FACT SHEET

01

MAY 2016

METALS ENVIRONMENTAL RISK ASSESSMENT GUIDANCE

MERAG

Risk characterisation

Check you have the most recent fact sheet by visiting www.icmm.com

ARCHE

Eurometaux
European Association of Metals

ICMM
International Council on Mining & Metals

CONTENTS

The content of the Metal Risk Assessment Guidance (MERAG) fact sheets reflect the experiences and recent progress made with environmental risk assessment methods, concepts and methodologies used in Chemicals Management programs and Environmental Quality Standards setting (soil, water, sediments, …) for metals. Because science keeps evolving, these fact sheets will be updated on a regular basis to take into account new developments.

1. INTRODUCTION

In the risk characterisation phase of a risk assessment, modelled or measured environmental concentrations are compared to toxicity values for each environmental compartment to identify risk magnitude and probabilities. The current fact sheet presents the general building blocks of a risk characterisation strategy that will allow compliance in an anticipative way with forthcoming legislative obligations while ensuring, at the same time, that the best option for managing risks presented by metals/metal compounds is considered. To this end, a tiered approach is advocated because data availability will depend on the type of metal/metal compound under investigation, allowing for further refinement of the assessment following two not mutually exclusive dimensions: refinement 1: total $\rightarrow$ dissolved $\rightarrow$ bioavailable $\rightarrow$ biogeochemical or metallo-regions and refinement; 2: deterministic $\rightarrow$ probabilistic.
The incorporation of the bioavailability concept into the risk assessment context of water, sediment and soils is the preferred way forward. Bioavailability concepts are discussed in detail in MERAG Fact Sheet 5. There, the bioavailability approach builds further on the total risk approach and can be seen as the scientifically most appropriate way in assessing risks for metals. However, it is acknowledged that in some particular cases (eg, setting of environmental effects thresholds) the use of the added risk approach may have its merits. A discussion on the assumptions/differences and limitations on the conventionally used total risk approach (TRA) versus the added risk approach (ARA) is further elaborated in Annex 1 to this Fact Sheet.

The remainder of this Fact Sheet discusses the general principles of risk assessment and explores more in depth of how risk assessments can be refined, taking into account bioavailability or using probabilistic techniques. Therefore, the term PNEC (Predicted No Effect Concentration) is used as an example of an environmental threshold value (ETV) throughout this section. Because metals in the environment most likely occur in mixtures, Annex 2 explores potential metal mixture toxicity approaches that could be used.

Figure 1 below outlines the generic tiered approach for the characterisation of risks to ecosystems associated with metals/metal compounds.

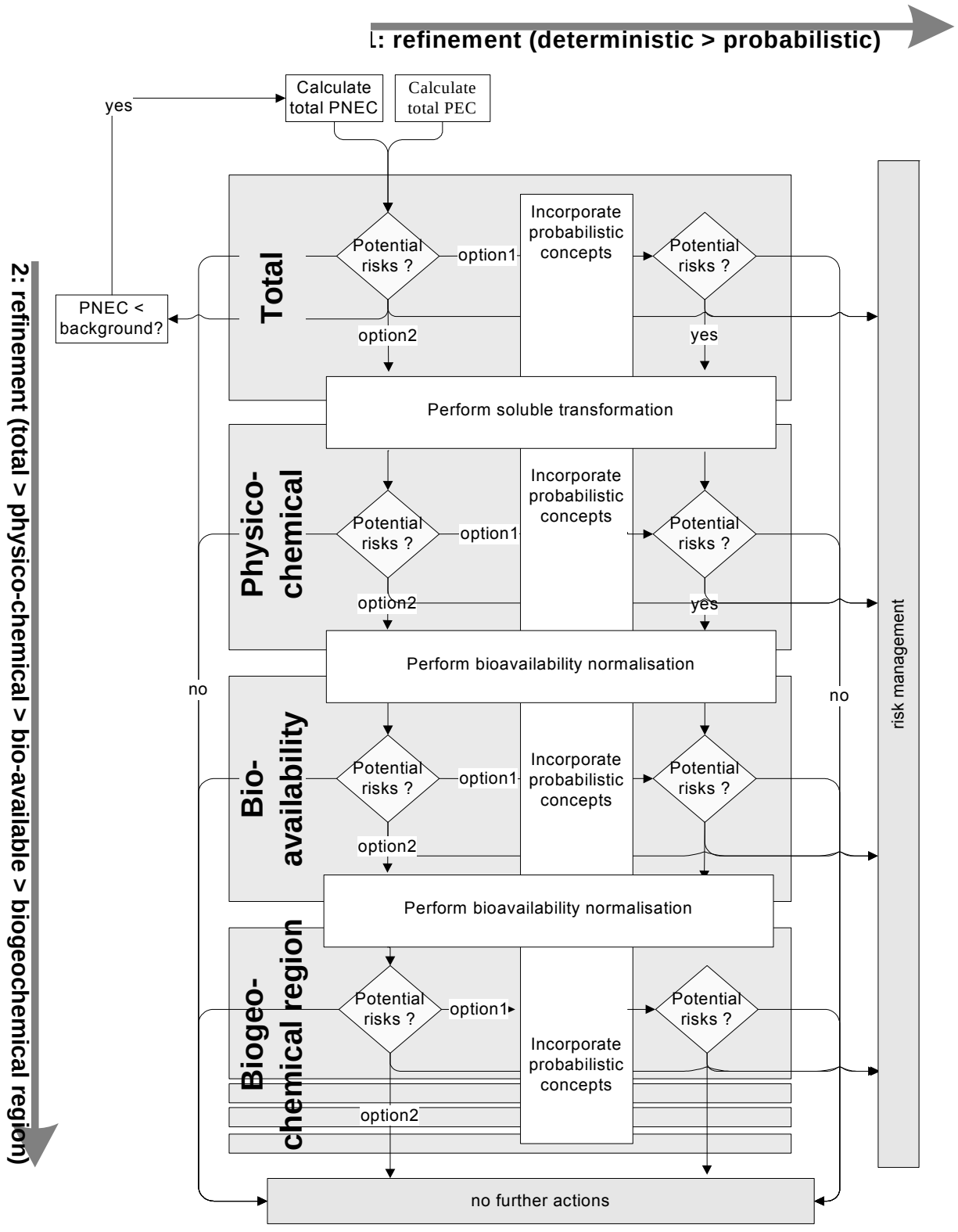


***Figure 1**: Generic tiered approach for performing the risk characterisation for metals/metal compounds (PEC: Predicted Environmental Concentration, PNEC: Predicted No Effect Concentration)*

The possibility for further refinement at every tier is governed by the availability of data, while the need for refinement results from the risk level and/or the magnitude of the required response.

Two dimensions are proposed for possible refinements, although they are not mutually exclusive (visualised as two axes in Figure 1). Concepts relative to bioavailability and biogeochemical regions can be applied to both deterministic and probabilistic assessments. Refinement 1 deals with assessing the bioavailable fraction. Incorporation of the bioavailability concept could be performed at different levels of refinement. A rudimentary but not preferred way of taking into account (bio)availability is the use of dissolved concentrations. The use of speciation models could help to determine the free metal ion concentration, quite often associated with metal toxicity.

But preferentially, the assessment should be performed on a 'bioavailable' basis. For this purpose ambient dissolved metal concentrations and appropriate toxicity-related bioavailability models (eg, Biotic Ligand Model) could be used. For further details see MERAG Fact Sheet 5). It should also be recognized that due to local or regional differences in geochemistry, the physico-chemical parameters influencing bioavailability can be quite different, in a similar way, metal (natural) background will vary to a large extent (see more information in MERAG Fact Sheet 2). A local or regional environmental compartment (water, soil, and sediment) is hence not characterised by one single set of abiotic factors/background, but rather is represented by a range of abiotic factors/metal backgrounds. The abiotic factors variation in space may have a significant impact and should be taken fully into account in the risk assessment process. It is therefore critical to understand which geochemical characteristics influence the toxicity of each metal and metal compound and different biogeochemical ecoregions should be identified where possible. Because biology also plays an important role in determining the level of response to a given metal concentration, this concept may be extended to include the premise that those species that are not present in the region under investigation should be excluded in the environmental threshold derivation (ETV). Examples of ETV's are Predicted No Effect Concentrations (PNEC); Environmental Quality Standards (EQS), etc derivation. Potential risks that metals may pose should be assessed within properly defined specific river/stream/lake eco-regions.

Currently, guidance on the application of the biogeochemical region concept is being developed for the aquatic compartment (Annex 1), but the same concepts apply to the other environmental compartments (sediments and soil).

In the second axis of refinement, ie moving from a deterministic to a probabilistic approach, the inherent spatial and temporal variability and estimate or measurement uncertainty of exposure concentrations and the inter-species variability of effects are fully integrated into the risk analysis. The initial (or screening) deterministic approach uses a simplified and often

unrealistic worst-case single extreme exposure concentration (EEC) (for example Predicted Environmental Concentration (PEC) and single ETV (example PNEC), in which the risk is subsequently quantified as a quotient of single values. This results in a “bright line” where “risk” is assumed if the exposure estimate is greater than the environmental threshold value and “no risk” is ascribed to the alternative. It provides no information about the probability of the occurrence of an adverse effect, which is the true definition of risk. However, because the deterministic quotient is based on worst-case estimates, if a finding of “no risks” is identified at this stage, no further action is required. When sufficient data are available, single point estimates can be replaced by probability distributions which allow assessors to understand the variability and uncertainty associated with both the exposure and effects sides of the risk assessment. Generally, more realistic scenarios are developed, and the probabilistic risk assessment (PRA) results in an evaluation of the probability of occurrence as well as the magnitude of effect.

It should, however, be acknowledged that a PRA is slightly more complex to compute and can be more difficult to communicate to risk managers than a deterministic approach that simply compares two numbers. Therefore, PRA may be more valuable when the risk boundary is approached and less valuable when the deterministic approach indicates a very low or very high risk. Finally, in addition to the PRA, a weight-of-evidence approach (eg, including field assessments, direct toxicity testing, and predictive modelling) can be used to develop more robust risk estimates (for more information on the weight-of-evidence approach, see Fact Sheet 9 on this issue).

2. RISK CHARACTERISATION: DETERMINISTIC VERSUS PROBABILISTIC APPROACH

The key question of environmental risk characterisation of metals is to answer: “What is the likelihood (ie probability) of adverse effects occurring to exposed ecological systems due to exceedance of a toxicity level by an environmental metal concentration?” This question assesses both the probability of occurrence (exposure) and the magnitude of effects. However, for data-poor metals, the key question is usually simplified to: “Is it likely that adverse effects occur to exposed ecological systems due to exceedance of a no-effect level by an environmental concentration?”

2.1 Deterministic risk characterisation approach

Environmental risks are typically estimated in a deterministic way using single point estimates for both exposure and effects. For example, the level corresponding to the protection of 95% of the species, ie the PNEC value, is compared to a reasonable worst-case exposure concentration in the environment, ie the PEC value, estimated as a high-end value (eg, 90th percentile) (see Figure 2). This is done separately for each of the environmental compartments of concern.

Inland environmental compartments that are distinguished in this regard are, for example, in Europe (TGD 2003):

- Aquatic ecosystem (including sediment);
- Terrestrial ecosystem (including both the below- and above-ground compartments);
- Atmosphere;
- Aquatic and terrestrial top predators;
- Micro-organisms in sewage treatment plants.

Marine environmental compartments:

- Aquatic ecosystem (including sediments);
- Top predators.

The estimations of PEC and PNEC are considered in other Fact Sheets. A list of the different PEC/PNEC ratios that could be considered for the inland and marine environments is given in Table 1.

Local scale	Regional scale
$PEClocal_{water}/PNEC_{water}$*	$PECregional_{water}/PNECwater$*
$PEClocal_{sediment}/PNEC_{sediment}$*	$PECregional_{sediment}/PNEC_{sediment}$*
$PEClocal_{soil}/PNEC_{soil}$	$PECregional_{agr.soil}/PNECsoil$
$PEC_{stp}/PNEC_{micro\text{-}organisms}$	
$PEClocal,oral_{fish}$ vs $PNEC,oral_{fish}$*	
PEClocal, $oral_{worm}$ vs $PNEC,oral_{worm}$	

Table 1: *Overview of PEC/PNEC ratios considered in the EU for inland risk assessment and marine risk assessment (marine indicated with * if applicable) for different geographical scales*

The potential risks of the metal in each environmental compartment are calculated as point estimates, being the quotient of single values representing exposure and effects (ie

PEC/PNEC also known as the Risk Characterisation Ratio (RCR) ratio[3] or Risk Quotient (RQ)). **A RCR value smaller than one (1) indicates that no further actions are required. A RCR value exceeding one (1) suggests that the metal is present at levels that may pose a risk to ecological receptors.** Further refinement on the exposure side (additional monitoring data, using site-specific information instead of defaults, reconsideration of operational conditions and/or risk management measures) or a reality check of the derived PNEC value (eg. if the PNEC is close to or even below reported background concentrations, the PNEC could be revisited) is required until RCR is below one (1). This can require several iterative loops. If no further refinement by taking into account bioavailability is possible or feasible, risk reduction measures could be considered on the basis of a RCR.

2.2 Probabilistic risk characterisation approach

2.2.1 General

Single point or deterministic modelling involves using a single "best guess" or "worst-case" estimate of each variable within a model to determine the model's outcome(s). "What if" scenarios are then conducted to determine how much that outcome might vary, depending upon which input value is selected (for example, for metals, lower and upper estimates for partitioning coefficients are typically used in the exposure assessment). Probabilistic risk assessment is similar to developing "what if" scenarios in that it generates a number of possible results and their attendant probabilities. However, it goes one step further by effectively accounting for every possible value that each variable could take and weighting each possible scenario by the probability of its occurrence. Probabilistic risk assessment achieves this by applying a probability distribution to each variable. Guidance on probabilistic risk assessment methods can be found in U.S. programs (ECOFRAM 1999; U.S. EPA 2001), EU research programs on plant protection products (Hart 2001; EUFRAM 2005), and scientific literature (Warren-Hicks and Hart 2010).

In a PRA, the point estimates (PEC and PNEC), used in the deterministic approach, are replaced by probability distributions representing the inherent variability (and uncertainty in case variability and uncertainty cannot be properly distinguished) in both the exposure and effect parameters (see Figure 2). Variability represents inherent heterogeneity or diversity in a well-characterised population or measurement method. Fundamentally a property of nature, variability is not reducible through further measurement or study. Uncertainty, which can also be incorporated into the probability distribution, represents partial ignorance or lack of perfect

[3] Note that in some risk assessment schemes (eg, plant protection products in Europe), the RCR value is expressed as the inverse of this (ie PNEC/PEC); as a consequence, an RCR<1 indicates risk.

information about poorly characterised phenomena or models (eg, sampling or measurement error) and is, however, reducible, generally through generation of more data to increase the number of measurements. For more information, a separate MERAG Fact Sheet (Fact Sheet 7) is dedicated to uncertainty analysis.

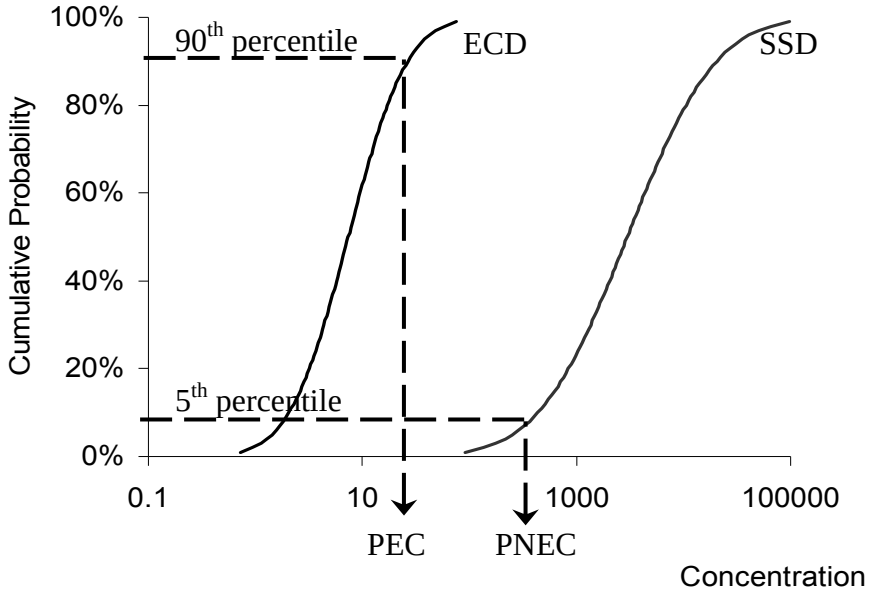


***Figure 2**: Visualisation of the deterministic concepts PEC (Predicted Environmental Concentration) and PNEC (Predicted No Effect Concentration) versus the probabilistic concepts of ECD (Exposure Concentration Distribution) and SSD (Species Sensitivity Distribution)*

Temporal and spatial variations of metal concentrations in the environment are captured in a variability distribution, called the Exposure Concentration Distribution (ECD) (see Figure 2 left side). The different sensitivities of various species to a metal are described in a variability probability distribution could be called the effect concentration distribution. The most common effect concentration distribution is the Species Sensitivity Distribution (SSD) and represents inter-species variability (see Figure 3 right side). Both ECD and SSD can be represented as probability density functions or cumulative probability distributions (Figure 3 presents cumulative probability distributions). Note that the probability distributions can have different interpretations depending on the data that were used to estimate them. For example, the probability distribution on the effects side could also represent the spatial variability of the PNEC due to spatial variability of bioavailability or the individual dose response curve of one particular species (eg, top predator). Possible representations of the exposure and effects distribution are:

Exposure: - Spatial variations of the exposure concentration
- Temporal variations of the exposure concentration (eg, at a local site)
- A combination of the representations above (as eg, in a regional assessment)

Effects: - Inter-species sensitivity (ie SSD, this is the most common form)
- Spatial/Temporal variability of PNEC (following variability in bioavailability)
- Intra-species sensitivity (dose-response curve of one species)
- A combination of the representations above

The guidance on the characterisation of the ECD and the SSD is considered in the Fact Sheets #2 and #3 on exposure and effects assessment, respectively.

Figure 3 provides guidance on how to characterise and interpret probabilistic risk given the ECD and the SSD. Furthermore, guidance is given on how to determine the magnitude of effects and identify the sources of exposure (probability of occurrence) leading to potential risk scenarios. Several methods are possible, each with their strengths and weaknesses. Probabilistic risk assessment is an evolving field for contaminants analysis. The proposed set of methods reflects the current state-of-the-art.

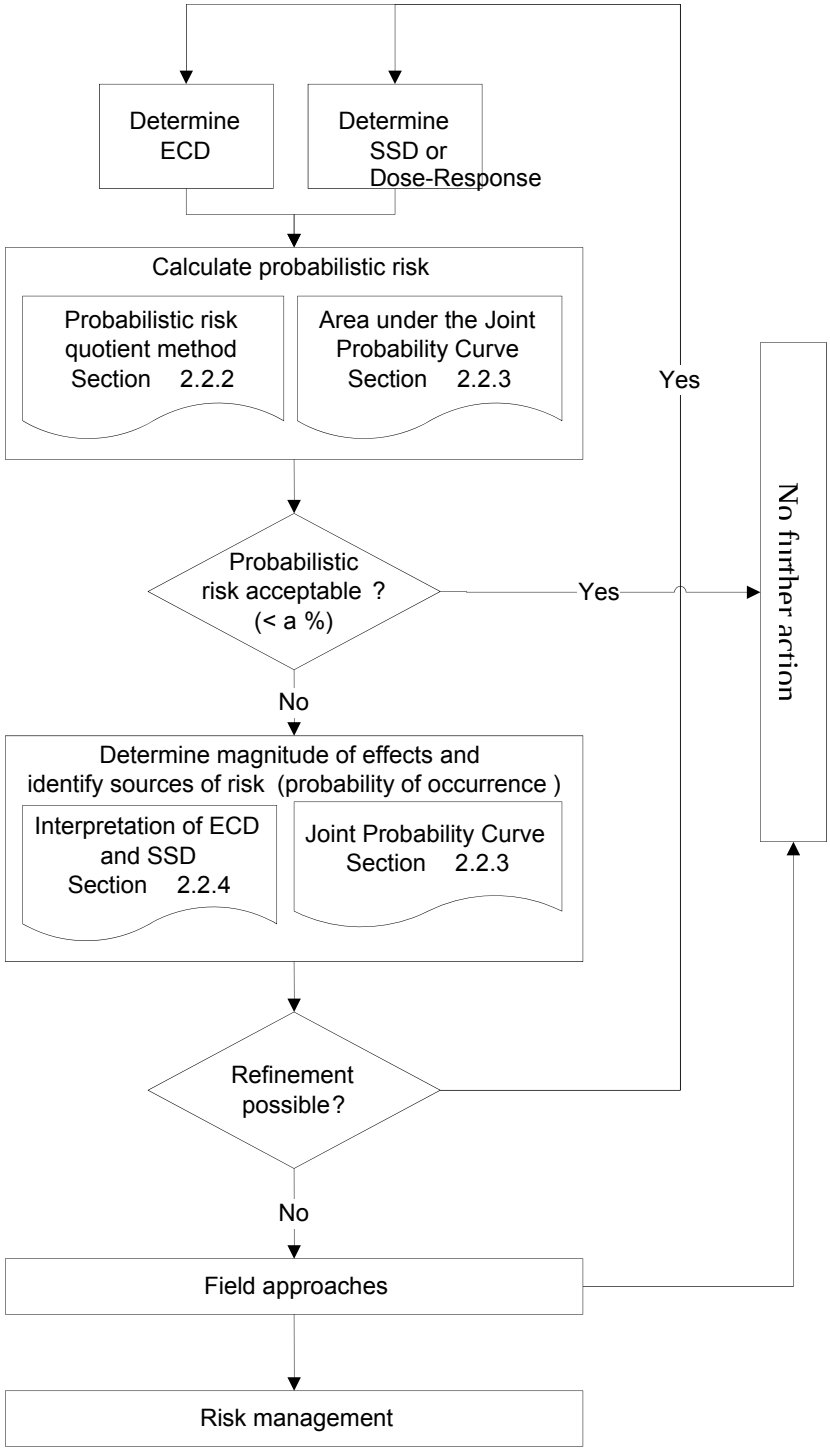


***Figure 3**: Guidance of risk characterisation, interpretation and refinement (field approaches have not yet been completely developed)*

The first step is to calculate the probabilistic risk (see Figure 3). If the calculated risk level is acceptable, no further actions are deemed necessary (in analogy with the deterministic risk characterisation). The probability of some randomly selected exposure concentration exceeding a randomly selected species sensitivity or toxicity value has been demonstrated to

be a common measure of risk (an overview is given in Aldenberg et al (2002)). Guidance on how to derive exposure concentration or toxicity value (eg, one single species value or a geometric mean of values) can be found in the respective Fact Sheets on exposure and effects assessment.

$$Risk = P\left(Exposure\ Concentration > ToxicityValue\right)$$

where *P*( ) denotes "the probability of"

The probabilistic risk can alternatively be defined as the probability that the risk quotient becomes larger than one. This can be written as:

$$Risk = P\left(\frac{ExposureConcentration}{ToxicityValue} > 1\right) = P\left(Risk\ Quotient > 1\right) \qquad \text{Equation (1)}$$

This definition is intuitively easier to understand because it is an extension of the well-known and widely accepted Risk Characterisation Ratio (RCR) or PEC/PNEC ratio of the deterministic risk assessment (see previous section). The main difference is that the inherent variability of exposure and effects quantified in the ECD and the SSD are considered instead of deriving point estimates as PEC and PNEC. Other probabilistic risk definitions, in which either the exposure concentration or toxicity value is fixed in combination with a probability distribution for, respectively, the toxicity value or exposure concentration, are also possible. For example, the Potentially Affected Fraction (PAF) has been considered as an alternative risk outcome. The PAF assessed the percentage of potentially affected species for a fixed exposure concentration.

The probabilistic risk definition, as defined in equation 1, is more general and considers all possible "what if"-scenarios. This comprises all possible combinations of the exposure concentration and the toxicity values (both toxicity values above and below the deterministic PNEC and both exposure concentrations above and below the deterministic PEC) because these combinations also occur in the real environment, although with differing probability of occurrence. Both (very) sensitive and insensitive species can be exposed to both low and high concentrations in a particular location/region or during a particular season. Or in other words, a probabilistic risk accounts for both the probability of occurrence (expressed by ECD) and the magnitude of effect (expressed by SSD).

Note that a probabilistic risk does not require the specification of the level of protection in the effects assessment (as eg, 95% protection level in SSD) and the exposure assessment (as eg, 90th percentile for PEC). Instead, an acceptability criterion only needs to be specified in the risk characterisation phase. Acceptability criteria for risk management currently are lacking. For deterministic assessments, it is generally accepted that a PEC/PNEC >1 is not acceptable (and becomes less so as the quotient gets larger). But there is no consensus on an acceptable *probability* of this happening, or whether the acceptable probability level changes as the ratio increases. Different acceptable thresholds on probabilistic risk could be defined at the regional and local scales. If the estimated probabilistic risk is smaller than that threshold, no further action is needed. Identification of potential risks (when exceeding that threshold) could be a trigger for further in-depth analysis (eg, considering spatial variability; incorporation of bioavailability) as indicated in Figure 3.

Knowing the probability of risk does not decrease the actual risk. Instead, it provides a better understanding of the risk estimate because likelihood of occurrence of an adverse effect of different magnitudes is provided. This allows the risk manager to differentiate risk statements such as eg, “negligible risk”, “low risk”, “medium risk”, “high risk” or other categories and which risk category is most likely. A deterministic risk estimate only provides a “yes” or “no” answer, without any statement of the likelihood associated with either outcome.

The probabilistic risk can be quantified using several methods (see Figure 3) of which the two most important ones, reflecting the current state-of-the-art, are a) the probabilistic risk quotient method (described in 2.2.2) and b) the area under the joint probability curve (described in 2.2.3). Mathematically, it can be shown that both methods result in the same risk estimate (Aldenberg et al 2002). Consequently, the two methods are equally valid and either method can be used to estimate the probabilistic risk. The risk assessor can therefore apply the method that is in his/her opinion easier to understand, apply, and communicate.

Box 1: Consideration of disadvantages of probabilistic risk characterisation	
Criticism/disadvantage	**Clarification**
No common standard/consensus on methods to be used	Several frameworks in literature and ongoing initiatives strive for standardisation and guidance (eg, ECOFRAM, EUPRA, EUFRAM).
Complex output/complicated, difficult to communicate and interpret	This is an issue for some of the probabilistic outputs (eg, joint probability curve). However, some probabilistic concepts are easily accessible, interpretable and communicable because these are extensions of the deterministic concepts (eg, exposure concentration distribution, species sensitivity distribution and risk quotient distribution).
How to deal with probabilistic risk in decision-making? (acceptability criteria)	Acceptability criteria for risk management are currently still lacking.
Lack of experience	On an academic level, there is a lot of literature illustrating probabilistic assessments. In risk assessment practice, there is already experience in other fields (eg, EU Water Framework Directive, UK consenting of dangerous substances in discharges to surface waters, U.S. EPA Superfund). In addition, “lack of experience” is a weak argument because it can be used against any scientific development. Also, probabilistic methods are well established in other fields such as engineering and finance.
Probabilistic risks contain less conservatism or are a mathematical artifact to decrease risk	A probabilistic risk does not decrease the actual risk. Instead, it is a true, more robust estimate of the risk and therefore allows the risk manager to differentiate between different risk levels or the probability of occurrence of an adverse outcome. Probabilistic methods deal with uncertainty differently (by separating it from risk characterisation) and are for this reason a precautionary-driven approach (Verdonck et al 2005).

To assist with the risk communication, the species that will be impacted or the amount of impact to an individual species (ie magnitude of effect) should be quantified, and which monitoring sites or exposure scenarios result in different risk probabilities should be identified (i.e probability of occurrence). In this way, different management actions can be implemented depending on the probability of occurrence (ECD) in combination with the magnitude of effects (SSD).

2.2.2 Probabilistic risk quotient method

General case

This method is the direct translation of the mathematical definition of probabilistic risk (the probability of some randomly selected exposure concentration exceeding a randomly selected toxicity value):

$$Risk = P\left(\frac{ExposureConcentration}{ToxicityValue} > 1\right) = P\left(Risk\,Quotient > 1\right) \quad \text{Equation 1}$$

Exposure and effects are characterised by probability distributions ie respectively, the ECD and the SSD. Many random samples are drawn (typically Monte Carlo[2] techniques are used) from both ECD and SSD distributions and for each set of samples, the ratio Exposure Concentration/Toxicity Value is calculated. All these ratios form the risk quotient distribution. The obtained risk quotient distribution is used to express the probability that the exposure concentration exceeds the toxicity value (Figure 4). This probability of some randomly selected environmental concentration exceeding some randomly selected toxicity value for the metal/metal compound under consideration is equal to the probability that the risk quotient becomes larger than 1 and can therefore be regarded as a measure of adverse effects. It can also be used to determine the probability of a larger effect, eg, the probability of the risk quotient exceeding 10 or 100. More information can be found in Verdonck et al (2003). In case the ECD and SSD are both (log)normally distributed, the lookup Table 5.3 of Aldenberg et al (2002) can also be used. In the example of Figure 4, there is 13% probability that any possible exposure concentration will exceed any possible toxicity value (both larger and smaller than the deterministic PNEC, derived as 5th percentile from SSD).

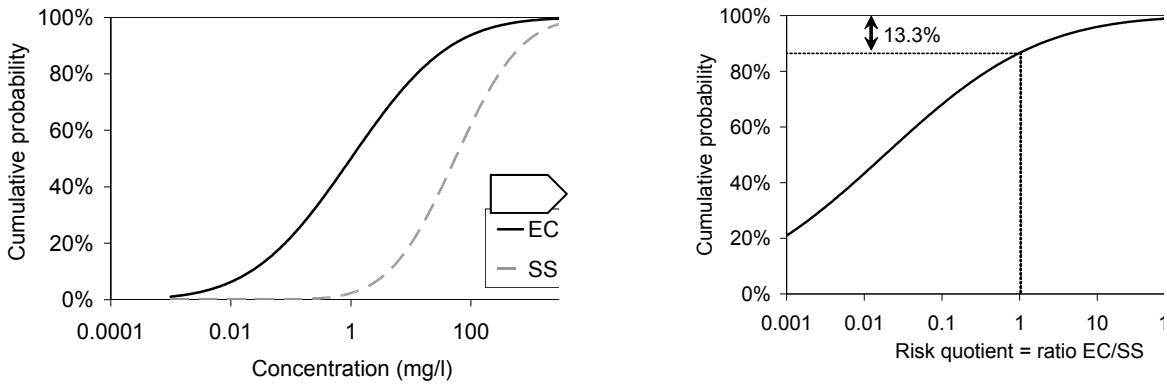


***Figure 4**: Probabilistic framework in case extensive exposure/effects data are available*

Specific sub-cases

In the literature, special cases of probabilistic risk (usually of a semi-probabilistic nature) are used in which a fixed PEC or fixed PNEC are compared with a probability distribution, respectively a SSD or an ECD. These do not include all information on exposure and effects (and therefore are neglecting species with toxicity values smaller than the PNEC or exposure concentrations larger than PEC). These hybrid-versions add to the complexity of the interpretation of possible probabilistic outcomes. Nevertheless, they can be useful in cases where there is sufficient information to estimate a probability distribution for either exposure or effects but data are lacking for, respectivel, effects or exposure. Special attention should, however, be paid to the interpretation.

2.2.3 Joint probability curve

Another way of integrating the ECD and the SSD is through the use of so-called Joint Probability Curves (JPCs) (ECOFRAM 1999; Giesy et al 1999). In JPCs, the cumulative probabilities of the ECD and the SSD for each concentration are plotted in a graph. An example is given in Figure 5. For concentration a, the fraction of species affected, 20% (ie the cumulative probability of the SSD or the magnitude of effects), is plotted against the exceedance exposure probability 22% (ie the complement of the cumulative probability of the ECD) (see line a in Figure 5). The same exercise is repeated for concentration b and for any other concentration (see line b in Figure 5). The resulting JPC presents the fraction of species affected for each exposure exceedance or the exposure exceedance for each fraction of species affected. JPCs come in several forms. Aldenberg et al (2002) gives an overview.

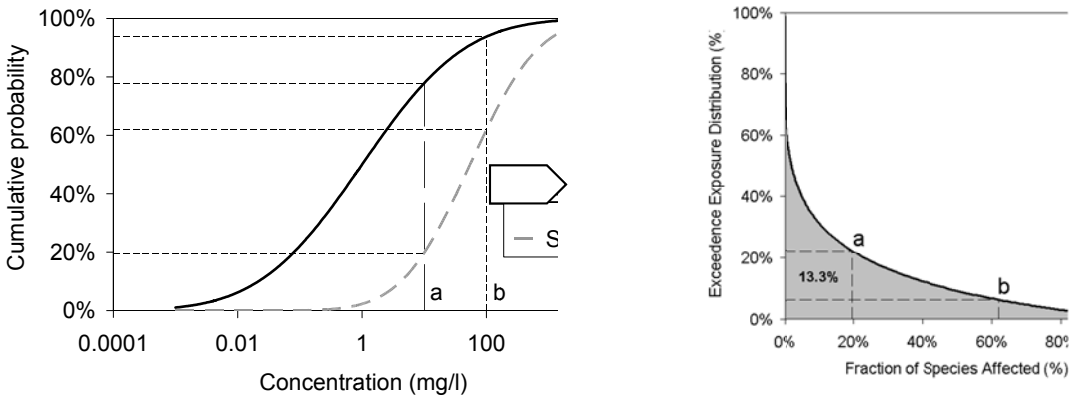


Figure 5*: Exposure Concentration Distribution (ECD), Species Sensitivity Distribution (SSD) and Joint Probability Curve (JPC) (type cumulative profile plot) with its Area Under the Curve (AUC)*

JPCs can be used for:

1. Calculation of the probabilistic risk: The area under the joint probability curve (shaded in Figure 5) is equal to the probabilistic risk and offers an alternative way of calculating the probabilistic risk. This probability of an exposure concentration exceeding a toxicity value is 13.3% in the hypothetical example of Figure 5.
2. Exploration of the magnitude of effects versus probability of occurrence: All possible combinations of the protection level (eg, fraction of species affected or percent mortality for a single species) versus percentage of exposure concentrations exceeded are plotted in one graph. The derivation of the JPC offers a useful tool for communication of risks because it allows "what-if" questions to be addressed. It also provides the risk assessor and risk manager a method for assessing the effects of changes in assumptions, such as the choice of a different protection level (eg, percentile of species affected).

JPCs often result in interpretation and communication issues by non-experts. For this reason, the interpretation of the ECD and/or SSD curves is much easier and straightforward as risk assessors and managers are more familiar with these curves (see next section). The ECD and/or SSD curves contain the same information as in a JPC.

2.2.4 Interpretation of ECD and/or SSD curve

Some risk assessors prefer to interpret the ECD and SSD curves directly. One could define an acceptable effect level (fixed PNEC) and calculate the probability that the exposure concentrations exceed this level. An example is given in Doyle et al (2003). Depending on the type and amount of data available, the fixed PNEC can be derived from assessment factors or, when sufficient data are available, from an SSD (as in Figure 6) or dose-response function. In the hypothetical example illustrated in Figure 6, the exposure concentration in 42% of the

monitoring locations will exceed the PNEC (defined as 95% protection level from the SSD). In addition, the locations of the monitoring stations or the particular exposure scenarios leading to exceedance of the PNEC can also be identified.

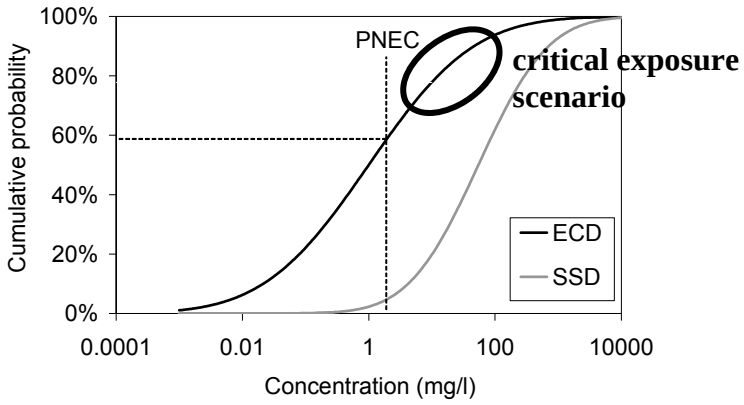


***Figure 6**: Exposure Concentration Distribution and Species Sensitivity Distribution*

Similarly, a fixed exposure level (fixed PEC) can be determined and the percentage of species affected at that level can be calculated (no example shown here). It is recommended that this exercise be repeated for several exposure and effect levels when exploring the sensitivity of varying threshold levels. When only a single, fixed PNEC is compared with an ECD, although relatively easy to interpret, only a one-sided view on the actual risk is obtained.

2.2.5 Spatially referenced regional risk characterisation

In a standard risk assessment, worst-case approaches are typically used, but unfortunately these do not account for the large spatial variation in both exposure and effect concentrations. As a consequence, exposure and effect concentrations for metals typically overlap at regional level (Figure 7), and worst-case assumptions for both parameters (ie high exposure and low effect concentrations) may result in overly conservative conclusions.

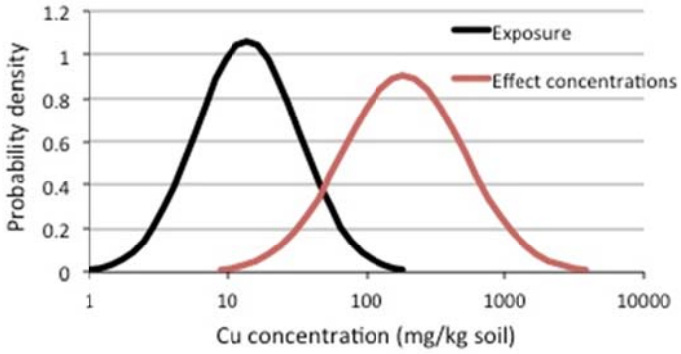
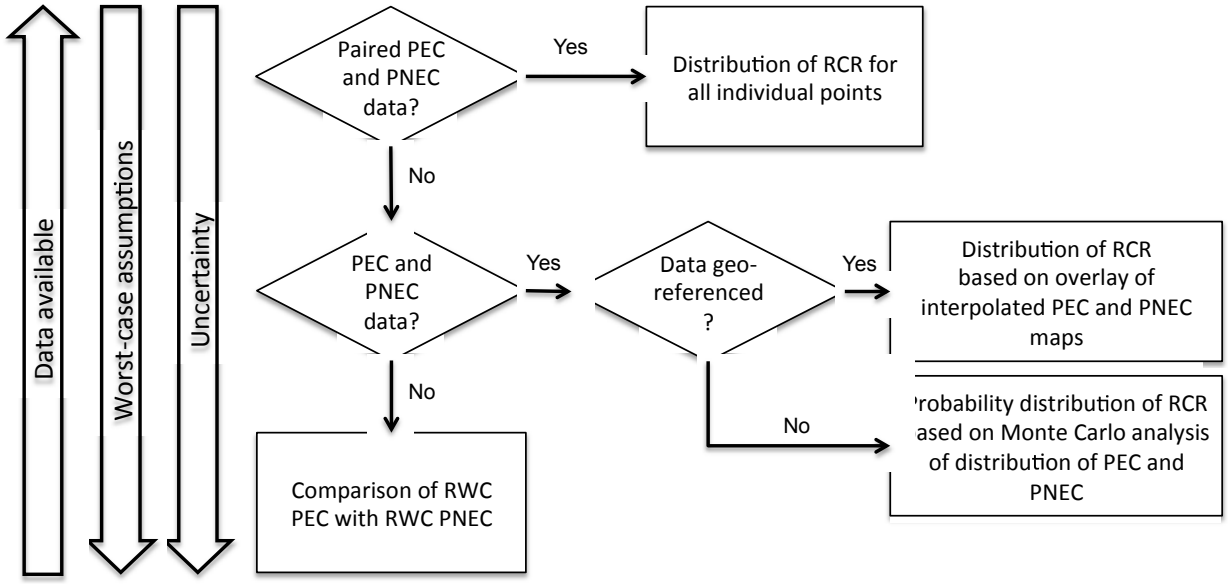


***Figure 7**: Probability distribution of Cu exposure concentrations in agricultural soil and selected effect concentrations (no observed effect concentration (NOEC) or effect concentration affecting 10% of organisms (EC10)) without bioavailability correction*

A sound risk assessment for metals in water, sediment, or soil must preferentially take into account the spatial variation of both exposure and effects concentrations. Data availability for metal concentrations and physico-chemical parameters influencing the toxicity of metals differs largely across different countries or regions, resulting in varying degrees of (worst-case) assumptions on exposure and effects of metals (Figure 8). The use of different sampling protocols and analytical methods further complicates comparison and consolidation of differently generated monitoring data sets. Based on harmonised datasets, it becomes clear that metal bioavailability (effects) and background concentrations (exposure) are often significantly correlated and therefore, exposure and effects data should preferentially not be treated independently to derive generic reasonable worst-case (RWC) scenarios for risk assessment. Whenever possible, regional and local environmental risk assessments for metals must be based on comparison of site-specific exposure and effects data that account for local bioavailability and species sensitivity differences, and the distribution of the resulting site-specific risk characterisation ratios (Oorts and Schoeters 2014).



PEC = Predicted Environmental Concentration
PNEC = Predicted No Effect Concentration
RCR = Risk Characterisation Ratio, i.e. PEC/PNEC
RWC = Reasonable Worst Case

Figure 8: *Data availability and uncertainty for regional risk assessments for metals*

ANNEX 1: ADDED VERSUS TOTAL RISK APPROACH AND ITS USE IN RISK ASSESSMENT AND/OR ENVIRONMENTAL QUALITY SETTING

1 INTRODUCTION

The presence of metals in the environment due to natural processes (resulting in a natural background concentration of metals in all environmental compartments, including organisms) and the chemical processes that affect the speciation of metals in the environment have implications for both the environmental exposure and effects assessment of metals and thus for the risk characterisation/environmental quality setting of metals in general.

In order to deal with the presence of a natural background, different concepts have been developed such as the *Added Risk approach*[4] *(ARA) or the Total Risk approach* (TRA). The total risk approach (TRA) assumes that "exposure" (PEC_{TOT}) and "effects" ($PNEC_{TOT}$) should be compared on both the fraction comprising the natural background and the added anthropogenic component. The risk characterisation can be done at different levels, for example, on total, total dissolved, or bioavailable fractions. The added risk approach (ARA) assumes that only the anthropogenic added fraction of a natural element contributes to the risk for the environment.

Although the ARA approach acknowledges that negative effects from the bioavailable fraction of the background concentration on some organisms in the ecosystem may occur or that organisms may even become acclimated/adapted to it, from an environmental policy point of view such effects may be ignored and may even be regarded as desirable, because these effects theoretically may lead to an increase in ecosystem differentiation or biodiversity (Crommentuijn et al 1997).

For the soil compartment, a significant difference in extractability between the added fraction and the natural background concentration present in soil results in a significant difference in bioavailability of both fractions. If this difference persists after long-term equilibration of added metals in soil, this can also be a reason to select the added approach instead of the total approach. Vanadium and boron are examples of elements that show low partitioning to soil

[4] The concept was developed and published by: T Crommentuijn et al (1997). Maximum permissible concentrations and negligible concentrations for metals, taking backgrounds concentrations into account, Netherlands, Institute of Public Health and the Environment, RIVM, Bilthoven, RIVM report N° 601501001

and hence high water extractability of the added fraction compared to the natural background concentration. In theory, the use of the ARA avoids the potential problem of deriving Predicted No Effect Concentration (PNEC) / Environmental Quality Standard (EQS) values below the natural background concentration, as could be the case when the TRA is used. In the ARA, both the "Predicted Environmental Concentration"(PEC) and the "Predicted No Effect Concentration" (PNEC) are expressed as anthropogenically added metals, resulting in an "*added* Predicted Environmental Concentration" (PEC_{ADD})[5] and "*added* Predicted No Effect Concentration" ($PNEC_{ADD}$)[6], respectively.

Currently, no clear guidance is available on how to deal with elements that have a natural background concentration in the environment, such as metals. Both approaches have been used in the EU Risk Assessments for metals: eg, "added risk approach" (according to Struijs et al 1997 and Crommentuijn et al 1997) – cfr. Zn RAR - and the "total risk approach" – cfr. Cd RAR, Pb RAR and Cu RAR.

In general, it can be stated that the total risk approach may be the most scientifically defensible option in the context of a risk assessment, but for regulatory purposes (eg, the setting of environmental quality standards) the added risk approach may have merits. Therefore preferably, environmental risks or compliance checking should be based on the TRA. However, PNEC/EQS values in this approach below natural background levels may be generated if:

- The PNEC/EQS has been set to an unrealistically low level simply because of a (too) conservative approach adopted in the PNEC/EQS derivation (ie a large assessment factor (AF)) to compensate for uncertainties arising from a lack of reliable (eco)toxicological data.
- The PNEC/EQS was set using ecotoxicity tests with organisms cultured/tested under conditions of low metal concentrations compared with the surface water background levels (ie organisms locally may have adapted to higher natural concentrations). This may occur, especially for metals with a significant background concentration in relation to the estimated PNEC/EQS.

Setting PNEC/EQS below the natural background level would result in a PNEC/EQS ratio that serves little regulatory purpose and is scientifically indefensible. Furthermore, many water bodies would fail the PNEC/EQS even though there is no risk to biota. A pragmatic way to

[5] $PEC_{add} = PEC_{total} – Cb_{region/site}$
[6] $PNEC_{add} = PNEC_{tot} – Cb_{culture\ medium}$

overcome this problem is:

- to evaluate the scope for refining the PNEC/EQS by reducing uncertainty (including making a correction for bioavailability- BRA approach) and/or
- to use the added risk approach (ARA).

Guidance on the use of the total risk approach (TRA) and added risk approach (ARA) is further outlined in detail below. More guidance on how to establish the natural background can be found in MERAG Fact Sheet 2.

2 USE OF TRA AND ARA CONCEPTS IN THE CONTEXT OF CHEMICAL SAFETY MANAGEMENT (EG, RISK ASSESSMENT AND ENVIRONMENTAL QUALITY STANDARD SETTING)

2.1 Application

Potential environmental risks (RCR) for use in both chemicals safety management and EQS setting are characterised in the TRA approach based on the following quotient:

$$RCR = PEC_{TOT}/PNEC_{TOT}$$

In the ARA the following approaches are used depending on the regulatory context:

- Use in chemicals safety management

Potential environmental risks (RQ) are characterised based on the following quotient:

$$RCR = PEC_{ADD}/PNEC_{ADD}$$

Where $PEC_{ADD} = PEC_{TOT} - Cb_{site/region}$ and $PNEC_{ADD} = PNEC_{TOT} - Cb_{culture\ medium}$

With $Cb_{site/region}$ the background concentration of the specific site/region under investigation; $Cb_{culture\ medium}$ the metal concentration in the culture media.

- Use in EQS settings

Although the same principles apply for EQS settings, the added risk approach is used somewhat differently. Indeed compliance of the monitoring data (PEC_{TOT}) with the proposed EQS (ie PNEC) is estimated after addition of the $Cb_{site/region}$ to the $PNEC_{ADD}$. Compliance checking is therefore realized by comparing:

PEC_{TOT} with $PNEC_{ADD}$ (ie $PNEC_{TOT} – Cb_{culture\ medium}$) + $Cb_{site/region}$

2.2 Further considerations when using the added risk approach

However, the added risk approach should be considered with caution for the following reasons:

- This approach ignores the possible contribution of the natural background ($Cb_{culture\ medium}$ /$Cb_{site/region}$) concentration to the toxic effects of metals to ecological systems. As currently used in risk assessment exercises (eg, Zn RAR), only the anthropogenic added fraction of a natural element that contributes to the risk for the environment is considered. However, organisms are not able to distinguish between the natural and the anthropogenic bioavailable part of the metal present in the environment. Consequently, part of the natural background will be bioavailable and could therefore contribute to the total bioavailable metal concentration to which the organisms are exposed and to which organisms could have been adapted, too.

- In order to use this approach correctly, the natural background of a particular location and/or a specific region ($Cb_{site/region}$) needs to be established (see MERAG Exposure Fact Sheet #2). Limited knowledge of the geographical distribution of metal background concentration in ecological systems may hamper the proper implementation of the ARA. However, significant work is ongoing in relation to soil and sediments in the UK, Australia, EU, US and some other countries. Significant efforts have been made to use extensive databases and intrinsic knowledge of the relationships between soil and sediment structural components and geogenic metal concentrations.

- To apply the ARA also involves correctly quantifying the metal concentration to which the test organisms are adapted/acclimatised ($Cb_{culture\ medium}$). Indeed, for several metals (particularly essential metals) a relationship has been demonstrated between the sensitivity of the organism and the metal concentrations of the standard culture condition. Organisms cultured in media with low metal concentrations (which is often the case in standard media) generally are more sensitive to added metals than those cultured in higher metal concentrations. However, organisms often are cultured in media (eg, treated tap water or natural water) with varying metal background concentrations or even with unknown metal concentrations, which therefore complicates the proper interpretation of test results. It must be stressed that culture media often differ from the standard test media used in the toxicity tests, suggesting

that test organisms may not be acclimatised/adapted to the metal background concentrations in toxicity tests. Moreover, metal background concentrations in the culture media ($Cb_{culture\ medium}$) may not be representative of the site/regional background concentrations ($Cb_{site/region}$). It should be noted that proper application of the TRA is also hampered in case only the added metal concentration is known and no information on the metal concentration in the culture medium is reported.

- The ARA 'pragmatically' accounts for the effects of acclimation/adaptation on the sensitivity of the organisms. Indeed, accounting for higher $Cb_{site/region}$ will result in higher region/site EQS/PNEC values[7] (lower sensitivity) or lower potential risks[8] (lower sensitivity). This approach therefore suggests a relationship between the natural background concentration of the site/region ($Cb_{site/region}$) and the sensitivity of the organisms.

- The remaining uncertainty on the effects assessment should be properly characterised. Indeed, the ARA 'allows (opens the door to)' the application of overly conservatism (eg, using large assessment factors, AF to the HC5) because the reality check will always result in EQS/PNEC values ($PNEC_{TOT}$) above the natural background concentrations of the site/region under investigation ($Cb_{site/region}$)[9] (because the AF is not applied to the background).

2.3 Further considerations when using the total risk approach

The total risk approach is based on the following assumptions:

- Contrary to the added risk approach, the total risk approach suggests the natural background ($Cb_{culture\ medium}$ /$Cb_{site/region}$) concentration contributes to the toxic effects of metals on ecological systems. As currently used in risk assessment exercises (eg, Pb VRAR), it assumes that the natural background is physiologically available, thus contributing to the toxicity.
- Following the reasoning that background concentration especially in aquatic culture media are generally lower than those encountered in the environment ($Cb_{site/region} > Cb_{culture\ medium}$), the total risk approach will be more conservative than the added risk

[7] $PNEC_{total;site/region} = PNEC_{add} + Cb_{site/region}$
[8] Added Risks = $(PEC_{TOT} - Cb_{site/region})/PNEC_{ADD}$
[9] $PNEC_{TOT} = PNEC_{ADD} + Cb_{site/region} = (HC5_{ADD}/AF) + Cb_{site/region}$

approach (ie a lower RQ is noted in the added risk approach compared with the total risk approach).

- This results in EQS/PNEC settings based on organisms acclimatised/adapted towards metal background concentrations prevailing in culture media. Such metal concentrations in the culture media often do not reflect those encountered in the environment. Compared to natural levels occurring especially in the aquatic environment, such concentrations are generally low (or even deficient for essential elements). This therefore suggests a higher sensitivity of the organisms, thereby leading to conservative EQS/PNEC settings. Consequently, if background concentrations affect the sensitivity of the organisms, the total EQS/PNEC value only reflects adaptation/acclimation effects to metal background concentrations of the culture media. Ideally, the organisms should have been cultured under conditions relevant for the region under investigation.

- The remaining uncertainty surrounding the effects assessment should also be properly characterised. As a reality check, it is suggested to compare the total EQS/PNEC against the total natural background, to check the environmental relevancy of the effects database used or the EQS/PNEC derived. A revision of the toxicity data set or the derivation approach (eg, size of assessment factors) would be required if the EQS/$PNEC_{total}$ is below background concentration ($Cb_{site/region}$).

2.4. Proposed most scientific approach

Based on the above considerations, the most accurate and ecologically relevant risk characterisation should be made by establishing - on a site-specific-, watershed/basin- or regional basis - both exposure and effects data sets expressed as *bioavailable total fraction* in the environmental compartment/medium ($PEC_{bioavailable}$) and the bioavailable total no effect concentrations (EQS/$PNEC_{bioavailable}$). Tools for assessing and predicting metal bioavailability are available or are being developed for a number of metals (eg, BLM model for water and the AVS-SEM model for sediment).

The bioavailability concept as described here could be further extended to an even more refined approach where both geographical/geological and biological characteristics are considered. This approach is often called the “metallo-region driven approach” (or biogeochemical region concept).

This biogeochemical-region approach arises from the fact that different ecoregions can be identified in terms of the physico-chemical characteristics and boundaries of the environmental compartment as well as in terms of their representative species. Within ecoregions, sub-ecoregions can be differentiated on the basis of the natural background concentration of the metal under consideration and the presence of well-defined abiotic factors that influence metal bioavailability. This concept therefore recognises that bioavailable background concentrations of a metal in a given ecoregion can differ from one ecosystem to the other, resulting in different sensitivities of organisms to the toxic effects of metals due to adaptation. This approach further suggests that when characterising the sensitivity of the ecosystem, instead of using generic species sensitivity distributions comprised of test organisms from any location, it is preferable to use endemic test organisms representative for the natural environment under investigation (Figure A1).

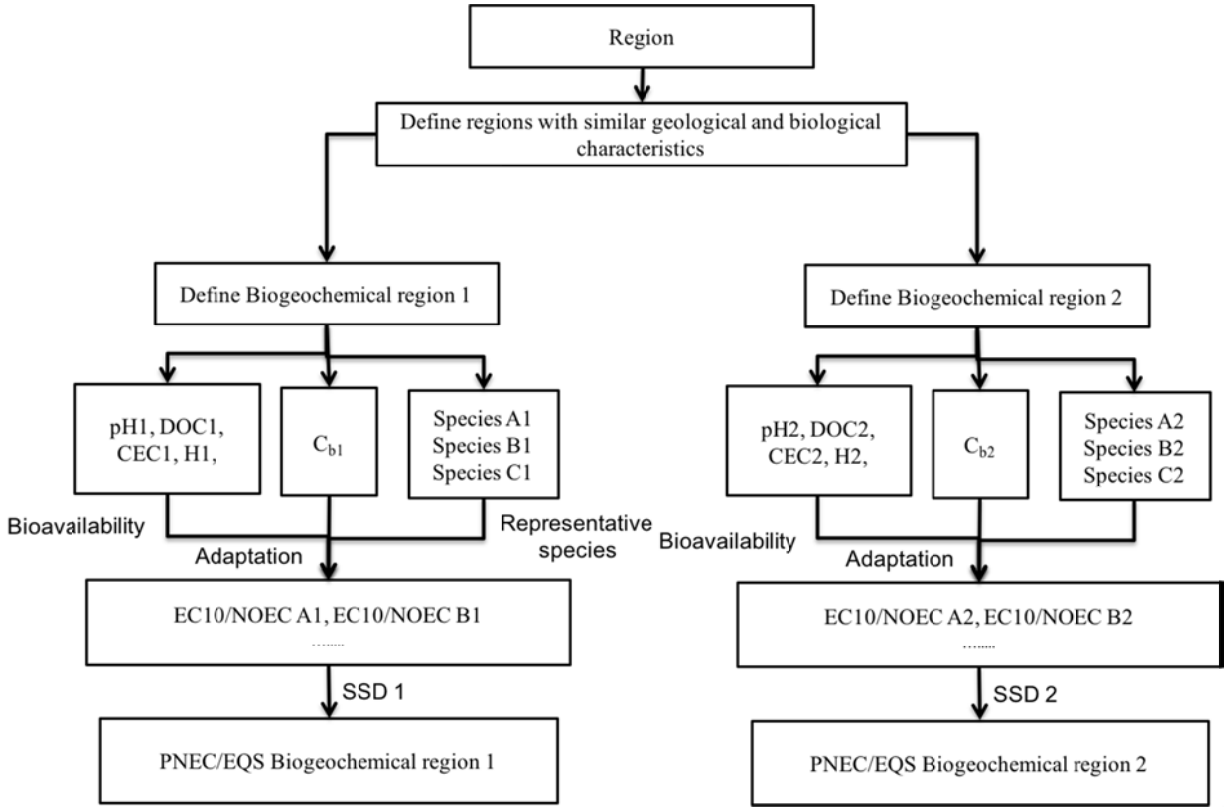


Figure A1: *Schematic overview of the biogeochemical region concept*

The Biogeochemical-region approach will further strengthen the understanding of the *biogeochemical-region specific biodiversity* related to metal background levels. The need for the Added Risk concept for the environmental risk assessments of metals within Chemical Safety Frameworks and EQS settings, would disappear when bioavailability is fully integrated into both the effects and exposure estimations. The risk assessors and risk managers would need to know specific biogeochemical region class(es) relevant for the region(s) under assessment, and their associated characteristics.

2.5 Proposed pragmatic tiered approach

Some regulatory initiatives (eg, the Water Framework Directive) require that the biogeochemical-region concept be further developed before it can be applied. Consequently, in Figure A2, a tiered decision tree is presented to facilitate the expert judgment choice for using either the ARA or TRA in the absence of biogeochemical models. The choice of the approach is mainly based on the comparison of the PNEC/EQS values and natural background levels (see Section 1 of Annex 1) but can also be driven by data availability or by requirements set out in a regulatory context. If the data allows it, preference should be given to

the TRA with bioavailability incorporation (tier 2-3). However, if the data and/or models are not available, the exercise could be started with approaches that require fewer resources and efforts, such as tiers 1 and 1'. In any event, if the effects data are considerably above the background concentration, the difference between using the added or total risk approach could be negligible.

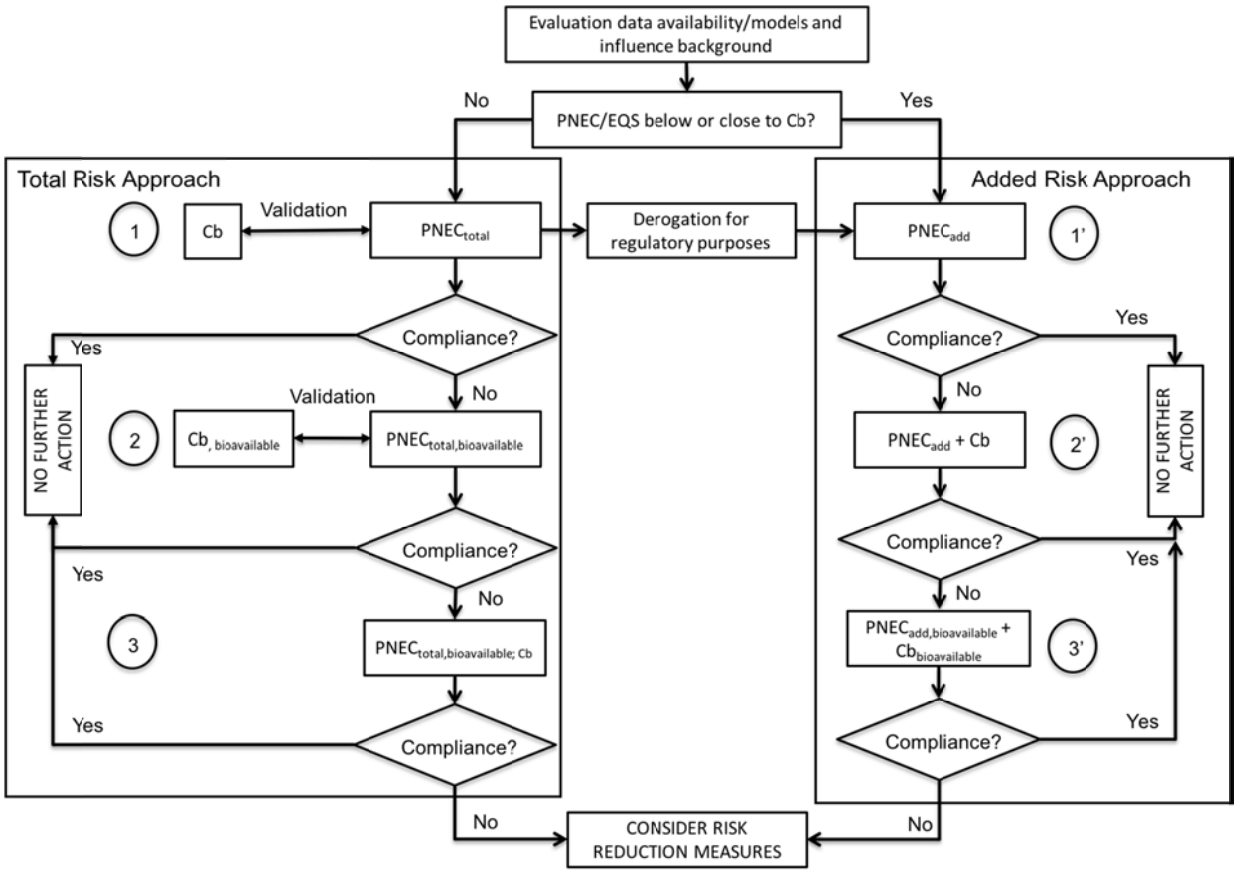


Figure A2: *Tiered approach on potential application of total versus added risk concept*

The individual steps of the decision tree are described below for both approaches.

Total Risk Approach

1. As a first step, it is strongly recommended to check the ecological relevancy of the proposed PNEC value by comparing the total PNEC with the natural background of the site/region ($Cb_{site/region}$). A revision of both the data set and/or the derivation approach would be required if the $PNEC_{TOT, total\ dissolved} < Cb_{site/region, total\ dissolved}$.

- Use in chemicals safety management

Potential environmental risks (RQ) are characterised based on the following quotient:

$$RQ = PEC_{TOT, total\ dissolved} / PNEC_{TOT, total\ dissolved}$$

- Use in EQS settings

Compliance checking is therefore checked by comparing:

$$PEC_{TOT, total\ dissolved} \text{ with } PNEC_{TOT, total\ dissolved}$$

2. If no compliance can be reached, a further refinement is possible when models are available to account for bioavailability of metals in the environmental matrix of concern. In the case of the TRA, both the PNEC and PEC should be corrected for bioavailability (see Fact Sheet 5 for further details). As a validation step, it is strongly recommended to check the ecological relevancy of the proposed PNEC value by comparing the *bioavailable* PNEC with the *bioavailable* natural background of the site/region ($Cb_{site/region;\ bioavailable}$). A revision of both the data set and/or the derivation approach would be required if the $PNEC_{TOT,\ bioavailable} < Cb_{site/region, bioavailable}$.

- Use in chemicals safety management

Potential environmental risks (RQ) are further characterised based on the following quotient:

$$RQ = PEC_{TOT, bioavailable} / PNEC_{TOT, bioavailable}$$

- Use in EQS settings

Compliance checking is therefore checked by comparing:

$$PEC_{TOT, bioavailable} \text{ with } PNEC_{TOT, bioavailable}$$

3. The most accurate and ecologically relevant approach would be to correct the effects and exposure data for bioavailability and acclimation or adaptation differences (~Cb). As the bioavailable fraction of both the natural background concentration and the anthropogenic amount of the metal are considered as potentially contributing to toxic effects, the use of the total risk approach is recommended, resulting in a $PNEC_{TOT,\ bioavailable;\ Cb}$.

- Use in chemicals safety management

Potential environmental risks (RQ) are characterised based on the following quotient:

$$RQ = PEC_{TOT,\ bioavailable} / PNEC_{TOT,\ bioavailable;\ Cb}.$$

- Use in EQS settings

Similarly, compliance of the proposed EQS with the monitoring data is based on the comparison between the site/region specific $PEC_{TOT,\ bioavailable}$ and the $PNEC_{TOT,\ bioavailable;\ Cb}$

Added Risk Approach

1'. The first tier in compliance checking in a regulatory context when using the ARA would be to correct the PNEC for background concentration and therefore to compare the $PEC_{TOT,\ total\ dissolved}$ with the $PNEC_{ADD,\ total\ dissolved}$. If the $PEC_{TOT,\ total\ dissolved}$ is below the $PNEC_{ADD,\ total\ dissolved}$ then consideration of the background (as in tier 2') will only make this difference bigger. This simple first step would ensure that only sites of concern are taken through the tiers.

- Use in chemicals safety management

Potential environmental risks (RQ) are characterised based on the following quotient:

$$RQ = PEC_{TOT,\ total\ dissolved} / PNEC_{ADD,\ total\ dissolved}$$

Where $PNEC_{ADD,\ total\ dissolved} = PNEC_{TOT,\ total\ dissolved} - Cb_{culture\ medium,\ total\ dissolved}$

- Use in EQS settings

Compliance checking is checked by comparing:

$PEC_{TOT,\ total\ dissolved}$ with $PNEC_{ADD,\ total\ dissolved}$ (ie $PNEC_{TOT,\ total\ dissolved} - Cb_{culture\ medium,\ total\ dissolved}$).

2'. In the second tier, both the PEC and PNEC are corrected for background concentrations. This approach also suggests the 'correct' estimation of the culture medium and natural site/region background concentrations.

- Use in chemicals safety management

Potential environmental risks (RQ) are characterised based on the following quotient:

$$RQ = PEC_{ADD,\ total\ dissolved} / PNEC_{ADD,\ total\ dissolved}$$

Where $PEC_{ADD,\ total\ dissolved} = PEC_{TOT,\ total\ dissolved} - Cb_{site/region,\ total\ dissolved}$ and $PNEC_{ADD,\ total\ dissolved} = PNEC_{TOT,\ total\ dissolved} - Cb_{culture\ medium,\ total\ dissolved}$

- Use in EQS settings

Compliance checking is checked by comparing:

$$PEC_{TOT,\ total\ dissolved} \text{ with } PNEC_{ADD,\ total\ dissolved} \text{ (ie } PNEC_{TOT,\ total\ dissolved} - Cb_{culture\ medium,\ total\ dissolved}) + Cb_{site/region,\ total\ dissolved}$$

3'. In the third tier, in case the ARA is used and no compliance is reached, bioavailability can be taken into account, similar to the TRA. In such case the PEC, PNEC and the background values should be corrected for bioavailability. However, care should be taken in how the background correction is done (see below).

- Use in chemicals safety management

Potential environmental risks (RQ) are characterised based on the following quotient:

$$RQ = PEC_{ADD,bioavailable} / PNEC_{ADD,\ bioavailable}$$

Where $PEC_{ADD,\ bioavailable} = (PEC_{TOT} - Cb_{site/region})_{bioavailable}$ and $PNEC_{ADD,\ bioavailable} = (PNEC_{TOT} - Cb_{\ culture\ medium})_{\ bioavailable}$

- Use in EQS settings

Compliance checking is therefore checked by comparing:

$$PEC_{TOT,\ bioavailable} \text{ with } PNEC_{ADD,\ bioavailable} \text{ (ie } PNEC_{TOT,\ bioavailable} - Cb_{culture\ medium,\ bioavailable}) + Cb_{site/region,\ bioavailable}$$

Conclusions

The above discussion shows that both the total and the added risk approach may be used for chemicals management purposes as well as for EQS setting. The added risk approach may be employed as a pragmatic solution facilitating risk management to account for the impact of background concentrations if strict data conditions are fulfilled and when more robust approaches (eg, the biogeochemical region approach) are not available.

ANNEX 2: COMBINED RISK ASSESSMENT/COMBINED TOXICITY

Disclaimer: the current text is largely based on the information gathered from Meyer et al (2015) as part of the Metal Mixtures Modelling evaluation project. This special Environmental Toxicology and Chemistry issue was published in 2015 and consists of 11 peer-reviewed publications.

Although organisms in real-world aquatic systems usually are exposed to mixtures of metals and other substances instead of only one metal at a time (USEPA 2007), metals are still regulated only on a metal-by-metal basis (EU 2008; USEPA 2013) except in Australia and New Zealand (ANZECC 2000). This metal-by-metal regulatory approach has, in part, been adopted because of the perceived complexity of mixture toxicity and because of difficulties in modelling metal-mixture toxicity. Two basic models are commonly used to define and test for mixture toxicity: *concentration addition* (also called simple similar joint action) and response addition (also called independent action or independent joint action) (Newman 2013). In concentration-addition models, the toxicants are assumed to have the same mechanism of action at the same toxicity site(s), and only differ in potency. In contrast to concentration-addition models, response-addition models assume the toxicants in a mixture have different mechanisms of action and act jointly but independently of each other (eg, Borgmann 1980). No clear pattern has emerged to allow *a priori* qualitative (much less quantitative) prediction of whether a given mixture of metals will produce less-than-additive, additive, or more-than-additive toxicity compared to the concentration-addition or response-addition models.. Therefore, there is a need to understand how metals interact in mixtures and to predict their toxicity accurately (Van Genderen et al 2015).

Australia and New Zealand are the only countries that explicitly incorporate calculations for mixture toxicity into their regulations for metals (ANZECC 2000). Under that framework, a sum-of-toxic-units approach is recommended for determining regulatory exceedance if a mixture contains less than or equal to 5 “significant toxicants” (regardless of whether they are organic chemicals, metals, or other compounds) and if their toxicity is known to be additive. However, if the toxicity of that mixture is known to be non-additive or if the interaction is uncertain, and/or more than 5 “significant toxicants” are in the mixture, those guidelines recommend that direct toxicity assessment (ie a whole effluent toxicity test) should be used to determine whether the mixture exceeds a regulatory limit. In the European Union (EU), mixture toxicity for ecological receptors in receiving environments is regulated in specific legislations, such as for biocides or plant protection products (eg, ECHA 2014). On the other hand, mixture toxicity assessment is indirectly required for compliance with the European REACH

Regulations for the assessment of complex multi-metallic substances based on information on their individual metal constituents. Kortenkamp et al (2009) reported that, out of 21 pieces of legislation they reviewed, only 4 deal explicitly with exposure to chemical mixtures. Kortenkamp et al (2009) recommended using concentration addition as a default first-tier approach in an assessment of potential mixture toxicity, and ECETOC (2001) recommended "…the assumption of additivity [of acute toxicity of metals] is probably the most balanced choice, unless there is clear evidence in the literature that mixtures of the metals under examination behave differently." Therefore, it appears that additivity would be a generally safe regulatory assumption about the **acute** toxicity of the majority of metal mixtures. **The paucity of metal-mixture toxicity data for chronic endpoints makes it currently difficult to draw meaningful conclusions about interactions in long-term chronic exposures to metal mixtures**.

There is, however, growing evidence that the concentration-addition model is also a conservative and scientific-justified generic first-tier approach to assess chronic combined effects of metal mixtures because there are only few indications for synergistic (more-than-additive) effects when compared to the concentration addition (CA) approach. On the other hand, synergistic effects relative to the independent action approach are more commonly observed when studying chronic toxicity of metal mixtures. Unfortunately, the information on chronic effects of metal mixtures still falls short compared to data on acute toxicity.

Recent initiatives in Europe have considered how to regulate chemical mixtures (eg, Backhaus et al 2011; EC 2012; Kortenkamp et al 2013). Some of the approaches include treating all chemicals in a mixture equally and thus dividing the regulatory limit for each chemical by the total number of "significant" chemicals in the exposure water (ie to provide a an assessment or safety factor to protect against the combined toxicity of the mixture). The problem is that differences in potency are not considered in such an approach. The relative contribution of all mixture constituents should be preferably considered by multiplying by a potency factor. Approaches that would apply a uniform safety factor to decrease the regulatory-acceptable concentration of metals (and other chemicals) in a mixture below that deemed acceptable for single-metal exposures run the unintended risk of regulating the concentrations of essential metals (eg, Cu, Zn) in receiving waters into the deficiency range and/or below natural background concentrations (Janssen and Muyssen 2001). In the new EU Biocidal Product Regulation, additivity of long-term PEC/PNEC ratios has also been suggested as a conservative, precautionary approach.

Summation of long-term PEC/PNEC ratios immediately faces two important concerns for metals:

- First of all, because of the natural occurrence of metals and the conservatism built into the PNECs derivation, the simple sum up of the RCRs values of metals even at *background* levels may already result in a sum >1, and this before any possible anthropogenic metal production/use. To resolve this, the added risk approach has been proposed (see Annex 1). This way, any hypothetical contribution to the risk ratio due to the natural presence of metals (which does not lead to ecotoxicological effects) is excluded.
- Secondly, the simple sum up entails that the considered toxicity values refer to the same species and endpoint. For metals, however, the most sensitive trophic level or species in a specific compartment may differ from one metal to the other (eg, fish for Ag, bacteria for Ni…) and one will need to consider this species sensitivity as well as the compartment specificity. This approach can be further refined and the risk for multiple metals can be assessed by calculating the $RCR_{mix,j}$ for every trophic level or species/endpoint separately.

These considerations place increased importance on development of methods to quantitatively predict metal-mixture toxicity, and mathematical models will probably play an important role. In particular, BLM models could be useful here. Although no multiple-metal bioavailability model has yet been adopted for regulatory use, BLM type of mechanistic, bioavailability-based models might help to understand interactions among metals in a mixture and might also predict metal-mixture toxicity. Bioavailability models that incorporate metal-metal interactions and the myriad interactions of metals with other chemical components in water offer promise that metal-mixture toxicity might be reliably predicted in the future. As a potential key to advancing the understanding and prediction of metal-mixture toxicity, it is hypothesised that the toxicity of metal mixtures will be additive when based on concentrations of metals accumulated at sites of toxic action on or within organisms, even though the mixture toxicity might appear to be less-than-additive or more-than-additive based on dissolved-metal concentrations. The use of critical body burdens could be considered in this regard (McCarty et al 1993).

REFERENCES

Aldenberg, T, Jaworska, JS.,Traas, TP (2002). Normal species sensitivity distributions and probabilistic ecological risk assessment. Pages 49-102 *in* Posthuma, L, Suter, GWII, Traas, TP (eds). *Species sensitivity distributions in ecotoxicology.* Lewis Publishers, London, UK.

ANZECC (Australian and New Zealand Environment and Conservation Council) and ARMCANZ (Agriculture and Resource Management Council of Australia and New Zealand). (2000). *Australian and New Zealand Guidelines for Fresh and Marine Water Quality. Volume 2. Aquatic Ecosystems – Rationale and Background Information.* Australian Water Association, Artarmon, New South Wales, Australia; New Zealand Water & Wastes Association, Onehunga, Auckland, New Zealand.

Backhaus, T, Cedergreen, N, Hutchinson, T (2011). 3rd SETAC Europe Special Science Symposium, "Prospective and Retrospective Environmental Risk Assessment of Mixtures: Moving from Research to Regulation". *SETAC Globe* 12(4), April 14.

Borgmann, U (1980). Interactive effects of metals in mixtures on biomass production kinetics of freshwater copepods. *Can. J. Fish. Aquat. Sci.,* 37, 1295-1302.

Crommentuijn, T, Polder, M, Van de Plassche, E (1997). Maximum permissible concentrations and negligible concentrations for metals, taking background concentrations into account. RIVM, Report 601501001.

Doyle, PJ, Gutzman, DW, Sheppard, MI, Sheppard, SC, Bird, GA, Hrebenyk, D (2003). An ecological risk assessment of air emissions of trace metals from copper and zinc production facilities. *Human and Ecological Risk Assessment,* 9(2), 607-636.

ECETOC (European Centre for Ecotoxicology and Toxicity of Chemicals) (2001). *Aquatic Toxicity of Mixtures. Technical Report No. 80.* European Centre for Ecotoxicology and Toxicity of Chemicals, Brussels, Belgium.

ECOFRAM (1999). *ECOFRAM Aquatic and Terrestrial Final Draft Reports*. U.S. Environmental Protection Agency, Washington, DC.

EC (2012). *The Combination Effects of Chemicals*: *Chemical Mixtures.* Communication from the Commission to the Council. COM(2012) 252 Final. European Commission, Brussels,

Belgium.

European Union (2008). Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on Environmental Quality Standards in the Field of Water Policy, Amending and Subsequently Repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and Amending Directive 2000/60/EC of the European Parliament and of the Council. *Official J European Union* 24.12.2008:L 348/84 - L 348/97.

EUFRAM (2005). EUFRAM is a Concerted Action coordinated by CSL and supported by European Commission's 5th Framework Programme, contract number QLK5 - CT 2002 01346. http://www.eufram.com/

Giesy, JP, Solomon, K, Coats, JR, Dixon, KR, Giddings, JM, Kenaga EE (1999). Chlorpyrifos, ecological risk assessment in North American aquatic environments. *Reviews in Environmental Contamination and Toxicology*, 160, 1-129.

Hart A (2001). *Probabilistic risk assessment for pesticides in Europe (EUPRA): implementation and research needs*. A report from the European workshop on probabilistic risk assessment for the environmental impacts of plant protection products, June 2001, The Netherlands. Central Science Laboratory, Sand Hutton, UK. ISBN 185 945 010 5.

Janssen, C, Muyssen, B (2001). *Essentiality of Metals: Consequences for Environmental Risk Assessments*. International Council on Metals and the Environment, Ottawa, ON, Canada.

Kortenkamp, A, Backhaus, T, Faust, M (2009). *State of the Art Report on Mixture Toxicity.* The School of Pharmacy, University of London, London, UK.

McCarty, L S, Mackay, D (1993) Enhancing ecotoxicological modeling and assessment. *Environ. Sci. Technol*., 27(9), 1719−1728.

Meyer, JS, Farley, KJ, Garman, ER (2015). Metal Mixtures Modeling evaluation: 1. Background. *Environ. Toxicol. Chem*., 34(4), 726-740. DOI: 10.1002/etc.2792.

Newman, MC (ed. ?)(2013). *Quantitative Ecotoxicology*. 2nd ed. CRC Press, Boca Raton, FL, USA.

Oorts, K and Schoeters, I (2014). Use of monitoring data for risk assessment of metals in soil under the European REACH regulation. In: Reimann, C, Birke, M, Demetriades, A, Filzmoser, P, O'Connor, P (eds), 2014. *Chemistry of Europe's agricultural soils – Part B: General*

background information and further analysis of the GEMAS data set. Geologisches Jahrbuch (Reihe B), Schweizerbarth, Hannover. pp.189-202.

Struijs, J, Van de Meent, D, Peijenburg, W, Van den Hoop, M, Crommentuijn, T (1997). Added risk approach to derive maximum permissible concentration for heavy metals: how to take into account the natural background levels? *Ecotoxicology and Environmental Safety,* 37, 112-118.

TGD (2003)

USEPA (2001). *Risk assessment guidance for superfund (RAGS): Volume III - Part A. Process for conducting probabilistic risk assessment*. U.S. Environmental Protection Agency.

USEPA (2007). *Framework for Metals Risk Assessment*. EPA 120/R-07/001. U.S. Environmental Protection Agency, Washington, DC, USA.

USEPA (2013). National Recommended Water Quality Criteria, Aquatic Life Criteria Table. http://water.epa.gov/scitech/swguidance/standards/criteria/current/index.cfm#altable

Van Genderen, E, Adams, W, Dwyer, R, Garman, E, Gorsuch, J (2015). Modeling and interpreting biological effects of mixtures in the environment: Introduction to the Metal Mixture Modeling Evaluation Project. *Environ. Toxicol. Chem.,* 34(4), 721-725.

Verdonck, FAM, Aldenberg, T, Jaworska, JS, Vanrolleghem, PA (2003). Limitations of current risk characterization methods in probabilistic environmental risk assessment. *Environ. Toxicol. Chem.*, 22(9), 2209-2213.

Verdonck FAM, Van Sprang P and Vanrolleghem PA, 2005. Uncertainty and precaution in European environmental risk assessment of chemicals. *Water, Sci. Technol.., 52(6), 227-234.*

Warren-Hicks. WJ and Hart, A (eds). 2010. *Application of uncertainty analysis to ecological risks of pesticides.* SETAC Press, Pensacola, FL. 190pp.