EBRC EUROFER EuroMetaux ICMM International Council on Mining & Metals

HERAG

Health Risk Assessment Guidance for Metals

Contents

Foreword

Assessing and managing potential risks from the production and use of metals and inorganic metal compounds is an increasingly important consideration for mining and metals companies. As well as demonstrating enhanced responsibility, it is becoming necessary to perform such assessments to align practices with new trends in chemicals management policies – for example the Registration Evaluation and Authorisation of Chemicals (REACH) legislation in the EU and by the UN's Strategic Approach to International Chemicals Management (SAICM) globally.

Access to markets will become ever more dependent on the ability of companies to prove a substance can be produced and used safely, and this in turn requires accurate and robust risk assessment methodologies. The Health Risk Assessment Guidance for Metals (HERAG) has been published in response to these challenges. Launched jointly by ICMM, Eurofer and Eurometaux, it has assembled a set of the most advanced and appropriate methods available for human-health based risk assessment of metals.

HERAG is intended to address the specific properties of metals, metal compounds, alloys and other naturally occurring inorganic substances. It describes current knowledge on metal-specific human health risk assessment approaches and provides guidance for the scientific and regulatory community with the aim of reducing uncertainty in future risk assessments. This is crucial because, in many cases, existing guidance focuses on organic chemicals and fails to adequately address specific characteristics that must be taken into account when assessing metals.

The critical scientific concepts are presented in the series of 'fact sheets' on the CD-ROM inside the back cover of this publication. Each fact sheet has been reviewed by a panel of leading independent scientists.

It is our intention that this publication, through periodic updates, will continue to provide a solid basis for sound health risk assessment processes for metals and we encourage all parties to use the material (for updates please visit www.metalsriskassessment.org). We welcome any comment on the publication as feedback enables us to provide further guidance as the science evolves.

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Abbreviations

CMR
Carcinogenic, Mutagenic and/or Reproductive toxin

EASE
Estimation and Assessment of Substance Exposure (model), see reference Creely et al. (2004)

ESR
'Existing Substances Regulation': European Council Regulation No 793/94 on the evaluation and control of the risk of existing substances. May also refer to the associated Commission Regulation EC 1488/94 laying down the principled for the assessment of risk to man and the environment of existing substances in accordance with Council Regulation (EEC) No793/93.

GHS
Globally Harmonized System of Classification and Labelling of Chemicals

GI
Gatro-Intestinal (tract)

IWGT
International Working Group on Genotoxicity Testing

LOAEL
Lowest Observed Adverse Effect Level

MMAD
Mass Median Aerodynamic Diameter

MPPD
Multiple Path Particle Deposition (Model), name of the current version

MW
Molecular Weight

OECD
Organisation for Economic Co-operation and Development

OEL
Occupational Exposure Limit

PSD
Particle Size Distribution

QSAR
Quantitative Structure Activity Relationship

RA(R)
Risk Assessment (Report)

RWC
Reasonable/Realistic worst case exposure value (usually the 90th or 95th percentile of a data set of measured values)

TDI
Tolerable Daily Intake

TGD
Technical Guidance Document in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market.

TLV
Threshold Limit Value

TYP
Typical exposure value (usually derived from the median of a set of measured exposures)

VRA
Voluntary Risk Assessment

WEL
Workplace Exposure Limit

HEALTH RISK ASSESSMENT GUIDANCE FOR METALS

PURPOSE AND INTENDED USE

01

01. Purpose and Intended Use

The principal purpose of this Health Risk Assessment Guidance for Metals (HERAG) is to provide the worldwide regulatory and scientific community with an overview of the most recent developments in risk assessment methodologies for metals and inorganic metal compounds, with the aim of reducing uncertainty in future risk assessments.

The guidance and concepts presented have been built on the experience gained with previous or ongoing risk assessments for metals under the EU Existing Substances Regulation (ESR, Council Regulation EEC 793/93) and of voluntary risk assessments conducted in the EU in accordance with the same legislation. However, reference has also been made to other national or international institutions (e.g. US EPA, WHO, OECD).

To allow for adaptation of this guidance and the underlying concepts to a broader legislative context, HERAG follows a 'building block' approach (see *'Scope and Organization'*). Each building block addresses a particular aspect of risk assessment, which enables the methodologies to be used in other applications, such as chemicals management systems and occupational exposure monitoring.

HERAG is intended to aid professionals in the field of human health risk assessment, particularly regulatory authorities and industry professionals, either at a national or international level. Whereas the general concepts presented may be useful for anyone interested in human health assessment of metals and inorganic compounds, it is assumed that the reader already has a good understanding of the basic principles of human health risk assessment.

Several of the fact sheets that accompany this publication have identified the need for further research and model development specifically for metals and inorganic compounds. In view of this and considering that the science of metals continues to evolve, it is anticipated that some of the recommendations presented in this document and the corresponding fact sheets will, in the course of time, require modification or updating.

HEALTH RISK ASSESSMENT GUIDANCE FOR METALS

SCOPE AND ORGANIZATION

02

02. Scope and Organization

2.1 Scope

Experience in recent risk assessments of metals and their inorganic compounds has led to the recognition that existing frameworks and associated guidance (e.g. US-EPA, EU TGD guidance) are not appropriate. This is largely because these systems for assessing the risk associated with the production and use of chemicals were initially developed with an emphasis on organic chemicals.

HERAG was therefore established to summarize existing knowledge on metal-specific issues that are relevant to human health risk assessment. Furthermore, some of the concepts presented may also be applied in chemicals management and in occupational exposure surveillance in particular.

To facilitate this, a team of metal industry experts from companies and associations previously or currently involved in metal risk assessments, conducted a point-by-point analysis of existing concepts on exposure assessment and hazard characterization to identify those that are truly specific for metals.

For the purpose of this document, the term 'metal(s)' refers also to semimetals (metalloids). For increased readability, this term also frequently refers to inorganic metal compounds as well as the pure metal. However, organometallic compounds[1] are currently outside of the scope of HERAG.

HERAG specifically focuses on risk assessment issues associated with inorganic metal compounds. However, some elements addressed in HERAG are not essentially unique to metals and may also be applied to a wider range of compounds. For example, the data-richness of some metals in previous risk assessments has required a specific focus on quality screening of available data, accordingly this topic is addressed in a separate fact sheet.

[1] IUPAC Definition of 'Organometallic Compounds' (abbreviated): Classically compounds having bonds between one or more metal atoms and one or more carbon atoms of an organyl group. (...) In addition to the traditional metals and semimetals, elements such as boron, silicon, arsenic and selenium are considered to form organometallic compounds (...). The status of compounds in which the canonical anion has a delocalized structure in which the negative charge is shared with an atom more electronegative than carbon, as in enolates, may vary with the nature of the anionic moiety, the metal ion, and possibly the medium; in the absence of direct structural evidence for a carbon–metal bond, such compounds are not considered to be organometallic.

2.2 Organization – building block approach

The HERAG project employs a building block approach (see Figure 1) to ensure that its methodologies are useful for different jurisdictions and that the presented concepts are also useful for chemicals management in general. Nevertheless, the established building blocks were based on general risk assessment methodology, which is principally conducted in three steps: effects assessment, exposure assessment and risk characterization.

The following key building blocks were established:

Exposure Assessment

The quantification (by measuring or modelling) of human exposure to a chemical is called exposure assessment. Conventionally, this assessment is performed for three human population subgroups:
(i) those occupationally exposed during production or use of the substance;
(ii) those exposed because the chemical is contained in and potentially released from consumer products; and,
(iii) those exposed indirectly via the environment, to which the chemical is emitted during production and use and may reach the individual for example via food, water or air.

As for the effects assessment, three routes of exposure (inhalation, oral, dermal) are considered. Previous metals risk assessment experience has shown that for the following topics there is a clear need for metal-specific guidance:

- inhalation and dermal exposure, both especially relevant under occupational conditions;
- oral exposure, including the fate of metals once they reach the gastrointestinal tract (systemic absorption and use of toxicokinetic models).

Though not strongly metal-specific, the assessment of consumer exposure and indirect exposure via the environment is addressed in some detail by HERAG, particularly since conventional diffusion-based exposure models are found to be inapplicable to metals, and numerous metal-specific consumer scenarios have been identified.

Effects Assessment

Effects assessment involves the investigation of the effect that a chemical exerts on human health because of its intrinsic toxicological properties using *in vitro* or *in vivo* methods (also called hazard identification). The effects assessment furthermore

Figure 1: **Overview of key building blocks**

includes the investigation of a dose (concentration) – response (effect) relationship and the derivation of no-adverse-effect levels/concentrations, where appropriate. Three routes of exposure need to be considered: inhalation, ingestion and dermal exposure. The spectrum of possible health effects that need to be covered are acute toxicity, repeated dose toxicity, irritation/corrosivity, sensitization, mutagenicity, carcinogenicity and reproductive toxicity. Of these effects, particularly the last four were identified as needing metal-specific attention and are therefore addressed separately within HERAG.

Risk Characterization

A risk assessor finally compares the quantitative and/or qualitative information on human exposure for the human population to the no-adverse-effect levels established in the effects assessment for the various effects, a process called risk characterization. In consideration of the uncertainties that are associated with both the effects assessment and the exposure assessment, so-called assessment factors (or safety factors) are usually introduced. In this context, experience has shown that special attention is required for metals to ensure a realistic risk assessment. In contrast to most anthropogenic organic substances, several metals play an essential role for the functioning of life and are ubiquitous in the environment. The choice of

assessment factors in risk assessments for metals should therefore take into account the sometimes low margin between toxicological endpoints and deficiency levels, and the existence of natural background levels.

Fact Sheets

Based on these building blocks, a series of fact sheets was developed (these are included as pdf files on the enclosed CD-ROM). The fact sheets contain the core guidance elements and provide the reader with state-of-the-art techniques and tools for assessing metals.

In contrast to the more elaborate and detailed guidance provided in the extensive fact sheets (which mostly also include concise summaries of relevant aspects from previous metal risk assessments), the subsequent chapters of this summary document outline the main concepts and key conclusions on metal-specific methodologies referred to in the different fact sheets. Suggestions for further research, indications of currently developed models and limitations in the application of methods are addressed where relevant.

Finally, some of the topics initially identified were considered not to warrant the publication of a full fact sheet at this time, either because they were judged not intrinsically metal-specific, or because the status of development based on available knowledge is insufficient. However, further development of these fact sheets is foreseen in the future. Whereas these are not included on the attached CD-ROM, working documents are available upon request from ICMM/EBRC and further comment or input to these fact sheets is welcomed. Further details of these fact sheets are included on the enclosed CD-ROM.

HEALTH RISK ASSESSMENT GUIDANCE FOR METALS

EXPOSURE ASSESSMENT

03

03. Exposure Assessment

For human health risk assessment, a correct assessment of exposure is essential and for metals, a considerable improvement of existing knowledge has occurred recently during the evaluation of zinc, nickel, lead, copper and antimony (as trioxide).

Inhalation is a key route of exposure, especially at the workplace, since metals and inorganic metal compounds are frequently produced and used in powdery, dusty forms. A considerable portion of the material entering the body through the nose or mouth is translocated to the gastro-intestinal tract and this indirect route of ingestion may contribute significantly to total systemic exposure.

Discussion among industry experts also identified ingestion by hand-to-mouth transfer, as well as inadvertent ingestion from the peri-oral region after facial deposition as additional routes of exposure with a need for further research.

Further to exposure via inhalation, the handling of powdery substances can also lead to exposure of the skin, followed by percutaneous absorption. Three separate HERAG fact sheets extensively discuss the metal industry's experience concerning 'dermal exposure' (No. 01), 'inhalation exposure' (No. 02), and 'gastrointestinal uptake' (No. 04). The key concepts and guidance elements with respect to exposure assessments are summarized below. However, because of the complex nature of these topics, it is explicitly recommended that the reader and users of the given guidance refer to the full fact sheet.

Finally, in addition to the workforce, consumers and humans indirectly exposed via the environment also need to be considered in chemicals risk assessments. HERAG addresses these issues in a further, separate fact sheet (No. 03).

3.1 Assessment of occupational exposure

3.1.1 Inhalation exposure

Inhalation is probably the most important exposure route to consider in the assessment of human risk from solid inorganic substances – in particular from metals in the workplace, and to a certain extent where consumer products entail exposure to an aerosol.

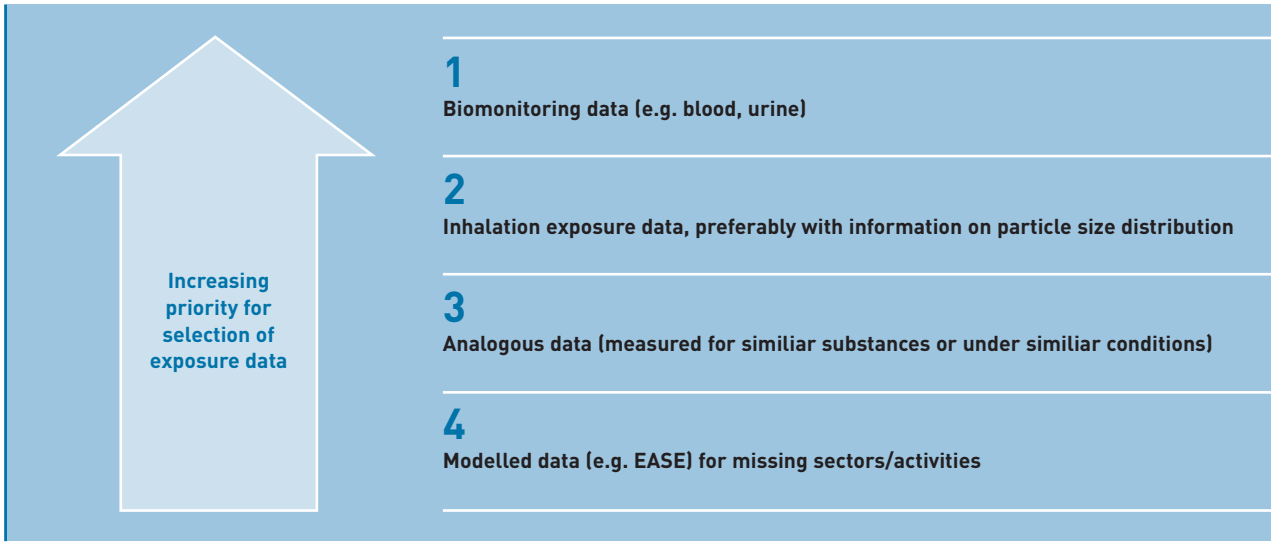
For some substances (examples: lead and cadmium), a large amount of biomonitoring data may be available. Given that biomonitoring data reflect actual body burdens most correctly by reflecting intakes as well as absorption/toxicokinetics, these should be given preference over 'external' exposure data that are intrinsically affected by uncertainties, and which require 'translation' into systemic body burdens via absorption factors which add to the uncertainty of any assessment. The priority of exposure data according to their relevance for risk characterization can be schematically summarized in Figure 2.

For many metal compounds however, biomonitoring data will not be readily available or at least not to an extent that it allows a thorough risk assessment. Furthermore, even when biomonitoring is available, this data considers the sum of all routes of exposure. Thus, a quantitative assessment of external exposures is required to identify the most quantitatively relevant sources of exposure, so that, if required, correct recommendations for appropriate risk reduction measures can be given.

The focus therefore of the fact sheet on inhalation exposure is on the collection of data of high relevance. The concepts and methodologies presented are based on the experience gained during previous risk assessments for metals and metals compounds, with a strong emphasis on the assessment of occupational exposure.

Another key issue is the influence of particle-size distribution of any inhaled material on its fractional deposition in the various regions of the respiratory tract. The use of particle-size distribution data for the assessment of inhalation absorption has been successfully used in previous risk assessments, and is described in detail in the toxicokinetics section of the fact sheet.

Figure 2: **Priority ranking of exposure data by relevance for risk assessment of occupational inhalation exposure**



Historically, there are regulatory limits (designated as OELs, TLVs or WELs, etc.) in place for many metals or metal compounds, which are generally aimed at the control of airborne dust or fume concentrations. As a consequence, a large body of data exist that were generated to monitor compliance with these levels. However, the existing differences in methods of sampling which influence the quality and relevance of these data has been recognized and methodological issues of aerosol sampling techniques have been addressed in detail.

In this context, it is noted for the sake of completeness, that the International Council on Mining & Metals (ICMM) has recently launched an initiative to promote a global harmonization of the way in which such regulatory limits on workplace exposure are set[2]. Further information may be obtained from ICMM (www.icmm.com). The issue of the setting of regulatory limits is not further addressed within HERAG, since the setting of such limits and the conduct of risk assessment occurs according to different legal standards.

Finally, whereas this chapter addresses particle-size as relevant for occupational inhalation risk assessment, nanoparticles are not currently considered; under most (albeit not all) occupational circumstances, particles in workplace aerosols aggregate or agglomerate to rather large particles. However, some exceptions for much smaller particles (<100nm) are given in this fact sheet (such as zinc and lead), but none of these essentially qualify as what is commonly designated a 'nanoparticle'. Since nanoparticles and their toxicological characterization are currently subject of extensive research without definitive conclusions being available at this time, the aspect has not yet been considered within HERAG.

Aerosol sampling techniques and methodology

Reviews of available measurement techniques and comparisons of sampling equipment have been conducted previously for various purposes, and extracts of these are summarized in the fact sheet. On workplace inhalation exposure sampling, Witschger (2001) extensively reviewed the monitoring devices and methods used in aerosol sampling studies in workplaces for exposure assessment. Whereas small parts of the document deal with radiation dosimetry issues, the major part addresses aerosol sampling issues in general. This exercise was conducted in the context of the SMOPIE[3] project.

[2] Towards a harmonized approach to setting occupational exposure limits, Report of an ICMM-sponsored workshop (9–11th November 2005), ICMM, London, May 2006.

[3] SMOPIE: Strategies and Methods for Optimisation of Internal Exposures of workers. Funded by the European Commission in 2001. For more information see www.nrg-nl.com/product/re/norm/smopie001.html

Different measurement methods and sampling devices are in use across the EU for the assessment of inhalation exposure at the workplace, and several studies were conducted to describe the performance of sampling devices in relation to the three biologically relevant aerosol fractions (inhalable, thoracic and respirable fraction (CEN, 1993; ISO, 1992)). The focus of most studies comparing the various types of samplers is on the sampling efficiency for the inhalable fraction. This specific methodical aspect of sampling efficiency has been discussed in the sections on occupational exposure assessment in the EU RARs on nickel and copper, and is further discussed in the HERAG fact sheet and its appendices.

Collection of occupational monitoring data for risk assessment purposes

For many metals or metal compounds, a large body of occupational exposure data exist that were generated in the past during compliance monitoring. However, for the purpose of retrospective analysis of such existing data, not only the measurement result itself is required, but further information on the situation under which the sample was taken, e.g.

- process descriptions,
- frequency and duration of exposure,
- amount and nature of substance handled,
- engineering controls and PPE in use,
- sampling details and quality controls.

Based on the principles given in the EU TGD, the experiences gained in previous data collection exercises and a consideration of available scientific literature (Ritchie and Cherrie 2001; Rajan et al. 1997; Vincent 1998), a generic questionnaire template has been developed within HERAG and is provided in the fact sheet as a starting point for future data collection exercises.

3.1.2 Dermal exposure

Uptake of metals through skin has been a major factor contributing to predicted risk in previous EU risk assessments, particularly when insufficient measured data was available and highly conservative default model predictions of exposure were coupled with current guidance on defaults for dermal absorption (i.e. 10%). Therefore, this topic is addressed in HERAG with the aim of providing guidance on how to assess occupational dermal exposure more precisely. The project findings focus primarily on solid, powdery/dusty, inorganic contaminants, and do not consider liquids or vapours of any kind.

Whereas very little published information on monitoring of dermal exposure for metals and their inorganic compounds is available, such data were generated only very recently within EU RARs or VRA processes, usually in the form of unpublished reports which are not generally accessible to the scientific community.

As a consequence of the lack of measured dermal exposure data, model calculations have often been used as an alternative in regulatory assessments. For EU Risk Assessments, extensive use has been made of the EASE model, the validity of which is uncertain because the dermal exposure component is partly based on experiments conducted with liquids and partly on expert judgement – with little actual measured data to support it. Another weakness is that EASE merely assigns a rather wide 'range' of exposures (based on a simple decision tree). In the absence of measured data and as an alternative to modelled exposure, increasing use is being made of 'analogous' dermal exposure data. For this purpose, either *potential dermal exposure*[4] data on calcium carbonate (Lansink, 1996), or the only publicly available data set (to date) on *actual dermal exposure* to zinc oxide (Hughson and Cherrie, 2002) have been used previously. For obvious reasons, it is necessary to understand whether it is appropriate to extrapolate from such data to other compounds, and based upon which argumentation.

Available dermal exposure data from EU RARs and comparison to EASE predictions

The HERAG fact sheet on occupational dermal exposure and absorption provides a comprehensive compilation of actual dermal exposure data generated in the context of risk assessment in the zinc, lead, nickel and antimony trioxide industries. Together with the exposure data, detailed information is available on the tasks performed with the compounds at the workplaces where the exposure was measured. Since EASE described the tasks only by a set of rather simplistic exposure descriptors (as presented in Table 1), it was therefore possible to compare the measured exposure with the exposure modelled by EASE.

[4] Definitions: *Potential exposure* is measured with surrogate techniques such as patches, cotton gloves etc. outside the clothing and any protective equipment. In contrast, *actual exposure* is measured by sampling any material that is actually deposited on the skin of a volunteer, e.g. by wipe-sampling, and is thus more reflective of practical workplace conditions.

Table 1: EASE exposure descriptors

Pattern of use (PU)	Pattern of control (PC)	Contact level (CL)
closed system	no direct handling	none
inclusion onto matrix	direct handling	incidental
non-dispersive use		intermittent
wide dispersive use		extensive

The selection of 'no direct handling' as a pattern of control leads to the qualitative prediction 'very low' independently of the two other parameters. Therefore, a comparison of EASE predictions to measured data in various industries was conducted only for 'direct handling'. For the pattern of use, either non-dispersive or wide dispersive use was selected (abbreviated 'Wide' or 'Non'), whereas for the contact level, distinction was made between intermittent and extensive contact only (abbreviated 'Int' or 'Ext'). See Figure 3.

A key finding is that EASE consistently over-predicts dermal exposure to metals and their inorganic compounds, in many cases by up to two orders of magnitude. The fact that EASE predicts the highest range of exposure for a workplace where the highest exposures are actually measured shows that some of the factors that determine exposure are indeed captured by the model's simplistic exposure descriptors. However, the absolute, quantitative figures are obviously inappropriate and it is therefore concluded that the dermal module of EASE is not suitable for regulatory risk assessment.

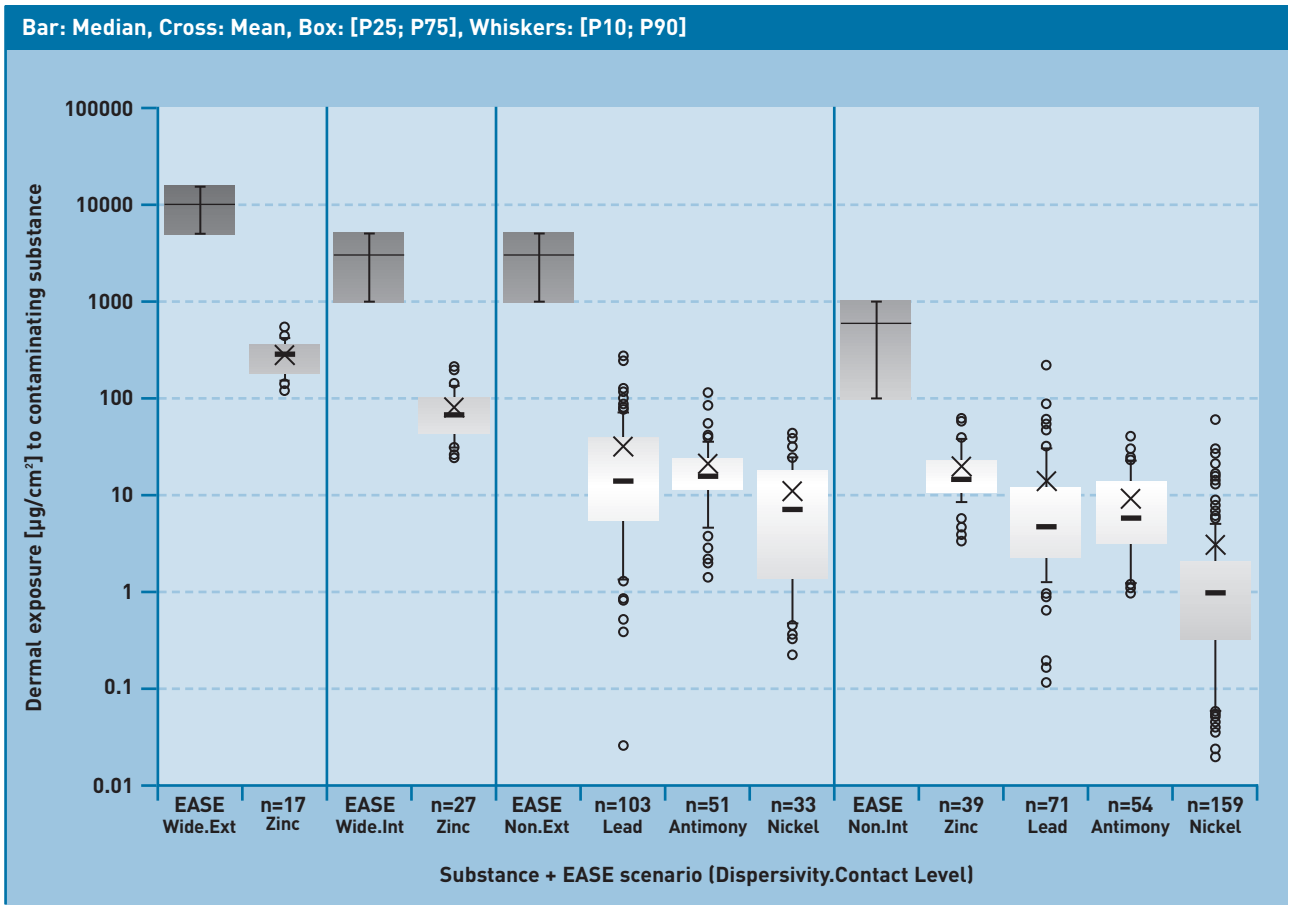
Perception of hazard and resulting pattern of control as an exposure modifier

The differences between actual measured dermal exposure data for zinc, lead, antimony and nickel compounds may be hypothesized to reflect the level of control implemented in these industries, resulting from the perception of risk associated with the skin contact with these substances – which is low for zinc and zinc oxide, medium for lead and antimony compounds, and high for nickel and its compounds. This is mirrored by the observation that the correct use of gloves (low usage for zinc, higher usage for lead, antimony, nickel or the respective compounds) and even beyond this, other levels of control (automated packaging for nickel) make a substantial impact on levels of dermal exposure.

Dermal exposure measurements – methodological aspects

Further to the compilation of measured dermal exposure data and its comparison with EASE model predictions, the HERAG fact sheet addresses key methodological aspects of dermal exposure measurements. Existing sampling techniques cannot continuously sample the changing dynamics of surface deposition and clearance of the skin contaminant layer. Saturation phenomena may occur, and thus dermal loading may not increase linearly with time. For this reason, samples taken during the course of a shift should preferably not be pooled in order to avoid potential over-sampling. The collection of individual samples should be given preference also because it allows for an assessment of variation of exposure during a shift. Based on a methodical comparison of available sampling techniques and in particular in consideration of the more recent experience gained from dermal exposure monitoring in various lead, antimony, nickel and zinc industries, it is concluded that neither the use of cotton gloves nor the bag-wash method with their inherent limitations are preferable methods. Particularly in the case of dermal exposure monitoring of inorganic compounds, it is proposed for future measurements to make use of the wipe-sampling methodology. The degree of standardization and validation obtained with this method to date should facilitate the collection of a comparable dataset for the future.

Figure 3: **Dermal exposure levels for different chemical agents and activities, in comparison to EASE predictions**



EASE use pattern: wide or non-dispersive use; contact level (direct handling): Ext = extensive, Int=intermittent

Alternative model approach (screening model)

Considering the limitations of existing models as outlined above, but also the time, effort and cost for properly conducted sampling, a screening model approach was suggested, which utilizes an 'analogous' approach for (occupational) scenarios with an absence of measured data.

In the case that exposure data for a particular substance are not available, but data do exist either for other substances derived from the same metal, or for completely different metals/substances, then an 'analogous approach' can be taken, provided a subset of data can be selected from the data base which comply with the exposure characteristics outlined as follows, and which may justify the choice of a particular analogy. Two main characteristics which are thought to influence the level of dermal exposure can be summarized as follows:

(i) Intrinsic substance properties:
- physical form, dustiness, particle size, hygroscopicity, agglomeration tendency;
- chemical speciation, water solubility.

(ii) Process conditions and pattern of control:
- conditions of handling, use of tools and PPE (such as gloves);
- degree of involvement (i.e., direct handling vs. use of automation);
- where no direct occurs, indirect exposure may result, for example from contaminated surfaces; thus, the level of ventilation controls and resulting air may influence deposition.

There is no single criterion that can be applied to justify the extrapolation from one data set to another. Instead, a combination of the aspects above should be considered. In the case that no data for a particular substance or any other substance derived from the same metal are

Table 2: **Ranges of exposure**

Range	RWC	TYP	Description
0-5 µg/cm²	5	1	Low dermal loading, no direct handling (analogy: Ni)
5-50 µg/cm²	50	10	Medium dermal loading, limited direct handling (analogy: Pb, Sb, etc.)
50-500 µg/cm²	500	100	High dermal loading, direct handling (analogy: Zn compounds)

available, then the following 'screening model' approach is suggested, by comparing the circumstances under which any particular 'analogous' data set was collected, with features characteristic of the 'new' occupational setting to be modelled. Then, the three ranges of exposure set forth in Table 2 may be used for model screening purposes.

The proposed typical (TYP) values were based on a level with greatest proximity to the median of a particular group of data sub-sets. The worst-case (RWC) values were selected because of proximity to the 90th percentile of the underlying data sub-sets. Whereas the use of EASE as a model is explicitly discouraged for metals, the advantage of the above 'screening model' approach is that it allocates data to several of the relevant exposure categories of EASE, thus facilitating continued use of conventional risk assessment considerations.

This model approach is intended to be of use in, for example, iterative approaches as foreseen in the development of exposure scenarios under REACH. Although this provides a valuable initial tool, it was recognized within HERAG that there is a clear future need to generate further dermal monitoring data, and to facilitate the development of more metal-specific dermal exposure models.

3.1.3 Exposure via ingestion

It is well-known that ingestion can play a major role in the way a metal may enter the body. For example, during occupational exposure to lead, poor personal hygiene behaviour can contribute to systemic intake, by inadequate washing of hands, poor maintenance of work clothing, and (previously) lack of control of feeding and drinking habits as well as smoking during work. As a result, ingestion by hand-to-mouth transfer can occur. There is to date no accepted methodology to quantity this route of exposure.

Another route of exposure is inadvertent ingestion from the peri-oral region after facial deposition that occurs as a function of airborne level of contaminants. None of the previous metal risk assessments have addressed this however, and although HERAG does not contribute to this, concepts are being developed elsewhere (Cherrie et al. (2006).

3.2 Indirect exposure via the environment and consumer exposure

Exposure to chemical substances during production and subsequent downstream or end-use may affect the general population in two ways:

- humans may be exposed to chemical substances released to the environment during production and/or use, which may reach humans indirectly via the environment, primarily through inhalation of ambient air, or ingestion of water and food;
- consumers may be exposed to hazardous substances intentionally or unintentionally released from consumer products or articles.

Whereas both aspects are not strictly metal-specific and extensive risk assessment guidance is already available, it was considered that there are several issues which are particularly relevant for metals and which are not appropriately covered by the standard TGD assessment approaches. Therefore, the aim was to capture these metal-specific issues in order to facilitate exchange of such knowledge on a broader basis for the metals industry in order to improve further risk assessment exercises (fact sheet No. 03).

3.2.1 Indirect exposure via the environment

Indirect exposure of humans may, in principle, occur via the typical exposure pathways – inhalation, ingestion and dermal contact. The following exposure scenarios are most commonly considered for the general public:

- exposure via inhalation of air;
- exposure via drinking water; and
- exposure via food intake.

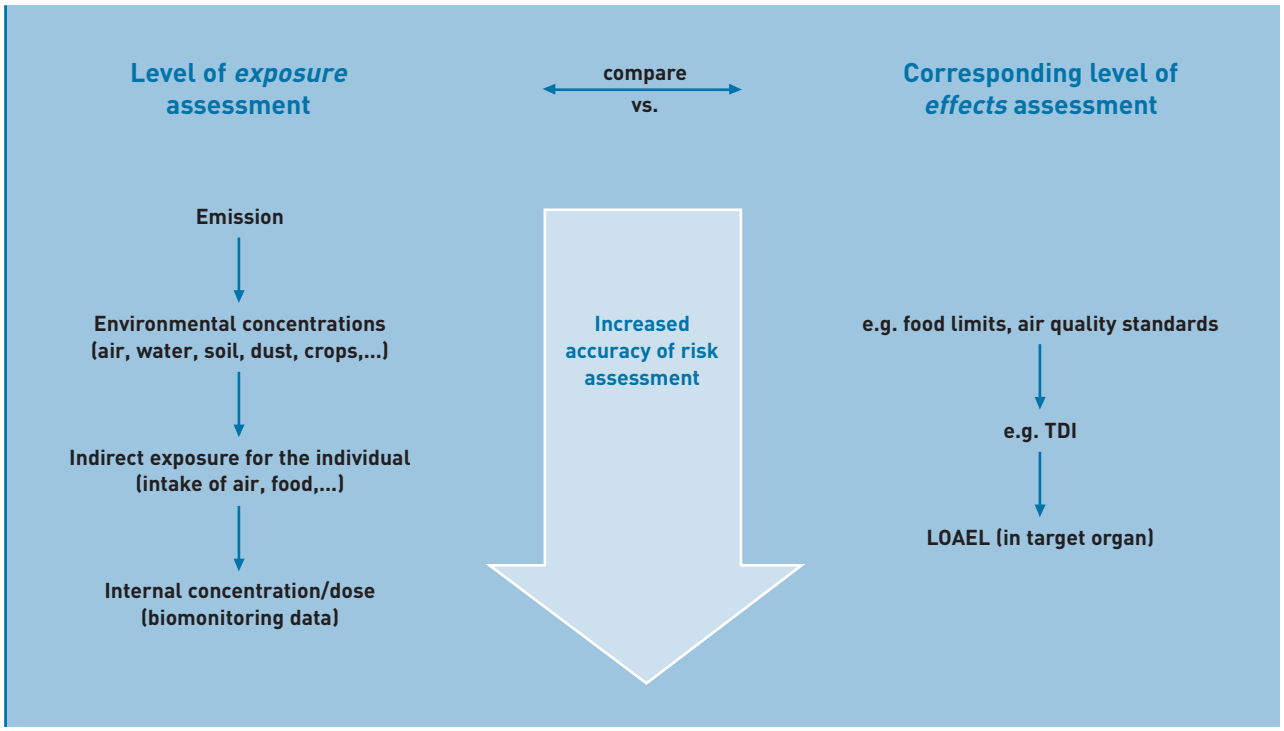
In some instances, further exposure routes may need consideration for sub-groups of the population, e.g. intake by infants via mother's milk. In current EU TGD guidance, exposure via soil ingestion and dermal contact is discounted because it is considered to be very unlikely (extremely polluted soils e.g. land fill sites or accidental releases are listed as exemptions). However, whereas the dermal route has indeed been shown to be irrelevant for 'indirect exposure' to metals because of their very low dermal absorption (see section 4.1.3), the ingestion of soil and dust has been found to be worthy of consideration especially for children as further discussed below.

In general terms, a risk characterization for indirect exposure via the environment can be conducted at several different levels, as shown in Figure 4, in hierarchical order of complexity and relevance.

If regulatory limit values like air quality standards or food limits exist for a given substance, a direct comparison with environmental concentrations may be feasible at the first level. As a more refined approach, a comparison of actual intake with limit values such as a TDI (tolerable daily intake) can be performed. At the final and principally most accurate level, the actual internal dose (biomarkers) of individuals is compared with the lowest observed adverse effect level (LOAEL), preferably in a specific target organ for repeated dose toxicity.

For metals, preference should be given (where available) to internal over external concentrations for risk characterization; the evaluation of biomonitoring data is discussed further in the HERAG fact sheet, based on examples from the risk assessments of lead (blood data) and cadmium (urinary data).

Figure 4: Conduct of risk characterization for indirect exposure at different levels of accuracy



If such biomarkers of exposure are not available then accurate absorption factors are required for a reliable conversion of external exposures (via food, water and air) into systemic uptakes. It is not uncommon for absorption to vary as a function of the level of intake (i.e., saturation; for examples, refer to the risk assessments on zinc and copper). Thus, precise oral absorption factors are likely to be required to assess intake from dietary sources (relevant for consumers and indirect exposure) and these will differ considerably from those applicable to occupational circumstances for example. For more details, please refer also to section 4.1.2 and to the separate fact sheet on GI uptake and toxicokinetic models.

Similarly, inhalation uptake will vary considerably between the occupational setting and situations where humans are exposed via ambient air. In the latter case, chemicals are commonly assumed to be adsorbed onto fine (sub-micron) particulate matter, which is assumed to penetrate to a high extent to the pulmonary region of the lung, with potentially very high uptake rates, for which 100% absorption is often assumed by default (for examples, refer to the EU risk assessment on lead). In contrast, workplace aerosols are often characterized by the mass-median aerodynamic diameters of airborne particles well above 10 microns. This means that the bulk of inhaled material will usually be redirected to the GI tract, with absorption rates usually much lower than 100% (for more details, see fact sheet on inhalation exposure/absorption).

Even when biomonitoring is available however, the quantitative assessment of external exposures is essential to identify the most relevant sources of exposure, so that if required, correct recommendations for appropriate risk reduction measures can be given.

Metal specific issues and exposure routes

In order to facilitate the indirect exposure assessment section, previous risk assessments reports conducted under the ESR or as voluntary risk assessments were screened for issues of 'indirect exposure via the environment', and in addition key metal industries provided input on their direct experience with these issues. For ease of reference to these previous metal risk assessments, the fact sheet contains an extensive appendix, giving detailed extracts of the indirect exposure assessments for individual metals.

In contrast, the main body of the fact sheet focuses on deviations from the TGD approach and summarizes metal specific issues (by route of exposure) which have been identified to require special attention in future metal risk assessments.

For example, for the assessment through the intake of drinking water, a set of definitions and defaults was proposed that may allow a more consistent approach to metals for which this is a relevant route of exposure. In addition, default (age-dependant) uptake factors beyond the abbreviated approach in the TGD are proposed for drinking water. Among other scenarios, further guidance is given on the assessment of metal exposure via cigarette smoking, via ingestion of soil and via consumption of food.

General recommendations

The assessment of indirect exposure to humans via the environment employs a considerable overlap with the assessment of possible risk to environmental ecosystems. Therefore, reference is made at this point to the MERAG[5] project. This project aims to provide the regulatory community at regional and international level with scientific and regulatory guidance on the most advanced status of environmental risk assessment concepts for metals and inorganic metal compounds. The included concepts of bioavailability, bioconcentration, bioaccumulation and biomagnification of metals and/or metal compounds are also applicable when assessing the possible exposure of humans via the environment, e.g. via the ingestion of food.

A further general conclusion is that the model approaches suggested by the EU TGD, which are based on partition equilibria, are applicable to metals only to a very limited degree. Depending on the level of data available, it may be possible to assess indirect exposure to some metals at a rather sophisticated level (i.e. using biomonitoring data) compared to the basic modelling of concentrations in air, water and food. Where relevant, the assessment of indirect exposure via the environment should be performed separately for susceptible or particularly sensitive sub-populations (for an example, please refer to the VRA for lead, where exposure of children is addressed in detail).

[5] The scientific and technical recommendations of MERAG can be found at www.metalsriskassessment.org

The general use of 90th percentiles of quantitative exposure measures as recommended in the EU TGD is likely not to be applicable to metals. This is because a multiplication of such values for concentration in environmental media and their intake rates may result in overestimates of internal exposure. However, the use of RWC values may, under certain circumstances, allow consideration to be given to (potentially sensitive) known sub-populations.

Metals are natural components of the earth and therefore reflection must be given to a correct distinction between natural ambient and anthropogenic concentrations. This will be of particular relevance when certain CMR labelled metals are discussed for risk through indirect exposure because of the conflict with the 'no threshold concept' for genotoxicity and carcinogenicity.

3.2.2 Consumer exposure

Similar to 'indirect exposure via the environment', the assessment principles for 'consumer exposure' are not metal-specific *per se*. Nevertheless, the experience in previous metal risk assessments has shown that several individual scenarios exist, where consumers are in (sometimes regular and extensive) contact with metals in products and articles of daily life.

The currently available risk assessment reports on metals and metal compounds were therefore screened for consumer exposure issues which were deemed to be quantitatively relevant for human health risk assessment. In the attached fact sheet, the resulting (non-exhaustive) tabular summary of consumer exposure scenarios potentially relevant for metals is presented, as well as a discussion of several aspects of common interest for which discrepancies between various existing metal risk assessments have been observed. Examples for metal specific scenarios addressed in previous assessments are contact with batteries, jewellery, coins, food-packaging materials, crystal-glassware, soldering material, household and artist's paints.

In the appendix to the fact sheet, more extensive summaries of previously undertaken consumer exposure assessments are given as a background document, from which more detailed information may be extracted as guidance for future assessments.

This compilation of scenarios may be helpful in future assessments, particularly because existing model concepts (such as ConsExpo) were designed for organic substances, and are based on diffusion-related calculation models. Since these rely predominantly on physico-chemical properties (such as vapour pressure and octanol/water partition coefficient), they are considered to be unsuitable for metals and metal compounds.

Based on a retrospective analysis of the way in which consumer exposure was addressed in several risk assessments, some general guidance for the future assessment of consumer exposure to metals and metal compounds is summarized in this fact sheet, as follows:

- It is recommended to conduct a quantitative exposure assessment for each consumer scenario, and not to exclude any particular use a *priori*. Previous experience with metals for example has shown that the designation of a particular scenario as 'negligible' inevitably opens a discussion on the 'cut-off' value for the metal, since the various existing routes of exposure may cumulate to critical total body burdens.
- The assessment of exposure via dermal contact should make use of default assumptions for release rates only for initial screening purposes; for a refined assessment, it is recommended to rely on (experimentally verified) release rates of the metal from the product (preferably in appropriate physiological media).

HEALTH RISK ASSESSMENT GUIDANCE FOR METALS

EFFECTS ASSESSMENT

04

04. Effects Assessment

4.1 Toxicokinetics

4.1.1 Inhalation absorption

Inhalation absorption factors are not commonly available for most metals, and are also difficult to measure. In the absence of substance-specific inhalation absorption factors, the initial approach in previous EU risk assessments has been to use 100% as a default absorption factor (75% is recommended for inhalation absorption for indirect exposure via the environment). For occupational risk assessment of metals, this is an unrealistic and unnecessarily conservative assumption.

The fundamental basis for assessment of absorption of inhaled particles is the aerodynamic-size dependant deposition of the particles in three distinct zones of respiratory tract. This has been elaborated upon in detail elsewhere (ICRP, 1994). This model leads to the conclusion that (i) large inhaled material is deposited in the extra-thoracic region by impaction, subject to rapid clearance to the gastro-intestinal (GI) tract; (ii) material deposited in the tracheo-bronchial region by sedimentation is similarly subject to clearance (although somewhat more slowly) to the GI tract; (iii) finally, the retention of material that penetrates to the alveolar/pulmonary fraction of the lung is subject to diffusion, so that as a conservative default assumption, 100% of this material may assumed to be absorbed.

In the case that detailed particle size distribution (PSD) data for a particular substance and a specific occupational setting are available, then a mass-median-aerodynamic diameter together with its geometric standard deviation can usually be calculated. Fractional deposition in the respiratory tract can then be predicted with the aid of the MPPD model (Asgharian and Freijer, 1999[6]). Since workplace aerosols commonly are composed of rather large particles (i.e. MMAD >10 microns), and if a precise rate of oral absorption is available, then such particle size distribution data together with deposition modelling can be used to refine the risk characterization considerably. A fully worked example of fractional deposition and inhalation absorption using workplace particle size distribution data as used in the (EU) zinc risk assessment is given in the HERAG fact sheet on this subject (No. 02).

[6] In the meantime, a revised version of the original MPPDep v1.11 model is available (MPPD 2.0, see annex A2.2 to the HERAG fact sheet and www.ciit.org/techtransfer/tt_technologies.asp

4.1.2 Oral absorption

Ingestion is a relevant route of exposure not only for dietary intake (relevant for consumer and indirect exposure), but is also of importance in the occupational setting (hand-to-mouth transfer, inadvertent intake from peri-oral exposure via facial deposition). In addition, translocation of large inhaled particles to the GI tract renders this the most relevant route of intake.

Absorption after intake via ingestion is known to vary strongly between metals, and is can be influenced considerably by chemical speciation, solubility, dietary composition and nutritional status. Metal-metal interactions are also known to occur: examples are copper-zinc or copper-iron where any one of these essential elements at high intakes is thought to compete with transport mechanisms of the other and thereby possibly induce deficiency; an alternative example is lead, which has no known physiological function in the human body, but partly enters the body by utilizing calcium transport mechanisms. Finally, non-linear kinetics usually govern the absorption of metals from the GI tract, with saturation occurring at higher intake rates.

Thus, for metals it is relevant to distinguish between (i) usually low intakes of the general population via food, ambient air, drinking water, or consumer articles/products, and (ii) usually considerably higher intakes from occupational exposure. In order to develop this issue further, metal- or metal compound-specific information on oral bioavailability was collected to derive general conclusions on GI uptake as well as information on modifying factors, such as speciation, particle size, solubility etc.

As a background document to the underlying fact sheet (No. 04), a collection of information available on gastro-intestinal uptake of several metals is presented in an appendix, this comprises extracts from previous and current risk assessments and other sources.

The second focus of this fact sheet is on physiologically based toxicokinetic and toxicodynamic models, which are in most cases intrinsically linked to the aspect of GI uptake. Such models use mathematical descriptions of the uptake and distribution of chemical substances to quantitatively describe the relationships among critical biological processes. A catalogue of such toxicokinetic models for metals was collected from the industries participating in the HERAG project in order to extract any aspects available for a particular metal that are of a more general nature and perhaps useful for other metals. Whether the basic input parameters of any of these models could be used for future human health risk assessments for other metals was also considered. Summaries of such models and where available or feasible, the underlying principles together with advantages and disadvantages are discussed metal-by-metal in appendices to this fact sheet.

In risk assessment for a wide range of metal compounds, extrapolation between different metal compounds is necessary and the fact sheet gives the following recommendations:

- For a differentiation between soluble vs. poorly soluble or insoluble forms, water solubility is often used as a surrogate for bioavailability. For example in the assessment of nickel and zinc, it has been experimentally verified (*in vivo*) that large variations exist between soluble salts of a metal, and the metal itself, or the oxides or other very poorly soluble substances. This principle has also been established for cobalt, based on *in vitro* data.
- As a warning, it has also been shown that this concept is not applicable to all metals. For example, the VRA for lead has shown that these differences in solubility do not necessarily impact bioavailability under physiological circumstances. In consequence, extrapolation based on solubility alone can not be assumed a priori, but should be demonstrated to exist as a phenomenon for a particular metal on a case-by-case basis.
- Where robust toxicokinetic data are not available, *in vitro* 'bioaccessibility'[7] testing may be performed to substantiate read-across arguments.

[7] The term 'bioaccessibility' refers to experimental (*in vitro*) testing of solubility in synthetic physiological media.

4.1.3 Dermal absorption

Current guidance documents suggest that in the absence of data on dermal absorption, a choice between two default values (10% and 100%) may be made, based on observations with organic molecules where substances with MW >500 and extreme log P_{ow} values (under -1 or above +4) display a limited extent of skin permeation. These considerations do not apply to metals as inorganic compounds require dissolution involving dissociation to metal cations prior to being able to penetrate skin by diffusive mechanisms.

However, current (EU TGD) guidance also suggests that where data are available (e.g. data on water solubility, ionic state, 'molecular volume', oral absorption and dermal area dose in exposure situations in practice) which indicate that the use of an alternative dermal absorption percentage value is appropriate, then this alternative value can be used, and scientific justification for the use of alternative values should be provided. A fact sheet on this aspect has therefore been developed within HERAG to provide such argumentation. For this purpose, all previously available information (as validated during recent or on-going risk assessments) on dermal absorption of metals was collected, and alternative default absorption factors were proposed.

Current models[8] for the prediction of dermal absorption were found to be inappropriate for metals, since they are also based on considerations of diffusion-mediated processes, depending on the liphophilicity (i.e. log P_{ow}) and molecular weight of a compound, and in some instances also to a certain degree on concentration. It may also be questioned whether the establishment of such QSARs is at all feasible, since (i) metals and their compounds may deposit on skin in many different physical forms (fine powders, coarse crystalline materials, or liquid paste or solubilized forms) which in turn will influence the availability of 'free' metal ions, and (ii) the solubility in water or a physiological medium such as sweat will vary strongly, depending on the solubility product of any given metal compound and the possible anions present in such a medium.

The focus of the work in preparation of this fact sheet (No. 01) was therefore on the collation and screening of the relevance of existing data on

[8] SKINPERM (ten Berge, 2006); Corish and Fitzpatrick, 2002; Moss et al. 2002; Krüse et al (2007); Cleek and Bunge (1993); Bunge and Cleek (1995); Bunge et al. (1995).

dermal absorption of metals. Test systems for percutaneous transfer have now been standardized to allow reliable measurement. *In vitro* studies of several metals (Zn, Ni, Cd, Sb, Cu, Pb) have demonstrated that the penetration of the dermis by dissolved metal cations is generally low, i.e. in the range of 0.1-1%, depending on the resolution of the test system. In the case of lead, a combination of *in vitro* testing plus toxicokinetic modelling has demonstrated that the assumption of a dermal absorption rate in excess of 0.01% would be in conflict with available biomonitoring data (blood lead) and is therefore implausible.

The fact sheet on dermal absorption however also concludes that future studies of metals and metal compounds could be undertaken with a view to establishing the maximum transfer rate of metal ions through skin, and the extent of dermal loading required to achieve the concentration gradient that is the determinant of this maximum. It is also proposed that an extensive validation exercise on existing dermal absorption studies should be undertaken with the purpose of proposing alternative, more realistic default dermal absorption factors.

Based on currently available data which were also validated and used for risk characterization in current EU risk assessments, the following conclusions were derived:

- Considering that under industrial circumstances many applications involve handling of dry powders, substances and materials, and since dissolution is a key prerequisite for any percutaneous absorption, a lower default absorption factor may be assigned to such 'dry' scenarios where handling of the product does not entail use of aqueous or other liquid media (like in the *in vitro* experiments).
- The following default dermal absorption factors (reflective of full-shift exposure) for metal cations may be tentatively proposed for screening risk assessment purposes, until more sophisticated guidance becomes available:
  - from exposure to liquid/wet media: 1.0%
  - from dry (dust) exposure: 0.1%

It remains a matter for debate in dermal absorption testing whether the assessment of material retained in the skin (and not released to the receptor fluid during the exposure period or thereafter) must be considered as 'potentially absorbable'.

4.2 Acute toxicity, irritation and corrosivity

This aspect is mentioned here merely for reasons of completeness. Discussions during the HERAG project did not identify any points of particular relevance to metals. One point worthy of mention however is that for acute inhalation toxicity testing, and for interpretation and extrapolation of test results for one compound to others, use should be made of the detailed particle-size argumentation in the fact sheet on inhalation exposure and absorption, as well as the fact sheet on classification, read-across and derogation (currently under development).

4.3 Sensitization

For the numerous metals, positive confirmation of sensitizing effects have been reported, these include beryllium, vanadium, chromium(VI), cobalt, nickel and platinum. In contrast, previous as well as current EU ESR and VRAs have concluded on a lack of sensitization for the metals copper, lead, cadmium and antimony. Only for nickel is a detailed risk assessment available. Within HERAG a retrospective analysis of experience from EU risk assessments on skin sensitization was undertaken with the exercise restricted to Cd, Zn, Ni, Cu, Sb and Pb. Since only one of these metals with sensitizing properties was reviewed within EU RAR procedure (nickel), the sensitization fact sheet was deemed upon peer review to be insufficiently developed for publication. Further input on this subject from beyond the current framework of the HERAG project is however welcome and interested parties can obtain the draft fact sheet from ICMM or EBRC.

4.4 Repeated-dose toxicity

At an early stage in the HERAG project, this endpoint was deemed not to be associated with many metal-specific aspects. Nevertheless, metal-metal interactions were identified as one major area of relevance. Whereas one metal may not exert any particular toxic effect at a given concentration, it may nevertheless modify the effect of another in situations of co-exposure.

Further, the relevance of particle-size dependant deposition on the respiratory tract was recognized for its relevance for route-to-route extrapolation, and for the correct assessment of target tissue (lung) dose assessment.

4.5 Mutagenicity/genotoxicity

The mutagenic and/or genotoxic properties of a substance are an important property upon which hazard classification of substances is based. Although new classification criteria may evolve with the progressive adoption of the United Nations' Globally Harmonized System (GHS), criteria for mutagenicity classification should be similar to those presently in place within the EU. Mutagenic properties will also be of fundamental importance with the adoption of REACH, serving as a potential mandatory 'trigger' for REACH authorization provisions. In addition, mutagenic potential can also be of importance within risk assessments and can affect the fashion in which dose response relationships are evaluated for other health endpoints. For example, genotoxic carcinogens can be presumed to exert this effect without a threshold dose/concentration, which is in contrast to *'No Observable Effect Levels'* that characterize several other end-points like acute toxicity or irritation.

The mutagenic effects of metals and their compounds have been evaluated within the context of several EU Risk Assessments and were further the subject of a workshop convened in Hannover, Germany on 28–29 November 2005. The workshop assembled external independent experts from government and academia to address key issues such as testing strategies, classification criteria and risk assessment principles that might be appropriate for metals. From this workshop, and as refined in subsequent stakeholder consultations, the conclusion has emerged that testing strategies developed for the classification of organic substances are not fully appropriate for metals and that alternate approaches for *in vitro* and *in vivo* genotoxicity testing should be adopted.

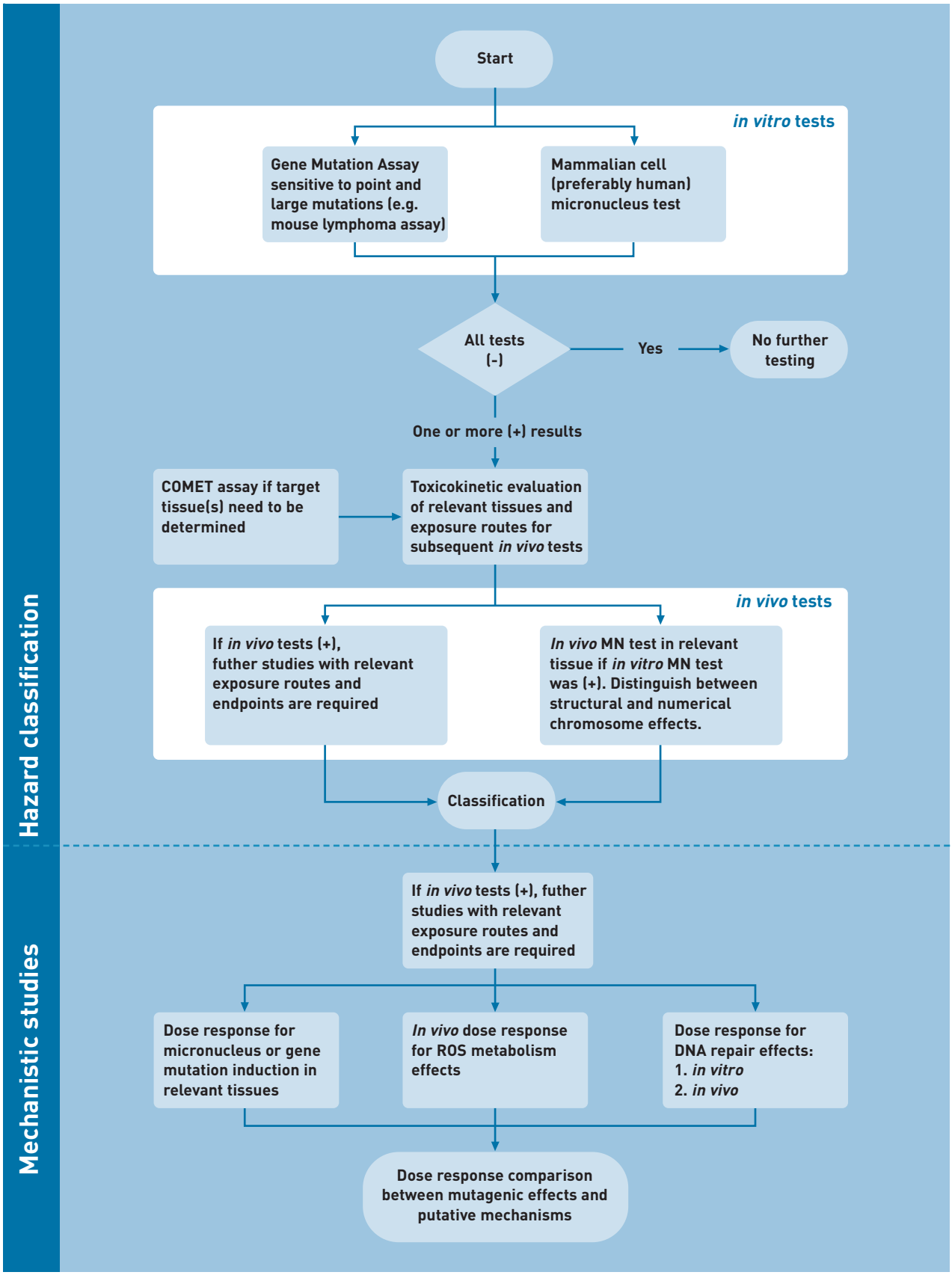
The attached HERAG fact sheet (No. 05) reviews the experience with test systems currently and previously applied to metals and metal compounds, focusing upon the findings of recent EU risk assessments. The response profile for these metals is presented and metal-specific mechanisms of mutagenicity are discussed. From these considerations, a mutagenicity testing strategy specifically for metals and metal compounds is proposed in the format of a decision tree (see Figure 5).

This decision tree for metals and metal compounds eliminates mutagenicity testing in bacterial systems due to a lack of sensitivity related to either probable mechanism of action or lack of metal uptake. Although some metals will induce mutations in bacteria, this would appear to be more the exception than the rule. Testing in mammalian cell culture assays for forward mutations is instead proposed as part of the base testing data set, preferably in a system sensitive to the large DNA deletions believed to the predominant form of damage induced by the indirect mechanisms of action that characterize many metals. In addition to a gene mutation assay, chromosome effects would be assessed in mammalian cells. The micronucleus test, incorporating appropriate staining procedures to distinguish aneugens from clastogens, would be appropriate for use as a second test.

Further testing might not be required if the materials tested were negative in both type of *in vitro* assays. However, based upon the collective experience of metal risk assessments conducted to date, it is expected that most metals will elicit responses in the micronucleus test and potentially assays for gene mutations. The tendency of metals to produce positive *in vitro* assay results is likely due to the high metal concentrations that can be achieved in cell culture and the multiple metal binding sites that exist on key cellular macromolecules. Indirect mechanisms for genotoxicity, triggered by either nonspecific metal binding or substitution of metals being tested for essential metals contained within metalloproteins, are expected to produce positive responses that will require follow-up in appropriately designed *in vivo* systems. The challenge that is presented for follow-up testing is a determination of whether or not positive *in vitro* responses are induced via mechanisms that are plausible for intact organisms.

Follow-up *in vivo* studies would ideally be conducted to evaluate the genetic endpoint of concern from *in vitro* testing (gene mutations or chromosome effects), coupled with an understanding of the toxicokinetic properties of the substance under study. Tissues known to accumulate high concentrations of metal, or to be the targets of metal toxicity, would be assigned priority for evaluation. If toxicokinetic information is lacking, indicator tests such as the Comet assay could be applied to identify potential target tissues for in depth study with mutagenicity tests. The route,

Figure 5: **Proposed mutagenicity testing strategy for metals and metal compounds**



intensity and duration of exposure would be selected with a view to both maximizing mutagenic responses and avoiding high dose effects (such as tissue necrosis or apoptosis) that may produce artifactual false positives. While control for sources of artifactual responses is advised for any substance, it is particularly important in the testing of metals since essential metals appear to be involved in key processes that regulate cell division, differentiation and apoptosis.

Since the uptake and distribution of many metals is governed by specific metal-binding carrier proteins, use of physiological routes of exposure would be most likely to yield exposure in tissues of greatest relevance to both hazard identification and subsequent risk assessment. Non-physiological routes of exposure (e.g. intravenous or intraperitoneal injection) can increase the precision of dosing but may bypass physiological carrier systems and fail to reproduce patterns of tissue specificity that would characterize oral or inhalation exposures. There may further be concern that non-physiological exposure routes, in bypassing carrier protein systems, result in levels of internal exposure to free metal ions and induce indirect mechanisms of effect that could not be plausibly achieved via oral or inhalation exposure.

Should positive findings be obtained during *in vivo* testing, appropriately designed tests will have laid the foundations for follow-up studies that would be critical for quantitative risk assessment. For example, if indirect mechanisms for mutagenicity are suspected, the induction of mutations may occur with sharply non-linear or quasi-thresholded dose response functions. An evaluation of the dose response functions for both suspected mechanisms and mutagenic effects could be initiated in relevant target tissues with guidance from the base set testing data.

4.6 Carcinogenicity

The ability of a substance to induce the cellular changes which lead to cancer (i.e. its carcinogenic properties) is an important factor for hazard classification within the context of the Existing Substances Regulation (ESR) of the EU. Carcinogenic properties will also be of fundamental importance with the adoption of REACH, serving as a potential mandatory trigger for REACH authorization provisions whereby classified substances must obtain approval prior to use in consumer products. Carcinogenic potential can also be of importance within risk assessments, with the potential for risk being introduced for individuals experiencing occupational exposure, exposure from consumer products, and indirect exposure via the environment. The manner in which dose response relationships are evaluated for carcinogenic substances is in part influenced by mechanistic assumptions made regarding the induction of carcinogenic responses. For example, genotoxic/mutagenic carcinogens are currently presumed to exert effects without a threshold and to exhibit low dose linearity for the induction of effects. Conversely, for non-genotoxic carcinogens, thresholds may be presumed to exist if adequate dose response and/or mechanistic information is available to support this contention.

Existing guidelines for classification and risk assessment for the carcinogenicity of metals and metal compounds are less than optimal and consideration needs be given to the special properties of metals when deciding upon strategies for testing. This consideration should focus upon both practical complexities of the occupational exposure environments for metal production and use, and the mechanistic complexity (i.e. indirect mechanisms) that may underlie the carcinogenic potential of some metals.

A number of metals have been demonstrated to be carcinogenic in animals, but the mechanism by which carcinogenic responses are induced, and the significance of animal responses for humans, must be conducted via a careful weight-of-evidence evaluation. Indirect mechanisms appear to be responsible for many carcinogenic responses. Given that the mechanism of action of many metals studied to date appears to be unique, demonstration that a given mechanism of action is, or is not, relevant to human must be conducted on a case-by-case base. The principal probable exception to this would be instances of pulmonary tumours produced by particulate overload mechanisms in the rat. The 'generic' mechanism would be common to inert, poorly soluble substances that induce tumour of alveolar origin in the rat following chronic inhalation exposure to high (e.g. 50 mg/m^3) levels of a given substance. Such substances would not induce tumour in other experimental animal species and could produce a stronger response in female rats than male rats. Substances exhibiting such a response profile should be carefully evaluated and potentially exempted from classification.

Distinctions between genotoxic and non-genotoxic carcinogens are also problematic when applied to

metals. Virtually all metals tested are genotoxic *in vitro* and most will also induce weak positive responses for *in vivo* genotoxicity. The presence of *in vitro* genotoxicity, and potentially *in vivo* genotoxicity, is thus uninformative with respect to determining whether or not a metal is carcinogenic. Given the uncertain relationships between genotoxicity and carcinogenicity for metals, it further follows that carcinogenic metals should not be automatically assumed to exert effects via a genotoxic mechanism. Alternate rules of procedure are needed whereby the relevance of genotoxicity for metal carcinogenicity can be assessed and applied to risk assessment. These might include, but would not be limited to, similarity in the dose response for induction of carcinogenic and genotoxic effects and patterns of tissue specificity for both effects.

Epidemiology studies have suggested associations between numerous metals and human cancer. However, in a number of striking cases, initial assumptions regarding causal relationships between specific metals and human cancer have been shown to be the result of co-exposures to other metals in the workplace. While confounding by co-exposures is not a specific property of metals *per se*, it is reflective of the long industrial history of metal production and a failure to fully recognize and evaluate the complex co-exposures associated with metallurgical processes. The older human epidemiology literature must thus be viewed with caution. In particular, co-exposures to arsenic may have been responsible for some of the associations that have been reported. Better understanding of the dosimetry of arsenic's effects would aid interpretation of the historical literature as well as future epidemiology studies. This highlights the need for more comprehensive and refined exposure assessments to be incorporated into future epidemiological studies of metals. Metal ore bodies are, by their intrinsic nature, extremely complex mixtures and the exposure environments at primary metallurgical facilities are more complex than had been initially realized. While excess cancer may exist at a number of primary metallurgical facilities, the causative agents that are responsible for these excesses can only be defined if more comprehensive and refined exposure assessments are conducted.

4.7 Reproductive toxicity

The reproductive effects of exposure to any substance (loosely defined as any adverse impact upon any aspect of mammalian reproduction) can be an important property upon which hazard classification and risk assessment are based. This is true within the context of the ESR, and is expected to be of fundamental importance with the adoption of provisions within the new EU Chemicals Policy (REACH). Thus, impacts upon the ability to conceive (fertility) or upon pregnancy outcome (inclusive of developmental effects) will be critical determinants of classification.

The reproductive effects of metals have been evaluated within the context of EU Risk Assessments (e.g. Cd, Cu, Ni, Pb, Zn). Through examination of existing risk assessments, and on the basis of consultations with experts who have evaluated the reproductive effects of metals, it would appear that technical procedures for the evaluation of reproductive risk developed for organic substances are largely suited for the evaluation of metals and their compounds. However, the design and interpretation of studies of reproductive impacts needed to consider the toxicokinetic properties of metals and, in certain instances, the unique mechanisms through which metal interactions could influence reproductive system function.

Metals are diverse in their ability to impact on reproductive organs and/or to cross the placenta to impact upon the developing foetus, but it has become evident that specific mechanisms exist that can regulate the ability of metals to reach target tissues. This is most evident for metals that are under tight homeostatic control (e.g. copper, zinc) or which bind to common carrier systems and sequestration proteins that modulate the pharmacokinetics and homeostasis of essential metals. Under conditions of excessive exposure, this binding can in result in perturbations of trace mineral homeostasis that can have adverse impacts upon development through indirect mechanisms of action. Thus excessive amounts of zinc can induce copper deficiency in the developing foetus and it is suspected that cadmium may exert adverse impacts via the induction of zinc deficiency. In the instance of both cadmium and zinc, effects are not mediated by the intrinsic capacity of the material to impair processes such as foetal development but by indirect mechanisms (disruption of homeostatic control mechanisms for trace mineral metabolism) that may be more properly

regarded as manifestations of maternal toxicity. That cadmium should be classified for reproductive toxicity, and zinc is not, in part reflects the quality of the data demonstrating the probable mechanism of zinc's impact relative to that for cadmium. Essential nutrients required for reproductive function are also less likely to be classified as toxic for reproduction if the public health risks associated with deficiency are perceived to be greater than those associated with exposure excess.

Interactions are to be expected between metals and, when these interactions mediate effects upon reproduction though the induction of trace mineral deficiency or perturbations in basic homeostatic control mechanisms, such fundamental mechanisms should be more explicitly and transparently considered in the evaluation of data for classification and risk characterization. Towards this end, guidelines should acknowledge that nutritional deficiency and perturbations in basic homeostatic control mechanisms for essential metals are both manifestations of systemic toxicity. Careful weight-of-evidence evaluations can thus be required to determine whether reproductive effects reflect unusual sensitivity of the developing foetus (or placenta) to a metal or are reflective of a more generalized systemic perturbation in homeostasis. Specific examples illustrating this are limited, but should be expected to increase in number as testing is extended to a broader range of metals and their compounds. Guidelines for the definition and demonstration of toxicity mediated through induction of perturbations in homeostasis for essential metals, and the subsequent induction of nutritional deficiency are needed.

Interpretation of toxicological studies, and extrapolation from animal studies to humans, is also facilitated if the basic dose response for deficiency and the regulation of metal uptake, distribution, and excretion by homeostatic control mechanisms is fully documented. Such information facilitates understanding of the potential mechanisms that may underlie adverse effects, sets bounds to the exposure levels that may or may not be of concern, and assists in the identification of effects that may reflect gross perturbations in fundamental homeostatic control mechanisms that should be regarded as systemic toxicity.

4.8 Quality screening procedures for health effects literature

Prior to initiating the effects assessment for a chemical, the data and information available may safely be assumed to vary considerably in extent and quality. As one extreme, there may be little or no information at all, meaning that new experimental data needs to be generated before an assessment is possible. On the other hand, 'data-rich' substances may exhibit a wealth of data on various health end-points.

This could include toxicological studies, published articles, earlier toxicological review, hand book data and even epidemiological studies for substances available and used for a longer period of time, requiring for a scoring for reliability and quality. Depending on the extent of the data set, systematic evaluation procedures need to be applied, which may differ in detail and extent between e.g. animal toxicity testing reports, human epidemiological studies and other published literature. The need for a relevance and reliability screening for health effects literature may not intrinsically appear to be a metal-specific issue in risk assessment. However, since some metals (such as lead and copper) have been found to be very data-rich in previous EU risk assessments, specific quality and relevance scoring and evaluation systems have already been developed in this context. To support similar such efforts in the future, the HERAG fact sheet (No. 06) provides some generic guidance and also provides specific examples of systematic health effects data evaluation procedures.

Animal test data

HERAG has acknowledged the continued usefulness of the scheme by Klimisch et al. (1997) for animal studies to assess data for reliability, relevance and adequacy, as also endorsed by the OECD in their Existing Chemicals Programme, as reflected in their 'Manual for Investigation of HPV Chemicals'. This ranking of individual experimental data is recommended since it has facilitated transparency in documenting how health end-points for risk characterization were selected based upon a weight-of-evidence approach.

Human (epidemiological) data

The assessment of the quality and relevance of human data is a more complex matter that has been dealt with at varying levels of detail in previous EU risk assessments. The examples for

Cu, Zn, Pb, Cd and Ni presented in the fact sheet illustrate that the diversity between nature and extent of data sets for various metals implies that there likely cannot be one common approach for all metals, and that a case-by-case approach needs to be developed. In some cases, an end-point by end-point scheme had to be developed. No single approach was found to be clearly superior to the others. The examples presented may help to select the most suitable approach, or at least provide guidance on relevant aspects which need to be considered in such an exercise. In doing so, one needs to consider the level of detail required for some of the approaches given in the fact sheet. If too much detail is required, the screening criteria may become so burdensome that they will be unlikely to be readily adopted. Therefore, the final procedure should be simple enough to not require excessive resources to complete while providing sufficient clarity regarding the quality of the study. Finally, for data rich substances, the application of screening criteria provide the basis of establishing exclusionary criteria for the conduct of sophisticated statistical exercises (e.g. meta-analyses) that can be used to integrate estimates of effect and/or dose response from multiple studies of exposure human populations.

Genotoxicity/mutagenicity data

Numerous test systems have been developed for the detection of mutagenic and genotoxic properties of substances, and test systems evolve on a continuous basis. No single set of quality assessment criteria can be applied to all testing data, and studies must be evaluated on a case by case basis. OECD protocols exist for some tests and OECD guideline compliance can be determined as a first step in study quality assessment. Other tests have been evaluated by groups such as the International Working Group on Genotoxicity Testing (IWGT) and detailed protocol recommendations published. IWGT recommendations, which tend to be published as separate papers as opposed to being compiled in a single repository for easy reference, serve as an additional useful source of quality screening criteria.

As a generalization, higher quality tests examine the effects of multiple doses in an effort to determine whether dose-dependent effects can be detected using concentrations of a test substance that extend into cytotoxic ranges while at the same time avoiding excessive cytotoxicity. Inclusion of positive and negative controls further aids in the evaluation of test data and controls for conditions known to produce artefactual positive responses (e.g. necrosis or apoptosis). As further addressed in section 3.2 and the corresponding mutagenicity fact sheet, special consideration should be given to the properties of metals when planning, conducting and evaluating experimental investigations concerning their mutagenic and/or genotoxic potential. Although no single set of metal specific guidelines can be put forward, due consideration must be given to the observation that most metals appear to act via indirect mechanisms which, in many instances, entail perturbations in metal control mechanisms and/or the ability of nonessential metals to substitute for essential metals in processes related to DNA repair and the metabolism of reactive oxygen species.

Metals also modulate processes (e.g. apoptosis and mitogenesis) that may influence assay outcomes and which therefore must be controlled if assay data are to be interpreted in an appropriate fashion. Finally, an understanding of metal toxicokinetics, and the capacity-limited processes that govern the uptake, transport, distribution, and excretion can be critical for the design of adequate *in vivo* studies. Combined, these factors introduce study quality issues different from those that would be important for the study of organic substances.

HEALTH RISK ASSESSMENT GUIDANCE FOR METALS

RISK CHARACTERIZATION

05

05. Risk Characterization

Extensive debate during the HERAG project did not yield major concerns for the application of current methodologies to metals and their inorganic compounds. However, some aspects of exposure assessment were thought to be of particular relevance for the refinement of the risk characterization and these are summarized below.

5.1 Proposed scheme for the refinement of occupational inhalation exposure and subsequent systemic absorption

The risk assessment of inhalation exposure (see fact sheet No. 02) for any hazardous substance may ultimately lead to a decision about which control measures are required, and which exposure limit standards need to be met to ensure adequate control. For this, a most precise assessment of exposure is needed, together with correspondingly accurate predictions of systemic intake and/or lung tissue target dose. For this purpose, a **step-wise procedure** was developed as shown in Figure 6.

The individual stages of this stepwise procedure are described in detail in the fact sheet. In principle, the scheme proposes a logical sequence starting with highly conservative assumptions for exposure and absorption, leading in an iterative process to the use of more sophisticated modelling and a combination of particle-size distribution and workplace monitoring data.

5.2 Proposed tiered-approach for dermal exposure assessment

Similar to inhalation exposure, a tiered approach for the refinement of systemic uptake via the dermal route was developed, as presented in Figure 7 (see also fact sheet No. 01). This approach reflects the consideration that currently existing models provide little guidance for metal-specific exposure scenarios, and also the necessary time, effort and costs for a properly conducted sampling campaign.

This tiered approach proceeds through various hypothetical situations, starting from the ideal position that adequate monitoring data are available, through to where assumptions can be made based upon available data on analogous materials, and finally to the extreme, where suitable data neither exist nor can be modelled, and where generation of monitoring data is the only alternative. The various steps including the screening model for dermal exposure are described in detail in the corresponding fact sheet

For risk characterization, these exposure estimates must be coupled to appropriate values for the likely dermal absorption; again, the fact sheet makes recommendations on the choice of default dermal absorption factors, or (where required) on the experimental design suitable for the investigation of measure uptake rates.

Figure 6: Decision tree for the refined assessment of inhalation absorption using particle size distribution data

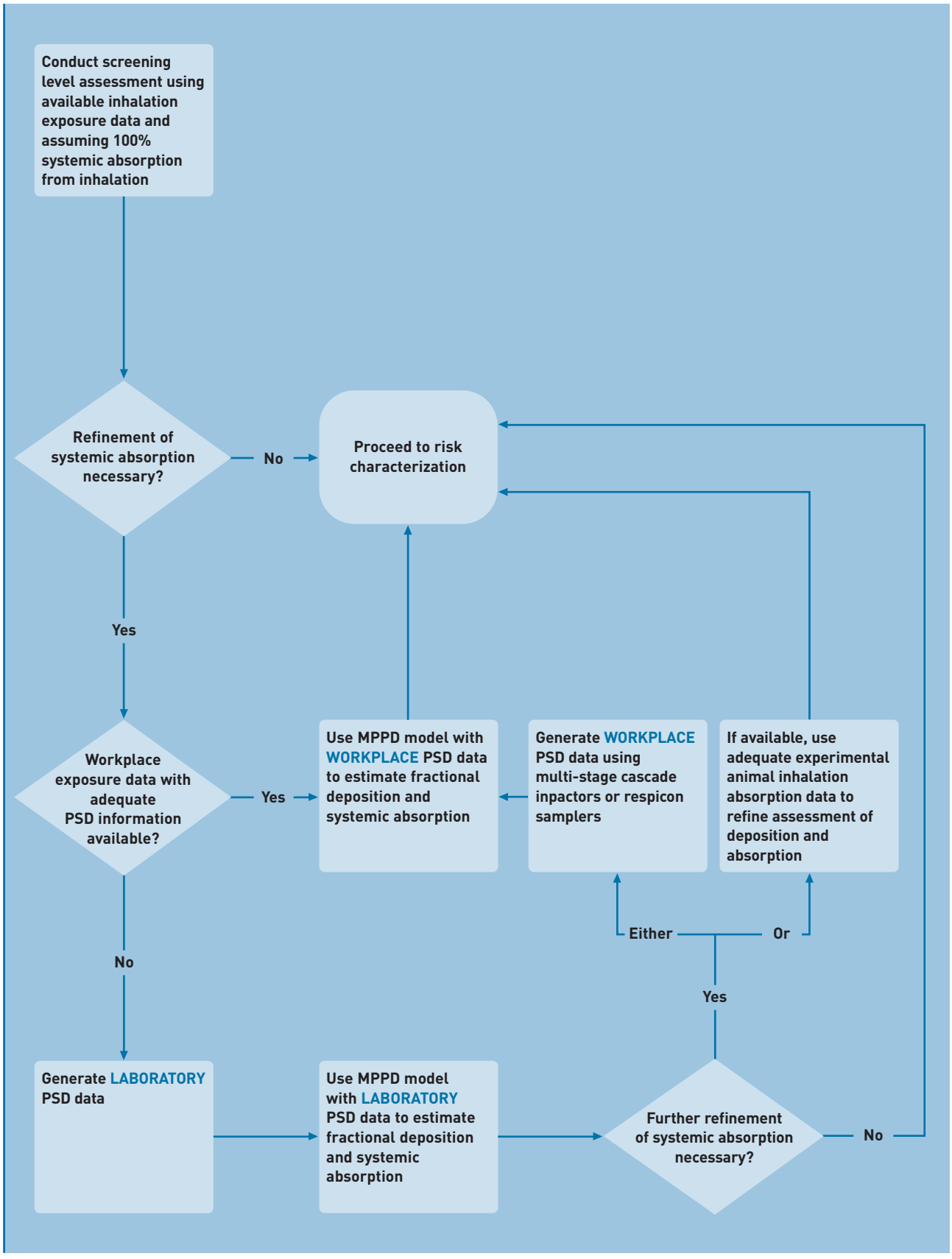
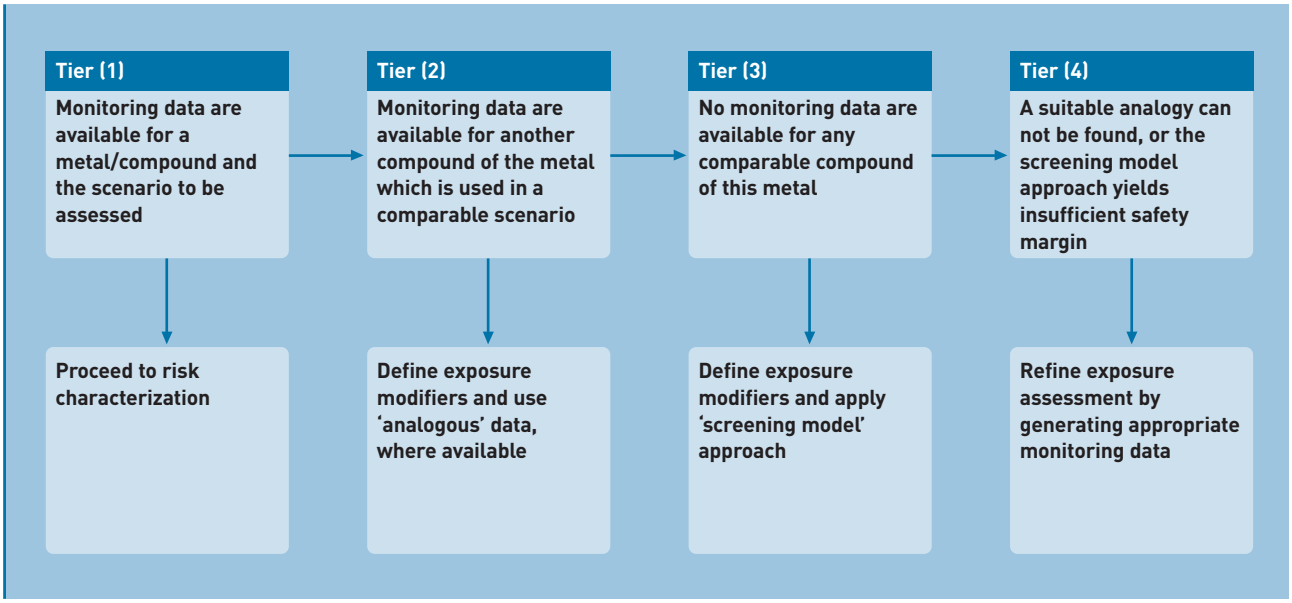


Figure 7: **Tiered approach for the assessment of dermal exposure**



5.3 General considerations for the choice of assessment factors in risk characterization of metals

In several of the previous and current EU risk assessments, considerable deviations from 'conventional' approaches of applying a standard set of assessment factors have been made. The intention of setting assessment factors is to account for uncertainty (see fact sheet No. 08).

This uncertainty may result from the reliability and quality of data that form the basis of a risk assessment; for this reason, such procedures were described in a separate fact sheet on 'quality screening of published data'. Similarly, uncertainty may also arise from inadequate or modelled exposure data – for this purpose, separate fact sheets on dermal, inhalation, indirect and consumer exposure were generated. Uncertainty in exposure assessment will be lowest when systemic exposure biomarkers (e.g. levels of a metal in blood) are available. Finally, uncertainty may also originate from the need to extrapolate from observations based upon experimental animals to humans. However, several metals have a substantial data base of human data, these include cadmium and lead, from which effect levels for different health endpoints based upon measures of systemic exposure can reliably be established. For these reasons, a fact sheet was established to document these approaches with the aim of providing guidance for future metal risk assessments. Some of the conclusions reached can be summarized as follows:

The choice of assessment factors in risk assessments for metals should consider the existence of natural background levels – the assumption of 'zero' exposure is irrelevant for most metals, because humans are subjected to a multitude of metal compounds through ambient environmental concentrations. This necessitates a verification of no-effect-levels against environmental background for plausibility; the documentation of 'baseline intake rates' and resulting body burdens for metals should be envisaged in future assessments.

In addition, the occasionally small differences in exposure levels that separate toxicological effects from exposure excess and deficiency for essential trace elements also need to be addressed (see section 5.4). The application of traditional assessment factor approaches to such substances results in permissible exposure levels that may be detrimental to health since they would induce deficiency.

For acute effects, HERAG does not provide any relevant basis for setting of such values in addition to that of the TGD, recognizing at the same time that there is currently no uniform, standardized approach available.

A systematic approach is however suggested in the fact sheet for the deviation from standard assessment factors for repeated dose toxicity, in three different situations:

- For non-essential elements with toxicity data largely derived from animal testing, the application of the standard (EU TGD) approach is recommended (example: nickel).
- For non-essential elements with relevant human data, it may argued (depending on data quality and extent) for a considerable reduction of assessment factors down to as little as 1-3 (example: cadmium and lead).
- For essential trace elements, where adequate human data are available for relevant endpoints, a minimal assessment factor of '1' may be adopted (example: zinc).

Particle size and chemical speciation

The extrapolation of effects seen in animal studies to human exposure situations should recognize the differences in particle sizes between laboratory experiments (usually micronized materials) and workplace exposures (usually much larger aerosol particles). As an example, the zinc RAR clearly distinguishes between effects elicited by ultra-fine zinc oxide particles and by aerosols reflective of the occupational setting.

In addition, particle-size dependant deposition may deviate considerably in view of the variances in airway morphometry between animals and humans. Furthermore, chemical speciation and dissolution kinetics will influence the translocation of deposited particles in the respiratory tract.

5.4 The influence of essentiality on risk assessment of metals

The World Health Organization regards the following trace elements as essential for human health: copper, zinc, iron, chromium, molybdenum, selenium, cobalt and iodine; a second group of elements is classified by the WHO as 'probably essential for humans': silicon, manganese, nickel, boron and vanadium.

Previous risk assessments have focused primarily on the effect of high doses of chemicals, which ultimately may induce toxicity; however, for several metals which are essential to life, harmful effects also occur at very low levels of intake due to deficiency. This challenges risk assessment paradigms that aim to minimize exposure as far as possible. Unbalanced concern over high dose effects of essential elements may result in recommendations that lead to harm from deficiency.

Therefore, a separate HERAG fact sheet (No. 07) has been prepared with the aim of providing guidance for careful consideration of both nutritional essentiality and high dose toxicity in the overall risk assessment and risk characterization procedures for essential metals and their compounds. The reader is cautioned to the fact that this fact sheet was largely based on a retrospective analysis of the zinc and copper risk assessments. Whereas it is acknowledged that the aspect of essentiality has also been recognized for other metals (such as iron and selenium), none of these have been subject to a comprehensive (EU) risk assessment, and therefore experience in the reflection of this aspect in the establishment of assessment factors is not available.

In brief the definition of essentiality for human health is that absence or deficiency of any such element from diet produces either functional or structural abnormalities related to or a consequence of specific biochemical changes that can be reversed by the presence of the essential metal. Essential trace elements are subject to homeostatic control mechanisms that may include regulation of absorption and/or excretion and tissue retention, and enable adaptation to varying nutrient intakes to ensure a safe and optimum systemic supply.

A structured scheme for the assessment of essentiality (depending on the quality and extent of data available) is suggested. In this, in order to avoid confusion with the concept of 'no effect levels' used for high dose toxicity, the new terms 'sufficient dietary intake[9]' (SDI) and 'deficiency effects level[10]' (DEL) as developed in the copper VRA are proposed as boundary terms for effects at low intakes.

For such an assessment, data need to be extracted largely from nutritional studies, which have intrinsic limitation; therefore, a separate set of quality screening criteria (Plunkett, 2004) have been developed. Klimisch criteria are not useful in this context as they were not designed to assess the potential adverse consequences of deficient exposures.

Given the current restriction of previously conducted work to copper, it would be desirable to have the same concept and level of detail applied to other elements such zinc and possibly also iron as further examples. It was recognized that such work is outside the current scope of the HERAG project, and is therefore highlighted as an issue for future consideration.

[9] The dose/intake level in a given study at which no adverse health consequences associated with intake are observed in any of the measured endpoints.
[10] The dose/intake level at which potentially adverse health consequences associated with deficiency are first observed. For studies with only one experimental dose, the DEL is considered to be that dose if adverse health consequences are observed relative to controls (basal diet).

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06

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