Fact Sheet on
Environmental Risk Assessment

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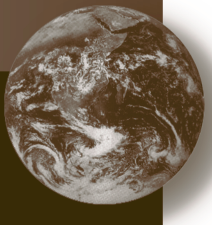

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ESSENTIALITY OF METALS:
CONSEQUENCES FOR ENVIRONMENTAL RISK ASSESSMENTS

Colin Janssen and Brita Muyssen

Ghent University
Laboratory for Environmental Toxicology and Aquatic Ecology

Introduction

Life has evolved in the presence of metals, some of which — the essential metals — have become incorporated into metabolic processes crucial to the survival, growth and reproduction of organisms. Additionally, organisms have developed several mechanisms — with varying efficiencies — for the uptake and excretion, regulation and detoxification of both essential and non-essential metals.

Like all materials, metals may present risks to humans and the environment and therefore scientifically sound assessments of these risks are required. In recent years, it has been recognized that standard risk assessment procedures developed and routinely used for man-made organic chemicals may not be appropriate to accurately assess the true impact of metals on human health and the ecological quality of terrestrial and aquatic systems (Bergman and Dorward-King, 1997). Recognition of the above-mentioned biochemical and physiological processes and their incorporation in risk assessment procedures are crucial to the correct evaluation of the hazards and risks of metals to humans and the environment.

This paper summarises the importance of considering the essentiality of some metals and the role of physiological phenomena such as metal regulation and acclimation in risk assessment procedures. It should be recognised, however, that essentiality is only one of several factors that differentiate the science of ecological-based risk assessment of metals and inorganic substances from that of organic substances (for a review: see Janssen et al., 2000 and other ICME *Fact Sheets*).

Metal essentiality: background

It is well demonstrated that a number of metals are essential for various biological functions and are critical in many of the enzymatic and metabolic reactions occurring within an organism. An element is considered essential when:

- it is consistently present in all healthy living tissues within a biological family, whereby tissue concentrations from species to species should not vary by a wide range;
- deficiency symptoms are noted with depletion or removal of the element and disappear when the element is returned to the tissue; and
- the deficiency symptoms are attributed to a distinct biochemical effect (at the molecular level).

In the highly specific metallo-enzymes, the metal is firmly associated with the protein and catalyses only one specific reaction or type of reaction (Wittmann, 1979). Several elements (e.g. sodium, potassium, magnesium, and calcium) occur in large concentrations in organisms. A second set of metals, termed trace metals, occurs at much lower concentrations (normally < 0.01%) in organisms. Table 1 gives an overview of the known essential elements and some of their biological functions. Some metals, such as Fe, Mn, Zn, Cu, Co, and Mo, have been identified as essential for all living organisms, while the essentiality of other metals, such as Ni, V, I, Cr, and Se, has only been established for a limited number of species.

For essential metals, each species has an optimal range of concentrations required for normal metabolic functioning (Figure 1A). This "Window of

Table 1: Trace metals and examples of their biological functions

Metal	Examples of function
Iron (Fe)	Present in hemoglobin for oxygen transport
Manganese (Mn)	Present in pyruvate carboxylase required for the metabolism of sugars Involved in synthesis of fatty acids and glycoproteins
Cobalt (Co)	Present in vitamin B12, required for the formation of hemoglobin Plays a role in biological N_2-fixation
Copper (Cu)	Present in cytochrome and hemocyanin, molecules involved in (cellular) respiration
Zinc (Zn)	Necessary for the function of dehydrogenases, aldolases, isomerases, transphosphorylases, RNA and DNA polymerase, carbonic anhydrase, Cu-Zn superoxide dismutase and more
Molybdenum (Mo)	Involved in electron transfer processes Nitrogen fixation is also coupled to a molybdenum process
Selenium (Se)	Activates glutathione peroxidase to scavenge free radicals
Chromium (Cr)	Involved in glucose metabolism (insuline)
Nickel (Ni)	Component of urease and thus a part of the CO_2 metabolism
Vanadium (V)	Regulation of intracellular signalling Cofactor of enzymes involved in energy metabolism Possible therapeutic agent in diabetes
Iodine (I)	Present in thyroxine and related compounds for proper functioning of the thyroid system

Essentiality" (Hopkin, 1989) or "Optimal Concentration Range for Essential Elements (OCEE)" (Van Assche et al., 1997) is determined by both the natural (bioavailable) concentrations of the essential metal in the species' habitat and the species' homeostatic capacity, which allows it to regulate its internal metal concentration to an optimal level. An organism's homeostatic capacity has limits, however, and when the external concentration of an essential metal becomes too high or too low, regulation will fail and toxicity or deficiency (respectively) will occur. Organisms have developed a variety of homeostatic control mechanisms to regulate internal metal concentrations, which vary considerably between species or groups of species. The following main categories of regulation can be distinguished (Brix and DeForest, 2000):

- active regulation (stable tissue concentrations are maintained by the excretion of metal at rates comparable to the intake rate);
- storage (large concentrations of metals can be stored in a detoxified form); and
- a combination of both.

Figure 1 illustrates that homeostatic regulation occurs for both essential (Fig. 1A) and non-essential (Fig. 1B) metals. For both groups, adverse effects on the biological activity of organisms occur when homeostatic regulation mechanisms fail.

For essential metals, either a shortage or an excess of the metal in the environment will lead to detrimental effects on organisms, populations and ecosystems. Deficiency effects induced through limitation or

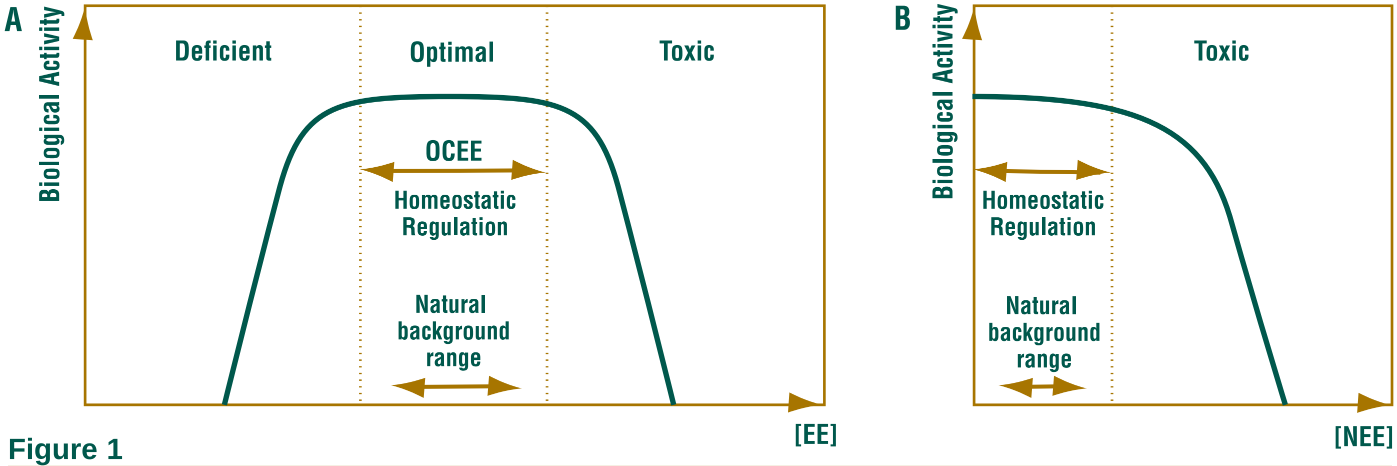

Figure 1

A. Biological activity as a function of the essential element concentration (EE). OCEE is the Optimal Concentration range for Essential Elements for a species in a given environment (Van Assche et al., 1997).
B. Biological activity as a function of the non-essential element concentration (NEE).

absence of essential metals have been reported for terrestrial and aquatic organisms. For non-essential metals, only excess environmental concentrations will cause adverse effects. For both metal groups, however, there is a clear concentration 'window' within which the internal metal concentration of the organism is regulated without resulting in detrimental effects.

Essentiality and acclimation in ecological/environmental risk assessments of metals: current practices and needs

Introduction: organisms only respond to bioavailable metals

Current water quality standards and risk assessment procedures for metals are predominantly based on total or dissolved metal concentrations. However, there is extensive evidence that neither total nor dissolved aqueous concentrations of a metal are good predictors of its bioavailability and toxicity.

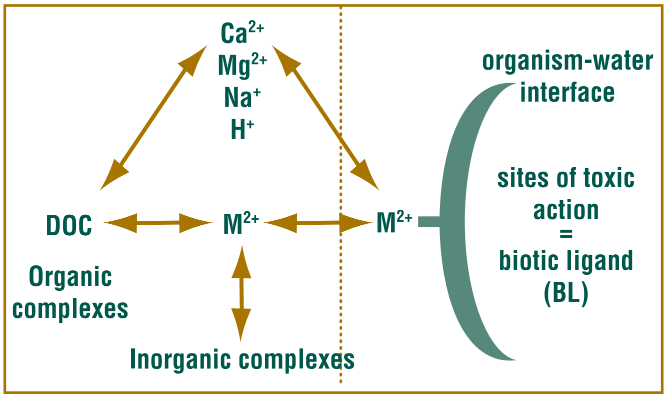

Figure 2

Simplified representation of the Biotic Ligand Model which predicts the 'bioavailable' — the ecotoxic — fraction of a metal in aquatic environments. Chemical reactions (left of dotted line), dependent on environmental characteristics, determine how much of the metal will interact with the organisms (right of dotted line).

Metal toxicity to freshwater organisms has been shown to be highly dependent on a variety of ambient water quality characteristics, e.g. pH, hardness, dissolved organic matter. Recent research efforts led to an improved understanding of how water chemistry affects bioavailability, how metals interact with aquatic organisms to exert toxic effects at the organism site of action, and how toxic effect levels can be predicted. The integration of these approaches has resulted in the development of (mechanistic) toxicity-related bioavailability models commonly referred to as Biotic Ligand Models – BLM (Figure 2) (Playle et al., 1992, 1993; Di Toro et al., 2000; Paquin et al., 2000, De Schamphelaere et al., 2001).

Although an in-depth treatment of metal bioavailability issues is not the purpose of this paper, it should be clear that when metal essentiality is discussed, the bioavailable concentration should be considered, rather than the total amount of metal present in the environment. The incorporation of bioavailability models such as the BLM in risk assessment procedures is central to the scientific relevance of these exercises. Consequently, all concentrations noted in the figures ([EE] or [NEE]) should be interpreted as bioavailable metal concentrations.

Acclimation to metals: laboratory evidence for field phenomena?

Many recommended standard artificial culture and test media contain no or very few essential metals. It has been demonstrated that organisms (e.g., waterfleas and frogs) cultured in media with low essential metal concentrations (e.g., Cu and Zn) exhibit an overall decreased fitness (Caffrey and Keating, 1997; Elendt, 1990; Elendt and Bias, 1990; Fort et al., 1998).

Furthermore, organisms cultured at these low metal concentrations acclimate to these conditions and become more sensitive to stress, including exposure to metals (Muyssen and Janssen, 2001). Conversely, organisms cultured in media with elevated metal concentrations (e.g., natural waters or contaminated waters) may become less sensitive (Figure 3).

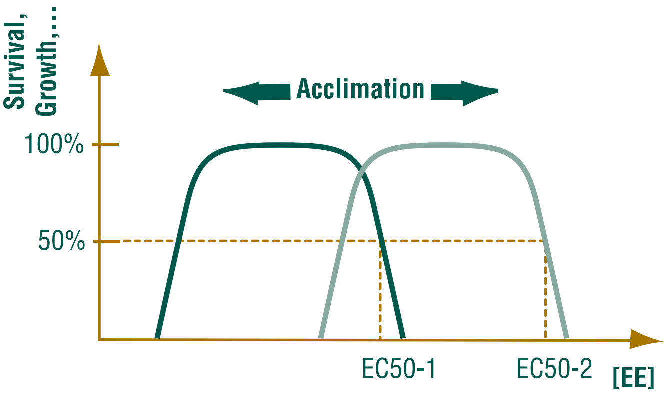

Figure 3

Representation of potential shift of the optimal concentration curve (OCEE) when organisms are cultured in media containing a low (left) or high (right) concentration of an essential metal. Note the concurrent shift in the sensitivity (expressed as EC50) of the organisms.

Considering that laboratory toxicity data are used for water quality criteria (WQC) derivation and the establishment of a Predicted No Effect Concentration (PNEC) in risk assessments, these acclimation-induced sensitivity shifts may affect the (ecological) relevance and effectiveness of these and other environmental quality criteria (EQC).

Acclimation to metals may be considered a natural phenomenon developed by organisms, in the course of evolution, to cope with fluctuating natural (i.e. non-anthropogenic sources) metal concentrations in the environment. In the context of EQC derivation, acclimation to essential metals should be considered at two levels:

- At the laboratory level: the relevance of toxicity data should be evaluated; toxicity test results used for EQC derivation should be screened to ensure that the test organisms used were not cultured in media containing too low or too high concentrations of essential metals.
- At the field level: although very little scientific data are available, acclimation — and associated sensitivity shifts — may also occur in natural environments. Geographic and seasonal variability in natural background concentrations of essential metals may be at the basis of this phenomenon. This issue is discussed in the next section.

Do differences in metal background concentrations induce differences in the sensitivity of local communities?

The fact that metals are naturally occurring elements with varying background concentrations in different habitat types has, to date, not been considered in most generic and regional (large-scale) environmental risk assessments. Depending on the metal background concentration, biological communities in these different systems may have differentially acclimated/adapted to the natural presence of the metal concentrations, resulting in varying community sensitivities (Figure 4). The term “metalloregion” has been coined to describe the interrelatedness of naturally occurring metals and the biotic community (to be covered in a later *Fact Sheet*).

To allow for the possible incorporation of such data into a regulatory framework, an evaluation is required of natural differences in community sensitivities due to either natural variation in metal background exposures or possible differences between the sensitivity of laboratory species and that of field-collected species (Janssen et al., 2000). Again, current scientific (field) evidence does not allow the further development of these concepts and their incorporation in regulatory systems.

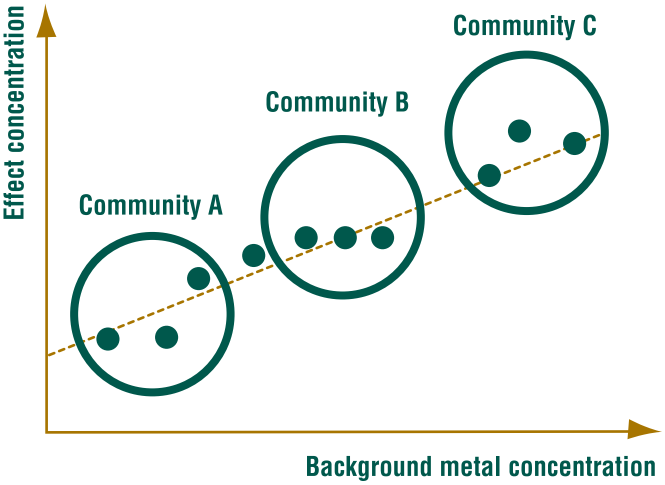

Figure 4

Hypothetical changes in the overall sensitivity of biological communities in environments with a different natural background concentration of a metal.

Essentiality and PNEC derivation

Current methods for the determination of the PNEC include: (a) the “safety factor” approach (TGD, 1996) in which a fixed factor (e.g. 10, 100, 1000), dependent on the quantity and type of available toxicity data, is applied to the lowest toxicity test result, and (b) the statistical extrapolation model(s)

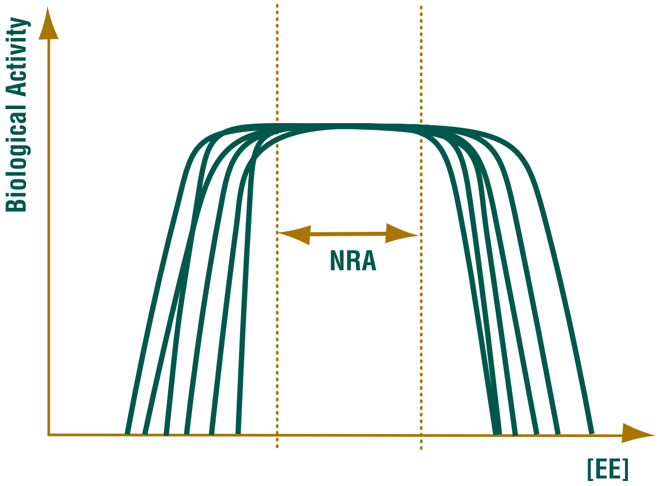

Figure 5

Hypothetical presentation of the OCEE curves (see Fig. 3) of all organisms in a given environment. The inner envelope of these curves represents a No Risk Area (NRA) in which all organisms are protected from both deficiency and toxicity effects.

approach (e.g., Aldenberg and Slob, 1993) in which all toxicity data are used to establish a species sensitivity distribution from which a "safe concentration" for a certain percentage of all species is derived (see *Fact Sheet* No. 3: "Distribution-Based Extrapolation Approaches in the Risk Assessment of Metals in the Environment").

When these techniques are applied to the essential elements, several conceptual problems and inconsistencies with biological/ecological reality arise. The "safety factor" approach often leads to PNECs well below the essential element's natural concentration range and may therefore be situated at concentrations that are deficient for (some) organisms in a given ecosystem. As the extrapolation statistical model(s) approach uses a statistical (e.g. log-logistic) distribution based on ecotoxicity data and does not consider possible adverse effects due to deficiency, resulting PNECs also may be at the lower end (or beyond) the homeostasis range of some organisms. Van Assche et al. (1997) proposed the "No Risk Area" (NRA) concept as a basis for PNEC determination for essential elements. The NRA is determined by the inner envelope of the overlapping OCEE curves of a group of species belonging to a given habitat-type, i.e. organisms adapted to the same metal background concentration (Figure 5). Within the NRA, none of the species is subjected to deficiency or toxicity stress. The NRA's upper (toxicity) boundary being determined by the biological species with the lowest toxicity value, the deficiency boundary would then be determined by the species with the highest deficiency value. Using this approach, the EQC can then be presented as a concentration range or concentration window, i.e. the NRA. Recognizing that the use of an "EQC window" may pose a problem for applying this concept in a regulatory framework, it may be suggested that the PNEC could also be set at the NRA's median or upper boundary, thus protecting all organisms in that environment from both toxicity and deficiency.

Whatever approach is used, it is clear that, when recognizing the essentiality and acclimation processes associated with essential metals, different types of habitat or environment may have different EQCs. Currently, the scientific or field evidence for the further development of these concepts and their incorporation in regulatory systems is not available.

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About the Authors:

Colin R. Janssen, Ph.D., is professor of Ecotoxicology at Ghent University, Belgium, where he directs the Environmental Toxicology Research Group, Department of Applied Ecology and Environmental Biology at the Faculty of Applied Biological and Agricultural Sciences. He teaches undergraduate and graduate courses in aquatic ecology, population ecology, marine ecotoxicology and environmental toxicology and risk assessment. C. Janssen currently heads a research team of 18 collaborators and (on average) a dozen thesis students/year that are actively studying bioavailability and ecological risks of metals in aquatic and terrestrial systems, detection of endocrine disruption effects in freshwater and marine environments, and ecological risk assessment procedures for contaminated effluents and sediments.

C. Janssen is a guest professor at three universities in Europe and directs research projects in West, East and Central Europe, South Africa and the USA. His research activities have resulted in 160 national and international publications and more than 120 lectures and presentations worldwide. C. Janssen and members of his research team have been the recipients of five scientific awards.

He is a member of the Publication Advisory Committee and the Metal Advisory Group of the Society of Environmental Toxicology and Chemistry and acts as European Newsletter editor for the same professional society. He is a full member and chair of the Ecotox group of the Belgian Health Council and acts or has acted as external advisor to various national environmental agencies and international organizations such as the OECD, EU and WHO. In his capacity of external expert to the above-mentioned organizations, he has provided independent scientific advice on regulatory issues concerning classification and labelling of substances, environmental quality criteria setting and the risk assessments of new and existing substances. He was recently appointed as a member of the EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (SCTEE).

Brita Muyssen is a Ph.D. student at Ghent University and team member of the above-mentioned research group. She is currently finalising her research concerning the influence of essential metals on the tolerance of aquatic organisms. Her work is aimed at elucidating and understanding the biochemical, physiological and population level consequences of metal acclimation and adaptation.

Fact Sheet on Environmental Risk Assessment

This is the fifth in an occasional series of *Fact Sheets* to be produced by ICME on metal-specific issues in environmental risk assessment. Authorship selection and editorial review are coordinated by Dr. Anne Fairbrother of Parametrix, Inc. Each *Fact Sheet* is reviewed for technical merit by Dr. Erik Smolders of Katholieke Universiteit (Catholic University) Leuven, Belgium, and by a panel of experts on metal-related regulatory issues. While the *Fact Sheets* reflect the views of the authors, they are intended to provide an objective review of each topic. ICME hopes these publications provide insights into complex issues in regulatory science, and welcomes questions and comments.

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**The International Council on
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294 Albert Street, Suite 506
Ottawa, Ontario, Canada K1P 6E6
Tel.: (+1 613) 235-4263 Fax: (+1 613) 235-2865
E-mail: info@icme.com
Web site: www.icme.com

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