HEALTH RISK ASSESSMENT GUIDANCE FOR METALS

FACT SHEET

HERAG 08

CHOICE OF ASSESSMENT FACTORS IN HEALTH RISK ASSESSMENT FOR METALS

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1. Introduction

One of the issues considered specific for metals within HERAG was the choice of assessment factors, since 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. It is therefore the purpose of this fact sheet to document these approaches with a perspective of providing guidance for future metal risk assessments.

Given that all previous EU Risk assessments were conducted according to principles laid down in the Technical Guidance Document (TGD), it is inevitable that the terms "MOS" (margin-of-safety) and "reference MOS" (MOS_{ref}) are used. It is recognised that under REACH, the derivation of DNELs (derived no-effect levels) will supersede this approach.

Whereas this retrospective analysis within the HERAG project repeatedly uses the previous terminology, the focus is in fact not on these concepts, but instead on the choice of assessment factors when deriving reference values for health endpoints and the criteria for doing so, in order to facilitate consistent approaches to be developed in future assessments.

The choice of assessment factors in risk assessments for metals should not only consider the sometimes low margin between toxicological endpoints and deficiency levels, but also the existence of natural background levels. The TGD (2003) proposes a fixed set of factors based upon which a so-called "reference MOS" is derived. However, in previous risk assessments the deviations from this principle were in fact considerable.

Therefore, this fact sheet is targeted at cataloguing the previous approaches, with a perspective of providing arguments for deviating from default approaches.

Key metal industry contact points were therefore approached with a request to provide (where applicable) a short response on MOS values which had been attributed to a particular metal or its compounds in previous assessments, or whether any other information was available on this topic (for details, see chapter 3).

Based upon this collection of cases, and after discussion within the HERAG project group, a set of conclusions and recommendations (see chapter 4) was derived.

Finally, the setting of assessment factors is always also a reflection of uncertainty. During peer review of this fact sheet, it was stressed that the reliability and quality of data that form the basis of a risk assessment should be documented. To this, the authors of this fact sheet would like to point out that such procedures are laid out for human health effects data in a separate fact sheet on "quality screening of published data", and for human exposure in separate fact sheets on dermal, inhalation, indirect and consumer exposure.

2. Definition of "margin of safety" (MOS)

Human health risk characterisation according to the current EU technical guidance document (TGD 2003) is conducted in the following way:

(1) First, health hazards for relevant endpoints are described by corresponding no-observed-adverse-effect-levels (NOAEL) or lowest-observed-adverse-effect-levels (LOAEL). On the other hand, actual typical and worst-case human exposure is assessed either by monitoring or modelling.

(2) A "margin of safety" (MOS) is calculated as the ratio of the outcomes of the effect assessment and the exposure assessment, by dividing the N(L)OAEL (usually given in mg/kg bodyweight/day) by the corresponding measured or predicted exposure (also in mg/kg bw/day). In some cases the risk assessors have derived MOS values using other units, e.g. for nickel, where the N(L)OAEL values and exposures levels were both given in mg metal/m^3.

(3) Then, a so-called "reference MOS" (MOS_{ref}) is derived. The MOS_{ref} is an overall assessment factor which incorporates differences between animal experimental data and human exposure, and also supposed to reflect inter- and intra-species variability and uncertainty. The MOS_{ref} is derived by combining a number of individual assessment factors (see below).

(4) Finally, risk is concluded in those cases where for a particular end-point the MOS is below the MOS_{ref}.

Note on uncertainty analysis: The derivation of each MOS may be assumed to intrinsically reflect either (i) an additional safety margin for example where very conservative assumptions were used, or (ii) a level of uncertainty usually related to the extent or quality of the data base or lack of accuracy in fundamental parameters such as toxicokinetics. Therefore, as a general principle, the uncertainty implicated in the procedure of deriving a MOS value should explicitly be stated.

This margin of safety approach as described above is commonly used where a threshold mechanism is plausible and a N(L)OAEL or a N(L)OAEC ("…adverse effect *concentration*") can be identified, such as in the case of repeated dose toxicity and reproductive toxicity.

However, for endpoints such as mutagenicity and carcinogenicity, usually a non-threshold mechanism is assumed, except where for the latter a threshold level of exposure below which there is no increased risk can be derived.

The TGD provide detailed guidance on the derivation of MOS_{ref} values applied in the assessment procedure for threshold endpoints. This primarily involves a selection of assessment factors used to address differences between experimental animal data and humans and to address inherent uncertainties, which are multiplied to arrive at an overall MOS_{ref} value.

When extrapolating from animal experimental data to humans, assessment factors are introduced to address (among others) inter-species differences, intra-species differences, differences in duration of exposure (i.e. extrapolation from semi/sub-chronic to chronic, subacute to chronic, or subacute to semi/sub-chronic), uncertainty in route-to-route extrapolation, and dose-response related issues including the severity of effects.

For comparison with the subsequent sub-chapters, the default assessment factors currently proposed by the recently (2005) revised risk characterisation section of TGD (2003) can be given as follows:

assessment factor	reasoning	default value
inter-species	- correction for differences in metabolic rate per body weight - remaining differences	AS 2.5
intra-species	- worker	5
	- general population[1][2]	10
exposure duration	- subacute to sub/semi-chronic	3
	- sub/semi-chronic to chronic	2
	- subacute to chronic	6
route-to-route extrapolation	- difference between human and experimental animal exposure route	1
dose response	- issues related to reliability of the dose-response, incl. LOAEL/NAEL extrapolation and severity of effect	1

AS = factor for allometric scaling (range: 1.4 -7)

(1) The intra-species assessment factor may be divided into a toxicokinetic and a toxicodynamic component (each contributing ~3.3).

(2) Higher intra-species extrapolation factor for children from 10 to 100 may be considered when the following three criteria are fulfilled:
- one or more exposure scenarios point to specific exposure of very young children
- there are indications or suspicions, obtained from, for example, experiments in adult animals, epidemiological studies, *in vitro* experiments and/or SARs (Structure Activity Relationships), of effects on organ systems and functions that are especially vulnerable under development and maturation in early life (in particular the nervous, reproductive, endocrine and immune systems and also the metabolic pathways), and
- there are deficiencies in the database on such effects in young animals.

Whereas the approach stated above principally is of a generally applicable nature, in practice it focuses on repeated dose toxicity. In contrast, the TGD is less specific on this procedure for acute effects.

Finally, it is also noted that for mutagenic and carcinogenic substances which act with no threshold or lack acceptable proof of a threshold mode of action, this approach is not applicable.

3. Previous experience in EU risk assessments

The widely differing approaches used for the derivation of reference MOS values in previous mandatory (according to the Existing Substances Regulation, ESR) and voluntary risk assessment are presented below in individual subchapters for each metal for which data have been made available. Where applicable, criticism to the approaches used by the respective rapporteur is included.

The following table gives an overview, for which compounds and endpoints the MOS approach was applied and where available the derived reference MOS value. Where the derived MOS deviated from the "standard approach", this value is highlighted in the third column (MOS_{ref}) by placing it in bold and italic letters. It should be noted that most of the evaluated risk assessment reports are currently still in a draft status and are not yet publicly available. Finalised reports are available from the European Chemicals Bureau.

Summary of reference MOS values as derived in previous EU risk assessments[1]

Substance	Endpoint	MOS_{ref}
antimony trioxide	not available *	
cadmium, cadmium compounds	repeated dose toxicity (workers)	***minimal MOS: 3***
cadmium, cadmium compounds	repeated dose toxicity (general population)	***minimal MOS: 3***
chromium, trivalent compounds	not available *	
copper, copper compounds	acute inhalation toxicity	no MOS derived
copper, copper compounds	acute oral toxicity (from drinking water)	***minimal MOS: 1***
copper, copper compounds	chronic (oral)	general population:200 ***workers: 100***
lead, lead oxides, lead stabilisers	repeated dose; occupational settings and indirect exposure via the environment	***minimal MOS: 1***
lead, lead oxides, lead stabilisers	repeated dose; consume exposure	Although not explicitly noted as such, the effectively applied MOS is 10 for single product applications.
lead, lead oxides, lead stabilisers	acute toxicity	not required (lack of effects)
nickel, nickel compounds	acute oral toxicity	not included in RAR
nickel, nickel compounds	acute inhalation toxicity	not specified
nickel, nickel compounds	chronic inhalation toxicity	workers: 200 (metal) workers: 50 (soluble)
nickel, nickel compounds	fertility effects	workers: 10
nickel, nickel compounds	developmental effects	workers: 50
zinc (metallic), zinc oxide, zinc sulphide, zinc chloride, zinc sulphate, zinc distearate, zinc phosphate	repeated dose	***minimal MOS: 1***
zinc oxide	respiratory irritation	not specified
zinc oxide (dust)	acute inhalation toxicity; occupational risk assessment	not specified
zinc oxide (fume)	acute inhalation toxicity; occupational risk assessment for the process "welding"	not specified

*) Risk Assessments on antimony trioxide and on trivalent chromium compounds are currently being conducted, so that relevant information on this issue is not yet available for these compounds.

[1] Sources: Cadmium RAR (ECB, 2004a), Zinc (ECB, 2004b), Nickel RAR (ECB, 2005), Copper VRA (ECI; 2005), Lead VRA (LDAI, 2005)

3.1. Zinc (ECB, 2004)

(i) MOS values for acute effects

The following two examples are summarised for zinc oxide. We merely note here that acute effects were also assessed for zinc chloride and zinc sulphate, but are not further described here for the sake of brevity.

Acute inhalation toxicity (zinc oxide dust): For occupational risk assessment, the short-term inhalation exposure level (3.8 mg Zn/m^3, corresponding to 4.8 mg ZnO/m^3) was compared to LC_{50} values of 2500 mg/m^3 in mice and > 5700 mg/m^3 in rats. The resulting MOS values (521 - > 1188) did not give rise to concern, but it was noted that the MOS values are calculated for a severe effect (lethality). A MOS_{ref} was not specified.

Acute inhalation toxicity (zinc oxide fume, during welding): In consideration of the "metal fume fever" phenomenon, a risk assessment for short-term inhalation exposure to very fine particles was considered relevant. Such metal fume fever symptoms have been observed in humans exposed for 2 hours to 5 mg/m^3. Short-term inhalation exposure in welding was assessed at 1.6 mg/m^3, resulting in a MOS = 3 for the risk of metal fume fever during welding (unprotected workers). A MOS_{ref} was not specified.

Respiratory irritation (zinc oxide): In an acute toxicity study, local lung effects were observed after exposures to 5.41 g Zn/m^3. No risk was concluded based on a comparison of this level with the short-term occupational exposure level (10 mg/m^3), resulting in a MOS of 541.

(ii) MOS values for repeated dose

An NOAEL of 50 mg Zn^{2+}/day was derived from a 10-week oral study with human female volunteers, yielding an "internal NOAEL" of 10 mg Zn^{2+}/day by correction for oral absorption (20 %). Occupational health risks due to zinc exposure were determined by comparing the internal NOAEL of 10 mg Zn^{2+}/day with the internal occupational exposure, derived form inhalation and dermal exposure and application of previously defined absorption factors. For metallic zinc, zinc oxide and zinc sulphide, 20 % respiratory absorption was assumed; for dermal absorption, 0.2 % was considered for exposure to dust. The MOS values for each scenario were then evaluated by comparison with a "minimal MOS". Since the NOAEL used as a starting point was derived from a study with human volunteers, a minimal MOS of 1 was considered appropriate.

(iii) Other endpoints

For lack of any other critical health end-points, no further MOS values beyond those for acute effects and repeated dose were derived.

(iv) Reflection of natural background levels in the RAR

The zinc RARs concluded that the most important exposure to zinc for the general population is via ingestion of foods (especially meat and meat products, milk and milk products, bread and starchy foods). The average adult dietary intake of zinc via food by adults in nine European countries was reported to be 9.1-12.3 mg/day. Beyond this, given that according to monitoring data drinking water and ambient air are minor sources of zinc intake, the contribution by the latter two sources was considered negligible.

In the introductory sections of the chapters on human health effects assessment and risk characterisation, it is mentioned that "it is assumed that the influence of the background intake levels of zinc cations in animal studies will be the same for humans". Furthermore, the risk characterisation for systemic effects is made (among others) under the assumptions that (i) the background intake of zinc in the experimental situation (human) and in workers are comparable, and (ii) background intake via food is considered to be comparable in the different EU countries.

3.2. Lead (LDAI, 2005)

A determination of the presence or absence of risk for lead exposure in the occupational setting and from indirect exposure via the environment entail comparison of observed and/or predicted blood lead levels and NOAEL's. Initial Risk Characterisations were conducted utilizing a MOS of "1" where blood lead levels in excess of the NOAEL provide an indication of risk and blood lead levels equal to, or lower than, the NOAEL indicate the absence of risk. A MOS of "1" was recommended by the Scientific Review Panel but has not yet been endorsed in discussion with member states. The following rationale supported this minimal MOS:

1) The NOAEL's were identified from multiple (in some case in excess of 100) scientific studies of human populations. This permitted detailed evaluation of issues such as age, gender, ethnicity, intensity of exposure and duration of exposure that can be sources of uncertainty (i.e. intra-species variation) in effects assessment and the identification of sensitive sub-populations for Risk Characterisation. No extrapolation from animal studies was conducted.

2) Blood lead levels in the occupational setting were routinely monitored and an extensive database had been compiled to document exposure. Occupational exposures could thus be defined with a good deal of certainty.

3) General population blood lead levels were estimated by both observational studies and by modelling from an extensive database on the presence of lead in environmental media. Good concordance was observed between observational and modelled data.

4) Reliance on established biomarkers for systemic exposure (PbB) eliminated uncertainties associated with extrapolation from external occupational or environmental exposures.

5) NOAEL's had been proposed for the most sensitive subsets of the population and defined blood lead levels protective against subtle effects.

6) The effects that were the basis of the NOAEL's lacked functional or clinical significance for the individual and could not be detected at the level of the individual. Protection was thus being sought against effects which, by many definitions, would not be considered as adverse.

7) The most sensitive NOAEL's in adults protect against effects known to be reversible if exposure were reduced.

8) For occupational exposures, there is strong non-linearity in the toxicokinetics of lead. Thus, more significant health effects occurring at blood lead levels above the most sensitive NOAEL's required substantial increases in external exposure.

For consumer exposures the process of Risk Characterisation was slightly more complex since the impact of individual product applications had to be evaluated separately from multiple other sources of environmental lead. The estimation of the potential significance of individual exposure sources was performed in two ways: Product exposures were compared to an internationally accepted index of external exposure (PTWI or Provisional Tolerable Weekly Intake) and compared to an estimated increase in blood lead. Exposures considered acceptable were those that corresponded to less than 10 % of the PTWI and which yielded an increase in blood lead less than 1 µg/dL. Although not explicitly noted as such, this effectively applied a MOS of 10 to single product applications.

<u>Reflection of natural background levels in the VRA:</u>

This is a highly contentious issue for lead in view of dispersive uses such as lead in gasoline, which continue to be reflected in ambient air, water, soil and food, despite a marked and continuous decline of these levels after phasing-out of such uses. Thus, the definition of a "natural" background does not appear feasible at this point. However, since not only the exposure assessment but also the health effects assessment are both based on human blood lead levels, this intrinsically entails that ambient exposures via air, water and food are reflected in these biomonitoring data. Particularly noteworthy is that uptake of lead via ingestion of soil (as a very relevant route of intake for children) has been well-studies, and sophisticated toxicokinetic models have been developed to characterise this.

3.3. Nickel (ECB, 2005)

Some of the assessment factors used in the RAR for risk characterisation of nickel substances were already based on the new version of the TGD (2003); the chosen factors used to derive a reference MOS for nickel substances when starting from animal data are listed below:

- Inter-species factor=3 for respiratory (local) effects, 10 for fertility/developm. (systemic) effects.
- Intra-species factor to account for intra-worker variability = 5 [Other metal RA documents used 3]
- factor of 3-5 from LOAEC to NOAEC extrapolation
- factor of 2 for lung particle accumulation seen in rat studies (if retention half life is long). [Other metal RA documents have taken the view that these effects are not significant because rats are known to be very sensitive to effects of particulates. In the Chromium(III)oxide RA document, not only was an extra factor of 2 not used but an interspecies assessment factor of 2 was used (instead of 3) because interspecies variation was not expected to be high due to the local (lungs) type of effect and rats were considered as a sensitive species for particle mediated effects.]
- factor of 3 for extrapolation from sub-chronic to chronic duration of study
- factor of 2-3 for severity of effect for perinatal mortality

Differences in particle size of aerosols used in animal studies (MMAD = 1.9 µm) versus workplace aerosols (containing a large distribution of particle sizes up to 100 µm) were not considered in the risk characterisation for respiratory or systemic effects. Depending on the exact particle size distribution of animal and workplace aerosols, the respiratory endpoint of concern, the duration of exposure in the animal study, and the models used, factors of up to 40 can be derived for nickel substances. Note: The EU-RA documents for nickel metal contain risk characterisation sections for endpoints for which there is no classification. For example (as summarised in the tables below), in the nickel metal risk assessment there is a risk characterisation section for fertility effects (based on data for nickel sulphate) that resulted in a “risk conclusion” (designated as “conclusion (iii)” according to TGD terminology[2]) in worst case exposure scenarios, although neither nickel metal nor nickel sulphate are classified for fertility effects.

MOS values for selected endpoints, Nickel RAR

Health Effects	NOAEC-LOAEC	NOAEC-LOAEC/typical exposure	acceptable MOS is over	conclusion (iii) derived for
Nickel metal				
Chronic inhal. toxicity	1.0 mg Ni/m^3	2 - 250	200	all typical & worst case
Fertility	0.45 mg/m^3 (sol)*	33 - 4,300	10	most worst case
Developmental effects	1.1 mg/kg (sol)*	1 - 1,800	50	some typical & all worst case
Soluble nickel compounds				
Chronic inhal. toxicity	0.056	0.2 - 14	50	all typical & worst case
Fertility	0.45 mg/m3	1.7 - 113	10	many typical & all worst case
Developmental effects	1.1 mg/kg	1 - 69	50	all typical & worst case

* NOAEC-LOAEC values of water soluble compounds were also used for nickel metal for lack of studies on the metal itself

Reflection of natural background levels in the VRA:

At the time of release of this fact sheet, this chapter of the risk assessment on nickel and nickel compounds had not yet been concluded.

[2] The TGD discriminates between three possible conclusions of a risk assessment:
(i): There is need for further information and/or testing
(ii): There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already
(iii): There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account

3.4. Copper (ECI, 2005)

Acute toxicity and repeated dose toxicity represent the most significant end-points in relation to human health for the copper substances covered by this risk assessment. Oral and inhalation exposure present the most significant routes of exposure.

Acute effect – inhalation
A data gap was identified because of a lack of relevant exposure and/or effects data, so that no MOS_{ref} was derived.

Acute effect – oral – drinking water
The most likely potential source of acute exposure is from drinking water. A human NOAEL of 4 mg/L, assuming an intake of 200 mL, is derived from a well-conducted study with humans. Therefore a MOS of 1 is considered sufficient.

Repeated dose
In this risk characterisation all MOS values are derived from internal NOAELs and absorbed doses. A MOS_{ref} is derived from the study of Hebert (1993) as follows:

The TGD indicates an AF of 10 for animal to human extrapolation (4 for toxicokinetics and 2.5 for toxicodynamics). An AF for inter-individual variability is given as 10 for the general population and 5 for workers, the latter on the basis that working populations exclude the most vulnerable individuals. A factor of 2 is given for sub-chronic (90 day) to chronic extrapolation. This gives a combined AF of 10 x 10 x 2 = 200 for the general population and 10 x 5 x 2 = 100 for workers. No guidance on the use of AFs for essential trace elements (ETEs) is given in the TGD which is geared towards assessment of organic compounds with no requisite physiological functions and thus makes no allowance for essentiality.

IPCS (2002) has reviewed the application of AFs ("uncertainty factors" in the alternative nomenclature) in relation to ETEs. They cite 10 x 10 x 2 = 200 as the conventional AF for the assessment of exogenous substances for the general population in agreement with the TGD. However, the application of this AF to ETEs, for which deficiency must also be considered, is questioned and alternative methods are explored. However, no clear guidance on the general application of AFs to ETEs is given. For further details on this issue please refer also to the separate HERAG fact sheet on "Essentiality".

Consequently, the derivation of AFs to calculate MOS_{ref} values is problematical. Application of a 10 x 10 x 2 = 200 AF directly (without correction for absorption) to the animal NOAEL (16.3 mg/kg bw) from the Hebert et al. (1993) study gives a human NOAEL of 5.7 mg Cu/day (using 70 kg as a default body weight). However, in the human volunteer study of Pratt et al. (1985), subjects supplemented with 10 mg/day (and consuming daily dietary intakes of approximately 1-2 mg Cu/day, giving a total intake estimate of 11-12 mg/day) showed no alteration in a number of biochemical parameters. Although this study was clearly limited in its scope, these findings suggest that absorption of intakes of this magnitude is subject to efficient homeostatic control. Based on numerous studies showing that systemically absorbed dietary copper decreases with increasing dose, the estimated systemic absorption of these intakes (5.7 and 11-12 mg/day, respectively) is almost equal. An AF of 10 x 10 = 100 is therefore considered appropriate for adults.

Reflection of natural background levels in the VRA:

The main source of indirect exposure to copper is through food and drinking water: dietary intakes for adults depending on the type of study typically range from 1.0-1.3 mg Cu/day (90^{th} percentiles 1.4-2.0 mg Cu/day), with some exceptional intakes as high as 1.8 and 2.2 mg Cu/day. Apart from this, the mean intake from alcoholic drinks was estimated to 0.05 mg Cu/day, based on monitored concentrations (0.03-0.77 mg/litre) and WHO statistics of alcohol consumption. The most relevant indirect exposure is from drinking water, with typical (range: 0.01-0.,72 mg/l) and worst-case exposures (0.07-2.11 mg/l) yielding estimated intakes of 0.01 (typical) and 0.84 mg/day (worst-case) for adults.

Despite monitoring data for copper in air being rather sparse, the available data (UK urban levels 21-64 ng/m^3, UK rural levels 11-27 ng/m^3) suggest that intake (estimated at 0.002 mg/day) from environmental inhalation exposure is a quantitatively insignificant route compared to dietary exposure.

Ingestion of dust by children was estimated based on a median of 250 mg Cu/kg of soil (ranges: 160-299 mg/kg) and default soil uptake rates of the IEUBK model, yielding ingestion rates of 13-135 mg Cu/day, varying with age.

Whereas background levels of copper in the environment did not directly impact the choice of assessment factors, the risk characterisation for repeated dose effects was performed in consideration of the essentiality of copper and associated risk of deficiency.

3.5. Cadmium (ECB, 2004)

MOS values for acute effects:

Acute inhalation toxicity: For occupational risk assessment, the available inhalation (worst-case) exposure level for each occupational scenario was compared to the LOAEL of 437.5 µg Cd/m³ (lowest dose causing mild pulmonary changes in rats). A minimal MOS of 10 was recommended to take into account both interspecies differences and nature and severity of the effect. The resulting MOS values gave rise to concern for three exposure scenarios with potential exposure to cadmium oxide fumes ("Cd metal production", "alloys" and "brazing, "soldering and welding").

Respiratory irritation: No MOS was calculated in the absence of available N(L)OAEL, but it was concluded, on the basis of the reported acute and chronic respiratory effects of cadmium, that cadmium oxide and cadmium metal are irritant for the respiratory tract.

MOS values for repeated dose:

The determination of the presence or absence of risk after repeated exposure to cadmium in occupational settings and from indirect exposure via the environment entailed the comparison of observed or modelled urine cadmium levels and LOAELs. At low and moderate exposure conditions, urine cadmium levels are acknowledged as mainly reflecting the cadmium body burden. Such levels are routinely monitored in workers, and occupational (typical and worst-case) exposure values were considered as being reliable for estimating risk in workers. For the general population, indirectly exposed to cadmium, urinary cadmium levels were either measured or derived from cadmium uptake in various scenarios (diet, smoking, air, soil, and drinking water). The conversion of cadmium intake/uptake to cadmium levels in urine required the use of a toxicokinetic model.

The LOAEL of 2 µg Cd/g creatinine in urine was derived from multiple epidemiological studies and should be understood as a composite level that endeavours to aggregate data both on the renal and on the bone effects that have been associated with cadmium exposure in human populations. The same LOAEL was used for occupationally and environmentally exposed populations, as (i) cadmium is cumulative, (ii) it has been suggested that cadmium exposure may interact with pre-existing or concurrent renal disease to produce adverse renal effects, and (iii) as workers should be offered the same degree of protection as they may suffer from such disease during or after their occupational career.

The MOS values for each scenario were then evaluated by comparison with a minimal MOS. Since the effect level used as a starting point was derived from studies conducted among the general population, including more sensitive subgroups, a minimal MOS of 3 was considered to be sufficient to take into account the conversion of an LOAEL to an NOAEL.

Note: A MOS was also calculated for respiratory effects in the general population living around point sources. In this scenario, the most important route of exposure could be inhalation. The LOAEL of 10 µg CdO dust/m³ was derived from an animal study (hamsters) and compared to the reasonable worst-case estimate of cadmium in air. The minimal MOS had to be at least 100 to take into account inter- and intra-species differences.

Reflection of natural background levels in the RAR:

Average Cd levels in air in EU countries range from <1-5 ng/m^3 in rural areas to 15-50 ng/m^3 in industrial areas, but daily uptakes via this route were considered small compared to that from food or from smoking. Drinking water usually contains low cadmium levels (<1 µg/l), so that uptake from water is also relatively unimportant.

Dietary intake is the major source of Cd exposure for the non-smoking general population, ranging in European countries from 5 to 90 µg/day, but with most values ranging between 10 and 35 µg/day. For the general population living in uncontaminated areas, smoking is another main sources of Cd exposure.

Since tobacco plants naturally contain high Cd concentrations (1-2 µg Cd/cigarette), for example, smoking a packet of 20 cigarettes daily results in a net uptake of 0.5-2 µg. This value is large compared to the daily Cd uptake from air (0.02 µg) and in the same range of the daily Cd uptake from food Cd (0.35-1.6 µg). Cd intake through smoking 20 cigarettes per day increases the Cd systemic dose 1.2 to 7 fold above that in non-smoking individuals with equivalent Cd intake through other sources.

Ingestion of dust and/or soil by young children was not considered a dominating exposure route for Cd, estimated to a daily uptake of 0.035 µg/day, which is less than 10% of the total daily uptake.

In conclusion, the risk characterisation for cadmium was performed with a very detailed assessment of all environmental exposure routes at hand. Further, similar to lead, the health effects assessment is based predominantly on biomonitoring (urinary cadmium).

3.6. Other metals

Apart from the 5 metals reviewed above, the authors are only aware of one other EU metal compound risk assessment, namely Diantimony trioxide. However, the draft that is currently available is under considerable revision, which is why a consideration at this point is considered premature. It has also been brought to the attention of the authors that a voluntary risk assessment is being conducted for Chromium (3+). Any other metals have not yet been subjected to risk assessments under the TGD approach, and are therefore not considered here.

4. Conclusions and recommendations

In consideration of previous experience in the conduct of TGD compliant risk assessments for metals and their inorganic compounds, the discussion within the HERAG project group on the correct derivation of MOS_{ref} values can be summarised by the following recommendations. The term MOS (although superseded under REACH by the required derivation of DNELs) is continuously used in this fact sheet since this document represents a retrospective analysis of previous risk assessments, with the purpose of extracting common aspects that may be of use in future such assessments.

Reflection of background concentrations:

The assumption of "zero" exposure is irrelevant for most metals, because humans are subjected to a multitude of metal compounds through ambient environmental concentrations. Thus, for "non-essential" elements, the derivation of MOS_{ref} values should be verified against environmental background for plausibility. However, the definition of such a level may be difficult because of non-linear kinetics assumed to be in place especially at low intake levels corresponding to what could be designated as a background level. Nevertheless, for future consideration, the documentation of "baseline intake rates" and resulting body burdens for metals should be envisaged.

Consideration of essentiality:

For essential trace elements, a formal consideration of deficiency effect levels should be included when deriving MOS_{ref} values. For more details on this aspect, reference is made to the separate fact sheet on essentiality.

MOS_{ref} values for repeated dose toxicity:

For the derivation of MOS_{ref} values that reflect systemic effects of exposure to metals and their inorganic compounds, it is proposed to group metals into three categories:

(i) Non-essential elements with toxicity data largely derived from animal testing: In these cases (example: nickel), the application of the standard TGD approach is recommended, as no arguments are seen that would support an alternative approach.

(ii) Non-essential elements with relevant human data: Depending on the quality and extent of the data base for any specific health end-point, a case should be argued for the establishment of a MOS_{ref} in the range of 1-3 (example: cadmium). Where health end-points are solidly based on biomarkers of systemic exposure, a minimal $MOS_{ref} = 1$ should be proposed (example: lead).

(iii) Essential elements: Where human data are available for relevant endpoints, a minimal $MOS_{ref} = 1$ should be adopted (example: zinc). In those cases in which an essential element is assessed based on animal toxicity data, the feasibility of a case-by-case argumentation should be considered to deviate from the standard TGD approach (example: copper). In the latter context, explicit reference is made to the separate HERAG fact sheet on "Essentiality" as supportive argumentation.

MOS_{ref} values for acute effects:

The discussion within HERAG has not provided any relevant basis for setting such values in addition to that of the TGD, at the same time recognising that there is currently no uniform, standardised approach available.

Uncertainty:

Any uncertainties in this procedure may be considered to be covered when strictly adhering to the approach suggested by the TGD risk characterisation section on the derivation of MOS_{ref} values, which assigns a set of assessment factors applied to any NOAEL/LOAEL to account for variability and sensitivity. In contrast, in cases where deviations are made from the standard approach, it was agreed in the discussions that any uncertainty will be intrinsically addressed in the detailed argumentation that is put forward in each case in support of a "deviating" MOS_{ref}.

In particular, established biomarkers for systemic exposure (e.g. blood lead, urinary cadmium and antimony) effectively reduce uncertainties associated with extrapolation from external occupational or environmental exposures and resulting systemic exposure (Yin et al., 2005).

Especially in the latter context, the richness of the data base on human health effects and the resulting requirement to apply a weight-of-evidence approach in the assessment of the data needs careful consideration.

Particle size and chemical speciation:

When extrapolating from effects seen in animal studies to the human exposure situation, the differences in particle sizes between laboratory animal experiments (usually especially micronised forms, according to the requirements of the guideline) and workplace exposures (most commonly much larger that those encountered in the laboratory) should be taken into account.

As an example, a clear differentiation was required in the zinc RAR between effects elicited by ultra-fine zinc oxide particles and aerosols in the occupational setting with usually much coarser particle size distributions. This aspect will certainly require more attention in future assessments on the impact of nano-technologies.

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

5. References and abbreviations

References

ECB (2004a)	EU RARs Cadmium and Cadmium oxide, final drafts September 2004, European Chemicals Bureau, Rapporteur:
ECB (2004b)	EU RARS on Zinc and Zinc compounds, final reports 2004, European Chemicals Bureau, Rapporteur:
ECB (2005)	EU RARs Nickel and Nickel sulphate, final drafts June 2005, European Chemicals Bureau, Rapporteur:
ECI (2005)	VRA on Copper and Copper compounds, first draft report May 2005
Hebert (1993)	Hebert, C.D.: NTP working group, Toxicity Report Series; 29. Toxicity Studies of Cupric Sulfate. Administered in Drinking Water and Fed to F344/N Rats and B6C3F1 mice. Nat. Toxicol. Prog., U.S. Dept. Health Hum. Serv., Public Health Serv., Nat. Inst. Health; Research Triangle Park, NC, USA, 1993.
Hebert et al. (1993)	Hebert, C.D.: Subchronic toxicity of cupric sulfate administered in drinking water and feed to rats and mice. *Fund. Appl. Toxicol*. 21, 461-475
IPCS (2002)	International Programme on Chemical Safety (IPCS). Environmental Health Criteria No. 228. Principles and Methods for the Assessment of Risk from Essential Trace Elements. Geneva 2002
LDAI (2005)	VRA on lead and lead compounds, first draft report May 2005
Pratt et al. (1985)	Pratt, W.B. et al.: Lack of effects of Copper gluconate supplementation. *Am. J. Clin. Nutr.* 42, 681-682
TGD (2003)	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 (2nd Edition, 2003)
Yin et al. (2005)	Air samples versus biomarkers for epidemiology, Occ. Env. Med. 62, 750-760

Abbreviations

AF	assessment factor
ESR	Existing Substances Regulation, Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances.
ETE(s)	essential trace element(s)
EU	European Union
LC50	Lethal concentration at which 50% of the tested animals died.
LOAEL / LOAEC	lowest observed adverse effect level / concentration
MMAD	mass median aerodynamic diameter
MOS	margin of safety
MOS_{ref}	reference MOS
NOAEL / NOAEC	no observed adverse effect level / concentration
PTWI	Provisional Tolerable Weekly Intake
RA(R)	Risk Assessment (Report)
TGD	Technical Guidance Document on Risk Assessment. See references.