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REVIEW ARTICLE

Heavy Metal Pollutants and Chemical Ecology: Exploring New Frontiers

Robert S. Boyd

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Abstract Heavy metals are an important class of pollutants with both lethal and sublethal effects on organisms. The latter are receiving increased attention, as these may have harmful ecological outcomes. For example, recent explorations of heavy metals in freshwater habitats reveal that they can modify chemical communication between individuals, resulting in "info-disruption" that can impact ecological relationships within and between species. Info-disruption can affect animal behavior and social structure, which in turn can modify both intraspecies and interspecies interactions. In terrestrial habitats, info-disruption by metals is not well studied, but recent demonstrations of chemical signaling between plants via both roots and volatile organic molecules provide potential opportunities for info-disruption. Metals in terrestrial habitats also can form elemental plant defenses, in which they can defend a plant against natural enemies. For example, hyperaccumulation of metals by terrestrial plants has been shown to provide defensive benefits, although in almost all known cases the metals are not anthropogenic pollutants but are naturally present in soils inhabited by these plants. Info-disruption among microbes is another arena in which metal pollutants may have ecological effects, as recent discoveries regarding quorum sensing in bacteria provide an avenue for metals to affect interactions among bacteria or between bacteria and other organisms. Metal pollutants also may influence immune responses of organisms, and thus affect pathogen/host relationships. Immunomodulation (modification of immune system function) has been tied to some metal pollutants, although specific metals may boost or reduce immune system function depending on dose. Finally, the study of metal pollutants is complicated by their frequent occurrence as mixtures, either with other metals or with organic pollutants. Most studies of metal pollutants focus on single metals and therefore oversimplify complex field conditions. Study of pollutant impacts on chemical ecology also are difficult due to the necessity of studying effects at varying ecological scales: "dynamic scaling" of chemical ecology studies is rarely done completely. It is clear that much remains to be learned about how heavy metal pollution impacts organisms, and that exciting new research frontiers are available for experimental exploration.

Keywords Behavior · Elemental defense · Heavy metals · Immunomodulation · Information disruption · Infochemical effect · Pollution · Quorum sensing

Introduction

Humanity's ability to mine and use metals has played a major role in development of modern human society (Wilson 1996). Many metals have a wide range of uses, but these have come at a significant environmental price: some (generally called heavy metals) have serious negative environmental consequences, yet our dependence on them continues to result in large inputs into our environment (Han et al. 2002). Heavy metals are an important category of pollutants and as such have major detrimental impacts on both human health (Duruibe et al. 2007) and the health of terrestrial and aquatic communities and ecosystems (Sánchez 2008). A number of metals have been included in the term "heavy metal," but the term has not been used consistently in the literature (Sánchez 2008). The primary focus here will be on those commonly

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R. S. Boyd (✉)
101 Life Sciences Building, Department of Biological Sciences,
Auburn University,
Auburn, AL 36849-5407, USA
e-mail: boydrob@auburn.edu

studied as pollutants (Han et al. 2002), including Cd, Cu, Cr, Hg, Pb, Ni, and Zn.

Much research on heavy metal pollutants has focused on their direct negative effects on organisms. These direct effects stem from the general toxicity of heavy metals to a variety of biological processes. The negative effects often result in serious toxicological symptoms, including mortality. These effects are generally dose-dependent, but some heavy metals are required in relatively small amounts as micronutrients for many organisms, so that low doses can have positive direct effects (Lefcort et al. 2008). In addition to direct effects, pollutants may have indirect effects through their impact on the structure of food webs in communities (Fleeger et al. 2003). For example, Lefcort et al. (2002) reported that snails in a heavy metal-polluted lake were less sensitive to the metals than their internal parasites, so that parasite loads were markedly reduced in the polluted lake and this resulted in greater abundance of the snail. In another example, Stepanauskas et al. (2006) dosed freshwater microcosms with a range of Cd or Ni concentrations and found that bacterioplankton densities increased at very low metal concentrations. They explained this effect as a consequence of low metal doses suppressing growth of bacteriovore eukaryotes. There are many cases in which organisms differ in susceptibility to pollutants, and hence community structure is altered in polluted locations by both direct and indirect effects.

Recently, there has been recognition that serious sublethal direct effects of many pollutants (including heavy metals) can occur. These may have subtle impacts on species performance that in turn can lead to important indirect effects. “Info-disruption” is a recently defined category of sublethal direct effect (Lürling and Scheffer 2007) in which a pollutant interferes with the chemical communication networks that inform organisms about their biotic and abiotic environments. For example, a review by Lürling and Scheffer (2007) described the importance of the “smellscape” to organisms and how pollutants can alter their perception of it. Klaschka (2008) referred to info-disruption as the “infochemical effect” and provided an additional recent review of this burgeoning field. Klaschka (2008) points out that the ecological importance of info-disruption, in both laboratory and field studies, is greater than was previously believed. Both these reviews broadly illustrate how anthropogenic pollutants (including heavy metals) can affect organismal ecology and summarize recent advances in this area.

This mini-review is not intended to comprehensively cover the literature regarding all heavy metals and their ecological effects. Instead, I seek to extract from recent literature concepts regarding the biological effects of metal pollutants that might be of interest to chemical ecologists. My emphasis is in illustrating these concepts to demonstrate their potential ecological importance and as a stimulus for additional research. Because most of the research regarding info-disruption by pollutants has emerged from studies in freshwater aquatic systems (Lürling and Scheffer 2007; Klaschka 2008), those systems will be the starting place for this review. From there, I will move to terrestrial systems and examine how concepts being developed from aquatic systems might apply to relationships in terrestrial habitats. Then, I will summarize some of the recent excitement in microbiology regarding chemical communication (and potential social organization) in bacteria, thus illustrating the potential for heavy metals to impact these aspects of microbial biology and touching upon two other metal/microbial issues of great recent interest, antibiotic resistance and immunomodulation. Finally, I will review briefly some other issues that complicate our understanding of heavy metal pollutant effects on organisms and communities (including impacts of multiple pollutants, and how issues of scale add complexity to ecological studies), and conclude with a few considerations of future research directions.

Heavy Metals in Aquatic Communities

Heavy Metals and Predator/Prey Relationships Perhaps the most active research area regarding info-disruption by heavy metals in aquatic communities deals with the effects of metals on predator/prey interactions. The concern is that heavy metals can influence predator/prey interactions by degrading the ability of prey to respond to predators, ultimately resulting in decreased prey population sizes due to increased predator success (McPherson et al. 2004). Another reason for the interest in heavy metals and behavior in aquatic communities is that heavy metals may have behavioral effects at concentrations much less than at which they have lethal effects (Scott and Sloman 2004), suggesting that regulatory pollution limits based upon standard toxicological studies may be too high to prevent damage to aquatic communities through these sublethal behavioral effects. This realization has led to calls for increased integration of behavioral studies into ecotoxicological investigations (e.g., Clotfelter et al. 2004; Klaschka 2008).

With regard to predator/prey relations, a number of investigations have shown decreased ability of fish exposed to heavy metals to respond to skin extracts, which can serve as an alarm signal for prey species (Smith 1992; Kats and Dill 1998). Heavy metal pollutants for which these effects have been shown include Cu (Carreau and Pyle 2005; Pyle and Mirza 2007), Cd (Honda et al. 2008; Kusch et al. 2008), and Hg (Smith and Weiss 1997). Some studies have taken these investigations into the field to show that fish in metal-contaminated lakes respond differently from fish in uncontaminated lakes. For example, McPherson et al. (2004) showed that prey fish in a Ni/Zn contaminated lake did not respond to skin extract of another prey species, whereas prey fish in an uncontaminated lake did. In other cases, fish from polluted and uncontaminated lakes have been brought into the laboratory for comparison of responses to skin extracts. Mirza et al. (2009) studied wild yellow perch (*Perca flavescens*) from a lake contaminated by a mixture of heavy metals (mainly Cu, Ni, and Zn), finding that the fish from the contaminated lake did not respond to a chemical alarm cue whereas those from an uncontaminated lake did.

Although the studies referred to above have focused upon ability of prey to detect and avoid predators, heavy metals may affect mechanisms other than escape behavior that are used by prey to avoid predation. For example, the bioluminescence ability of some marine organisms (or the presence of bioluminescent organisms as symbionts in hosts) is thought to be an anti-predator behavior (Buskey and Swift 1983; Jones and Nishiguchi 2004; Cronin 2005), and there is evidence that heavy metal pollution can affect bioluminescence ability. For example, Deheyn et al. (2000) collected individuals of an echinoderm, the brittle star *Amphipholis squamata*, along a heavy metal (Cd, Cu, Fe, Pb, Zn) gradient in a polluted bay in Spain. Those from the most polluted area had less intense and more slowly generated bioluminescence responses, and bioluminescence responses of individuals transferred from a less- to a more-polluted area became weaker and slower. The authors suggest that, since light production is a defense for some bioluminescent organisms, this defense would be less effective for this species in polluted areas. Bioluminescence of marine organisms also may play a role in mate attraction (Deheyn and Latz 2009) or attraction of prey (Cronin 2005), so that interference with bioluminescence by heavy metals may impact other organismal interactions.

While most studies show that info-disruption can result in lowered defensive ability and thus increased predation, info-disruption may act to enhance predator defense in some cases. I know of no case involving heavy metals in which prey defense against predation is enhanced by a metal pollutant, but Lürling (2006) reported that an organic pollutant (the surfactant FFD-6) affects a green alga (*Scenedesmus obliquus*) in a way that mimics effects of predator compounds that stimulate an anti-predator trait (formation of relatively large colonies of cells). Presumably, algal cells in the larger colonies formed in a polluted lake would be less susceptible to predation by zooplankton (Lass and Spaak 2003). Info-disruption also may benefit prey by negatively affecting predator search ability. For example, Smith and Weiss (1997) studied effects of Hg pollution on the behavior of mummichogs (*Fundulus heteroclitus*), a tidal creek fish that preys upon invertebrates but in turn is preyed upon by blue crabs (*Callinectes sapidus*). Fish from a polluted site attempted to capture prey less frequently than those from an unpolluted site, and the polluted site fish also were more likely to be captured by blue crabs. Although the effects of Hg were not shown to be due to info-disruption (rather than other sublethal effects), these results suggest that the net result of info-disruption will depend on the suite of species involved, their sensitivities to the pollutant, etc.

Another way by which a heavy metal can affect an organism negatively is for the metal to prevent that organism from detecting and avoiding areas that contain toxic heavy metal concentrations. Hansen et al. (1999a) found that low levels of Cu can damage olfaction in Chinook salmon (*Oncorhynchus tshawytscha)* and rainbow trout (*Oncorhynchus mykiss*), and fish actively avoided Cu-contaminated water. However, if fish were exposed to sublethal Cu levels that damaged their olfactory abilities, they were unable to detect waters containing lethally high Cu concentrations, thus suggesting that exposure to low levels of metal pollutants may result in mortality if fish are later exposed to greater concentrations.

Although I have emphasized studies of fish behavior in the previous sections, studies of invertebrates have shown heavy metal effects on their behavior as well. For example, Vuori (1994) concluded that sublethal concentrations of Cd changed behavior of caddisfly larvae. Larvae exposed to low (12 μg/L) Cd were less aggressive in intraspecific encounters, and behavior of both intruder and resident larvae that had been exposed to this low concentration of Cd differed from that of larvae not exposed to Cd. In a second example, Michels et al. (2000) showed that sublethal doses of Cd affected the phototactic behavior of the crustacean *Daphnia magna*. A recent review of chemically-induced predator defenses in plankton summarized a number of cases of behavioral predator defenses present in this invertebrate group (Lass and Spaak 2003), illustrating the potential for heavy metals to impact these and thus affect ecological relationships.

To this point I have discussed how heavy metals may influence predator/prey interactions via info-disruption, by affecting the ability of prey to detect predators or vice versa. Heavy metals may influence predator/prey interactions in ways other than through their effects on behavior, such as through effects on physical defenses. Physical defense (involving a change in morphology) is common in plankton (Lass and Spaak 2003), and a number of studies have reported morphological reactions of plankton species to the presence of predator kairomones. For example, *Daphnia* produce neckteeth that reduce the rate of predation by *Chaoborus* midge larvae (Parejko 1991). Mirza and Pyle (2009) reported that low levels of Cu (10 μg/L) interfered with ability of *Daphnia* to respond to the *Chaoborus* midge kairomone that induces neckteeth formation. *Daphnia* exposed to Cu and kairomone had fewer and smaller neckteeth than those exposed to kairomone alone. These less well-defended offspring had lower survival when exposed to predators (*Chaoborus* midge larvae).

Heavy Metal Effects on Social Structure and Reproductive Behavior The effects of heavy metals on an animal species are likely complex, and one of the factors that can add to that complexity is the social structure of the organism(s) involved. Social structure is important in many organisms, especially vertebrates such as fish, and a recent review by Sloman (2007) of trace heavy metal effects on salmonid fish social hierarchies illustrates how sociality can influence pollutant effects on species. Her review shows that social status can change the physiology of an individual and, as a result, its susceptibility to pollutants. Furthermore, uptake may vary among heavy metals depending upon the physiological effects of a fish's social status. For example, she reported that dominant fish accumulated less Cu (Sloman et al. 2002; Sloman 2007) whereas studies of Cd showed that dominant fish accumulated more Cd (Sloman et al. 2003). In this case, the specific effect may depend on the mechanism by which the heavy metal is taken up by cells. Copper is taken up via Na transport pathways (Sloman et al. 2002), and subordinate fish have increased Na uptake due to increased social stress (Sloman et al. 2004). On the other hand, Cd crosses gills via Ca transport pathways (Sloman 2007). If dominant fish take up more Ca to support the higher growth rates that result from their social position, then Cd uptake may be greater than for subordinate fish (Sloman et al. 2003). In addition to an impact of hierarchical position on metal effects, heavy metal pollutants also can affect social hierarchy formation itself (Sloman 2007). For example, Sloman et al. (2003) showed that rainbow trout exposed to Cd formed social hierarchies more quickly. The reason for this more rapid hierarchy formation was unclear, as Cd both increased fish growth rate and also damaged olfactory sensing cells. Interestingly, waterborne Cu (Sloman et al. 2002) or Cd (Sloman et al. 2003) did not affect hierarchies that had been formed in fish populations prior to exposure to the heavy metals.

The route of exposure of a heavy metal may determine if social structure will affect metal concentration in a fish species (Sloman 2007). For example, if exposure is dietary rather than waterborne, then a fish's social status and a contaminated food item's perceived value may influence metal intake. This could occur if a dominant individual that monopolizes a prized but contaminated food source receives an increased dose, whereas a subordinate forced to eat less prized but less contaminated foods will have lesser exposure. This scenario suggests an interesting possibility for accelerated social turnover, where dominants are harmed by diet, become less aggressive and/or are less healthy, and are replaced by subordinates, which in turn become harmed, etc.

Reproductive behaviors are another arena in which heavy metals may exert negative effects on aquatic species. The above information regarding chemical cue detection and social hierarchies illustrates two ways in which metals may affect reproductive behaviors, since reproduction in aquatic animals often involves chemical cues (Paul and Ritson-Williams 2008) and may involve social hierarchies (Sloman 2007). However, heavy metals also may directly affect gamete interactions, as illustrated by a study of the effects of Cu on fertilization of eggs of an intertidal polychaete, *Galeolaria caespitosa* (Hollows et al. 2007). This worm is a broadcast spawner, so that the sperm are diluted rapidly over distance. Laboratory tests showed that Cu had stronger effects on fertilization at low sperm concentrations than at high ones. The authors also took their study into the field, finding that Cu also reduced fertilization success there. They concluded that eggs needed to be much closer to a sperm source in the presence of Cu for successful fertilization to occur in the field. Relatively sedentary aquatic species may require a minimum population density to be reproductively successful. This is an example of an Allee effect in population ecology, broadly defined as a positive relationship between individual fitness and population size or density (Stephens et al. 1999). Hollows et al. (2007) point out that their research on *Galeolaria caespitosa* shows that Cu pollution can magnify an Allee effect: the negative effect of Cu on fertilization success means that successful fertilization will occur at greater population densities than when Cu pollution is absent. Given that Allee effects are increasingly recognized as important in ecology and conservation biology (e.g., Levitan and McGovern 2005; Liu et al. 2008), potential effects of metal pollutants on reproductive processes deserve more investigation.

Mode of Action of Heavy Metals Reports of the effects of heavy metals on behavior have stimulated researchers to investigate the mechanisms by which those effects operate. Some studies of fish suggest that heavy metals directly damage sensing cells in the olfactory epithelium (e.g., Hansen et al. 1999b), but in some cases fish that return to unpolluted conditions recover their olfactory function (e.g., Beyers and Farmer 2001; Baldwin et al. 2003; Sandahl et al. 2006), depending on the degree and extent of exposure to the metals. More recent research has revealed cases of lasting damage from short-term embryonic exposure. For example, Carreau and Pyle (2005) showed that short (5–7 days) embryonic exposure of fathead minnows (*Pimephales promelas*) to Cu caused decreased olfactory function several months after they were removed from Cu-contaminated conditions. A study by Blechinger et al. (2007), using embryos of zebrafish (*Danio rerio*) exposed for 3 hr to Cd, documented olfactory cell death, the effects of which decreased olfactory ability 4–6 weeks later.

Besides direct effects on sensing cells, there is an additional pathway by which heavy metal pollutants can interfere with fish senses. As summarized by Sloman (2007), certain metals (Cd, Hg, Ni, Mn) can be transported along nerves into more central portions of the nervous system and can exert disruptive effects there. Therefore, the examination of the olfactory epithelium for damage to detect olfactory impairment may not reveal functional failure. For example, Mirza et al. (2009) studied yellow perch from unpolluted and metal-contaminated lakes in Canada. They found that fish from the contaminated lakes had functional olfactory epithelium, but failed to respond to chemical alarm cues. They hypothesized that heavy metals of these chronically exposed fish may be accumulating in signal generating olfactory cells and interfering with signal processing rather than signal reception.

Heavy Metals as Elemental Defenses It also is possible that heavy metals have a direct chemical defense function. In general, studies of chemical defense in both marine (summarized in Pawlik 1993; Hay 1996) and terrestrial (summarized in Dearing et al. 2005; Schowalter 2006) environments have focused on the tremendous variety of organic chemicals (termed secondary chemicals) that are produced by organisms and that protect them from natural enemies. Elemental defense, a concept that has emerged mainly from studies of some terrestrial systems (see terrestrial system section below), suggests that certain elements present at high concentrations in an organism's tissues may protect it from natural enemies (Boyd 2004). In general, elemental defenses differ from secondary chemicals because they are not carbon-based structures synthesized via the metabolic pathways that generate secondary chemical defenses but instead are based upon other elements absorbed from the environment (Martens and Boyd 1994).

Elemental defense by heavy metals has been suggested in a few instances from studies in marine environments. For example, Capon et al. (1993) reported extremely high concentrations of Cd and Zn in an Antarctic marine sponge (*Tedania charcoti*) and demonstrated that those concentrations were capable of antibacterial effects. A recent survey of Antarctic sea spiders (Pycnogonida) found high levels of Cd, Cu, Ni, or Zn in some samples (Jöst and Zauke 2008): the authors suggested that the high Ni levels in some samples (up to 200 mg/kg on a dry mass basis) may have defensive effects, although no experimental investigation was done. In another example, Pawlik (1993) suggested that some tunicates that contain high levels of metals (notably V, but also Cr, Fe, Mg, Mn, Mo, and Ti) may be protected by those elements. In particular, feeding experiments with V (Stoecker 1980) showed that artificial food amended with V was less palatable to two species of representative generalist marine predators. Recently, Odate and Pawlik (2007) tested whether the high V concentration in a marine tunicate has a defensive effect. They were unable to confirm that V in the form present in the tunicate was defensively active, and suspected that low tissue pH was the primary chemical defense in the case they examined. Thus, unlike in terrestrial systems, there currently is little evidence that heavy metals (including metal pollutants) have defensive effects in marine systems. The topic, however, is not well explored.

Heavy Metals in Terrestrial Communities

Heavy Metals and Plant Behavior/Communication Whereas the literature from aquatic (particularly freshwater) communities suggests heavy metals may be important info-disruptors, similar effects have not been reported from terrestrial communities. This may be due to fundamental differences between aquatic and terrestrial habitats (Zimmer and Zimmer 2008): for example, heavy metals in above-ground terrestrial communities generally are not suspended in the medium (air) in high concentrations, whereas heavy metals in polluted aquatic communities usually are dissolved in the medium that bathes those organisms. On the other hand, effects of some heavy metals (e.g, Hg and Pb) on the nervous systems of terrestrial animals are well known, and these can include effects on behavior (Duruibe et al. 2007), illustrating a potential for heavy metal effects on terrestrial animal behavior.

The lack of information on heavy metal info-disruption in terrestrial communities might also stem from a lack of investigation. For example, the section above on effects of metals on aquatic animal behavior brings up the question of whether metals in soil might affect plant root behavior. Whether plants "behave" in a way that is analogous to animals is debatable (Trewavas 2009), but McNickle et al. (2009) have attempted to define common ground for studies of both animal and plant "behavior." In terms of plant root foraging, it has long been known that plant roots respond to heterogeneity in the soil environment (Hodge 2009), and research on the Zn hyperaccumulator plant *Thlaspi caerulescens* revealed existence of "zincophilic" foraging (Schwartz et al. 1999;

Haines 2002), the preferential proliferation of roots in high-Zn soil patches. Studies of plants that hyperaccumulate other metals (e.g., Liu et al. 2009) have documented similar cases of root proliferation in high-metal soil patches. The opposite situation, plant roots avoiding high-metal soil patches (perhaps in response to metal pollution of the soil), may exist for less metal tolerant species. Thus, soil heavy metal concentration may affect root growth patterns of plants and thus root behavior.

Direct response of plant roots to soil heavy metals may be analogous to direct responses of aquatic animals to waterborne heavy metals, but the more subtle info-disruption effects of heavy metals that are beginning to be identified in aquatic communities are difficult to relate to plants. Recent research, however, suggests plant roots may be more environmentally aware than previously thought. In particular, studies have suggested that roots can discriminate between self- and non-self roots (e.g., Falik et al. 2003; Gruntman and Novoplansky 2004). Furthermore, Dudley and File (2007) reported that roots of sea rocket (*Cakile edentula* var. *lacustris*) detect and respond to roots of conspecifics, and particularly suggested that they are capable of kin recognition. Debate has occurred regarding both the claim of kin selection by plants (Klemens 2008; Milla et al. 2009) and root mediated kin recognition (Hess and de Kroon 2007), but the field seems open for further experimental work (de Kroon 2007). Early work with desert plant roots suggested that *Larrea tridentata* and *Ambrosia dumosa* shrubs can detect roots of heterospecifics (Mahall and Callaway 1992, 1996) and the concept of chemical signaling between plant roots seems generally accepted (Hodge 2009).

Plant communication is not limited to the belowground realm. Communication between plants by volatile airborne chemicals has attracted interest since at least the 1970s, but the signals may be non-specific and susceptible to “eavesdropping” by neighboring plants (e.g., Karban et al. 2004). A recent report (Karban and Shiojiri 2009) showed that sagebrush (*Artemisia tridentata*) individuals discriminate between self-generated and non-self-generated signals. In this study, herbivore damage was significantly less when a clone of the target plant generated a volatile signal that induces herbivore chemical defense (compared to a volatile signal generated by a non-clone plant). Volatile chemical communication provides another pathway by which info-disruption may occur. The ability of a plant to detect volatile chemical signals may be changed due to exposure to heavy metals, most likely through impacts of metal-contaminated soil. Stress from exposure to the contaminated soil (Koricheva et al. 1998) may affect a plant’s physiology and thus the volatile chemical signaling system. Dry deposition of metal-containing dust is another avenue by which heavy metals can impact plants. Entry of metal-laden dust into stomata, or dissolution of metals from dust during rain or dew deposition, may allow metals to penetrate directly into tissues and ultimately cells (Greger 2004). How metal exposure may influence volatile chemical generation or detection remains to be explored.

The existence of chemical signaling between plants provides an opportunity for heavy metal pollutants to interfere with these signal mechanisms, perhaps in ways similar to the info-disruption documented in aquatic animal research. As in aquatic systems, signal disruption may occur in several ways: heavy metals may prevent the signal from reaching the receptor, interfere with the receptor’s reception, or interfere with signal transmission. To my knowledge there is no evidence of such info-disruption, but now that the question has been raised it can receive research attention.

Heavy metal pollutants, via other indirect pathways, also may influence plant interactions with natural enemies. As with other pollutants, heavy metal pollutants cause stress that changes plant characteristics, including secondary chemistry. Mithöfer et al. (2004) pointed out that heavy metals may stimulate production of oxylipins in plants: some of these, such as jasmonic acid, have well investigated roles as plant defense signals (e.g., Kessler et al. 2004). Koricheva et al. (1998) reviewed papers regarding the plant stress hypothesis: the concept that increased stress may cause changes in plant chemistry that favor natural enemy performance. They concluded that the hypothesis was supported in some cases but not in others, depending on many factors including the type of stress and insect feeding mode. It is clear from their review, however, that stress caused by heavy metal pollutants is another pathway by which plant ecological relationships with natural enemies can be impacted.

Heavy Metals as Elemental Defenses Heavy metal pollutants in terrestrial environments may directly affect plants by providing an elemental defense against plant natural enemies. The elemental defense hypothesis was originally applied to plants that accumulate extraordinary concentrations of elements, often heavy metals, in their tissues (Boyd and Martens 1992). These “hyperaccumulator” plants most often occur in habitats that contain naturally elevated levels of the element the plants accumulate. For example, many hyperaccumulators of Ni (Ni hyperaccumulators are the most numerous category of hyperaccumulators: Baker et al. 2000) occur on serpentine soils, and these often are naturally Ni-rich (Alexander et al. 2007). Tests of elemental defense (reviewed by Boyd 2007) have reported defensive effects (in some but not all cases) for a number of elements (As, Cd, Ni, Se, and Zn), most of which are heavy metals. These elements and others can be pollutants, leading to the question of whether a heavy metal pollutant might form an elemental defense for a plant exposed to that pollutant.

I know of one study that may illustrate an elemental defensive effect by a pollutant. Scheirs et al. (2006) studied effects of Cd pollution on herbivory by a leaf-mining fly (*Chromatomyia milii*) on the grass *Holcus lanatus*. Plants were exposed to a range of relatively low Cd concentrations, and their suitability as hosts was determined by monitoring the performance of both adult flies and their offspring. Plant growth decreased in response to Cd treatments, and plant tissue Cd concentrations increased. Feeding and oviposition by adult flies, as well as performance of fly offspring, decreased as Cd concentration in plant tissues increased. Although this experiment showed plants exposed to Cd pollution were less suitable hosts, the authors were unable to determine if this was a direct effect of Cd or an indirect effect of plant host quality changes that occurred due to Cd exposure (in this case, for example, soluble sugar concentrations in plant tissues decreased with increasing Cd exposure). Thus, it cannot be concluded that the pollutant was directly responsible for the defensive effect, but this study does provide an example of a metal pollutant changing a plant-herbivore relationship in favor of the plant.

The concept of elemental defense is not limited to the producer trophic level. Elements (including heavy metals) found at relatively high concentrations in herbivores (or higher trophic levels) may have defensive benefits (Boyd and Martens 1998), but they have rarely been investigated. Nickel hyperaccumulator plants in serpentine ecosystems can be fed upon by specialized herbivores that themselves have high whole-body Ni levels (Boyd 2009). If high body Ni concentrations have defensive effects, these “high-Ni insects” (Boyd 2009), defined as those containing >500 μg Ni/g (on a whole-body, dry mass basis), are good choices for experimental tests of elemental defense against predators or pathogens. An initial investigation (Boyd and Wall 2001), that used the high-Ni mirid bug *Melanotrichus boydi,* found that mortality of crab spiders (*Misumena vatia*) was significantly greater when they were fed the high-Ni insect compared to those fed low-Ni prey. No defensive effect was found, however, for tests of two other predators (Boyd and Wall 2001) or for several pathogens (Boyd 2002), so that no general conclusion about elemental defense in this high-Ni herbivore could be reached. Elemental pollutants other than heavy metals also may have defensive effects in herbivores: Vickerman and Trumble (2003) showed that consumption of high-Se herbivore prey negatively affected the predacious bug *Podisus maculiventris*. Elemental defensive benefits likely will be positively correlated with heavy metal concentration. Biomagnification (sometimes used synonymously with bioconcentration) is generally defined as an increased element concentration in one trophic level relative to the previous one (Gray 2002). If biomagnification were to occur with a heavy metal, defensive metal effects would be more likely for organisms higher in a food web due to their higher body concentrations of that metal. Many studies have examined biomagnification, with mixed evidence that heavy metals biomagnify (e.g., Goodyear and McNeill 1999; Gray 2002; Burger 2008). Focus of elemental defense studies on systems that show biomagnification would be most likely to demonstrate elemental defense at higher trophic levels: yet even without biomagnification, differing abilities to bioaccumulate can result in defensive metal effects at higher trophic levels.

Heavy Metals and Pathogen/Microbial Communities

Heavy Metals as Pathogen/Microbial Info-disruptors Chemosensation is a vital way in which bacteria gain information about their environment. During the last 20 years, microbiologists have been excited to learn that chemical signaling among bacteria can be extensive and can lead to behaviors that suggest analogies to animal behaviors (West et al. 2007). For example, quorum sensing is the production of molecules by bacterial cells that indicate bacterial density and stimulate a population to act in a coordinated fashion (West et al. 2007; Williams et al. 2007). Discovery of this phenomenon stimulated much research into the mechanisms involved (Waters and Bassler 2005), the potential uses of these molecules in treating diseases (Ni et al. 2009), and even exploration of social phenomena (West et al. 2007) such as kin selection (Diggle et al. 2007) and cheating (Zhang et al. 2009) in bacteria. Although not all microbiologists are in agreement regarding the phenomenon’s behavioral analogies with eukaryotes (Turovskiy et al. 2007), it is interesting to consider how metal pollutants might impact the behavioral ecology of microbes.

Metals have some direct connections to quorum sensing. For example, Fe is an important and often limiting resource for bacteria, and they may produce chelating chemicals (siderophores) in order to sequester it from their environment (Challis 2005). These siderophores may have multiple functions, including acting as quorum sensors or antibiotics (Schertzer et al. 2009). Tolerance of some bacteria to heavy metals is increased greatly by formation of a bacterial biofilm, and biofilm formation can be controlled by quorum sensing molecules (e.g., Sarkar and Chakraborty 2008). At least one quorum sensing molecule contains a heavy metal (Zn) ion as part of its structure (Hilgers and Ludwig 2001).

Recognition of the importance of chemical signaling to microbes raises questions regarding the potential for heavy metal pollutants to disrupt communication similar to those discussed for macrobiotic organisms in the preceding sections. Do heavy metal pollutants interfere with signal production, inactivate a signal, or interfere with signal reception? And, if they do, then what are the consequences for ecological relationships between organisms? Research on quorum sensing disruption appears to focus primarily on organic molecules: recent reviews (González and Keshavan 2006; Rasmussen and Givskov 2006; Ni et al. 2009) do not mention interference by heavy metals yet contain a plethora of examples involving organic compounds. The potential for pollutants to interfere with quorum sensing appears unevaluated, but there are tantalizing glimpses of how this could work. For example, the green alga *Chlamydomonas reinhardtii* produces organic chemicals that apparently mimic quorum sensing molecules produced by some bacteria (Teplitski et al. 2004). In another case, Manefield et al. (2002) report that a red alga (*Delisea pulchra*) produces organic chemicals (halogenated furanones) that interfere with quorum sensing of bacteria and may prevent algal biofilm formation on the surface of the algal thallus. There also are many examples in which chemicals produced by eukaryotes influence bacterial quorum sensing (e.g., González and Keshavan 2006; Ni et al. 2009), providing chemical interactions that might be influenced by heavy metal pollutants.

Heavy Metals and Antibiotic Resistance Another connection between heavy metals and disease incidence is concern that metal pollutants may act as co-selection agents for antibiotic resistance in bacteria. Co-selection occurs when selection for one trait simultaneously selects for a second trait: in this case, selection for metal resistance also selects for resistance to antibiotics (Baker-Austin et al. 2006). In fact, one explanation for the evolution of antibiotic resistance genes, some of which have had extensive evolutionary histories prior to widespread human uses of antibiotics, is their ability to function in heavy metal resistance (Aminov and Mackie 2007): essentially pre-adapting them to current human uses of antibiotics. Antibiotic resistance is a serious threat to human health, and how such resistance evolves and the role of the environment in this process is of increasing interest (Baquero et al. 2008). One reason for this interest is that antibiotics may degrade in the environment but metals do not, and heavy metal pollution continues to increase (Han et al. 2002). Thus, heavy metal pollution may help maintain antibiotic resistant bacterial strains even if input of antibiotics into the environment is reduced. For example, chloramphenicol has been banned in China since 1999 (Dang et al. 2008). A recent survey (Dang et al. 2008) of antibiotic-resistant bacteria found resistant bacteria remained in Jiaozhou Bay, and suggested that pollutants (including heavy metals) were providing a reinforcing selective pressure that maintained the antibiotic resistance of bacterial populations. This indicates that antibiotic resistance, once evolved, will be difficult to eradicate and thus will remain a serious human health concern.

Co-selection includes two mechanisms: co-resistance and cross-resistance. In co-resistance, a gene that confers heavy metal tolerance is present on the same genetic element as a gene for antibiotic resistance. Aminov and Mackie (2007) point out that antibiotic resistance genes may occur on plasmids large enough to include other genes, including heavy metal resistance genes. In such situations, a bacterium that possesses that plasmid would benefit from the physiological capability to resist both stresses. In cross-resistance, the same gene codes for resistance to both heavy metals and antibiotics. Baker-Austin et al. (2006) point out that cross-resistance is probably common because resistance to stresses induced by both heavy metals and antibiotics rely on similar cellular mechanisms. Co-selection also may occur because of a bacterial behavior (such as biofilm formation) that indirectly increases resistance to both heavy metals and antibiotics (Baker-Austin et al. 2006).

Evidence for co-resistance between heavy metal pollutants and antibiotics takes two forms. First, studies of metal polluted versus unpolluted areas show greater antibiotic resistance in bacteria from the polluted areas. For example, Stepanauskas et al. (2005) measured both heavy metal and antibiotic resistance of bacterial communities both before and after they were exposed to metal-polluted wastewater, finding significant increases in resistance to both stressors after metal exposure. In a study of freshwater microcosms, Stepanauskas et al. (2006) showed that bacteria from Cd- and Ni-treated microcosms were significantly more resistant to antibiotics than those from controls. A number of studies, in a variety of environments exposed to a variety of heavy metals, have shown similar results, suggesting that co-selection is widespread (Baker-Austin et al. 2006). Second, co-selection has been demonstrated experimentally by adding heavy metals to a system and measuring antibiotic resistance change. Berg et al. (2005) found that Cu-amended soils contained more Cu-resistant and antibiotic-resistant bacteria than unamended soils.

Heavy Metals as Immunomodulators The previous section regarding antibiotic resistance and heavy metals suggests a related issue that has been connected to metal pollutants: immunomodulation. Immunomodulation is a change in immune system function due to effects of a chemical (Lawrence and McCabe 2002), including pollutants such as heavy metals: it includes immunotoxicity (or immunodepression), a suppressing effect on the immune system, as well as immunostimulation (an accelerating effect). Either of these phenomena can negatively affect an organism's health. As with other heavy metal effects, immune system effects can vary depending on metal dose (Lawrence and McCabe 2002). For example, low doses of some heavy metals, such as Cd, Hg, and Pb, can improve immune system function, whereas higher doses are suppressive (Cabassi 2007). Many studies have shown immunomodulation associated with sublethal metal exposure in the environment or in experimental laboratory settings (e.g., Lawrence and McCabe 2002; Dietert and Piepenbrink 2006; Ilbäck et al. 2008). Most studies have targeted vertebrates, but recent work has revealed negative effects of heavy metal pollutants on host defense response systems of marine invertebrates (e.g., Oweson and Hernroth 2009; Vijayavel et al. 2009) as well as terrestrial insects (e.g., Sorvari et al. 2007; van Ooik et al. 2008).

Although there are many reports of effects of heavy metals on immune system function, in general the ultimate mechanisms are not clear. One mode of action is for metals to affect directly the ability of the immune system to identify and respond to pathogen attack. In other words, the complicated chemical communication that occurs during generation of the immune response provides an opportunity for info-disruption by metals. In a simple example, phagocytic activities of cells, measured by their ability to engulf labeled particles, may decrease in the presence of some heavy metals (Fournier et al. 2000). Furthermore, Bishayi and Sengupta (2003) showed that chemotaxis was impaired in mouse splenic macrophages when animals were treated with As or Pb. It is not clear whether these effects stem from info-disruption or more direct effects of heavy metals on cellular health, but the potential parallel with the info-disruption issues being investigated by aquatic biologists is interesting.

Final Considerations

A complicating factor for studies of pollutants (including heavy metals) is that contamination by multiple pollutants often occurs (Fleeger et al. 2003). With regard to metals, these may be multiple metals or one or more metals mixed with one or more organic chemical pollutants. Despite the prevalence of mixtures, toxicological studies often focus on effects of single pollutants (Yang 1994) and so may not be realistic models for judging actual impacts. Generally, combinations of potentially toxic materials may act additively, synergistically, or antagonistically, and all of these effects have been observed in some cases for some heavy metals. For example, additive effects occur when one chemical acts independently of another. Jhee et al. (2006) explored the effectiveness of combinations of certain plant elemental defenses toward an herbivorous moth (*Plutella xylostella*) using an artificial diet amended with metals. When Zn was combined in a pairwise fashion with Cd, Ni, or Pb, toxic effects were additive, and the combination treatments caused greater mortality than single metals alone. Synergy occurs when chemicals interact in a way that increases their joint toxicity beyond that expected if their effects were additive. Jensen et al. (2006) reported an example of synergy of methylmercury and selenate in a study of effects of these chemicals on an insect detritivore (the fly *Megaselia scalaris*). Mixtures containing as little as the LC5 (Lethal Concentration 5%) of both chemicals resulted in 100% larval mortality. Finally, antagonism occurs when effects of one chemical can reduce a negative impact of another. For example, Sanchez-Dardon et al. (1999) studied effects of heavy metals on the immune system of rainbow trout. They found that individual doses of Cd, Hg, or Zn affected immune system function, but when Zn was combined with Cd or Hg no changes occurred. The positive effect of a small dose of a potentially toxic substance is termed a "hormetic effect" (Lefcort et al. 2008), and antagonism is one mechanism by which hormetic effects of a heavy metal pollutant can occur.

Another complicating factor for studies of pollutant impacts is that of scale. While the challenges of scale to ecological studies have been recognized for a long time, Zimmer and Zimmer (2008) point out that these are especially important in chemical ecology. In their recent review, Zimmer and Zimmer (2008) discuss dynamic scaling: the need to scale chemical ecology studies to the physical and chemical environments in which chemical ecology occurs. They point out that complete dynamic scaling is usually not done in laboratory or field studies and this can make it difficult to judge actual ecological effects. They also conclude that many chemical ecology studies have an organism-level emphasis, and point out that including population, community, and ecosystem scales is important to achieve a full understanding of ecological effects. These points certainly apply to studies of metals as info-disruptors, and illustrate the extensive and careful research needed to explore these aspects.

This mini-review has covered a number of ways in which anthropogenic heavy metal pollution may affect organisms and their interactions. It is interesting to consider how the human-generated increase in heavy metal concentrations in biological communities may be affecting evolution of species within them. It is clear that heavy metal pollution (or in fact, release of many pollutants) has provided an opportunity for some species to evolve tolerant populations. In the case of heavy metals, examples range from prokaryotes (e.g., Piotrowska-Seget et al. 2005) to eukaryotes (Janssens et al. 2009). In light of the concept of elemental defenses: is human-caused increase in heavy metal availability providing an opportunity for metal-based defenses to become more frequent? There are two ways this may occur: 1) through changes in host traits (other than metal concentration) that occur as consequence of exposure to the heavy metal, 2) directly through increased heavy metal concentration serving as an elemental defense. The latter case (increased heavy metal concentration) occurs when organisms are exposed to heavy metal pollutants, and it depends on the balance of intake and excretion. The evolution of metal tolerance in organisms exposed to metal pollutants is a first step in formation of an elemental defense, allowing subsequent evolution of uptake and sequestration mechanisms that may result in concentrations of heavy metals adequate to deter natural enemies. It is difficult, however, to differentiate between direct and indirect effects of heavy metal pollutants. For example, in the section on terrestrial communities (above), the study of Scheirs et al. (2006) showed that Cd exposure of the grass (*Holcus lanatus*) negatively impacted an herbivore (the fly *Chromatomyia milii*). However, the authors were unable to determine if this was due to the direct effect of Cd on the fly, or an indirect effect of plant host quality changes that also changed due to Cd exposure.

Bioaccumulation of heavy metals may be another example by which metal pollutants can have defensive effects. In fact, in a sense this has been the case in some polluted locations where animals that contain dangerous levels of pollutants have been banned from human consumption. If this resulted in decreased human predation upon those animals, then a heavy metal pollutant would function as an elemental defense against humans. For example, in 2001 the U.S. government recommended that pregnant women limit intake of some fish (notably tuna) due to Hg contamination, and consumption by this target group decreased significantly (Oken et al. 2003). This apparently is not (at least not yet) an effective defense, as overfishing of tuna continues (e.g., MacKenzie et al. 2008), but it serves to illustrate a potential defensive consequence of heavy metal pollution.

Future Research Directions

Most of this mini-review has suggested future research directions, but I will close with some summary considerations. Research on direct toxic effects of heavy metals on organisms, a research area that has received much attention, needs further exploration. The discovery of important sublethal metal effects, however, provides a new area for research. The concept of info-disruption, now well established in freshwater systems, may be extended into other habitats and could uncover previously unrecognized heavy metal pollution impacts. For example, are there parallels between the effects of metals on immunomodulation in animals and effects of heavy metals on plant responses to pathogen attack? Poschenrieder et al. (2006) suggested there are, for example, pointing out that Cd treatment can induce production of plant signal molecules (e.g., jasmonic acid, ethylene) that mobilize plant defenses against natural enemies.

The concept of elemental defense is another research area in need of investigation. Examples from communities that are exposed to naturally elevated heavy metal levels, such as terrestrial serpentine communities (Boyd et al. 2009), suggest ways to explore similar questions in metal polluted situations. Finally, there are opportunities to explore the effects of heavy metal pollutants on ecological units larger than species. Communities and ecosystems are difficult to study due to their complexity, but a complete understanding of metal pollutant effects cannot be accomplished without such studies. Hopefully, a more complete understanding will enable us to limit harmful effects of anthropogenic heavy metal pollutants on Earth's biota.

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