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Nordic comments on the Health Risk Assessment Guidance for Metals

HERAG Fact Sheets

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Contents

Summary and conclusions

The proposed guidance document for metals that the HERAG project has presented in so called facts sheets (FSs) is at a general level and might be applicable to all substances, not only metals. Risk assessment of existing chemicals should be done according to the EU Technical Guidance Document (TGD, 2003). The experience from the implementation of the Existing chemicals regulation (793/93/EC) risk assessments, which are done according to the TGD methodology, is that TGD allows deviations when required, as long as they are justified and done in a transparent way. The reason for establishing a separate health risk assessment guidance document for metals remains questionable. There is no reason to believe that special aspects of metal toxicology could not be considered under RIP (REACH Implementation Projects) projects.

Concerning the FSs, there is no clear definition given which elements and compounds are included in the term "metals". In most cases, the chemical form (species) of an element (oxidation state, molecular structure etc) is important for the uptake and toxicity. In some cases it is obvious that inorganic metal compounds are included. We assume that semimetals such as arsenic and selenium are included. Organic metal compounds have been omitted in most cases. This further emphasizes the difficulties in having a separate guidance document for metals.

The FSs do not give a solution how to group or create categories for read across purposes concerning metals and metal compounds (inorganic and organic). The problems involved are mainly due to the differences e.g. in the toxic profile(s) of different oxidation states (e.g. Cr^{III} and Cr^{VI}), water solubility, physical form and combination of these.

The selection of metals that are covered in the FS documents is mainly restricted to a few metals (mainly copper, zinc, lead and cadmium) for which there are EU risk assessment reports (RARs for existing chemicals regulation) and voluntary risk assessment reports prepared by industry (VRAs). The examples given are too few to draw more general conclusions, but they do not indicate any reason to apply specific risk assessment methodologies for metals. Besides, the VRAR on copper is a voluntary risk assessment report, prepared by the copper industry, and should thus not be given the same weight as the other EU RARs, which have passed several independent expert reviews. For other metals that are known to be toxic, for example mercury and arsenic, there are other solid risk assessment reports, e.g. from the WHO, that could also be used for discussions and conclusions regarding risk assessment of metals.

Too much emphasis is put on the fact that some metals are essential. We disagree that this should warrant special consideration in risk assess-

ment. Evaluation of recommended intakes to meet the physiological requirements is handled by food agencies and should not be re-evaluated in the context of toxicological risk assessment. Instead, in the regulatory risk assessment the main issue is to ensure that the exposure is below the levels that may entail a risk of toxic effects. We do agree that risk management of essential metals should not result in recommendations that lead to lower intakes than are physiologically required.

In conclusion, it is obvious that the guidance present in the current TGD (2003) allows performance of risk assessment(s) also for metals and metal compounds on a 'case-by-case' basis with 'expert judgement' following the principle of transparency concerning the possible deviations form TGD. Thus, there are no arguments for a separate guidance document for metals.

Background

The HERAG (Health Risk Assessment Guidance Project) was initiated and financed by metal industry associations, represented by the International Council on Mining & Metals (ICMM), the European Confederation of Iron and Steel Industries (Eurofer) and the European Association of Metals (Eurometaux).

The HERAG project consisted of 3 main building blocks (exposure assessment, effects assessment and risk characterisation). From these a set of key-topics were selected for which Fact Sheets (FSs) were developed in order to improve risk assessment guidance for metals and inorganic metal compounds. The EBRC Consulting GmbH (Hannover, Germany) was chosen to develop the project Fact Sheets (FSs).

FSs focus on the evaluation of the applicability of the current Technical Guidance Document (TGD, 2003) on risk assessment of chemicals under the EU Existing Substances Regulation (ESR 793/93/EC), which guidance was mainly derived for organic chemicals.

Introduction

The Nordic Chemicals Group of the Nordic Council of Ministers initiated a critical review of the HERAG FSs. Nordic experts from the Institute of Environmental Medicine at the Karolinska Institute, (IMM, Sweden), Danish Working Environment Authority, Danish Institute for Veterinary and Food Research, Technical University of Denmark and Finnish Institute of Occupational Health (see front page) acted as reviewers.

In this report, the main contents of the FS summary is presented first, then some aspects of the EU Technical Guidance Document (TGD, 2003) principles and after that some of the the main issues extracted from the Nordic comments, which are presented in full in the Annexes of this report (Annexes 1-12).

Table 1. Fact Sheets, the date of the version commented and the Annexes of this report where the detailed comments are in full by the authors.

FS no	Fact Sheet name	Version dated	Comments Annex no
FS 1	Assessment of occupational dermal exposure and dermal absorption for metals and inorganic metal compounds	21 Aug 2006	Annex 1A
			Annex 1B
FS 2	Assessment of occupational inhalation exposure and systemic inhalation absorption	2 Oct 2006	Annex 2A
			Annex 2B
			Annex 2C
FS 3	Mutagenicity	13 Aug 2006	Annex 3
FS 4	Read across, Derogation criteria, Classification and labelling	9 Oct 2006	Annex 4
FS 5	Essentiality	10 Aug 2006	Annex 5A
			Annex 5B
FS 6	Choice of assessment factors in health risk assessment for metals	9 Oct 2006	Annex 6
FS 7	Gastrointestinal uptake and absorption, and catalogue of toxicokinetic models	3 Oct 2006	Annex 7
FS 8	Indirect exposure via the environment - Consumer exposure	6 Sep 2006	Annex 8
FS 9	Carcinogenicity	13 Aug 2006	Annex 9
FS 10	Quality screening of health effects literature	4 Sep 2006	Annex 10
FS 11	Reproduction toxicity	13 Aug 2006	Annex 11
FS 12	Sensitisation	9 Oct 2006	Annex 12

FS 1:
Assessment of occupational dermal exposure and dermal absorption for metals and inorganic metal compounds

Main issues in the Fact Sheet

One of the biggest concerns by the industry is the dermal absorption default set by TGD (10% is used in cases where MW>500 and log Pow<-1 or >4, otherwise 100%; TGD, Appendix IVB).

FS argumentation as direct citations:

- 'Most inorganic metal species do not permeate the membranes that separate organism from the external environment by passive diffusion. Instead, the uptake of metals largely depends on the presence of specific transport systems that provide biological gateways for the metal to cross the membrane'.
- 'Dissolution of an inorganic metal compound or the metal itself on skin will intrinsically require dissociation, and ultimately liberation of free metal cations.'
- '... assigning a dermal absorption rate (namely molecular weight) is irrelevant for metals, since under no circumstances is it feasible that any metal cation may exceed the cut-off value of 500'.

In case the skin is not healthy, how much the actual absorption could change compared to the healthy skin, was one of the questions raised in the Workshop in Brussels (12–13.10.2006). Are there any data available on the destroyed skin and metal (compound) exposure(s)?

Principles in the TGD (2003)

TGD (2003) gives choices based on available information and recognises modifications of substantial differences (See eg. TGD p. 54, Fig.2) in dermal exposure assessment. TGD clearly prefers measured data: '*...for dermal exposure is to use measured data for scenarios when they are available (including use of analogy reasoning) and to use EASE of other appropriate models if measured data on the scenario is not available.* TGD recognises the limitations of EASE model (See eg. TGD, p. 55, 2.2.5.1. Measured data): '*... because all the model approaches lead to highly uncertain results due to the limited overall knowledge on dermal exposure'.* TGD gives very thorough guidance on dermal exposure also in Appendixes IA, IB, IC and IE and there is and has been recognised way to use expert judgement, when the substance characteristics so require.

TGD shows clear green light to deviate from the defaults given (Appendix IVB 'Default values for dermal absorption'): 'The lower limit was

chosen, because there is evidence in the literature that substances with MW and/or logP values at these extremes can to a limited extent cross the skin. If data are available (e.g. data on water solubility, ionogenic state, 'molecular volume', oral absorption and dermal area dose in exposure situations in practice) which indicate the use of an alternative dermal absorption percentage value is appropriate, then the alternative value can be used. Scientific justification for the use of alternative values should be provided.'

Biological monitoring is discussed in the TGD in chapters 2.2.6 and 2.2.7. and concludes: '... that biological monitoring results reflect an individuals total exposure to that substance from any relevant route, i.e. from consumer products, and/or from the environment and not just occupational exposure.

Main issues in the Nordic comments (detailed comments in Annex 1A and 1B):

The FS should be in compliance with the technical specifications concerning 'Strategy for the evaluation of dermal exposure (CEN/TS 15278:2006)' and 'Measurement of dermal exposure - principles and methods (CEN/TS 15279:2006)' (Annex 1A):

- FS focuses on methodological aspects and the sampling strategy for measurements is missing.
- EASE (Estimation and Assessment of Substance Exposure) model should be used as initial exposure assessment, which does not exclude the proposed screening model for metals and inorganic metal compounds.
- To make exclusive use of the wipe-sampling methodology to facilitate the collection of comparable data sets.
- Tiered approach is proposed to be done by expert-judgement and the three basic criteria: 1) intrinsic substance properties, 2) process conditions, control measures and influence of PPE (Personal Protective Equipment) and 3) perceptual factors derived from hazard assessment are to be met in order to accept a data set as valid. This could improve the transparency of the approach.

We agree with the general messages and conclusions of the document, with three important exceptions, given below (Annex 1B):

- The dermal absorption part of the document focuses very much on percent absorbed dose. However, the absorption rate is related to the concentration at the skin surface rather than the applied amount (as already stated in the document). Furthermore, dissolution and absorption are continuous processes as long as depletion does not occur. Thus, both the percentage dissolved and the percentage

absorbed will increase over time. Giving merely a numerical value for percent absorbed therefore has no or limited value unless additional information is given, most importantly the duration of exposure and the applied amount per unit area. In our experience (mainly from organic chemicals and not metals), both the amount applied and the exposure duration may vary widely over several orders of magnitude. An approach, based upon Ficks' law of diffusion, focusing on dermal absorption and penetration at steady-state (flux, J_{ss}) and permeability coefficient (K_p) (*fig 1 and eq 1*), rather than percent absorbed, would be preferable. This has been done e.g. for cobalt by Filon *et al.* (*see table 21*) (see also Details, item 1). Given specified exposure conditions (e.g. concentration, C), flux and K_p data can then easily be translated to systemic dose for use in risk assessment.

- The document further suggests that the presently used default assumptions of 100% and 10% absorption of dermal load, should be replaced by other default values (1% for wet/liquid exposure, 0.1% for dry/dust exposure). We agree that the bases for the present defaults (molecular weight and $\log P_{ow}$) are not applicable to metals and inorganic metal compounds. However, in our opinion, the data presented in the document are not sufficient to support the new recommendation.
- There is no discussion (or even mentioning) of biological exposure in the document. In view of all the difficulties encountered in assessing dermal exposure and absorption, biomonitoring is often a very efficient tool for verifying, excluding and/or quantifying systemic absorption via the dermal route. This is recognized for example by the Scientific Committee for Occupational Exposure Limits (SCOEL) of the European Commission. SCOEL has decided to always seek to propose a Biological Limit Value whenever a substance is assigned with a Skin notation (update of SCOEL Key Document to be published).

Conclusions:

- There is no need for a metal-specific approach in addition to the guidance given in the TGD, because the TGD guidance allows the use of other default values than 10% and 100%, when scientifically justified.
- In order to improve EASE or any other model, there is need for good and relevant data for the development of the model.

FS 2: Assessment of occupational inhalation exposure and systemic inhalation absorption

One of the biggest concerns by the industry is the inhalation absorption defaults (100% and if not known then use 75%) set by the TGD (2003).

Main issues in the Fact Sheet

- The use of particle size characterisation in derivation of inhalation absorption factors, by predicting inhalation deposition behaviour.
- Description of the basic methods used to generate such particle size distributions.
- A model approach for assessing particle size distributions during normal handling and use, based on dustiness testing combined with PSD analysis.
- Validation status and/or needs for this model approach and its limitations.
- Examples from previous or current risk assessment work on the use of such an approach.
- FS presents decision trees for systemic and local absorption from inhalation exposure.

Principles in the TGD (2003)

TGD (2003) gives guidance concerning inhalation exposure assessment and (Chapters 2.2.3. and 2.2.4., Appendix I D) the core information requirements for exposure assessment (Fig. 1). This includes also the considerations of the data reliability and representativeness (e.g. were the data collected according to the defined sampling strategies, e.g. EN 689).

The exposure levels (reasonable worst case and typical exposure levels by scenarios) taken forward to risk characterisation are described in TGD (2003, Chapter 2.2.7) including the uncertainty or variability of the data, particle size distribution (whether inspirable dust or respirable dust are measured) and type and duration of the air sampling data.

In case where biomonitoring data is used, a number of parameters should be given, like sampling strategy (spot sample at the end of work shift, or 24 hour sample, the biological half time of the measured substances) and any data (inhalation or dermal, duration and possible health outcomes) which could help in the interpretation of the data.

The route-to-route extrapolation is important in calculating the absorption in case of systemic effects. Toxicokinetic data, when available, should be taken into account. TGD prefers the measured values but modelled data analysis can be used in cases where there is insufficient measured data available. (2003, 3.3.3.2. Approximate inhalation NAEL from oral NOAEL; Appendix 1A, Appendix 1C, TGD, 2003).

Main issues in the Nordic comments (detailed comments in Annex 2A, 2B and 2C):

The quality of the data used for valid assessment of exposure by inhalation depends on the sampling strategy used for collecting the data, including also the sampling technology (Annex 2A).

- The strategy used for the collecting the data sets should be valid and transparent and the methods used for the collection and analysis of the samples should be well established.
- FS focus on methodological aspects and the sampling strategy for measurements is missing.
- A separate FS on sampling strategy is proposed, which should provide answers to questions such as: 'where to sample', 'how often to sample', how many samples per shift' and 'how many workers to sample per shift'. Guidance in design of a sampling strategy is given in the European Standard (CEN 689).
- The detailed comments on the evaluation of the production and use of MPPD and RDDR models and PSD data is given in the light of the available European standards in the specific comments (Annex 2).

The document focuses on the assessment of inhalation exposure and absorption of metals and metal compounds under occupational exposure situations. Inhalation is probably the most important exposure route to consider in the assessment of human risk from solid inorganic substances and in particular from metals in the workplace. Two distinct aspects are addressed: assessment of external exposure, and the proportion of material that is retained and absorbed into the body (Annex 2B).

- The document is far from complete as nanoparticles, welding fumes and vapours (e.g. mercury) are not included. A discrepancy compared to the other HERAG fact sheet was also noted (e.g. the one on GI absorption) in that the present document only covers occupational exposure.
- Exposure levels and exposure variability are the most important factors. Therefore, sampling techniques, strategy and sample size are very important. It is acknowledged that this has been done by others and that it suffices to refer to one or two reviews (as done on page 15). However, the different sources of error and variability in assessing systemic exposure need both to be addressed and put in perspective. As the document is written now, the reader is given the impression that deposition fractions, inhalation absorption fractions, and correction factors for samplers are the key/critical issues. The document would benefit from rearrangement, so that it starts with inhalation exposure followed by systemic inhalation absorption.
- The key concept of "*inhalation absorption*" should be defined and explained early in the text (no such definition was found in the document).

- The models chosen to estimate regional deposition seem appropriate. The MPPD model is gaining more and more use. The RDDR model for species to species extrapolation is to our knowledge the best of the easily available methods.
- Welding fumes should be included (not excluded) in step 2 and/or step 3 in the stepwise procedure (*page 12-14*). Welding is an important source of exposure to metals for many workers. The particles generated by welding generally have smaller diameters (often < 1 μm) and may have different solubility characteristics than those formed in other industrial processes.
- ”Total dust” be should be addressed. At present, the term is merely mentioned in passing in Appendix 5.1. Many old reports, that may still be very useful in risk assessment, only have data on total dust. Further, many occupational standards, including those of Sweden and SCOEL, still use total dust for some OELs.
- The differences between measured concentrations of “total dust” and inhalable dust, regarding which particle sizes are collected, must be expressed and evaluated correctly. Particle size distributions should not be assumed to be uni-modal unless they can be shown to be so.
- If terms are defined differently in toxicology, occupational medicine and/or occupational hygiene, define them explicitly. Don’t invent terms that are not defined.
- Dustiness testing should not be used as a method for obtaining the particle size distribution of a material identical to that generated when it will be/is handled at workplaces. Dustiness testing gives only a (method-dependent) measure for a material when it is handled in a standardized way.

Conclusions

- TGD (2003) methodology takes into account practically everything which is presented in this FS and TGD also stresses the need for industrial hygiene expertise when exposure data is assessed. Therefore, it is difficult to see the rationale for separate guidance for metals, because TGD allows deviation from the guidance case-by-case basis and expert judgement with the principle of transparency.

FS 3: Mutagenicity

Main issues in the Fact Sheet

- The FS states that 'Bacterial mutagenicity tests appear to have little utility for the testing of metals (test results are almost always negative) and should be replaced with mammalian cell test systems.' FS

proposes a tiered testing strategy presented in the Fig. 1 (Proposed mutagenicity testing strategy for metals and metal compounds).

Principles in the TGD (2003)

In the TGD (2003) the Summary of the mutagenicity testing strategy is described in Table 6 (p. 154), where the possibility of negative and equivocal positive findings are applied also for other substances and compounds.

Main issues in the Nordic comments (detailed comments in Annex 3):

The suggested test battery for hazard classification, with the exclusion of bacterial mutagenicity assays, seems appropriate based on the knowledge on mechanisms of metal mutagenicity.

Mechanistic follow up studies including in vivo and in vitro dose response measurements for identified endpoints are highly relevant especially if they are directed towards oxidative mechanisms. Co-mutagenic action of metals is a critical aspect of metal mutagenicity and carcinogenicity, why combined dose-response studies with known mutagenic regimes should be recommended. Mutagenicity assays using transgenic animals are relevant for the in vivo point mutation tests. Such tests are available for chemical screening purposes and protocols that allow detection of mutation frequency for different tissues have been developed and evaluated by IPCS/WHO (Environmental Health Criteria no 23. Transgenic Animal Mutagenicity Assays, WHO, Geneva 2006).

Concerning administration, the route should be chosen which is relevant for the particular substance and for the expected target organ and the dose levels should also cover doses that produce some toxicity (minimal to zero mortality). Concerning the intrinsic property/hazard evaluation any route could be used (including i.v.).

Conclusions

- The suggested test battery for hazard classification is appropriate based on the knowledge on mechanisms of metal mutagenicity. Mechanistic studies including *in vivo* and *in vitro* dose response measurements for identified endpoints are highly relevant as suggested.
- Concerning the intrinsic property/hazard evaluation any route could be used.

FS 4: Read across, Derogation criteria, Classification and labelling

Main issues in the Fact Sheet

- 'Read across can be defined as an extrapolation of known data from one substance to another substance on the basis of assumptions leading to a conclusion that the two substances will cause similar biological responses.'
- 'However, for metal substances, it should be considered that the simple presence of a metal cation in a substance, does not necessarily transfer the biological properties of the metal ion to that substance and also not to the same extent for different anions. It is the target site bioavailability of the metal cation (or a redox form of this ion) that is required for such read-across to be accurate.'

In the conclusions FS focuses on read across for C&L purposes in extrapolating from one metal to another with similar properties, the term 'similar' becomes for a key importance. Toxicokinetic data are usually sparse and therefore guidance is needed how oral, inhalation and dermal absorption available for one metal could be used for the other also in relation to health effects. The occupational exposure data may be available for primary metals. The establishment of criteria how this exposure data could be used for another metal exposure assessment. The conclusion to read across from an endpoint in a particular animal study from one route of exposure to another - without additional testing.

Particle size distribution, speciation and dissolution in aqueous media need to be considered both for inhalation and dermal exposures. For oral absorption there is a proposal in case of the lack of specific toxicokinetic data, *in vitro* bioavailability may be assessed by testing a compound, metal or alloy *in vitro* for 'bioaccessibility'

Derogation needs to be decided on a case-by-case basis, however, unnecessary animal testing can primarily be avoided by applying grouping of compounds according to similar toxicokinetics or if it can be shown that substance 'is not systemically available'

Principles in the TGD (2003)

TGD (2003, 3.9.6.2. General principles, p. 131): 'The decision whether the escape clause or derogation can be accepted for a new or an existing chemical substance is made on a case-by-case basis, e.g. derogation / escape may be considered in cases where there are data on a closely related substance that could be read across to fill the particular requirement or where a substance undergoes immediate disintegration and there are sufficient data on the cleavage products.'

TGD (2003, 3.2.2.5. (Q)SARs) states that the methods SAR and especially QSAR are not well developed for mammalian toxicology, and recommends their use with 'expert-judgement'.

The TGD (2003) does not have at present clear view on how read-across and grouping of chemical compounds should be done, although in the ESR program those have been used on 'case-by-case basis' and with 'expert judgement'. TGD (Part 4, 2003) has only one paragraph concerning the use of (Q)SARs in human health risk assessment and recommends when ever (Q)SARs are used to give the specified information on the used methodology in a transparent manner.

RIP 3.3-1, Information Working Group 3, TAPIR Final report Appendix 9, p.5 (direct citations):

- 'Read-across/analogue - normally involves using data/information on one chemical structure and making some assessment about the relevance of that information for a second chemical structure.
- SAR - normally involves using data from a training set of many chemicals and their structures, the development of rules based on 'expert judgement' and then applying the rules to another chemical structure.'
- QSAR - normally involves the development of a mathematical (statistical) based equation, based on the data from a training set of many chemicals and their structures/properties, which may then be applied to another chemical structure.'
- Chemical category/grouping - normally involves collecting chemical structures/substances using some measure of commonality and assessing the available data. From this analysis, data gaps fro some of the substances may be interpolated.

Main issues in the Nordic comments (Annex 4):

Read-across principles are described in the FS for oral, inhalation and dermal bioavailability, uptake and toxicity. The central issues are the use of toxicokinetic data, bioaccessibility, water solubility (it is not self evident that good water solubility guarantees bioavailability), particle surface and bioavailability. FS also recognises that '*tentative information shows that not only particle size, but particle surface may play an important role in the bioavailability of a particle'*

FS does not give a clear answer, what is meant with 'similar and similarity' between metals. In many of the FSs the use of toxicokinetic data has regarded for high importance and on the other hand the FS conclusions state that the availability of the toxicokinetic data is sparse. Also in REACH, it is recommended to use toxicokinetic data, but not obligatory. FS focuses on proposing (screening) testing which is not at present available as validated.

Many of the FS proposals are valid not only for metals and metal compounds but are rather by nature in fact more general. The intrinsic properties of metals and metal compounds vary substantially and guidance to cover the different situations (water solubility, particle size and surface, bioavailability, toxicokinetics etc.) is definitely difficult to give. This is also seen in the FS, which recognises these different parameters influencing the read-across and final grouping of metals (speciation) and metal compounds, but does not give clear guidance how to do it.

Conclusions:

- It is recommended to continue classification, read-across and derogation according to the current guidance to do the risk assessments of metal and metal compounds on 'case-by-case basis' and 'using expert judgement', as guided in the TGD and wait for the outcome of the international guidance development going on at the OECD level (Manual of investigation of HPV chemicals Chapters 3.2. and 3.3). In the EU, the development of guidance for REACH is going on in the RIP-projects.

FS 5: Essentiality

Main issues in the Fact Sheet

- The conventional risk assessments 'focus on the effects of high doses of chemicals which tends to neglect that several metals are essential to life, and that harmful effects occur both at very low and very high levels of intake.'
- FS proposes - in order to avoid confusion with the concept of 'no effect levels' used for high dose toxicity, the new terms: 'sufficient dietary intake' (SDI) and 'deficiency effects level' (DEL).

Principles in the TGD (2003)

TGD (2003) does not cover the essentiality concept.

Main issues in the Nordic comments (detailed comments in Annex 5A and 5B):

The recommended dietary intakes of essential trace elements (ETEs) in order to prevent deficiencies are set up by the food administrations (e.g. for the Nordic countries “The Nordic Nutrition Recommendations”) (NNR, 2004). There is no reason why this should be re-evaluated in this document. The parts discussing the recommended dietary intakes of ETEs should be omitted. Besides, the document generally arrives at rec-

ommended dietary intakes which are higher than those set up by food agencies.

We object to the new term SDI (safe threshold for deficiency, sufficient dietary intake). It is not clear if SDI is similar to NOAEL. If this is the case, NOAEL should be used instead.

Too much emphasis is put on deficiency in relation to toxicity (most of the considerations given on page 13-14 focus on deficiency). When toxic effects / NOAELs are established only the right part of the U-shaped effect curve is of interest. The fact that an element is essential does not exclude toxic effects at higher doses.

In the consideration of essentiality and toxicity it is important to consider differences in the susceptibility in different groups of the population. Different genetic composition or diseases may affect the essentiality or the toxicity of the metals.

It is well known that uptake and function or toxicity of trace elements may be influenced by intake of other trace elements or pollutants. This is to a limited extend included in the description or the three metals but as it is an important issue more efforts should be made on this area.

Because the expected use and purpose of this fact sheet is unclear, and because the evaluation so far is incomplete, we are reluctant to give more detailed comments on specific contents here. For specific comments we refer to the Annex.

Conclusions

- The present document should not focus on the prevention of deficiencies, which is outside the scope of risk assessment.

FS 6: Choice of assessment factors in health risk assessments for metals.

Main issues in the Fact Sheet

FS states that the assumption of 'zero' exposure is irrelevant for most metals due to the ambient environmental concentrations. 'For future consideration, the documentation of 'baseline intake rates' and resulting body burdens for metals should be envisaged. For essential trace elements, a formal consideration of deficiency effect levels should be included when deriving MOSref values.'

FS MOSref values for repeated dose toxicity, it is proposed to group metals into three categories:

- For non-essential elements with toxicity data largely derived from animal testing FS supports the TGD approach.

- For non-essential elements with relevant human data, depending on the quality and extent of the data base MOS_{ref} in the range of 1-3, and where health end points are solidly based on biomarkers of systemic exposure, MOS_{ref} =1 should be proposed.
- For essential elements MOS_{ref} =1 should be proposed.
- FS supports the MOS_{ref} values for acute effects as in TGD
- FS agrees also with the approach concerning uncertainty suggested by the TGD.
- FS is the opinion that the differences in particle sizes between laboratory animal experiments and works place exposures should be taken into account.

Principles in the TGD

It is difficult for the reader to identify which version of the technical guidance document (TGD) that has been used for the comparisons, because the TGD from 2003 does not contain the risk characterisation part referred to. According to the Swedish National Chemicals Inspectorate, this chapter has been worked on during several years, but has never been published. ESR program has used for a couple of years the MOS_{ref} approach, which is an overall assessment factor addressing differences between experimental effect assessment data (animal studies) and human exposure situation with uncertainty and variability.

In the HERAG document reference is made to "the current EU technical guidance document" as TGD 2003, 2nd edition. We are not aware of such a second edition, only a Human Health Risk Characterisation revised chapter, final draft, dated 10.11.2005. It is important to clarify which version is cited in the document.

Main issues in the Nordic comments (detailed comments in Annex 6):

Section "Reflection of background concentrations". It is difficult to establish background exposures for metals that are widely distributed in the environment because of present and previous emissions. The suggested "baseline intake rates" will also vary between countries and regions.

Section "MOS_{ref} values for repeated dose toxicity". We do not agree on the proposed MOS_{ref} values (1-3) for case (ii), non-essential elements with relevant human data. That deviates largely from the TGD default values (minimum 10). Considering the serious health effects of many metals, the prevalent variation in susceptibility, and the fact that metals are persistent in the human environment, we strongly recommend that the TGD values are used as defaults. Deviations depending on data availability, toxic effects and variation in susceptibility can then be considered.

Some reasons for maintaining a high MOS_{ref} :

- Long-term exposure to metals like lead and cadmium may give rise to a range of severe health effects.
- Several of the metals pass the placenta, implying that exposure starts already prenatally. This is of special concern, as the developing organism is particularly vulnerable. Other metals, e.g. cadmium, accumulate in the placenta and may cause indirect effects on the fetus.
- In most instances, the environmental exposure is via food and drinking water, which means that exposure starts very early in life.
- In most cases people are exposed to a number of metals, as well as other pollutants, simultaneously, which is not considered in the risk assessment of each individual metal. Little is known about the combined effects, but there is increasing evidence of additive or even synergistic effects (see e.g. de Burbure et al, Environ Health Perspectives 114(4):584-90, 2006).
- History shows that improved research methodology tends to lower the NOAELs.

For group (iii) essential elements, a MOS of 1 may not be sufficient, depending on the toxicity and data on variation in sensitivity. Obviously, a comparison with recommended daily doses should be made. It should be noted that the homeostasis is often not fully developed during infancy.

Section "Particle size and chemical speciation". It is correct that both the different particle size distributions between laboratory animal exposures and work place atmospheres, and the different deposition and clearance patterns between animals and humans should, if possible, be considered in the risk assessment process. However, it is not obvious that more detailed considerations will always lead to lower human risk estimates than default assumptions. While it is true that a finer particle size distribution of experimental aerosols will give higher deposition in the deeper regions of the respiratory tract than do coarser workplace aerosols, the much more efficient filtering action of nose-breathing rodents will give lower deep lung exposures to coarser aerosols than is the case for often mouth breathing humans in a strenuous work place. It is also too categorical to say that work place aerosols are always coarser than those used in animal experiments. There are a number of processes used in industry that may generate fine to ultrafine condensation aerosols from metal fumes such as welding, heavy brakes and milling machines.

Conclusions

- There is no need for a metal-specific guidance concerning the choice of assessment factors, because the guidance at present in the TGD (2003) and the ESR MOSref approach allows to do the risk assessment(s) also for metals and metal compounds on a 'case-by-case' basis with 'expert judgement' following the principle of transparency concerning the possible deviations form TGD.

FS 7: Gastrointestinal uptake and absorption and catalogue of toxicokinetic models

Main issues in the Fact Sheet

This FS reviews the existing information on GI uptake of metals concerning nickel (EU RAR), zinc (EU RAR), cadmium (EU RAR), lead (VRA), copper (VRA), arsenic (ASTDR, WHO), beryllium (ASTDR, WHO), manganese (ASTDR, WHO), mercury (ASTDR, WHO), selenium (ASTDR, WHO), titanium (ASTDR, WHO), vanadium (WHO). Metal industry associations made oral absorption data available concerning cobalt, aluminium, iron and chromium.

FS comes to the general conclusion that for the majority of the work places GI uptake is the most relevant route of exposure at the workplace. Dermal absorption has been shown to be minimal for a large number of metals, and in most occupational settings, the particle size distribution of aerosols will cause the bulk of the inhaled material to be deposited in the upper respiratory tract, with rapid subsequent translocation to the GI tract.

Principles in the TGD (2003)

In many parts of the TGD the possibility of exposure, absorption, uptake and excretion via GI-tract is mentioned: Excretion via GI tract TGD p. 103; Chapter 3.5.7. Use of toxicokinetic data in risk assessment;

Chapter 3.6.2.1. Minimum data requirements p. 107 discussing the possibility of 'uptake or deposition in the respiratory tract is likely may indicate the need for an acute inhalation study'; Chapter 3.9.1.1. Definition of repeated dose toxicity' in relation to the possible systemic toxicity; Chapter 3.9.4. 'Assessment of the dose-response relationship' p. 128 in relation to the possible local effects in the upper GI tract due to the treatment procedures in data evaluation; In Chapter 3.10. 'Testing strategy' and 3.10.5.2. 'Preliminary considerations' p. 149 TGD states, that *'certain substances may need special consideration, ...the use of test methods that can be applied to the respiratory tract, upper gastrointestinal tract and ... may be appropriate. ...'The validity and utility of such tests and the selection of protocols should be assessed by experts from regulatory authorities and industry on a case-by-case basis.'* and in Chapter 3.10.5.6. Substances for which an *in vitro* test is positive' p. 152 TGD states that 'For insoluble substances, the possibility of release of active molecules in the gastrointestinal tract may indicate that a test involving the oral route of administration is particularly appropriate.'

Main issues in the Nordic comments (detailed comments in Annex 7A and 7B):

We do not agree that GI uptake is the most relevant route of exposure. In many cases, effects in airways or skin are the critical ones (e.g. cobalt may cause irritation, lung function impairment, asthma, skin sensitisation and cancer (hard metal dust)). The authors are probably referring to systemic dose, but this needs to be clearly stated

- The influence of dose on absorption is only addressed for lead (A 1.1.4). Thus, there is a sublinear relation between lead ingestion and blood lead (*figure on page 12*) suggesting decreasing absorption at higher doses. Such an effect is also discussed for some other metals (zinc, cadmium), yet the doses used is neither described nor discussed for any of the other metal or metal compounds.
- The text is sometimes too condensed. Thus, it is difficult to find the basis for some statements. References to major conclusions (main papers and/or appendices) should be included in the main text. The main text would also benefit from some brief examples (see several suggestions under Details). All major statements should be described in more detail in the appendices. This would make it easier for the reader to check the validity of the statements.
- The grouping of the Appendix A1 into EU, peer-reviewed and metal industry risk assessments is misleading. The first category (EU) contains also a lead (VRA) and copper (no reference to any RA). Further, specific references to the RARs are lacking in Appendix A1. The reference to e.g. zinc and zinc compounds is unacceptable since there are several RARs for specific zinc compounds.
- There should be more focus on differences between sub-populations. One example is the difference of the toxicokinetic of cadmium in smokers and non-smokers due to the high content of cadmium in tobacco. Smokers and non-smokers must therefore be considered separately in the models. The blood-brain barrier in small children is not completely developed and may permit larger transport of the elements over the barrier. This is for example important for manganese.
- The speciation of the metals is an important subject, which is not considered sufficiently. Many metals may exist in different states of oxidation with different toxicokinetic properties. Each of the naturally occurring state of oxidation of the metals should be considered separately. The difference in solubility of different inorganic metal compounds is also important. On the other hand, some organo-metallic compounds of manganese and mercury are included. As the toxicokinetic properties of these and other organo-metallic compounds is not always determined by the metal and because there exist several other organo-metallic compounds, which is not included in the fact sheet, we suggest that only inorganic metal compounds are considered.

Conclusions

- There is no need for an additional metal-specific guidance, because TGD covers the different aspects of the GI tract and allows the risk assessment to be done in cases where GI tract is one of the main routes of exposure, and real absorption/uptake really happens in the GI tract. Also, the role of the GI tract as the route of exposure can be taken into account in testing. These should be done again following the principle of transparency.

FS 8: Indirect exposure and consumer exposure

Main issues in the Fact Sheet

The fact sheet on "Indirect exposure via the environment and consumer exposure" summarises the experience gained by industry in previous and current ESR and VRAR on theses aspects, and it is concluded that there are several issues that are particularly relevant for metals and not properly covered by the TGD assessment approaches.

FS discusses the current principles of the assessment of consumer exposure and exposure indirectly via the environment. This is mainly done focusing on the sources, because the inhalation and dermal exposure FSs are separate. Biomonitoring has also been taken into account, which is especially relevant for metals, although biomonitoring combines all the possible sources of exposure and it is not always possible to distinguish between the metal oxidation states.

Principles in the TGD (2003)

Consumer exposure and humans exposed via the environment (TGD, 2003) does not make any strict lists which sources are e.g. part of the consumer exposure, like on p. 65, '*exposures to substances released or leached from articles..'*. This includes also the direct contact with metal containing objects (e.g. jewerly) etc.

TGD (2003) allows also the sources for consumer exposure and human exposure via the environment to be done in reasonable way, following the principle of transparency.

Main issues in the Nordic comments (detailed comments in Annex 8):

The overall effort of the HERAG FS seems to aim at showing that the TGD procedures results in unreasonably high exposure estimates, especially for metals. To prove that, FS examples are only given for certain exposure situations or scenarios in which the exposure can be estimated to be lower than in other situations. One example concerns the oral intake

of lead via soil and a reduced gastrointestinal lead absorption due to matrix effects. This may be the case in some situations but not in others. Therefore, it is necessary to account for interindividual variations in soil intake and g.i. absorption as well as in matrix effects, which in many situations may lead to higher absorption. Another example concerns cadmium for which it is pointed out that the life-long (50 yrs) average g.i. absorption of cadmium is lower than the average absorption during the fertile period of women. However, the fertile period of women is associated with a higher absorption rate due to low iron status. Thus, Cd is accumulated to a higher extent in women during a major part of life, which put women at higher risk for Cd induced health effects.

The fact sheet states that the TGD model is inadequate to assess the exposure via inhalation of metals related to local point sources (stack emission modelling) and via ingestion of foods (by use of biotransfer factors). Instead, the use of measurement data was recommended. No advice or alternatives are given on how to model such exposures when measured data is lacking. Further, if measured data is to be used for exposure assessment, the database must be large enough so that results can be extended to the general population or specific sub-populations of interest.

Biomonitoring was suggested as a more sophisticated way of measuring indirect exposure to metals via the environment than the modelling approach suggested by the TGD. However, at the same time it is recommended to distinguish between natural and anthropogenic concentrations in the environment and to exclude exposure which is caused by historical soil contamination. This is not possible with biomonitoring, and not useful in the risk assessment. Biomonitoring is very useful when measuring total exposure (or fraction absorbed) since it integrates over all sources of exposure, but cannot provide information of the contribution of each exposure source (which is needed for effective exposure reduction strategies). If biomonitoring data is to be used for exposure assessment, the database must be large enough so that results can be extended to the general population or specific sub-populations of interest.

Conclusion:

- There is no need for a special document on indirect exposure and consumer exposure for metals.

FS 9: Carcinogenicity

Main issues in the Fact Sheet:

FS discusses widely the evaluation of the carcinogenicity both concerning classification and labelling and risk assessment, scoping especially to

testing, epidemiological studies and human genotoxicity biomarkers. In the recommendations, Fig. 1, biomarkers and monitoring are proposed as one of the steps.

However, in the Workshop in Brussels, there was general understanding, that the biomarkers should be explained more and the role of biomarkers need to be clarified in the evaluation of carcinogenicity. Biomarkers of exposure may allow link of cancer to specific metal in addition to animal cancer studies. There was also general understanding that quite few scientifically agreed biomarkers are available, although the term 'biomarker' was understood widely (to include also the biomonitoring of metals in serum or urine). Evaluation should be done on case-by-case basis. This would need more generic guidance and it is not only metal specific issue.

Principles in the TGD (2003)

TGD (2003) describes and reviews very widely in Chapter 3.11.2.2. 'Data which may already be available', like human data (epidemiological studies), biomonitoring and molecular epidemiology as markers of both exposure and effects especially when combined with classical epidemiological observations and/or animal data, wide variety of animal in *in vitro* data. In the evaluation for carcinogenicity TGD stresses the need for consideration of a large set of data. An important part being the evaluation of the mode of action, human relevance, existence of thresholds (genotoxicity) and comparability of structurally related carcinogens - to be done with expert judgement.

TGD summarises (p. 160) the assessment of carcinogenic potential of a substance to be done by integrating many different categories of the data. '*The assessment should consider the whole set of information available, i.e. evidence in humans and animal species as well as the results of genotoxicity tests, structure activity analysis, the biological mechanisms and the metabolic processes identified, the toxicokinetic and physiological data for interspecies scaling of dose. Expert judgement is required on the weight of evidence data.* Therefore there is no need for metal and metal compound specific separate guidance concerning carcinogenicity.

Main issues raised in the Nordic comments (detailed comments in Annex 9)

This document is well written and highlights many problems associated with risk assessment of carcinogens in general and emphasizes obstacles complicating risk assessments of carcinogenic metals in particular. A general comment is that many issues are common to all carcinogenic chemicals and that these problems are discussed in a way that might give the impression that they are specific for carcinogenic metals. Thus, *chapter 5 (Recommendations, page 18)* lists a number of critical issues that are

important for carcinogen risk assessment in general. It is not hard to agree that these issues are critical and that lack of comprehensive knowledge can be an obstacle. Controversies or interpretation problems may arise in the risk assessment of single metals, as well as in risk assessment of other chemicals. For example, caution is always prudent when extrapolating from animals to humans.

Conclusions

- There is no need for metal specific guidance concerning carcinogennicity. The problems associated with risk assessment of carcinogens in general raised in FS could be taken forward when revising TGD and/-or to the RIP projects.

FS 10: Quality screening of health effects literature

Main issues in the Fact Sheet

This Fact Sheet states clearly, that this is not a metal specific issue and a wide range of studies scoring systems are needed according to the experiences with the risk assessments of data-rich substances. FS refers to the EU regulatory context to validate animal experimental studies for chemical substances according to the scheme by Klimisch et al, (1997).

Principles in the TGD (2003)

The description of the evaluation of the quality of the risk assessment data and test results is given in the Chapter 3.2. 'Evaluation of the data' of the TGD. The aspects of quality screening in risk assessments which should be taken into account are: 1) completeness of the data according to the requirements; 2) adequacy of the data (reliability and relevance); reliability of the test data (GLP and standardisation of the test data); 3) human data (epidemiological studies); 4) *in vitro* data; 5) relevance of the data; 6) (Q)SARs.

Main issues raised in the Nordic comments (detailed comments in Annex 10):

FS gives quite heavy critics to the EU RARs concerning Cd (cadmium metal and cadmium oxide) and Ni (nickel and nickel compounds). This critics is very odd, because, these EU RARs both cadmium & cadmium oxide and nickel & nickel compounds have been through very thorough peer review procedure where all the member states competent authorities, their scientific experts have had the possibility to comment, discuss and

agree the conclusions of the risk assessment report according to the TGD guidance. Industry has been involved in the procedure.

The FS introduces separately the utility rating system for deficiency studies. Thus, the present document should not focus on the prevention of deficiencies, which is outside the scope of risk assessment, as stated in the comments to the FS 5. FS introduces also the Severity-of-Effect-Criteria, which in the ESR programme has been done under 'expert judgement' when evaluating the data for its final use and weight of evidence.

Conclusions

- The approaches how to carry out the quality screening of the data, differ between the FS and TGD, but are partly overlapping. The 'expert judgement' with the principle of transparency in the TGD covers many issues introduced in the FS. The need and usefulness of such lists should be evaluated.

FS 11: Reproduction toxicity

Main issues in the Fact Sheet

The summary and conclusions of the FS concerning reproduction toxicity states that the interpretation and evaluation of reproductive toxicity data can be significantly improved. FS points especially the need for guidelines for the definition and demonstration of toxicity mediated through nutritional deficiency.

Principles in the TGD (2003)

TGD (2003) guides the evaluation of the data concerning reproductive toxicity carefully both for fertility and developmental toxicity as well as developmental neurotoxicity and reproductive toxicity via lactation.

Main issues in the Nordic comments (detailed comments in Annex 11):

Although a number of metals have well documented reprotoxic effects, the focus of the FS discussions on reproductive impact of metals is on essential metals. In order to arrive at an acceptable guidance document for reprotoxic effects of metals, examples from several well documented reprotoxic metals need to be reviewed and discussed. Metals, such as mercury, which is known to induce adverse effects in the progeny surprisingly, are not considered. Also the effects of lead on human development are given little attention and mainly with focus on effects on fertility at high exposure levels. Even though there are no final RAR documents

for those well established reproductive metals, there are a number of internationally accepted risk assessment documents, including EHO/IPCS and US National Academy of Sciences.

As stated in the FS, evidence for neurobehavioural deficits associated with developmental toxicity has generally been reliably and convincingly demonstrated in studies of exposed human populations. There are well standardised tests to evaluate neurobehavioural deficits, and they are routinely used in the field of neuroscience as well as neurotoxicology. Many of the published behavioural data from animal experiments are reliable, convincing, and in agreement with what observed in exposed human population, as in the case of methylmercury and lead.

Concerning the discussion of guidelines for the detection of more subtle developmental effects, we would like to emphasize again that there are numerous studies on the neurodevelopmental effects of e.g. lead and there is increasing evidence of effects already at very low exposure levels.

Late effects of early life exposure should be discussed.

The discussion on mechanisms of action deals exclusively with effects of metals on kinetics and homeostasis of essential elements. Although there are certain evidence for effects of zinc and cadmium on the transfer of essential trace elements to the fetus, there are, obviously, several other important mechanisms responsible for the reproductive effects of metals, in particular effects of e.g. oxidative stress on the developing brain and immune function. Probably, those mechanisms are more common for the major reproductive metals. Also, the observed endocrine effects of e.g. arsenic and cadmium need to be commented. All these relevant mechanisms of action should be reviewed and discussed.

It cannot be concluded that some essential trace elements are less likely to be toxic to reproduction because of a general high prevalence of deficiency.

We agree with the FS that interactions between metals are to be expected, but not only when the mechanism is perturbation of homeostasis.

We do not agree that compound specific bioavailability complicates exposure estimations. On the contrary, this is preferred to generalized default values. Obviously, lack of data requires conservative default values.

Although we agree that the NOAEL and the margin of safety (MOS) need to be discussed in relation to the required daily intake doses for essential elements, it has to be emphasized that these are separate evaluations. While daily requirements of trace elements concern dietary intake, toxicity to metals may be derived from various exposure routes, some of which lack homeostatic control. Also, the homeostasis is often not fully developed during early age, and may be affected by excess intake of toxic metals.

Conclusions

There is no need for specific guidance concerning metals and metal compounds, because the TGD gives a wide range of possibilities for assessing the reproductive toxicity of a compound using the 'case-by-case' approach and expert judgement with the principle of transparency.

FS 12: Sensitisation

Main issues in the Fact Sheet:

FS reviews the ESR RAs, VRAs and international reviews such as EHC, CICAD and ATDSR. FS recognises that for the dermal sensitisation validated (animal) test systems exists (Buehler test, Guinea Pig Maximisation Test, GPMT and Local Lymph Node Assay, LLNA). FS states, that caution over the use of the LLNA assay for metals and their compounds concerning false negative or positive findings with certain metals has been expressed by several organisations. FS also reviews the human assays used for investigate the sensitisation potential.

The criteria for respiratory sensitisation are less well established. FS states that there are currently no concepts or sets of criteria that would allow the setting of elicitation thresholds for respiratory sensitisation.

Principles in the TGD (2003)

TGD guides the evaluation of the available animal and human data and how the testing conditions should be taken into account. For the assessment of the dose-response relationship, the possibilities for sensitisation potency consideration is explained. Although neither the GPMT/Buehler nor the standard LLNA is designed to evaluate the skin sensitisation potency of test compounds, they could be used to identify the sensitisation potential and estimation of potency.

Main issues in the Nordic comments (detailed comments in Annex 12):

A list of sensitising metals is mentioned in the introduction, which list should also include mercury, gold and palladium. FS states that ECVAM and US EPA have reservations about the use of LLNA to test metals, but it is not mentioned if the findings by Basketter et al (1999) has been taken into account. The FS document relies heavily on the EU RARs on nickel and nickel compounds and does not raise new or controversial views on sensitisation, or risk assessment of metals concerning sensitisation.

Conclusions

There is no need for additional metal or metal specific guidance in addition to the TGD (2003).

Annex 1A.

Specific comments on FS 1: Assessment of occupational dermal exposure and dermal absorption for metals and inorganic metal compounds

Dr. Niels Oluf Breum, WEA

High quality data are required for a valid assessment of dermal exposure. The quality of the data depends on the sampling strategy used for collecting the data but the sampling technology is also important. The present fact sheet has focus on methodical aspects of the sampling technology. Below is given general and specific comments to the fact sheet.

General comments

Comment #1

The fact sheet shall be in compliance with the following technical specifications:

- CEN/TS 15278:2006 Workplace exposure – Strategy for the evaluation of dermal exposure
- CEN/TS 15279:2006 Workplace exposure – Measurement of dermal exposure – Principles and methods

Note that the period of validity of the specifications is limited initially to three years. After two years the members of CEN will be requested to submit their comments, particularly on the question whether the specifications can be converted into European Standards.

At present stage the fact sheet has focus on methodical aspects while information on the sampling strategy is missing. The sampling strategy used for collecting a data set is an important aspect to consider in an assessment of exposure. A strategy that is not well designed can produce an apparently reassuring bulk of data but the real information content may be low and interpretation with any degree of confidence extremely difficult. Thus the fact sheet shall include a comprehensive section on the design of sampling strategies. As quoted from CEN/TS 15278:2006 “an appropriate sampling strategy related to the sampling objectives should include the selection of the relevant agent, workplace, population/jobs/tasks, sample size, time of sampling, sampling duration, frequency of sampling, body locations, and sampling methods”.

Analysis of data on dermal exposure indicate a generally higher within-worker variability than between-worker variability in levels of dermal contamination, so it appears important to include repeated sampling over 'relatively 'long' periods of observations (more than one week), i.e. high sampling frequency over tasks or shifts. The reliability of the estimate will be determined more by the number of samples than by the accuracy of the individual sample.

Comment #2

The fact sheet summarise some studies on dermal exposure in various zinc, lead, antimony and nickel industries. The fact sheet has a detailed comparison of the data sets with the EASE model, and EASE was prone to over-predict by one to two orders of magnitude. From three exposure descriptors (pattern of use, pattern of control, and contact level) the dermal module of the EASE model allows an estimate of dermal exposure. Although EASE is simple the model captures some of the factors that determine exposure. Taking the complexity of workplace conditions into account one should not expect a "low" (less than a factor of e.g. 10) bias from an EASE estimate and for regulatory risk assessment it is an advantage to know that the model over-predicts exposure. Taking the "large" bias from EASE into account the fact sheet concludes (section #4.1) "that the dermal module of EASE is not suitable for regulatory risk assessment". Although the bias may be "large" the conclusion shall be rephrased to accept the EASE as a tool for an initial exposure assessment. Note that the rephrasing shall not exclude use of the proposed screening model for metals and inorganic metal compounds (see comment #5).

Comment #3

For the assessment of occupational dermal exposure the fact sheet proposes (section #4.1) to make exclusive use of the wipe-sampling methodology to facilitate the collection of comparable datasets. In principle several materials and procedures can be used for wipe-sampling (see CEN/TS 15279:2006) and a detailed manual on the sampling strategy and methodology is needed for the harvest of comparable data sets.

Comment #4

In section #4.1 the following tiered approach is proposed as an alternative dermal exposure assessment strategy.

- Tier #1 is for a scenario where measured data are available.
- Tier #2 is for a scenario where monitoring data are available for another compound of the metal which is used in a comparable scenario. The assessor is to define exposure modifiers and use "analogous" data.

- Tier #3 is for a scenario where no monitoring data are available for any comparable compound of the metal. The assessor is to define modifiers and apply "screening model" approach.
- Tier #4 is for a scenario where no monitoring data are available. A suitable analogy can not be found and the screening model approach yields insufficient safety margins. For this scenario the exposure assessment shall be refined by the generation of appropriate monitoring data.

Transparency and high quality data is a must for a risk assessment report to be useful. It is noted that tier #2 / #3 involves use of exposure modifiers defined by the assessor. In general little scientific data is available for the assessor to derive validated exposure modifiers and more often than not the modifiers are derived from "expert judgement". For the assessor it may not be easy to do a transparent "expert judgement", and the approach may leave the reader with a data set of unknown validity and it is difficult to estimate the safety margin in the risk. Thus the fact sheet shall give high priority to measured data as compared to data derived from "expert judgement", and the present tier #4 shall become tier #2.

Comment #5

It is noted (section #1, introduction) that in current risk assessment reports increasing use is being made of "analogous" dermal exposure data rather than model data, and it is necessary to understand whether it is appropriate to extrapolate from these data to other metals, and based upon which argumentation. A tiered approach is proposed (section 4.1) for the assessment of dermal exposure. For tier #2 ("analogous" approach) three basic criteria are to be met to accept a data set as valid for the approach

- intrinsic substance properties
- process conditions, control measures, and influence of PPE
- Perceptual factors derived from hazard assessment

Transparency is a must for a risk assessment report to be useful, and the three basic criteria should be considered a conceptual approach for an improved transparency. Many parameters acting in concert is important for dermal exposure in workplaces, and a large set of high quality data is required to develop a validated decision tree from the basic criteria. Perhaps more often than not the data set is not available for the assessor, and for such a situation the fact sheet shall emphasize that tier #2 is based on "expert judgement". Note that tier #2 ("analogous" approach) shall become tier #3 (see general comment #4).

Comment # 5

A tiered approach is proposed (section 4.1) for a simple but realistic assessment of dermal exposure. For tier #3 ("screening model" approach) the dermal exposure is estimated at levels given in the table below. In

terms of exposure descriptors the model is simple in having a single descriptor (pattern of control) while EASE has three (contact level, pattern of control, pattern of use).

Exposure descriptor	Exposure µg/cm^2		
	Typical	Reasonable worst case	Range
No direct handling	1	5	0-5
Limited direct handling	10	50	5-50
Direct handling	100	500	5-500

The "screening model" is restricted to the handling of metals and inorganic metal compounds. The exposure levels given were derived from exposure measured in various zinc, lead, antimony and nickel industries. The data available are listed as an appendix in details, but to improve transparency the reader needs a table listing the following information pr level of the descriptor: (**i**) the number of samples, (**ii**) the range, (**iii**) the median, and (**iiii**) the 90 percentile. Holding the listed typical levels against measured values (median) given in Table 16 the estimated levels are biased towards low levels. Perhaps it is not possible to hold data in Table 16 against the proposed screening model, but to avert the reader from such comparison more detailed information is needed on the approach taken to derive the exposure levels used for the screening model.

Specific comments

Page #7, last paragraph

The reader of the paragraph is left with the feeling that dustiness is the most important governing parameter for dermal exposure in handling Calcium carbonate. At present stage no data are available to support the hypothesis of a significant positive correlation on dermal exposure vs. dustiness. For workers it has to be expected that many parameters (including dustiness) in concert govern the dermal exposure.

Annex 1B.

Specific comments on FS 1, Assessment of occupational dermal exposure and dermal absorption for metals and inorganic metal compounds

Dr. Bengt Sjögren, IMM, Prof. Gunnar Johansson, IMM
Assoc. Prof. Per Gerde, IMM

The document aims to provide guidance on how to assess occupational dermal exposure and how to measure and evaluate dermal absorption of metals and inorganic metal compounds for the purpose of risk assessment.

General comments

We agree with the general messages and conclusions of the document, with three important exceptions, given below.

- The dermal absorption part of the document focuses very much on percent absorbed dose. However, the absorption rate is related to the concentration at the skin surface rather than the applied amount (as already stated in the document). Furthermore, dissolution and absorption are continuous processes as long as depletion does not occur. Thus, both the percentage dissolved and the percentage absorbed will increase over time. Giving merely a numerical value for percent absorbed therefore has no or limited value unless additional information is given, most importantly the duration of exposure and the applied amount per unit area. In our experience (mainly from organic chemicals and not metals), both the amount applied and the exposure duration may vary widely over several orders of magnitude. An approach, based upon Ficks' law of diffusion, focusing on dermal absorption and penetration at steady-state (flux, J_{ss}) and permeability coefficient (K_p) (*fig 1 and eq 1*), rather than percent absorbed, would be preferable. This has been done e.g. for cobalt by Filon *et al.* (*see table 21*) (see also Details, item 1). Given specified exposure conditions (e.g. concentration, C), flux and K_p data can then easily be translated to systemic dose for use in risk assessment.
- The document further suggests that the presently used default assumptions of 100% and 10% absorption of dermal load, should be replaced by other default values (1% for wet/liquid exposure, 0.1% for dry/dust exposure). We agree that the bases for the present defaults (molecular weight and $\log P_{ow}$) are not applicable to metals and inorganic metal

compounds. However, in our opinion, the data presented in the document are not sufficient to support the new recommendation.

- For zinc oxide, a potentially absorbed dose of 14.9% (sum of recoveries in receptor fluid, stratum corneum and residual skin) is reported from an in vitro study by Grötsch (*page 35*). It is further stated that the zinc bound to skin may become systemically available at a later stage, as indicated by some studies in patients. Yet it is concluded that the default absorption for solutions/suspensions of zinc compounds should be 2%. The support for 2% is that the release of zinc is so slow that it is not expected to disturb the homeostatic zinc balance. This may be correct as a standalone statement, i.e. when referring to exposure conditions similar to that of the referred experiment, but becomes absurd when making general conclusions on the quantitative systemic absorption of zinc oxide independent of amount and exposed area. The description of the more recent tape-stripping study by Gamer *(page 36, 4th paragraph*), suggesting less than 0.1% absorption, is non-informative, as the time of tape-stripping is not given.
- For copper, conclusions are drawn from two unpublished studies that are not described in the document.
- The data on nickel (metal and salts) are inconclusive, as described in the document.
- Cobalt metal powder (*page 38*) was tested suspended in artificial sweat for 30 min. The percentage of dissolved cobolt (and thus available for dermal absorption) after 30 min was 0.13%. The dissolution kinetics is not known (or reported) and the percentage dissolved after e.g. 8 h is unknown but can be expected to be at least one order of magnitude higher. Furthermore, the relevance of the in vitro test system for the in vivo situation is not known (e.g. the composition of the sweat and the very high cobalt concentration of 50 g/L).
- The experimental conditions regarding aluminium chlorohydrate and cadmium (*page 39*) are not described, hence the percent absorbed is uninformative.
- The study on antimony trioxide (only a draft so far, and thus not available to us) indicates an absorption of about 0.1%, however, the substance was not suspended in sweat, thus the relevance for the in vivo situation is not known.
- For titanium, no details are given on amount applied, exposure duration, observation time and amount in skin. Thus, the <0.1% value has no meaning. Further, sweat was apparently not studied.
- Overall, although it is acknowledged that the dissolution of the metal (compound) particles may be a rate limiting factor, little attention is paid to the major determinants of dissolution: sweat, particle size, time. In conclusion, we fear that adoption of the 1% and 0.1% default values, might results in serious underestimates of absorbed dose for some substances and/or particle types.

- There is no discussion (or even mentioning) of biological exposure in the document. In view of all the difficulties encountered in assessing dermal exposure and absorption, biomonitoring is often a very efficient tool for verifying, excluding and/or quantifying systemic absorption via the dermal route. This is recognized for example by the Scientific Committee for Occupational Exposure Limits (SCOEL) of the European Commission. SCOEL has decided to always seek to propose a Biological Limit Value whenever a substance is assigned with a Skin notation (update of SCOEL Key Document to be published).

Details

The term "dermal absorption rate" is used repeatedly throughout the document to denote per cent dermal absorption. This is misleading or at least confusing, as the term "rate" is related to time whereas the percent values contain no such information.

The list of abbreviations is incomplete (e.g. TGD) or inconsistent (e.g. RAR vs RA(R)).

Tables 2 and 5-14: The column "Counts" needs an explanation.

Table 4: Explain "n".

Page 14, paragraph 3: "There are no known adverse systemic or dermal health effects associated with this". Bold statement, more appropriate would be: "At present, there are no known …".

Page 14, paragraph 4:

> "We note that supplemental investigations have also been conducted which identified approx. 700 µg/cm² as a maximum dermal loading level for zinc oxide, obtained from measurements that involved volunteers immersing their hands in a bowl filled with the powder material." Reference to the statement is missing.

Page 19: Figures 4 and 5 are difficult to interpret. More details are needed in the figure legends.

Page 24, section 3.3: It is unclear what the given example has to do with material bound in/on skin, the way the data is presented.

Page 26: It is unclear why the use of skins with varying background levels would result in increased problems to reach the detection limit. On the contrary, one might think that it is even more important to use several donor skin when varying background levels are expected.

Annex 2A.

Specific comments on: FS 2. Assessment of occupational inhalation exposure and systemic inhalation absorption

Dr. Niels Oluf Breum, WEA

High quality data are required for a valid assessment of exposure by inhalation. The quality of the data depends on the sampling strategy used for collecting the data but the sampling technology is also important. The present fact sheet has focus on methodical aspects of the sampling technology. Below is given general and specific comments to the fact sheet.

General comments

Comment #1

To enter an assessment of exposure by inhalation a data set has to meet two basic sets of criteria:

1. the strategy used for collecting the data sets shall be valid and transparent and,
2. the methods used for the collection and analysis of the samples shall be well established.

At present stage the fact sheet has focus on methodical aspects (criteria set #2) while information on the sampling strategy is missing. It is noted that the fact sheet has a section (#A 7) on a generic occupational inhalation exposure questionnaire and this section is an important part of a sampling strategy. The strategy used for collecting a data set is an important aspect to consider in an assessment of exposure. A strategy that is not well designed can produce an apparently reassuring bulk of data but the real information content may be low and interpretation with any degree of confidence extremely difficult. Thus the fact sheet shall include a comprehensive section on the design of sampling strategies. Perhaps, as an alternative, a separate fact sheet on sampling strategy is more useful. In general a strategy is developed from the purpose of the sampling campaign and should provide answers to questions such as “where to sample”, “how often to sample”, “how many samples per shift” and, “how many workers to sample per shift”. Guidance in the design of a sampling strategy is given in a European Standard (CEN 689: Workplace atmospheres – Guidance for the assessment of exposure by inhalation to chemical agents for comparison with limit values and measurement strategy).

Comment #2

Taking advantage of the Multiple Path Particle Deposition (MPPD) model or the Regional Deposited Dose Ratio (RDDR) model the fact sheet suggests the use of particle size characterisation in the derivation of inhalation absorption factors. High quality data on the particle size distribution (PSD) are required for the approach and highest relevance should be attributed to workplace PSD data, particularly where process conditions heavily may influence particle size and composition of aerosols.

For mechanical handling of bulk materials where no workplace PSD-data is available the fact sheet suggests generation of PSD-data from dustiness testing in the laboratory. The European Standard on dustiness testing (EN 15051:2006 – Workplace atmospheres – Measurement of the dustiness of bulk materials – Requirements and reference test methods) specifies two reference test methods for the reproducible production of dust from a bulk material under standard conditions, and the measurement of the inhalable, thoracic and respirable fraction. Method A (rotating drum method) produces dust by a multiple continuous dropping process of the bulk material, whereas Method B (continuous drop method) produces dust by dropping the bulk material once under gravity. The standard was developed based on the results of the European research project SMT4-CT96-2074 (Development of a method for dustiness testing, SMT4-CT96-2074, Final Report, April 2000). It is noted that neither of the methods produce PSD-data.

For some years two EC member countries have had national standards on dustiness testing (UK: MDHS 81; Germany: VDI 34921 pt1). The fact sheet recommends the widely used Heubach rotating drum tester (DIN 34921 pt1) for the dustiness testing. The recent European project (SMT4-CT96-2074) observed that this tester cannot separate the biological fractions (inhalable, thoracic, and respirable). The project included dustiness testing with the Heubach tester interfaced with a seven stage precision cascade impactor (PCI) with cut points between 0.3-30 μm [the PCI is no longer commercially available]. The Heubach-PCI tester samples the total dust produced and by modelling the biological fractions are calculated from the seven size fractions collected (the method of calculation is in-house knowledge of DMT (Deutche Montane Technology)). In dustiness testing the amount of bulk material used and the time of generation are important variables in the amount of dust released. The Heubach-PCI tester varies the amount of bulk material and time to keep the loading on the impactor within a specified range. The narrow range in acceptable loading of dust onto the PCI is a severe constraint of the tester, and neither the Heubach tester nor the Heubach-PCI tester entered the European Standard. Note that the narrow range makes it difficult to use the Heubach-PCI method for comparison of dustiness of different substances. Note that DIN 34921 pt1 has no description of the Heubach-PCI tester. It is emphasized that the PSD obtained from a Heubach-PCI test is for the

"total" dust leaving the rotating Heubach drum, but a PSD determined in this way may be used in turn to calculate the masses contained within individual health-relevant particle size fractions of interest (e.g., inhalable, thoracic and respirable). Further calculations are required to derive the PSD for the inhalable fraction. Recently INCO funded a study on the PSD of nickel species; a modified cascade impactor was used for static sampling of aerosols and by contrast to the "total" aerosol fraction a substantial different PSD was seen for the inhalable fraction (see Fig. 8 in Kerr *et al*.: Ann Occup Hyg 45(7), 555-568, 2001).

While the Heubach-PCI tester has an advantage in producing PSD-data, the use of the tester is complicated by the lack of a European standard for the tester. Method #A of EN 15051:2006 has the advantage of giving data on dustiness in terms of the respirable, thoracic and inhalable dust. As a further advantage of EN 15051:2006 a chemical analysis of the three fractions of dust is rather simple. Although EN 15051 is a very recent standard Method #A has been used for some years and the fact sheet shall exclude the Heubach-PCI tester and take advantage of the methods given in EN 15051:2006.

For exposure assessment the MPPD-model of the human airway has the advantage in giving an estimate of the regional deposition of the inhaled aerosols. Detailed PSD-data are required as input to the model, but very often such data are not available from workplaces. At workplaces exposure by inhalation of dust shall be measured by samplers meeting the criteria of an European Standard (EN 481:1995 – Size fraction definitions for the measurement of airborne particles in the workplace). Thus the fact sheet shall focus on data collected with samplers meeting EN 481 leading to PSD data for the inhalable fraction of dust. In case the sampler does not meet the criteria of EN 481 the PSD data shall be converted to be valid for the health-relevant particle size fractions of interest (e.g., inhalable, thoracic and respirable).

Comment #3

Section A 3.1 (Measurement of particle size; laboratory methods) of the fact sheet recommends the Heubach-PCI method for dustiness testing and for the assessment of the particle size distribution of the dust. This method, as mentioned above, was not included in the European standard for dustiness testing (EN 15051:2006). Thus the fact sheet shall exclude the Heubach-PCI method and focus on the methods given in EN 15051:2006.

To demonstrate the use of the Heubach-PCI tester the fact sheet has examples (Section A 4, Workplace particle size data from previous/current EU Risk Assessments) of data from dustiness testing of Lead and Zinc compounds. Dust leaving the tester at outlet of the drum is collected by the PCI and the particle size distribution is estimated from the mass of the collected seven size fractions of particles. The dust fraction entering the PCI is the "total" fraction of dust. As mentioned above (comment #2) a PSD de-

termined in this way may be used in turn to calculate the masses contained within individual health-relevant particle size fractions of interest (e.g., inhalable, thoracic and respirable). For the reader of Section A 4 it is difficult to see if the size distributions are for the "total" fraction or for the inhalable fraction. If a size distribution is for the "total" fraction it has to be expected that the size distribution by contrast to the inhalable fraction is biased towards a high MMAD. The bias depends on the size distribution – the coarser the dust is the larger is the bias.

Comment #4

The fact sheet has a full section (page #28. Section A 3.2: Workplace particle size monitoring, Multi-stage cascade sampling) on the measurement of particle size distributions (PSD). Any PSD depends on the particles entering the measuring equipment. Recently ILZRO funded a study on PSD in a primary lead smelter facility, and it was noted that the aspirated fraction (in relation to total fraction) is important for the estimated PSD (see Spear *et al.*, Ann Occup Hyg 42, 73-80, 1998). Furthermore it was noted, that the mass collected in the entry section of a cascade impactor is important for the estimated PSD. For occupational exposure assessment focus is on health-relevant particle size fractions (e.g., inhalable, thoracic and respirable). Thus the fact sheet shall stress, that the equipment used for PSD analysis shall allow a valid estimate of the health-relevant fractions. Unfortunately some cascade impactors sample "total" dust (i.e. an unknown fraction), and such data are difficult to use for an exposure assessment. As an example it is difficult to see the fraction ("total" or inhalable) used for estimation of the PSD-data on zinc compounds (Page #29. Section A 4.1: Zinc, Fig. #1-3) and lead (Page #33. Section A 4.2: Lead, both figures shown). The fact sheet recommends the Heubach tester for dustiness testing. As mentioned above (general comment #2/#3) this tester was not included in the European standard for dustiness testing (EN 15051:2006). Thus the fact sheet shall not mention the Heubach but focus on the methods given in EN 15051:2006.

Comment #5

A step-by-step procedure is suggested (Section #4) for assessing systemic absorption from inhalation exposures. For step #2 of the scheme dustiness testing is suggested as the method to obtain data on a particle size distribution (PSD). For a refined assessment (step #3a) workplace PSD data can be used.

In the occupational setting airborne particulate matter will be characterized by a process- and substance-driven particle size distribution, and the fact sheet shall emphasize that it is difficult to relate the size distribution of aerosols generated in the laboratory (dustiness testing) to the size distribution experienced in workplaces particularly where process conditions heavily may influence particle size and composition of aerosols. For

the suggested scheme the fact sheet shall emphasize that it is difficult to simulate workplace conditions in the laboratory and for occupational exposure workplace PSD data should always be given preference over dustiness testing in the laboratory. In case of no workplace PSD data a field study might prove more productive than dustiness testing in the laboratory. As mentioned above (comment #2/3) no standard method is available to generate PSD-data from dustiness testing.

Specific comments

Page #25. A 1: Definitions. Aerodynamic diameter:

By definition the aerodynamic diameter (d_a) is the diameter of a sphere with unit density that has aerodynamic behaviour identical to that of the particle in question. Particles having the same aerodynamic diameter may have different dimensions and shapes. For a smooth sphere (diameter d_p; density ρ_p) the aerodynamic diameter d_a is given by the relation (ρ_u is unit density)

$$d_a = d_p \times \sqrt{\rho_p / \rho_u}$$

Note that the particle has to be a smooth sphere for the relation to be valid. The fact sheet should stress this important limitation to the given simple relationship between the physical and the aerodynamic diameter.

Page #25. A 1: Definitions. Dustiness:

The European standard (EN 15051:2006) has two methods for dustiness testing: (**i**) a rotating drum method and, (**ii**) a single drop method. Dustiness as derived from the rotating drum is reported in terms of the three health related fractions (inhalable, thoracic and, respirable dust). For the single drop method dustiness is given in terms of the inhalable and the respirable fraction. For both methods the dust fractions are collected on foams and a filter (rotating drum) or on filters (single drop). Thus neither of the methods allows an easy access to detailed data on the particle size distribution of the collected airborne dust. As mentioned above (general comment #2 / #3) the Heubach "rotating-drum" method is not included in the European Standard on dustiness testing of bulk materials (EN 15051:2006). Thus the Heubach method shall not enter the fact sheet.

Page #25. Line #5 from bottom and line #2 from bottom:

The GSD is given as 1.5 µm. Please note that a GSD is a non-dimensional parameter.

Page #27. A 2.2:

Models relevant for derivation of inhalation absorption factors. MPPD model: Note that version 2.0 of the MPPD model was released October 2006. The link to the download page (link checked 2006-10-26) is: http://www.ciit.org/mppd .

Page #28. A 3.1:

Laboratory methods (Measurement of particle size): As mentioned above (general comment #2 / #3) the Heubach-PCI tester is not included in the European standard on dustiness testing. The Heubach-PCI tester varies the amount of bulk material and time to keep the loading on the impactor (PCI) within a specified range. The narrow range in acceptable loading of dust onto the PCI is a severe constraint of the tester. The accuracy of the method will depend on the efficiency that the coarse fraction is collected and the number and spacing of the fractions used. For a comparison of dustiness of different materials to be valid it is important to keep all important parameters (including the amount of bulk material and testing time) at a fixed level. The Heubach-PCI tester does not meet this requirement. Thus the fact sheet shall not mention this method but recommend dustiness testing according to EN 15051:2006.

Page #28. A 3.2:

Workplace particle size monitoring: For the multi-stage cascade sampling the presentation shall emphasize that the estimated particle size distribution shall be valid for the health-relevant particle size fractions (e.g., inhalable, thoracic and respirable).

Page #29-35. A 4.1 (Zinc) and A 4.2 (Lead):

As already mentioned (general comment #4) it is difficult to see the fraction ("total" or inhalable) used for the estimation of the PSD-data shown in the graphs.

Page #42, Section A 7:

Generic occupational inhalation exposure questionnaire: Section 2 of the questionnaire (Measurement procedure and strategy) requires information on particle size/fraction [e.g. total inhalable dust etc]. The concept "total inhalable dust" is confusing. Perhaps the sentence shall read "total or inhalable dust"?

Annex 2B.

Specific comments on: FS 2, Assessment of occupational inhalation exposure and systemic inhalation absorption

Med.Dr. Bengt Sjögren, IMM, Prof. Gunnar Johansson, IMM
Assoc. Prof. Per Gerde, IMM

The document focuses on the assessment of inhalation exposure and absorption of metals and metal compounds under occupational exposure situations. Inhalation is probably the most important exposure route to consider in the assessment of human risk from solid inorganic substances and in particular from metals in the workplace. Two distinct aspects are addressed: assessment of external exposure, and the proportion of material that is retained and absorbed into the body.

General comments

Some important / general comments are given below, followed by minor ones at a more detailed level.

- We note that the document is far from complete in that nanoparticles, welding fumes and vapours (e.g. mercury) are not included. We also note a discrepancy compared to the other HERAG fact sheet (e.g. the one on GI absorption) in that the present document only covers occupational exposure.
- We believe that the by far most important factors concern exposure le -vels and exposure variability. Therefore, the importance of sampling techniques, strategy and sample size are very important. We acknowledge that this has been done by others and that it suffices to refer to one or two reviews (as done on page 15). However, the different sources of error and variability in assessing systemic exposure need both to be addressed and put in perspective. As the document is written now, the reader is given the impression that deposition fractions, inhalation absorption fractions, and correction factors for samplers are the key/critical issues. The document would benefit from rearrangement, so that it starts with inhalation exposure followed by systemic inhalation absorption.
- The key concept of "*inhalation absorption*" should be defined and explained early in the text (we found no such definition in the document).
- The models chosen to estimate regional deposition seem appropriate. The MPPD model is gaining more and more use. The RDDR model

for species to species extrapolation is to our knowledge the best of the easily available methods.

- Welding fumes should be included (not excluded) in step 2 and/or step 3 in the stepwise procedure (*page 12-14*). Welding is an important source of exposure to metals for many workers. The particles generated by welding generally have smaller diameters (often < 1 um) and may have different solubility characteristics than those formed in other industrial processes.
- ”Total dust” be should be addressed. At present, the term is merely mentioned in passing in Appendix 5.1. Many old reports, that may still be very useful in risk assessment, only have data on total dust. Further, many occupational standards, including those of Sweden and SCOEL, still use total dust for some OELs.

Details

Page 4, bullet points:
The descriptions of the mechanisms of deposition in the airway regions are too categorical, suggested modifications are underlined:

- Large-size material is deposited in the extra thoracic region <u>largely</u> by impaction, and is subject to rapid clearance (usually within 2-5 minutes) and translocation to the gastro-intestinal (GI) tract. Thus, assuming minimal absorption through skin and mucous membranes in the extra thoracic region, the GI uptake factors will actually determine the systemic bioavailability of such a compound.
- Material is deposited in the tracheo-bronchial region by <u>impaction, sedimentation and diffusion and is</u> then subject to clearance usually on a scale of 15-20 minutes, and also then translocated to the GI tract. Similarly assuming minimal absorption through mucous membranes in this region, GI uptake factors will again apply.
- Material that penetrates to the alveolar/pulmonary fraction of the lung is <u>predominantly</u> subject to diffusion. Information on clearance from this area is rarely available, so as a conservative default assumption, 100 % of this material may assumed to be absorbed.

Page 13, line 13: A clearance of particles with the mucociliary escalator from the entire TB region within 15-20 min seems very fast. Within that time frame only the trachea and the two main bronchi will have cleared their mucus to the larynx. The major fraction of particles deposited in the TB will need 1-24 hrs and even longer to clear to the GI tract. If material in the deeper TB region is assumed to clear by dissolution and absorption to the circulation this needs to be clearly stated.

Pa*ge 24, Abbreviations*: OEL means Occupational Exposure <u>Limit,</u> not <u>Level.</u>

Page 29, paragraph 6: "Inhalation studies in human volunteers (Gordon et al 1992) have reported subjective symptoms (fever, chills, dry/sore throat, chest tightness, headache) of metal fume fever at and above exposure levels of 5 mg/m^3 already after 2 hours of exposure. The zinc oxide fume was generated in an electrical furnace, with an aerosol particle size typically below 0.1 μm. "

Some later studies present a slightly different result: In a study by Fine and coworkers (1997), volunteers were exposed to zinc particles which were generated in an electrical furnace under inert gas protection. The zinc vapours reacted with oxygen to form zinc oxide which condensed to ultrafine particles. These primary particles aggregated in chains to form secondary particles with a mass median diameter of 0.3 μm. Two hours exposure to 2.5 mg/m^3 resulted in an increased plasma concentration of interleukin-6 and increased body temperature. No effects were observed after two hours inhalation of 0.5 mg/m^3 zinc oxide (Beckett et al 2005).

Fine JM, Gordin T, Chen LC, Kinney P, Falcone G, Beckett WS. Metal fume fever: Characterization of clinical and plasma IL-6 responses in controlled human exposures to zinc oxide fume at and below the Threshold Limit Value. JOEM 1997; 39: 722-726.

Beckett WS, Chalupa DF, Pauly-Brown A, Speers DM, Stewart JC, Frampton MW, Utell MJ, Huang L-S, Cox C, Zareba W, Oberdörster G. Comparing inhaled ultrafine versus fine zinc oxide particles in healthy adults. Am J Respir Crit Care Med 2005; 171: 1129-1135.

Thus, these more recent studies should be included as they demonstrate metal fume fever at lower concentration than the study cited in the document.

Page 30, Discussion: This section is confusing as it discusses risk (of zinc oxide) rather than the influence of particle size on absorption. One of the paragraphs goes on to dismiss metal fume fever as a consequence of improper use or omission of RPEs. This deals with risk management and is beyond the scope of risk assessment. It is definitely beyond the scope of occupational inhalation exposure and systemic inhalation absorption.

Page 42, Questionnaire Section 2 Medical biomonitoring: It is important to note also when sampling was performed in relation to exposure, e.g. before shift, after shift, first day in the week, last day in the week, first day after vacation, last day after a long working period etc.

Annex 2C.

Specific comments on FS 2, Assessment of occupational inhalation exposure and systemic inhalation absorption

Assoc. prof. Göran Lidén, SU

At several places in the document the formulations of the authors indicate that they are not well enough familiar with their subject.

3.1 second part (and other places): A particle size distribution, (assumed) uni-modal, with GSD≥4 indicates that the assumption of uni-modality is wrong, i.e. the size distribution is bi- or tri-modal. Each mode may be lognormal by itself. In order to get relevant results, the estimations must be based on a better representation of the underlying particle size distribution than what was obtained by a uni-modal lognormal distribution. See for example the table with size distributions for copper aerosols on page 10. Therefore the method on page 13 should begin with determining the number of modes, and for each mode, its concentration, MMAD and GSD.

3.1 second part (and other places, e.g. page 18 and the conclusions on page 20): The described simulation model only works for particles ≤20 μm. All inhaled particles that exceed 20 μm will deposit in the extrathoracic region of the respiratory tract. Later the report discusses the difference between "total dust" and inhalable dust, assumes a ratio of "total dust"/inhalable dust equal to 0.5, and goes on to correct the concentration for all particle sizes by the same factor. This is completely wrong. Almost the whole difference between "total dust" and inhalable dust occurs for particle sizes ≥20 μm. It is therefore only the deposition in the extrathoracic region that will exceed those estimated based on concentrations of "total dust".

It is important to know what the terms used stand for. In work environments, inhalable dust is specified in EN481 and ISO7708. In work environments, "total dust" is *not* the concentration of all airborne particles. When this concept was introduced (in the sixties-seventies) it was *believed* that a so-called "total dust sampler" (which could vary in design from country to country) sampled the concentration of all airborne particles. This has since been proved to be wrong, instead the "total dust" concentration is generally lower than the inhalable concentration. To complicate matters, USEPA uses a concept termed "inhalable coarse particles", but this is only the differential fraction between PM2.5 and PM10, that is considerably smaller particles than those that in most cases dominate the mass of "total dust" or inhalable dust.

3.1 third part: The term “respirability” is probably derived from the concept “respirable aerosol fraction" used in occupational hygiene. This concept does not designate particles that may be respired, i.e. inhaled. This term designates the aerosol fraction that can reach (=penetrate down to) the gas-exchange region, i.e. not only the fraction depositing in the gas-exchange region. The respirable aerosol fraction (respirable dust) is defined in EN481 and ISO7708.

Table Zinc-B (and other occurrences): There are no references for the values for absorbed fraction.

Page 12, last paragraph: "... measurement of total dustiness including particle size distribution ... is considered to adequately reflect the particles size of aerosols under conditions of mechanical handling, and as such is useful in the assessment of the PSD [Particle Size Distribution] under workplace conditions (such as for example packaging, weighing or mixing of a substance/product)." This is overstating the capacity of a dustiness test. Dustiness is not a definite property of a compound, as for example boiling point, density, etc. Measured dustiness (and hence also measured PSD) is very dependent on how the test is performed. The determined dustiness value is only a standardized measure when the original material is handled in a well-defined way, and this may vary considerably from what will be obtained at real-existing workplaces and work practices. Dustiness testing cannot be used to investigate the dust released when solid materials are mechanically reduced (e.g. cut, crushed) or to test handling procedures for the materials. See the standard EN15051, and Lidén, *Ann. Occup. Hyg. 50*(5):437-439, 2006 (http://annhyg.oxfordjournals.org/cgi/content/full/50/5/437).

A report like this should only be based on well-specified references in the open literature or possibly on published reports that can be obtained from the issuing institute.

Dustiness page 25: The authors of the report ought to study CEN standard on dustiness testing, EN15051, and the final report of the EU project that preceeded the CEN standard, HSL report IR/L/MF/00/11 *Development of a Method for Dustiness Testing – Final report EU contract smt4-ct96-2074*.

Size fractions for relevant inhalation toxicology, page 25: This part includes several misunderstandings that are quoted almost verbatim from one of the cited references, though not the original source, EN481 or ISO7708.

- inhalable fraction: The inhalable fraction is not defined for particles exceeding 100 µm. This is generally interpreted to mean that tests are not carried out for larger particles than this, not that samplers for inhalable dust should be prohibited from sampling particles exceeding 100 µm (i.e. that it would be a requirement that the sampling efficiency of samplers for inhalable dust should be zero for particles exceeding 100 µm.)

- thoracic fraction: The clause "the median value of the particle size is 11.64 µm with a geometric standard deviation (GSD) of 1.5 µm." expresses a misunderstanding. The sampling convention for thoracic dust is formulated mathematically as the product of the sampling convention for inhalable dust, I(Dae), and a curve T(Dae)=(1-F(x(Dae))), where F is the cumulative normal distribution function and x=ln(Dae/D.T)/ln(GSD.T). In the expression for x, D.T=11.64 µm (this is the particle size for which T(Dae)=F(x)=0.5) and GSD.T=1.5 (*no µm*) is the slope of the curve T(Dae). [It is formally correct that D.T and GSD.T by themselves describe a lognormal size distribution. But, in this case the curve is used without any implied particle size distribution with a median size=11.64 µm and a geometric standard deviation=1.5.] The value for D.T is expressly chosen in order that I(10 µm)*T(10 µm)=0.50000.

- respirable fraction: Similar comment. The clause "the median value of the particle size is 4.25 µm with a geometric standard deviation (GSD) of 1.5 µm." expresses a misunderstanding. The sampling convention for respirable dust is formulated mathematically as the product of the sampling convention for inhalable dust, I(Dae), and a curve R(Dae)=(1-F(y(Dae))), where F is the cumulative normal distribution function and y=ln(Dae/D.R)/ln(GSD.R). In the expression for y, D.R=4.25 µm (this is the particle size for which R(Dae)=F(y)=0.5) and GSD.R=1.5 *(no µm*) is the slope of the curve R(Dae). [It is formally correct that D.R and GSD.R by themselves describe a lognormal size distribution. But, in this case the curve is used without any implied particle size distribution with a median size=4.25 µm and a geometric standard deviation=1.5.] The value for D.R is expressly chosen in order that I(4 µm)*T(4 µm)=0.50000

A.5.1 fourth paragraph and the following four indents: The problem that the report authors are referring to is neither any general "undersampling in laboratory studies" as two different samplers are compared simultaneously (both in a lab and at workplaces) nor any of the factors listed in their four bullets. The crux of the matter is rather that a wind-tunnel test is a standardised test, and that this test is more relevant for work outdoors, in spray booths and in mine galleries and other tunnels, than at indoor workplaces with low air speeds (2-25 cm/s). In lab tests performed with almost calm air (see for example Kenny et al., *J. Aerosol Sci. 30*(5):627-638,1999) a much better correspondence between lab tests and workplace tests is obtained (see for example Lidén & Harper, *J. Occup. Environ. Hyg.* **3**(10):D94-D101, 2006).

Annex 3.

Specific comments on: FS 3, Mutagenicity

Assoc. Prof. Agneta Rannung, IMM

Document No 3 describes the testing strategies for mutagenic and genotoxic properties of metals and metal compounds on which a hazard classification can be based. It differs in several aspects from the Current EU Genotoxicity Testing Guidelines and its minimal data requirements, which was developed for the classification of organic substances. The document also suggests a strategy for follow-up dose response and mechanistic studies of importance for risk assessment.

Based on the identification of a number of indirect mechanisms of mutagenic action that are atypical for mutagenic organic substances, an alternate tiered testing strategy was developed and presented that can be used both for hazard identification and risk assessment.

In the "decision tree" suggested, the bacterial mutagenicity assays are omitted and particular mammalian cell test systems that have the capacity to detect both large and small scale mutagenic events are recommended to be used. Assays for chromosomal damage are suggested to be performed under conditions of high cell survival and include markers for apoptosis and necrosis. The testing strategy is also recommended to provide information on toxicokinetics and target organ specificity and preferentially use mutagenesis assays in transgenic animals for gene mutation endpoints. Conduct of dose response and mechanistic studies, especially directed towards oxidative mechanisms is recommended in order to improve risk assessment. Dominant lethal mutation tests are suggested to be used only for the purpose of quantifying risks of germ cell mutations if enough data suggest such risk.

General comment

The suggested test battery for hazard classification is appropriate based on the knowledge on mechanisms of metal mutagenicity. Mechanistic studies including in vivo and in vitro dose response measurements for identified endpoints are highly relevant as suggested. Mutagenicity assays using transgenic animals are relevant for the in vivo point mutation tests. Such tests are available for chemical screening purposes and protocols that allow detection of mutation frequency for different tissues have been developed and evaluated by IPCS/WHO (Environmental Health Criteria no 23. Transgenic Animal Mutagenicity Assays, WHO, Geneva 2006).

Concerning administration, the route should be chosen which is relevant for the particular substance and for the expected target organ and the dose levels should also cover doses that produce some toxicity (minimal to zero mortality). Concerning the intrinsic property/hazard evaluation any route could be used (including i.v.).

There are some more aspects with relevance for testing of metals, along with some other comments, which need to be addressed as detailed below.

Specific comments

In section 2.1, page 5 paragraph 3, first sentence: define "biological relevance".

In the *same section, page 9 paragraph 3, row 3*. fast ligand should read Fas ligand.

The sectio*n 2.2 gives on page 10 and 11* a valuable and in depth description of several indirect mechanisms that may account for possible co-mutagenic (and co-carcinogenic) properties of metals such as free radical production, oxidative stress, DNA repair and effects on the mitotic spindle. However, the effects of metal compounds on phase I and phase II biotransformation enzymes, on cellular stress responses such as kinase activated cell proliferation and on levels of cellular antioxidants are not mentioned. Such effects may be particularly relevant for the observed co-mutagenic effects of metal compounds with PAH or cigarette smoking. Also epigenetic effects such as DNA methylation ought to be mentioned.

In *section 2.3, page 12*, the table showing The Summary Result of Genotoxicity Testing and Carcinogenicity Evaluations for Selective Metals should be complemented with data for arsenic for comparison with results presented in the fact sheet on carcinogenicity.

In *section 3, page 15*, in vivo follow-up dose response studies are suggested that could provide critical data for conduct of risk assessment. Whether germ cell clastogenicity in rodent spermatogonial cells is a useful endpoint should be discussed.

As commented above, the co-mutagenic actions of metals is a critical aspect of metal mutagenicity and carcinogenicity, which should be investigated by performance of combined dose-response studies with known mutagenic regimes such as alkylating agents, PAH and UV. It is appropriate to focus the testing strategies on responses that have been observed at low doses in earlier studies such as cell stress responses, including oxidative stress, and proliferation which may affect the susceptibility also of germ cells to DNA damage.

Annex 4.

Specific comments on: FS 4. Read across, Derogation criteria, Classification and labelling

Dr. Marita Luotamo, FIOH

Read-across principles are described in the FS for oral, inhalation and dermal bioavailability, uptake and toxicity. The central issues are the use of toxicokinetic data, bioaccessibility, water solubility (it is not self evident that good water solubility guarantees bioavailability), particle surface and bioavailability. FS also recognises that '*tentative information shows that not only particle size, but particle surface may play an important role in the bioavailability of a particle*'

FS does not give a clear answer, what is meant with 'similar and similarity' between metals. In many of the FSs the use of toxicokinetic data has regarded for high importance and on the other hand the FS conclusions state that the availability of the toxicokinetic data is sparse. Also in REACH, the toxicokinetic data is recommended to use, but not obligatory. FS focuses on proposing (screening) testing which is not at present available as validated.

The TGD (Part 1, 2003) does not have at present clear view on read-across and grouping of chemical compounds, although it has been done in the ESR program on 'case-by-case basis' and with 'expert judgement'. TGD (Part 4, 2003) has only one paragraph concerning the use of (Q)SARs in human health risk assessment and recommends when ever (Q)SARs are used to give the specified information on the used methodology in a transparent manner.

Many of the FS proposals are valid not only for metals and metal compounds but are rather by nature in fact more general. The intrinsic properties of metals and metal compounds vary substantially and guidance to cover the different situations (water solubility, particle size and surface, bioavailability, toxicokinetics) is definitely difficult to give. This is also seen in the FS, which recognises these different parameters influencing the read-across and final grouping of metals (speciation) and metal compounds, but does not give clear guidance how to do it.

Conclusions:

- Therefore it is recommended to continue according to the current guidance to do the risk assessments of metal and metal compounds on 'case-by-case basis' and 'using expert judgement', as guided in the TGD and wait for the outcome of the international guidance develop-

ment going on at the OECD level (Manual of investigation of HPV chemicals Chapters 3.2. and 3.3). In the EU, the development of guidance for REACH is going on in the RIP-project.

Annex 5A.

Specific comments on: FS 5, Essentiality

Dr. Agneta Åkesson, IMM, Prof. Marie Vahter, IMM
Prof. Monica Nordberg, IMM

General comments

The recommended dietary intakes of essential trace elements (ETEs) in order to prevent deficiencies are set up by the food administrations (e.g. for the Nordic countries "The Nordic Nutrition Recommendations") (NNR, 2004). Thus, the present document should not focus on the prevention of deficiencies, which is outside the scope of risk assessment. The parts discussing the recommended dietary intakes of ETEs should be omitted. Besides, the document generally arrives at recommended dietary intakes which are higher than that set up by food agencies.

We object to the new term SDI (safe threshold for deficiency, sufficient dietary intake). It is not clear if SDI is similar to NOAEL. If this is the case, NOAEL should be used instead (WHO, 2002).

Also it is important to notice that the essentiality and the NOAEL of ETEs is very much dependent on the exposure route and chemical species of the compound. Thus, exposure to Zn via food is very different from exposure to ZnO via inhalation.

Section 3.1.1 Copper

The EU's Scientific Committee on Food has evaluated the Tolerable Upper Intake level of Copper (SCF, 2003). Strangely, this evaluation is not referred to by the HERAG document.

The HERAG document has a long section on Cu-deficiency while the section on copper excess is short and incomplete. It should be noted that Cu-deficiency is considered a very rare condition almost never occurring in circumstances outside severe illness.

Most data seem to support an average requirement of 0.7 mg Cu/d for adults. With a coefficient of variation of 15%, the US Food and Nutrition Board calculated the RDA to be 0.9 mg/day (which was also adopted in the Nordic nutrition recommendations) (NNR, 2004). In contrast, the HERAG document states that an intake below 1 mg/day may be insufficient to maintain copper status.

The paragraph on adverse effects due to copper excess is very short (page 6). It should include symptoms of excess intake, situations where excess intake can occur, vulnerable groups and information on the diseases related to copper toxicity (Wilson, Indian liver cirrhosis).

A NOAEL of 16.3 mg Cu/kg bw is mentioned in the HERAG document based on an animal study. Using an assessment factor of 200 this document arrived at 5.7 mg Cu/day for adults. Recently, the EU's Scientific Committee on Food has proposed a tolerable upper intake level of 5mg/day to be safe for adults. This is based on the absence of negative effects during copper supplementation and includes a safety factor of 2. It seems more appropriate to use the Tolerable upper intake level set by the Scientific Committee on Food.

Last paragraph on page 7 deals with Cu deficiency (commented on above): omit this part.

Section 3.1.2. Zinc

The recommended zinc intake mentioned in the HERAG document, from 5 mg Zn/day in infants to 19 in lactating women, is higher than that in NNR (11 mg Zn /day in lactating women). See general comments in the introduction.

The NOAEL used was 50 mg Zn/day based on a study on humans. It is not clear if this was the value HERAG arrived at.

EU Scientific Committee on Food used an assessment factor of 2 on the NOAEL of 50 mg Zn/day and arrived at a tolerable upper intake level of 25 mg Zn/day and 12.5 mg Zn/day for children.

Section 3.2.1 Iron

Paragraph 5, page 11: Postmenopausal women and elderly men are not at a high risk of iron deficiency.

The health consequences (metabolic syndrome) in the offspring due to maternal iron deficiency is not well substantiated

Iron toxicity due to accidental intake of iron supplement in children should be mentioned.

Chapter 4. Summary and conclusions

Too much emphasis is put on deficiency in relation to toxicity (most of the considerations given on page 13-14 focus on deficiency). When toxic effects / NOAELs are established only the right part of the U-shaped effect curve is of interest.

Appendix

The purpose of the appendix is not clear. Apparently it is written based on personal communication with the European Copper Institute, and other references are missing. We suggest that the appendix is omitted as it is not possible to evaluate in its current form. Figure D is probably of great importance in the interpretation as it deals with the copper dose-response curve. However, based on the limited information given in the 7document and the very small pictures it is impossible to evaluate.

References

NNR, 2004; Nordic Nutrition Recommendations 4th edition, Nord 2004:13.

WHO, 2002; Principles and Methods for the Assessment of Risk from Essential Trace Elements, World Health Organization, Geneva, Series Environmental Health Criteria, No 228, ISBN 92-4-157228-0.

SCF, 2003; European Commission, Scientific Committee on Food, 2003 http://ec.europa.eu/food/fs/sc/scf/out176_en.pdf

Annex 5B.

Specific comments on: FS 5, Essentiality

Dr. Max Hansen, DTU, Dr. Ole Ladefoged, DTU

General remarks:

We find that the organisation of the document and the presentation of data need to be more structured. The aim of the fact sheet should be better defined. Who is expected to use it and for what purpose. This fact sheet contains many statements and many data without references. These statements and data must either be followed by a reference or excluded.

The presentation of intake data is insufficient. We suggest that intake data are presented as mean or median intake with 5^{th} and the 95^{th} percentile including a reference to the study. In studies on human intake large food survey must be preferred for small studies. It is also important to consider the differences in intake in different regions due to different food habits and varying concentration of trace elements in the drinking water and soil.

On the essentiality and toxicity of each element we suggest that human or animal studies are presented with the following data: Number of participants or animals. The length of the intervention or dosing period. The critical effect(s). The critical study. Where it is considered appropriate also the most important methods.

In the consideration on essentiality and toxicity it is important to consider differences in the susceptibility in different groups of the population. Therefore upper and lower limits must always be specified for different age groups and in some cases also for each sex. Different genetic composition or diseases may affect the essentiality or toxicity of the trace elements. These groups should be included in the fact sheet.

It is well known that uptake and function of trace elements may be influenced by intake of other trace elements or pollutants. This is to a limited extend included in the description or the three metals but as it is an important issue more efforts should be made on this area.

On the other hand, too much effort has been put into the description of the traditional methods for toxicological risk assessment. The use of NOAEL with the application of uncertainty factors and MOS based on animal studies is for obvious reasons only partial relevant in the assessment of essentiality and toxicity of essential elements. Animal's studies should be used with particular caution because there are huge differences in the action of trace elements between different animal species.

As a minor point we would prefer that the word "absorption" be changed to the more precise word "uptake" where it is relevant. It would increase the readability of the text if there was used fewer abbreviations.

Specific remarks

I our opinion this fact sheet must be re-written. Therefore, we are not going to give comments in detail. The general comments are valid for the three elements.

Introduction:

In the introduction it is mentioned that "unbalanced concern over high dose effects may lead to recommendations that lead to harm form deficiency". This statement is of cause true but we are not aware that this has happened. Statements like this must be documented.

Copper:

Interaction between copper and other trace element or pollutants is important. One example could be the interaction between cupper and molybdenum, which may be included. It is correct that there are large amount of animal studies for assessment of adverse health effects of high copper intake. But it is not correct that there are many human studies, which can be used for this purpose. The lack of human data is actually a major problem in the determination of an upper safe level as animal studies, as mentioned earlier, is of restricted value.

In the part "reflection of deficiency in human health risk assessment" the use of uncertainty factors is discussed. This could be replaced by reflection over the differences in bioavailability of different copper compound. Also the difference in the toxicity of copper given in the drinking water compared to copper given in the food deserves attention. The toxic endpoint may even change by selection of administration route.

Zinc: The effect of high intake of zinc on semen quality or testis function should be included. Zinc interacts with other trace elements or pollutants. As an example it could be mentioned that zinc reduces the toxicity of cadmium. Also the risk of copper deficiency due to high intake of zinc deserves attention. Of cause speciation is of importance.

Iron: Many of the general comments are relevant in this part. Although excess intake of iron is not common it may be mentioned that some few men have probably too high intake of iron. It is surprising that high levels of iron has been associated with increased severity of rheumatoid arthritis and heart disease. It is on of the many places where a reference would be desirable. Iron has two state of oxidation with different toxicity. It would be relevant to include the consequences of this.

Conclusion:

It is true that the essentiality has only been considered in EU in few cases but assessments made by different groups in WHO may be considered as very good substitute for the lacking EU assessments. On the other hand we do not agree that the voluntary risk assessments should be considered as being on the same level EU assessments as it is difficult to ensure the quality and the independency of the voluntary risk assessments.

Step-wise approach:

Several of general remarks should be implemented in the step-wise approach. In (4) it is mentioned that the quality of the animal study should be identified. It is true but it may be more important to identify the relevance of the animal study.

Annex 6.

Specific comments on: FS 6, Choise of assessment factors in health risk assessments for metals.

Assoc. prof. Katarina Victorin, IMM, Prof. Marie Vahter, IMM

This HERAG document reviews how the margin of safety values (MOS) have been applied in a number of EU risk assessment reports (RAR) for metals, and a comparison is made with recommendations concerning MOS in the EU technical guidance document (TGD) on risk assessment for new notified substances, existing substances and biocidal products. Based on this information a set of conclusions and recommendations is presented. We think that this approach, in principle, is acceptable, but we have some critical remarks:

General comment

It is difficult for the reader to identify which version of the technical guidance document (TGD) that has been used for the comparisons, because the TGD from 2003 does not contain the risk characterisation part referred to. According to the Swedish National Chemicals Inspectorate, this chapter has been worked on during several years, but has never been published. In the HERAG document reference is made to "the current EU technical guidance document" as TGD 2003, 2nd edition. We are not aware of such a second edition, only a Human Health Risk Characterisation revised chapter, final draft, dated 10.11.2005. It is important to clarify which version is cited in the document.

Chapter 1. Introduction and 2. Definition of "Margin of safety" (MOS)

In the introduction of the HERAG document it is stated that the TGD proposes a fixed set of factors based upon which a so-called "reference MOS" is derived. However, the factors are default assessment factors, as cited in section 2, which can be subject to deviations. The corresponding table in the TGD contains several footnotes with references to explanatory texts. For example, if the starting point for the MOS calculation is a LOAEL instead of a NOAEL an assessment factor between 3 and 10 is suggested to be used instead of the default value of 1, or preferably a Benchmark dose approach (dose response). Also, the severity of the effects needs to be considered when deciding on MOS. More of these explanatory texts should have been included in the HERAG document.

The statement that "MOS settings for metals should observe a low margin between toxicological endpoints and natural background or deficiency levels" *(first sentence second paragraph under Introduction)* needs clarification. We do not agree to have a general recommendation of low MOS_{ref} values, if that is the meaning. Also, it is important that the total exposure is considered. It should be pointed out that, for many metals, previous anthropogenic emissions have resulted in "background levels", meaning unpolluted areas, that are clearly elevated above natural background levels.

In the HERAG document there is no discussion about exposure assessment. The margin of safety (MOS) is calculated as the ratio between the NOAEL and the exposure, and can be compared with the reference MOS (MOS_{ref}). Thus, an essential part of the risk characterisation is reliable and representative exposure estimates for different scenarios. A critical question is whether the average or worst case exposures should be used. In the TGD it is recommended that the "reasonable worst case" should be used initially (taken from the upper end of the exposure distribution, e.g. 90^{th} or 95^{th} percentile). Typical values can then be used as well. A statement on exposure should be added.

Chapter 3. Previous experience in EU risk assessments

We recommend references in the text to the RAR documents and other references listed in section 5. It has not been possible for us to localize and read all the different risk assessment reports, but we still would like to give some comments.

3.1 Zinc. The fact that zinc is an essential element and the type of adverse effects at elevated exposure are not mentioned. In relation to the reference to a NOAEL based on a study with human volunteers, the number and type of volunteers as well as the time period of exposure need to be mentioned. Also, possible variations in susceptibility should be discussed.

3.2. Lead. In the first paragraph it should be clarified whether such a low MOS as 1 was really recommended in the RAR for both the occupational setting and indirect exposure via the environment. And, what was the NOAEL? Does the points 1) – 8) refer to the occupational setting? History shows that the NOAEL or LOAEL for lead has been continuously revised from a "safe" blood lead level of 300 µg/L in the early 1980ies to 100 µg/L and below 20 years later. In fairly recent years, a number of studies revealed effects at blood lead levels below 100 µg/L including immune effects (Critical Rev. Toxicol. 36, 359-385, 2006), hearing loss (Osman et al. Environ. Res., 80(1), 1-8, 1999), and increased mortality in cardiovascular effects and cancer already at blood lead levels of 50-100 µg/L (Schober et al, EHP 114(10)1538-1541, 2006). In addition, there is increasing evidence for increased risk of cancer in occupationally exposed individuals (Van Wijngaarden et al, Int. j. Cancer 119,

1136-1144, 2006). Indeed it can be questioned whether a scientifically sound NOAEL has been established. Therefore, a MOS of 1 is too low.

3.3 Nickel. Nickel allergy should also be considered. Was that not considered in the risk assessment report? According to the TGD, the MOS approach can be used for sensitisation if a robust NOAEL for induction or elicitation can be derived. If a NOAEL is not available, the risk cannot be characterised, and therefore emphasis should be placed on controlling exposures to as low as possible.

3.4. Copper. The reported indications of associations between copper in drinking water and child diarrhoea should be mentioned. We also refer to our comments on Document 5, Essentiality.

3.5. *Cadmium, MOS values for repeated doses*. We would like to point out that the LOAEL of 2 µg Cd/g creatinine in the RAR contains significant uncertainty and does not imply a conservative assessment. Furthermore, the exposure assessment in the RAR is based on average exposure in the general population (which means that half the population have higher exposure levels) and not "reasonable worst case", as recommended in the TGD. The minimal MOS of 3 as used in the RAR only covers the conversion of LOAEL to NOAEL, and thus, according to our view, does not provide sufficient protection. Benchmark dose calculations for renal effects of cadmium in a female population with low environmental exposure in Sweden gave a BMDL of 0.7-1.2 µg Cd/g creatinine concerning effects on glomerular filtration rate (corresponding to an additional risk of 5 or 10 %) in a study at our institute (Suwazono et al, Environ Health Perspect 114, 7, 1072-1076, Åkesson A, et al., Environ. Health Perspect. 113(11), 1627-1631, 2005). A lower BMDL for women (1.6 µg/g creatinine) than for men was obtained in recent Japanese studies (Kobayashi et al, J Appl Toxicol. 2006 Jul-Aug;26(4):351-5). In addition, recent studies indicate an association between cadmium exposure and kidney effects also in children living in the vicinity of historic nonferrous smelters in France, Czech Republic and Poland (de Burbure et al, Environ Health Perspect 114(4):584-90, 2006).

Chapter 4. Conclusions and recommendations

Section "Reflection of background concentrations". It is difficult to establish background exposures for metals that are widely distributed in the environment because of present and previous emissions. The suggested "baseline intake rates" will also vary between countries and regions.

Section "MOS_{ref} values for repeated dose toxicity". We do not agree on the proposed MOS_{ref} values (1-3) for case (ii), non-essential elements with relevant human data. That deviates largely from the TGD default values (minimum 10). Considering the serious health effects of many metals, and the fact that metals are persistent in the human environment, we strongly recommend that the TGD values are used as defaults. Devia-

tions depending on data availability, toxic effects and variation in susceptibility can then be considered.

It should be specified if the mentioned MOS_{ref} values for cadmium and lead should be applied to a NOAEL or a LOAEL. In case of a LOAEL a MOS of 1 or 1-3 is totally inadequate. In case of a NOAEL a MOS of 1 does not provide sufficient protection, even in a case such as lead, where health endpoints are based on biomarkers of systemic exposure (see discussion of lead and cadmium above).

Some reasons for maintaining a high MOS_{ref} :

- Long-term exposure to metals like lead and cadmium may give rise to a range of severe health effects.
- Several of the metals pass the placenta, implying that exposure starts already prenatally. This is of special concern, as the developing organism is particularly vulnerable. Other metals, e.g. cadmium, accumulate in the placenta and may cause indirect effects on the fetus.
- In most instances, the environmental exposure is via food and drinking water, which means that exposure starts very early in life.
- In most cases people are exposed to a number of metals, as well as other pollutants, simultaneously, which is not considered in the risk assessment of each individual metal. Little is known about the combined effects, but there is increasing evidence of additive or even synergistic effects (see e.g. de Burbure et al, Environ Health Perspect 114(4):584-90, 2006).
- History shows that improved research methodology tends to lower the NOAELs.

For group (iii) essential elements, a MOS of 1 may not be sufficient, depending on the toxicity and data on variation in sensitivity. Obviously, a comparison with recommended daily doses should be made. It should be noted that the homeostasis is often not fully developed during infancy.

Section "Particle size and chemical speciation". It is correct that both the different particle size distributions between laboratory animal exposures and work place atmospheres, and the different deposition and clearance patterns between animals and humans should, if possible, be considered in the risk assessment process. However, it is not obvious that more detailed considerations will always lead to lower human risk estimates than default assumptions. While it is true that a finer particle size distribution of experimental aerosols will give higher deposition in the deeper regions of the respiratory tract than do coarser workplace aerosols, the much more efficient filtering action of nose-breathing rodents will give lower deep lung exposures to coarser aerosols than is the case for often mouth breathing humans in a strenuous work place. It is also too categorical to say that work place aerosols are always coarser than those used in animal experiments. There are a number of processes used in industry

that may generate fine to ultrafine condensation aerosols from metal fumes such as welding, heavy brakes and milling machines.

Annex 7A.

Specific comments on: FS 7, Gastrointestinal uptake and absorption and catalogue of toxicokinetic models

Prof. Gunnar Johansson, IMM , Prof.. Monica Nordberg, IMM
Dr. Agneta Åkesson, IMM

The fact sheet focuses on experiences on gastrointestinal uptake and absorption of metals as gained from risk assessments and from toxicokinetic and to some extent toxicodynamic models.

General comments

1. The fact sheet is easy to follow in that the main text is kept short and focuses on conclusions and recommendations.
2. The influence of dose on absorption is only addressed for lead (A 1.1.4). Thus, there is a sublinear relation between lead ingestion and blood lead (*figure on page 12*) suggesting decreasing absorption at higher doses. Such an effect is also discussed for some other metals (zinc, cadmium), yet the doses used is neither described nor discussed for any of the other metal or metal compounds.
3. The text is sometimes too condensed. Thus, it is difficult to find the basis for some statements. References to major conclusions (main papers and/or appendices) should be included in the main text. The main text would also benefit from some brief examples (see several suggestions under Details). All major statements should be described in more detail in the appendices. This would make it easier for the reader to check the validity of the statements.
4. We appreciate that a number of metals have been addressed in the appendices.
5. The grouping of the Appendix A1 into EU, peer-reviewed and metal industry risk assessments is misleading. The first category (EU) contains also a lead (VRA) and copper (no reference to any RA). Further, specific references to the RARs are lacking in Appendix A1. The reference to e.g. zinc and zinc compounds is unacceptable since there are several RARs for specific zinc compounds.

Details

Check the list of acronyms for completeness (e.g. SRP).

Page 3, section 1 1), 1st bullet: It should be added that hand-to-mouth transfer is of particular importance for children, who may also constitute a vulnerable group.

Page 4, 4th paragraph: (example: zinc) should be (example: zinc metal and zinc oxides versus zinc salts).

Page 5, Occupational exposure, 1st bullet: We do not agree that GI uptake is the most relevant route of exposure. In many cases, effects in airways or skin are the critical ones (e.g. cobalt may cause irritation, lung function impairment, asthma, skin sensitisation and cancer (hard metal dust)). The authors are probably referring to systemic dose, but this needs to be clearly stated.

Page 5, Indirect exposure, 1st bullet: Give examples to 1st statement; which metals, magnitude of effect of diet, references.

Idem, 2nd bullet: Give examples; which metals, magnitude of effect of diet, references. What is meant by "individual matrix components" ?

Page 6, 1st bullet: Again, examples could be given for specific metals. What is the expected magnitude of the error introduced by assuming 100% bioaccessibility and bioavailability?

Page 6, last bullet: The example of cobalt is not substantiated in any of the appendices. Is in vivo bioavailability higher or lower than the in vitro bioaccessibility? How big errors are introduced?

Page 7, section 3.1: PBDK should be PBTK

Annex 7B.

Specific comments on: FS 7, Gastrointestinal uptake and absorption and catalogue of toxicokinetic models

Dr. Ole Ladefoged, DTU

General remarks:

The fact sheet gives a good overview on the subject and the quality is in general good. However, we have some comments, which may improve the sheet further.

There should be more focus on differences between sub-populations. One example is the difference of the toxicokinetic of cadmium in smokers and non-smokers due to the high content of cadmium in tobacco. Smokers and non-smokers must therefore be considered separately in the models. The blood-brain barrier in small children is not completely developed and may permit larger transport of the elements over the barrier. This is for example important for manganese.

The speciation of the metals is an important subject, which is not considered sufficiently. Many metals may exist in different states of oxidation with different toxicokinetic properties. Each of the naturally occurring state of oxidation of the metals should be considered separately. The difference in solubility of different inorganic metal compounds is also important. On the other hand, some organo-metallic compounds of manganese and mercury are included. As the toxicokinetic properties of these and other organo-metallic compounds is not always determined by the metal and because there exist several other organo-metallic compounds, which is not included in the fact sheet, we suggest that only inorganic metal compounds are considered.

The impact of the different route of ingestion is described too simplistic. It is true that inhalation of large particles will be transferred to the gastro-intestinal tract, but small particle may be taken up via the lungs. This is of special importance in occupational health in the metal industries and should be considered. The toxicokinetic of orally ingested elements is dependent on several factors. The toxicokinetic properties of elements ingested via drinking water is often different from the toxicokinetic properties of elements ingested intake via food. It is also of importance whether food is ingested in an empty stomach or in a full stomach.

Soil is treated as one substance although there are large differences in bioavailability of elements between different types of soil. Also “ageing” of soil and environmental factors like the pH of the soil-water influence the bioavailability of some elements. Aluminium hydroxide is an exam-

ple of a substance where the solubility and thereby the bioavailability is pH dependent.

In the chapter on models it should be stated whether the model is validated or not. This is important, as only very few of these models have been formally validated.

A minor point is that some of the references seem rather old. They should be updated and especially it should be checked if JECFA has new relevant documents.

Finally, it is disturbing that the word rate is used incorrect. As an example absorption rate is used on page 13 where the meaning seem to be uptake of a quantity of a substance. This should be corrected in the entire document.

Specific remarks:

The following list is not intended to be complete.

P. 4: The meaning of line starting with "in other cases….." is not clear.

P. 5: It is not completely documented that arsenic and mercury are metabolised in the GI tract.

P. 7: In line 2 moles should probably be models. We do not agree that extrapolation from route to route and between subpopulations is possible.

P. 13: There seem to be few data to support the extrapolation in the figure. This must be commented.

P. 14: The different species of the metals should be included in the table. It should be mentioned that many of rodents eat faeces, which may influence the toxicokinetic.

P. 17: It should be mentioned that small children has a less developed blood-brain barrier, which permit manganese to enter the brain.

P. 21: It should be checked that the compound mentioned in line 21 really is sulfhydral and not sulfhydryl.

P. 18 The paragraph on organic manganese should be deleted.

P. 23: Other aluminium compounds could be included in the table.

P. 24: It must be mentioned that the chapter on chromium only concern Cr^{III}. It has been suggested that endogene redox processes may oxidise Cr^{III} to Cr^{VI}. It would be interesting to include a discussion of this possibility.

P. 26: In about line 26 we suppose that toxicokinetic models for Risk Assessment should be of lead and not cadmium.

P. 27: It is mentioned that the uptake of lead from the gastrointestinal tract in adults is assumed to be 8 %. It seems to be very low and if it is correct the statement must be followed by a reference.

P. 29: It should be checked whether the EPA revision of the model is available now.

P. 30: It should be mentioned that the models is not suitable to analyse smokers due to the high content of cadmium in tobacco.

P. 34: There is a reference Turnlund 2005 – in press. This paper has been published. The reference should be updated.

P. 35: Check if a new JECFA reference exists.

P. 38: The model for methyl mercury should be excluded.

Annex 8.

Specific comments on: FS 8, Indirect exposure via the environment - Consumer exposure

Dr. Marika Berglund, IMM

It is stated in the introduction of the fact sheet that the purpose is to cover issues which are not covered by the TGD, in particular those relevant for metals. The fact sheet gives an overview of the current principles for the assessment of indirect exposure via the environment and consumer exposure.

Section 2.3.1 Blood lead biomontoring

It is stated that the gastrointestinal absorption of lead is 50% in children and 5-10% in adults from food, and that the absorption from soil is reduced due to matrix effects. It should be noted that these default values are average absorption factors, and that variation probably is considerable.

Section 2.3.2. Urinary cadmium biomonitoring

It is stated that on average, over a long period (50 yrs), an absorption factor of 3% for Cd is more relevant than 10%, which may be correct for men but probably not for women. However, it should be borne in mind that since Cd has a very long half-life in the body, a higher exposure/absorption during the period of about 30 years in which women are in childbearing age may result in a higher average absorption than 3 % and adverse effects showing up earlier in life in women than in men.

Section 2.4.1. Inhalation route

The fact sheet point to the inadequacy of the TGD model for exposure assessment via inhalation of metals related to local point sources (stack emission modelling). However, no advice is given on how to handle it or how to perform a relevant exposure assessment for metal exposure via air/inhalation.

A lot of emphasis is put on describing metal exposure via smoking, and especially Cd (what other metals in tobacco smoke are relevant for health risk assessment?). Statistical descriptors of national cigarette consumptions are given (mean, 90 percentiles, etc). It is not clear if these numbers also include non-smokers or not. We recommend to perform

exposure and risk assessment for smokers and non-smokers separately, since smoking is a voluntary activity.

Section 2.4.2. Dermal contact

It is correctly pointed out that dermal contact may lead to significant metal exposure in children via the hand-to-mouth exposure route, even if the exposure via dermal absorption is negligible. It may also be noted that in cases of soil contaminated with organo-metal compounds the dermal absorption can be significant.

According to this fact sheet, the TGD does not consider dermal exposure in the indirect exposure section, because exposure via dermal contact is considered very unlikely. It should be mentioned here that many areas formerly used for industrial activities, heavily contaminated, and which used to be situated far from the cities and communities, are now being exploited for residential purposes. This can make exposure via contaminated soils to a more common scenario.

For further comments see our comments on HERAG document No 1.

Section 2.4.3. Oral intake

It is pointed out in the fact sheet that exposure via soil is not covered by the current TGD, and that lead (and other metals) exposure in children is largely a function of soil/dust ingestion. We agree that the soil/dust exposure route should be considered in the TGD. Detailed guidance is given in the fact sheet of how to calculate the exposure in children with the example of lead.

However, it is concluded that since the model suggested (IEUBK, USA) is overestimating the EU blood lead levels when comparing measured and modelled data, the default soil intakes should be lowered substantially compared to the model. This is based on the statement that the information for the bioavailability of lead (what about other metals?) is detailed. It should be noted that the bioavailability of lead (and other metals) is to a large extent dependant on chemical form and the soil/particle type. We agree that soil concentrations should be based upon soils to which children most likely are exposed to. The bioaccessibility of the metals, e.g. the type of soil and source of the metals, should also be considered. It should also be noted that for arsenic, soil levels in areas with historical releases can be high enough to give rise to acute effects in children.

2.4.3.2. Ingestion of foods. No suggestions are given except that an alternative to the use of biotransfer factors needs to be considered. The examples given on Pb, Cu and Cd do not provide any further guidance of how to perform the exposure assessment for metals via food ingestion.

*2.4.3.3. Ingestion of drinking water***.** Only metals deriving from piping materials are mentioned (Pb, Cu).). Other metals of concern in drinking water are not mentioned and should be included, such as arsenic.

It was suggested that the US EPA age specific default values for children and adolescents for drinking water intake, ranging from 0.6 to 0.97 L/day, are used since the TGD does not provide such. It can be mentioned that WHO (Drinking water guidelines, 3rd edition) uses a default value of 2 L/day for adults, 1 L/day for children assumed to weigh 10-kg or 0.75 L/day for a 5-kg bottle-fed infant. The corresponding daily fluid intakes are higher for children than for adults on a body weight basis.

Chapter 3. Consumer exposure

Table page 19: When should an exposure be classified as high? It seems strange that the only exposures which are ranked high are Ni exposure via jewellery and food contact materials. For example, inhalation of metals via cigarette smoke and (burning) of candles with lead wick cores is ranked as moderate exposure. And there are several other examples in the list which are doubtfully classified as moderate.

3.3.1. Inhalation

3.3.1.1. Smoking: The argumentation that smoking is a voluntary individual choice but inhalation of metals via cigarette smoke is not ("beyond the influence of an individual") is odd. Active smoking is a consumer exposure.

3.3.1.2. Metal compounds as pigments in household paints: It is first stated that besides lead pigments other metals may become relevant, and that exposure via paint dust inhalation and ingestion (for children) may occur. Then it is suggested to assess this exposure within "indirect exposure via the environment". The basis for that conclusion is missing. In our opinion pigments in household paints are consumer products, and should be assessed as such.

3.3.3. Oral intake

3.3.3.2. Dietary supplements: We agree that the composition of market products and the frequency of use in the general population must be established.

3.3.3.3. Drinking water (pipes): Copper and lead is mentioned. Is it possible that other metals used in plastics need to be assessed?

Chapter 4. Summary and conclusions

4.1. Indirect exposure via the environment: Reference is made to the MERAG project which is discussing bioavailability, bioconcentration etc. Biomonitoring is suggested as a more sophisticated way of measuring

indirect exposure to metals via the environment than the modelling approach suggested by the TGD. It should be mentioned that biomonitoring gives a measure of the total exposure (or fraction absorbed), but cannot alone provide information on which sources of exposure are the most significant, which is needed for effective exposure reduction strategies.

We agree that assessment should also be performed for the susceptible groups of the general population.

It is stated that 90th percentiles should not be used when assessing exposure to metals based on environmental concentrations because it may lead to overestimates of internal exposure. We find no reason why the use of 90th percentiles should not apply to metals.

The last section in 4.1, General recommendations is odd. It is not meaningful to distinguish between natural and anthropogenic environmental concentrations of a metal (or other) when performing risk assessment. The risk manager may consider naturally high background levels in standard and guideline setting.

For the assessment of exposure via drinking water age-dependant default values for intake is proposed referring to US EPA (1997), page 17. No uptake factors, as stated in the summary section (page 23, second bullet, "Relevant compartment-specific conclusions"), is given.

It is not clear why distinction should be made between historically and currently polluted soils when performing exposure assessment of metals in soil.

In the "Relevant compartment-specific conclusion" for ingestion via food it is stated that metal-metal interactions, where known, need to be addressed. It is not explained how interactions such as decreased gastrointestinal absorption of lead in the presence of calcium should be performed in reality.

Overall comments

- The use of measurement data was recommended in preference to modelled/predicted data in the exposure assessment. It is important, however, that the data base is large enough and that the results can be extended to the general population or specific sub-populations (statistical sample of general population).
- There are no examples with mercury
- There is no discussion on organic metal compound exposures, e.g. methylmercury

Annex 9.

Specific comments on: FS 9, Carcinogenicity

Prof. Johan Högberg, IMM

General comments

This document is well written and highlights many problems associated with risk assessment of carcinogens in general and emphasizes obstacles complicating risk assessments of carcinogenic metals in particular. A general comment is that many issues are common to all carcinogenic chemicals and that these problems are discussed in a way that might give the impression that they are specific for carcinogenic metals. Thus, *chapter 5 (Recommendations, page 18)* lists a number of critical issues that are important for carcinogen risk assessment in general. It is not hard to agree that these issues are critical and that lack of comprehensive knowledge can be an obstacle. Controversies or interpretation problems may arise in the risk assessment of single metals, as well as in risk assessment of other chemicals. For example, caution is always prudent when extrapolating from animals to humans.

Specific comments

The document highlights the problem of co-exposure and confounding in epidemiological studies. It is possible that that mixed exposures is more common in metal cancer epidemiology, and that extra care should be taken to analyze this question. However some examples in this document seem misleading. *See e.g. chapter 4.5, page 16,* where nickel and co-exposure is discussed. The arguments used here can be applied on many non-metallic carcinogens and their effects on humans. It seems that many inherent problems in cancer epidemiology in general is discussed here as a problem specific for metals.

Another example (*chapter 3.2, page 10-11)* is presented as a problem with "cobalt". However the literature referred to deals with "hard metal" (which is a mix of cobalt and tungsten). Thus, if "hard metal" is assessed several problems can been avoided. This is the way the Swedish Criteria Group and a CICAD document handled the assessment. These two groups independently considered a ref. (Moulin et al. Am J Epidem. 1998,148, 241-248) as central, but this ref. is not motioned here. Instead the document refers to a paper by the same authors, but which seems to deal with another exposure scenario involving arsenic. This creates confusion, especially as the *summary table on page 11* gives the impression that the evidences for cobalt carcinogenicity are insufficient.

Another problem with the table *on page 11* is that the data by Waalkes on intra-uterine arsenic exposure of mice (see e.g. Waalkes et al. 2006 Toxicol Appl. Pharmacol. 215, 295) seem not to have been considered.

Yet another confusing example the citation of Englyst et al., *2001 (chapter 3.2 p 10 and chapter 4.1 page 14).* The document claims that this citation suggests that excess lung cancer incidence is due to a synergistic interaction between arsenic and cigarette smoking. However this seems to be a misinterpretation. Englyst et al. state (on page 80 in their publication): "No information about smoking habits is available for workers in these two subcohorts. However, there is no reason to believe that confounding from smoking could explain more than a minor part of the increased SIR-values for lung cancer (Sandström and Wall, 1995; Lundström et al., 1997)."

The reference (COC, 2004), mentioned on *page 9,* is missing in the reference list.

We find that the recommendations in the last bullet point on page 19 is very important and therefore should be among the first recommendations given in the list. In order to improve cancer risk assessment it is crucial to understand the mechanism of action of metals and to use mechanistically relevant endpoints. This is in line with the recommendations for mutagenicity testing in the accompanying fact sheet and is highly relevant taken into account that most metal compounds lack direct reactivity with DNA and in many cases have been found to act as co-mutagens and co-carcinogens.

Annex 10

Specific comments on: FS 10. Quality screening of health effects literature

Dr. Marita Luotamo, FIOH

FS gives quite heavy critics to the EU RARs concerning Cd (cadmium metal and cadmium oxide) and Ni (nickel and nickel compounds). Industry claims that the data was not systematically evaluated and most of the reviews did not take the speciation into account, leaving uncertainties to the effects specially associated to the two cadmium compounds to be assessed.

Concerning nickel and nickel compounds, FS argues that '... the Danish Rapporteur in the EU RARs of nickel and nickel compounds, no established criteria for evaluating study reliability were apparently applied in the human health component of these RAs. However, the Danish rapporteur explicitly required data quality assessments in the environmental component of the nickel/nickel compound RAs.'

This critics is very odd, because, these EU RARs both cadmium & cadmium oxide and nickel & nickel compounds have been through very thorough peer review procedure where all the member states competent authorities, their scientific experts have had the possibility to comment, discuss and agree the conclusions of the risk assessment report according to the TGD guidance. Industry has been involved in the procedure.

As general recommendations, FS proposes that the use of suitable biomarkers enhance the credibility of a particular report/study (Pb and Cd as examples); the relevance of confounders in epidemiological studies; and background levels for all metals. The metal-specific issues raised were connected to the essentiality / non-essentiality of the metals; confounders and retrospective exposure assessment in epidemiological studies (in particular As); as well as speciation.

The FS introduces separately the utility rating system for deficiency studies. Thus, the present document should not focus on the prevention of deficiencies, which is outside the scope of risk assessment, as stated in the comments to the FS 5. FS introduces also the Severity-of-Effect-Criteria, which in the ESR programme has been done under 'expert judgement' when evaluating the data for its final use and weight of evidence.

Annex 11.

Specific comments on: FS 11, Reproduction toxicity

Prof. Sandra Ceccatelli, IMM, Prof. Marie Vahter, IMM

This Document is intended to review the risk assessment procedures of effects of selected metals on reproductive toxicity, defined as "any adverse effect induced by a substance upon any aspect of mammalian reproduction". This includes all phases of reproductive cycle, male and female reproductive function and capacity, as well as the induction of non-inheritable adverse effects due to exposure *in utero* or during lactation. Based on this information a set of conclusions and recommendations is presented. We have some critical remarks:

Introduction

It is not clear how the selection of the metals to be included in the evaluation was made. Metals, such as mercury, which is known to induce adverse effects in the progeny surprisingly, are not considered. Also the effects of lead on human development are given little attention with focus on effects on fertility at high exposure levels. Even though there are no final RAR documents for those well established reproductive metals, there are a number of internationally accepted risk assessment documents, including EHO/IPCS and US National Academy of Sciences.

Apart from mercury and lead, other metals such as arsenic, manganese, metals for semiconductor applications and catalytic converters may be taken into consideration.

Chapter 2. Definition of "Reproductive toxicity"

The statements at the end of page 3 "Protocol modifications are possible to more explicitly evaluate potential functional deficits associated with developmental toxicity, but many of these (e.g. for neurobehavioural deficits) are non-standardised and can be difficult to extrapolate to humans. Evidence for neurobehavioural deficits associated with developmental toxicity has generally been most reliably and convincingly demonstrated in studies of exposed human populations." is unacceptable and shows that a large part of the existing literature on metals was overlooked. There are well standardised tests to evaluate neurobehavioural deficits, and they are routinely used in the field of neuroscience as well as neurotoxicology. Many of the published behavioural data from animal experiments are reliable, convinc-

ing, and in agreement with what observed in exposed human population, as in the case of methylmercury and lead.

There is a contradiction that needs to be clarified. In spite of the inclusion of lactational transfer among the exposure routes leading to reproductive toxicity *(page 3),* manifestation of reproductive toxicity "through impacts upon lactation" are not considered *(page 4).*
Where are these effects going to be assessed? Why should they be evaluated separately?

Section 3.2. Reproductive Impacts of Metals

Concerning the discussion of guidelines for the detection of more subtle developmental effects, we refer to our comment above on section 2. There are numerous studies on the neurodevelopmental effects of e.g. lead and there are increasing evidence of effects already at very low exposure levels.

Late effects of early life exposure should be discussed.

3.2.1. Problems related to mechanism of action. This section deals exclusively about effects of metals on kinetics and homeostasis of essential elements. Although there are certain evidence for effects of zinc and cadmium on the transfer of essential trace elements to the fetus, there are, obviously, several other important mechanisms of reproductive effects of metals, in particular effects of e.g. oxidative stress on the developing brain and immune function. Probably, those mechanisms are more common for the major reproductive metals. Also, the observed endocrine effects of e.g. arsenic and cadmium need to be commented. All these relevant mechanisms of action should be reviewed and discussed.

It cannot be concluded, as in *the last sentence of the first paragraph*, that some essential trace elements are less likely to be toxic to reproduction because of a general high prevalence of deficiency.

Second paragraph: Indeed, interactions between metals are to be expected, but not only when the mechanism is perturbation of homeostasis. This needs to be discussed.

3.2.2. Problems of Data Interpretation. Although there may be lack of suitable biomarkers of exposure to zinc, this is not generally applicable to all essential trace elements.

We do not agree that compound specific bioavailability complicates exposure estimations. On the contrary, this is preferred to generalised default values. Obviously, lack of data require conservative default values.

3.2.3. Nutritional vs. Toxicological Data. Although we agree that the NOAEL and the margin of safety (MOS) need to be discussed in relation to the required daily intake doses for essential elements, it has to be emphasized that these are separate evaluations. While daily requirements of trace elements concern dietary intake, toxicity to metals may be derived from various exposure routes, some of which lack homeostatic control.

Also, the homeostasis is often not fully developed during early age, and may be affected by excess intake of toxic metals.

Chapter 4. Summary and Conclusion

Although a number of metals have been reviewed for impacts on reproductive function, including lead, a well documented reprotoxic metal, the focus of the discussions of reproductive impact of metals, mechanisms of action and summary and conclusion is on essential metals. In order to arrive at an acceptable guidance document for reprotoxic effects of metals, examples from well documented reprotoxic metals need to be reviewed and discussed.

Annex 12.

Specific comments on: FS 12. Sensitisation

Dr. Charotte Madsen, DTU

Introduction

The fact sheet on sensitisation comprises a nine-page text. The rest of the document is text that has been copied from international reviews on metals. Some of these are resent some are quite outdated.

The fact sheet 1-6

A list of sensitising metals is mentioned in the introduction. The list should also include mercury, gold and palladium.

There are general texts on classification, skin sensitisation methods in animals and humans and alternative tests.

It is correctly stated that there are no QSAR models covering sensitisation with metals (skin and respiratory).

In the paragraph on scientific and regulatory acceptance of existing assays it is mentioned that ECVAM and US EPA have reservations about the use of LLNA to test metals because of false negatives. It is not mentioned if this reservation has been cancelled after new data from Basketter et al 1999 has been presented (see later).

The lack of test methods for respiratory sensitisation is mentioned. In the paragraphs on elicitation thresholds and cross-sensitisation text from the EU RAR on nickel has been copied.

Summary and recommendations

The following sentence is not followed by a conclusion: ‘Caution over the use of LLNA for metals and their compounds has been expressed by several organisations in view of false negative or positive findings in the LLNA with certain metals’.

Comment

A paper from Basketter et al 1999 shows that LLNA correctly predicts 7/8 sensitising metals and 4/5 non-sensitising metals. This gives and overall predictive accuracy of 11/13 (85%). The false negative chemical is nickel. This chemical is a notorious contact sensitiser in humans. It has also proven to be difficult to show this in GPMT. The false positive che-

mical is Cu. A possible but not conclusive explanation is irritation induced by the Cu concentrations used in the LLNA. Overall LLNA does not seem to be less able to predict sensitising potential of metals than GPMT.

It is mentioned that the testing strategy should include considerations on availability of metal ions from metals and poorly soluble metal compounds.

Comment

This may be true for nickel and nickel salts, but there may not be data to make this a statement that is true for all metals and metal salts. The same comment can be made about the documents mention of elicitation thresholds.

Conclusion

The document raises the flag about the use of the LLNA in assessing sensitisation to metals, without any conclusions. The document relies heavily on the EU RARs on nickel and nickel compounds from 2004 and does not raise new or controversial views on sensitisation, or risk assessment of metals in relation to sensitisation.

Reference

Basketter et al (1999) Identification of metal allergens in the local lymph node assay. Am. J. Contact Dermatitis, 10, 207-212

Sammanfattning och slutsatser

De förslag till vägledningsdokument för metaller som HERAG-projektet har tagit fram i olika s.k. fact sheets (faktablad) är generella och skulle kunna vara tillämpliga på alla kemiska ämnen och inte bara metaller. Riskbedömning av existerande ämnen görs enligt EUs vägledningsdokument (TGD, 2003). Erfarenheterna från existerande ämnesprogrammet (regulation 793/93/EC), är att riskbedömningarna enligt TGD tillåter avvikelser om det behövs samt är motiverade och görs på ett klart sätt. Skälet till att ta fram särskilda vägledningsdokument för metaller kan därför ifrågasättas. Det finns ingen anledning att tro att särskilda aspekter på metalltoxikologi inte skulle kunna beaktas i RIP (REACH implementation projects).

I faktabladen finns inte någon klar definition av vilka ämnen som inkluderas i begreppet ”metaller”. I de flesta fall är ett ämnes kemiska form (oxidationsstadium, molekylstruktur etc.) viktig för dess upptag och toxicitet. I vissa faktablad inkluderas uppenbarligen oorganiska metallföreningar. Möjligen ingår även element som arsenik och selen. Organiska metallföreningar ingår i de flesta fall inte. Detta understryker problemen med separat vägledningsdokument för metaller.

Faktabladen presenterar inte någon lösning på hur man skulle kunna gruppera eller skapa kategorier av metaller och metallföreningar (oorganiska och organiska) för jämförande eller övergripande analyser, s.k. read across. Svårigheterna med sådana grupperingar beror f.a. på skillnader i t.ex. toxikologisk profil mellan olika oxidationsstadier (t.ex. Cr^{III} och Cr^{VI}), vattenlöslighet och fysikalisk form samt en kombination av dessa.

Urvalet av metaller som täcks i faktabladen är i de flesta fall begränsat till de få metaller (huvudsakligen koppar, zink, bly och kadmium) för vilka det finns EU-riskbedömningsrapporter eller frivilliga riskbedömningsrapporter från industrin. De exempel som ges är för få för att tillåta generella slutsatser, men de pekar inte på någon anledning att använda särskild riskbedömningsmetodik för metaller. Dessutom är dokumentet om koppar en frivillig riskbedömningsrapport som tagits fram av kopparindustrin, och bör därför inte ges samma vikt som de andra EU-riskbedömningsrapporterna som har genomgått flera oberoende expertgranskningar. För andra kända toxiska metaller, som t.ex. kvicksilver och arsenik, finns det andra gedigna riskbedömningsdokument från t.ex. WHO, som också skulle kunna användas för diskussioner och slutsatser beträffande riskbedömning av metaller.

Alltför stor vikt har lagts vid det faktum att vissa metaller är essentiella. Vi håller inte med om att detta kräver särskilt övervägande i riskbedömningen. Utvärdering av rekommenderade intag (för att möta det fysi-

ologiska behovet) hanteras av livsmedelsmyndigheter, och bör inte utvärderas på nytt i samband med toxikologisk riskbedömning. I stället är huvudfrågan vid regulatorisk riskbedömning att försäkra sig om att exponeringen är lägre än de nivåer som kan medföra en risk för toxiska effekter. Däremot håller vi med om att riskhanteringen av essentiella metaller inte bör resultera i rekommendationer som leder till ett lägre intag än vad som är fysiologiskt önskvärt.

Sammanfattningsvis så är det uppenbart att det nuvarande EU-vägledningsdokumentet (TGD 2003) medger riskbedömningar också för metaller och metallföreningar, med expertbedömningar från fall till fall och med tydlighet och klarhet vad gäller eventuella avvikelser från TGD. Det saknas därför skäl för särskilda vägledningsdokument för metaller.

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