USE OF READ-ACROSS IN THE HEALTH RISK ASSESSMENT OF FERROCHROMIUM ALLOYS UNDER REACH

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ABSTRACT

In REACH regulation there is a category of substances called special preparations, to which alloys belong. In the assessment of special preparations not only the bulk composition of an alloy, but also the way the constituent metals are bonded in the chemical matrix, shall be taken into account. The surface of the alloy may limit the ability of constituent metals to be released from the matrix and thus affect the toxicological profile of an alloy. Therefore, the surface characteristics and the release rates of metals shall be taken into account.

Finnish Institute of Occupational Health has been carrying out REACH-compliant chemical safety assessment of ferrochromium in collaboration with International Chromium Development Association. Ferrochromium is composed mainly of chromium and iron with small amounts of other metals, e.g. nickel. Since almost no studies have been published on the health effects of ferrochromium, the assessment of ferrochromium should be based on its constituent metals.

An approach used in this study included the use of data on surface composition and release of metal constituents from ferrochromium. The chromium oxide surface layer limits the release of nickel and other constituents from ferrochromium and affects the toxicological profile. As a result it can be concluded that ferrochromium alloys can be likened to chromium metal and stainless steel when assessing their health hazards. Thus, the risk assessment can be based largely on existing human, animal and in vitro toxicity data on chromium metal, chromium(III)oxide and stainless steel. By referring to this data, it was possible to make conclusions on health hazards of ferrochromium without need to carry out any new toxicity tests.

1 INTRODUCTION

1.1 REACH and alloys

The European Union legislation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) applies to the manufacture, placing on the market and the use of chemical substances on their own, in preparations or in articles. A substance is defined in REACH as a chemical element or its compounds with additives necessary to preserve its stability and impurities deriving from the process used. A preparation means a mixture or solution composed of two or more substances [1]. Alloys do not fit either of these definitions. However, there is a special category called special preparations in REACH to which alloys belong. No specific definition is, however, given for special preparations.

REACH sets a general provision to register substances on their own or in preparations. Registration includes the chemical safety assessment of these substances. In the REACH regulation it is stated, that in the assessment of special preparations not only the bulk composition of an alloy, but also the

way the constituent metals are bonded in the chemical matrix, shall be taken into account [1]. However, there is no further guidance how this should be performed. Currently, the work is going on to develop guidance on the health risk assessment of alloys under the HERAG platform [2]. This study presents an approach for the chemical safety assessment of ferrochromium using information on surface properties and release of individual elements from alloy matrix *in vitro* to support the read-across.

1.2 Ferrochromium

Ferrochromium is a smelted alloy produced mostly as a high-carbon ferrochromium by direct carbothermic reduction of chromite ore in three-phase submerged electric arc furnace. It has a minimum chromium content of 45.0 wt%, and a maximum chromium content of 95.0 wt% depending on the type of the ferrochromium [3]. Iron is the other main constituent of ferrochromium, constituting most of the remaining alloy. Minor elements in ferrochromium include for example silicon, nickel and vanadium. Nickel and silicon may be present at levels up to 0.5 and 1 wt%, respectively.

It is well known in metallurgy and material and corrosion science that on contact with air or other oxygen-containing media, elemental chromium and other engineering metals rapidly oxidise, resulting in a thin layer of oxides on the surface of the metal or alloy. This passivation layer very effectively separates the bulk material from the surrounding medium. If the layer becomes damaged (e.g. by scratching) it immediately self-heals by oxidation. In ferrochromium, this layer of chromium oxide limits the release of iron, nickel and other constituents. Therefore, it is likely that this layer affects also the toxicological properties of ferrochromium. However, so far no toxicological data is available on the possible health effects of ferrochromium. Thus, the assessment of ferrochromium should be based on read-across from constituent metals or similar alloys taking into account these specific alloy properties, which affect the release of the elements from the alloy matrix.

1.3 Release rate data in the human health hazard assessment

Release rates have been used to assess the nickel release from stainless steel. European Nickel Directive 94/27/EEC[4] sets a limit of 0.5 µg/cm^2/week for the nickel release from nickel containing metals or alloys. This limit has been shown to reduce the nickel release at such a low levels that the risk of nickel sensitization in contact with the material is low [5]. According to new EU regulation on classification, labelling and packaging of chemicals [6], alloys containing nickel are classified for skin sensitisation when the release rate of 0,5 µg Ni/cm^2/week in artificial sweat, as measured by the European Standard reference test method EN 1811, is exceeded.

Although the use of release data in the assessment of the risk of nickel sensitization by nickel containing alloys is accepted at regulatory level, in the case of other toxic endpoints and other elements the use of this knowledge on the release rates of individual constituents from the alloy matrix is still under development.

1.4 The aim of the study

The aim of this study was

1) to develop a read-across based method to assess the health hazards of ferrochromium using information on surface properties and bioaccessibility of individual constituents from the alloy matrix, and
2) to carry out the human health hazard assessment of ferrochromium. The outcome of the study would be the derivation of REACH DNEL (derived no effect level) for FeCr and a decision whether there is any need for further tests.

2 MATERIALS AND METHODS

The approach used in this study to assess the health hazards of ferrochromium is presented in Figure 1.

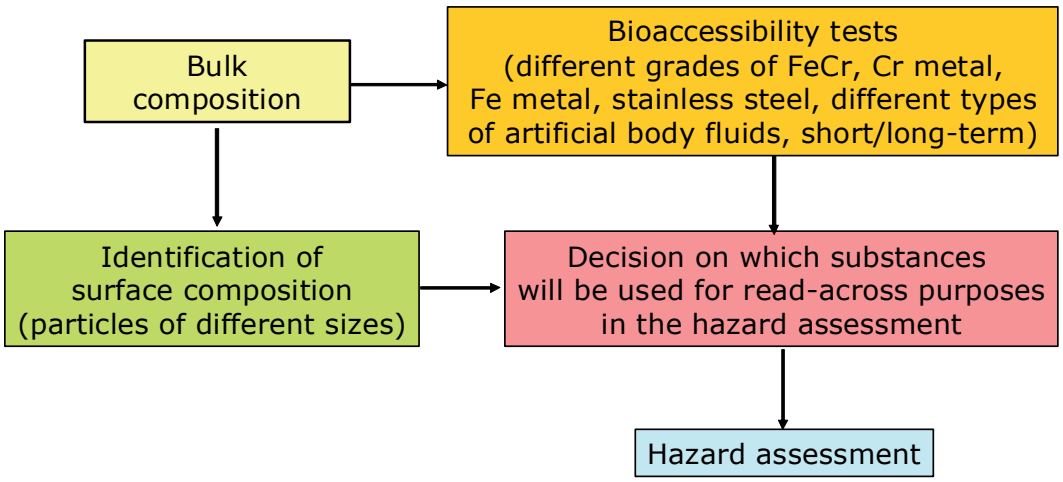

Figure 1: Workflow for hazard assessment of FeCr

Briefly, the data on FeCr surface properties and release of different elements from ferrochromium, chromium, iron and stainless steel were collected and evaluated. Based on the obtained data it was possible to decide, which is the main component of ferrochromium determining its toxic properties. Decisions on grouping and source substances were made and the assessment was based on read-across from the source substance(s).

The toxicological data on substance(s) selected as source substance(s) for read across was collected and evaluated. Toxic endpoints relevant in REACH, which were considered in the assessment, are listed in Table 1. Also available epidemiological data from ferrochromium industry was taken into account. Based on this data, decisions on the possible hazards, further data needs and a suggestion on DNEL were made.

Table 1: Toxic endpoints needed to be covered in REACH at >1000 tonnes level [1].

Skin irritation or corrosion	Mutagenicity
Eye irritation	Repeated dose toxicity**
Acute toxicity	Reproductive toxicity**
Toxicokinetics	Carcinogenicity**
Skin sensitization	

** Studies which usually provide quantitative data for derivation of DNELs/DMELs

3 RESULTS

3.1 Available data on the surface composition and the release of elemental constituents from FeCr

The general bulk and surface composition of ferrochromium has been described in common handbooks. Midander et al. [7] studied the surface composition of ferrochromium particles (<63 µm) and confirmed that the surface is composed mainly of chromium and iron oxides but there is also some enrichment of silicon (a few percents when the bulk content of silicon is 1 wt%).

Bioaccessibility tests have been performed with chromium particles, iron particles and ferrochromium particles [7,8,9,10] in different artificial body fluids. Comparative data on the release rates of chromium, iron and nickel from stainless steel and pure metals has also been published [7-11].

Midander et al [7,9] studied the release of chromium and iron from fine sized (<20 µM) particles of chromium, iron and ferrochromium during one week of incubation in artificial lysosomal fluid with pH

of 4.5. This fluid mimics the inflammatory conditions in the lysosomes of alveolar macrophages eliminating particles from lungs[12]. The results show that ferrochromium particles (Cr 67 wt%, Fe 25 wt%) have a similar low release of chromium as pure chromium particles. Chromium is released as trivalent chromium and no hexavalent chromium could be identified [7,9]. Iron release from ferrochromium is about a hundred fold lower than from pure iron particles. Similar pattern was also reported by Ullmann [8] on the release of chromium and iron from chromium, iron, ferrochromium and stainless steel particles (< 63 µm) incubated in synthetic sweat for one week. Examples of results on these studies are presented in Tables 2 and 3.

Table 2: Table 2. The release of iron and chromium from fine (<20 µm) FeCr, Cr and Fe particles in ALF expressed as total amount released during 168 h incubation as µg/cm^2 [7]

	FeCr	Cr fine	Fe
Fe	1.3+/-0.07	-	131+/-1.7
Cr	0.08+/-0.02	0.01+/-0.002	-

Table 3: Table 3. The release of iron and chromium from coarse (<63 µm) FeCr, Cr and Fe and stainless steel particles during 168 h incubation in artificial sweat calculated as µg/cm^2/week [8,9]

	FeCr	AISI 316L	Cr fine	Fe
Fe	0.08+/-0.02	0.11+/-0.06	-	8.62+/-5.1
Cr	0.015+/-0.0002	0.007+/-0.001	0.0012+/-0.003	-

Similarly, the release of chromium from stainless steel sheets is the same as from pure chromium sheets but the release of iron and nickel is about 1000-fold lower from stainless steel than from pure iron and nickel sheets [11].

The release of minor constituents has also been studied [7]. Nickel release has been tested e.g. in synthetic gastric fluid (pH 1.6) and in artificial lysosomal fluid (pH 4.5-5) which are more aggressive fluids than synthetic sweat (the test solution used in the standard EN 1811 test). The results show very low release of nickel (below 0.5 µg Ni/cm^2/week) even under these aggressive conditions. In ALF, like in more pH-neutral solutions (PBS and in Gambles fluid) the release was below the detection limits [7]. This suggests that nickel bioaccessibility from ferrochromium is very low regardless of route of exposure of ferrochromium. Also silicon release was very low or undetectable as well as the release of other minor ferrochromium constituents [7,9,10].

3.2 Grouping

Chemicals can cause adverse effects either at the site where they first are in contact with the body (local effects) or in distant organs after the absorption of the substance into the systemic circulation. Systemic toxic effects of the metallic alloys are dependent on the amount of components available for systemic absorption (bioaccessibility). Also local effects, like irritation or sensitization depend on the ability of the substance to dissolve and modify body macromolecules, causing either inflammation or immunological reactions. For example, when rats were exposed at the same Cr exposure level for 13 weeks to poorly water soluble chromium(III)oxide no signs of respiratory tract irritation were seen, whereas soluble basic chromium sulphate caused widespread inflammatory changes in the respiratory tract [13]. On the other hand, readily soluble compounds are faster eliminated from the lungs than the sparingly soluble compounds.

The release data cited above was used to assess the potential bioaccessibility of ferrochromium components from the alloy matrix and compared to the bioaccessibility of pure metals. The data shows that when FeCr enters the body, the exposure of humans to chromium(III) ions from FeCr particles is likely to be the same as the exposure to chromium from chromium particles. Thus, the bioaccessibility of chromium from ferrochromium particles is similar to the bioaccessibility of chromium released from chromium particles.

On the other hand, the exposure of humans to iron released from FeCr particles containing ~25wt% iron is substantially (>100-fold) lower compared with the release of iron from the same mass of iron particles, meaning that the bioaccessibility of iron from ferrochromium is more than 100-fold lower than iron released from iron particles. This means, from a metal release perspective, that the alloy behaves like particles containing less than 1 wt% of iron in any inert matrix.

Taken together, this data shows that the health effects of ferrochromium can be predicted mainly from the health effects of trivalent chromium and the significance of iron is very limited. Thus, from a health hazard perspective, ferrochromium containing 67 wt% chromium and 25 wt% iron can be considered as an impure form of chromium with only small amounts (<1 wt%) of "active" iron. The health hazard assessment can, therefore, be largely based on the toxicity of chromium. Also the relevance of nickel and e.g. silicon in the health hazard assessment of ferrochromium is very low because of their limited release.

In addition to chromium metal, ferrochromium resembles stainless steel. The surface of stainless steel is also mostly composed of chromium oxide, and it releases chromium at similar amounts as chromium metal. Due to its passive properties, iron and nickel are released from stainless steel at significantly lower levels than from nickel and iron particles [11]. Thus, also stainless steel data can be used for read-across, if available.

3.3 Evaluation of human health hazards

Since trivalent chromium is the main determinant affecting the health hazard profile of ferrochromium, toxicological data on metallic and trivalent chromium were evaluated. Two recent toxicological evaluations on trivalent chromium compounds summarize all the available data on their toxicity [14,15]. The toxicological database on chromium metal is very limited, but since particles of metallic chromium are always covered by chromium(III) oxide, the toxicity of metallic chromium has been concluded to resemble that of chromium(III)oxide, which has similar solubility [14,15]. Thus, data on chromium(III)oxide is mainly used as a source for read across instead of the scanty data on chromium metal. In addition to trivalent chromium, in the case of some endpoints, also data on other components of ferrochromium may become relevant and their potential contribution to the toxicity has to be considered.

3.1.3 Acute toxicity, irritation and corrosivity of ferrochromium

Chromium metal has not been tested for acute toxicity but there is data available on chromium(III)oxide showing low acute toxicity (oral LD_{50} >5000 mg/kg) of trivalent chromium [14,15]. Since ferrochromium is considered as a "preparation" in REACH, classification and labelling rules for mixtures have also to be considered. The assessment of acute toxicity of preparations with several components is based on the additivity equation [6]:

$$100 / ATEmix = 100 / \sum Ci / ATEi \quad (1)$$

in which:

Ci = concentration of ingredient i (% w/w or % v/v)
i = the individual ingredient from 1 to n
n = the number of ingredients
ATE_i= Acute Toxicity Estimate of ingredient i.

Based on the release rate data, however, the active concentration of iron was estimated to be less than 1%. When this is taken into account, it means that even with the highest acute oral toxicity value for soluble iron salt (132 mg/kg [16]), the acute toxicity of ferrochromium remains above the classification limits. Similarly, if active concentration of iron is used instead of bulk concentration in the assessment of irritancy and corrosivity of ferrochromium, the assessment can be justified to be based on the data on trivalent chromium. According to CLP, the lowest concentration limit of ingredients classified for skin/eye corrosive/irritant hazard that triggers classification of the mixture as corrosive/irritant is 1%. Chromium(III)oxide has not shown any skin or eye irritant properties [14,15].

3.2.3 Sensitization

Metallic chromium or insoluble chromium(III)oxide has not shown any ability to cause skin sensitization [13,14]. Considering the sensitizing properties of ferrochromium, the critical component is nickel, which can be present in ferrochromium at levels higher than 0.1 wt%. A bulk composition of 0.1% is the lowest cut-off limit in CLP for ingredients of a mixture containing classified skin sensitizers that trigger the classification of the mixture [6]. However, alloys containing nickel are classified for skin sensitisation when the release rate of 0.5 µg Ni/cm^2/week, as measured by the European Standard reference test method EN 1811, is exceeded [6]. The release rate of nickel remained well below this limit [7,9].

3.3.3 Repeated dose toxicity

There is no data on the repeated dose toxicity of chromium metal but a standard guideline based 13 week inhalation toxicity study has been conducted with insoluble Cr(III)oxide at concentrations of 4.4, 15 and 44 mg/m^3[13]. This study showed no systemic effects related to the exposure to chromium(III)oxide. However, lungs revealed an accumulation of groups of pigmented alveolar macrophages accompanied with slight inflammation in alveolar epithelium at all dose levels. Some minor changes were observed also at the lowest exposure level (4.4 mg/m^3) after the 13-week recovery period. It may be speculated whether the effects seen were mainly particle effects or caused specifically by trivalent chromium. In addition, some studies on FeCr plant workers working in the crushing and sintering department showed respiratory symptoms related to sustained irritation at total dust levels of 2.5 mg/m^3 [17,18]. No other effects have been observed in humans [17,18]. The assessment of the repeated dose toxicity of ferrochromium can be based on the trivalent chromium data. Iron is unlikely to affect the repeated dose toxicity of ferrochromium because of its restricted release.

3.4.3 Mutagenicity, carcinogenicity and reproductive toxicity

If a substance or preparation contains mutagenic or carcinogenic category 1A or 1B impurities or ingredients at levels exceeding 0.1%, the whole preparation shall be classified in the similar category [6]. In the case of ferrochromium attention should involve nickel. Many nickel compounds are known carcinogens. However, evidence on metallic nickel is not so clear. Nickel was evaluated in EU existing substances program and the draft report on the nickel assessment is available [5]. In addition, cancer bioassay to study the carcinogenicity of nickel has been performed. This did not show clear carcinogenic effects [19]. Also the genotoxicity of nickel metal is equivocal. Nickel (metal) is currently classified in EU to carcinogenicity category 3 corresponding cat 2 in the CLP system. For CLP category 2 carcinogens, the classification and labelling cut-off limit is 1%, which is above the bulk concentration of nickel in most grades of ferrochromium. In addition, as described earlier, nickel release from ferrochromium is very limited, which supports the lack of hazard. For chromium, regardless of the huge number of studies, no clear evidence of mutagenicity or carcinogenicity of inorganic trivalent chromium is presented [14,15]. Some limited data on reproductive and developmental toxicity of chromium(III)oxide suggest the lack of reproductive effects [14,15]. Based on bioaccessibility studies ferrochromium is likely to resemble chromium(III)oxide also in this respect.

3.4 Setting of DNEL for ferrochromium

Inhalation exposure limit values for chromium(III)oxide and metallic chromium were set in the human health hazard assessment of trivalent chromium compounds published by ICDA [14] and in the CICAD on inorganic chromium(III) compounds by WHO [15]. The conclusions were based on the repeated dose inhalation study [13] showing a LOAEL of 4.4 mg/m^3 (=3 mg Cr/m^3). Application of 2 and 3-fold inter- and intraspecies assessment factors resulted in a limit value for workers of 0.5 mg Cr/m^3[14,15]. Based on the metal release and surface composition of ferrochromium, the same value is suggested as a DNEL relevant for ferrochromium, as well.

4 CONCLUSIONS

REACH regulation encourages taking all available data into account when assessing the health hazards of chemicals. It also states that the alloy matrix shall be considered when assessing special preparations like alloys. In this study, the information on the release of individual components from the alloy matrix was applied to the assessment of human health hazards. The approach was based on the fact that the systemic toxic effects of an alloy depend on the systemic exposure to the alloy components, independent on if they are available for systemic absorption (bioaccessible) at significant amounts or not. Also local effects, like irritation or sensitization are dependent on the ability of the substance to be released and react with body macromolecules causing either inflammation or immunological reactions.

Based on the release rate data it was possible to conclude that ferrochromium alloys can be likened to chromium metal, chromium(III)oxide and stainless steel in their health hazards. Iron and other minor components are likely to a have minimal effect on the toxicity of ferrochromium due to their restricted bioaccessibility demonstrated in *in vitro* metal release tests [7,8,9,10].

The assessment of ferrochromium could therefore be based on the toxicity of metallic chromium and chromium(III)oxide (source substances for read across) and a DNEL of ferrochromium based on chromium and chromium(III)oxide was proposed. Available human epidemiological data on ferrochromium dust exposure and respiratory symptoms supported this conclusion [16,17]

When considering exposure assessment and REACH exposure scenario (ES) building, trivalent chromium is the best exposure indicator in the FeCr work. The trivalent chromium air levels can be compared to ferrochromium DNEL, which is based on the toxicity data on trivalent chromium. However, it should be noted that in the case of ferrochromium, generation of REACH ES is not needed if chromium/ferrochromium is not classified.

To conclude, data on surface composition and results of *in vitro* metal release tests bring relevant information on the ability of the alloy surface and matrix to restrict the release of some alloy constituents. This information helps to group alloys together and to conduct the read-across. The application of this hazard assessment approach to other alloys demands the generation of bioaccessibility data also on those alloys and their constituent metals.

5 ACKNOWLEDGEMENTS

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