# Guidance on the classification of inorganic UVCB substances for human health hazards

16 April 2020

**Summary**

Several substances in the inorganic industry are UVCB substances: substances of Unknown or Variable composition, Complex reaction products or Biological materials. Such substances are often defined at least partly by the industrial process and the source material from which they are produced. They present specific challenges for their assessment under current classification schemes, such as in the UN GHS and EU CLP. Examples of inorganic UVCB substances include ores, concentrates, intermediates, final slags, and recyclables. The composition of these inorganic UVCB substances may vary considerably depending on the material used as input for the process. Furthermore, due to the mineralogical complexity and technical limitations in the best available analytical techniques, it may not be possible to fully and reliably characterize (i.e. provide speciation) and quantify all trace constituents. Toxicity tests on UVCB substances are not often available. Given the number, variability, and complexity of UVCB substances, in most cases it is not feasible nor desirable, from an animal welfare perspective, to perform toxicity tests.

This guidance document describes a tiered approach and its application to hazard classification of inorganic UVCB substances for **human health hazards**. The information necessary to conduct the assessment is identified at 3 levels: elemental composition, mineralogy / speciation, and information on bioaccessibility. This information is used to establish a hazard classification by treating the UVCB substance as if it were a mixture of its constituents. It has a built-in mechanism to ensure a sufficiently precautionary approach: the assumptions on the exact constituents depend on the level of information that is available. If only the elemental composition is available, worst-case assumptions ensure that the outcome of the assessment is precautionary. More realistic assumptions are made as more information becomes available. In particular, the use of bioaccessibility data for the purposes of classifying UVCB substance for systemic human health endpoints is discussed in detail.

The tiered methodology described here has been implemented in the online tool MeClas which complies with the UN GHS and EU CLP classification procedures and is available free of charge at www.meclas.eu. Examples confirm that, using this guidance document, it is possible to assess the hazards of inorganic UVCB substances in a consistent, transparent, and scientifically sound way.

**Glossary**

| | |
|---|---|
| Constituent | Any single species present in a substance that can be characterised by its unique chemical identity (ECHA Guidance on Substance Identity). |
| Constituent element | The chemical elements present in a UVCB substance. The speciation of some of these constituent elements may not be known in full detail. |
| Mixture rules | The mixtures rules (Section 1.6.3.3 of the EU CLP Guidance) are rules to classify mixtures based on information on their ingredients. They are either based on additivity and calculation rules or on cut-off values and concentration limits. |
| UVCB substance | Substances of Unknown or Variable composition, Complex reaction products or Biological materials (ECHA Guidance on Substance Identity). |

## 1. Inorganic UVCB substances

### 1.1. Definition of UVCB substances

Substances of Unknown or Variable composition, Complex reaction products or Biological materials – briefly referred to as UVCB substances – are defined in the ECHA Guidance on substance identity (Box 1). Well-defined substances can be fully identified by their chemical composition. These may either be mono-constituent or multi-constituent substances, and may in addition contain impurities and additives. In contrast, the UVCB substances cannot be completely identified by their chemical composition, because:

- The number of constituents is relatively large, and/or
- The composition is, to a significant part, unknown, and/or
- The variability of composition is relatively large or poorly predictable.

**Box 1: Definition of UVCB substances according to ECHA (2017).**

"Substance identification should be based on at least the substance identification parameters listed in REACH Annex VI, section 2. Therefore, any substance needs to be identified by a combination of the appropriate identification parameters:

- The IUPAC- and/or other name and other identifiers, e.g. CAS-number, EC-number (Annex VI, section 2.1);
- The molecular and structural information (Annex VI, section 2.2);
- The chemical composition (Annex VI, section 2.3);

A substance is completely identified by its chemical composition i.e. the chemical identity and the content of each constituent in the substance. Although such straightforward identification may be possible for most substances, for certain substances it is not feasible or not adequate within the scope of REACH and CLP. In those cases, other or additional substance identification information is required.

Thus, substances can be divided into two main groups:

- Well defined substances: Substances with a defined qualitative and quantitative composition that can be sufficiently identified based on the identification parameters of REACH Annex VI section 2.
- UVCB substances: Substances of Unknown or Variable composition, Complex reaction products or Biological materials. These substances cannot be sufficiently identified by the above parameters."

### 1.2. Characteristics of inorganic UVCB substances

Inorganic UVCB substances most often vary widely for some of its constituents. Examples include slimes and sludges, slags, matte, doré, flue dusts, ores, concentrates, sinter, and many others. These substances are complex in nature, and their composition varies significantly depending on the source materials and process parameters used when they are produced. A detailed account of the various inorganic UVCB substances and their characterization can be found in Verougstraete et al. (2018).

The key levels of characterization for inorganic UVCB substances, relevant for the assessment of human health hazards under UN GHS and EU CLP, can be grouped as follows:

Level 0. The elemental composition

Level 1. The mineralogical composition or speciation

Level 2. Information on bioaccessibility

Level 3. Results from direct toxicity testing

The elemental composition of inorganic UVCB substances (Level 0) may be determined using various methods, as described in Chapter 6 of Verougstraete et al. (2018). The elemental composition is generally well known, and detailed information is typically available even on the concentrations of elements present in trace amounts. The term "constituent element" is used in this document to denote the chemical elements present in a UVCB substance. The speciation of some of these constituent elements may not be known in full detail.

The mineralogical composition (Level 1) reveals information on the form (or "speciation") under which the constituent elements occur. It is usually determined using X-ray diffraction and/or advanced microscopy techniques, which are more qualitative methods as described in Chapter 6 of Verougstraete et al. (2018). All known constituents, and all constituents present at concentrations ≥ 10%, should be specified by at least a IUPAC name, preferably a CAS number, and the typical concentrations and concentrations ranges (ECHA, 2017). The mineralogy of the major constituents is usually well known. In contrast, an accurate characterization of the trace constituents of some UVCB substances, even with the most sophisticated techniques available, has proven challenging (Piatak et al., 2015).

Bioaccessibility information (Level 2) may be available for some UVCB substances and may help to further refine the assessment.

Finally, data may be available from toxicity testing on the UVCB substance itself (Level 3).

### 1.3. Implications for hazard classification approaches

The definition of UVCBs as substances, their complex characteristics, and their variable and partially unknown composition has important implications for hazard assessment. According to the CLP guidance, section 1.1.6, "*the classification of a substance is based on the relevant information available on its hazardous properties. This information can include experimental data generated in tests for physical hazards, toxicological and ecotoxicological tests, historical human data such as accident records or epidemiological studies, or information generated in in vitro tests, (Quantitative) Structure Activity Relationships ((Q)SAR), read-across, or grouping approaches. CLP does not require new testing for the purpose of classification for health or environmental hazards*."

The classification assessment of UVCB substances must recognize these principles. However, for inorganic UVCB substances, a number of unique specificities need to be taken into account:

- The elemental composition is typically well known, but can present high variability as it is to a large extent determined by the source material that was used to produce the UVCB substance. The chemical speciation may be known in less detail as it can be extremely complex.
- The high variability complicates fulfilling the normal toxicity and ecotoxicity requirements for substances. Selection of a representative sample is problematic. Subjecting all individual inorganic UVCB substances to toxicological and ecotoxicological tests is not feasible and not defensible from a resources and animal welfare perspective. Therefore, with some exceptions, test data on UVCB substances are often not available. A weight of evidence approach using expert judgement will need to be applied (CLP, art. 9).

- Many metals and metal compounds, the constituents of inorganic UVCB substances, are well-characterized through e.g. risk assessments, voluntary risk assessments, REACH dossiers, high tier test data available, and peer reviewed scientific papers. Ample data, expertise and experience are available on these individual constituents and are shared among the inorganic sector. Relying on these data implies less uncertainty in the assessment of the UVCB substance;

- In many cases, it is not technically possible to accurately identify or quantify all constituents of a UVCB, or to relate them back to known substances. Indeed, while the major constituents for many UVCB substances are known, trace constituents can often not be fully and reliably characterized (Piatak et al., 2015, section 3.1.2). Indeed, it may not be possible to clarify under which chemical form or species trace elements are present (e.g. as a metal, a sulphide, a carbonate, an oxide…). Alternatively, the element may occur under a variety of poorly defined forms which cannot be easily related back to known pure substances with known properties. The example of final slags clearly illustrates this case (Section 3).

As basis for the human health hazard classification, all available information on the UVCB substance is considered, in particular the 3 types of information listed in Section 1.2 and information on the hazard classification of the identifiable constituents. The hazard classification of the UVCB substance is established based on the classifications of the constituents. A tiered approach has been established in order to conduct the assessment in a transparent way (Section 2). The assessment scheme is based on the available information on the UVCB substance, the available information on the hazard classification of its constituents, and established assessment methods for mixtures. The scheme considers that, for the purposes of the hazard classification assessment, the UVCB substance may in many cases effectively be assessed as if it were a mixture of its identifiable constituents. The approach contains a built-in level of precaution that depends on the amount of available information on the UVCB substance.

## 2. A tiered approach

A tiered approach has been developed for the purposes of hazard classification of complex inorganic materials (Figure 1). The tiers 0, 1 and 2 are implemented in MeClas (Verdonck et al., 2017). MeClas is an online tool that was developed to address the specific challenges associated with the human health and environmental hazard assessment and classification of complex inorganic materials under the EU CLP and UN GHS. It has been made freely available for industries and authorities since 2010 and is accessible at www.meclas.eu. Physical hazards are not in the scope. The tool is compliant with the requirements of UN GHS, EU CLP, and US OSHA. The tiered approach relates the classification of the complex inorganic material to known substances with known classifications. When considering classification under the EU CLP Regulation, these substance classifications may use the harmonized classifications as specified in Annex VI of the EU CLP Regulation, or self-classifications by industry, for those substances not subject to harmonized classifications. These classifications are included in the background database of MeClas. As explained below, MeClas addresses the UN GHS human health and environmental hazard endpoints, is based on an unambiguous algorithm defined under the UN GHS and EU CLP classification systems, has a well-defined domain of applicability, and robust predictability.

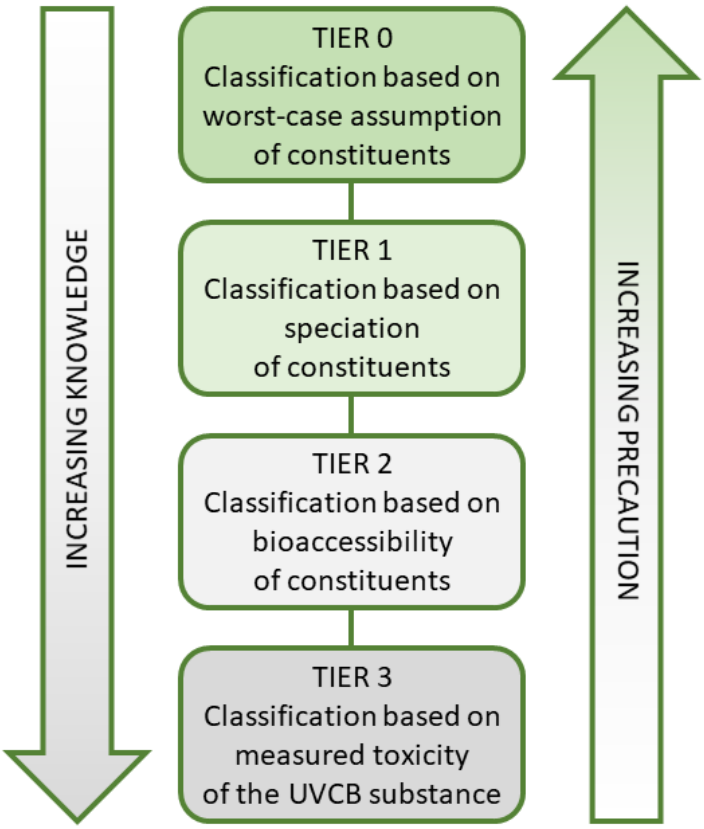


Figure 1: Tiered approach for hazard assessment of UVCB substances. Adapted from Verdonck et al. (2017).

The underlying philosophy of the tiered approach is that the assessment starts from precautionary (worst-case) assumptions, but that these assumptions can progressively be refined and made more realistic if more knowledge about the substance or mixture is available. In order to refine an assessment, the assessor can therefore take the initiative to gather additional information in order to progress to higher tiers. The tiered approach is applied separately for each endpoint to determine the hazard profile of the complex inorganic material.

The mixture rules play a central role in the tiered approach. In the UN GHS and EU CLP classification systems, the available hazard data on a substance or mixture as a whole, or on a similar substance or mixture, should primarily be used to determine the hazard classification. However, as pointed out above, for UVCB substances such data is often lacking. The assessment of the classification of a substance or mixture must then be based on the available information on the individual ingredients (when assessing mixtures) or constituents (when assessing substances), using the mixture rules as summarized in Section 1.6.3.3 of the EU CLP Guidance. The mixtures rules are either based on additivity and calculation rules (for endpoints like acute toxicity, skin irritation/corrosion or aquatic toxicity) or on cut-off values and concentration limits (for endpoints like reproductive toxicity or mutagenicity). The cut-off values are the minimum concentrations for a substance to be taken into account for classification purposes. Concentration limits are established for substances, and indicate a threshold at or above which the presence of that substance in another substance or in a mixture triggers the classification of the substance or mixture as hazardous (EU CLP, Article 10).

This section further details the tiered approach as applied in the specific context of UVCB substances.

0. Tier 0 uses the mixture rules as defined in the UN GHS and EU CLP classification systems. The Tier 0 assessment uses as basis the most stringently classified compound of each constituent element that is present in the UVCB substance. These are typically soluble compounds. In order to determine the classification outcome, the UVCB substance is effectively treated as if it was a mixture of metal compounds, using the mixture rules.

1. Tier 1 considers a similar approach; however, it considers as basis the classification of those substances that, from a chemical speciation perspective, most closely resemble the constituents of the UVCB substance.

2. Tier 2 uses a combination of mixture rules and bioaccessibility testing of the UVCB substance itself. The bioaccessibility of the constituents in the UVCB substance is determined by testing the UVCB substance *in vitro* in a relevant mimetic fluids or media, according to the exposure pathway. The classification is subsequently derived based on comparison of the bioaccessibility with a reference to establish the classification, using mixture rules. A homologous methodology is used in the context of environmental hazard classification; the Transformation-Dissolution protocol as prescribed in Annex 10 of the UN GHS, and the concept of the Ecotoxicity Reference Value (CLP Guidance, Annex IV) is used as reference. As example, for the evaluation of human health hazards via the oral route, bioaccessibility tests in gastric fluid can be used, and the reference is a pure (mono-constituent) substance with known classification which has been tested in the same fluid.

3. Tier 3 considers testing on the UVCB substance itself. The classification is derived based on the rules foreseen for substances in the EU CLP and UN GHS classification systems.

The tiered approach is precautionary by nature. In the absence of detailed information, a precautionary approach is adopted (Tier 0). The assessment can progressively be refined to become more realistic and accurate if more information is available. The result of the higher tiers may lead to

a less stringent classification, because the lower tiers do not consider several factors that could mitigate the toxicity, such as speciation, particle size, or low bioavailability due to occlusion of certain constituents in other mineral phases. For example, if the Tier 0 assessment shows there is no need for classification of the UVCB substance for a particular endpoint, it is very unlikely that a toxicity test with the UVCB substance would lead to a classification. However, in order to take into account all available information and arrive at the most realistic classification outcome, the assessor should proceed as far along the scheme as the available information allows.

The application of the tiered approach to the classification of UVCB substances is further detailed in the next sections.

### 2.1. Tier 0: Mixture rules with worst-case speciation assumptions

The Tier 0 assessment only requires information on the elemental composition of the UVCB (Level 0). Consistent with the precautionary principle, due to the level of uncertainty it assumes the worst-case classification species for every constituent element of the material (Verdonck et al., 2017). Concretely, for each constituent element, the corresponding substance with the most stringent classification is identified. A molecular weight correction is applied to convert the elemental composition into the concentration of the selected substances. The classification of the UVCB substance is finally calculated based on the mixture rules. For the purposes of deriving a classification, the UVCB substance is effectively regarded as a mixture of worst-case constituents.

It should be noted that, in order to ensure a precautionary classification at this tier, the assumed speciation for the same UVCB substance may differ depending on the endpoint. This is the case if, for a certain element, different substances of the element are classified more stringently for different endpoints.

### 2.2. Tier 1: Mixture rules considering the speciation of the constituents

The Tier 1 assessment requires information on the elemental composition and the speciation (mineralogy) of the constituents of the UVCB substance (Levels 0 and 1). In particular, sufficiently detailed speciation information is necessary on those constituent elements that are relevant for the hazard endpoint that is assessed. Based on this information, for each constituent element, a corresponding substance with similar speciation is selected, and the classification of that substance is considered. For example, if mineralogical information reveals that the constituent element copper in a UVCB substance is present as chalcopyrite, a mineral containing copper and sulphide, then the substance chalcopyrite and its corresponding hazard profile and classification will be considered in the assessment. A molecular weight correction should be applied to convert the elemental composition into the concentration of the selected substances. The classification of the UVCB substance is finally calculated based on the mixture rules. For the purposes of deriving a classification, the UVCB substance is effectively regarded as a mixture of constituents with a speciation that matches the speciation of the UVCB substance.

It should be noted that, in some cases, detailed speciation information will be available for most but not all constituents of a UVCB substance. This is a consequence of the defining properties of UVCB substances, i.e. the composition may be to a significant part unknown. It applies in particular to trace constituents present at quantities around or below 1%, for which even advanced analytical techniques may not allow to reliably establish the speciation. Such trace constituents may still be relevant for certain hazard endpoints. For those constituent elements where no or limited information on the

speciation is available, a substance with the worst-case classification (i.e. the substance with the most stringent classification for the endpoint that is assessed) is selected. The classification of the UVCB substance is finally calculated based on the mixture rules and concentration limits as defined in the UN-GHS or EU-CLP Regulation.

In general, Tier 1 is a precautionary assessment of the hazard profile of a UVCB substance. This is because it does not consider several factors that could mitigate the toxicity, such as large particle size, or low bioavailability due to inclusion of certain constituents in other mineral phases. There may be exceptional cases where information is available to indicate that the hazard of the UVCB substance is higher than that of its constituents. For example, this may be the case if a constituent of a UVCB substance is more soluble than the corresponding pure substance, e.g. due to a very high exposed surface area (e.g. in a porous structure) or due to electrochemical interactions between constituents. The Tier 1 assessment is not valid if the available information indicates that the bioaccessibility of any of the relevant constituents in the UVCB substance may be higher than that of the pure substance. In such exceptional cases, the assessor is required to conclude based on the Tier 0 assessment, or to gather additional information and proceed to Tier 2.

### 2.3. Tier 2: Classification based on bioaccessibility data

The Tier 2 assessment requires information on the elemental composition, the speciation / mineralogy, and information on bioaccessibility (Levels 0, 1, and 2). For the assessment of human health hazards, Tier 2 only applies to those endpoints and those metals for which it is demonstrated that systemic absorption, i.e. dissolution of the metal ion and subsequent uptake, precede the observed effects. In practice, this includes the endpoints carcinogenicity, mutagenicity, reproductive toxicity, and specific target organ toxicity with repeated exposure (STOT-RE). Acute toxicity via the oral route is also included if the effects are due to systemic absorption. This Tier does not apply to local effects, such as skin irritation after dermal exposure, or local lung effects after inhalation exposure.

The application of the Tier 2 assessment in this document focuses on systemic effects occurring after oral exposure, which is useful to determine classification for systemic endpoints in case the route of exposure is not specified. A test protocol for assessing the bioaccessibility of UVCB substances via the oral route, in gastric fluid, is available. It has been reviewed by EURL ECVAM in 2020 and is subsequently under discussion at OECD. For other routes of exposure, in particular the inhalation route, several approaches are currently being developed to assess the bioaccessibility of metals.

#### 2.3.1. Definitions

Bioavailability refers to the portion of the total quantity of a chemical present that is absorbed by a living organism, and reaches the central (blood) compartment (Lowney, 2017). Bioelution refers to the in vitro extraction methods used to measure the degree to which a substance is released in artificial biological fluids, i.e. the bioaccessibility of a substance. In situations where the bioavailability of a substance/material is not known or where it is not feasible to determine this in vivo, bioaccessibility may be used as a conservative estimate of bioavailability.

According to Lowney (2017), the term “bioaccessibility” refers to the solubility of a chemical under physiological conditions. It most commonly is used to express solubility of a chemical under simulated physiological conditions (e.g., simulated gastrointestinal fluid), and referred to interchangeably in the

published literature as “bioaccessibility,” “bioelution”, “bioelution test data,” or “in vitro bioaccessibility.”

### 2.3.2. Application to the classification of UVCB substances

In the Tier 2 assessment, the hazards classification of UVCB substances can be further refined by considering the bioaccessible metal concentrations determined using in vitro bioelution tests. The assessment considers the classification of the UVCB substance based on the element release from the UVCB substance and from a “reference substance” with known classification for the endpoint that is considered. The relative bioaccessible concentration (RBC) of a constituent element in a UVCB substance is then calculated relative to the reference substance, and is usually expressed as %

$$RBC = \frac{mg\ metal\ ion\ released\ per\ g\ UVCB\ substance\ tested}{mg\ metal\ ion\ released\ per\ g\ reference\ substance\ tested} \cdot 100\%$$

The selection of the appropriate reference substance is key. An appropriate reference substance must be a well-defined and well-characterized substance with a known classification, and robust and reproducible bioaccessibility data must be available.

In some cases, it may be possible and appropriate to consider a reference substance that is identical to the mineralogy or speciation of the relevant element in the UVCB substance. Such may e.g. be the case when the relevant constituents of the UVCB substance can be very clearly and unambiguously identified. Alternatively, the selection may be informed by considering the central assumption of the bioaccessibility approach: the toxic effects are preceded by dissolution and uptake of the metal ion. Based on this, it would be appropriate to select a soluble compound as reference substance, which fully dissolves to release metal ions. These fully soluble substances have a well-established toxicological profile, since key toxicological studies used to establish the hazard profile of metals are typically conducted with e.g. a chloride, nitrate, sulphate or acetate salt. In most cases, the choice for considering the soluble compound as reference substance includes a level of conservatism: such soluble compounds are usually classified more stringently than other less soluble compounds, such as oxides, sulphides, or metallic forms. In all cases, the choice of the reference substance must be transparently documented and substantiated.

After selecting the reference substance and calculating the relative bioaccessible concentration, the relative bioaccessible concentration is compared to the relevant concentration limit. The relevant concentration limit is the generic or specific concentration limit (under the mixture rules of EU CLP and UN GHS classification systems) that is associated with the studied endpoint and with the chosen reference substance.

The approach has been implemented in MeClas, and a calculator is provided to facilitate the conversion (see Figure 3 in section 3.2). The calculator also reminds users that the value to be entered into MeClas is the relative bioaccessibility, which is different from the RBC as defined above. The relative bioaccessibility (expressed as %) can be calculated as:

the RBC (expressed as %)

divided by

the total concentration of the element of interest in the UVCB (expressed as g of element of interest / g of UVCB).

### 2.4. Tier 3

If test data on the UVCB substance itself are available, the classification assessment can be conducted based on the rules for classifying substances as reflected in UN GHS and EU CLP classification systems. A justification should be available that a representative sample has been selected.

## 3. Examples

### 3.1. Hypothetical Ni-containing UVCB

#### 3.1.1. Characterization

A hypothetical UVCB substance is assessed for its carcinogenicity. The only constituent element which may exhibit carcinogenicity is Ni. The UVCB substance contains 0.25% by mass of the constituent element Ni.

#### 3.1.2. Tier 0 assessment

Among all Ni containing substances, nickel compounds such as nickel sulphate ($NiSO_4$) have the most stringent classification for this endpoint (cat. 1A) under GHS and CLP. Due to the molecular weight correction, a nickel sulphate content of 0.66% is considered. This exceeds the relevant concentration limit of 0.1%. Therefore, with the available information, this UVCB substance would be classified as carcinogen cat. 1A. However, more information may be gathered to refine this assessment.

#### 3.1.3. Tier 1 assessment

Additional mineralogical analysis reveals that the nickel is exclusively present as nickel metal. This additional information allows for a more refined assessment of the carcinogenicity of this UVCB substance . Nickel metal is classified as a carcinogen cat. 2 under GHS and CLP. The concentration limit for classifying mixtures as carcinogen cat. 2 is 1%. As the content of nickel metal is below this threshold, the UVCB substance is not classified for carcinogenicity. Extensive data from product testing and use show that the UVCB substance only releases minimal Ni compared to pure nickel powder and therefore enhanced metal release compared to pure nickel powder is not expected. This confirms that the Tier 1 assessment is appropriate.

### 3.2. Final copper slag

#### 3.2.1. Characterization

Final slag is a UVCB substance co-produced out of the process to smelt and recover metals from primary and secondary raw materials. The final slag resulting from smelting copper is considered here as example. Final copper slag consists primarily of iron silicate and calcium-aluminium silicates. These phases act as a host for the other phases, which typically appear as inclusions. Concentrations of other metals have been reduced to the lowest levels that are economically and technically feasible. These metals are mainly present as droplets and as inclusions within the silicates. The slags are a valuable product used in a massive, granulated or powder form in various applications, e.g. as construction material.

In most final copper slags, amorphous glass phases and iron calcium silicates explain over 90% of the slags' mineral composition. They contain iron silicate in amorphous glass (18—99%) or fayalite (15—73%) and silicates of aluminum and calcium. Traces of copper, zinc, lead, and other metals may occur in various forms and species, e.g. metallic forms, sulphide forms, oxide forms, and inclusions in silicate phases.

As example, a characterization of one final copper slag is provided below. For the purpose of assessing the reproductive toxicity of this UVCB substance, one relevant trace constituent (lead) is characterized in detail. Elemental composition was determined after dissolution using anion chromatography and inductively coupled plasma-optical emission spectroscopy (ICP-OES). Mineralogical characterization was determined using X-ray diffraction, optical microscopy, and scanning electron microscopy with X-ray fluorescence (XRF). The bioaccessibility in gastric fluid was determined according to the Eurometaux SOP (version 2018).

The final slag considered here occurs as large stones with $D_{50}$ equal to 18 cm, which corresponds to the size of a massive material. The final slag principally contains very large grains of a CaMgFe silicate (95.5%) which act as a host to many other minerals found within the slag. Minerals appearing alongside and in particles with the CaMgFe silicate include fayalite (1.5%). Magnetite (0.8%) is found as inclusions, intergrowths, and as skeletal growths in the CaMgFe silicate. Copper minerals, such as bornite (0.16%), chalcocite (0.19%), and metallic copper (0.05%) appear as extremely fine droplet inclusions within the host CaMgFe silicate.

Lead is the only relevant constituent element for assessing the reproductive toxicity of this UVCB substance. The final slag contains 0.277% lead, which is present in various forms: metallic lead, oxidized lead (PbO), galena (PbS), and anglesite ($PbSO_4$). These are distributed amongst the copper-bearing minerals and within host CaMgFe silicate phases as finely disseminated minerals. However, one coarse particle containing oxidized lead, anglesite, and a zinc oxide phase were encountered. A bioelution test in gastric fluid showed that the bioaccessibility of the lead is minimal: only 3.8% of the lead in the slag was released, and 96.2% was not released. This corresponds to a release of 0.105 mg Pb per g of final slag tested.

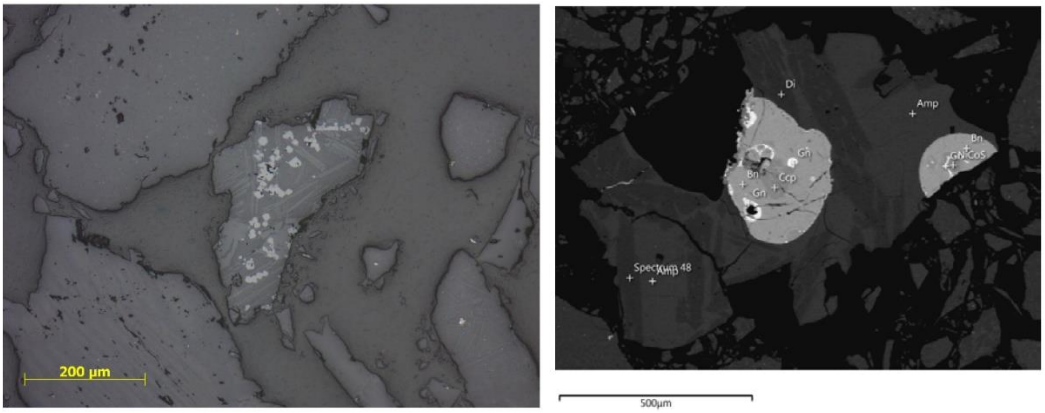


Figure 2. Left: microphotograph of a final copper slag. Dark areas comprise most of the sample and consist of large CaMgFe silicate host phases (95.5%). Bright minerals consist of magnetite and droplets of copper-bearing minerals. Right: Back-scattered electron emission image of one large inclusion as example. In this particular inclusion, bornite ($Cu_5FeS_4$), chalcopyrite ($CuFeS_2$), and galena (PbS) minerals are locked into a CaMgFe silicate host phase.

### 3.2.2. Tier 2 assessment

The final slag is assessed for its reproductive toxicity. The only constituent element that bears a classification relevant for this endpoint, is lead (Pb). The characterization includes elemental composition, speciation information, and bioaccessibility data. Therefore, sufficient information is available to apply the Tier 2 assessment.

For the calculation of the relative bioaccessible concentration, a reference substance must be selected. The speciation of lead in the final slag is very complex, with multiple forms present as inclusions in other minerals. This prevents the speciation from being used as a meaningful criterion to inform the selection of a reference substance. Instead, the selection of the reference substance is informed by the toxicological data used to establish the classification of lead substances as reproductive toxicants. Lead is a very well-studied metal. Under EU CLP, lead metal and all lead compounds are all classified as Repr. 1A. However, in the REACH registration dossier for lead, all available experimental studies on reproductive toxicity were conducted with lead diacetate, a soluble lead compound. In the EU CLP regulation, lead diacetate has a harmonized classification as Repr. 1A with a generic concentration limit of 0.3%. Lead diacetate is therefore selected as reference substance. The relative bioaccessible concentration of lead in the slag can now be calculated, with lead diacetate as reference substance. Bioelution data show that lead diacetate fully dissolves in gastric fluid. Due to the molecular weight correction, this corresponds to a bioaccessibility of 634 mg per g substance tested. The relative bioaccessible concentration of lead in the final slag therefore equals

$$0.105 / 634 * 100\% = 0.017\ \%$$

The relative bioaccessible concentration of lead in the final slag is far below the concentration limit of 0.3% which applies to the selected reference substance. The final slag is therefore not classified for the endpoint reproductive toxicity.

The correction for bioaccessibility has been implemented in MeClas, and a calculator is provided to the user. A screenshot of the calculator is provided in Figure 3, with the data for the above example filled in.

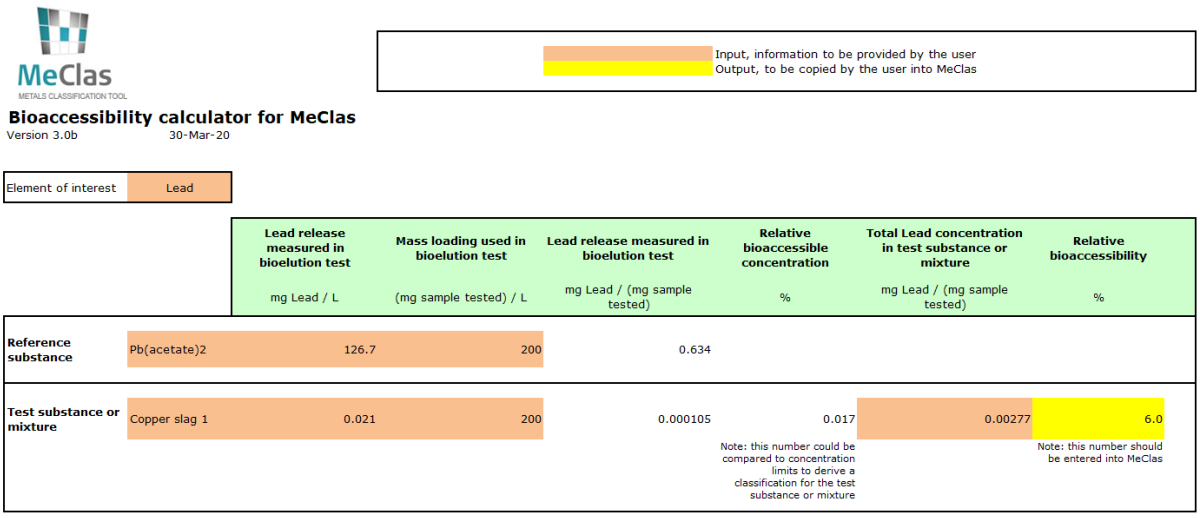


Figure 3: Bioaccessibility calculator for MeClas, completed with the data corresponding to the copper slag discussed in this section.

## 4. References

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