Review Article

A Gateway to Metal Resistance: Bacterial Response to Heavy Metal Toxicity in the Biological Environment

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Abstract

Heavy metals and metalloids are dangerous because they have the tendency to bioaccumulate in biological organisms over a period of time. However, it is conceived that a number of phytochemical agents as well microorganism can act as heavy metal removing agent both from human beings and the environment surrounding. For instance, microbes are used for the removal of heavy metals from the water bodies including bacteria, fungi, algae and yeast. This review shows that bacteria can play an important role in understanding the uptake and potential removal behaviour of heavy metal ions. The bacteria are chosen based on their resistance to heavy metals (incl. their toxicities) and capacity of adsorbing them. Due to specific resistance transfer factors, cell impermeability is drastically inhibited by several ion (i.e. mercury, cadmium, cobalt, copper, arsenic) forms. Between these elements, free-ion cadmium and copper concentrations in the biological medium provide more accurate determination of metal concentrations that affect the bacteria, than with most of the other existing media. Metal toxicity is usually assessed by using appropriate metal ion chelators and adjusting pH factor. Bacteria and metals in the ecosystem can form synergistic or antagonistic relationships, supplying each other with nutrients or energy sources, or producing toxins to reduce growth and competition for limiting nutritional elements. Thus, this relation may present a more sustainable approach for the restoration of contaminated sources.

Introduction

The elements which are known collectively as the "heavy metals" are a fairly ill-defined group. Generally they include many of the transition series of metals and some of the metals and metalloids in groups IIIB, IVB, VB and VIB of the periodic table. Although many of them are micro-nutrients, they are primarily of interest because of their toxic properties to all forms of life [1].

Probably the most important feature which distinguishes the heavy metals from other toxic pollutants is that they are not biodegradable, and having entered the environment where their potential toxicity is controlled to a great extent by biological and geochemical factors [2]. The toxicity of heavy metals to plants [3,4] and animals [5] is well known. It is primarily the avidity of heavy metals for natural metal-binding agents which determine their toxicity. They may cause disruption of enzyme structure and function by binding with thiol and other groups on protein molecules which may replace metals naturally occurring in enzyme prosthetic groups [6]. Metals have also been shown to bind with and disrupt deoxyribonucleic acid (DNA) [5]. The bioaccumulation of some metals is an important aspect of their toxicity [7,8] which may result in the appearance of symptoms after prolonged exposure; their accumulation may also lead to mobilisation through food chains [9] with possible effects on higher organisms.

There is convincing evidence that some metals, notably chromium and nickel, can cause cancer, and tentative evidence for many more [10]. The form of metals may increase their toxicity: dimethyl mercury and tetraethyl lead are particularly dangerous since they may easily enter the body and remain there as a result of their high lipid solubility [4,11]. Volatile metals and their compounds may also be dangerous since they may enter the body through the lungs [12], while organomercurials may pass through the placenta [13].

As a group, the bacteria are important agents in determining the form and distribution of metals in the environment. They play a major part in the modification, activation and detoxification of heavy metals [14]. However, they may themselves be subject to metal toxicity. This is of importance in some key processes, such as biological waste treatment [15,16] and also in the field of medicine [17].

Heavy metal toxicity to bacteria

Several workers have studied the toxicity of heavy metals to pure bacterial cultures. Although it is apparent that different species have different responses [18], some trends are evident. Waturangi et al. [19], found for the species they tested, that actinomycetes were more tolerant to cadmium than Gram negative bacteria, which were more tolerant than Gram positive bacteria. These differences may be due to the different biochemical and morphological characteristics of the groups. This may be reflected in the distribution of metals in cellular fractions. During an investigation of the effects of inorganic lead salts on *Azotobacter sp.* and *Micrococcus luteus* [20], 37.6% of the lead immobilised by *Azotobacter sp.* was found in the cell wall, compared to only 9.5% of that immobilised by *M. luteus.*

The outer layers of cells are probably very important in determining how much of a metal penetrates the cytoplasm. Of the lead abstracted from a medium containing 600 mg/L lead bromide or lead nitrate by *M. luteus,* 75 to 82% was found in lipid extracts of the cells [21]. Analysis showed that no specific plumbated lipids were present, thus it appears that only a natural mixture of cell lipids had the capacity for lead retention [22].

The lead caused structural inconsistency of the cytoplasmic membrane, and attempts to prepare protoplasts by treatment of cells with lysozyme often resulted in protoplasmic lysis [23]. Some other bacteria have been shown to undergo plasmolysis and changes in mesosomal structure indicative of membrane disruption [24]. Treatment of the extracted lipid fraction with tris (hydroxymethyl) aminomethane and ethylenediaminetetracetate (EDTA) or reduction of thiol groups with p-chloromercuric phenylsulphonic acid had little effect on lead retention [25].

A fairly common feature of the effects of sub-lethal concentrations of metals on bacteria is retardation of the onset of growth. Methylmercury acetate extended the lag phase of cultures of *Rhodopseudomonas capsulata,* but cultures which did begin to grow reached limiting cell densities similar to that of a control [26]. Cadmium had the effect of extending the lag phase of cultures of *Escherichia coli,* but normal proliferation was observed at the end of the lag phase [27]. During lag phase 95% of cells lost viability, and various structural abnormalities were observed, but by the middle of the lag phase cells had resumed normal morphology. Extension of the lag phase by mercuric chloride was also accompanied by a decrease in viability of *R.capsulata* although the turbidity remained the same [28]. This effect would therefore not be observed if culture turbidity was used solely as a measure of growth. It was suggested that growth would only occur when the available metal had been reduced to a threshold concentration, and that this may have been brought about by cell lysis during the decrease in viability [29]. However, in the case of *E. coli,* Mokkapati et al. [30] have suggested that the cells develop some mechanism of molecular accommodation during this phase. This concept is supported by the changes in cellular distribution observed during growth.

Species specific sensitivity to heavy metals may have pronounced effects on natural microbial populations. Although effects on total viable counts may be minimal, the sensitivity of one type or group of organisms may result in an appreciable change in the behaviour of the population [31]. Singleton and Guthrie [32] studied the effects of added copper and mercury on aerobic, heterotrophic bacterial populations of two aquatic systems. Although 2 mg/L copper or mg/L mercury caused an increase in the total number of colony forming units, the colony type diversity decreased in both systems. Additions of copper and mercury also stimulated an increase in uptake of a number of other elements [33]. Albright and Wilson [34] found that the heterotrophic activity (based on uptake and mineralisation of 14Cglucose) of a natural population decreased on addition of 10 µg/L copper and 50 µg/L mercury, but the numbers of viable heterotrophic bacteria were unchanged. However, the addition of 10 and 50 µg/L copper to two marine ecosystems led to a marked increase in the relative numbers and activity of heterotrophs [35].

Biological waste treatment processes employ natural microbial populations to treat organic wastes. Bacterial sludge has an ability to remove metals from solution [36] but they are also subject to the toxic effects of such metals. The toxic effects of metals include deflocculation [37] and a decrease in the respiratory activity of the sludge [38] leading to poor effluent quality. Anaerobic digestion is also susceptible to metal toxicity [39].

Metal form and toxicity

Several factors affect the form of metals, and thus their potential toxicity. These include pH, concentration of chelating agents, concentration of inorganic anions and competition from other cations. Shi et al. [40] found that the toxicity of cadmium to some bacteria was enhanced at alkaline pH, while for others it was independent of pH. It would have been virtually impossible to determine metal form because of the complex nature of the growth medium used. Precipitation of a metal may cause a reduction in toxicity by preventing its access to bacteria. It was found that inhibitory concentrations of copper in a seawater medium had no effect on the growth of *E. coli,* when added to the medium before autoclaving [41]; seawater precipitates considerably on heating. Soltani and Shaheli [17] suggested that precipitated metals may exert an effect on bacteria, but this was based on the assumption that metals retained in solution by chelating agents would be available to exert a toxic effect on the bacteria.

A number of natural and synthetic chelating agents can reduce the toxicity of heavy metals. Cysteine has been shown to protect bacteria against the toxicity of methyl mercury acetate [42], EDTA abolished the toxic effect of added copper to *Nitrosomonas* [43] and cysteine hydrochloride promoted more rapid onset of growth in cultures of *E. coli* retarded by copper [44]. Nitrilotriacetate and citrate have also been shown to protect fish from copper and zinc toxicities [45]. Cadmium sensitive strains of *Staphylococcus aureus* pre-treated with cysteine were protected from penetration of the metal into the cells, but treatment after metal uptake had occurred did not lead to release of cadmium from the cells [46]. Clay minerals have been shown to influence the toxicity of cadmium to bacteria. Montmorillonite, and to a lesser extent, kaolinite, decreased the inhibitory effects of cadmium [47]. The greater protective effect of montmorillonite was correlated with its higher cation-exchange capacity (CEC). However, clays homoionic to cadmium (i.e. already saturated with the metal) enhanced the toxicity of exogenous cadmium, montmorillonite again having the greatest effect due to its higher CEC [48].

Metals may also have their toxicity reduced by common components of nutrient media. Leitao and Sa-Correia [49] found that growth of *Pseudomonas aeruginosa* in the presence of inhibitory concentrations of copper was improved by increasing the concentrations of nutrients in the medium. It has been demonstrated that three
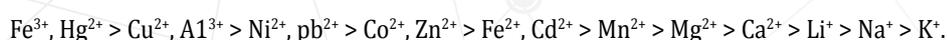
common agar media neutralised to differing degrees the bacteriostatic effects of silver [50]. These examples indicate that media constituents should be taken into account where studying metal toxicity to bacteria and that such study may not reflect the real situation in a natural environment.

Another aspect of metal form which may influence toxicity is the valence of metal ions and their compounds. Panda and Sarkar [51] found Cr^{3+} to be less toxic to *K. aerogenes* than CrO_4^{2-}. A 24% reduction in glucose oxidation by the bacteria in a laboratory scale continuous flow reactor was induced by 12.4 mg/L Cr^{3+}, whereas only 4.9 mg/L CrO_4^{2-} caused a reduction of 45% [52]. Both Cr^{6+} and Cr^0 are known to induce cancer in experimental animals, but there is no evidence that Cr^{3+} has a similar effect [53]. A mixed microbial population from activated sludge was inhibited during lag phase of growth to a greater extent by Cd^{2+} than $Cd(CN)_4^{2-}$, but there were no differences between them in the effects on substrate utilisation [54]. Other metals may have similar properties. The fact that, a strain of *S. aureus* has been found to possess a plasmid carrying separate resistance determinants for arsenate and arsenite [55] suggests that the properties of arsenic in these two anionic species axe significantly different, and this may influence their toxicity.

Obviously, it is unlikely that in a natural environment, bacteria are exposed to the effects of a single metal. Synergism or antagonism may occur with mixtures of metals. Babai [56] found that growth of *E. coli* was inhibited at very low concentrations of nickel, cobalt, cadmium, zinc and manganese when magnesium was not present in the medium. Their toxicity was markedly reduced in the presence of magnesium. Magnesium had similar effects on the toxicity of nickel and cobalt to *Aerobacter aerogenes*, and it was found that higher levels of magnesium reduced the amounts of these metals bound by the cell [57]. Tsai [58], in a study of chromium and copper sensitivity in *K. aerogenes*, found both have synergistic and antagonistic effects. Very low concentrations of Cd^{2+} or Zn^{2+} potentiated the lethal action of Cu^{2+}, mixtures of Cu^{2+} and CrO_4^{2-} gave an additive response, and mixtures of Cd^{2+} with CrO_4^{2-} were antagonistic.

The antimicrobial activity of some toxic compounds may be increased by heavy metals. Heavy metal derivatives of sulphonamide drugs were found to have greater antimicrobial activity than the parent compounds [59]. Copper ions were shown to increase the growth inhibitory effect of 2,2'-bipyridyls on mycoplasmas [60]. A strong inhibitory effect on *Mycoplasma gallisepticum* was noted only in the presence of exogenous Cu^{2+}. The tetrahedral complexes formed by Cu^{2+} (and Zn^{2+} and Cd^{2+}, which had lower activity) with 2,2'-bipyridyls are highly stable and lipophilic, which probably allows them easy access to the cell [61]. Other examples of augmentation of the toxic effect of metals by chelation include the formation of a lethal complex between 8-hydroxylquinoline and a metal, even when the concentration of the metal itself (for example iron) is not toxic [62]. The toxic action of the 8-hydroxylquinoline iron complex can be antagonised by cadmium, cobalt, zinc and nickel [63].

Obviously, some metals are intrinsically more toxic than others. Since heavy metals act primarily as a result of their affinity for chelating agents, an assessment of the degree of affinity may indicate the comparative toxicity of a metal. Dipu et al. [64] has stated that most chelating agents show approximately the same order of preference for metals. For decreasing order of affinity this series is:

Fe^{3+}, Hg^{2+} > Cu^{2+}, Al^{3+} > Ni^{2+}, pb^{2+} > Co^{2+}, Zn^{2+} > Fe^{2+}, Cd^{2+} > Mn^{2+} > Mg^{2+} > Ca^{2+} > Li^+ > Na^+ > K^+.

However, there are many cases of departure from this series. Madoni et al. [65] found that Hg^{2+} was less toxic to heterotrophs than Cu^{2+} and Ni^{2+}, and lead was found to be adsorbed by activated sludge more efficiently than copper and cadmium. It is apparent, therefore, that although a general trend may be evident; this alone has limited value in the estimation of toxicity.

Bacteria and metal form

Bacteria can, to some extent, determine the forms of heavy metals to which they are exposed. This may occur by transformation to less toxic forms, immobilisation by uptake or mobilisation from sinks. The mechanisms involved may be specific for the metal or non-specific.

Immobilisation of metals by bacteria is an important feature of the activated sludge process [66]. Gu et al. [67], have suggested that it may be possible to develop a practical microbiological process to remove metals from water. They evaluated the potential of *Zoogloea ramigera* cellflocs for removal of cadmium and mercury from solution, and found that cells grown in an arginine-glucose medium accumulated considerably less mercury than cells cultivated in trypticase soy broth. The possibility that affinity for metals is influenced by nutrient source and metabolism has also been considered by Abdulaziz et al. [68]. Cell-associated radioactive zinc in growing cultures of *Z. ramigera* was found to decrease between the fifth and seventh day of growth. This release from the cell floc may indicate a conversion from one metabolic activity to another.

Although it is unlikely that insoluble metal precipitates could exert a toxic effect on bacteria, they may be mobilised by the bacteria themselves. Chen and Weimer [69] showed that the solubility of copper in the absence of bacteria was increased three fold in their presence. It was suggested that this was due to the production of chelating agents by the bacteria. However, the distinction made between soluble and insoluble metal here may be misleading. Metals may form many different species, and it is probably an over simplification to suggest that only two classes of metal species (i.e. precipitated and those apparently in solution) are significantly different in their toxic effects. *Pseudomonas fluorescens* may mobilise and accumulate metals from sediment and river water [70]. A multicompartment system of bacteria accumulated about twenty times more than the sediment. The bacteria were also able to remove mercury from the sediment at a rate much higher than the normal rate of adsorption. This may be significant since sediment acts well as a sink, and in highly polluted waters may have loads of greater than 9000 mg/L of mercury [71].

Some microorganisms are thought to guard against mineral deficiencies by providing themselves with chelating agents which may aid in the absorption and conservation of essential trace elements. Compounds may be released into the medium in conditions of iron deficiency. Upon re-entry of the iron complex into the cell, the compounds are broken down enzymatically to release the iron [72]. Although synthesis of iron-fixing compounds usually only occurs in conditions of iron deficiency, the complexation of iron by EDTA and α,α'-dipyridyl in a medium containing plentiful amounts has been shown to reduce the free concentration of the metal such that synthesis of iron-fixing catechols by *K. aerogenes* was induced [73]. It is probable that uptake of the complexes is associated with specific transmembrane pores, since acquisition of a new transport system by strains of *E. coli,* originally deficient in iron-uptake capability, has been associated with the loss of two major outer membrane proteins [74].

Bacteria may produce more or less toxic forms of metals by transformation [75]. Some metals may be methylated by bacteria [76] and other organisms [77]. Mercury may be methylated by the transfer of methyl groups from methylcobalamine in extracts of ethanogenic bacteria [76] and microorganisms present in lake sediment can transform inorganic lead compounds into volatile tetramethyl lead in anaerobic conditions [78]. Kobza [79] has suggested that it may be possible to predict which metals could be methylated. Methylcobalamine does not transfer methyl groups to lead, cadmium and zinc, but may to tin, palladium, platinum, gold and thallium. The isolation of tetramethyl lead [4,80] suggests, therefore, that other mechanisms of methylation may occur. The stability of alkylmercurials may result in mercury releases into the environment being more dangerous than other metals, whose alkyls are relatively unstable.

Although methylation is known to occur in aquatic environments, the failure by many workers to isolate methyl mercury maybe due in part to the presence of bacteria capable of degrading methyl mercury [81]. Aerobic incubation of sediment containing Hg^{2+} gave rise to the production of methyl mercury during the first day, but this was followed by a rapid decrease in methyl mercury concentration concomitant with a rapid increase in the amount of volatile Hg^0 produced [82]. Wright and Hamilton [83] stated that, for a given culture, neither the type of substrate its concentration nor its rate of addition, had any effect on the rate of aerobic decomposition of methyl mercury and they suggested that an actively growing population is not necessary for decomposition, and that an enzyme system may be involved.

It was found that the induction period before the onset of degradation was decreased by pre-incubation of river sediment in increasing concentrations of methyl mercury, and that the mineralising activity appeared to be lost on prolonged incubation in the absence of mercury [84]. The authors suggested that preincubation in the presence of methyl mercury favours the development of a sub-population capable of degradation, while in non-preincubated cultures that part of the population having degradative activity was present at such a low level that the rate of mineralisation was below the detection limit initially.

The decomposition of phenylmercuric acetate to benzene and Hg^0 by a *Pseudomonas sp.* from soil [85] was found to be mediated by an enzyme designated metallic mercury-releasing enzyme (MMR-enz). The enzyme was induced by phenylmercuric acetate, p-chloromercuric benzoate, sodium ethyl mercuric thiosalicylate, mercuric chloride and metallic mercury; D-glucose: NAD oxidoreductase (or L-arabinose: NADP oxidoreductase) and cytochrome C, were required for activity [86]. The phenylmercuric acetate was only degraded once it had entered the cell. A large amount of radioactive phenylmercuric acetate was absorbed by the cells, and this disappeared during the logarithmic phase of growth although hardly any free phenylmercuric acetate disappeared from solution [87].

Oxidation of Hg^0 by several bacterial species has also been observed. Graham et al. [88] studied the stability of Hg^0 in two culture media. In a glucose medium it was stable, but in yeast extract medium it was slowly oxidised. Growth of the bacteria significantly increased the oxidation of Hg^0, as did a sterile filtrate from a 48 h culture of *Bacillus megaterium.* The conversion of Hg^{2+} to Hg^0 may be regarded as a detoxification mechanism since Hg^0 is more readily lost from the aquatic environment. In fact, all interconversions are cyclic, and unless disruption occurs, equilibrium will be maintained [89].

Resistance

Two types of resistance are discussed here: non-specific resistance arising from differences in physiological state of the organism, and inheritable specific resistance factors for particular heavy metals. Both may be important for different reasons. Impermeability or detoxifications by chelation are both non-specific mechanisms of resistance. The formation of a complex or chelate with bacterial extracellular polymers is an important aspect of metal removal from wastewaters. Krul [90] studied the uptake of metals by *Z. ramigera* strain 115, which produces a gelatinous matrix, and strain I-16-M. Strain 115 showed a high affinity for cobalt, copper and iron, took up about twice as much metal as strain I-16-M. Work with capsulated and non-capsulated strains of *K. aerogenes* showed that the capsulated strain survived better in the presence of copper and cadmium (10 mg/L) [91]. Extracellular polymer extracted from one strain, when mixed with the metals, exerted a protective effect on the non-capsulated strain. Analysis by ion-selective electrodes (ISE) showed that, at the concentrations used, the extracted extracellular polysaccharide complexed 54% and 9% of the copper and cadmium respectively [91].

Brandt et al. [92], found that periphytic *Pseudomonas spp.* produced significant quantities of extracellular polymers, and that growth in the presence of copper did not stimulate that production. Of the copper taken up by the cells, most was found immobilised in the polymer layer, and very little gained access to the cytoplasm. An *Azotobacter sp.* was found to be more efficient in immobilisation of lead than *M. luteus* [93], this probably being due to the large quantity of capsular material surrounding the cells (*M. luteus* is non-capsulated). The relative sensitivity of *Nitrosomonas* to chromate compared with *Nitrobacter* may be due to differences in intracytoplasmic membranes [94]. These encircle the entire cell of *Nitrosomonas,* but are restricted to lesser areas of *Nitrobacter.*

The density of a bacterial culture or population may also influence the toxicity of heavy metals. The inhibitory effects of copper on the growth of bacterial cultures can be eliminated by the addition of more living or dead cells [95]. The toxic effects of metals on the activated sludge process may be alleviated by increasing the suspended solids (biomass) concentration [96]. Resistant species which can accumulate metals may exert a protective effect on sensitive species in the same system by removing the metal from the system. A strain of *E. coli* which was twenty times more resistant to mercuric chloride and merbromin than *S. aureus* caused a decrease of 50% in sensitivity of the latter when suspensions of the two were mixed [97]. *E. coli* suspensions took up about five times as much mercury than *S. aureus*, and the protective effect was amplified by the secretion by *E. coli* of glutathione into the medium, which when added to mercury-inhibited cultures of *S. aureus* could relieve the toxic effects of the metal.

The introduction of antibiotics in recent years has led to the appearance of specific resistance factors to these agents in a number of bacteria. Similarly, resistance factors to a number of heavy metals have occurred. These factors are determined by extrachromosomal genetic material called plasmids. These genetic elements, which are self-replicating, may be transferred to bacteria of the same and similar species; hence they are often known as Resistance Transfer Factors (RTFs) [98].

Specific resistances to metals, which are often found linked to antibiotic resistances, can make the bacteria which possess them resistant to as much as one thousand times the concentration causing inhibition of sensitive strains. In contrast, a plasmid carrying determinants for increased sensitivity to mercuric chloride and cobalt chloride in some strains of *E. coli* K-12 has been discovered [99].

Götz et al. [100], found that penicillinase plasmids of *S. aureus* carried determinants for resistance to arsenate, arsenite, lead, cadmium, mercuric and bismuth ions. Resistances to antimony and zinc were also found, but these were not distinguishable from resistance to arsenite and cadmium respectively. This is probably because the chemistry of cadmium and zinc, at least, are essentially homologous [101]. Resistance factors for organomercurials have also been discovered [102]. The mechanisms of resistance to mercury and cadmium mediated by the penicillinase plasmid of *S. aureus* were found to be entirely different [100]. The resistance to mercury was probably inducible since during the lag phase of growth cells lost viability followed by a gradual increase to the level of the control. The resistance to cadmium was probably due to an impermeability barrier [103], which is specific since the uptake of other essential metals (magnesium and calcium) was not affected [104]. An impermeability barrier to Co^{2+} has been observed in a resistant strain of *E. coli B*. Electrophoretic analysis of membrane proteins showed slight differences between the strains, suggesting a modification in the specific membrane transport system for cobalt [105].

The possession of drug resistance RTFs by coliform bacteria has lead to concern about water quality standards and public health [106]. However, drug resistances have been found associated with heavy metal resistance factors in samples from sewage [107], polluted sites [108] and clinical sources [109,110]. In fact, resistance to heavy

metals is virtually always found associated with resistance to antibiotics [111,112] and the frequency of heavy metal resistance is often the same as or higher than the frequency of drug resistance [113]. Resistant *Bacillus* populations have a greater frequency in sites polluted by mercury containing sewage sludge than in unpolluted sites, and ampicillin resistance follows the same pattern [114-116]. The fact that *Bacillus spp.* with the combined resistance were six times more frequent in the sludge dump site, suggested that resistances may be co-selected for, and that metal pollution may exert a selection pressure for antibiotic resistances, thus further increasing their clinical importance.

Conclusion

Bacteria are generally the first organisms to be affected by discharges of heavy metals into the environment. Each of the wide range of species may be affected in a different way, and although low concentrations of metals may have only imperceptible effects on total viable counts of natural populations, the balance of species, and thus the metabolic characteristics of the population, may be drastically affected.

The major factor determining the toxicity of heavy metals to bacteria is probably the extent to which they penetrate the cytoplasm. Many bacteria appear to have the capacity for adsorbing metals in the outer layers of the cell. The synthesis of capsules by some species is important both in terms of resistance to toxicity and in detoxifying the environment by removal of metals from solution. Metals may also be prevented from entering the cell by the formation of complexes or chelates with several metal-binding agents. Although these agents may serve to protect microbial populations, their influence on metal uptake may have serious effects in waste-treatment processes where immobilisation of metals by the biomass is the most important mechanism of metal removal.

Apart from their role in immobilising heavy metals, bacteria may affect their environmental distribution in other ways. Some metals are particularly susceptible to alkylation by some bacteria, and subsequent dealkylation by others. Metals may also be mobilised from sinks either by accumulation or by complexation with excreted metabolic products.

In recent years the increasing frequency of antibiotic resistance in bacteria has been correlated with specific determinants for heavy metal resistance. Although, bacterial populations having resistance to high concentrations of heavy metals may be advantageous, the association with antibiotic resistance may lead to co-selection, thus enhancing the clinical importance of antibiotic resistance.

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