Eurometaux

EBRC
Services for the Chemical Industries

Brief profiles on systemic toxicological effects of common counter-ions in metal substances:

Cover note

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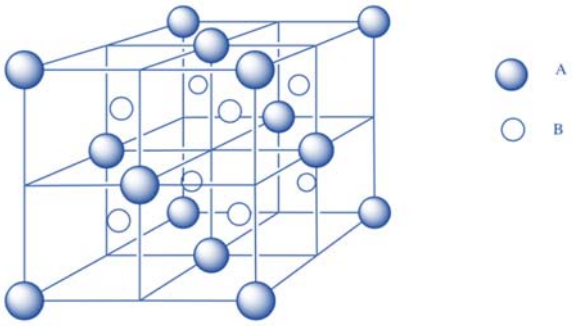

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0. Cover note:

Cations:

1	Calcium, Ca^{2+}	2	Magnesium, Mg^{2+}	3	Potassium; K^{+}	4	Sodium, Na^{+}	5	Ammonium, NH_4^{+}

Anions:

6	Sulfate, SO_4^{2-}	7	Chloride, Cl^{-}	8	Nitrate, NO_3^{2-}	9	Carbonate, CO_3^{2-}	10	Phosphate, PO_4^{3-}

Introduction

Grouping or category approaches are often applied when conducting human health risk assessments for inorganic metal substances. The main assumption underlying such grouping is that toxicological properties of a group of substances are likely to be similar or follow a similar pattern as a result of the presence of a common metal ion. If scientifically justified, read-across can be conducted within the group, to predict hazard data for substances where no substance-specific information is available. Whereas the focus will be on the metal ion that drives the toxicity, the potential contribution of other moieties in the different substances cannot be disregarded. Here, these other moieties are referred to as “counter ion(s)”. At least basic information on the counter ion must available to show either that it will not be toxic “on its own right”, or at least that it contributes less to the toxicity of the substance(s) than the “driving” metal (ion) under consideration.

Based on a selection on behalf of Eurometaux, ten brief toxicological profiles were compiled by EBRC Consulting GmbH on “counter ions” that are most commonly found in metal compounds. **The focus of these documents is on systemic toxicity and the oral uptake route** (but would “by default” also include the assessment of particulate substances which upon inhalation are translocated to a substantial degree to the gastrointestinal tract, or those which are already readily absorbed in the respiratory tract without any particular local effects.

The aim of these brief toxicological profiles is to assist the assessor of health hazards of metal substances in determining whether these “counter ions” contribute to the overall toxicity of the substance. **An exemplary calculation is included in this cover note demonstrating how it can be documented that a particular “counter ion” does not contribute to the toxicity of a metal substance.**

Background

When conducting risk assessments for inorganic metal substances, they are often grouped by the metal moiety that is considered as the driver of toxicity.

> *"The main assumption underlying the grouping of metal compounds is that toxicological (and ecotoxicological) properties are likely to be similar or follow a similar pattern as a result of the presence of a common metal ion (or ion complex including a hydrated metal ion). It is the bioavailability of the metal ion (or a redox form of this ion) at target sites that, besides the toxicity potency, will determine the occurrence and severity of the effects to be assessed. This is a reasonable assumption for the majority of inorganic compounds and some organic compounds (e.g. metal salts of some organic acids), in the absence of demonstrated relative differences in bioavailability."* (OECD, 2014)

For example, various cobalt substances, such as cobalt sulfate, cobalt chloride or cobalt nitrate can be assessed together as a group or category, since the systemic toxicological effects of these substances are driven by the metal moiety / i.e. in this case the released cobalt cation. Another example, where the key moiety forms an oxoanion instead, is the category of inorganic molybdenum substances, including sodium molybdate, ammonium molybdate(s), calcium molybdate and others. Often, read-across is used within these groups to avoid conducting toxicological studies for each and every substance. In the examples above, toxicological data may be available for cobalt chloride or sodium molybdate, but not for other members of the respective category.

Under EU REACH, such read-across/grouping can be used in adaptations of standard data requirements for substance registration, but requires sufficient documentation and justification. A framework for assessing the validity of read-across/grouping approaches has been established by ECHAs, the so called Read Across Assessment Framework (RAAF).

Whereas the focus will be on the metal ion that drives the toxicity, the possible contribution of other moieties in substances cannot be disregarded (e.g. sulfate and nitrate in the cobalt category, or ammonium and calcium in the molybdate category), and must therefore be assessed. These other moieties are also referred to as "counter ion(s)".

At first it should be reported and explained whether and how the counter ion affects the bioavailability of the metal constituent. This aspect would usually be covered with information on bioavailability on every substance in the category. Whereas water solubility can be a first indicator of bioavailability, bioelution data in artificial physiological media are preferred, when in vivo information is not available (or not on all substances). This topic is not addressed here.

Secondly, at least basic information on the counter ion must be provided to show that it is not toxic "on its own right", or is at least less toxic than the "driving" metal. In other words, it needs to be demonstrated that the toxicity of the metal substances in the category is caused by the driving metal ion, and not by the counter ion. In the context of ECHA's RAAF, this should be addressed under the Assessment Element "Formation and impact of non-common compounds".

To support the MISA consortia/associations that use such read-across/category approaches for REACH registrations with regard to this second aspect, ten individual brief toxicological profiles on counter ions commonly associated with metals were prepared. These documents are intended to assist the assessor to determine whether the counter ion moiety contributes to the overall toxicity of the substance or not.

Scope:

The focus of these documents is on systemic toxicity and the oral route (but "by default" also includes particulate substances translocated to the gastrointestinal tract upon inhalation, or those that are readily absorbed in the respiratory tract without any particular local effects). These documents do not address local effects such as irritation/corrosion, or sensitisation in detail. Although data on acute toxicity are also cited, most relevance is assigned to repeated/long-term systemic exposure.

These documents do not review primary literature or studies in detail, and collection and review of primary references were not within the remit of this project. Instead, reference is primarily made to one (or more) recently published authoritative reviews, such as from the European Food Safety Authority or from WHO, or to publicly available datasets for example the OECD Screening Information Datasets (SIDS). Since literature searches and reviews have already been conducted within these authoritative reviews, no new literature searches were conducted.

Toxicological studies can obviously not be conducted with ions, but instead only with substances as a whole. The data presented in these ten documents follow the authoritative reviews by for example EFSA, in that usually only data on substances are presented that allow an assessment of the hazard of the ion of interest. For example: to assess the toxicity of "nitrate", information on potassium or sodium nitrate could be useful, since potassium or sodium are generally considered as "benign". In contrast, toxicological tests conducted with nickel- or cobalt nitrate would rather inform about the toxicity of nickel or cobalt, but not about nitrate. Therefore, such data are usually not cited in the counter ion documents.

All documents follow the same structure as far as possible - after an introduction, they provide summaries on the following aspects: natural occurrence, physiological function and dietary intake, toxicokinetics, acute toxicity, (skin) sensitisation, repeated dose toxicity, mutagenicity/genotoxicity, reproductive toxicity and carcinogenicity. The documents conclude with a discussion, and where applicable the identification of the key/leading systemic health effects of the ions.

Exemplary calculations: does the "counter ion" contribute to the toxicity of a metal substance?

To facilitate a quantitative assessment of the contribution of the respective ion to the systemic toxicity of a substance, numerical toxicological descriptors or thresholds are presented in the counter ions documents where possible. Depending on the available information and the source of the data, these figures can be of various types or use different terminology: e.g.: NOAELs from animal studies or Upper Limits (UL) or Acceptable Daily Intakes (ADI) derived for humans. The user of these counter ions documents can use these figures for the counter ion on a case-by case basis to put them into context with available toxicological thresholds for their toxicity driving metal ion. The figures are usually valid for healthy adults in the general population. On a case-by-case basis, different age groups and/or sensitive sub-populations may have to be considered by the assessor.

Such an assessment should usually be based on the most critical toxicological effect (i.e. the effect described by e.g. the lowest DNEL) that drives the risk assessment. Where numerical toxicological thresholds are not applicable (e.g. from non-thresholds effects), a semi-quantitative assessment may be required. An underlying assumption in these assessments is that the toxicity driving metal and the counter ion do not cause the same type of toxicological effects in the same target organ. Usually, the two moieties / ions of interest will be a cation and an anion, from whom it may be assumed that their toxicokinetic and toxicological profiles are quite different (e.g. different mechanisms of ADME, different target organs, different toxicological modes of action). Only if this would not be the case, the possible additivity of the toxicity of the driving metal(ion) and the counter ions would have to be considered.

The following actual case is provided as an example for a quantitative demonstration that a counter ion does not contribute to the toxicity of a metal salt. Calculations similar to this example can be conducted for different combinations of driving metal and counter ion:

Example: Demonstration that sodium does not contribute significantly to the toxicity of sodium molybdate and that the assessment of systemic toxicity can be based on the molybdenum moiety.

In the category of molybdenum substances, the molybdate ion (MoO_4^{2-}) is the ion that drives the hazard assessment. The key (lowest) DNEL for systemic, long-term effects (oral route) for the general population, expressed on the basis of molybdenum (Mo) is 3.4 mg $Mo/kg_{bw}/d$, corresponding to ca. 238 mg Mo/d for a 70-kg person. The DNEL is based on a NOAEL from a sub-chronic oral study (acc. to OECD TG 408).

The category substance sodium molybdate, Na_2MoO_4, has a molecular mass of 205.9, the atomic masses of sodium and molybdenum are 22.99 and 95.96, respectively.

Thus, the Mo-based DNEL above can be converted into a substance-specific DNEL for sodium molybdate:

DNEL (Na_2MoO_4) = DNEL (Mo) / 95.96 * 205.9 = 3.4 / 95.96 * 205.9 = 7.3

The substance-specific DNEL for sodium molybdate is 7.3 mg $Na_2MoO_4/kg_{bw}/d$.

Next, the dose of sodium is calculated to which a person would be exposed to, when exposed to sodium molybdate at the Mo-based-DNEL level:

Dose of sodium at Mo-based DNEL for sodium molybdate = DNEL (Na_2MoO_4) / 205.9 * 2 * 22.99 = 7.3 / 205.9 * 2 * 22.99 = 1.63

When exposed to sodium molybdate at Mo-based-DNEL level, the person would be exposed to ca. 1.63 mg $Na/kg_{bw}/d$. For a default 70-kg person, this would be ca. 114 mg Na per day.

Based on the counter ion document on sodium, an intake of up to 2 g Na per day (2000 mg/d) is considered as safe for adults. Thus, a (70 kg) person exposed to sodium molybdate at the Mo-based DNEL would ingest less than 6% of the safe dose of sodium (114 / 2000 = 5.7 %).

In conclusion, sodium does not contribute significantly to the systemic toxicity of sodium molybdate and it can there considered justified to base the hazard assessment for sodium molybdate on the molybdenum moiety in this substance.

References:

OECD, 2014: Guidance on grouping of chemicals, Second Edition, Series on Testing & Assessment No. 194, ENV/JM/MONO(2014)4

RAAF, 2017: European Chemicals Agency (ECHA): Read-Across Assessment Framework (RAAF), Reference: ECHA-17-R-01-EN.