidic species such as sulfates and hydrids. Generally, Ce(III) is more soluble than Ce(IV), for Ce(IV) is known to undergo hydrolysis reaction to generate insoluble $Ce(OH)_4$ (solubility product of $K_{sp} = 2 \times 10^{-48}$), whereas K_{sp} of $Ce(OH)_3$ is 1.6×10^{-20} (Channei et al. 2017; Dahle et al. 2015). Nevertheless, Ce(III) could form the insoluble P compound of $CePO_4$ with K_{sp} of 1.0×10^{-23} (Xu et al. 2018). Some other common O-donor organic (oxalate and tartrate) complex with Ce(III) to form products of $Ce_2(C_2O_4)_3{\cdot}9H_2O$ (K_{sp}: 3.2×10^{-26}) and $Ce_2(C_4H_4O_6)_3$ (K_{sp}: 1.0×10^{-19}) (Dahle et al. 2015). These resulting transformations of CNPs will impact their fate, transport, and toxic properties. The physicochemical and biological conditions favoring the formation of complex are reviewed in the following sections considering various environmental scenarios.

3.1 Speciation and Ecological Effect of CNPs in Aquatic Environments

As Ce exhibit various possible redox states, the chemical stability of CNPs can vary in aquatically environmental conditions, as schematically illustrated in Fig. 2.

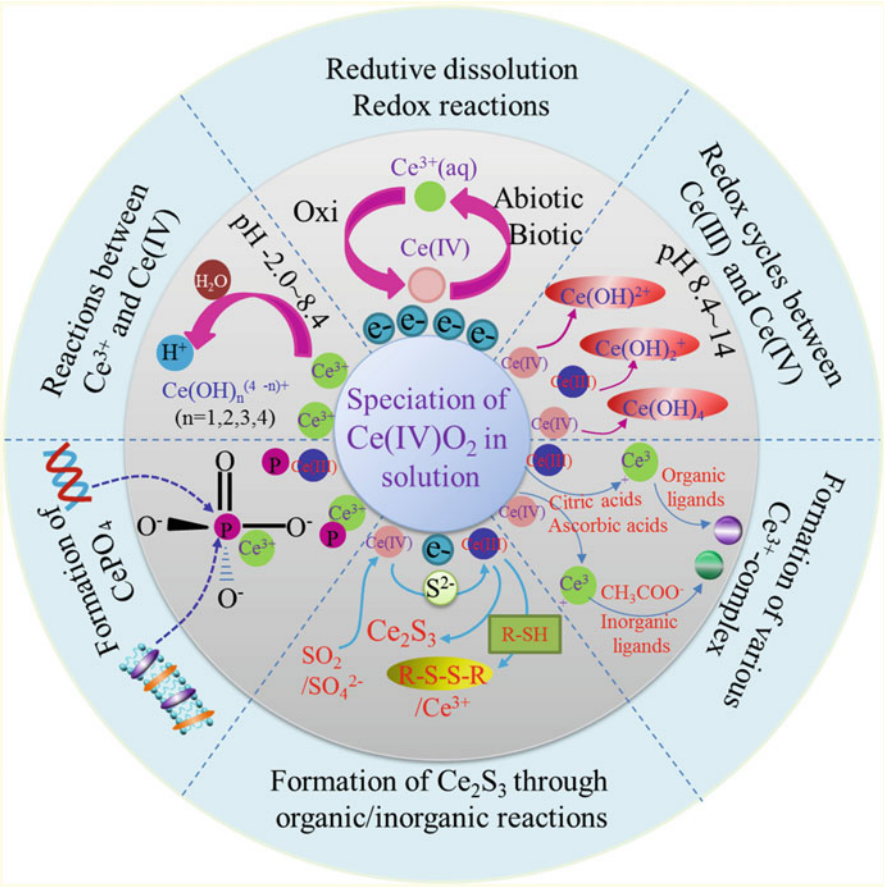

Fig. 2 Speciation and transformation of CNPs in the aquatic system. The three parts in the top show the calculated speciation for Ce^{3+}-H_2O, Ce^{4+}-H_2O, and Ce-H_2O. Details about aqueous speciation of each ion, polycomplex of specific valence, and Pourbaix diagram are given in Channei et al. (2017). The other three parts illustrate the transformations of CNPs in environmental medium with both organic and inorganic ligands in biological system. Detailed information is also given in Sect. 4

Pourbaix diagrams using thermodynamic data were introduced to dictate the speciation of Ce in solution by the simultaneous indications of chemical (as a function of pH) and electrochemical reactions (as a function of electrochemical potential (pe, calculated as pe = 16.9 E_H (V) at 25°C)). As an example, in Channei et al. (2017), the speciation diagrams for the simple system of Ce^{3+}-H_2O, Ce^{4+}-H_2O, and E_H-pH diagrams for Ce-H_2O were respectively displayed. It can be found that Ce(IV) on the surface of CNPs is not in equilibrium with water in the section of water stability, so the reduction of Ce(IV) to Ce(III) occurs spontaneously (Channei et al. 2017; Cui et al. 2014). Therefore, the composition is shifted into the Ce^{3+} predominance region. Then, Ce^{3+} hydrolyzes to $Ce(OH)^{2+}$ and the end products of $CeO_2 \cdot 2H_2O$

Table 2 Electrochemical potentials required for redox reactions (E) for Ce species corresponding to speciation diagrams (Brookins 1983; Channei et al. 2017; Hayes et al. 2002; Yu et al. 2006)

No.	Coupled redox reaction	pH range	E range
Reactions between Ce^0 with Ce(III)			
1	$Ce^{3+} + 3e^- \rightarrow Ce^0$	−2.0 to 8.4	2.32 (pH independent)
2	$Ce(OH)^{2+} + H^+ + 3e^- \rightarrow Ce^0 + H_2O$	8.4–9.1	−2.15 to 0.02 pH
3	$Ce(OH)_2^+ + 2H^+ + 3e^- \rightarrow Ce^0 + 2H_2O$	9.1–9.7	−1.97 to 0.04 pH
4	$Ce(OH)_3 + 3H^+ + 3e^- \rightarrow Ce^0 + 3H_2O$	9.7–14	−1.78 to 0.06 pH
Reactions between Ce^{3+} with Ce(IV)			
5	$Ce^{4+} + e^- \rightarrow Ce^{3+}$	−2.0 to –0.76	1.74 (pH independent)
6	$Ce(OH)^{3+} + H^+ + e^- \rightarrow Ce^{3+} + H_2O$	−0.76 to 0.72	1.69–0.06 pH
7	$Ce(OH)_2^{2+} + 2H^+ + e^- \rightarrow Ce^{3+} + 2H_2O$	0.72–1.5	1.74–0.12 pH
8	$Ce(OH)_3^+ + 3H^+ + e^- \rightarrow Ce^{3+} + 3H_2O$	1.5–2.6	1.83–0.18 pH
9	$Ce(OH)_4 + 4H^+ + e^- \rightarrow Ce^{3+} + 4H_2O$	2.6–8.4	1.98–0.24 pH
Reactions between Ce(III) with Ce(IV)			
10	$Ce(OH)_4 + 3H^+ + e^- \rightarrow Ce(OH)^{2+} + 3H_2O$	8.4–9.1	1.48–0.18 pH
11	$Ce(OH)_4 + 2H^+ + e^- \rightarrow Ce(OH)_2^+ + 2H_2O$	9.1–9.7	0.94–0.12 pH
12	$Ce(OH)_4 + H^+ + e^- \rightarrow Ce(OH)_4 + H_2O$	9.7–14	0.37–0.06 pH

(s) and $Ce(OH)_4$ (gel) as the pH progresses toward neutral. $Ce(OH)_2^+$ and $Ce(OH)_3$ are not formed since their predominance fields do not adjoin that of Ce^{3+} (Channei et al. 2017). Correspondingly, the electrochemical potential required for redox reactions (E) for Ce species is also given in Table 2. A more thorough description of the stability fields for water can be found in Channei et al. (2017). It is clear from these thermodynamic simulations that Ce speciation in waters will be more strongly dependent on redox conditions than pH. Thus, the identity of these phases will have to be examined experimentally.

The redox activity of CNPs is often associated with the hypothesis of their high oxygen nonstoichiometry. A range of techniques such as UV-Vis spectroscopy, X-ray photoelectron spectrum (XPS), X-ray absorption near-edge structure spectrum (XANES), electron energy loss spectroscopy (EELS), X-ray scanning transmission microscopy (STXM), and high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) have been largely used to determine the redox state of CNPs both in vivo and in vitro. In the studies of van Hoecke et al. (2009), Thill et al. (2006), and Zhang et al. (2012), Ce in the CNPs is present as Ce(IV), and no reduced Ce(III) was observed in OECD medium, Luria broth (LB) growth medium, as well as individual exposure medium by using XANES. However, once the species related to Ce(IV) have been hydrolyzed, the tendency of the redox reaction (Table 2) is enhanced by high IS (Channei et al. 2017). For example, the redox and crystallinity changes of CNPs in environmental and toxicological media were illustrated by Merrifield et al. using HAADF-STEM and EELS (Merrifield et al. 2017). They found that CNPs were changed to mixed Ce(IV, III) NPs at high IS although the exact mechanism is not clear, whereas the presence of NOM stabilized the oxidation state and increased crystallinity. Since the toxicity of CNPs

is associated primarily with high E_H of Ce(IV) and their ability to oxidize biomolecules (Plakhova et al. 2016), the results of Merrifield et al. (2017) and Wu et al. (2018b) further confirmed the roles of NOM in controlling CNPs transformation to alleviate toxicity.

Taking account of interactions with biomass, a measurable reduction of Ce(IV) to Ce(III) has been observed with *E.coli*, activated sludge, nematodes, and plants (Thill et al. 2006; Barton et al. 2014; Collin et al. 2014; Ganguly et al. 2018; Ma et al. 2015, 2017; Marie et al. 2014; Zhang et al. 2012), which linked to the occurrence of a strong cytotoxicity. It was believed that the microreducing zones produced by microbial metabolism and the reducing molecules, like amino acids, released by the bacteria were able to cause the reduction of CNPs (Thill et al. 2006; Xu et al. 2018). Barton et al. indicated preferential accumulation of CNPs in biosolids where reductive transformation occurred (Barton et al. 2015). Zhang et al. (2012) and Ma et al. (2015) further demonstrated that the reducing substances like ascorbic acids, and organic acids like citric acids, secreted by root in hydroponic studies are necessary conditions for the reduction and dissolution of CNPs. To go a step further, the formation of stable Ce^{III}-organic complexes (Bayülken and Saraç 1996), $CePO_4$ in the root (Zhang et al. 2012), $Ce(CH_3COO)_3$ in the shoot (Zhang et al. 2012), and Ce_2S_3 in the anaerobic digestion (Barton et al. 2014) was determined. Specific studies in relation to such transformations on toxicity are discussed in Sect. 4.

Inevitably, in the aquatic case, the oxidation and hydrolysis of Ce may lead to the formation of an insoluble oxide surface coating on CNPs which may passivate the surface. It is also likely that the biomass, NOM, reducing agents, and even clays play vital roles in the stability of CNPs. Moreover, hard basic ligands are undoubtedly important in predicting the environmental transformations of CNPs. However, whether the formation of complex induces or reduces the toxicity of CNPs should be addressed in detail.

3.2 *Transfer and Transformation of CNPs in Terrestrial System*

Concerns about the possibility of NPs transport from the soils to agricultural crops and ultimately bioaccumulation in the food chain or leaching to the groundwater are in a state of developing. Thus, increasing efforts are dedicated to evaluating the bioavailability (from the soil solution to the plant root) and transformation of CNPs in the terrestrial system, as displayed in Fig. 3.

Zhang et al. demonstrated that the bioavailability of CNPs was positively linearly correlated to the sum of exchangeable, reducible, and oxidizable fractions (i.e., Ce bound to organic matter) of Ce in both loamy sand soil and silty loam soil (Zhang et al. 2015). Cornelis et al. further investigated the primary mechanisms determining CNPs bioavailability in soils by relating retention (K_r) values to the physicochemical properties of 16 kinds of Australian soils (Cornelis et al. 2011). They found that the

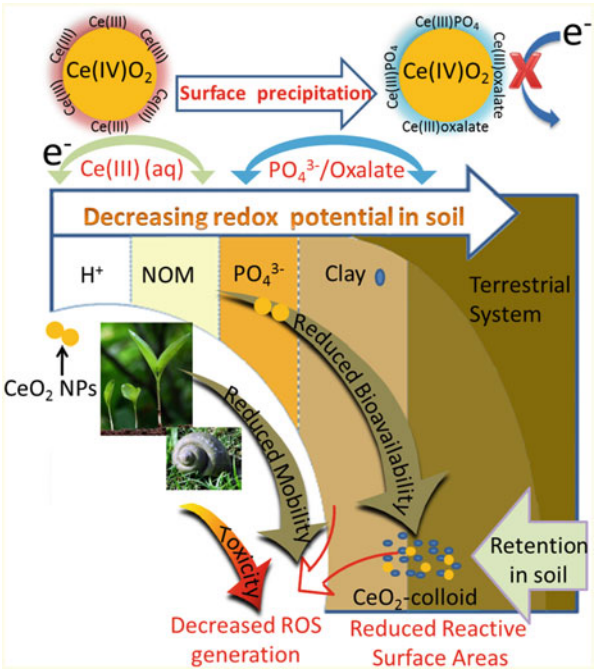

Fig. 3 Schematic illustration for the transfer and transformation of CNPs in terrestrial system controlled by the properties and compositions of soils. The bioavailability and further toxicity of CNPs in the terrestrial system were reduced in the presence of natural organic matter (NOM), phosphate (PO_4^{3-}), or oxalate through surface passivation and redox reduction

fraction of clay was the main physicochemical driver determining K_r values ahead of the concentration of P or the pH of the soil (52% of the total sum of squares was caused by the percentage of clay, 14% by P concentration, and 6% by pH) (Cornelis et al. 2011). Layet et al. (2017) developed ISO-standardized RHIZOtest to comprehensively decipher the factors determining CNPs phytoavailability, and they reported that the clay colloids reduced Ce uptake, which was consistent with Cornelis et al. (2011). Surprisingly, this work combined with other studies provided new evidence that NOM enhanced the phytoavailability of CNPs (Layet et al. 2017; Majumdar et al. 2016a, b; Zhao et al. 2012a, b). The authors suggested that NOM tended to coat CNPs, limiting their homo(hetero)aggregation and therefore rendering CNPs more phytoavailable. Moreover, both CA and Alg coatings were observed to facilitate CNPs phytoavailability relating to the increased mobility, whereas the enhancing effects depend on soil type and NOM content (Layet et al. 2017; Zhao et al. 2012a). This phenomenon could also explain the limited effects of CA coating on the bioavailability of CNPs in Cornelis et al. (2011).

Another intriguing observation is that the disparity of roots and shoots with regard to CNPs accumulation is controlled by the properties of soils. Recent studies demonstrated that the presence of NOM and negatively charged colloids in soil could complex with positively charged CNPs and reduce their mobility. As a result, the upward transport of CNPs from roots to shoots will be limited in the kidney bean plants, *Raphanus sativus L.*, and corn plants (Majumdar et al. 2016a, b; Zhang et al. 2015; Zhao et al. 2012a). Additionally, the extent of CNPs translocation in soil

grown plants might depend significantly on the standard of water-soluble fraction (Zhang et al. 2015). There have also been some progresses in assessing the bioaccumulation and trophic transfer of CNPs within terrestrial and specifically agricultural food chains. Findings showed that CNPs may be taken up by plants and transferred to consumers along food chains, which may affect food safety (Hawthorne et al. 2014; Ma et al. 2018; Majumdar et al. 2016a, b). Majumdar et al. further suggested that the bioaccumulation and biomagnifications of Ce in the mature stages of primary and secondary consumers (Mexican bean beetles and spined soldier bugs) feeding on kidney bean plants exposed to CNPs were observed, due to the higher content of ingestion than excretion (Majumdar et al. 2016a, b).

To reveal the favorable reaction path to make CNPs more bioavailable, the chemical fate of CNPs in both soil and plants was evaluated. Arai and Dahle showed that CNPs of 30 nm and 78 nm were strongly adsorbed (>98%) by soils (Arai and Dahle 2017). Under the oxic condition, >90% of CNPs remained as $Ce(IV)O_2$, and a small portion of $CePO_4$ were identified in XANES analysis. Interestingly, under anoxic conditions, the reduction was more pronounced in small CNPs, which is considered to be highly related to bioavailability. However, the greater concentration of exchangeable Ce(III) in large CNPs facilitated the formation of Ce(III)P/oxalate surface precipitates, suppressing the bioavailable and thus reducing cytotoxicity (Arai and Dahle 2017). Upon uptake, both the geochemical modeling and XANES analysis of the roots failed to correlate the CNPs phytoavailability with different Ce speciation in the soil solution, since Ce is mainly present as $Ce(IV)O_2$ inside the root tissues (Layet et al. 2017; Ma et al. 2018; Zhao et al. 2012b). Nevertheless, biotransformation of CNPs to Ce(III)P/carboxylate complexes has been observed in root in hydroponic cucumber plants (Rui et al. 2015; Zhang et al. 2012). These results further reveal the lower levels of bioavailability, transformation, and phytotoxicity of CNPs in soil than in aqueous media (Layet et al. 2017; Majumdar et al. 2016a, b; Zhang et al. 2015; Zhao et al. 2012a, b). Notably, in the trophic transfer experiment, the reduction of Ce(IV) to Ce(III) did not occur in plants and snail faces, and did only in the digestive gland of snail (Ma et al. 2018), which raises the question whether this reduction creates potential risk to humans through the food supply.

In short, though hydroponics studies provided valuable information about the chemical fate and plant uptake of CNPs, the soil properties (porosity, pH, IS, NOM, and mineral composition) played decisive roles in the bioavailability, migration, chemical transformation, and their interactions at the nano-bio interface in soils. Therefore, it is imperative to study the behavior of CNPs in the terrestrial system in realistic conditions to determine if CNPs can be put in the food chain threatening the ecosystems and human health.

3.3 Uptake and Toxicity of CNPs Through Air Exposure

As the increasing release of CNPs into the atmosphere through vehicles emissions (Hong et al. 2014), plants could be exposed to unusual high concentrations of CNPs

via aerial exposure. Thus, besides through the roots (aquatic and soil exposure), the interactions between atmospheric CNPs and plants through the leaves (i.e., aerial/rain deposition) were examined to provide more comprehensive and informative picture on the actual influences of CNPs contamination toward plants.

Findings highly suggested that CNPs could be adsorbed on and further incorporated in leaves through both powder and suspension spraying (Birbaum et al. 2010; Hong et al. 2014; Jie et al. 2016; Ma et al. 2018; Salehi et al. 2017). An effective uptake and translocation of CNPs through leaves to the plants tissues was observed in *Lactuca sativa* (Ma et al. 2018), cucumber (Hong et al. 2014; Ma et al. 2017), and *Phaseolus vulgaris L.* (Salehi et al. 2017), while contradicted results of Birbaum et al. in maize plants were reported (Birbaum et al. 2010). In Ma et al., no significant difference in plant growth between the control and group treated with foliar exposure was detected (Ma et al. 2018). However, Hong et al. revealed that low concentrations of CNPs (40 and 160 mg/L) in contact with leaves could interfere the enzyme activities, whereas high concentration (320 mg/L) caused toxicity (Hong et al. 2014; Jie et al. 2016). These results were further evidenced by Salehi et al. through morphological, proteomic, and metabolomic data (Salehi et al. 2017). These marked differences could be related to the influencing factors such as the plant species, size and type of CNPs, as well as environmental conditions (e.g., wind, moisture). Particularly, the exposure route of airborne was suggested to pose a more marked effect toward bean than soil exposure (Salehi et al. 2017). Besides, when exposed through foliage, the differences in particle size were less significant compared to root-based exposure (Jie et al. 2016). These strong differences are because CNPs might be modulated by hydroponic cultures or soil factors such as pH, root exudates, and microorganisms (Thill et al. 2006; Xu et al. 2018). Then, the bioavailability, influenced by adsorption-desorption and mobility processes in soil, would be limited, thus decreasing the root uptake (Cornelis et al. 2011).

In addition to the plants, the increased ambient air concentrations of CNPs could also contribute to the exposure of animals and humans. Most studies on the health effects of CNPs pay attention to the lung cells, since the most likely route of exposure is through inhalation (Cassee et al. 2011). The uptake of 20–50 nm CNPs by human lung 3T3 fibroblasts was examined in vitro, and results showed that CNPs internalization occurred linearly with exposure time at concentrations as low as 100 ng/g cells (Limbach et al. 2005). The tissue distribution of inhaled CNPs in rats was determined in a 28-day exposure study. After 6 h exposure, CNPs were translocated to the liver, kidney, spleen, brain, testis, and epididymis (Geraets et al. 2012). The biotransformation of CNPs in the vasculature of rat's brain was conducted by EELS, and the ratio of Ce^{3+}/Ce^{4+} was not changed after 20 h (Hardas et al. 2010). However, when the liver was tested by HRTEM after 90 days, CNPs showed rounded edges and corners with the increased surface Ce^{3+} (Graham et al. 2015), which was described as the basis of the genotoxicity toward human fibroblasts (Auffan et al. 2009). The toxic effects of CNPs on human mesothelioma were examined by measuring metabolic activity and cell proliferation, which showed that the metabolic activity and DNA content reduced by approximately 50% after 3 days of exposure (Brunner et al. 2006).

It has been concluded that acute CNPs exposure from hours up to 1 day via the inhalation route might induce cytotoxicity via oxidative stress and would lead to a chronic inflammatory response, while the levels of exposure concentration are orders of magnitude higher than the real condition in the environment (Yokel et al. 2014). An inhalation study in mice exhibited that at an aerosol concentration of 2 mg/m^3 for 7, 17, or 28 days, CNPs can induce pulmonary and extrapulmonary toxicity (Aalapati et al. 2014). When a truly nanoscale aerosol exposure atmosphere was used, inflammation of neutrophils after 24 h exposure was observed, while the markers of pulmonary response returned to the control levels 84 days post-exposure (Demokritou et al. 2013). Fall et al. (2007) also explored the biological influence of engine emissions using a CNPs fuel additive compared to that of a reference fuel and an organotypic culture of lung slices from rat. The authors demonstrated that the biological impacts of CNPs fuel additive are very limited and there was no influence of CNPs aerosol on lung tissue viability. Similarly, Park et al. (2008a) also concluded that no effects were observed on the viability of the lung tissue slices when exposed to a continuous flow of CNPs aerosol. However, with longer exposure duration, accumulation can occur and lead to a dose that causes adverse health effects. Regrettably, there is no data on the inhalation toxicity of chronic exposure to CNPs under realistic conditions.

In summary, CNPs could penetrate the leaf surface through aerosol exposure, while their translocation through the leaf tissue and adverse effects are contradictory among studies under various test conditions. Besides, pulmonary exposure to high concentrations of CNPs led to pulmonary inflammation and alveolar interstitial fibrosis. Considering the risks that atmospheric CNPs could be directly stored in or adsorbed by the fruit of plants, the skin or lung, studies are needed to determine the chronic threat for environmental and human health through trophic transfer and inhalation.

4 Chemical Transformation of CNPs Core and Associated Effects on Toxicity

The formation of environmentally relevant Ce species described in Sect. 3 has been investigated to partly evaluate the impact of such transformations on toxicity. In some cases, these transformations may promote toxicity potential (e.g., dissolution reactions that produce excessive ROS) (Seal 2008). In other cases, these transformations have been shown to reduce effects (e.g., the formation of $CePO_4$ decreased the cytotoxicity of CNPs toward wastewater biofilm (Xu et al. 2018) and plants (Zhang et al. 2016). Some transformations can potentially limit CNPs persistence in the environment (e.g., dissolution and redox reactions). Importantly, many transformations are slow or irreversible and cannot necessarily be predicted using thermodynamics. Thus, some main transformations are discussed in more in-depth in the following sections.

4.1 Reductive Dissolution of CNPs and Related Toxicity Effects

It is generally accepted that CNPs have extremely low solubility, and the dissolved Ce ions have little or even no impacts on its cytotoxicity. However, numbers of researches have shown that CNPs undergo partial dissolution under specific conditions (Dahle et al. 2015; Plakhova et al. 2016; Zhang et al. 2012). In addition, toxicity of CNPs is largely associated with high redox potential (E_H) of tetravalent and trivalent Ce ions and their ability to oxidize biomolecules. Thus, the dissolution of CNPs to form Ce ions is one of the main environmental risk issues.

Extensive data indicated that CNPs solubility is strongly dependent on pH (Auffan et al. 2017b), as shown in Fig. 4a. As an example, CNPs dissolution was lower than or close to detection limits (0.1 nM) at pH 7 and 9, but 3.1% (i.e., 29 μM) CNPs dissolved at pH 4 in artificial soil solution (AS) (Cornelis et al. 2011). Similarly, CNPs dissolution was reported to be significant at pH $<$ 5 and pH $<$ 4.5 by Dahle et al. (Dahle et al. 2015) and Plakhova et al. (2016), respectively, indicating the promoted dissolution by proton. According to the measurements of E_H values, the solubility-pH dependence could be associated with differing redox conditions of pe-pH dependence (Fig. 4b) (Plakhova et al. 2016). Hence, the different solubility behavior of CNPs at pH 1.5–4.5, pH 4.5–7, and pH $>$ 7 can be explained by the different redox conditions. It has also been concluded that CNPs appeared to be more soluble in AS relative to 0.1 mM NaCl, possibly because of both ionic Ce(III) and Ce(IV) forming pairs with inorganic oxyanions, thus enhancing solubility (Cornelis et al. 2011). Through complexation, the presence of NOM like arabic gum and organic ligands like ethylenediaminetetraacetic acid (EDTA) and CA were found to enhance CNPs dissolution (Schwabe et al. 2014; Zhang et al. 2012) as demonstrated in Fig. 4c.

Cornelis et al. proposed that through geochemical modeling in PHREEQC, Ce (IV) ion concentration was much higher than that in equilibrium with CNPs and Ce $(OH)_4$. Therefore, it is speculated that part of Ce which dissolved from CNPs may occur as Ce(III) (Cornelis et al. 2011). The available Pourbaix diagrams shown in Channei et al. verified that at pH $<$ 7, the predominant cerium species in solution is Ce(III) (Channei et al. 2017). Namely, the more thermodynamically probable solubility mechanisms of CNPs are reductive dissolution, where Ce(IV) would be reduced to a more stable soluble species of Ce(III) (Fig. 4a). This phenomenon was highly consistent with the considerations of Zhang et al. that with the assistance of reducing substances secreted by roots, CNPs might be first reduced and then released as Ce(III) (Zhang et al. 2012). Based on the environmental data with pH ranging from 2 to 7 in Fig. 4a, a reductive dissolution model was proposed by Plakhova et al. (2016). The solubility process of CNPs can be depicted by the following equation:

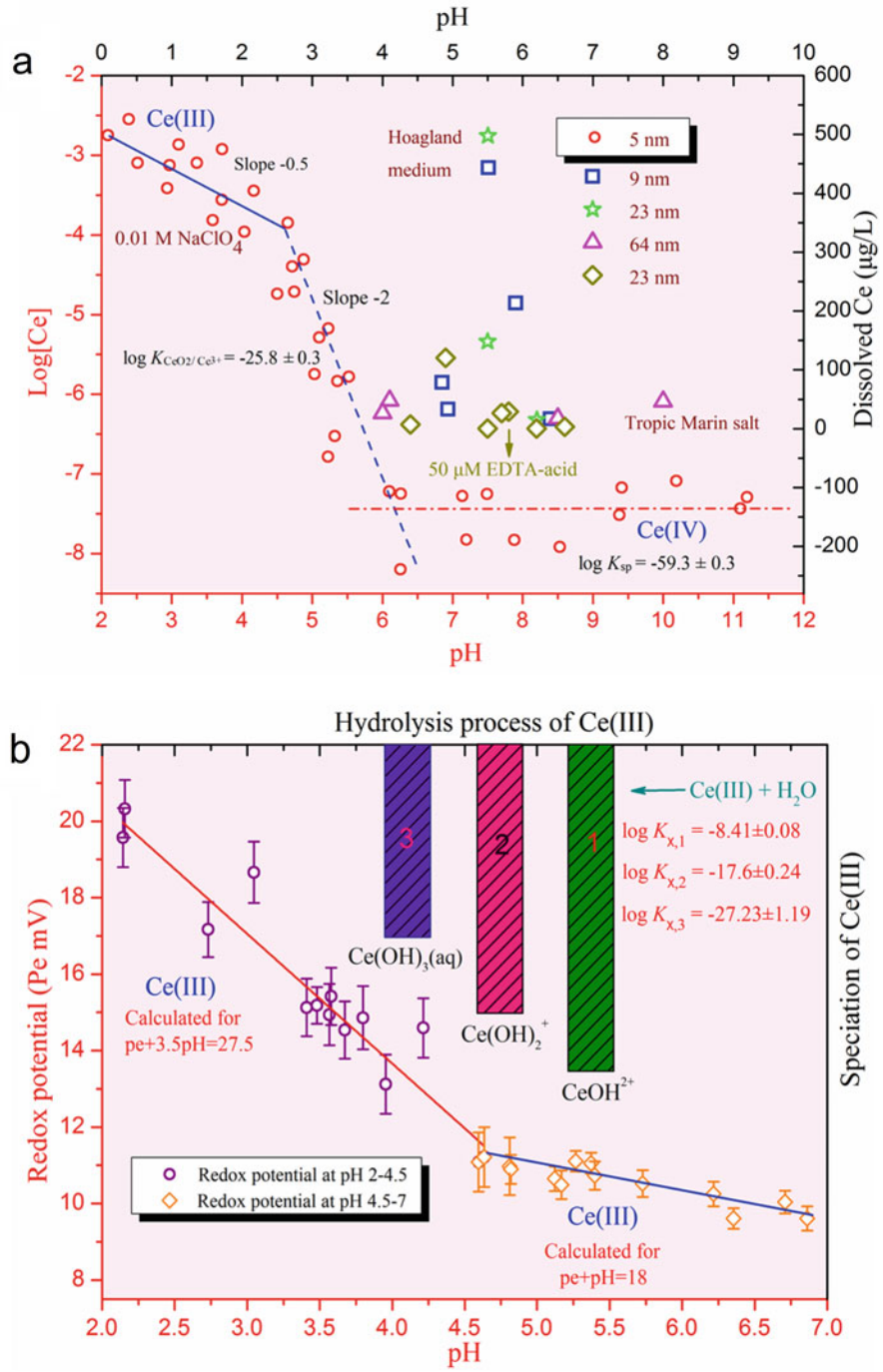

Fig. 4 Panel (**a**) Concentration of dissolved Ce in medium against the pH value. The red circle is related to the left and bottom axis, while other symbols representing CNPs with different size are related to the right and top axis. The corresponding labels like $NaClO_4$ indicate the medium used in

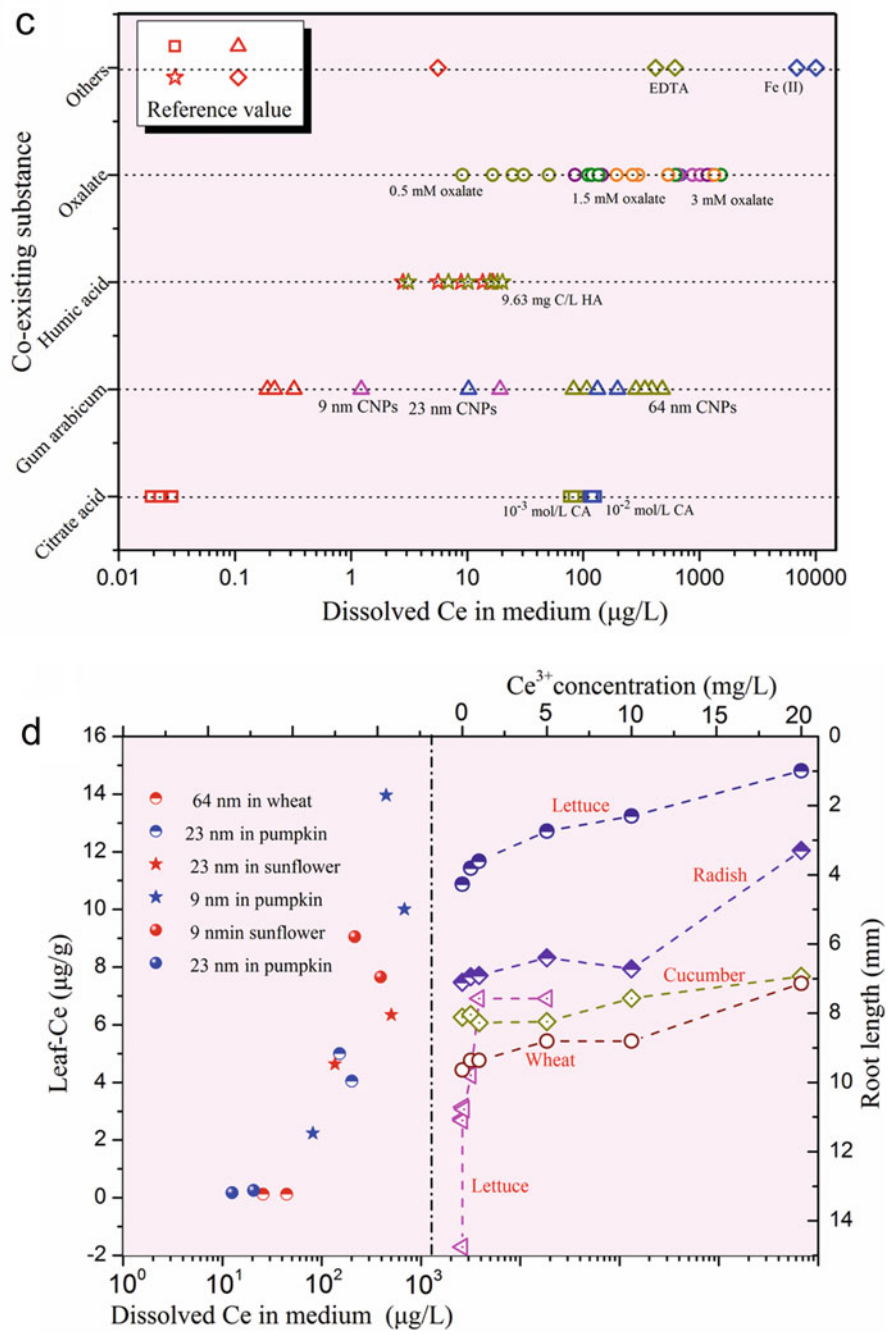

Fig. 4 (continued) individual experiment. The slope –0.5 and –2 is correlated to the blue solid and dotted line. Panel (**b**) The experimental redox potential data collected from pH 2 to 7 and the related Ce^{3+} hydrolysis products. Columns 1, 2, and 3 represent the further hydrolysis products of released Ce^{3+} in solution, with the qualitative analysis of $CeOH^{2+}$ being the most and $Ce(OH)_3$ being the

$$CeO_2 + e^- + 4H^+ \rightarrow Ce^{3+} + 2H_2O \quad (1)$$

with $\log K_{CeO2/Ce}{}^{3+} = \log[Ce^{3+}] + pe + 4pH$. The total trivalent cerium concentration in the solution was calculated as:

$$[Ce(III)]_{total} = \left[Ce^{3+}\right] + \left[CeOH^{2+}\right] + \left[Ce(OH)_2{}^{+}\right] + \left[Ce(OH)_3\right] \quad (2)$$

Upon fitting the data obtained in acidic pH region, the equilibrium constant for reductive dissolution and non-redox dissolution reaction was developed: $\log K_{CeO2/Ce}{}^{3+} = -25.8 \pm 0.3$ and $\log K_{sp} = -59.3 \pm 0.3$ (Lee and Byrne 1992).

Reduction reactions of CNPs and the subsequent valence state transformations from Ce(IV) to Ce(III) have been demonstrated to be toxic to organisms, as previously discussed. Reductive dissolution of CNPs is also an important step in the biotransformation process, which may have been a more favorable reaction to make Ce more bioavailability (Fig. 4d). Schwabe et al. declared that dissolved Ce(III) contributed to uptake of CNPs in different plants (Schwabe et al. 2015). The species-specific toxicity of CNPs to *Lactuca* plants cultured in hydroponic and agar media was associated with the small amount of released Ce(III) ions (Cui et al. 2014; Zhang et al. 2013). Zhang et al. also reported that smaller CNPs with higher reactive activity released more Ce^{3+} ions in plant roots (Zhang et al. 2013), which was in line with the toxicity observations listed in Sect. 2 and Table 1. Importantly, reducibility of CNPs determines their activity in biochemical process (especially activation of ROS and other free radicals like $SO_4^{\cdot-}$ in living cells). Toxicity of Ce(IV) compounds is attributed primarily to high E_H of Ce^{4+} ions and their ability to oxidize biomolecules. The standard E_H of Ce(IV)/Ce(III) (+1.44 V) is much higher than the oxidation potential of the most organic compounds (as an example, for the growth nutrient of Dulbecco's Modified Eagle's Medium, this value ranges from −0.38 to +0.34 V).

Fig. 4 (continued) least. The log*K*x,1, log*K*x,2, and log*K*x,3 are their individual hydrolysis constants. The corresponding slopes of red and blue solid line could be fitted using the linear equations pe + 3.5pH = 27.5 (at $2 \leq pH \leq 4.5$) and pe + pH = 18 ($4.5 < pH \leq 7$). Panel (**c**) Effects of co-existing substance on CNPs dissolution. The red symbols represent the dissolution of CNPs in ultrapure water. The symbols with different shapes and colors represent the influence of the respective co-existing substance marked by the labels in the plot area on CNPs dissolution. Panel (**d**) Concentration of dissolved Ce in medium from CNPs with various diameter against Ce concentration in the leaves of wheat, pumpkin, and sunflower (related to the left and bottom axis) and the root length of head lettuce, cucumber, wheat, and radish treated with Ce^{3+} ions (related to the right and top axis) for 5 days. The Ce content accumulated in the leaf was determined by ICP-MS. Data are cited from Arai and Dahle (2017), Auffan et al. (2017b), Cui et al. (2014), Lee and Byrne (1992), Plakhova et al. (2016), Schwabe et al. (2014, 2015, 2015), Tella et al. (2015), Xu et al. (2018), and Zhang et al. (2013)

4.2 Reaction of Ce with Phosphate

Several researchers have also put forward that the thermodynamically favorable reactions of Ce(IV) and Ce(III) with various (in)organic ligands should be considered, which might interfere with their intrinsic and toxic properties. The high binding affinity of released or exchangeable Ce(III) to P groups has been observed in different contexts, such as formation of cerium phosphate at CNPs surface (Singh et al. 2011), in plants roots (Rui et al. 2015; Zhang et al. 2012), algal cells (van Hoecke et al. 2009), and activated sludge (Barton et al. 2014). Cerium phosphate nucleation on CNPs {111} surface was shown to preferentially affect their surface properties (van Hoecke et al. 2009), redox reactivity (Singh et al. 2011), dissolution rate (Dahle et al. 2015), and further partitioning and retention in soil (Cornelis et al. 2011).

Wang et al. exhibited that DNA, lipids, and various P species (including orthoP, pyroP, sodium trip/trimetaP, and polyP) could tightly adsorb on CNPs surface (Wang et al. 2018a). Li et al. and Jiang et al. also stated that Ce(III) could strip P from lipid bilayer (Li et al. 2014) or react with P released from inside the yeast cells (Jiang et al. 2010), while pretreatment of CNPs with P prevented their biotransformation and thus toxicity (Li et al. 2014). In plants, Ce(III) speciation mostly exhibited as $CePO_4$ in roots, since roots were completely immersed in the nutrient solution and abundant in P (Rui et al. 2015; Zhang et al. 2012, 2017). As most of the released Ce(III) was precipitated as insoluble $CePO_4$ and immobilized in roots, only a small part of Ce(III) may be transported to the other tissues, which directly reduced the bioavailability of CNPs.

Following incubation with phosphate buffer (50 mM), the strong association of Ce(III) with P at the surface of CNPs led to the changes of surface chemistry and thus the redox behavior of CNPs (Singh et al. 2011). Moreover, the readily occurred complexation of P with Ce(III) at the ceria-water interface induced the formation of insoluble surface precipitates, which would effectively suppress the electron transfer reaction and/or further ligand-promoted dissolution (Arai and Dahle 2017; Cornelis et al. 2011). Dahle et al. also illustrated that the chelation of P with exchangeable Ce (III) on CNPs surface in a binary model system could inhibit the dissolution of CNPs (Dahle et al. 2015).

According to Cornelis et al. (2011), both sets of partitioning (K_d) values for Ce (III) and Ce(IV) in soil were positively correlated with cation exchange capacity (CEC). However, due to the low solubility of Ce(III)-P, K_d of Ce(III) was found to be also correlated with the soluble (<0.45 μm) P concentration according to the following equations (Cornelis et al. 2011):

$$\log K_{d,Ce(IV)} = 2.486 + 0.805x \log (CEC) \left(r^2 = 0.55\right) \quad (3)$$

$$\log K_{d,Ce(III)} = 4.126 + 0.726x \log (CEC) + 0.243x \log [P] \left(r^2 = 0.64\right) \quad (4)$$

Also, the presence of P notably lowered the retention (K_r) values of CNPs, since P significantly decreased the charge of natural colloids. The multiple linear regression that best described the variation in K_r values was (Cornelis et al. 2011):

$$\log K_{r,CNPs} = -3.96 + 0.038x(\text{clay}\%) - 0.4262x \log [\text{P}] + 0.3x\text{pH} \left(r^2 = 0.72\right) \quad (5)$$

These three equations clearly indicated that the presence of P alters the chemical stability and dispersion characteristics of CNPs in soils, which theoretically confirmed the interference of P with the reactivity, bioavailability, transformation, and persistence of CNPs.

The researches mentioned above suggest that the solubility of CNPs is controlled by reductive dissolution of Ce(IV)O_2 and then followed by the complexation of P. Notably, cerium-P formation would block the redox cycling between Ce(III)/Ce (IV), showing a good relationship with the toxicity attenuation of CNPs. Therefore, reaction process of ceria with P should be of consideration in protecting the microbial and agricultural ecosystems, since P is ubiquitous in the biochemical and biogeochemical systems.

4.3 Reaction of Ce with Sulfate/S^{2-}

Consistent with the properties of Class B soft metal cations (e.g., Ag, Zn, and Cu), the affinity of Ce ions for electron-dense sulfur molecules makes them highly reactive with both organic and inorganic sulfurs in natural environments. Ionic Ce (IV) has been shown to successively associate with sulfate ion to form $Ce(SO_4)^{2+}$, $Ce(SO_4)_2$, and $Ce(SO_4)_3^{2-}$ (Hardwick and Robertson 1951). The complexation between SO_4^{2-} with Ce(III) has also been previously proposed (Newton and Arcand 2002). Cornelis et al. reported that both ionic Ce(IV) and Ce(III) are expected to form ion pairs with SO_4^{2-}, which further enhances the solubility of CNPs (Cornelis et al. 2011). However, considering the valence state of Ce(IV) and Ce(III) on CNPs surface, whether SO_4^{2-} can directly complex with exchangeable Ce and further disturb their E_H have not been well understood at a fundamental level.

Under reducing conditions, $Ce_2(SO_4)_3$ would be further transformed to Ce_2S_3. Barton et al. illustrated that according to the thermodynamics arguments, the likely Ce(III) phase generated from CNPs would be Ce_2S_3 in anaerobic digesters (Barton et al. 2014). At high free S-bearing gases (H_2S, SO_2, and CS_2) concentrations, sulfidation may directly occur by conversion of released Ce(III) to Ce_2S_3. Previous study showed that the acute toxicity of Ag^+ to microorganisms was reduced in the presence of environmental relevant levels of sulfide (Bianchini et al. 2010). Thus, considering the toxicity-related bioavailability and Ce(III) content, it is expected that CNPs toxicity will be lowered in the presence of sulfide by forming relatively insoluble Ce_2S_3.

Importantly, Ce ions can also bind strongly with organosulfur compounds, with the greatest affinity for thiol-containing ligands. For example, Rollin-Genetet et al. and Han et al. concluded that Ce(IV) atoms present at the surface of CNPs could be reduced to Ce(III) to form stable Ce(III)-disulfide complex following interactions with thiol groups of cysteine (Han et al. 2010; Rollin-Genetet et al. 2015). Similarly, the redox reaction between Ce(IV) and glutathione (GSH) oxidized thiol group to its disulfide counterparts, leading to the formation of Ce(III)GSH (Han and Liu 2010). Moreover, due to the oxidation-reduction potential of Ce(IV)/Ce(III), the formation of Ce(III)-disulfide fluorescent complex would create an oxygen vacancy based on the previously advocated mechanism. Thus, the disulfide bridge formation for thiol-containing biomacromolecules could induce the toxicity of CNPs.

In short, CNPs and their released Ce species would undergo the process of sulfidation. Notably, the sources of sulfur might be wide-ranging, from sulfate to sulfur-bearing gas to organic species and even to metal sulfide minerals having a lower stability than Ce_2S_3 (e.g., ZnS, FeS, CuS, and Ag_2S). Thus, the process of sulfidation in the life cycle of CNPs is of great importance to evaluate their ultimate toxicity and environmental risk.

4.4 Reaction of Ce with Ferrous Ions

Several researchers have demonstrated the thermodynamically favorable reduction of Ce(IV) (aq) by Fe(II) (aq), with the standard E_H of Ce(IV)/Ce(III) being 1.44 V and Fe(III)/Fe(II) being 0.77 V. The Gibbs free energy ranges from −118.5 to −126.19 kJ/mol (Arai and Dahle 2017; Xu and Wang 2012). In Fe(II) solution, the colloidal stability of CNPs was enhanced, due to the redox reactions between Fe (II) and CNPs and thus highly increased zeta potential (Liu et al. 2015). Interfacial redox reactions between CNPs and Fe(II) lead to the generation of six-line ferrihydrite on the CNPs surface, while the dissolved Ce(III) is released from the $Ce(IV)O_2$ surface into the solution (Liu et al. 2015). The adsorption of Fe(II) and precipitation of Fe(III)(hydr)oxides could make CNPs surface more hydrophilic, which would be more stable in the aqueous phase (Azimi et al. 2013). The redox reaction can be described as (Azimi et al. 2013; Liu et al. 2015):

$$\begin{aligned} Ce(IV)O_2 + Fe(II)\ (aq) \rightarrow\ & Ce(IV)O_2 + Ce^{3+}(aq) + Fe(III) \\ & \times (hydr)oxides\ (e.g., ferrihydrite) \end{aligned} \tag{6}$$

Interestingly, when Fe oxides were produced by air oxidation of Fe(II) solution, further formed green rust played a catalytic role in the oxidation of Ce(III) to Ce (IV) by O_2, which was proved to be discrete nanocrystals of $Ce(IV)O_2(s)$ (Nedel et al. 2010). This process can realize the continuously removal of Ce(III) from the solution.

Involved in the series redox reactions, the production of ROS is another issue of consideration. Lu et al. reported that when continued to increase the concentration of Fe(II) from 0.6 mM, greater amount of ·OH was produced by CNPs in the presence of H_2O_2 (Lu et al. 2016). Xu et al. also proposed the generation of ·OH by the reaction of Fe(II) and Ce(III) species with H_2O_2 in the bulk solution (Xu and Wang 2012). Consequently, CNPs exhibited prooxidant activity. Additionally, Ce(III) in CNPs could transmit electrons to the iron oxide, leading to the dissolution and dispersion of Fe(III) and Fe(II) (Wang et al. 2014). This process may further initiate the decomposition of H_2O_2 and eventually produce ·OH (Xu and Wang 2012).

Consequential alterations in the physicochemical properties of CNPs during the redox reactions between CNPs and Fe(II) can further induce the toxicity of CNPs by mediating surface charge, dissolution of Ce(III), and generation of ROS. Besides Fe (II), other redox reactive elements (i.e., Mn^{2+}) or contaminants (i.e., As, Cr, and U) can also be adsorbed on and react with CNPs. These interactions need to be considered when assessing the chemical fate and risk of CNPs in aquatic environments.

5 Toxicity Mechanisms of CNPs Posed on the Organisms

There are several different mechanisms by which CNPs toxicants might inhibit the growth rate of microorganism and plant in terms of cell division, since the very small size of CNPs enables them to interact with biological systems at the subcellular scale (membranes, proteins, or DNA molecules). Direct or physical inhibition involves interaction of CNPs with cell itself or cytomembrane. Indirect or chemical inhibition occurs when CNPs interact with the environment, which can be related to chemical factors or reactions. A combination of these pathways may even be present, as demonstrated in Fig. 5.

5.1 Physical Damage

As highlighted in the literature, the direct adsorption of CNPs onto the cell outer membrane induces strong toxicity, and two mechanisms are probably involved. Firstly, potential toxicity of CNPs could be caused by an interference of the adsorbed CNPs shell with the nutrients reaching the cell surface and transport functions, changing pH or E_H in the external milieu (Rogers et al. 2010; Zeyons et al. 2009). Secondly, upon contact with the cell membrane, the abrasive nature of CNPs was reported to inflict non-specific physical damage. Indeed, when directly adsorbed onto the outer cell membrane, CNPs may modify the viscosity of the membrane, corrupt the specific ionic pumps, and thus strongly alter the transport exchanges of the cell with the media, which interfere with the growth of both microorganisms and plants (Rogers et al. 2010; Thill et al. 2006; van Hoecke et al. 2009; von Moos and Slaveykova 2014).

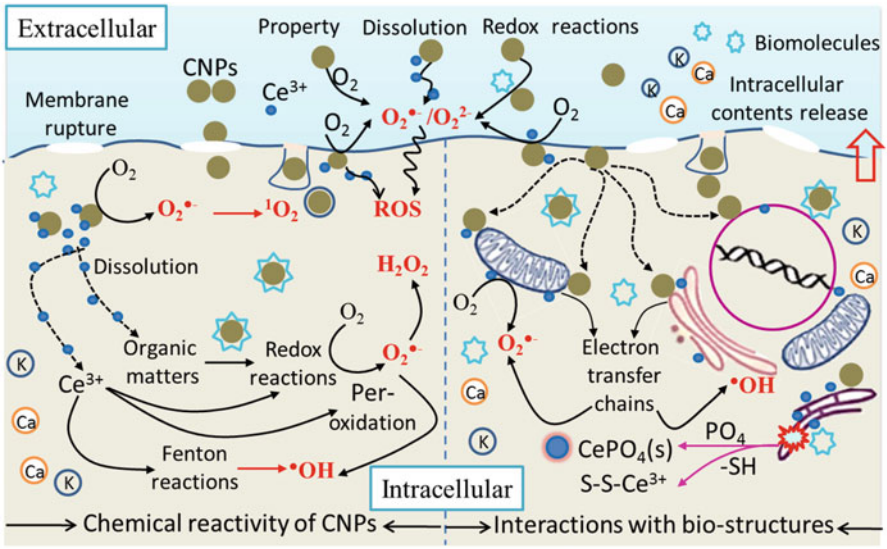

Fig. 5 Illustrations of CNPs toxicity mechanisms via the physical damage (membrane rupture and intracellular contents release) and chemical inhibition (ROS generation and reactions of CNPs with bio-structures). ROS generation can be divided into three parts: (1) the extracellular ROS generation (top) through direct redox reactions with biomembrane/biomolecules, dissolution, and the inherent property of CNPs; (2) intracellular chemical reactivity (left) involves redox cycling between CNPs or leached Ce ions and organic compounds yielding $^{\cdot}OH$, $O_2^{\cdot-}$, and $^1O_2$ through Fenton and per-oxidation reactions; (3) direct redox reactions between CNPs and subcellular structures or biomolecules (including enzymes, protein and nucleic acids) (right) are also known to trigger ROS generation through per-oxidation or electron transfer chain

5.2 *Chemical Inhibition*

The chemical inhibition most likely to take parts in promoting toxicity of CNPs includes the redox chemistry of cerium on the particles or in intracellular cells. The redox chemistry directly leads to the generation of ROS, which is considered damaging to cells, proteins, and DNA (Park et al. 2008b; Rogers et al. 2010; von Moos and Slaveykova 2014; Xu et al. 2018).

5.2.1 ROS Formation on CNPs

The redox properties of CNPs may lead to the reduction of Ce(IV) to Ce(III), which then directly induce ROS production inside CNPs' crystal lattice or engage in the ROS-generating Fenton reactions (Heckert et al. 2008; Huang and Fabris 2007; Li et al. 2012; Preda et al. 2011; von Moos and Slaveykova 2014). For example, Preda et al. confirmed that the interaction of O_2 with the $V_o^{\cdot\cdot}$ at CNPs surface resulted in the

formation of peroxo (O_2^{2-}) and superoxo ($O_2^{\cdot-}$) species (Preda et al. 2011). The process can be further described as:

$$\left[2Ce^{3+}, V_o^{\cdot\cdot}\right] + O_2 \rightarrow \left[2Ce^{4+}, O_2^{2-}\right] \quad (7)$$

$$\left[2Ce^{3+}, V_o^{\cdot\cdot}\right] + O_2 \rightarrow \left[Ce^{4+}, Ce^{3+}, O_2^{\cdot-}\right] \quad (8)$$

Under UV irradiation (365 nm), Li et al. showed that CNPs can generate $O_2^{\cdot-}$ and no $^{\cdot}OH$ was detected, since the E_H for $^{\cdot}OH$ generation (2.2 V at pH 5.6) is higher than the valence band (E_V) of CNPs (1.6 eV) (Li et al. 2012). However, Heckert et al. proposed that in the presence of H_2O_2, Ce(III) on the surface of CNPs is presumed to be an active site and produces $^{\cdot}OH$, behaving similarly to iron in a Fenton-like reaction (Heckert et al. 2008). The redox evolution at CNPs surface and generation of ROS species were therefore reported to pose oxidative damage to biomolecules in the surrounding medium (Park et al. 2008b). According to the current understanding, it is reasonable to say that the toxicity of CNPs is likely related to the catalytic properties and ensuing redox reactions in aquatic or biological media. However, the correlation successfully linking the physicochemical properties and ROS generation of CNPs needs to be further explored, which would provide guidance for the design of safe and environmentally benign CNPs.

5.2.2 ROS Generation in Intracellular Portions

At the nano-bio interface, physical interactions of CNPs with cellular structures can also lead to the formation of $^{\cdot}OH$, $O_2^{\cdot-}$, or $^1O_2$. The detections and observations of these ROS species have been demonstrated for CNPs in *E coil.*, wastewater biofilm, *Corophium volutator*, RLE-6TN rat cells, and lettuce, for instance (Dogra et al. 2015; Dunnick et al. 2015; Thill et al. 2006; Xu et al. 2018; Zhao et al. 2017). Consequently, these three types of ROS contribute to the major oxidative stress in biological system (Li et al. 2012). Furthermore, in the intracellular part, the negatively charged cell membrane, DNA and RNA attract metal cations to its polyanionic surface and therefore favor the production of $^{\cdot}OH$ by Fenton reactions (von Moos and Slaveykova 2014). Generally, $^{\cdot}OH$ is the major ROS generated in the CNPs exposed organisms, mediating DNA damage and polysaccharide cleaving (Xu et al. 2018; Zhao et al. 2017).

Regarding the induction of ROS by CNPs in cells, there is no clear explanation to date of the mechanisms involved. In the biotic system, a number of factors may trigger the redox-type reactions and ultimately ROS generation, such as reactions of CNPs with inorganic, organic, and liquid-phase ligands. Proposed mechanisms for in vivo ROS production from CNPs is displayed in the equations below (Brunet et al. 2009; Li et al. 2012; von Moos and Slaveykova 2014; Zhao et al. 2012b):

$$\mathrm{Ce(IV) + X_{red}}^{-} \rightarrow \mathrm{Ce(III) + X_{ox}} \quad (9)$$

$$\mathrm{Ce(III) + O_2 \rightarrow Ce(IV) + {O_2}^{\cdot -}} \quad (10)$$

$$\mathrm{2H^+ + 2{O_2}^{\cdot -} \rightarrow {}^1O_2 + H_2O_2} \quad (11)$$

$$\mathrm{H_2O_2 + Ce(III) \rightarrow Ce(IV) + OH^- + {}^{\cdot}OH} \quad (12)$$

$$\mathrm{LOOH + Ce(III) \rightarrow Ce(IV) + LO^{\cdot} + {}^{\cdot}OH} \quad (13)$$

where $\mathrm{X_{red}}^{-}$ refers to physiologically relevant reductant, $\mathrm{X_{ox}}$ is their oxidative state, and LOOH is alkoxyl radicals from lipid peroxidation. Further studies focusing on the site of catalysis by CNPs and untangling the molar ratio of the products might be helpful to elucidate the mechanisms involved. Moreover, the systematic study on subtle cellular alternations in the redox balance may also help to further fill the knowledge gaps by illustrating the mechanisms of action of ROS at the molecular level.

5.2.3 Distinct Types of Chemical Reactions

The chemical reactions of CNPs with biologically relevant molecules are of key importance to reflect the lethal mechanisms of CNPs. Firstly, it was demonstrated that CNPs led to biotic P complexation and resulted in organelle damage, because of stripping of P from the surrounding lipid bilayer (Li et al. 2014). The ability of CNPs to cleave the P ester bond in *p*-nitrophenyl P, adenosine triphosphate (ATP), and *o*-phospho-*L*-tyrosine was also illustrated (Kuchma et al. 2010). Secondly, the favorable interactions between CNPs and the electroactive substances in biological system lead to the toxicity of CNPs. For instance, the representative redox state of disulfide bonds of biomolecules (the intracellular protein metallothioneins and cysteine/disulfide redox control system) was reported to be oxidized and decomposed (Han et al. 2010; Rollin-Genetet et al. 2015). Thirdly, the biological activity of Ce(III) compounds is likely dictated by proximity of the ionic radii of $\mathrm{Ce^{3+}}$ and $\mathrm{Ca^{2+}}$ ions (1.01 and 1.00 Å, respectively). Consequently, $\mathrm{Ca^{2+}}$ might be partially replaced by $\mathrm{Ce^{3+}}$ in $\mathrm{Ca^{2+}}$-dependent proteins (Arai and Dahle 2017; Plakhova et al. 2016). As a result, the reduced Ce(III) in vivo leads to disruption of cell signaling pathways, cellular homeostasis, and thus cell inactivation (Horie et al. 2011).

6 Challenges and Perspectives

In this review, the latest knowledge about the physicochemical properties and environmental transformations of CNPs when addressing their toxicity and environmental risks are discussed and summarized. Although incipient surface chemistry of

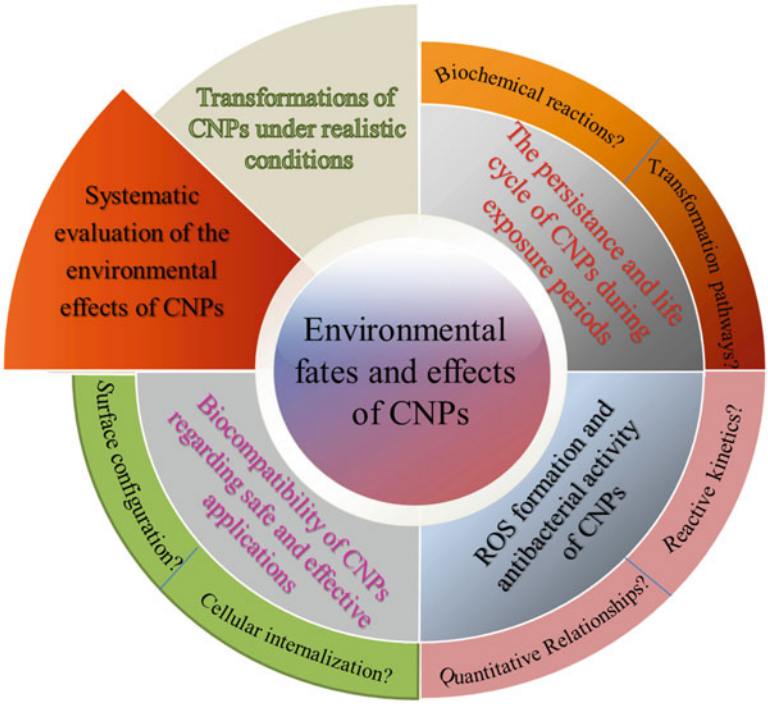

Fig. 6 Suggestions for future research challenges and priorities of the environmental fates and effects of CNPs. The questions in outer circle are urgently to be clarified to fill the knowledge gaps in the inner circle

CNPs has a profound influence on their toxicity, environmental transformations might decrease the effects of initial chemical conditions and render lower or higher toxic. Though knowledge about how CNPs transformations influence their toxicity are expanding, several research gaps and challenges important for better predicting the environmental fate and effects of CNPs need to be addressed. Specially, several critical research needs are generalized in Fig. 6.

6.1 Determining the Current States and Effects of CNPs in the Environment

Advanced analysis of the physical and chemical characteristics of CNPs under realistic environmental conditions will continue to be essential in discovering the relationship between their morphology, size, composition and their aggregation, reactive kinetics, and toxicity. Since the experimental model and related exposure conditions could influence the environmental transformation, translocation, and thus toxicity of CNPs (Ganguly et al. 2018; Rogers et al. 2010; van Hoecke et al. 2009),

researches are required to better track the rate and extent of CNPs transformations under realistic conditions, especially for illustrating the co-occurred multiple transformations. Completely understanding the diverse transformations of CNPs in the environment requires the ability to recover the products from environmental or biological matrices. Then, measuring the properties of these partially transformed CNPs or characterizing them in vivo/in situ is necessary. Additionally, scarcely any information is presently known about the toxicology under the relevant conditions regarding long-term exposure to low CNPs doses, which is necessary for better revealing the current effects of CNPs on the environment.

6.2 *Identifying the Toxicological Risk Factors of CNPs*

It has been widely known that ROS generation is closely related to the inhibition effects of CNPs (Park et al. 2008b; Rogers et al. 2010; von Moos and Slaveykova 2014; Xu et al. 2018). However, the information about the quantitative relationships between ROS formation and the toxicity effects of CNPs for rapid toxicological screening prior to in vivo testing is lacking. On the other hand, the possibility of changes in CNPs reactivity and biological molecules after their contacts has been examined (Li et al. 2014; Rollin-Genetet et al. 2015); thus further studies on kinetics and biochemical interactions of CNPs within organisms are imperative. These studies should include research on CNPs transformation pathways, interactions with cells, the receptors and signaling pathways involved, cytotoxicity, and surface functionalization for an effective cellular phagocytosis or internalization. Then, sufficient information to identify the toxicological risk factors including genotoxicity, induction of cell transformation, and also how the various physicochemical properties or biochemical reactions affect CNPs toxicity is critical. In order to clarify the risk factors mentioned above, nanoscale characterization techniques should be introduced to a larger extent to identify CNPs at intracellular sites in affected cells or tissues and to further establish the pertinent interaction mechanisms.

6.3 *Characterizing and Identifying the Potentially Safe Applications of CNPs in the Future*

Another important research topic to be pursued is to reduce the toxicological profiles of CNPs and maintain the functional properties of the core materials. According to the existing data discussed above, the anti- and prooxidant activity of CNPs depends on their physicochemical properties, reactive activity, and extent of cellular internalization. Thus, to avoid the environmental toxicity of CNPs, surface modification and configuration should be considered in the synthesis process to hinder the interactions between CNPs with biomolecules and other chemicals within

organisms. It will be essential to introduce the structural and reactivity data derived from material science and toxicology studies to the safer design of CNPs in the future. Knowledge about the fundamental characteristics of CNPs and ceria-based material, new characterization techniques, and powerful theoretical methods need to be developed to help us predict the biocompatibility of CNPs regarding safe and effective applications in nanotechnology. Moreover, research should be directed toward finding ways to decrease CNPs toxicity (such as antioxidants provided by dietary source and supplements, metal chelators, passivators).

7 Conclusion

In the present study, the important transformations of CNPs that need to be considered when addressing their environmental and ecological effects are discussed and summarized. The surface properties are crucial in understanding the environmental behavior of CNPs in relation to their stability against agglomeration, mobility, reactivity, and toxicity. The phase transformations of CNPs metallic core with (in) organic compounds in different environmental scenarios significantly influence their fate, transport, interactions with organisms, and consequence of bioaccumulation and toxicity. The roles of surface properties and environmental transformations of CNPs in the likelihood of toxicity mechanisms are further explored based on the physical damage and chemical inhibition. Finally, important questions and research directions in terms of identifying the toxicological risk factors and safer applications of CNPs are highlighted. Overall, the findings characterizing and predicting the environmental transformations and risks from manufactured CNPs should increase our awareness of CNPs pollution. With increased knowledge and ongoing study, we are urged to find strategies for mitigating the toxicities associated with CNPs exposure. More important, we should foresee a future with better-informed and, hopefully, more cautions manipulation for safe design and application of CNPs.

8 Summary

Increasing production and utilization of cerium oxide nanoparticles (CNPs) in recent years have raised wide concerns about their biotoxicity. Numerous studies have been conducted to reveal the toxicity of CNPs, but the results are sometimes contradictory. In this review, the most important factors in mediating CNPs toxicity are discussed, including:

1. the roles of physicochemical properties (size, morphology, aggregation condition, surface charge, coating, and surface valence state) on CNPs toxicity;
2. the phase transfer and transformation process of CNPs in various aqueous, terrestrial, and airborne environments;

3. the reductive dissolution and chemical reactions of CNPs core with phosphate, sulfate/S^{2-}, and ferrous ions.

Physicochemical properties of CNPs play key roles in their environmental transformations and consequently their interactions with organisms, reactivity, and toxicity assessment. Also, the speciation transformations of CNPs caused by reactions with (in)organic ligands in both environmental and biological systems would further alter their fate, transport, and toxicity potential. Thus, the toxicity mechanisms of CNPs are proposed based on the physical damage of direct adsorption of CNPs onto the cell membrane and chemical inhibition (including oxidative stress and interaction of CNPs with biomacromolecules). Finally, the current knowledge gaps and further research needs in identifying the toxicological risk factors of CNPs under realistic environmental conditions are highlighted, which might improve predictions about their potential environmental influences. This review aims to provide new insights into cost-effectiveness of control options and management practices to prevent environmental risks from CNPs exposure.

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Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Correction to: Feeding Behavioural Studies with Freshwater *Gammarus* spp.: The Importance of a Standardised Methodology

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Correction to:
Chapter "Feeding Behavioural Studies with Freshwater *Gammarus* spp.: The Importance of a Standardised Methodology"
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The original version of the chapter was inadvertently published with a couple of fundamental mistakes in the Conclusion section on page 36. The sentences on the 5th line from the top of page 36 should read as

"The authors recommend that the position of the constant is dependent on when the leaves are conditioned and dried. If the leaves are conditioned after being dried and weighed, the constant should multiply with the initial dry weight, so that it takes into consideration that the leaf disc might have lost more weight through being submerged in water during the experiment. However, if the leaf discs are dried and weighed after being conditioned, the final dry weight should be divided by the constant, because some of the leaf material might have been lost through leaching and not through Gammarid feeding."

The original article was corrected.

The updated version of this chapter can be found at
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