METAL MIXTURES MODELLING

www.metalsintheenvironment.com

METAL MIXTURE TOXICITY

Fact Sheet Three

Introduction

Although environmental regulations for aquatic ecosystems typically focus on individual substances, it is widely recognized that substances actually occur as part of a complex mixture of different chemicals. Substances in a mixture may or may not interact with each other both in solution and within an organism depending on their chemical properties and modes of action. Consequently, predicting the toxicity of mixtures, and developing regulations for mixtures, is more complicated than it is for individual substances. Metal mixtures are of interest because of the ubiquitous nature of metals in the environment, the tendency for metal containing discharges to include more than one metal, and, in some cases, their chemical similarity.

There are two general modelling approaches that can be applied to understanding the toxicity of chemical mixtures, these are concentration addition, where substances have a similar mode of action, and independent action (also known as response addition), where substances have different modes of action (see Meyer et al. 2015[1] for a more detailed discussion). Interactions between different chemicals are also possible and this could lead to different types of mixture toxicity effects. Currently, Australia and New Zealand are the only two countries that consider metal mixtures in their environmental regulations. They use a concentration addition approach when 5 or fewer significant toxicants are present and known to have additive toxicity. Other jurisdictions mention metal mixtures, but provide no specific regulations to deal with them. Importantly, because many metals are essential for organisms, the use of safety factors to address uncertainty in metal mixture toxicity would be inappropriate as it could result in scenarios where metals are regulated to concentrations below the essential requirements of organisms. Consequently, there is a need to improve our understanding of metal mixtures to allow development of evidence-based regulations.

How are effects of metal mixtures currently evaluated?

Three broad groups of potential scenarios associated with mixture effects have been identified and are often used. A variety of terminology has been used to describe the effects of mixtures relative to those of their component chemicals including terms such as synergism and antagonism. A recent workshop on metal mixtures, the Metal Mixtures Modelling Evaluation (MMME) programme, recommended consistent terminology be adopted when discussing mixtures to avoid confusion when evaluating mixture studies.

Specifically, the scenarios and the terminology recommended were:

Less-than-additive: Where the constituents of a mixture, added together, give an observed impact (toxic effect) that is less than would be predicted when the individual chemical toxicities are combined. For example, if the toxicity of metal A = 10, the toxicity of metal B = 6, and the toxicity of A+B = < 16

Additive: Where the observed impact is what would be predicted through adding the toxicities of the individual mixture components. For example, if the toxicity of metal A = 10, the toxicity of metal B = 6, and the toxicity of A+B = 16

More-than-additive: Where the impact is more than would be predicted by adding together the toxicities of the individual components. For example, if the toxicity of metal A = 10, the toxicity of metal B = 6, and the toxicity of A+B = > 16

A review of published data on the effects of metal mixtures on aquatic organisms was undertaken by Norwood et al. (2003). The authors identified 191 relevant tests, of which 156 were mixtures of two metals, 18 of three metals, with the rest being four or more metals. More than 60% of these tests examined acute or short-term effects. Analysis of the interactions observed in these tests by Norwood et al. (2003) and later by Meyer et al. (2015) categorised the mixture effects consistent with the terminology defined in Box 1.

Meyer et al. (2015) noted considerable variability in the toxicological responses to metal mixtures, even for tests with the same metal binary combinations. Some of this variability was attributed to different species being tested and the range (and ratios) of metal test concentrations used. A further potential confounding factor was the

[1] Meyer JS, Farley KJ, Garman ER. 2015. Metal Mixtures Modeling Evaluation project: 1. Background. Environ Toxicol Chem. 34:726–740.

statistical method used to interpret the type of interaction seen in the tests (eight different ones in all).

Importantly, the types of interaction were all determined based upon the measured dissolved metal mixture concentrations in the tests and not on a bioavailability scale. Therefore, the conclusions drawn from the studies did not account for what the organisms that were exposed to the metal mixture were actually experiencing.

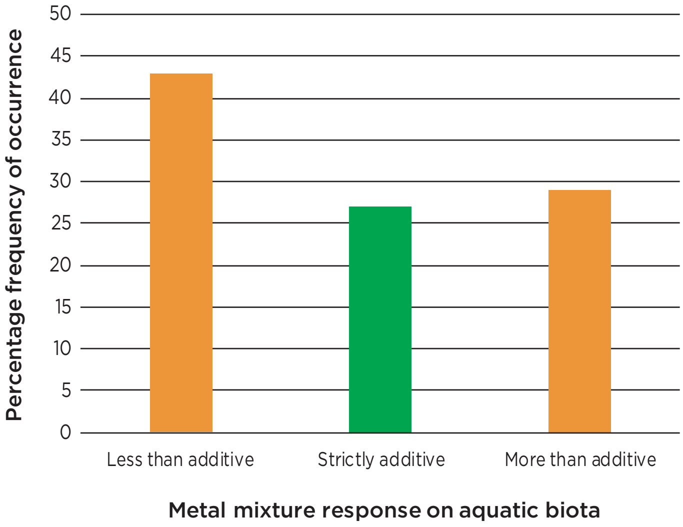

Figure 1. The interactions of metal mixtures from 191 chronic and acute ecotoxicity tests (data from Norwood et al. 2003[2]).

It may be reasonable to suggest from the analysis presented in Figure 1 that only equivocal conclusions can be made regarding metal mixtures and how ecological effects may be predicted from such environmental exposures (especially chronic or long-term ones).

Other reviews have reported broadly similar findings and overall it has been suggested that the assumption of additivity for metal mixtures would be sufficiently protective, from a regulatory perspective, approximately two thirds of the time.

Conclusion

There is a need, therefore, to develop an approach to facilitate the prediction a priori of the ecotoxicological outcomes of metal mixture exposures. Recent efforts to develop such an approach have focused on further developing existing single metal Biotic Ligand Models (BLMs; see Fact Sheet 2 for more information) in order to accommodate a mixture of metals to predict not only the effects of water chemistry, but also the effects of simultaneous exposure to multiple metals on bioavailability and toxicity. These models may be known as mixture BLMs (mBLMs). The basic assumption behind this is that a speciation-based approach, which takes account of accumulation of metals by the organism will be better able to predict the outcome of metal mixture toxicity experiments than approaches which are based on waterborne metal concentrations. More information on mBLM development can be found at metalsintheenvironment.com.

[2] Norwood WP, Borgmann U, Dixon DG, Wallace A. 2003. Effects of metal mixtures on aquatic biota: A review of observations and methods. Hum. Ecol. Risk Assess., 9:795–811.