

Use of an Effective Concentration Approach to Classify Alloys

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Abstract

- Most metals on the market are used as alloys; alloys are considered 'special preparations' of metals since their properties differ from those of their metal components.
- Appropriate chemical management practices, including classification, are essential to ensure the safe use of alloys (e.g., UN GHS and EU CLP).
- The default approach for the classification of alloys (as mixtures) is to directly compare the alloy content of classified metals to the classification criteria (i.e., summation rules or additivity formula for acute toxicity classification and cut-off concentration/limit approaches for the other toxicological endpoints).
- In general, the toxicity of metals and alloys is considered to be related to the bioavailability of the metal ion. Due to the alloys' properties, the extent of the metal ion release from alloys (and thus its bioavailability) can be significantly different from the releases from their pure metal constituents.
- Bioelution testing measuring metal ion releases in synthetic body fluids (bioaccessibility) relevant to each route of exposure can be used in the calculation of the effective concentration of classified metals in alloys.
- An overall framework for the human health classification of alloys is proposed, starting from the collection and evaluation of available data and following three tiers of assessment that range from using alloy-specific toxicity data for classification, to bridging information across alloy samples, to using effective concentration of classified metals in an analogous way as simple mixture concentrations.
- The bioelution-derived effective concentration of metals in alloys has been shown to be a better predictor of in vivo toxicity than concentration. The use of effective concentration of metals in alloys allows refinement of the classification for these special and important substances.

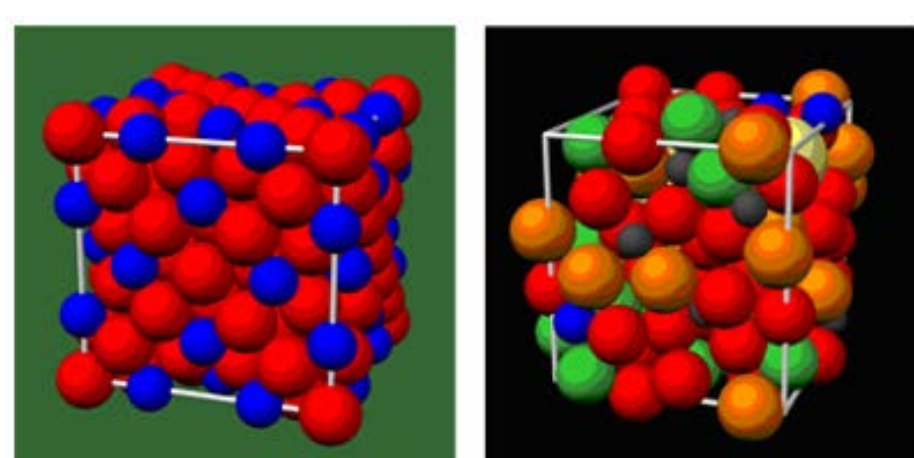
Introduction

- For mixtures (including alloys), regulatory frameworks such as the European Union (EU) Registration Evaluation and Authorisation of Chemicals Regulation (REACH, Regulation EC No 1907/2006) require hazard identification, classification and exposure scenarios to be developed and circulated throughout the supply/use chain, including their use in downstream applications.
- Furthermore, the classification of all alloys in commerce must be compliant with Classification, Labelling and Packaging (CLP) terminology and communicated to the supply chain as of June 2015.
- The fact that alloys largely exhibit different properties from their individual metal components and consequently have different hazard/risk profiles was recognised in 2002 when the UN established the GHS.
- In the EU, REACH designates alloys as a form of "special preparation" due to the potential difference in properties from their constituents and recognising that specific assessment methods will be required.

Alloys

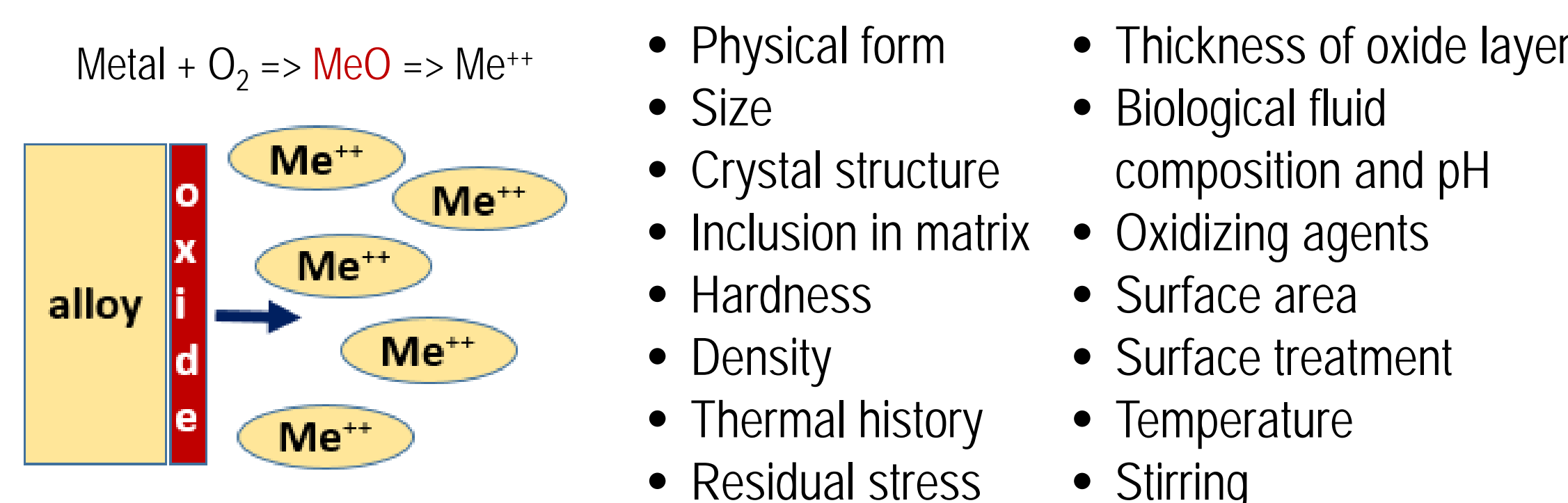
What are they made of?

- Alloys are defined as "...a metallic material, homogeneous on a macroscopic scale, consisting of two or more elements so combined that they cannot be readily separated by mechanical means" (REACH, 2006; UN, 2007).
- In general, a metallic alloy consists of a metal or a metalloid base element, constituting the largest percentage of the material and one or several intentionally added elements to achieve specific and improved mechanical, physical or chemical properties compared to its individual alloy constituents.
- For metal-containing materials, it is generally accepted that their toxicity will be related to the release of soluble metal ions and their uptake by the body and/or interaction at their target sites (i.e., bioavailability).



What drives the release (bioavailability) of metal ions?

- Metal release from alloys in biological fluids affected by:

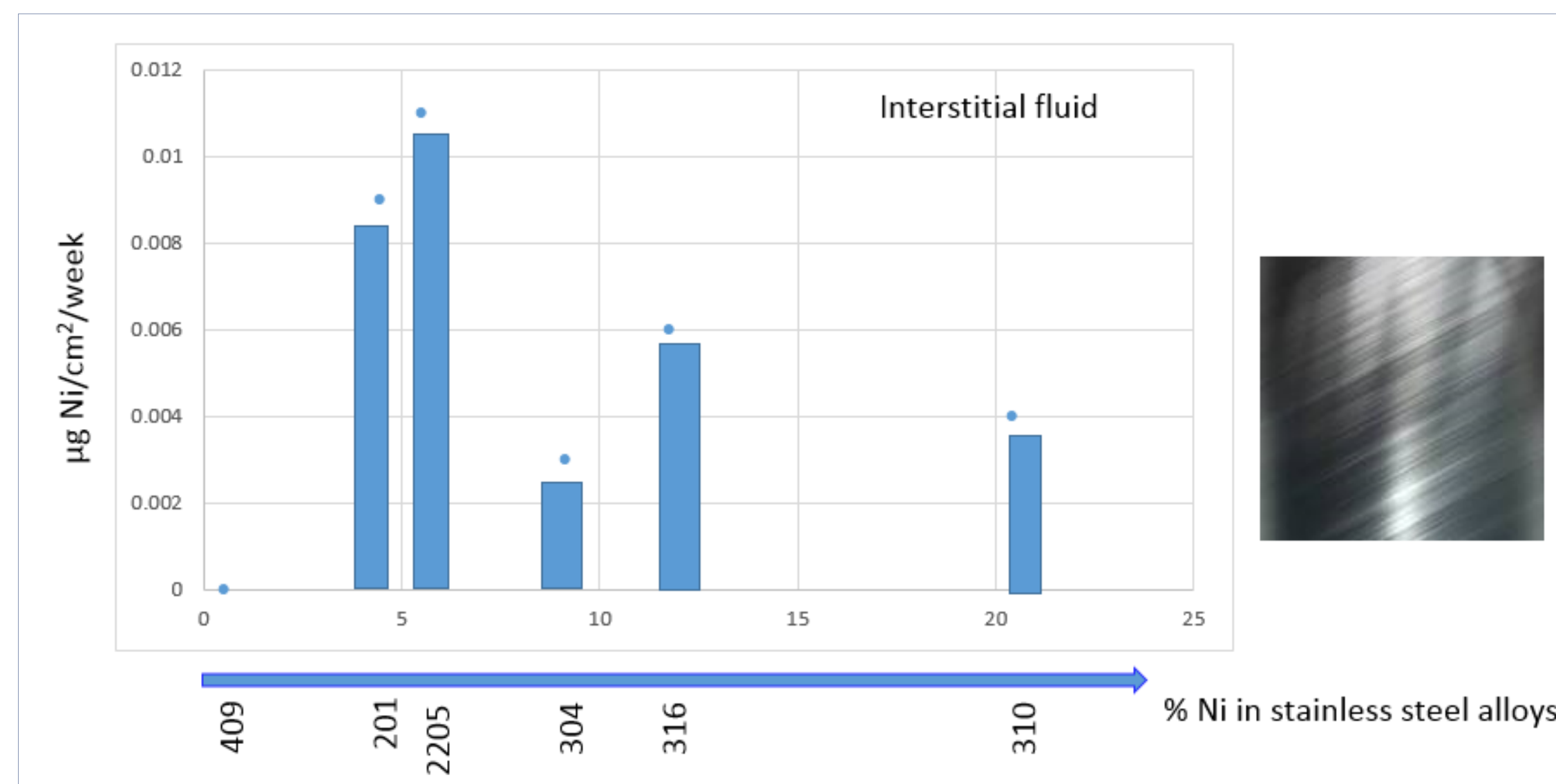


Definitions

- Bioavailability**—the extent to which a substance is taken up by an organism and is available for metabolism and interaction. The toxicity of most metals and metalloids is associated to a large degree with the release of soluble metal ions and, their uptake by the body and/or interaction at their target sites.
- Bioaccessibility**—the fraction of a substance that dissolves under surrogate physiological conditions and therefore is 'potentially available' for absorption into systemic circulation (systemic effects) or for interaction at port of entry sites (local effects). Bioaccessibility can be considered as a conservative estimate of bioavailability for metals.
- Bioelution**—the in vitro methods used to measure the degree to which a substance (e.g., metal ion) is released in artificial biological fluids. Such tests estimate a substance's bioaccessibility in the form of released metal ions (i.e., its solubility under physiological conditions).
- Effective Concentration**—the bioaccessible concentration of a constituent substance (e.g., metal) in the test material (e.g., alloy); it is based on the relative ion release from the test material (e.g., alloy) compared to the ion release from the reference material (e.g., pure metal with known toxicity profile).

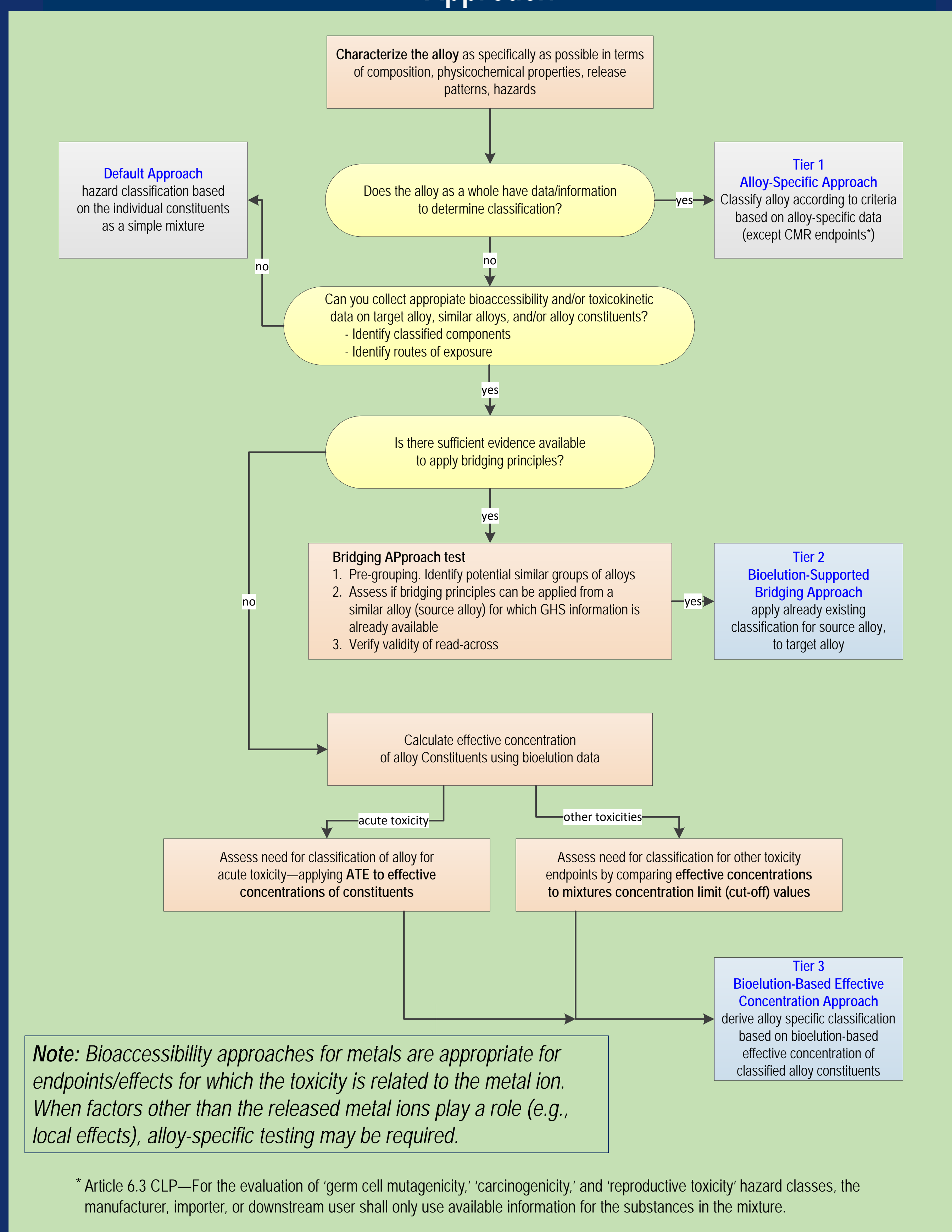
Alloys' Content and Release Do Not Correlate!

Same concentration of a metal in an alloy can lead to different metal ion releases depending on the other elements present in the alloy.

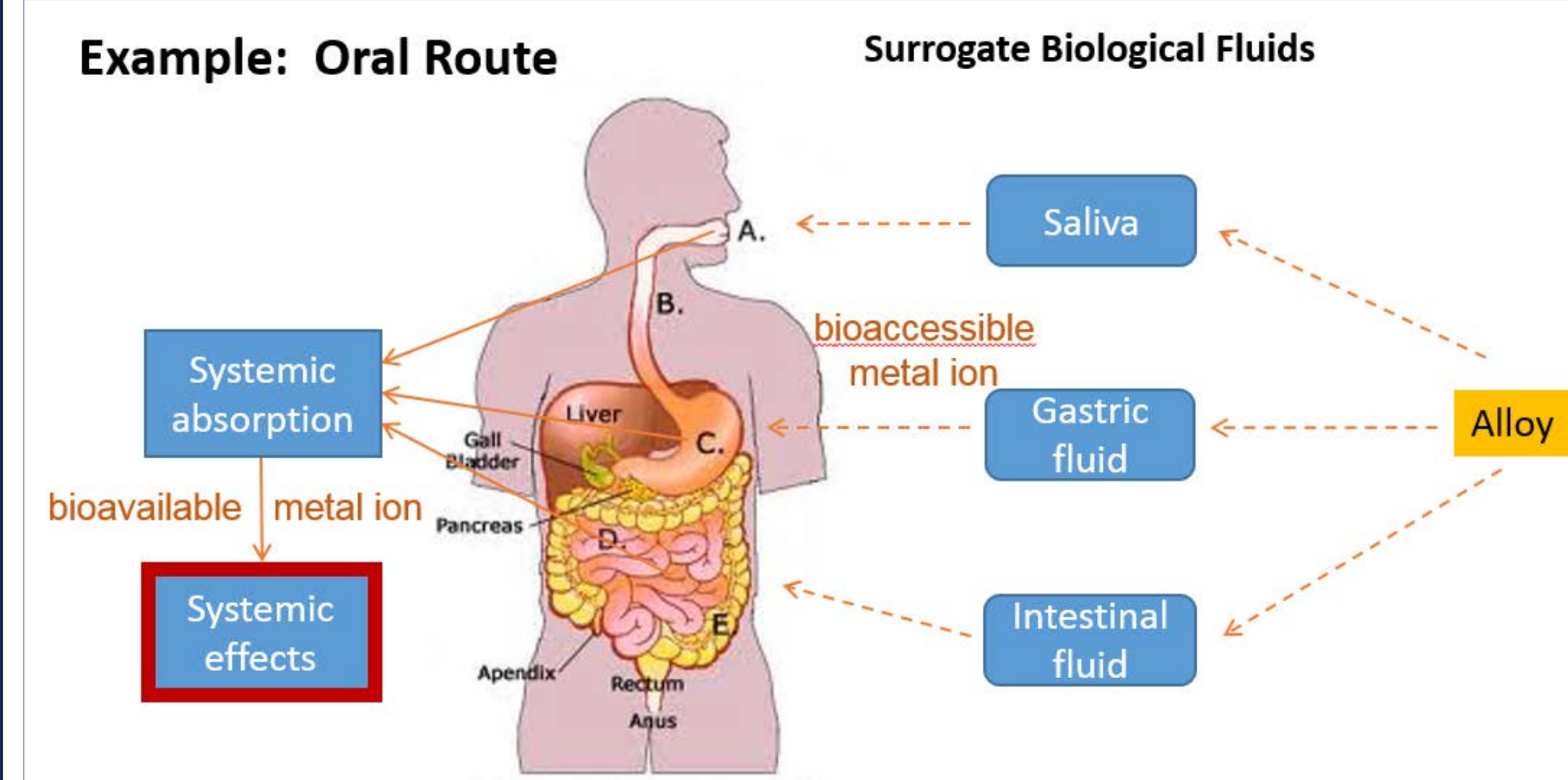


[Stainless steel grades 409, 201, 2205, 304, 316, 310, all contain Fe with >10.5% Cr but differ in the amount of Ni (0-22%) as well as the presence of generally low amounts of additional elements such as Mo, Mn, Si, etc.]

Approach



Bioelution Testing



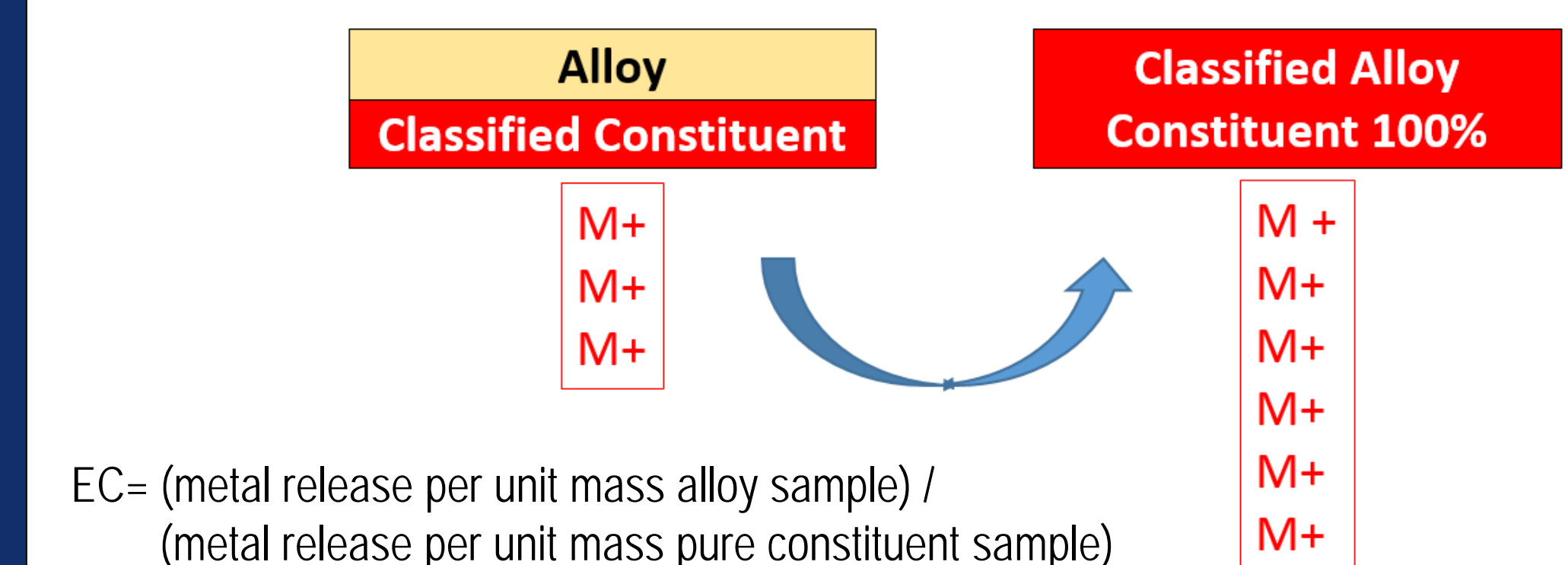
Metal ion releases have been used before for regulatory purposes in the context of human health.

- EN 71.3 & ASTM F-963**
Standard and methods for determining toy safety that specify limits for the migration of metals from toy materials
- REACH Restriction of Nickel & EN 1811**
Consider allowable nickel release from consumer articles intended for prolonged and direct skin contact and provide method to assess Ni release from articles
- REACH Restriction of Lead (Pb) in Consumer Articles** (<http://echa.europa.eu>; adopted opinions on restriction proposals)
Considers allowable lead release from consumer articles that can be mouthed by children (Urrestarazu et al. 2014, Environmental Health 13:66)
- CLP & EN 1811**
Addresses the classification of alloys as dermal sensitizers based on Ni release 12.91

Bioaccessibility Data—Relative Metal Release

Absolute metal releases are seldom used for classification in a human health context!
Exception: nickel release from alloys & dermal sensitization (CLP)

Effective Concentration (EC) is calculated based on the relative metal ion releases from the alloy and from the pure alloy constituents with known toxicity profile and tested under the same conditions.



Verification

Can effective concentration of metals in alloys predict in vivo toxicity better than concentration?

Example—Stainless steel 316L (10.5% Ni⁰, 17.5% Cr⁰, 72% Fe⁰)

Default Classification of SS316L Based on Cut-off Values for Ni	
≥10% Ni ⁰ content in alloy	
Skin Sens 1, Carc 2 (inhalation), STOT RE 1 (respiratory tract)	

- Based on Ni⁰ concentration, SS316L would be classified as STOT RE 1.
- Based on CLP STOT RE 1 classification criterion, inhalation of SS316 powder at >0.06 g/m³ (28-day study) is predicted to cause repeated toxicity in animals.

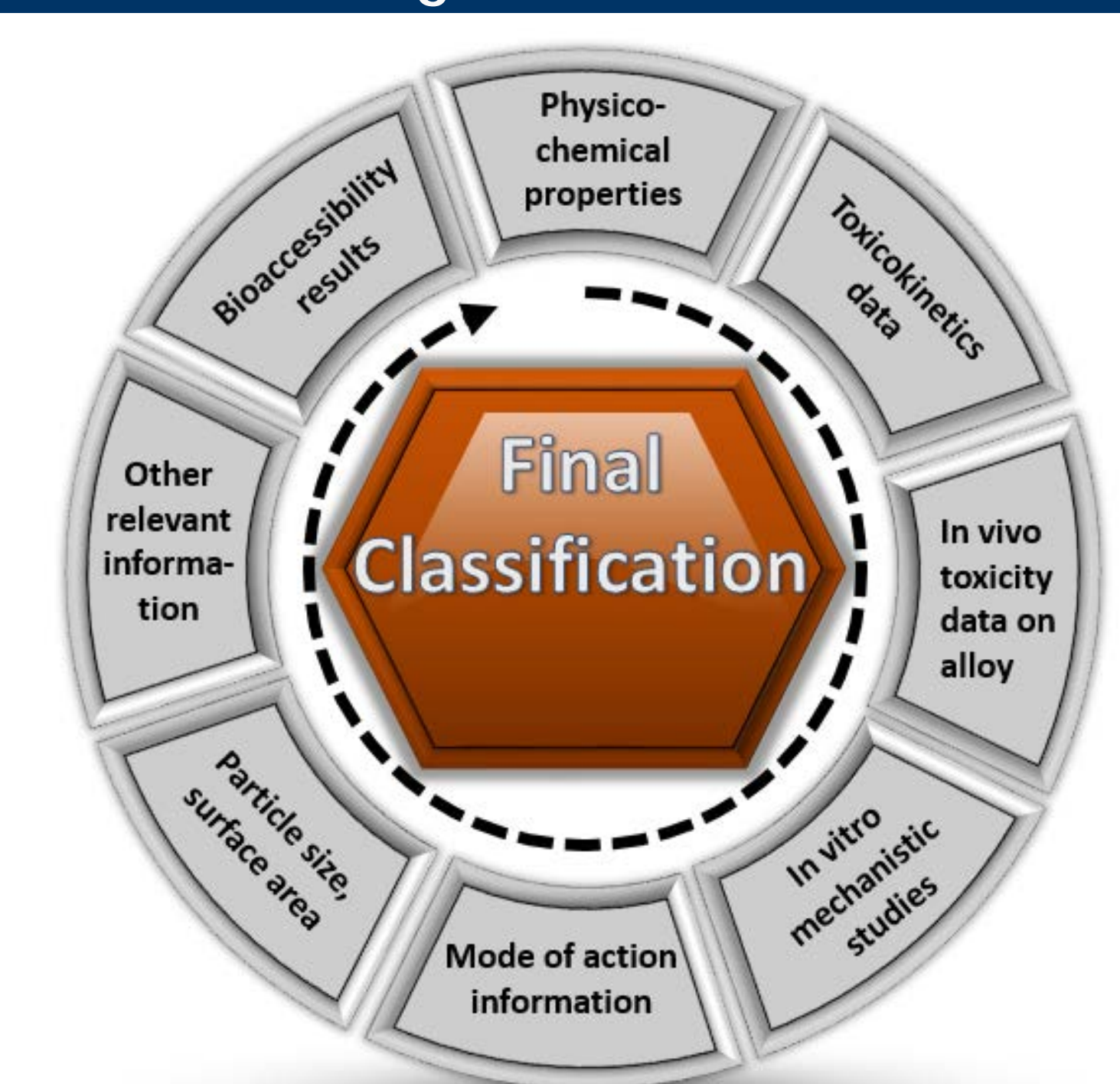
Results

Data Sets	Ni Metal Powder (MMAD = 1.8 µm)	SS316 Powder Predicted Based on Content	SS316 Powder (MMAD 2.5 µm) Observed	Fold-difference Between Predicted (based on Ni concentration) and Observed
Bioaccessibility: µg Ni ion/g sample (168h)	0.87	0.087	0.00088	100-fold
In vivo toxicity: No Adverse Effect Concentration (g/m ³) -28-day study-	<0.004	<0.04	≥ 1.0	> 25-fold

Stockmann-Juvala et al., 2013, HET 32(11): 1137-1154

- Inhalation toxicity of SS316L > 25-fold lower than predicted based on Ni content!
- Effective concentration predicts toxicity of SS316L to be 100-fold lower than that of Ni metal. Observed toxicity was at least 25-fold lower (no toxicity at highest exposure tested).
- SS316L NAEC > 1.0 g/m³ does not meet criterion for STOT RE 1 or STOT RE 2.

Weight of Evidence



Conclusions

- REACH designates alloys as a 'special preparation' recognizing the potential difference in properties from their constituents and that specific assessment methods and new exposure scenarios are required.
- When alloy-specific toxicity data are not available for classification, we propose the application of a tiered approach to the human health hazard classification of alloys that benefits from the use of bioaccessibility data in relevant fluids (e.g., bridging and effective concentrations approaches to classification). When no appropriate data (toxicity, toxicokinetic, or bioelution) on the alloy and/or the alloys constituents are available, the default approach (based on content of classified alloy constituents and cut-off limits for simple mixtures) is applied.
- The relative bioaccessibility data needed for this assessment has to be generated through reproducible and relevant methods.
- The bioelution derived effective concentration of metals in alloys has been shown to be a better predictor of in vivo toxicity than concentration.
- The use of effective concentration of metals in alloys allows refinement of the classification for these special and important substances.
- As for any proposed approach, a weight of evidence evaluation and some level of verification are needed to ensure that the requirements for correctly identifying and communicating the health hazards of alloys are met.

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