

## COMMITTEE OF EXPERTS ON THE TRANSPORT OF DANGEROUS GOODS AND ON THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS

Sub-Committee of Experts on the Globally  
Harmonized System of Classification  
and Labelling of Chemicals

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Item 2 (c) of the provisional agenda

### UPDATING OF THE SECOND REVISED EDITION OF THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS (GHS)

#### Environmental hazards

#### OECD work related to the validation of the Transformation/Dissolution Protocol

#### Transmitted by the Organisation for Economic Co-operation and Development (OECD)

In December 2002, the Sub-Committee requested the OECD to complete the work on the validation of the Transformation/Dissolution Protocol (T/DP).

Since then, two reports have been prepared by OECD.

The first report (*Report of the Ring Test and Statistical Analysis of Performance of the Guidance on Transformation/Dissolution of Metals and Metal Compounds in Aquatic Media (Transformation/Dissolution Protocol)*) was published in April 2008 as OECD document ENV/JM/MONO(2008)8 and circulated as information document UN/SCEGHS/15/INF.3 to the fifteenth session of the Sub-Committee.

The second report, containing a short discussion on the applicability of the Transformation/Dissolution Protocol (T/DP), is reproduced hereafter. A document concerning lessons learned from the ring test for improvements and clarification for the T/DP is attached as Annex 1 to the second report; a further statistical analysis is attached as Annex 2.

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**CONSIDERATIONS REGARDING APPLICABILITY OF THE GUIDANCE ON  
TRANSFORMATION/DISSOLUTION OF METALS AND METAL COMPOUNDS IN AQUEOUS  
MEDIA (TRANSFORMATION/DISSOLUTION PROTOCOL)**

**Environment Directorate  
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT  
Paris, June 2008**



## FOREWORD

The OECD is developing criteria and guidance proposals for classification and labelling in the area of health and environmental hazards, at the request of the United Nations Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals (UNSCEGHS). The *Guidance on Transformation/Dissolution of Metals and Metal Compounds in Aquatic Media* (Transformation/Dissolution Protocol: abbreviated to T/DP) was published in July 2001 in the OECD Series on Testing and Assessment (OECD, 2001) and as Annex 10 to the United Nations' Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (United Nations, first edition, 2003; first revised edition, 2005; second revised edition, 2007).

In January 2002, the OECD Task Force on Harmonisation of Classification and Labelling (HCL) discussed the approaches for the validation, and agreed to establish the Validation Management Group on the Transformation/Dissolution Protocol (VMG). In December 2002, the UNSCEGHS requested the OECD to complete work on the validation of the Transformation/Dissolution Protocol. The experimental work (the ring test) was conducted by four laboratories nominated by members of the Task Force on HCL: CANMET (lead laboratory), CIMM, ECVAM and LISEC NV. Following the ring test, the VMG developed the first report titled the *Report of the Ring Test and Statistical Analysis of Performance of the Guidance on Transformation/Dissolution of Metals and Metal Compounds in Aquatic Media (Transformation/Dissolution Protocol)* concerning the outcome of the results of the ring test and statistical analysis of performance of the T/DP under the supervision of the Task Force on HCL. The first report was published in April 2008 (OECD, 2008).

This document is a short discussion on the applicability of the T/DP. A document concerning lessons learned from the ring test for improvements and clarification for The T/DP is attached as Annex 1 to this document. A further statistical analysis which was conducted by the Nordic Council of Ministers and reviewed by the VMG is attached as Annex 2.

This document was developed by the VMG and reviewed by the Task Force on HCL. The VMG met in October 2007 and April 2008, and agreed to the final draft at the latter meeting. The final draft was provisionally approved with slight changes by the Task Force on HCL at its meeting in April 2008, and the approval was confirmed by the Task Force in May 2008 by a written procedure.

This document is published on the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology of the OECD.

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## DISCUSSION

1. The aim of this report is to present further considerations on the applicability of the *Guidance on Transformation/Dissolution of Metals and Metal Compounds in Aquatic Media* (Transformation/Dissolution Protocol: abbreviated to T/DP)<sup>1</sup> to the generation of data for the aquatic hazard classification of metal-bearing substances. The report is based on experience gained with the ring test exercise.
2. Within boundaries of the ring test, statistical analysis provides a robust outcome in terms of relating mass loading to dissolution. Those boundaries are however relatively specific, as discussed in the *Report of the Ring Test and Statistical Analysis of Performance of the Guidance on Transformation/Dissolution of Metals and Metal Compounds in Aqueous Media (Transformation/Dissolution Protocol)* (OECD, 2008). Although the number of metal-bearing substances examined in the ring test was limited, there was a wide distribution of concentrations. Furthermore, it is expected that the variability of such a physical process is much lower than the variability of biological systems.
3. The T/DP is guidance and therefore the extent of the applicability is not expected to be the same as for a Test Guideline.
4. It is recognized that the ring test has some limitations. For instance, the ring test covers fresh water but not marine conditions, and pH 6 and 8 rather than the range 5.5-8.5 specified in the guidance.
5. The ring test did not provide for comparisons of T/DP performance for different specific surface areas (m<sup>2</sup>/g) of a single metal. The relationship of metal concentration to surface area loading in such experiments is important for assessing the validity of the T/DP for classification purposes. However, such data are becoming available (Skeaff *et al.*, 2008).
6. Based on the variability of measured concentrations derived from the ring test, the report of the Nordic Council of Ministers ([Annex 2](#)) provided an approach for modeling false-decision rates in classification. These rates could be important (i) when the limit of detection is close to the Ecotoxicity Reference Values (ERVs) or (ii) when a sublinear relation between mass loading and concentration is observed. In these cases, decisions based on the T/DP could be less certain. These uncertainties should be considered when appropriate. However, uncertainties related to ERVs used for classification might be more relevant.
7. It is important to note that there were no classifications of poorly soluble metals and metal compounds before the T/DP became available. The only possibility was to classify the ions. Therefore, there is no reference classification to compare with classifications derived from the T/DP data. The T/DP conditions do not reflect the real environment. The aim is to classify metals; the T/DP was not designed for risk assessment.
8. Within the limitations of the ring test, intra- and inter- laboratory variability was acceptable. However, because of the limited scope of the ring test, classification of sparingly soluble metals and metal compounds must involve the use of judgement for interpretation of T/DP outcomes. All evidence must be weighed in a classification decision. This would be especially true for metals or metal compounds showing borderline results in the T/DP.

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<sup>1</sup> The T/DP was published in July 2001 in the OECD Series on Testing and Assessment (OECD, 2001) and as Annex 10 to the United Nations' Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (United Nations, first edition, 2003; first revised edition, 2005; second revised edition, 2007)

9. Based on the experience of the laboratories that have performed the T/DP on a number of metal bearing substances, a number of improvements and clarifications for the T/DP are recommended (see [Annex 1](#)).

10. A brief survey by industry shows that at least 31 metal and metal compounds have been tested with the OECD T/DP. The results demonstrate the discriminatory power for GHS aquatic hazard classification.

#### **ADDITIONAL ISSUES**

11. Further considerations should be given to;

- Issues on marine conditions
- Methodology for achieving the full range of pH as specified in the GHS strategy for metals (5.5-8.5)
- Does the Protocol reflect difference in dissolution rate /kinetics for individual metals of different specific surface areas?
- Behaviour of alloys (Skeaff *et al.*, 2008)

12. The GHS strategy has been used with the T/DP for some metals and metal compounds to date. However, in addressing the relevance of metals hazard classification using the T/DP, the extended VMG acknowledges how difficult it is to obtain a reference database of classified metals and metal compounds and verify its correlation to the real world. The metals classified present a greater variety of cases than those already evaluated in the ring test. These classifications could be further evaluated in light of the Nordic Council of Ministers' report *Environmental Hazard Classification of Metals and Metal Compounds - A Probabilistic Assessment of Classification Power for Data Generated by the T/D Protocol* ([Annex 2](#)). Classification probabilities can be calculated for these chemicals in the same way as for the chemicals in the ring test as provided in the Nordic Council of Ministers' Report, to evaluate the behavior of the system. If feasible, sets of metals with similar specific surface areas could be drawn from this list and evaluated to verify that the classification strategy using the result generated by the T/DP gives results consistent with anticipated hazard. If data are available for an individual metal-bearing substance with several different specific surface areas, the relationship of dissolution rate to surface area loading can be determined for internal consistency. Further evidence should be helpful to achieve this purpose.

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- United Nations (2003; first revised edition, 2005; second revised edition: 2007), *Globally Harmonized System of Classification and Labelling of Chemicals (GHS)*. United Nations, New York and Geneva.  
[http://www.unece.org/trans/danger/publi/ghs/ghs\\_welcome\\_e.html](http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html) [last accessed 14 April 2008]



## ANNEX 1: LESSONS LEARNED FROM THE RING TEST FOR IMPROVEMENTS AND CLARIFICATIONS TO THE T/DP

The Extended Validation Management Group (VMG) on the T/DP agreed to recommendations for amendments to the T/DP as follows:

- Temperature: reduce range of temperature  $\pm 1.5^{\circ}\text{C}$  in the range  $20^{\circ}\text{-}23^{\circ}\text{C}$ , replacing  $\pm 2^{\circ}\text{C}$  in the range of  $20^{\circ}\text{-}25^{\circ}\text{C}$
- T/DP: A 10.5.1.1 (k): the following sentence should be revised as follows:
  - analytical equipment for metal analysis [of] acceptable accuracy, preferably with a limit of quantification (LOQ) five times lower than the lowest chronic ecotoxicity reference value (ERV).
- T/DP: A 10.5.2.3.5 should be revised for laboratories as follows:
  - Use of training set for new laboratories;
  - One metal for standard control;
  - One or two laboratories should be responsible for reference chemicals. If necessary specific surface areas to be checked.
- Table A 10.1 could be revised based upon a proposal from Canada (CANMET);
  - Keep pH 6 and 7 tables as it is;
  - Add pH 8 and 8.5 columns to the table;
  - Add footnote “This does not prevent attaining pH 5.5, and composition for pH 8.5 has not been verified experimentally in presence of metal”.

Proposed revisions:

**Table A10.1: Recommended chemical composition of testing medium**

Chemical composition of medium	NaHCO <sub>3</sub>	6.5 mg/l	12.6 mg/l	<u>64.75 mg/l</u>	<u>194.25 mg/l</u>
	KCl	0.58 mg/l	2.32 mg/l	<u>5.75 mg/l</u>	<u>5.74 mg/l</u>
	CaCl <sub>2</sub> .2H <sub>2</sub> O	29.4 mg/l	117.6 mg/l	<u>294 mg/l</u>	<u>29.4 mg/l</u>
	MgSO <sub>4</sub> .7H <sub>2</sub> O	12.3 mg/l	49.2 mg/l	<u>123.25 mg/l</u>	<u>123.25 mg/l</u>
CO <sub>2</sub> concentration (balance is air) in test vessel	0.50%	0.10%	<u>0.038% (air)</u>	<u>0.038% (air)</u>	
Calculated pH	6.09	7.07	<u>7.98</u>	<u>8.5</u>	

***NOTE 1:** The pH values were calculated using the FACT (Facility for the Analysis of Chemical Thermodynamics) System (<http://www.crct.polymtl.ca/fact/fact.htm>).*

***NOTE 2:** This does not prevent attaining pH 5.5, and composition for pH 8.5 has not been verified experimentally in presence of metal.*

- A10.5.1.1: Add “Flush Acrodisc filter at least 3 times with fresh medium to avoid elevated trace metals in sample at time = 0 ”
- A10.5.2.3.3: Revise as follows: “...the solution is acidified with 1-2 drops of trace metal grade HNO<sub>3</sub> with the target pH -1 and analysed...”
- A10.5.4.3: Revise as follows: “... maintain the dissolved oxygen concentration above about 6.0 mg/L, which is 70% of the saturation level of 8.5 mg/L.”
- A10.5.1.7 & 10.5.1.8: Revise as follows:
  - methods for pH adjustment and buffering in Table A10.1;
  - no pH adjustment during the test using an acid or alkaline.



ANNEX 2



# Environmental Hazard Classification of Metals and Metal Compounds

– A Probabilistic Assessment of Classification  
Power for Data Generated by the T/D Protocol



# Environmental Hazard Classification of Metals and Metal Compounds

– A Probabilistic Assessment of Classification  
Power for Data Generated by the T/D Protocol

Reinhard Meister & Jonas Falck

## TemaNord 2008:518

### **Environmental Hazard Classification of Metals and Metal Compounds – A Probabilistic Assessment of Data Generated by the T/D Protocol**

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#### **Nordic Environmental Co-operation**

The Nordic Environmental Action Plan 2005-2008 forms the framework for the Nordic countries' environmental co-operation both within the Nordic region and in relation to the adjacent areas, the Arctic, the EU and other international forums. The programme aims for results that will consolidate the position of the Nordic region as the leader in the environmental field. One of the overall goals is to create a healthier living environment for the Nordic people.

#### **Nordic co-operation**

Nordic co-operation, one of the oldest and most wide-ranging regional partnerships in the world, involves Denmark, Finland, Iceland, Norway, Sweden, the Faroe Islands, Greenland and Åland. Co-operation reinforces the sense of Nordic community while respecting national differences and similarities, makes it possible to uphold Nordic interests in the world at large and promotes positive relations between neighbouring peoples.

Co-operation was formalised in 1952 when *the Nordic Council* was set up as a forum for parliamentarians and governments. The Helsinki Treaty of 1962 has formed the framework for Nordic partnership ever since. The *Nordic Council of Ministers* was set up in 1971 as the formal forum for co-operation between the governments of the Nordic countries and the political leadership of the autonomous areas, i.e. the Faroe Islands, Greenland and Åland.

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Svensk sammanfattning (Summary in Swedish) <b>[NB]</b> . Deleted from this OECD report.]	





## Preface

For the purpose of determining the rate and extent to which metals and sparingly soluble metal compounds can produce soluble available ionic and other metal-bearing species in aqueous media under a set of standard laboratory conditions representative of those generally occurring in the environment, a Test Guidance was designed (see A10 of /1/). The generation of Transformation/Dissolution (T/D) data according to this Test Guidance, which is referred to as the T/D protocol, is an integrated part of the recommended strategy to assess metals and metal compounds and transformation data can generally only be considered as reliable for the purposes of classification if conducted according to this Test Guidance (see A9.7.1.3 of /1/).

The present publication consists of *a probabilistic assessment of classification power for data generated by the T/D Protocol*, following the guidance on aquatic hazard classification of metals and metal compounds given in Chapter 7 of Annex 9 to /1/.

The assessment was conducted by Dr. Reinhard Meister, TFH Berlin – University of Applied Sciences, [meister@tfh-berlin](mailto:meister@tfh-berlin).

The publication is written by Reinhard Meister and Jonas Falck, Swedish Chemicals Agency, [jonas.falck@kemi.se](mailto:jonas.falck@kemi.se) and produced by The Nordic Council of Ministers.

The Nordic project group on Classification and Labelling is responsible for this report and the probabilistic assessment presented, apart from being issued by the Nordic Council of Ministers (NCM), is by permission from NCM also intended for publication by the OECD concerning the validation of the transformation/dissolution (T/D) protocol.

## Reports on "Environmental Hazard Classification and Labelling" issued by the Nordic Council of Ministers

The Nordic project on "Environmental Hazard Classification and Labelling" was launched in the spring of 1990. Until now, the results of the work have been presented in 15 reports issued by the Nordic Council of Ministers (see next page).

1. "Miljöfarliga kemiska ämnen och produkter- System för klassificering, märkning och varuinformationsblad", (Nord 1990:087), pp. 62. (Publication 2 but in Swedish)
2. "Substances and Preparations Dangerous for the Environment- A System for Classification, Labelling and Safety Data Sheet", (Nord 1990:087E), pp. 65.
3. "Environmental Hazard Classification - data collection and interpretation guide", (TemaNord 1994:589, 2nd edition 1995:581), pp. 167.
4. "Environmental Hazard Classification - classification of selected substances as dangerous for the environment (I)", (TemaNord 1994:643), pp 101.
5. "Environmental Hazard Classification criteria for chemical substances: Terrestrial environment – Fate in the soil and soil compartment effects", (unpublished, 1997), pp 192.
6. "Hazard classification of metals and metal compounds – Effect of pH on dissolution of priority substances", COWI Report: 29855-02, (unpublished, June 1997), pp 22.
7. "Modelling of metal speciation in Hazard Classification", COWI Report: 03, (unpublished, September 1997).
8. "Environmental Hazard Classification - classification of selected substances as dangerous for the environment (II)", (TemaNord 1997:549), pp 137.
9. "Environmental Hazard Classification – The N-CLASS Database", CD-ROM version, (TemaNord 1999:538), pp 44 and CD-ROM.
10. "Transformation/Dissolution of Specified Inorganic Metal Substances", VKI Project: 12434, (unpublished, December 1999), pp 22.

11. "Transformation/Dissolution Screenings Test of Inorganic Metal Compounds", DHI project: 50602.01, (unpublished, February 2000).
12. "The N-CLASS Database", Internet version release (2001).
13. "The N-CLASS Database", Folder on content and reliece of the New Internet 5.0 version (2004).
14. "Identifying relevant parameters that can be used for monitoring trends in the use of environmentally hazardous substances", (In Danish) (unpublished, 2004), pp 87.
15. "Environmental Hazard Classification of Metals and Metal Compounds - A Probabilistic Assessment of Classification Power for Data Generated by the T/D Protocol", (TemaNord 2008:518, present report).



## Executive Summary

This report serves as a guide for understanding the performance and reliability of a classification rule, when applied to data generated by Annex 10 to /1/ (the transformation/dissolution (T/D) protocol).

The classification of sparingly soluble metal compounds is based on ecotoxicity reference values (ERV) and on the measured concentrations of metal ions of experiments performed according to the T/D protocol and the operating procedure (OP, Annex 1 to /2/).

Experimental values have inevitably a component of random noise and classification of sparingly soluble metal compounds into category I – III cannot be made error free. Results of a statistical analysis in /2/ of the validation ring test of the T/D protocol allow, however, to derive a framework for assessing error rates and an approach tackling this rate is presented.

The summary of /2/ establishes constant variability on log scale (with respect to expected level of measurement) within and between laboratories can be assumed. In addition, a log-normal distribution of measured concentrations appears as a reasonable model for the data. Based on these findings, false negative and false positive decision rates can be calculated for hypothetical settings, if the ecotoxicity reference value as well as the T/D-characteristics (e.g. median concentrations for different loadings) are specified. Hence, the probability of classifying a substance into a given category can be predicted.

A 95% uncertainty-factor for classification can be calculated and the classification scenario can be studied, using a schematic plot of classification probabilities, assumed median concentrations and ERV. Thereby, based on the results from three laboratories, it can for concentrations measured at pH 6, be concluded that if the ratio (or its inverse) of the median concentration of a substance to the ERV is greater than 2, the false decision rate is below 2%.

As long as the T/D measurements show no extreme sublinear dependence on loading, misclassification is limited to a one-category difference. On the basis of the experimental findings, Cu<sub>2</sub>O, Co<sub>3</sub>O<sub>4</sub>, and Ni metal powder preparations from the validation ring test can be classified consistently for the three laboratories, providing examples of classification into categories I – III.



# 1. Background

## 1.1 Classification of metals and sparingly soluble metal compounds

The recommended strategy to derive an environmental hazard classification can be found in Annex 9, section A9.7, GHS, p. 483 of /1/. Most of the text under 1.1 and 1.2 in this publication is taken from Annex 9, section A9.7 of /1/.

The harmonized system for classifying chemical substances is a hazard based system, and the basis of the identification of hazard is the aquatic toxicity of the substances, and information on the degradation and bioaccumulation behaviour. The recommended strategy to classify aquatic hazardous metals and metal compounds deals only with the hazards associated with a given substance when the substance is dissolved in the water column. Exposure from this source is limited by the solubility of the substance in water and bioavailability of the substance in species in the aquatic environment. Thus, the hazard classification schemes for metals and metal compounds are limited to the hazards posed by metals and metal compounds when they are available (i.e. exist as dissolved metal ions, for example, as  $M^+$  when present as  $M-NO_3$ ), and do not take into account exposures to metals and metal compounds that are not dissolved in the water column but may still be bioavailable, such as metals in foods (see A9.7.1.1 of /1/).

The industry associations responsible for the supply of these materials have taken a positive attitude in seeking to assess the toxicity of their products. It has been agreed that, rather than conduct further aquatic toxicity testing, the key issue is to determine the extent to which bioavailable forms can be produced during standard conditions, the rate at which these forms are generated, and whether this rate and extent of formation should lead to classification.

The level of the metal ion which may be present in solution following the addition of the metal and/or its compounds, will largely be determined by two processes: the extent to which it can be dissolved, i.e. its water solubility, and the extent to which it can react with the media to transform to water soluble forms. The rate and extent at which this latter process, known as “transformation” for the purposes of the classification guidance, takes place can vary extensively between different compounds and the metal itself, and is an important factor in determining the appropriate hazard category (see A9.7.1.2 of /1/).



## 1.2 Intrinsic T/D properties and classification rule

Generally speaking, the rate at which a substance dissolves is not considered relevant to the determination of its intrinsic toxicity. For metals and many poorly soluble inorganic metal compounds, however, the difficulties in achieving dissolution through normal solubilization techniques is so severe that the two processes of solubilization and transformation become indistinguishable. Thus, where the short-term aquatic toxicity for the metal ions of concern (expressed as  $L(E)C_{50}$ ) is less than or equal to 100 mg/l and the compound is sufficiently poorly soluble that the levels dissolved following normal attempts at solubilization do not exceed the available  $L(E)C_{50}$ , consideration must be given to the data available on the rate and extent to which these ions can be generated from the metal or metal compound (see A9.7.1.3 of /1/).

For the purpose of determining the rate and extent to which metals and sparingly soluble metal compounds can produce soluble available ionic and other metal-bearing species in aqueous media under a set of standard laboratory conditions representative of those generally occurring in the environment, a Test Guidance was designed (see A10 of /1/). The generation of Transformation/Dissolution (T/D) data according to this Test Guidance, which is referred to as the T/D protocol, is an integrated part of the recommended strategy to assess metals and metal compounds and transformation data can generally only be considered as reliable for the purposes of classification if conducted according to this Test Guidance (see A9.7.1.3 of /1/).

Where such data are unavailable, i.e. there is no clear data of sufficient validity to show that the transformation to metal ions will not occur, the safety net classification (Chronic Category 4) should be applied since the known classifiable toxicity of these soluble forms is considered to produce sufficient concern (see A9.7.5.2.3 of /1/).

However, where data have been generated using the T/D protocol, the evaluation of the aquatic hazard of metals and sparingly soluble metal compounds is to be accomplished by comparison of (a) the concentration of the metal ion in solution with (b) appropriate standard ecotoxicity data as determined with the soluble metal salt, known as the ecotoxicity reference values (ERV). If the ERV is exceeded, irrespective of whether the toxicity and dissolution data are at the same pH and if this is the only data available then the substance should be classified. If other solubility data are available to show that the dissolution concentration would not exceed the  $L(E)C_{50}$  across the entire pH range then the substance should not be classified on its soluble form (see A9.7.2.3 of /1/).

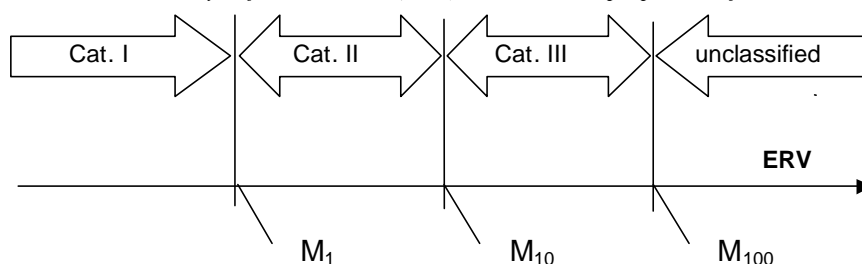
The aquatic hazard classification of metals and sparingly soluble metal compounds are based on the dissolved metal ion concentrations obtained after a seven day T/D period. Normally massive forms and/or powders are introduced into the aqueous medium at three different

loadings: 1, 10 and 100 mg/l. The loading that delivers a dissolved metal concentration that equals or exceeds the ERV, defines the classification level (see A10.2.3.1 of /1/).

If the 100 mg/L loading does not deliver a dissolved metal concentration exceeding the ERV, then the metal does not receive any of the core set of aquatic hazard classification categories (Category 1-3). For the purpose of this paper they will be called unclassified. They may, however, still be subject for a safety net classification (Chronic Category 4).

Basically, the classification considers the loading necessary to reach a limit where aquatic toxicity is expected. Thus the classification depends on both: the intrinsic toxicity of the metal-ions and the metal and/or its compounds ability to deliver certain concentrations of metal-ions in the aquatic medium. Figure 1 provides a condensed overview of this concept.

*Figure 1: Intrinsic T/D properties and classification rule. The classification depends on the actual ecotoxicity reference value (ERV) and the T/D properties of a substance*



*determined for different loadings (1, 10, 100 mg/L). The true median metal ion concentrations resulting from loadings of 1, 10, 100 mg/L are denoted by  $M_1$ ,  $M_{10}$ ,  $M_{100}$ .*

**Example:** Assume that a compound has true median concentrations ( $M_1$ ,  $M_{10}$ ,  $M_{100}$ ) of 7, 50, and 400  $\mu\text{g/L}$  corresponding to loadings of 1, 10, and 100 mg/L in a 7 day testing period. An ERV of 25  $\mu\text{g/L}$  should result in a classification into Category II while an ERV > 400  $\mu\text{g/L}$  should leave the sparingly soluble compound unclassified.

However, classification cannot be based on true median concentrations; experimentally derived values have to be used instead. All measurements come with an error causing unavoidable classification error, which is analysed in the following section.

### 1.3 Validation of the Transformation/Dissolution protocol

The T/D protocol was first published in 2001 as an OECD Test Guidance document (3) before it was incorporated into GHS as Annex 10 to (1).

As explained in the foreword of (3) the T/D protocol was considered provisional and subject to changes depending on the outcome of a validation work.

In January 2002, the OECD Task Force on Harmonisation of Classification and Labelling (HCL) discussed the approaches for the validation of the T/D protocol, and agreed to establish the Validation Management Group on the Transformation/Dissolution protocol (VMG) (see (4)). In December 2002, December 2004 and December 2006, the UN sub-Committee of Experts on GHS requested the OECD to complete work on the validation (see (5), (6) and (7)).

It had originally been agreed that the validation should not cover the metal strategy as described in Chapter 7 of Annex 9 to (1), but that the validation could cover both reliability (Phase 1) and relevance for classification purposes (Phase 2) of the T/D protocol, Annex 10 of (1) (see (4) and (6)).

It was later clarified that the Phase 2 validation on relevance could possibly also cover discussions on the utility and applicability of the classification strategy (see Forward to (2)).

A central part of the Phase 1 validation was a ring test on transformation/dissolution, performed in 2005 with three metal substances (Cu<sub>2</sub>O, Co<sub>3</sub>O<sub>4</sub>, and Ni powders) and one INVAR alloy to determine its potential to provide consistent results between laboratories.

Four laboratories participated in the ring test. Two of these laboratories had been involved in the development of the Test Guidance and had much experience prior to the ring test with performing tests using the T/D protocol. The same two laboratories had co-operated in writing the Operating Procedure (OP) for the ring test (Annex 1 to (2)). Two other laboratories participated with less or no experience of the protocol.

For one of the latter laboratories, the measured metal ion concentrations, as a result of the test performed, were in line with the first two laboratories. The fourth laboratory showed, however, obvious discrepancies.

These discrepancies were not limited to a single or few measurement. Nor were they limited to the measurement of a single metal or metal loading. For example, while the fourth laboratory measured near-zero copper concentrations, the other three laboratories identified significant levels of dissolution with an average dissolved concentration of 131 and 391 µg/l for the 7 day and 28 day test, respectively (target pH 6 and

loading of 1 mg Cu<sub>2</sub>O/l). Similar pattern was shown for target pH 8 (see Paragraph 50 and Figure 1.2a of /2/).

**Note:** Already back in 2001, the European Copper Institute (ECI) reported T/D test data on Cu<sub>2</sub>O following the T/D protocol. The report revealed for the target pH of 6 and a loading of 1 mg/l a measured copper concentration of 236 µg/l after 7 days (see /8/). Hence, the ECI results are very much in line with the results reported from three of the four laboratories in the validation ring test.

For the loadings of 10 and 100 mg Cu<sub>2</sub>O/L and target pH of 6 and 8, the laboratory that had shown obvious discrepancies reported significantly greater copper concentrations than the other three laboratories. And while the other three reported a significant difference in copper concentrations between the tests performed under the two target pHs the fourth laboratory could not show this clear difference (see Figure 1.2 a and 1.2.b of /2/).

**Note:** A linear regression of dissolved copper concentration, between pH 6 and 8 was studied and reported by the European Copper Institute in 2001, with thermodynamic calculation as supportive evidence (see /8/).

It is important to realise that just because the results from one laboratory in the ring test of a new protocol reported discrepancies in their measurements most assuredly does not mean that this laboratory will represent 1 in any 4 laboratories worldwide that may in the future conduct T/D testing. All this discrepancy means that procedures at one of the four participating laboratories alone were at some point faulty, somewhere.

Even if there are no obvious reasons at this time as to why there should be such considerable discrepancies between one laboratory and the other three laboratories, and a thorough investigation was not done to investigate this further, avoiding results like those of laboratory 4 is considered not to be a statistical issue. Therefore, laboratory 4 was excluded from the statistical analysis in /2/, as well as in this report.

From a statistical point of view, variability for the measured concentrations of the components of the alloy tested could not be assessed with sufficient precision. The alloy is not included in the probabilistic assessment in this report.



## 2. Classification and measurement error

In reality, classification is based on the experimentally determined dissolved concentrations  $C$ . In this section, the probability of a classification given a specific ERV and the T/D properties of a substance will be derived. As a first step, false-positive and false negative decision rates will be defined and a rule for their computation will be derived.

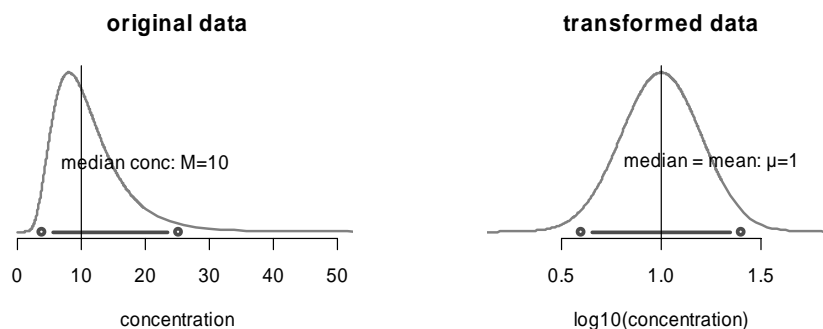
For the introduction of the concept, only one measurement and one loading is considered. More complicated cases, considering measurements for several loadings simultaneously are discussed later.

For understanding the formulae used in computation, the following note should be useful.

### 2.1 A note on logarithms and notation

It had been expected, and the data analysis of the ring test study results showed, that a logarithmic transformation of the concentration measurements is very convenient (*cf. /2/*). In particular, the Normal-distribution appears as acceptable model for characterizing the distribution of the log-transformed concentrations. Therefore, this report uses log<sub>10</sub>-transformed data for computations, and back-transformed values for presentations and graphs. When used for graphs, concentrations are displayed on logarithmically scaled axes.

Figure 2 displays some of the facts, helpful for understanding the transformation.



**Figure 2:** Distribution of concentration measurements, displayed on original and on logarithmic scale including prediction intervals (o--o), where a randomly sampled value will be observed with 95% probability.

The log10-transformation is monotonic, therefore percentiles are preserved. In particular, the median of the log-transformed concentrations equals the log-transform of the median of the original distribution. An example is given in Figure 2.

For understanding the behaviour of the classification procedure, it is important to know what to expect from a new concentration measurement of a given compound by a randomly chosen laboratory. Standard normal distribution theory gives the 95% prediction intervals for new measurements.

Assuming a normal distribution for the log-concentrations with expectation  $\mu$  and variance  $\sigma^2$ , a  $1-\alpha$  prediction interval is given by  $\mu \pm z_{1-\alpha/2} \times \sigma$ . For the example data in Figure 2 values approximately equal to  $1 \pm 2 \times 0.2 = (0.6, 1.4)$  are obtained when  $\alpha = 5\%$ . The anti-log transformation gives the interval  $10^{(\mu \pm z_{1-\alpha/2} \times \sigma)}$  approximately equal to  $(4, 25)$ . Using  $M = 10^1 = 10$  and  $f = 10^{2 \times 0.2} \approx 2.5$  it is obvious, that the boundaries of the interval are given by  $(M / f, M \times f)$ . One-sided limits (that is,  $(-\infty, M \times f)$  or  $(M / f, \infty)$ ) could be computed similarly, just replacing  $z_{1-\alpha/2}$  by  $z_{1-\alpha}$ .

Notations:

variable	original scale	log10 scale
concentration	$C$	$c$ or $\log_{10}(C)$
true median	$M$	$\mu$
stand.deviation		$\sigma$
ecotox.ref.val.	$ERV$	$erv$

## 2.2 Classification based on one measurement resulting from one loading

The classification rule is very simple given a specific ERV:

**Rule:** classify the substance if  $ERV < C$

There are four possible situations that have to be considered. These are explained in the table 1.

**Table 1: There are four possible situations when comparing the measured concentration (C) based on one measurement from one loading with the ecotoxicity reference value (ERV). M denotes the true median metal ion concentration.**

		<b>Not classified</b> <i>ERV &gt; C</i>	<b>Classified</b> <i>ERV &lt; C</i>
<b>True unclassified</b>	<i>ERV &gt; M</i>	correct	false positive
<b>True Cat. 1</b>	<i>ERV &lt; M</i>	false negative	correct

The probability for a classification decision can easily be calculated, after making some assumptions about the true intrinsic properties of a substance.

**Assumption:**  $\log_{10}(C) \sim N(\mu, \sigma^2)$  normally distributed  $\log_{10}$  transformed concentration measurements.

This assumption covers both aspects of the experimental determination of a concentration: the median value  $\mu$  and the standard deviation  $\sigma$  quantified on  $\log_{10}$  scale.

Given these intrinsic characteristics of the metal ion concentration observed after the T/D process at a certain loading, the probability of being classified is a function depending solely on the actual value of the ecotoxicity reference limit.

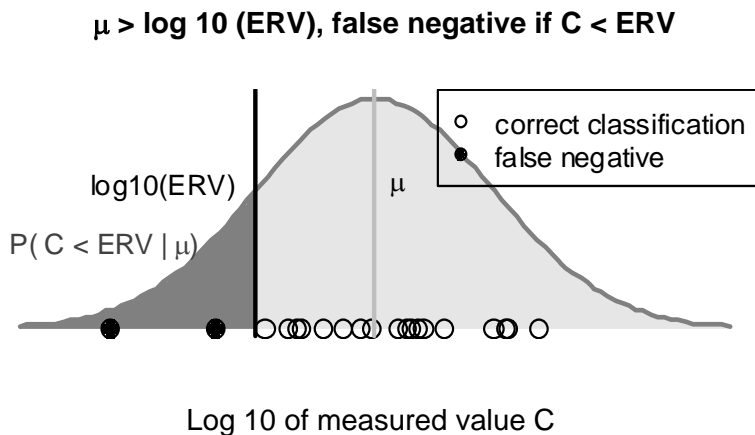
**Probability of classification:**

$$\begin{aligned}
 P(ERV < C) &= 1 - P(C \leq ERV) \\
 &= 1 - \Phi(\{erv - \mu\} / \sigma) \\
 &= \Phi(-\{erv - \mu\} / \sigma)
 \end{aligned}$$

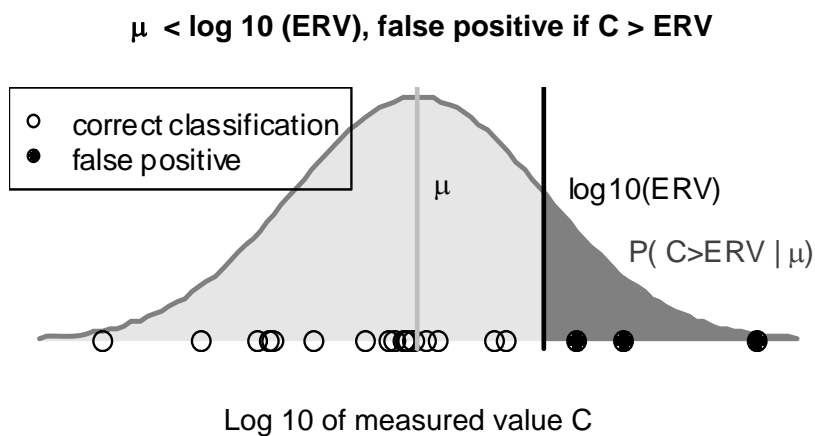
Here,  $\Phi$  denotes the cumulative distribution function of the standard normal distribution.

The calculation of expected classification rates is now straightforward, just by inserting numerical values into the equation given above. Figures 3 and 4 illustrate the cases of false negative and false positive classification.





**Figure 3:** Application of classification rule to measured concentrations. Probability of **false negative classification:** not classified, true mean above ERV. For illustration purpose simulated measurements, displayed as filled and empty circles, are added.



**Figure 4:** Application of classification rule to measured concentrations. Probability of **false positive classification:** classified, true mean below ERV. For illustration purpose simulated measurements, displayed as filled and empty circles, are added.

The concept described above will be used in the next part, considering the real procedure with three plus one categories.

### 3. Probabilities of Classification into Category I - III

In this part, probabilities for correct and for false classifications are derived. Obviously, these probabilities depend on the following variables:

- the ecotoxicity reference value
- the true median concentrations at the different loadings
- the variability of the measured concentrations

From the report on the “Statistical Reanalysis of the T/D Validation Study” (Meister 2006) two conclusions can be drawn:

- the T/D measurements are appropriately described by a lognormal probability distribution
- the variability within and between laboratories can be regarded as constant on log scale

For an evaluation of the performance of the classification scheme the probabilities needed can be calculated, under the assumptions mentioned above. Given the intrinsic log-median concentrations of a substance ( $\mu_1, \mu_{10}, \mu_{100}$ ) and the common standard deviation  $\sigma$ , the desired probabilities are derived under the assumption of independent measurements at different loadings. Again  $\Phi$  denotes the cumulative distribution function of the standard normal distribution.

**Table 2: Formulae for computing probabilities of classification into different categories**

<b>Classification</b>	<b>Event</b>	<b>Probability</b>
<b>Category I</b>	$C_{1mg} > ERV$	$1 - \Phi(\{erv - \mu_{1mg}\} / \sigma)$
<b>Category II</b>	$C_{1mg} < ERV \leq C_{10mg}$	$\Phi(\{erv - \mu_{1mg}\} / \sigma) \times [1 - \Phi(\{erv - \mu_{10mg}\} / \sigma)]$
<b>Category III</b>	$C_{1mg} < ERV \cap C_{10mg} < ERV \cap C_{100mg} > ERV$	$\Phi(\{erv - \mu_{1mg}\} / \sigma) \times \Phi(\{erv - \mu_{10mg}\} / \sigma) \times [1 - \Phi(\{erv - \mu_{100mg}\} / \sigma)]$
<b>unclassified</b>	$\neg(Cat.I \cup Cat.II \cup Cat.III)$	$1 - [P(Cat.I) + P(Cat.II) + P(Cat.III)]$

The derivation of the formulae given above is straightforward and on a basic level of probability calculus. Within the range of settings considered in this paper, the assumption of independent measurements is not critical and could be replaced by appropriate assumptions for intra-laboratory correlations, without making any substantial change to the classification probabilities derived. This has been demonstrated by some numerical integration.

### 3.1 Classification: hypothetical examples

A schematic plot of classification probabilities will be presented, illustrating the properties of the classification procedure. To this end information about the essential parameters is needed:

- assumed true median concentrations corresponding to different loadings
- assumed standard deviation of log10 transformed concentration measurements

#### *True median concentrations*

The assumed median concentrations differ from substance to substance. In addition, different behaviour of the T/D process results in different ratios of the medians corresponding to the loadings. For example 1:10:100 has linear behaviour, but 1:5:15 has extremely sublinear behaviour (observed if the T/D process shows an apparent plateau).

#### *Standard deviation*

The standard-deviation is taken as constant on the log scale. This assumption is fully supported for the substances tested in the validation study.

For further calculations a standard deviation of 0.14 on log10 scale is assumed. This value corresponds to the sum of variances within and between laboratories ( $\sigma = \sqrt{\sigma_{within}^2 + \sigma_{between}^2}$ ) derived in the validation ring test. A measurement taken in a randomly selected laboratory will have exactly this standard deviation under the assumptions made in the evaluation of the ring test.

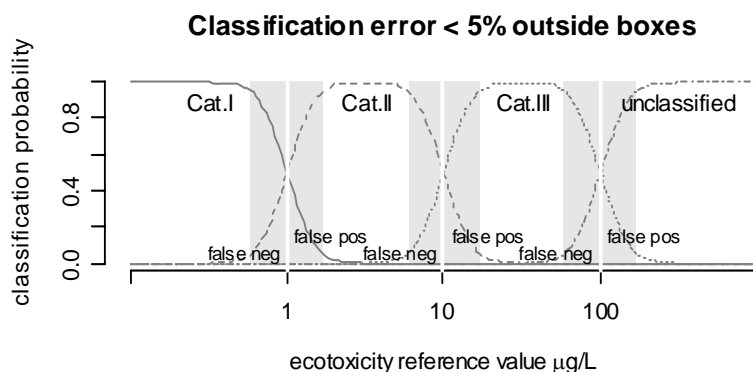
#### *Schematic plot*

The schematic plot (figure 5) displays the probabilities of classification into different categories.

Once the intrinsic properties of a metal are specified, this probability depends only on the magnitude of the ecotoxicity reference value (ERV). Therefore, the horizontal axis displays all potential values of ERV. Ticks and divided grey boxes indicate the assumed true median concentrations as well as regions of uncertainty in classification. The lower half of the boxes controls the false negative classification rate; the upper half controls the false positive rate. The horizontal axis displays original values using a logarithmic scaling.

The construction of the boxes follows the ideas presented in 2.1. One-sided limits ( $\alpha = 5\%$ ) are used with  $\sigma = 0.14$  as specified above. The width of the boxes  $w = z_{0.95} \times \sigma = 1.65 \times 0.14 = 0.23$  guarantees that the risk of a false classification is below 5% outside the boxes. Consider, for example, a situation where ERV is below the true median  $M_1$  for the 1 mg/L loading corresponding to a true Category I substance. The corresponding values on log10-scale will be denoted by  $erv$  and  $\mu_1$ . It could happen though, that a measured concentration  $C_1$  below the ERV is observed. This observation would result in a false negative classification into Category II. The dashed curve in figure 4 displays the probability of a Category II classification. The false negative rate  $P\{\log_{10}(C_1) < erv\}$  is smaller than 5% if  $erv < \mu_1 - w$  holds true. This condition can also be expressed for the original data. The false negative rate is below 5% if  $ERV < M_1 / (10^w)$ . With the values assumed the factor is  $10^w = 1.7$ .

**Note:** The calculation of classification probabilities is possible only if the true median concentrations are known. There is no way to estimate misclassification rates from single observed concentrations. However, if the ratio of a measured metal ion concentration to the ERV is larger than the factor given above (or smaller than its inverse), a misclassification appears unlikely.



**Figure 5:** Schematic plot: Probabilities of classification for an artificial substance. The true median concentrations corresponding to loadings of 1, 10, and 100 mg/L are assumed as 1, 10 and 100  $\mu\text{g/L}$ .

From figure 5 the behaviour of the classification scheme can be read off. As an example, the uninterrupted line gives the probability for classification into Category I. If the ERV is within the shaded box around the median concentration for 1 mg/L loading, a substantial risk of false classification occurs. ERV values outside the boxes would result in correct classification with a probability greater than 95%.

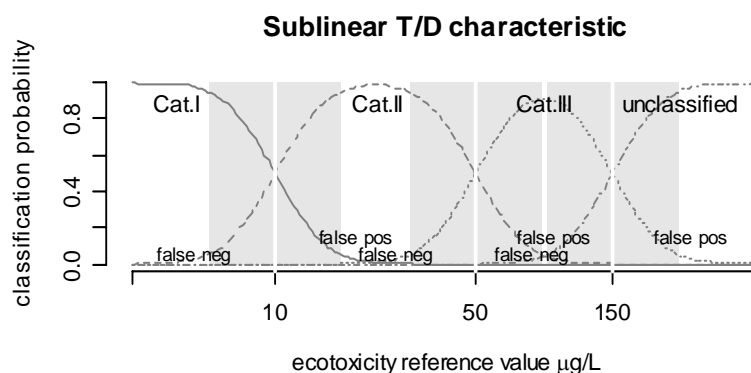
Numerical results are listed in table 3, which is just a read-out from figure 5.

**Table 3: Probabilities of classification for an artificial substance. The true median concentrations corresponding to loadings of 1, 10, and 100 mg/L are assumed as 1, 10 and 100  $\mu\text{g/L}$ .**

ERV	P(Category I)	P(Category II)	P(Category III)	P(unclass)
0.50	<b>0.98</b>	0.02	0.00	0.00
0.67	<b>0.90</b>	0.10	0.00	0.00
<b>1.00</b>	0.50	<b>0.50</b>	0.00	0.00
1.50	0.10	<b>0.90</b>	0.00	0.00
2.00	0.02	<b>0.98</b>	0.00	0.00
5.00	0.00	<b>0.98</b>	0.02	0.00
6.67	0.00	<b>0.90</b>	0.10	0.00
<b>10.00</b>	0.00	0.50	<b>0.50</b>	0.00
15.00	0.00	0.10	<b>0.90</b>	0.00
20.00	0.00	0.02	<b>0.98</b>	0.00
50.00	0.00	0.00	<b>0.98</b>	0.02
66.67	0.00	0.00	<b>0.90</b>	0.10
<b>100.00</b>	0.00	0.00	0.50	<b>0.50</b>
150.00	0.00	0.00	0.10	<b>0.90</b>
200.00	0.00	0.00	0.02	<b>0.98</b>

The behaviour of the classification probability is similar for all categories. This could be different, if the T/D process shows a sub-linear characteristic.

Such a case is provided by the situation shown in figure 6.



**Figure 6:** Probabilities of classification for an artificial substance. The true median concentrations corresponding to loadings of 1, 10, and 100 mg/L are assumed as 10, 50 and 150 µg/L.

Figure 6 demonstrates, that substantial sub-linear T/D characteristics of a substance can result in difficulties concerning a correct classification, if the ERV is in the range of the concentrations reached by the 10 and 100 mg/L loadings. This example, however, shows a very extreme case, not seen in the validation study for the powder preparations.

Numerical results are listed in table 4, which is just a read-out from figure 6.

**Table 4:** Probabilities of classification for an artificial substance. The true median concentrations corresponding to loadings of 1, 10, and 100 mg/L are assumed as 10, 50 and 150 µg/L.

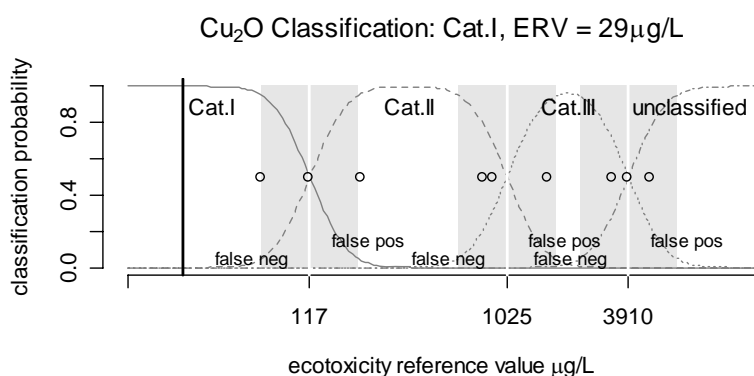
ERV	P(Category I)	P(Category II)	P(Category III)	P(unclass)
5.00	<b>0.98</b>	0.02	0.00	0.00
6.67	<b>0.90</b>	0.10	0.00	0.00
<b>10.00</b>	<b>0.50</b>	<b>0.50</b>	0.00	0.00
15.00	0.10	<b>0.90</b>	0.00	0.00
20.00	0.02	<b>0.98</b>	0.00	0.00
25.00	0.00	<b>0.98</b>	0.02	0.00
33.33	0.00	<b>0.90</b>	0.10	0.00
<b>50.00</b>	0.00	<b>0.50</b>	<b>0.50</b>	0.00
75.00	0.00	0.10	<b>0.88</b>	0.01
100.00	0.00	0.02	<b>0.88</b>	0.10
<b>150.00</b>	0.00	0.00	<b>0.50</b>	<b>0.50</b>
225.00	0.00	0.00	0.10	<b>0.90</b>
300.00	0.00	0.00	0.02	<b>0.98</b>

### 3.2 Classification: data from validation ring test

The concept given in the preceding paragraph is illustrated using data from the ring test study. The results from three laboratories and three substances are used. Here only concentrations measured at pH 6 are considered. The geometric mean of the concentrations provided by the

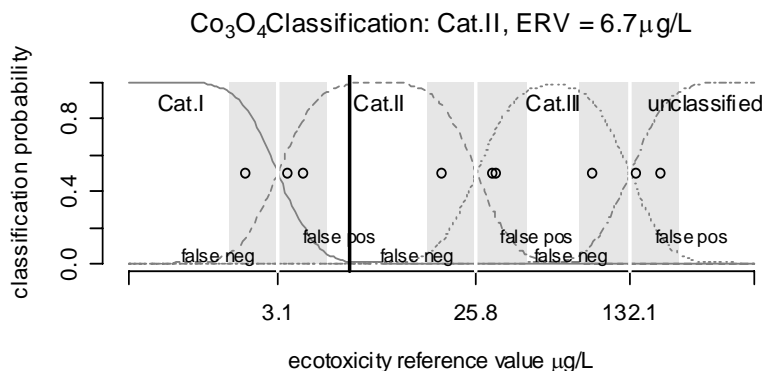
three laboratories is used as substitute of the true median concentration. The substances are classified identically when using the individual data from the labs.

**Cu<sub>2</sub>O:** For Cu<sub>2</sub>O the ERV equals 29µg/L, all measured concentrations are greater than this value, therefore, the substance is labelled as Category I (see figure 7). If the substitute median concentrations are taken as true, the chance of a false positive classification can be taken as zero.



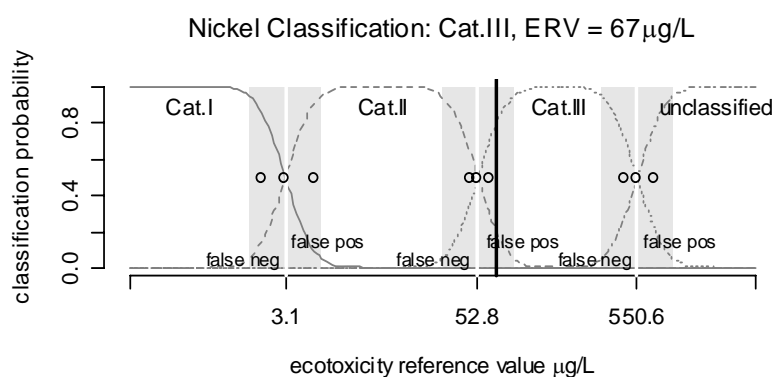
**Figure 7:** Classification of Cu<sub>2</sub>O, pH=6. The ERV is far below all measured concentrations, so Cu<sub>2</sub>O would be classified as Category I. Assumed median concentrations as indicated, individual measurements displayed as open circles.

**Co<sub>3</sub>O<sub>4</sub>:** The measured concentrations of Co<sub>3</sub>O<sub>4</sub> give a Category II result (see figure 8). The ERV of 6.7µg/L is far from the assumed true median concentrations (3.1 µg/L for 1mg/L loading and 25.8µg/L for 10mg/L loading). The probability of a correct classification equals virtually 100%.



**Figure 8:** Classification of Co<sub>3</sub>O<sub>4</sub>, pH=6. The ERV is well in between the measured concentrations at 1mg/L and 10mg/L loading, so Co<sub>3</sub>O<sub>4</sub> would be classified as Category II. Assumed median concentrations as indicated, individual measurements displayed as open circles.

**Nickel** is classified into Category III (see figure 9). The ERV of 67µg/L is just above the concentrations measured by the three labs for 10mg/L loading. Taking the geometric mean of 52.8µg/L as true median concentration, there would have been a chance of about 23% for a false positive classification into Category II. The observed per lab measurements, however, all result in a Category III decision.



**Figure 9:** Classification of Nickel, pH=6. The ERV is just above all measured concentrations at 10mg/L loading, so Nickel would be classified as Category III. Assumed median concentrations as indicated, individual measurements displayed as open circles.

For further clarification the information used in classifying the three compounds is included in tabular form. The assumed T/D properties, their relation to the ERV values and the probabilities of classification are provided in tables 5-7.

**Table 5: Numerical summary of T/D data. Ecotoxicity reference values and assumed median concentrations for loadings of 1, 10, and 100 mg/L at pH6 (Concentrations in µg/L).**

compound	ERV	M1	M10	M100
<b>Cu<sub>2</sub>O</b>	29	117	1025	3910
<b>Co<sub>3</sub>O<sub>4</sub></b>	6.7	3.1	25.8	132.1
<b>Nickel</b>	67	3.1	52.8	550.6

The ratios in table 6 show the relation between the ERV and the T/D response. Only one ratio lies within the interval (0.59, 1.7), where a substantial chance for misclassification exists: see Nickel and the ratio of M10 and ERV.



**Table 6: Ratios of assumed median concentrations to ERV.**

compound	M1/ERV	M10/ERV	M100/ERV
<b>Cu<sub>2</sub>O</b>	4.0	35	135
<b>Co<sub>3</sub>O<sub>4</sub></b>	0.5	3.9	19.7
<b>Nickel</b>	0.0	<b>0.8</b>	8.2

The fact, that M10 and ERV are rather similar for Nickel is expressed in a lower rate of correct classification (see table 7). Such behaviour is unavoidable in principle.

**Table 7: Probability of classification into different categories, given assumed median concentrations and ERV values of compounds. Correct classifications are indicated as bold.**

compound	Cat.I	Cat.II	Cat.III	unclass.
<b>Cu<sub>2</sub>O</b>	<b>1.00</b>	0.00	0.00	0.00
<b>Co<sub>3</sub>O<sub>4</sub></b>	0.01	<b>0.99</b>	0.00	0.00
<b>Nickel</b>	0.00	0.23	<b>0.77</b>	0.00

Probabilities are calculated according to formulae given in table 2.

## 4. Conclusions

- Classification of sparingly soluble metal compounds into category I – III cannot be made error free.
- Results of the statistical analysis of the validation ring test allow a framework for assessing error rates to be derived.
- False negative and false positive decision rates can be calculated for hypothetical settings, if the ecotoxicity reference value and the T/D-characteristics (e.g. median concentrations for different loadings) are specified.
- If the ratio (or its inverse) of the median concentration of a substance to the ERV is greater than 2, the false decision rate is virtually equal to zero.
- As long as the TD measurements show no extreme sublinear dependence on loading, misclassification is limited to a one-category difference.
- Classification scenarios can be studied, using a schematic plot of classification probabilities, assumed median concentrations and ERV.
- Metal powder preparations from the validation ring test were classified consistently for the three laboratories, thereby providing examples for categories I – III.

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