Metal release from stainless steel in biological environments: A review

Yolanda S. Hedberg, and Inger Odnevall Wallinder

Citation: Biointerphases **11**, 018901 (2016);
View online: https://doi.org/10.1116/1.4934628
View Table of Contents: http://avs.scitation.org/toc/bip/11/1
Published by the American Vacuum Society

Articles you may be interested in

Mechanism of Electrolytic Oxidation of Aluminum
Journal of Applied Physics **15**, 477 (1944); 10.1063/1.1707459

Incomplete Atomic Arrangement in Crystals
The Journal of Chemical Physics **3**, 592 (1935); 10.1063/1.1749733

Self-organized formation of hexagonal pore arrays in anodic alumina
Applied Physics Letters **72**, 1173 (1998); 10.1063/1.121004

Hexagonal pore arrays with a 50–420 nm interpore distance formed by self-organization in anodic alumina
Journal of Applied Physics **84**, 6023 (1998); 10.1063/1.368911

Self-repair of ordered pattern of nanometer dimensions based on self-compensation properties of anodic porous alumina
Applied Physics Letters **78**, 826 (2001); 10.1063/1.1344575

Fabrication of highly ordered metallic nanowire arrays by electrodeposition
Applied Physics Letters **79**, 1039 (2001); 10.1063/1.1389765

Spectra Simplified
Plot, compare, and validate your data with just a click
eSpectra: surface science
SEE HOW IT WORKS

Metal release from stainless steel in biological environments: A review

Yolanda S. Hedberg[a)]
KTH Royal Institute of Technology, School of Chemical Science and Engineering, Department of Chemistry, Division of Surface and Corrosion Science, Drottning Kristinas väg 51, Stockholm SE-100 44, Sweden and Unit of Occupational and Environmental Dermatology, Institute of Environmental Medicine, Karolinska Institutet, Box 210, Stockholm SE-171 77, Sweden

Inger Odnevall Wallinder
KTH Royal Institute of Technology, School of Chemical Science and Engineering, Department of Chemistry, Division of Surface and Corrosion Science, Drottning Kristinas väg 51, Stockholm SE-100 44, Sweden

(Received 17 September 2015; accepted 14 October 2015; published 29 October 2015)

Due to its beneficial corrosion resistance, stainless steel is widely used in, e.g., biomedical applications, as surfaces in food contact, and for products intended to come into skin contact. Low levels of metals can be released from the stainless steel surface into solution, even for these highly corrosion resistant alloys. This needs to be considered in risk assessment and management. This review aims to compile the different metal release mechanisms that are relevant for stainless steel when used in different biological settings. These mechanisms include corrosion-induced metal release, dissolution of the surface oxide, friction-induced metal release, and their combinations. The influence of important physicochemical surface properties, different organic species and proteins in solution, and of biofilm formation on corrosion-induced metal release is discussed. Chemical and electrochemical dissolution mechanisms of the surface oxides of stainless steel are presented with a focus on protonation, complexation/ligand-induced dissolution, and reductive dissolution by applying a perspective on surface adsorption of complexing or reducing ligands and proteins. The influence of alloy composition, microstructure, route of manufacture, and surface finish on the metal release process is furthermore discussed as well as the chemical speciation of released metals. Typical metal release patterns are summarized. © *2015 Author(s). All article content, except where otherwise noted, is licensed under a Creative Commons Attribution 3.0 Unported License.* [http://dx.doi.org/10.1116/1.4934628]

I. INTRODUCTION

Stainless steel is an iron (Fe) based alloy with at least 11 wt. % chromium (Cr).[1] It may also contain several other alloying elements, such as nickel (Ni), molybdenum (Mo), and manganese (Mn).[2] High corrosion resistance, in combination with good mechanical properties,[3] is the main reason for its wide use also in relatively aggressive environments, such as sea water, food, or the human body.

Even though the corrosion resistance is high, or very high for a given grade, low levels of metals can be released from the stainless steel surface in contact with different fluids. Metal release is here defined as all metal species released from the stainless steel surface into solution due to electrochemical (metal corrosion/oxidation), chemical/electrochemical (dissolution of the surface oxide), or physical processes (removal of metal or oxide particles via, e.g., friction). Knowledge on the extent of metal release is of highest concern in sensitive environments such as within the human body, upon skin contact, and if released into food and drinking water, as it, for instance, may induce allergic and toxic reactions.[4–8] Specific stainless steel grades are designed and used in biomedical applications, such as orthopedic, dental, or cardiovascular implants, to achieve biocompatibility and maintained function with time. These aspects are closely related to a very low extent of metal release, no active corrosion, and physicochemical surface properties that govern protein adsorption and bacteria adhesion.[9–12] Released levels of metals (Fe, Cr, Ni, Mn, or Mo) from stainless steels are generally low due to a high corrosion resistance and the continuous adjustment of the passive surface oxide to the environment. Active corrosion, caused by erroneous grade selection for a given environment, inadequate heating, surface or cleaning treatments, or a too corrosive chemical environment, may result in the enhancement of released metals.

The objective of this review is to compile and elucidate the state of knowledge on prevailing electrochemical, chemical, and physical mechanisms that govern metal release processes from stainless steel, the speciation of metals released into different environments, and the influence of microstructure, route of manufacture, and surface finish on the extent of metal release in selected biologically relevant environments including fluids that mimic human interactions and food contact. The main focus is placed on processes ongoing at the interface between the stainless steel surface and adsorbed organic species and proteins. Aspects of cell adhesion are not covered in any large detail.

II. ELECTROCHEMICAL, CHEMICAL, AND PHYSICAL MECHANISMS OF METAL RELEASE

A. Physicochemical properties of the passive surface oxide

The passive surface oxide of stainless steel is mainly composed of divalent or trivalent Fe and of trivalent Cr

[a)]Electronic mail: yolanda@kth.se

oxide.[13–15] Ni is typically not present in the outermost surface oxide, but is enriched in its metallic form beneath the surface oxide.[14,16–19] Oxides of Mn and Mo can be present in the surface oxide,[14–16,20–22] depending on the stainless steel grade and prevailing environmental conditions. The surface oxide composition, thickness, and other properties dynamically change with time and gradually adjust to the environment.[13,14,19,20,23] Chromium becomes, for example, enriched in the surface oxide at acidic conditions.[19,23–27] The surface oxide composition varies within the surface oxide, with trivalent Cr mostly enriched at the metal-oxide interface,[14,28,29] unless the surface oxide has been exposed to acidic or metal-complexing aqueous solutions for a sufficient time, conditions that result in an increased Cr content of the entire surface oxide.[30] The thickness of the passive surface oxide on stainless steels that is formed in air or water is typically 1–3 nm.[14,20] This thickness varies though depending on prevailing environmental conditions,[14,19] e.g., the surface oxide thickness of implanted surfaces of stainless steel increases with time, primarily due to the incorporation or adsorption of calcium and phosphate from the surrounding fluid.[15]

The passivity (barrier properties) of the surface oxide can be improved by reducing the number and size of inclusions in the bulk alloy[31] (e.g., by lowering the alloy contents of S, C, and N, or via different surface treatments). Passivation treatments[19,31–34] that aim on dissolving instable or less stable phases or elements from the surface oxide, and thereby enrich its Cr-content, can also be used to improve the passive properties.

Reported zeta potential or streaming potential measurements (indicative of the surface charge, but quantitatively possibly different[35]) generally suggest that the surface of stainless steels is negatively charged in solutions of a *p*H exceeding 3–5. The zeta potential is though dependent on the shape of the material (e.g., different charge for particles compared with massive sheet)[36] and on the specific surface finish/treatment.[23,37–41] The surface charge influences which species (e.g., anions, cations, charged small and hard proteins) that are electrostatically attracted, or repelled by the surface for equal charges.[42,43] Other driving forces, i.e., hydrophobic interactions and a net gain in entropy, are also important for proteins, especially if large-sized.[43] A perfectly clean stainless steel surface is hydrophilic, but already adventitious carbon contamination from the ambient air makes the surface close to, or totally, hydrophobic.[23,44,45] Water contact angle values between $<10°$ and 126° have been reported.[23,44–49]

B. Corrosion and passivity

1. Principles

Corrosion (oxidation) of metals in aqueous biological environments is an electrochemical process, which involves an anodic reaction (metal oxidation) and a cathodic reaction, such as oxygen reduction.[50–52] It requires furthermore the metal to be conductive for electrons, and the metal surface to be in contact with an ion-conductive fluid.[50–52] The cathodic and anodic currents (flows of electrons) are equal, which means that both reactions can limit the overall current. Most metals and alloys used in biological environments are passive by nature, which means that a surface oxide acts as an efficient barrier for corrosive species and thereby hinders the anodic reaction.[1,20,53] Once the surface oxide on stainless steel is damaged and the cathodic reaction rate is sufficiently rapid, it is reformed (repassivated/healed) within seconds to a thickness of 1–3 nm due to the ability of the bulk metal/alloy to form stable oxides upon oxidation.[20] This repassivation can take place if the oxidation potential is sufficiently high (e.g., in the presence of oxygen),[20] and if the chemical environment is not too corrosive to, e.g., induce pitting corrosion.[54]

2. Pitting corrosion

Pitting corrosion is one type of a localized corrosion process that can occur on stainless steel. Other corrosion types include crevice corrosion, intergranular corrosion (IGC), stress corrosion cracking, and microbially induced corrosion.[2] For all types of localized corrosion processes, the anodic and cathodic reactions occur spatially separated. Since the anodic area is usually significantly smaller compared with the cathodic area (the area of the intact passive surface oxide), the corrosion rate is comparably rapid. Pitting corrosion is mostly triggered and initiated by the presence of halide ions, especially chlorides in biologically relevant environments.[53] If this kind of active corrosion takes place, it may significantly contribute to the extent of released metals. This is also an effect in the case of metastable pitting, i.e., active pitting corrosion, but where the surface is able to rapidly repassivate and reduce the metal release process. Several pit initiation mechanisms have been suggested in the literature including a penetration mechanism, a film breakdown mechanism, adsorption mechanisms, a percolation model, a localized acidification theory, and a concept related to voids at the metal-oxide interface.[54] Prevailing surface and environmental factors determine the predominating mechanism. Once initiated, the pit either propagates or repassivates. Formation of stable pits (propagating pits) is more probable at higher temperatures, lower *p*H, lower amount of inhibitors (including alloying elements that increase the pitting corrosion resistance), higher amount of corrosive species such as chlorides, higher (more positive) potentials (once a passive film is formed), and if formed underneath a porous passive surface layer or a layer of salt.[54] Only a fraction of formed pit nuclei continues to grow as stable pits.[54]

C. Chemical and electrochemical dissolution of the surface oxide

The origin of released metals from actively corroding metals and alloys is predominantly from oxidized bulk material. This is not the case for stainless steel at passive conditions, where the released amount of metals is substantially

lower and predominantly related to chemical or electrochemical dissolution of the surface oxide and of inclusions, if present. Biological settings generally contain a relatively high amount of metal-complexing (chelating) species and biological molecules such as proteins. Such environments might further include oxidizing or reducing species, e.g., a high content of antioxidants (reducing species) in some food[55,56] or in the human body.[57] Theoretically, the stainless steel surface oxide can be dissolved by reduction (of Fe oxides) or oxidation processes (of the Cr oxide). It should however be noticed that the mixed Fe/Cr surface oxide of stainless steel has very different intrinsic properties and dissolution kinetics compared with the pure oxides of Fe and Cr.[13,58] The behavior of Fe- or Cr-(hydr)oxides might though provide important clues to understand surface oxide dissolution of stainless steels.

Several studies exist that describe complexation/ligand-induced dissolution, reductive or oxidative dissolution, or protonation, of Fe oxides and Cr hydroxide.[58–68] Reductive dissolution of trivalent Fe-oxides (or oxyhydroxides/hydroxides) is, for example, possible at anaerobic conditions in biological environments and is enhanced as the *p*H is reduced,[58,60] and with increasing concentration of reducing species on the surface.[59] Oxidative dissolution of $Cr(OH)_3$ takes place at a $pH > 8$, mediated by surface-deposited higher valent (III or IV) Mn-oxides at oxic conditions.[65] In some cases, chloride-[69] or sulfate-[61] ions have been shown to promote protonation-induced dissolution, acetate[64] to promote complexation/ligand-induced dissolution, and oxalate or carboxylate to promote reductive dissolution.[66] The presence of organic ligands,[58] or phosphate,[67] in solution may either enhance (ligand-induced dissolution),[58] or retard dissolution (by blocking surface sites).[58,67] If protonation, complexation/ligand dissolution, or reductive dissolution are combined, or if two of these processes occur at the same time, dissolution is faster compared with the effect of one of the mechanisms only.[60,70] All mechanisms require that protons, reducing species, and/or complexing species are adsorbed on the surface in a first step.[58,60,66–68] The rate-limiting step is, in the case of both protonation and complexation/ligand-induced dissolution, the detachment of Fe from the surface oxide.[60] For goethite, it has been shown that the adsorption equilibrium constants of some ligands (e.g., phosphate, acetate, and sulfate) could be correlated to the complex formation constants of the corresponding trivalent Fe-ligand complex in solution.[62] This finding agrees with the general observation that the highest (initial) extent of released metals (dominated by Fe) from stainless steel is induced by the ligand with the highest ligand-trivalent Fe-complex stability constant.[71–73] The stability of the surface complex may though not necessarily be the same as formed in solution.[58] Since both the charge of the surface (hydr)oxide and the charge of the ligands change with *p*H, there is often a certain *p*H at which maximum ligand-induced dissolution takes place,[74] e.g., at *p*H 4.5 in citric acid, and for hematite (α-Fe_2O_3).[75] This is also the case for adsorbed reductants and for reductive dissolution of Fe oxides.[63,67] The dissolution rate is further influenced by the type of oxide, e.g., goethite or hematite,[58,60,63] influence of UV-light,[58] and temperature.[74] Goethite that contains 7.8 mol. % Cr (substituted Fe) reveals, for example, a significantly lower dissolution rate in HCl (6 M at 25 °C) compared with pure goethite.[58] This underlines the importance of mixed oxides in the passive surface oxide. This effect has been highlighted for different alloys that possess mixed surface oxides of different, often more protective, properties compared with their corresponding pure oxides.[13,76–79] The crystallinity of the surface oxides are also important as amorphous oxides tend to be more easily dissolved by complexation-induced processes compared with crystalline oxides.[64,92] The presence of point defects, dislocations, microfractures, kinks, grain boundaries, corners, and edges/ledges have further been pointed out to be important for crystal dissolution.[81]

D. Metal release induced by protein adsorption and protein- and biofilm-formation

1. Adsorption of proteins

Surface adsorption of proteins (or ligands/species) is very important for both the metal release and the corrosion process. Adsorption of proteins on solid surfaces depends, e.g., on the protein properties, solution *p*H and ionic strength, the presence of other proteins, the charge of the solid surface, as well as on the surface heterogeneity, hydrophobicity, and the presence of specific surface groups.[43,80,82] In the presence of several different kinds of proteins, already adsorbed proteins may be exchanged in favor of larger proteins of higher binding affinity (known as the Vroman effect).[83] Attempts have been undertaken to modify the stainless steel surface by using irreversibly adsorbed proteins to enhance the attachment of endothelial cells, as this is anticipated to be beneficial for the clinical outcome of stainless steel cardiovascular stents.[84] Surface modification made to control protein adsorption at *in vivo* conditions is though not straightforward due to a very complex chemical environment.[82]

2. Protein-induced metal release

Although protein interactions with stainless steel surfaces (without considering the influence of friction) interact with corrosion processes at static conditions,[38] there are indications in some studies that ligand-induced dissolution, or protonation, of the surface oxide also are important to consider within the context of protein-induced metal release. This is summarized below:

(1) Interactions with bovine serum albumin (BSA) result in a Cr-enriched surface oxide on different stainless steel grades to an extent that could not be explained from the bulk solution *p*H or by a reduced surface *p*H induced by adsorbed albumin.[30,38]
(2) Correlations between the extent of metal release from different stainless steel grades and the adsorption of a specific protein.[23,38,85]

(3) Complexation between different proteins and ions of Fe (Refs. 86 and 87) and Cr.[87–91] Strong surface interactions (grade 316L) with adsorbed BSA and lysozyme (LSZ) from chicken egg white have been observed.[30]
(4) Delayed release of metals (from grade AISI 304) in the presence of albumin,[23] which is typical for ligand-induced dissolution due to the relatively slow detachment step.[58,92,93]
(5) Enhanced release of metals and enrichment of Cr in the surface oxide (grade AISI 316L) at increased albumin solution concentrations, despite the lack of significant change of the thickness and structure of the adsorbed albumin layer at albumin concentrations in solution above a threshold value.[38] This indicates that measured amounts of released metals in solution, at least to some extent, also involve surface-solution exchanged albumin.[23,38]

The structure and conformation of the adsorbed protein layer definitely plays a role for the metal release process,[38,87,94,95] and possibly also for the net charge of the adsorbed protein layer, since it may repel or attract positively, or negatively, charged metal ions/species.[94,95]

3. Influence of proteins and organic species on pitting corrosion

The role of organic species to inhibit or accelerate pitting corrosion is convoluted. Many organic species, including proteins, form complexes with metal ions, especially with Fe at the surface oxide, or when released into solution.[22,23,29,30,38,58,64,71,72,75,87,92,96] These processes assist in surface oxide passivation as their surface interactions may result in the enrichment of Cr in the surface oxide (due to preferential ligand-induced release of Fe from the surface oxide).[22,30,38] Their presence may also hinder repassivation or deteriorate the passivity of the oxide layer,[38,72,216] for example, due to the complexation of surface-bound or free metal ions (one out of many possible explanations). An adsorbed layer of proteins that has the same polarity of the surface charge (negative) compared with the stainless steel surface, such as albumin, may attract protons and therefore reduce the surface *p*H and thereby indirectly influence corrosion and/or metal release processes.[38] Positively charged proteins that are adsorbed on the negatively charged stainless steel surface may in a similar way attract negatively charged species, such as chlorides, which may trigger pitting corrosion.[38]

4. Biofilm formation

In biological environments, pitting corrosion often occurs due to the formation of a biofilm. The biofilm consists of microbes, e.g., bacteria, and extracellular slime.[10] In a first phase, bacteria are initially attached to the surface by long- and short-range interactions, such as electrostatic, hydrophobic, and polar interactions.[10] In a second phase, molecular and cellular interactions between the bacteria and the surface take place.[10] Many environmental factors (such as temperature, *p*H, and chlorides) that influence the corrosion process also influence the characteristics of the biofilm.[10] The presence of a biofilm can, in a similar way as metal-complexing ligands and proteins, accelerate or inhibit corrosion.[97] Biofilms of sulfate reducing bacteria, sulfur-oxidizing bacteria, Fe oxidizing/reducing bacteria, Mn-oxidizing bacteria, and bacteria producing organic and inorganic acids, slime, and volatile compounds, all influence the corrosion process.[98] The biofilm interacts with the metal or surface oxide in several ways; (1) by reducing the oxide,[98,99] (2) oxidizing the metal,[98–100] (3) accelerating or inhibiting corrosion due to the interaction of many different chemical species,[98,99,101–103] (4) mediating electrochemical reactions,[98,99] and (5) influencing the cathodic reaction due to its surface coverage, surface aeration, and *p*H.[87,104] Microbes can also produce strongly oxidizing species, such as H_2O_2 (Refs. 101, 102, and 105) or deposit Mn oxides on the surface,[101,103] which ennobles the stainless steel surface and may result in pitting-[101,103] or galvanic-corrosion.[105] Surface ennoblement can also occur via the interaction with enzymes in the biofilm matrix,[98] and the electrochemical reactions can strongly be influenced by complexation between Fe and macromolecules (e.g., proteins).[98] Diatoms (algae)[105] have been shown to be able to adjust to the cathodic currents on stainless steel.[105] On-going electrochemical reactions in the biofilm are often coupled with electrochemical reactions at the metal or surface oxide for which Fe ions within the biofilm matrix can have a catalytic effect.[98] Surface ennoblement induced by the interaction of diatoms is further strongly dependent on the access to light.[102,105]

E. Importance of friction for metal release

Friction, especially if continuous or frequently occurring, strongly influences both corrosion and metal release processes on stainless steel since the passive surface oxide may be locally destroyed by its action. At such conditions, corrosion and metal release may increase, and micron- and/or nanosized particles may be released into the proximate solution or tissue. This process depends on the prevailing chemical environment and on friction conditions, and is often denoted erosion corrosion[106] (induced on soft and passive metals and alloys, e.g., by particles or gas bubbles), tribocorrosion[53] (mechanical wear and corrosion), or fretting corrosion[53,107] (at the interface between two, closely fitting, surfaces, for example, relevant for articulating parts of prostheses in the human body). Fretting corrosion, alone or in combination with crevice corrosion, has shown up as a common corrosion mechanism on failed implants.[53]

The release of metals and the release of wear particles from, e.g., an implant may induce adverse effects on human health.[108] Even released amounts of metals that do not result in any direct implant failure may pose a risk. Tribocorrosion processes in biological environments are also influenced by the presence of biomolecules such as proteins. Generally, proteins act as lubricants and have been shown to lower the friction coefficient when adsorbed on stainless steel.[87,109,110]

Their efficiency depends on the water content of the adsorbed protein layer (an increasing water content lowers the friction coefficient),[110] and on the degree of protein aggregation, which is influenced by, e.g., *p*H,[111] shear flow,[112] and released metal ions.[113] Even though proteins have the capacity to lower the friction coefficient, their presence has shown to influence the corrosion process and enhance the rates of static corrosion[109] and of tribocorrosion.[114] An alternative explanation could be that the adsorbed protein layer retains wear particles and therefore increases the total wear volume.[115] Recent findings show no change or reduction of the total wear volume in the case of tribocorrosion of stainless steel grade AISI 316L when exposed to albumin concentrations of 20 g/l compared to lower concentrations.[107]

F. Synergistic or antagonistic effects induced by simultaneous metal release mechanisms

More than one mechanism, including corrosion phenomena, dissolution of the surface oxide, and/or friction, are typically taking place at the same time for a stainless steel surface exposed in a biological environment. The predominating metal release mechanism may change with time since the surface oxide, the adlayer and/or biofilm, and the environmental conditions change. All mechanisms may though not automatically result in an increased extent of released metals, their combination can be both synergistic and antagonistic, see examples below.

1. Dissolution or local destruction of the surface oxide

Surface oxide dissolution, or local destruction, occurs via protonation-induced dissolution, reductive dissolution, complexation/ligand-induced dissolution, and/or friction processes. These, or other mechanisms,[54] may also result in local pit initiation in the surface oxide.

2. Metal oxidation (corrosion)

Active corrosion requires the passive surface oxide to be locally ruptured (breakdown). This area then acts as the anodic site whereas the cathodic site is positioned on the non-ruptured passive surface oxide. Depending on the location of the anodic site, and on the biological and mechanical environment, pitting and crevice corrosion, microbially induced corrosion, intergranular corrosion, fretting corrosion (tribocorrosion), stress corrosion cracking, or several of these processes would typically occur.

3. Passivation of the surface oxide and surface adsorbants

Any of the above mentioned surface oxide dissolution mechanisms may passivate the surface oxide by preferentially dissolving Fe (resulting in Cr enrichment), dissolve inclusions or the oxide at unstable, defective sites, resulting in repassivation events. Passivation hinders/decelerates both surface oxide dissolution and corrosion. Surface adsorbed ligands may block sites for other more aggressive ligands, block cathodic or possibly anodic sites (hinder active corrosion), or (for macromolecules) act as lubricants and result in conditions of lower friction.

The same species, e.g., an organic acid or a protein, can hence either enhance or hinder the metal release process, depending on the stainless steel grade, the prevailing environment, and the surface history, since passivation of the surface oxide is the result of events of surface oxide dissolution and/or corrosion. Some important factors that govern corrosion and metal release processes at biological conditions, including the solution, the presence of a biofilm and adsorbed species, the surface oxide characteristics, and the metal substrate properties, are schematically illustrated for a pitting event in Fig. 1. The influence of friction is excluded from the figure. Other important factors not considered are

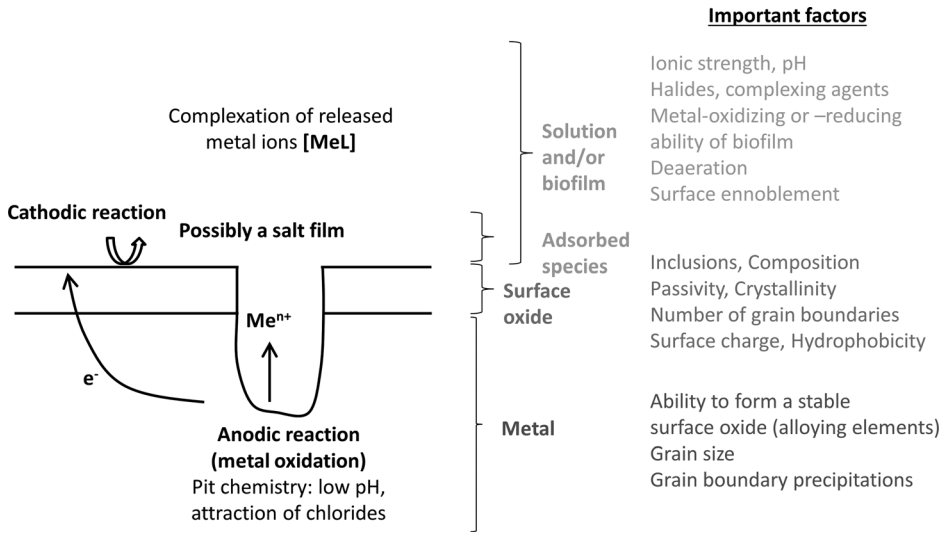


FIG. 1. Simplified illustration of a localized corrosion (pitting corrosion) event of stainless steel and some important factors that influence the extent of metal release in a biological environment.

the temperature, the pressure, the effect of light and applied potential, and conditions with coupled metals.

III. CHEMICAL SPECIATION OF RELEASED METALS

Released metals are in most biological environments very seldom present as free cations (e.g., Fe^{2+}, Cr^{3+}, and Ni^{2+}), but rather exist as different complexes of varying stability.[116] Depending on the prevailing release mechanism, released metals form complexes at the surface (that are later possibly detached), in any surface biofilm or when entering into solution. The chemical speciation of released metal species depends, for a given setting, on the solution composition and *p*H, the temperature, the redox potential, the concentration of released metal ions and of ligands, as well as on time.

The chemical speciation of released metals is important for assessing equilibrium constants (Nernst equation), dissolution kinetics, and precipitation of released species, and hence highly important for toxicological considerations. Knowledge on precipitation of released species is important for: (1) any (further) corrosion processes, as precipitated phosphates, for instance, might protect the surface, and/or induce crevice corrosion, (2) considerations of the fate of released metals as they, for example, might concentrate locally, and/or be transported/distributed in a different way compared to mobile metal species, and (3) experimental design of metal release studies and their interpretation, as the measured metal concentration in solution is the sum of background contamination and of released metal species in solution, i.e., with precipitated metal species subtracted. This effect has been clearly observed in several studies at neutral *p*H, where the aqueous metal concentration diminishes with time due to precipitation processes.[117–119] From this clearly follows that metal release studies performed at neutral or alkaline *p*H (for Fe, Cr, Mn, or Ni), or at acidic *p*H (for Mo),[76] should take into account potential precipitation effects of formed metal-complexes, and that measured amounts of released metals at such conditions might be underestimated.

The toxicity,[120] bioavailability,[121] skin diffusion,[122,123] and allergenic potential[124–127] of released metal ionic species are strongly dependent on their chemical speciation. Main focus has been given to the speciation of Cr since hexavalent Cr is significantly more toxic and allergenic compared with trivalent Cr. The release of hexavalent Cr (mono- or dichromate) is theoretically possible at very oxidative (e.g., strong applied oxidative potential) and/or at alkaline conditions, where it is thermodynamically stable in solution.[128] Only trivalent Cr (no hexavalent Cr) has been shown to be released from different stainless steel grades into: (1) phosphate buffered saline (PBS, *p*H 7.4),[77,117] (2) phosphate buffered saline with a physiologically relevant concentration of hydrogen peroxide (10 μM H_2O_2),[117] (3) gastric solution (*p*H 1.5),[77] (4) citric acid (5 g/l, *p*H 2.4),[22] (5) artificial lysosomal fluid (ALF, *p*H 4.5),[71,77] (6) artificial sweat (*p*H 6.5),[79,129] (7) artificial fresh water (*p*H 6.0 and 8.0),[118] (8) 0.9% saline,[129] (9) Gamble's solution (*p*H 7.4),[77] (10) Ringer's solution [*p*H 7.4, at oxidative potential below the breakdown potential (75 mA/cm^2 during 1 h)],[130] (11) artificial tap water (*p*H 7.5),[22] and (12) artificial tear fluid (*p*H 8.0).[79] Only one study claims that hexavalent Cr is released at both *in vivo* and *in vitro* conditions from stainless steel.[131] However, the surface was oxidatively pretreated (0.5 h at 0.5 V versus a saturated calomel electrode) in chloride-containing solution at neutral *p*H (Ref. 132) (conditions of high risk for pitting corrosion), and do hence not reflect realistic surface conditions.[131]

Predictions of the chemical speciation of released Fe, Cr, Mn, and Ni [using the JOINT EXPERT SPECIATION software, JESS, version 8.3 (Ref. 133)] from stainless steel grade AISI 304 (surface area to solution volume ratio of 1 cm^{-1}) are presented in Fig. 2 (based on measured released metal

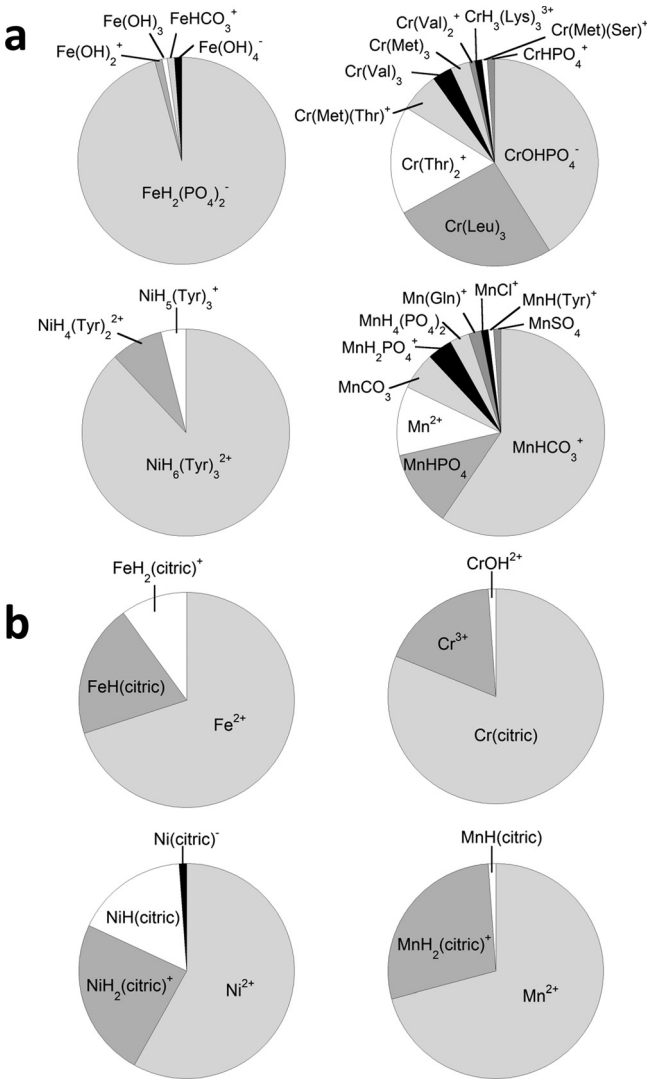


FIG. 2. Chemical speciation of released Fe, Cr, Ni, and Mn from stainless steel (grade AISI 304) in cell medium DMEM at *p*H 7.4 (a) and in 5 g/l citric acid at *p*H 2.4 (b) calculated using the JESS software. Predominant species greater than 0.5% prevalence (max. ten species) are shown in the graphs. Input data are given in Table I. Fe is at the given conditions predominantly present in both valence state +II and +III, Cr in valence state +III, and Ni and Mn in valence state +II. Leu, Leucine; Thr, Threonine; Val, Valine; Met, Methionine; Lys, Lysine; Ser, Serine; Tyr, Tyrosine; Gln, Glutamine; citric, $C_6H_5O_7$ (-III); and DMEM, Dulbecco's Modified Eagle medium.

concentrations in solution) for two different fluids to illustrate the importance of solution chemistry, and that free metal ions are not likely to exist to any large extent in complex biological solutions at neutral *p*H due the formation of different metal complexes.

The first example [Fig. 2(a)] is based on measured metal concentrations released from grade AISI 304 after 24 h in phosphate buffered saline (*p*H 7.4, 37 °C) containing BSA (10 g/l),[38] and is calculated for conditions of the chemically relatively complex cell medium Dulbecco's Modified Eagle medium (DMEM) at *p*H 7.4. The second example [Fig. 2(b)] is based on measured metal concentrations released from grade AISI 304 exposed in citric acid (5 g/l, *p*H 2.4) for 2 h at 70 °C followed by 24 h at 40 °C[134] and calculated for the same solution. All input values for the modeling are provided in Table I. Even if other valence states of the released metals are chosen, the same result will, due to thermodynamic reasons, be obtained. The reliability of chemical speciation modeling calculations strongly depends on the quality of the database. The reliability of the predicted speciation is higher in citric acid [Fig. 2(b)] compared with the more complex cell solution [Fig. 2(a)], which may be due to possible errors or lack of data in the database. Modeled speciation data for the cell medium should hence not be taken as absolute, but rather illustrate that free metal ions are not probable to exist at given released metal concentrations (relevant for stainless steel) in cell medium at *p*H 7.4. Another factor, as described above, is that released metals might form metal-complexes that precipitate (e.g., complexes with uncharged phosphates or hydroxides). The effect of precipitation has not been taken into account in these calculations. In citric acid of lower *p*H (*p*H 2.4), and lack of other organic/inorganic ligands, is the free metal ion fraction more pronounced for all released metals compared with DMEM.

Further measurements and predictions on the chemical speciation of released metals are though needed (and ongoing by the authors) to distinguish between equilibrium-driven dissolution (by sequestration of released metal ions) and ligand-induced dissolution (cf. Sec. II), and to further elucidate its importance to assess potential adverse effects induced by the release of metals from metal and alloy surfaces into biological settings.

TABLE I. Input values to chemical speciation calculations (using the JESS software) shown in Fig. 2.

DMEM [Fig. 2(a)]	Citric acid [Fig. 2(b)]
28.4 μM Fe^{3+}	38.3 μM Fe^{3+}
0.25 μM Cr^{3+}	3.9 μM Cr^{3+}
0.67 μM Ni^{2+}	0.73 μM Ni^{2+}
0.38 μM Mn^{2+}	0.25 μM Mn^{2+}
*p*H 7.4	*p*H 2.4
Redox potential: 308 mV (versus standard hydrogen electrode)	Redox potential: 308 mV (versus standard hydrogen electrode)
37 °C	40 °C
0.4 mM glycine (hydrophilic/hydrophobic)	0.026 M citric acid
0.4 mM L-arginine hydrochloride	
0.2 mM L-cystine 2HCl (S-S)	
4 mM L-glutamine (Neu)	
0.2 mM L-histidine hydrochloride-H_2O	
0.8 mM L-isoleucine (hydrophobic)	
0.8 mM L-leucine (hydrophobic)	
0.8 mM L-lysine hydrochloride	
0.2 mM L-methionine (Neu)	
0.4 mM L-phenylalanine (hydrophobic)	
0.4 mM L-serine (Neu)	
0.8 mM L-threonine (hydrophobic)	
0.08 mM L-tryptophan (hydrophobic)	
0.4 mM L-tyrosine disodium salt dihydrate (hydrophobic)	
0.8 mM L-valine (hydrophobic)	
0.009 mM folic acid	
0.02 mM pyridoxine hydrochloride	
0.001 mM riboflavin	
0.01 mM thiamine hydrochloride	
1.8 mM calcium chloride ($CaCl_2$) (anhyd.)	
0.0003 mM ferric nitrate [$Fe(NO_3)_3 \cdot 9H_2O$]	
0.8 mM magnesium sulfate ($MgSO_4$) (anhyd.)	
5.3 mM potassium chloride (KCl)	
44 mM sodium bicarbonate ($NaHCO_3$)	
110 mM sodium chloride (NaCl)	
0.9 mM sodium phosphate monobasic ($NaH_2PO_4 \cdot 2H_2O$)	
25 mM D-glucose (dextrose)	
0.04 mM phenol red	

IV. IMPORTANCE OF ALLOY COMPOSITION, MICROSTRUCTURE, ROUTE OF MANUFACTURE, AND SURFACE FINISH ON THE METAL RELEASE PROCESS

A. Alloy composition and comparison with corresponding pure metals

The release of metals from different stainless steel grades has been compared to metal release from Ni metal,[78,135–139] Cr metal,[77–79,118,135,138] and Fe metal[38,77–79,118,135,138] in protein (albumin) containing fluid,[38] in different artificial body fluids,[38,77–79,138,139] semiphysiological medium,[137] upon skin contact,[136,139] in artificial rain,[135] and in artificial surface water.[118] In all cases, the release of Cr from Cr metal was similar (within twofold),[77–79,135,138] or lower (7–20-fold),[78,118] compared with the release of Cr from stainless steel. The release of Ni was higher (30–5000-fold)[78,135–139] from Ni metal compared with stainless steel. Similar observations were evident for Fe (10–1150-fold times higher).[38,77–79,118,135,138] Similar and relatively low released amounts of Cr from Cr metal and stainless steel into the above mentioned media are related to the presence of a passive trivalent Cr-rich surface oxide on Cr metal, and a passive trivalent Cr-rich surface oxide on stainless steel.[13] The large discrepancy in released amounts of Ni and Fe from the alloy compared with the pure metals is attributed to the passive surface oxide properties of the alloy.[72,128]

The degree of alloying (Cr, Ni, Mn, Mo, etc.) and presence of impurities (C, S, N, etc.) influence the alloy microstructure, and hence the specific corrosion resistance

(e.g., pitting corrosion resistance, or intergranular corrosion resistance) for a given grade.[2,13,140,141] As discussed in Secs. IV B and IV C, these factors also influence the extent of metal release.

B. Microstructure and degree of alloying

Differences in the total (Fe + Cr + Ni + Mo) amount of released metals from stainless steel grades of different microstructure (AISI 201, 304, 310, 316L, 409, 430, and duplex EN1.4462) exposed for one week into Gamble's solution of relatively low metal complexation capacity and near-neutral *p*H conditions (*p*H 7.4) was less than tenfold among the investigated grades. This screening included also highly corrosion resistant grades that are not designed for an intended use in biological environments. The highly corrosion resistant austenitic grade AISI 310 (24.2 wt. % Cr, 19.1 wt. % Ni) released the lowest amount of metals, but there was otherwise no clear trend in terms of corrosion resistance for the other grades.[142] The difference was <20-fold in ALF of high metal complexation capacity (due to a high concentration of citric acid, 20.8 g/l) and a lower *p*H (*p*H 4.5). Grade AISI 310 was releasing the lowest amount of metals, and the ferritic grade AISI 409 (with the lowest Cr bulk content, 11.4 wt. %) released the highest amount among the investigated grades.[142] Fe was the predominating element released from all grades. The release of Ni, Cr, and Mo did not follow the same trends and could neither be correlated to the bulk content, the surface composition, nor the corrosion resistance. The release of Ni in ALF was, for example, highest for the austenitic grade AISI 316L, even though it is not the alloy of lowest corrosion resistance or alloying content.[142]

Similar observations have been made in a metal release study on different stainless steel grades (EN1.4003, AISI 430, 204, 201, 316L, 304, and duplex EN1.4162) in citric acid (5 g/l, *p*H 2.4).[134] The EN1.4003 (11 wt. % Cr) grade released most metals (Fe + Cr + Ni + Mn) and revealed the highest amount of released Fe, an amount that decreased with increasing Cr bulk content and corrosion resistance.[134] The release of the other elements (Cr, Ni, and Mn) did not follow such a trend, but was seemingly higher for the grades of higher corresponding bulk content of the same elements. For example, the highest Ni release was observed for AISI 304 and 316L, the highest Cr release for EN1.4162, and the highest Mn release for AISI 204 and 201.[134] However, the difference among the different grades was less than tenfold.[134]

A study on the release of metals from different ferritic stainless steels (bulk Cr content: 11–23 wt. %) in acetic acid with or without chlorides and hydrochloric acid showed reduced levels of released Cr for grades of increasing Cr bulk alloy content.[33]

The extent of metal release (Fe, Cr, Ni, Mn, and Mo) from seven different austenitic stainless steel grades, of which five were Ni-free and two contained Ni, was investigated in artificial sweat (*p*H 6.5) and bone plasma (*p*H 7.5).[143] The total amount of released metals did neither decrease with increasing Cr bulk alloy content nor did the alloying element bulk content correlate with the release of the alloying element.[143] The Mn-containing austenitic stainless steels released detectable amounts of Mn, and the Ni-containing stainless steels detectable amounts of Ni.[143] No correlation was observed between the extent of metal release and the corrosion behavior.[143] This indicates that passive conditions were prevailing during the metal release investigation.

Metal release studies (Fe, Cr, Ni, and Mn) have been conducted for different stainless steel grades (AISI 304, 310, 316L, 430, and duplex EN1.4462) exposed in PBS (*p*H 7.4), in PBS containing BSA (10 g/l), and in PBS containing lysozyme from chicken egg white (LSZ, 2.2 g/l).[38] While the difference in metal release among the grades was very small in the relatively nonaggressive fluids, PBS and PBS containing LSZ (less than twofold), the total metal release was the highest for the ferritic grade AISI 430 (16.0 wt. % Cr) and the lowest for the austenitic grade AISI 310 (24.2 wt. % Cr) in PBS containing BSA, though the difference was relatively small (less than sixfold).[38] Even though the total metal release from the investigated grades was relatively similar, the metal release mechanism in the protein-containing solutions was different. Very similar released amounts of metals were observed for the pitting corrosion resistant austenitic grade AISI 316L (containing Mo) in PBS compared with PBS containing LSZ, while the less pitting corrosion resistant grades AISI 304 (austenitic) and AISI 430 (ferritic) both showed statistically significantly higher amounts of released metals in PBS containing LSZ compared with PBS only.[38] In all studies reported above, Fe was preferentially released from all grades, and Cr and Ni were released to a less extent compared with their bulk alloy content.[38,134,142,143]

Relatively high amounts of released Ni were observed in a long-term (30–120 days) study investigating the release of Fe, Cr, and Ni from AISI 304, AISI 316, and AISI 444 in NaCl solutions (9–100 g/l).[144] High levels of released Ni and increasing metal release rates with time indicate active corrosion for all investigated grades. The underlying reason to why these surfaces corroded actively was not reported or investigated in the study,[144] but may be related to the occurrence of crevice corrosion due to an applied adhesive Teflon tape, the long immersion time period, and exposure conditions with relatively high amounts of chlorides.[144]

From these metal release studies, it seems that observed differences in the total amount of released metals is generally low among different grades as long as passivity is maintained. A higher bulk alloy content of Cr and a higher corrosion resistance results generally in a lower total amount of released metals (dominated by Fe), but not necessarily in a lower amount of released Cr, Ni, Mn, or Mo. The metal release mechanisms may differ, depending, e.g., on the pitting corrosion resistance of specific grade in a specific environment.

A study on the release of Ni into artificial sweat (*p*H 4.5, 6.5, and 6.6) from different austenitic stainless steels of large

differences in bulk alloy content of sulfur and in corrosion resistance (AISI 304, 304L, 304L+Ca, 304L+Cu, and 303) clearly shows that the high-sulfur containing grade AISI 303 releases greater than fivefold more Ni at similar conditions compared with the other grades (alloys with less inclusions).[145] Similar observations have been made in an earlier study by the same authors, where the metal release behavior of AISI 303 was compared to AISI 304, 316L, and 430.[139]

C. Route of manufacture and cooling rate

A series of studies on gas- and water-atomized AISI 316L stainless steel powder particles of different size (<45 and <4 μm) showed the importance of the route of manufacture and the cooling rate for their physical properties such as magnetic properties and crystallographic microstructure,[146] electrochemical properties (ennoblement),[29] surface oxide characteristics (composition, phases, phase distribution, inclusions, and crystallinity),[29,147] corrosion resistance,[29,148] and metal release into different solutions.[24,29,71,78,79,92] The particles, especially the smallest ones, were despite similar bulk composition very different in all these properties compared with corresponding massive sheet of the same stainless steel grade.[24,29] This is explained by the very rapid solidification process of the particles during their route of manufacture.[146,149–153] The presence of water vapor or oxygen during solidification also strongly influences the oxide composition and alloy microstructure.[29,147,154] Similar factors influence other kind of particles generated, e.g., during welding, particles that are very different in composition, microstructure, and solubility, compared with particles (independent of size) and sheet of stainless steel.[155]

Heat treatments applied in vacuum, air, or argon, and cooling (furnace or water-cooled) of orthodontic wires of unreported composition or grade have been shown to increase the release of Ni into artificial saliva compared with non-heat-treated control surfaces, and to result in substantial (greater than tenfold) differences in Ni release depending on treatment.[156]

Inclusions are important initiation sites for pitting, and possibly also important for metal release governed by dissolution. Inclusion density and shape depend on the grain orientation and route of manufacture, which can have a large effect on the metal release process. This has been shown in a Ni release study in artificial sweat (*p*H 4.5) when comparing cold-worked and annealed stainless steels (different AISI 316L type grades: DIN 1.4427So, DIN 1.4441, DIN 1.4435) of different transversal/longitudinal (grain) area ratios.[157] For each grade, the difference in Ni release increased between 1.8 and 52 times.[157]

D. Surface finish and roughness

The surface roughness and surface finish can also influence the extent of metal release for a given exposure condition. However, small differences in metal release (<1.5-fold) were observed for grade AISI 304 of different commercially available surface finishes upon exposure in ALF (*p*H 4.5).[158] A less than fourfold difference in metal release has been observed between abraded and as-received surfaces of grade AISI 316L immersed in ALF (*p*H 4.5) for one week.[138] Similar observations have been made for grade AISI 201 in citric acid (5 g/l, 2 h, *p*H 2.4, 70 °C).[22] A larger difference in metal release (less than tenfold) has been reported for grade AISI 430 of different surface finish exposed in acetic acid (3%, 40 °C).[159] Similar findings (tenfold) have been reported for polished and grit-blasted (higher surface roughness) surfaces of AISI 316LVM.[160] A 5–8-fold difference was observed in the case of the release of Ni and Cr from saucepans of an unreported grade of different surface finish (as-received, HNO_3/HF-treated, electropolished, and other commercial surface finishes) exposed to rhubarb food.[161] Differences less than 17-fold have been reported for the release of Cr from surfaces of AISI 410 of different surface roughness in acetic acid.[33]

A special surface finish is surface passivation, which usually is generated via acid treatments. Such a treatment is very effective to increase the corrosion resistance.[19,31–34] In terms of metal release, the extent of reduction depends on the solution composition and *p*H of the passivation fluid, and on the specific metal. While the release of Cr from a saucepan of grade AISI 304 exposed to rhubarb (*p*H 3.5) was not reduced by *a prior* HNO_3/HF surface treatment, the release of Ni revealed a threefold reduction.[161] The total metal release and the individual release of Fe, Cr, and Ni, respectively, from HNO_3 passivated grade AISI 316 were reduced about tenfold in Hanks' solution containing 100 mM H_2O_2 (*p*H 7.4), but not in Hanks' solution without H_2O_2.[162] HNO_3 passivation of grade AISI 304 has also been reported to reduce the release of Fe (17-fold) into citric acid (*p*H 2.4).[23]

V. EXTENT OF METAL RELEASE IN SELECTED BIOLOGICAL ENVIRONMENTS

When comparing the extent of metal release from stainless steels reported in different studies, it is essential to consider the following aspects, all known to influence the metal release process:

(1) Exposure conditions: Solution composition (especially chloride concentration and presence of complexing species), solution *p*H, exposed surface area to solution volume ratio, temperature, the presence of macromolecules and/or biofilms, exposure/immersion duration, friction/wear, and applied potential.
(2) Surface conditions: Surface cleaning, surface finish and roughness (e.g., blasting or abrasion), surface oxide composition, time, and storage conditions after surface treatment and the time of exposure, e.g., any passivation treatments, electrochemical treatments, heat treatments, etc.
(3) Alloy bulk conditions: Route of manufacture (e.g., any heat treatments), alloying elements, microstructure, heterogeneities (e.g., inclusions, secondary phases, etc.), shape and size (e.g., massive sheet or particles).

(4) Other experimental conditions: illumination, agitation, buffer capacity of the solution, access to oxygen (e.g., open or closed vessels), purity of water and chemicals used, possibility for bacteria growth in solution (influenced by, e.g., purity of water and chemicals, duration of immersion, *p*H, illumination, temperature, and the presence of any antiseptics), sealing of parts of the investigated surface (possibility of crevice corrosion).

Metal release data from different studies of massive sheet of stainless steel (reported data for particles are excluded due to large differences in surface oxide composition) of different characteristics is compiled in Fig. 3. To further limit the dataset, only data exposed for equal or longer periods than 1 day is included. All results are normalized to the exposed geometrical surface area and the solution volume, and presented as the released amount of metal per surface area ($\mu g/cm^2$). Studies in which information on surface area or solution volume is lacking are hence excluded. For specific numbers and uncertainty data, the reader is referred to the corresponding publication. All studies that at least report the release of Fe, Cr, and Ni (for austenitic grades) are compiled in Fig. 3(a). For clarity, only the highest values reported are included with the exception of three studies, refs. A, B, and C [left part of Fig. 3(a)].[117,144,162] For most studies (denoted C–M), Fe was the preferentially released element. The highest total amount of released metals was 8.6 $\mu g/cm^2$ for immersion time periods between 1 and 112 days, for different solutions of *p*H values ranging from 2 to 7.4 [these studies are shown in Fig. 3(b) at larger magnification]. There are two exceptions. In reference A,[144] preferential release of Ni could possibly be caused by the occurrence of crevice corrosion (applied Teflon tape to seal one sample side). In reference B,[162] Cr was preferentially released from as-received, polished, and passivated grades of AISI 304 and 316L immersed for 28 days in Hanks solution, a solution of relatively low corrosivity (relatively low levels of chlorides, some phosphates and carbonates, and glucose, *p*H 7.4).[162] The addition of H_2O_2 (100 mM) resulted in increased released metal quantities at levels proportional to the bulk alloy composition for nonpassivated surfaces, indicative of active corrosion.[162] This observation is very different from findings in a similar study [ref. C in Fig. 3(a)][117] of grade AISI 316L immersed in phosphate buffered saline (*p*H 7.4) for 28 days, and after addition of a physiologically relevant concentration of H_2O_2 (10 μM).[163]

Total amounts of released metals from grade AISI 316L (if available) are shown in Fig. 3(b) [refs. C-M of Fig. 3(a)] ordered by increasing solution *p*H and composition complexity. The figure clearly illustrates that both *p*H and solution composition influence the extent of metal release, whereas the immersion time period is of minor importance for surfaces that do not actively corrode. Similar trends were observed in refs. F (Ref. 119) (112 days) and M (Ref. 38) (7 days) that showed increasing released metal quantities with increasing bovine serum albumin solution concentration, Fig. 3(b).

Most published metal release studies investigate the release of Ni in different solutions. A compilation of findings from reported studies are made in Fig. 3(c) for a large variety of experimental conditions. The restriction limit for Ni-containing articles intended to come into direct or prolonged skin contact is included for comparison, a limit that is based on the release of Ni in artificial sweat (*p*H 6.5) after 7 days following an EN standard (EN 1811:2011).[164] Studies that observed higher amounts of released Ni compared with this limit were not performed in agreement with this standard protocol and were performed in solutions of lower *p*H [refs. N (Ref. 145) and O (Ref. 157) in Fig. 3(c)], or the surfaces were exposed for longer time periods than stipulated by the protocol [ref. F (Ref. 119) in Fig. 3(c)]. All other studies report lower, or significantly lower, amounts of released Ni from different grades than the threshold value, Fig. 3(c). It should be noted that reported amounts of, e.g., released Ni from pure Ni metal and a copper–nickel alloy (coins) are significantly higher at comparable conditions, i.e., 4.3–200 $\mu g/cm^2$ after 7 days in artificial sweat (*p*H 6.5).[139,165–167] This elucidates the importance of the passive surface oxide on stainless steel to hinder the release of metals, as discussed in more detail in Secs. II A and V C.

A. Food

Increased knowledge on the extent of released metals from stainless steel surfaces in food contact applications has been of considerable interest since stainless steel is widely used in a wide range of applications including food handling, cooking, and processing. Stainless steel is primarily present in its passive state, and as such, the extent of released metals is relatively minor. However, in the case of the occurrence of active corrosion, the situation becomes different. Cases where active corrosion have occurred have been reported and can generally be attributed to inappropriate grade selection for given conditions, faulty fabrication or design, and/or incorrect cleaning procedures, as previously summarized and reviewed.[168] Food and food processing can be very corrosive environments due to the presence of high amounts of halides (mainly chlorides), complexing agents and other corrosive components, very acidic or alkaline conditions, temperatures as high as 100 °C or higher, and the influence of friction and different mechanical stresses.[168] Except for different localized corrosion phenomena,[168] general corrosion can for instance occur at elevated temperatures,[168] as well as microbially induced corrosion.[169]

Metal release studies from different stainless steel grades in food-relevant solutions have been reported including; (1) acetic acid (*p*H 2.4 or lower),[22,25,33,159,170–172] (2) citric acid (*p*H 2.4–4.5, or unspecified),[22,173] (3) malic acid,[173] (4) oxalic acid,[173] (5) tartaric acid (*p*H 2.3),[171] (6) lactic acid (*p*H 2.3),[171] (7) distilled water (*p*H 7),[172] (8) artificial tap water (*p*H 6.6),[174] (9) *p*H-adjusted water (*p*H 2.5–11),[175,176] (10) sodium carbonate (*p*H 11.5),[172] (11) tomato sauce (*p*H 4.2–4.3),[176,177] (12) Indian drinks (*p*H 3.8–5.9),[171] (13) different menus (*p*H 7–8.7),[179] and (14) different foods or

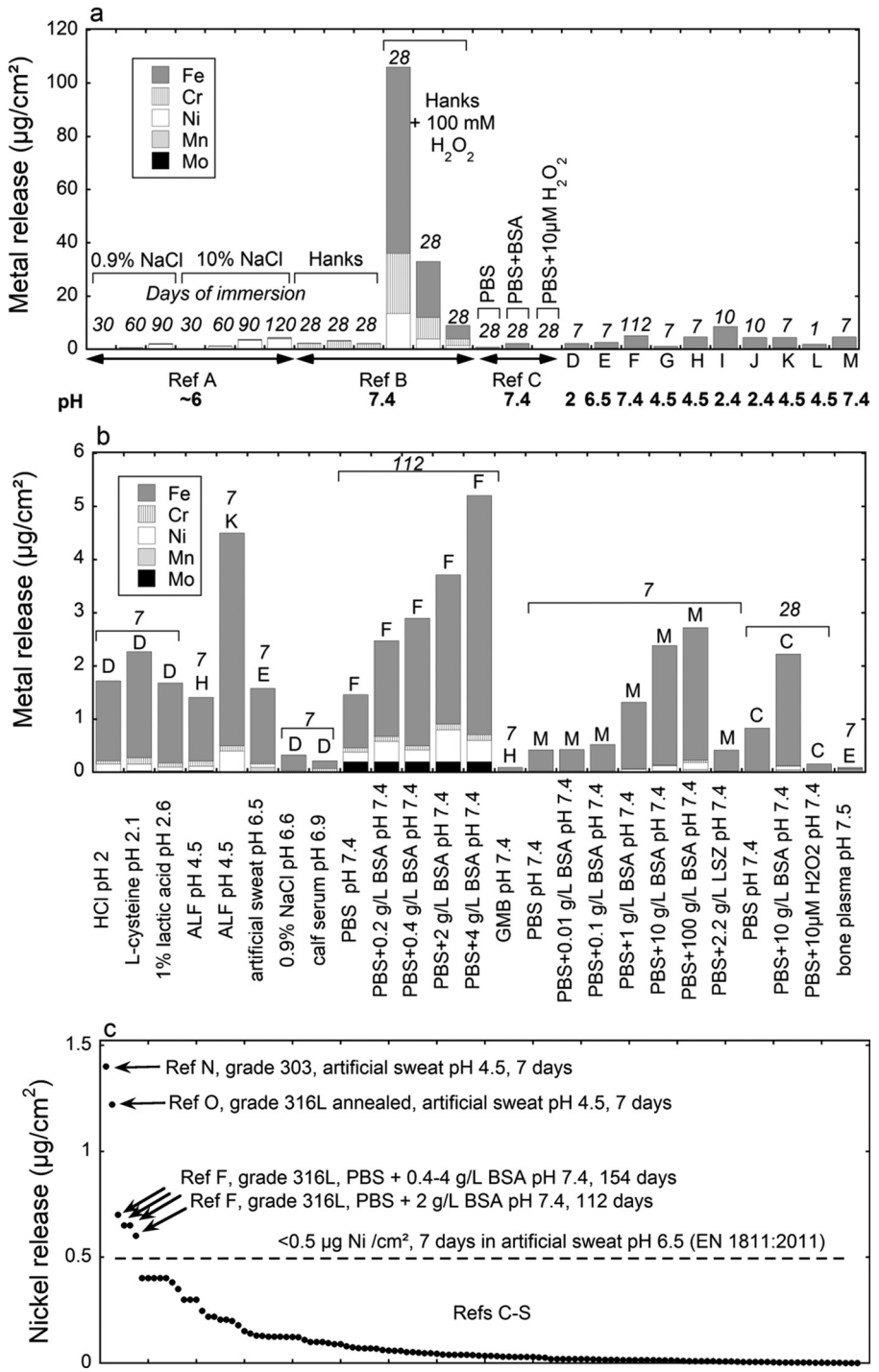


FIG. 3. (a) and (b) Total amount ($\mu g/cm^2$) of released metals (Fe + Cr + Ni + Mn + Mo) from different stainless steel grades into different solutions (days of immersion given above the bars). (c) Ni release ($\mu g/cm^2$) from different stainless steel grades into different solutions. PBS, phosphate buffered saline; Hanks, Hanks solution; BSA, bovine serum albumin; ALF, artificial lysosomal fluid; GMB, Gamble's solution. References: A (Ref. 144), B (Ref. 162), C (Ref. 117), D (Ref. 178), E (Ref. 143, F (Ref. 119), G (Ref. 158), H (Ref. 142), I (Ref. 159), J (Ref. 25), K (Ref. 138), L (Ref. 22), M (Ref. 38), N (Ref. 145), O (Ref. 157), P (Ref. 185), Q (Ref. 156), R (Ref. 187), and S (Ref. 180).

beverages (*p*H 2.0–6.9, or unspecified).[161,172,173,176] Unfortunately, many of these studies only report released metal concentrations neither in relation to the exposed surface area, nor to the solution volume. As information often also is lacking on the specific grade, no direct comparison between observed results can be done.

For similar solutions, an acidic solution *p*H [or alkaline *p*H (Ref. 172)] generally results in higher amounts of released metals compared with solutions of near-neutral *p*H conditions.[22,175,176] However, solution *p*H was seen to be of minor importance when comparing different solutions or foods/drinks containing metal complexing (chelating) species.[171,172,176]

Released levels of Ni or Cr were found to be relatively minor compared with levels known to, e.g., induce contact dermatitis for Ni- or Cr-allergic individuals,[161,174,175,179] or lower/similar compared with the recommended daily diary intake.[161,170–172,176,179] Exceptions (higher released concentrations into food than recommended) were observed for released Ni into curd and lassi (an Indian drink),[171] into oxalic acid and lemon juice,[173] into acetic acid (from some cookware),[170] and the release of Ni and Cr into tomato sauce.[177]

Investigations on how the extent of metal release changes during repeated usage are highly relevant for stainless steel surfaces in food contact. Most studies do however not consider this aspect and investigate only the initial release of metals, i.e., the first portion of metals released upon exposure. This portion is typically higher compared with subsequent exposures, see below. Measurements were in one study performed to assess the amount of released Ni and Cr from grade AISI 304 upon repeated exposure (consecutive cycles, each cycle 6 h) in boiling tomato sauce. Reduced amounts of released metals (approximately sixfold) were observed up to the sixth cycle, after which the amount remained relatively stable during subsequent exposure cycles (another 4 cycles).[177] In another study, the extent of released metals from grade AISI 201 into citric acid (*p*H 2.4, 100 °C) was determined during three consecutive cycles (each cycle 0.5 h). The extent of metal release was less than tenfold times lower (a significantly larger reduction for Ni) after the third cycle compared with the first cycle.[22] Similarly, fourfold lower amounts of Cr were released from grade AISI 430 exposed in acetic acid (*p*H 2.4, 100 °C) after the third cycle compared with the first cycle (each cycle 0.5 h).[159] Changes in released metal quantities of Cr and Ni with time were investigated for saucepans of different grade and different foods for 5 up to 23 repeated cooking cycles.[161] These investigations showed a reduced extent of released metals (approximately tenfold) up to the 16th cycle in rhubarb where after it did not increase noticeable, even after abrasion using a plastic mesh or soap-filled wire wool (an observation also made for cooking of apricots).[161] Similar observations have been made when cooking lemon marmalade, tomato chutney, and boiling potatoes in stainless steel saucepans of different producers (investigated up to the fifth cycle).[161]

To summarize, food contact, especially with foods containing ingredients of high metal complexation capacities and acidic foods, is a relatively corrosive setting for stainless steel that may trigger several of the metal release mechanisms as were discussed in Sec. II. Stainless steel is though generally considered safe to use in contact with food as long as the correct grade is used. Repeated usage generally results in reduced amounts of released metals.

Cases with active corrosion have been reported for certain conditions but are then usually related to an erroneous usage or grade selection for the given application.

B. Human body

Stainless steel is due to its high corrosion resistance and beneficial mechanical properties commonly used as orthopedic, dental, or cardiovascular implants. Production, friction, and wear during their processing might result in the unintentional inhalation, ingestion, or skin or eye contact with stainless steel particles. A large number of studies exists on the behavior of biomedical stainless steel grades (such as grade AISI 316L) at simulated biological conditions to estimate the extent of metals that can be released at real human body conditions. Several of these studies are summarized in Fig. 3.

Metal release studies have been performed in the following general and simple fluids of near-neutral *p*H; Hanks solution,[162] Ringer's solution,[160,180] phosphate buffered saline,[24,38,117,119,178,180–182] and 0.9% saline.[144,178,180,183,184] Studies have also been performed to investigate the effect of different proteins on the metal release process, e.g., albumin,[23,24,38,117,119,181] (an abundant blood protein) and other proteins,[38,85] and of solution *p*H[178,180,188,189] and different metal complexation species.[24,71,72] Investigations have also been accomplished in more complex fluids, such as bone plasma,[143] cell cultures,[185] cell medium,[178,180] and calf serum.[178,180] To simulate conditions of ingestion and the oral environment, metal release studies have been performed in artificial gastric fluid (*p*H 1.5)[77,92,186] and artificial saliva (*p*H 4.2–7.6).[156,178,180,187–191] Gamble's fluid (*p*H 7.4)[77,142,192] and artificial lysosomal fluid (*p*H 4.5)[71,77,78,92,138,142,158,182,186,192] are solutions that aim to simulate chemical conditions within cells and are hence relevant to predict the extent of metal release at inhalation scenarios. Artificial tear fluid (*p*H 8.0) is used to simulate eye contact.[79] Fluids of relevance for skin contact are presented in Sec. V C.

Several *in vitro* and *in vivo* studies[130,193–195] exist that attempt to study the biocompatibility of stainless steel in the human body, but fail to use relevant metal release fractions and aspects of chemical speciation when assessing risks. Corrosion initiated by deliberate anodic oxidation (dissolution) of the stainless steel surface is not relevant for the real situation and is of very low relevance to assess released metal species *in vivo*. Such deliberate anodic surface oxidation results in the release of hexavalent Cr and not as trivalent Cr (cf. Sec. III), conditions that do not reflect realistic conditions.

Several studies have investigated the release of metals from different stainless steel grades exposed to fretting corrosion (tribocorrosion) in simulated human body environments.[131,193] Such conditions have been shown to cause preferential release of Ni,[193] and the enrichment of Cr into red blood cells.[131] The investigators of this latter study interpreted this as the release of hexavalent Cr (no measurements were made) since this oxidation state is more readily taken up by red blood cells compared with trivalent Cr.[131] An alternative explanation could however be the release of Cr-rich nanoparticles (wear debris),[194–196] which are known to become phagocytized by cells.[196,197]

Increased concentrations of released metals were observed up to 12 weeks for grade AISI 316L implanted into rat tibia tissue, followed by reduced levels.[194] Another study

on the growth of human osteoclasts and on the extent of metal release from grade AISI 316L showed an increased and differentiated growth of osteoclasts on the stainless steel surface, processes that resulted in increased metal release and the secretion of proinflammatory cytokines.[198] A different study observed good cytocompatibility between osteoblastlike cells and stainless steel intended for cardiovascular stents.[199] The same study showed that an anodization treatment (made to thicken the surface oxide) completely failed in reducing the released amounts of metals into the blood stream as the released amounts of Ni and Cr instead increased (2–10-fold).[199] Patients, that showed allergic reactions to Ni or Mo, revealed a higher frequency of in-stent restenosis than patients without hypersensitivity, most probably due to the release of metal ions.[200]

An early study identified an increased risk of intestinal cancer for grinders of stainless steel surfaces, but no increased risk of lung cancer.[201] Very low levels of Cr and Ni were observed in urine and blood (whole blood and plasma) samples collected from stainless steel grinders.[202] Relatively low, or no, adverse health effects have been observed on stainless steel workers in other studies.[203–208] The only exception is stainless steel foundry workers,[204] who also are exposed to different fumes, silica, and polycyclic aromatic hydrocarbons. Several studies have investigated concentrations of Cr and Ni in saliva, blood, and serum of persons with orthodontic stainless steel appliances, or at *in vitro* conditions without finding any toxic levels.[183,209,210] The release of Ni and Co ions from orthodontic appliances (including stainless steel) has in one study been shown to induce deoxyribonucleic acid (DNA) damage in oral mucosa cells.[211] Another study observed active corrosion (localized corrosion) for 11 different failed stainless steel hip implants that had been in service between 9 and 21 years.[212]

To summarize, the chemical environment in the human body is complex and relatively corrosive, conditions that trigger several of the metal release mechanisms discussed in Sec. II. Biomedical grades of stainless steel possess very high biocompatibility, unless there is the occurrence of localized active corrosion induced by reasons described in Secs. II and IV. Hypersensitivity reactions to Cr or Ni need though to be considered and are described in more detail in Sec. V C.

C. Skin contact

Deposition of Ni and Cr ions on the skin can, at high concentrations, sensitize a person. For sensitized individuals, such deposition may at significantly lower concentrations cause (elicit) allergic contact dermatitis (eczema).[6,213] Concentrations when this occurs depend on the skin properties (e.g., skin barrier, damaged skin), and on the charge, size, and chemical speciation of deposited (released) Ni and Cr species.[122–127]

The lowest concentration of Cr found to elicit contact dermatitis for Cr-allergic individuals is 0.18 $\mu g/cm^2$ when exposed to trivalent Cr for 2 days (from $CrCl_3$ in water, *p*H 2) and 0.03 $\mu g/cm^2$ upon exposure to hexavalent Cr for 2 days (from $K_2Cr_2O_7$ in water, *p*H 7.5).[127] Since the release of hexavalent Cr is unlikely from a bare stainless steel surface in skin contact (cf. Sec. III) and released concentrations of trivalent Cr have been shown to be lower than 0.18 $\mu g/cm^2$ [see Fig. 3(b)], it is unlikely that Cr contact dermatitis will be induced as a result of skin contact with a bare stainless steel surface. The following released amounts of Cr have been reported for different stainless steel grades in artificial sweat (*p*H 6.5); 0.38 $\mu g/cm^2$ (2 days, a 21Cr10Ni4Mn2Mo alloy according to ISO 5832–9),[185] $<0.16\ \mu g/cm^2$ (7 days, 5 "Ni-free" stainless steel grades and AISI 316L and 904L),[143] and $<0.007\ \mu g/cm^2$ (7 days, AISI 316L powder).[79]

Allergic contact dermatitis to Ni is more common compared with Cr.[6] The release of Ni from surfaces (articles) that are intended to come into direct or prolonged contact with the skin is in the EU restricted to $<0.5\ \mu g/cm^2$/week in artificial sweat (*p*H 6.5), and to $<0.2\ \mu g/cm^2$/week for piercing items.[164,214] One study reports 10% of the Ni-allergic individuals to react with released amounts of Ni corresponding to 0.78 $\mu g/cm^2$ (after 2 days, applied in a closed patch test) and 22% of the same individuals to levels of 0.035 $\mu g/cm^2$ Ni per application for 1 week (applied twice a day as open exposure).[215] The following released levels of Ni from stainless steel in artificial sweat (*p*H 6.5) have been reported: (1) 0.3 $\mu g/cm^2$ (2 days, a 21Cr10Ni4Mn2Mo alloy according to ISO 5832-9),[185] (2) $<0.03\ \mu g/cm^2$ (1 week, grades AISI 304, 316L, and 430),[139] (3) approximately 0.5 $\mu g/cm^2$ (1 week, grade AISI 303),[139] (4) $<0.3\ \mu g/cm^2$ (1 week, *p*H 4.5–6.6, grades AISI 304, 304L, 304L+Ca, 304L+Cu),[145] (5) $<1.4\ \mu g/cm^2$ (1 week, *p*H 4.5–6.5, grade AISI 303),[145] (6) $<0.05\ \mu g/cm^2$ (1 week, grades AISI 305, 321, and 316L),[187] (7) $<0.07\ \mu g/cm^2$ (1 week, 5 Ni-free grades and AISI 316L and 904L),[143] and (8) $<0.003\ \mu g/cm^2$ (1 week, AISI 316L powder).[79] Very high released amounts of Ni were observed in one study at an extent that depended on the heat treatment and on the angle to rolling direction.[157] The study reports released amounts of Ni between 0.15 and 7.8 $\mu g/cm^2$ from grade AISI 316L (1 week in artificial sweat, *p*H 4.5), between 0.13 and 0.24 $\mu g/cm^2$ for grade DIN 1.4441 (a Cr-Ni-Mo stainless steel), and between 3.1 and 32 $\mu g/cm^2$ for DIN 1.4427So (a high-sulfur stainless steel).[157] A recent study investigated the release of Ni from grade AISI 316L (and other alloys and Ni metal) after short and repeated skin contact (by wiping) by using the index finger in contact with the surface, and after repeated, short immersions (3 s) into artificial sweat.[136] These exposures resulted in released amounts of Ni corresponding to 0.0045 $\mu g/cm^2$ for one wipe-off with a tissue wetted with artificial sweat, to 0.007 $\mu g/cm^2$ upon ten repeated wipe-offs, and to 0.024 $\mu g/cm^2$ after in total five wipe-offs (one wipe each at five replicate surfaces).[136] Repeated direct skin contact with the index finger and the stainless steel surface resulted in the deposition of 0.024 $\mu g/cm^2$ Ni (one touch), 0.05 $\mu g/cm^2$ (ten touches), and 0.059 $\mu g/cm^2$ (five touches of five replicate surfaces) onto human skin.[136] Lower amounts

of Ni ($<0.002\ \mu g/cm^2$) were released from the same surfaces after ten repeated immersions into artificial sweat.[136] These results are interesting from a mechanistic perspective, as it seems that direct skin contact with a surface of stainless steel results in an enhanced release of Ni compared to if the same surface is immersed in artificial sweat. This could be explained by (1) a wear effect, (2) differences between reactions in thin aqueous layers compared with immersion conditions, e.g., due to different surface area to solution volume ratios, and (3) atmospheric corrosion. Repetitive use is known to reduce the release of metals with time why a freshly prepared surface initially releases more metals compared with conditions of subsequent exposures. This kinetic effect has been described to take place in many different fluids ranging from rainwater[21,135] to acetic and citric acid[22,159] to synthetic body fluids.[38,138,186] No reactions were observed in contact with different stainless steel grades when investigating the potential for elicitation of contact dermatitis of Ni- or Cr-allergic individuals.[139,145,185,187] The only exception was in the case of skin contact with the resulfurized grade AISI 303 for which 4%–14% of the Ni-allergic individuals reacted.[139,145] However, this grade is not designed for an intended use of human contact.

To summarize, stainless steel is usually not associated with the elicitation of Ni or Cr contact dermatitis, since it releases very low levels of metals upon skin contact due to the properties of the passive surface oxide. However, grades of low corrosion resistance (not recommended for human contact), for example, high-sulfur containing grades may be of concern for Cr- or Ni-allergic individuals.

VI. SUMMARY AND CONCLUSIONS

This review aims to (1) elucidate differences in electrochemical, chemical, and physical metal release mechanisms for stainless steels exposed in biologically relevant environments including the human body, skin contact, and food relevant settings; (2) compile quantitative data on released metals; and (3) emphasize the importance of chemical speciation of released metals. The influence of microstructure, route of manufacture and surface finish on the extent of metal release is further highlighted.

The high amount of metal-complexing species, proteins, and other biomolecules, and the possible formation of biofilms in biological fluids strongly influence both corrosion-induced metal release and dissolution of the surface oxide. The metal release process is though often governed by combined mechanisms that not necessarily interact in an additive or synergistic way, as many factors that enhance the release of metals also increase surface passivity and thereby reduce the amount of released metals. Except for prevailing chemical conditions, also the stainless steel grade, surface finish, route of manufacture, heating treatments, and microstructure influence the metal release process. Their effects are relatively small since the passive surface oxide readily acts as an efficient barrier. However, if passivity is disabled and the surface hence not is able to repassivate, the extent of released metals may become of concern. Active corrosion may occur in biological environments if a grade of low corrosion resistance is used for a specific application that the grade is not intended for, or if inadequate surface treatments have been made that reduce or hamper the corrosion resistance of the passive oxide or change the microstructure. At such conditions and depending on different environmental factors (e.g., the presence of oxygen, solution *p*H, and temperature), unacceptably high amounts of metals can be released into solution. For example, the release of Ni in skin contact with resulfurized grade AISI 303, or the use of low quality grade stainless steel in cookware.

This review aims to provide a good basis for further studies of metal release processes for stainless steels used in biological environments. It should be considered that the stainless steel bulk properties (e.g., composition and microstructure), its physicochemical surface properties (e.g., surface oxide composition and surface charge), the adsorbed layer properties (e.g., net charge of proteins, thickness, and complexation capacity), and the formation of any biofilm or adhesion of cells, all are conditions and parameters that influence each other as well as the metal release process and its kinetics. Simplified studies that aim to, e.g., treat the stainless steel surface to become almost inert and not change with time, that do not consider metal-protein complexation, or that assume released metals to be present as free metal ions (usually not present in biological environments), are insufficient to understand prevailing metal release processes on stainless steels or to assess their effects.

ACKNOWLEDGMENTS

This work has been financially supported by the Swedish Research Council (VR, Grant No. 2013-5621), the Swedish Research Council for Health, Working Life, and Welfare (FORTE, postdoc Grant No. 2013-0054), Jernkontoret, Sweden, and KTH faculty grants. Jonas Hedberg, KTH Royal Institute of Technology, Sweden, and Peter May, University of Murdoch, Australia, are highly acknowledged for the JESS calculation and valuable comments. Jonas Hedberg is also gratefully acknowledged for critical reading.

[1]R. Adams, J. Vac. Sci. Technol. A **1**, 12 (1983).
[2]A. J. Sedriks, *Corrosion of Stainless Steels*, 2nd ed. (Wiley, New York, 1996).
[3]N. Baddoo, J. Constr. Steel Res. **64**, 1199 (2008).
[4]WHO, "Guidelines for drinking-water quality," 2011, www.who.int/water_sanitation_health/publications/2011/dwq_guidelines/en/index.html.
[5]CoE, *Metals and Alloys used in Food Contact Materials and Articles, A Practical Guide for Manufacturers and Regulators* (European Directorate for the Quality of Medicines & HealthCare (EDQM), Strasbourg, 2013).
[6]J. P. Thyssen and T. Menné, Chem. Res. Toxicol. **23**, 309 (2010).
[7]T. Santonen, H. Stockmann-Juvala, and A. Zitting, *Review on Toxicity of Stainless Steel* (Finnish Institute of Occupational Health, Helsinki, Finland, 2010).
[8]I. Milošev, Pure Appl. Chem. **83**, 309 (2010).
[9]N. Hallab, J. J. Jacobs, and J. Black, Biomaterials **21**, 1301 (2000).
[10]Y. H. An and R. J. Friedman, J. Biomed. Mater. Res. **43**, 338 (1998).
[11]G. Manivasagam, D. Dhinasekaran, and A. Rajamanickam, Recent Pat. Corros. Sci. **2**, 40 (2010).
[12]D. C. Hansen, Electrochem. Soc. Interface **17**, 31 (2008).

[13]P. Schmuki, J. Solid State Electrochem. **6**, 145 (2002).
[14]I. Olefjord and L. Wegrelius, Corros. Sci. **31**, 89 (1990).
[15]B. Pound, J. Biomed. Mater. Res. A **102**, 1595 (2014).
[16]I. Olefjord and B.-O. Elfstrom, Corrosion **38**, 46 (1982).
[17]T. Hanawa, S. Hiromoto, A. Yamamoto, D. Kuroda, and K. Asami, Mater. Trans. **43**, 3088 (2002).
[18]I. Olefjord, Mater. Sci. Eng. **42**, 161 (1980).
[19]K. Asami and K. Hashimoto, Corros. Sci. **19**, 1007 (1979).
[20]C.-O. A. Olsson and D. Landolt, Electrochim. Acta **48**, 1093 (2003).
[21]G. Herting, I. Odnevall Wallinder, and C. Leygraf, J. Environ. Monit. **10**, 1084 (2008).
[22]N. Mazinanian, I. Odnevall Wallinder, and Y. Hedberg, J. Food Eng. **145**, 51 (2015).
[23]Y. Hedberg, M.-E. Karlsson, E. Blomberg, I. Odnevall Wallinder, and J. Hedberg, Colloid Surf. B **122**, 216 (2014).
[24]Y. Hedberg, N. Mazinanian, and I. Odnevall Wallinder, Environ. Sci. Processes Impacts **15**, 381 (2013).
[25]G. Herting, D. Lindström, I. Odnevall Wallinder, and C. Leygraf, J. Food Eng. **93**, 23 (2009).
[26]S. Haupt and H.-H. Strehblow, Corros. Sci. **37**, 43 (1995).
[27]B. Elsener and A. Rossi, Mater. Sci. Forum **192–194**, 225 (1995).
[28]R. Frankenthal and D. Malm, J. Electrochem. Soc. **123**, 186 (1976).
[29]Y. Hedberg, M. Norell, P. Linhardt, H. Bergqvist, and I. Odnevall Wallinder, Int. J. Electrochem. Sci. **7**, 11655 (2012).
[30]Y. Hedberg, M. S. Killian, E. Blomberg, S. Virtanen, P. Schmuki, and I. Odnevall Wallinder, Langmuir **28**, 16306 (2012).
[31]J. Noh, N. Laycock, W. Gao, and D. Wells, Corros. Sci. **42**, 2069 (2000).
[32]D. Wallinder, J. Pan, C. Leygraf, and A. Delblanc-Bauer, Corros. Sci. **41**, 275 (1998).
[33]R. M. Wang, S. Z. Luo, and L. Z. Jiang, J. Iron Steel Res. Int. **21**, 131 (2014).
[34]B. G. Pound, Corros. Rev. **32**, 21 (2014).
[35]J. Lyklema, *Fundamentals of Interface and Colloid Science, Volume II: Solid-Liquid Interfaces* (Academic, London, 1995).
[36]M. P. Gispert, A. P. Serro, R. Colaço, and B. Saramago, Surf. Interface Anal. **40**, 1529 (2008).
[37]L. Boulangé-Petermann, A. Doren, B. Baroux, and M.-N. Bellon-Fontaine, J. Colloid Interface Sci. **171**, 179 (1995).
[38]Y. Hedberg, X. Wang, J. Hedberg, M. Lundin, E. Blomberg, and I. Odnevall Wallinder, J. Mater. Sci.-Mater. Med. **24**, 1015 (2013).
[39]S. Fukuzaki, H. Urano, and K. Nagata, J. Ferment. Bioeng. **80**, 6 (1995).
[40]C. Exartier, S. Maximovitch, and B. Baroux, Corros. Sci. **46**, 1777 (2004).
[41]G. Lefèvre, L. Čerović, S. Milonjić, M. Fédoroff, J. Finne, and A. Jaubertie, J. Colloid Interface Sci. **337**, 449 (2009).
[42]N. Chandrasekaran, S. Dimartino, and C. J. Fee, Chem. Eng. Res. Des. **91**, 1674 (2013).
[43]W. Norde, Macromol. Symp. **103**, 5 (1996).
[44]S. Flint, J. Brooks, and P. Bremer, J. Food Eng. **43**, 235 (2000).
[45]M. Mantel and J. Wightman, Surf. Interface Anal. **21**, 595 (1994).
[46]G. Anand, F. Zhang, R. J. Linhardt, and G. Belfort, Langmuir **27**, 1830 (2010).
[47]G. Lerebour, S. Cupferman, and M. N. Bellon-Fontaine, J. Appl. Microbiol. **97**, 7 (2004).
[48]G. Guillemot, G. Vaca-Medina, H. Martin-Yken, A. Vernhet, P. Schmitz, and M. Mercier-Bonin, Colloid Surf. B **49**, 126 (2006).
[49]H. Ksontini, F. Kachouri, S. El Abed, S. Ibnsouda Koraichi, H. Meftah, H. Latrache, and M. Hamdi, J. Adhes. Sci. Technol. **27**, 783 (2012).
[50]L. L. Shreir, *Corrosion: Metal/Environment Reactions*, 3rd ed. (Butterworth Heinemann, Oxford, 1994).
[51]D. E. J. Talbot and J. D. R. Talbot, *Corrosion Science and Technology*, 2nd ed. (CRC, Boca Raton, FL, 2007).
[52]Z. Ahmad, *Principles of Corrosion Engineering and Corrosion Control*, 1st ed. (Elsevier, Oxford, 2006).
[53]S. Virtanen, I. Milosev, E. Gomez-Barrena, R. Trebse, J. Salo, and Y. T. Konttinen, Acta Biomater. **4**, 468 (2008).
[54]J. Soltis, Corros. Sci. **90**, 5 (2015).
[55]A. Ismail, Z. M. Marjan, and C. W. Foong, Food Chem. **87**, 581 (2004).
[56]T. Katsube, H. Tabata, Y. Ohta, Y. Yamasaki, E. Anuurad, K. Shiwaku, and Y. Yamane, J. Agric. Food Chem. **52**, 2391 (2004).
[57]D. Koracevic, G. Koracevic, V. Djordjevic, S. Andrejevic, and V. Cosic, J. Clin. Pathol. **54**, 356 (2001).
[58]U. Schwertmann, Plant Soil **130**, 1 (1991).
[59]D. Suter, S. Banwart, and W. Stumm, Langmuir **7**, 809 (1991).
[60]B. Zinder, G. Furrer, and W. Stumm, Geochim. Cosmochim. Acta **50**, 1861 (1986).
[61]V. I. Bruyére and M. A. Blesa, J. Electroanal. Chem. Interfacial Electrochem. **182**, 141 (1985).
[62]L. Sigg and W. Stumm, Colloid Surf. **2**, 101 (1981).
[63]J. S. LaKind and A. T. Stone, Geochim. Cosmochim. Acta **53**, 961 (1989).
[64]R. F. Carbonaro, B. N. Gray, C. F. Whitehead, and A. T. Stone, Geochim. Cosmochim. Acta **72**, 3241 (2008).
[65]S. Namgung, M. J. Kwon, N. P. Qafoku, and G. Lee, Environ. Sci. Technol. **48**, 10760 (2014).
[66]M. Dos Santos Afonso, P. J. Morando, M. A. Blesa, S. Banwart, and W. Stumm, J. Colloid Interface Sci. **138**, 74 (1990).
[67]A. Amirbahman, L. Sigg, and U. von Gunten, J. Colloid Interface Sci. **194**, 194 (1997).
[68]M. A. Blesa, A. D. Weisz, P. J. Morando, J. A. Salfity, G. E. Magaz, and A. E. Regazzoni, Coord. Chem. Rev. **196**, 31 (2000).
[69]R. Cornell, A. Posner, and J. Quirk, J. Inorg. Nucl. Chem. **38**, 563 (1976).
[70]W. Stumm, G. Furrer, E. Wieland, and B. Zinder, *The Chemistry of Weathering*, edited by J. I. Drever (Springer, Dordrecht, the Netherlands, 1985), Vol. 149, pp. 55–74.
[71]Y. Hedberg, J. Hedberg, Y. Liu, and I. Odnevall Wallinder, BioMetals **24**, 1099 (2011).
[72]A. Kocijan, I. Milošev, and B. Pihlar, J. Mater. Sci. Mater. Med. **14**, 69 (2003).
[73]I. Milošev, J. Appl. Electrochem. **32**, 311 (2002).
[74]E. Baumgartner, M. A. Blesa, and A. J. Maroto, J. Chem. Soc., Dalton Trans. issue 9, 1649 (1982).
[75]Y. Zhang, N. Kallay, and E. Matijevic, Langmuir **1**, 201 (1985).
[76]A. Mörsdorf, I. Odnevall Wallinder, and Y. S. Hedberg, Regul. Toxicol. Pharm. **72**, 447 (2015).
[77]K. Midander, A. de Frutos, Y. Hedberg, G. Darrie, and I. Odnevall Wallinder, Integr. Environ. Assess. Manage. **6**, 441 (2010).
[78]Y. Hedberg, J. Gustafsson, H. L. Karlsson, L. Möller, and I. Odnevall Wallinder, Part. Fibre Toxicol. **7**, 23 (2010).
[79]Y. Hedberg, K. Midander, and I. Odnevall Wallinder, Integr. Environ. Assess. Manage. **6**, 456 (2010).
[80]P. M. Claesson, E. Blomberg, J. C. Fröberg, T. Nylander, and T. Arnebrant, Adv. Colloid Interface **57**, 161 (1995).
[81]J. Schott, S. Brantley, D. Crerar, C. Guy, M. Borcsik, and C. Willaime, Geochim. Cosmochim. Acta **53**, 373 (1989).
[82]E. A. Vogler, Biomaterials **33**, 1201 (2012).
[83]S. L. Hirsh, D. R. McKenzie, N. J. Nosworthy, J. A. Denman, O. U. Sezerman, and M. M. M. Bilek, Colloid Surf. B **103**, 395 (2013).
[84]J. Harvey, A. Bergdahl, H. Dadafarin, L. Ling, E. Davis, and S. Omanovic, Biotechnol. Lett. **34**, 1159 (2012).
[85]M. Lundin, Y. Hedberg, T. Jiang, G. Herting, X. Wang, E. Thormann, E. Blomberg, and I. Odnevall Wallinder, J. Colloid Interface Sci. **366**, 155 (2012).
[86]D. E. Wilcox, Inorg. Chim. Acta **361**, 857 (2008).
[87]C. Valero Vidal and A. Igual Muñoz, *Bio-Tribocorrosion in Biomaterials and Medical Implants* (Woodhead Publishing Limited, Oxford, UK, 2013), pp. 187–219.
[88]Y. Hedberg, M. Lundin, J. Jacksén, Å. Emmer, E. Blomberg, and I. Odnevall Wallinder, J. Appl. Electrochem. **42**, 349 (2012).
[89]J. Yang and J. Black, Biomaterials **15**, 262 (1994).
[90]C. Tkaczyk, O. L. Huk, F. Mwale, J. Antoniou, D. J. Zukor, A. Petit, and M. Tabrizian, J. Biomed. Mater. Res. A **94**, 214 (2010).
[91]K. Salnikow, A. Zhitkovich, and M. Costa, Carcinogenesis **13**, 2341 (1992).
[92]Y. Hedberg and K. Midander, Mater. Lett. **122**, 223 (2014).
[93]N. Mazinanian, Y. Hedberg, and I. Odnevall Wallinder, Regul. Toxicol. Pharmacol. **65**, 135 (2013).
[94]X. Wang, G. Herting, I. Odnevall Wallinder, and E. Blomberg, Langmuir **30**, 13877 (2014).
[95]X. Wang, G. Herting, I. Odnevall Wallinder, and E. Blomberg, Phys. Chem. Chem. Phys. **17**, 18524 (2015).

[96]L. A. García Rodenas, A. M. Iglesias, A. D. Weisz, P. J. Morando, and M. A. Blesa, Inorg. Chem. **36**, 6423 (1997).
[97]B. Little and R. Ray, Corrosion **58**, 424 (2002).
[98]I. B. Beech and J. Sunner, Curr. Opin. Biotechnol. **15**, 181 (2004).
[99]D. Jones and P. Amy, Corrosion **58**, 638 (2002).
[100]M. Moradi, J. Duan, H. Ashassi-Sorkhabi, and X. Luan, Corros. Sci. **53**, 4282 (2011).
[101]B. J. Little, J. S. Lee, and R. I. Ray, Electrochim. Acta **54**, 2 (2008).
[102]J. Landoulsi, K. Cooksey, and V. Dupres, Biofouling **27**, 1105 (2011).
[103]P. Linhardt, "MIC in hydroelectric power plants and approaches for risk assessment," *paper presented at the EuroCorr*, Estoril, Portugal, September 1–5 (2013), Paper No. 1279.
[104]Y.-C. Tang, S. Katsuma, S. Fujimoto, and S. Hiromoto, Acta Biomater. **2**, 709 (2006).
[105]P. Linhardt, Mater. Corros. (2015).
[106]R. J. K. Wood, Wear **261**, 1012 (2006).
[107]J. Geringer, K. Kim, J. Pellier, and D. D. Macdonald, *Bio-tribocorrosion in Biomaterials and Medical Implants* (Woodhead Publishing Limited, Oxford, UK, 2013), pp. 45–73.
[108]D. R. Haynes, T. N. Crotti, and M. R. Haywood, J. Biomed. Mater. Res. **49**, 167 (2000).
[109]Y. Yan, A. Neville, and D. Dowson, J. Phys. D Appl. Phys. **39**, 3206 (2006).
[110]T. J. Hakala *et al.*, RSC Adv. **2**, 9867 (2012).
[111]M. Parkes, C. Myant, P. M. Cann, and J. S. Wong, Tribol. Int. **72**, 108 (2014).
[112]C. Myant and P. Cann, J. Mech. Behav. Biomed. Mater. **34**, 338 (2014).
[113]Y. S. Hedberg, M. Pettersson, S. Pradhan, I. Odnevall Wallinder, M. W. Rutland, and C. Persson, ACS Biomater. Sci. Eng. **1**, 617 (2015).
[114]Y. Yan, A. Neville, and D. Dowson, Tribol. Int. **40**, 1492 (2007).
[115]M. Arenas, A. Conde, A. De Frutos, and J. de Damborenea, Corros. Eng., Sci. Technol. **49**, 656 (2014).
[116]P. M. May, P. W. Linder, and D. R. Williams, J. Chem. Soc., Dalton Trans. issue 6, 588 (1977).
[117]Y. Hedberg and I. Odnevall Wallinder, J. Biomed. Mater. Res. B **102**, 693 (2014).
[118]Y. Hedberg and I. Odnevall Wallinder, Mater. Corros. **63**, 481 (2012).
[119]S. Karimi, T. Nickchi, and A. M. Alfantazi, Appl. Surf. Sci. **258**, 6087 (2012).
[120]G. Morrison, G. Batley, and T. Florence, Chem. Br. **25**, 791 (1989).
[121]M. Ernest, *Metals and Their Compounds in the Environment: Occurrence, Analysis and Biological Relevance* (VCH, Weinheim, 1991).
[122]M. Samitz, S. Katz, and J. D. Shrager, J. Invest. Dermatol. **48**, 514 (1967).
[123]B. Gammelgaard, A. Fullerton, C. Avnstorp, and T. Menné, Contact Dermatitis **27**, 302 (1992).
[124]M. Samitz and J. Shrager, Arch. Dermatol. **94**, 304 (1966).
[125]U. Siegenthaler, A. Laine, and L. Polak, J. Invest. Dermatol. **80**, 44 (1983).
[126]E. Shmunes, S. A. Katz, and M. Samitz, J. Invest. Dermatol. **60**, 193 (1973).
[127]M. B. Hansen, J. D. Johansen, and T. Menné, Contact Dermatitis **49**, 206 (2003).
[128]M. Pourbaix, Biomaterials **5**, 122 (1984).
[129]G. Flint, S. Carter, and B. Fairman, Contact Dermatitis **39**, 315 (1998).
[130]M. G. Shettlemore and K. J. Bundy, Biomaterials **22**, 2215 (2001).
[131]K. Merritt and S. A. Brown, J. Biomed. Mater. Res. **29**, 627 (1995).
[132]S. A. Brown, L. J. Farnsworth, K. Merritt, and T. D. Crowe, J. Biomed. Mater. Res. **22**, 321 (1988).
[133]P. M. May, Appl. Geochem. **55**, 3 (2015).
[134]Y. S. Hedberg, N. Mazinanian, and I. Odnevall Wallinder, "Compliance tests of stainless steel as a food contact material using the CoE test guideline," 2014, http://www.euro-inox.org/pdf/health/KTH_report_EN.pdf.
[135]G. Herting, I. Odnevall Wallinder, and C. Leygraf, J. Electrochem. Soc. **152**, B23 (2005).
[136]B. Erfani, C. Lidén, and K. Midander, Contact Dermatitis **73**(4), 222–230 (2015).
[137]M. Assad, N. Lemieux, C. Rivard, and L. Yahia, Bio-Med. Mater. Eng. **9**, 1 (1999).
[138]G. Herting, I. Odnevall Wallinder, and C. Leygraf, J. Environ. Monit. **10**, 1092 (2008).
[139]P. Haudrechy, J. Foussereau, B. Mantout, and B. Baroux, Corros. Sci. **35**, 329 (1993).
[140]T. Suter and H. Böhni, Electrochim. Acta **43**, 2843 (1998).
[141]E. Bettini, U. Kivisäkk, C. Leygraf, and J. Pan, Int. J. Electrochem. Sci. **9**, 61 (2014).
[142]G. Herting, I. Odnevall Wallinder, and C. Leygraf, Corros. Sci. **49**, 103 (2007).
[143]L. Reclaru, R. Ziegenhagen, P. Y. Eschler, A. Blatter, and J. Lemaître, Acta Biomater. **2**, 433 (2006).
[144]A. Chiba, S. Sakakura, K. Kobayashi, and K. Kusayanagi, J. Mater. Sci. **32**, 1995 (1997).
[145]P. Haudrechy, B. Mantout, A. Frappaz, D. Rousseau, G. Chabeau, M. Faure, and A. Claudy, Contact Dermatitis **37**, 113 (1997).
[146]Y. Hedberg, O. Karlsson, P. Szakalos, and I. Odnevall Wallinder, Mater. Lett. **65**, 2089 (2011).
[147]Y. Hedberg, M. Norell, J. Hedberg, P. Szakálos, P. Linhardt, and I. Odnevall Wallinder, Powder Metall. **56**, 158 (2013).
[148]Y. Hedberg, S. Virtanen, and I. Odnevall Wallinder, Int. J. Electrochem. Sci. **7**, 11678 (2012).
[149]T. Kelly, M. Cohen, and J. van der Sande, Metall. Mater. Trans. A **15**, 819 (1984).
[150]T. Volkmann, D. Herlach, and W. Löser, Metall. Mater. Trans. A **28**, 461 (1997).
[151]W. Löser and D. Herlach, Metall. Mater. Trans. A **23**, 1585 (1992).
[152]W. Löser, T. Volkmann, and D. M. Herlach, Mater. Sci. Eng. A **178**, 163 (1994).
[153]T. Tunberg and L. Nyborg, Powder Metall. **38**, 120 (1995).
[154]L. Nyborg and I. Olefjord, Key Eng. Mater. **29–31**, 9 (1991).
[155]J. Antonini, J. Roberts, S. Stone, B. Chen, D. Schwegler-Berry, R. Chapman, P. Zeidler-Erdely, R. Andrews, and D. Frazer, Arch. Toxicol. **85**, 487 (2011).
[156]K.-T. Oh and K.-N. Kim, Eur. J. Orthod. **27**, 533 (2005).
[157]L. Reclaru, H. Lüthy, R. Ziegenhagen, P.-Y. Eschler, and A. Blatter, Acta Biomater. **4**, 680 (2008).
[158]G. Herting, I. Odnevall Wallinder, and C. Leygraf, Corros. Sci. **48**, 2120 (2006).
[159]G. Herting, I. Odnevall Wallinder, and C. Leygraf, J. Food Eng. **87**, 291 (2008).
[160]J. Galván, L. Saldaña, M. Multigner, A. Calzado-Martín, M. Larrea, C. Serra, N. Vilaboa, and J. González-Carrasco, J. Mater. Sci. Mater. Med. **23**, 657 (2012).
[161]G. Flint and S. Packirisamy, Food Addit. Contam. **14**, 115 (1997).
[162]M. Cieslik, W. Reczynski, A. M. Janus, K. Engvall, R. P. Socha, and A. Kotarba, Corros. Sci. **51**, 1157 (2009).
[163]S. Mueller, H. D. Riedel, and W. Stremmel, Anal. Biochem. **245**, 55 (1997).
[164]CEN, *Reference Test Method for Release of Nickel From All Post Assemblies Which Are Inserted Into Pierced Parts of the Human Body and Articles Intended to Come Into Direct and Prolonged Contact with the Skin* (European Committee for Standardization, Brussels, Belgium, 2011).
[165]C. Lidén, L. Skare, and M. Vahter, Contact Dermatitis **59**, 31 (2008).
[166]A. Julander, K. Midander, G. Herting, J. P. Thyssen, I. R. White, I. Odnevall Wallinder, and C. Lidén, Contact Dermatitis **68**, 323 (2013).
[167]J. P. Thyssen, D. J. Gawkrodger, I. R. White, A. Julander, T. Menné, and C. Lidén, Contact Dermatitis **68**, 3 (2013).
[168]M. S. Jellesen, A. A. Rasmussen, and L. R. Hilbert, Mater. Corros. **57**, 387 (2006).
[169]S. Durmoo, C. Richard, G. Beranger, and Y. Moutia, Electrochim. Acta **54**, 74 (2008).
[170]J. Kuligowski and K. M. Halperin, Arch. Environ. Contam. Toxicol. **23**, 211 (1992).
[171]P. Agarwal, S. Srivastava, M. M. Srivastava, S. Prakash, M. Ramanamurthy, R. Shrivastav, and S. Dass, Sci. Total Environ. **199**, 271 (1997).
[172]R. Kumar, P. Srivastava, and S. Srivastava, Bull. Environ. Contam. Toxicol. **53**, 259 (1994).
[173]R. Brun, Contact Dermatitis **5**, 43 (1979).
[174]T. Berg, A. Petersen, G. A. Pedersen, J. Petersen, and C. Madsen, Food Addit. Contam. **17**, 189 (2000).
[175]O. B. Christensen and H. Möller, Contact Dermatitis **4**, 343 (1978).
[176]E. G. Offenbacher and F. X. Pi-Sunyer, J. Agric. Food Chem. **31**, 89 (1983).

[177]K. L. Kamerud, K. A. Hobbie, and K. A. Anderson, J. Agric. Food Chem. **61**, 9495 (2013).
[178]Y. Okazaki and E. Gotoh, Biomaterials **26**, 11 (2005).
[179]M. Accominotti *et al*., Contact Dermatitis **38**, 305 (1998).
[180]Y. Okazaki and E. Gotoh, Corros. Sci. **50**, 3429 (2008).
[181]S. Karimi and A. M. Alfantazi, Mater. Sci. Eng. C **40**, 435 (2014).
[182]K. Midander, J. Pan, and C. Leygraf, Corros. Sci. **48**, 2855 (2006).
[183]T. Eliades, H. Pratsinis, D. Kletsas, G. Eliades, and M. Makou, Am. J. Orthod. Dentofacial **125**, 24 (2004).
[184]H. Kerosuo, G. Moe, and E. Kleven, Angle Orthod. **65**, 111 (1995).
[185]B. Summer, U. Fink, R. Zeller, F. Rueff, S. Maier, G. Roider, and P. Thomas, Contact Dermatitis **57**, 35 (2007).
[186]W. E. Hillwalker and K. A. Anderson, Environ. Pollut. **185**, 52 (2014).
[187]C. S. Jensen, S. Lisby, O. Baadsgaard, K. Byrialsen, and T. Menné, Contact Dermatitis **48**, 300 (2003).
[188]M. F. Sfondrini, V. Cacciafesta, E. Maffia, A. Scribante, G. Alberti, R. Biesuz, and C. Klersy, Am. J. Orthod. Dentofacial **137**, 809 (2010).
[189]M. F. Sfondrini, V. Cacciafesta, E. Maffia, S. Massironi, A. Scribante, G. Alberti, R. Biesuz, and C. Klersy, Angle Orthod. **79**, 361 (2009).
[190]G. Hultquist, C. Leygraf, and D. Brune, J. Electrochem. Soc. **131**, 1773 (1984).
[191]R. D. Barrett, S. E. Bishara, and J. K. Quinn, Am. J. Orthod. Dentofacial **103**, 8 (1993).
[192]K. Midander, J. Pan, I. Odnevall Wallinder, and C. Leygraf, J. Environ. Monit. **9**, 74 (2007).
[193]T. Hanawa, Mater. Sci. Eng. C **24**, 745 (2004).
[194]Y. Okazaki, E. Gotoh, T. Manabe, and K. Kobayashi, Biomaterials **25**, 5913 (2004).
[195]A. J. Hart, P. D. Quinn, B. Sampson, A. Sandison, K. D. Atkinson, J. A. Skinner, J. J. Powell, and J. F. W. Mosselmans, Acta Biomater. **6**, 4439 (2010).
[196]H. S. Gill, G. Grammatopoulos, S. Adshead, E. Tsialogiannis, and E. Tsiridis, Trends Mol. Med. **18**, 145 (2012).
[197]G. M. Keegan, I. D. Learmonth, and C. Case, Crit. Rev. Toxicol. **38**, 645 (2008).
[198]D. Cadosch, E. Chan, O. P. Gautschi, H.-P. Simmen, and L. Filgueira, J. Orthop. Res. **27**, 841 (2009).
[199]M. Díaz, P. Sevilla, A. Galán, G. Escolar, E. Engel, and F. Gil, J. Biomed. Mater. Res. B **87**, 555 (2008).
[200]R. Köster, D. Vieluf, M. Kiehn, M. Sommerauer, J. Kähler, S. Baldus, T. Meinertz, and C. W. Hamm, Lancet **356**, 1895 (2000).
[201]B. Svensson, V. Englander, B. Åkesson, R. Attewell, S. Skerfving, Å. Ericson, and T. Möller, Am. J. Ind. Med. **15**, 51 (1989).
[202]I. C. Stridsklev, K. H. Schaller, and S. Langård, Int. Arch. Occup. Environ. Health **80**, 450 (2007).
[203]M. Huvinen *et al*., Mutagenesis **17**, 425 (2002).
[204]J. J. Moulin, P. Wild, B. Mantout, M. Fournier-Betz, J. M. Mur, and G. Smagghe, Cancer Cause Control **4**, 75 (1993).
[205]J. J. Moulin, T. Clavel, D. Roy, B. Dananché, N. Marquis, J. Févotte, and J. M. Fontana, Int. Arch. Occup. Environ. Health **73**, 171 (2000).
[206]K. Jakobsson, Z. Mikoczy, and S. Skerfving, Occup. Environ. Med. **54**, 825 (1997).
[207]M. Huvinen, J. Uitti, P. Oksa, P. Palmroos, and P. Laippala, Occup. Med. **52**, 203 (2002).
[208]M. Huvinen, J. Uitti, A. Zitting, P. Roto, K. Virkola, P. Kuikka, P. Laippala, and A. Aitio, Occup. Environ. Med. **53**, 741 (1996).
[209]G. Ağaoğlu, T. Arun, B. İzgü, and A. Yarat, Angle Orthod. **71**, 375 (2001).
[210]S. E. Bishara, R. D. Barrett, and M. I. Selim, Am. J. Orthod. Dentofacial **103**, 115 (1993).
[211]F. Faccioni, P. Franceschetti, M. Cerpelloni, and M. E. Fracasso, Am. J. Orthod. Dentofacial **124**, 687 (2003).
[212]J. Walczak, F. Shahgaldi, and F. Heatley, Biomaterials **19**, 229 (1998).
[213]D. Bregnbak, J. D. Johansen, M. S. Jellesen, C. Zachariae, T. Menné, and J. P. Thyssen, Contact Dermatitis **73**, 261 (2015).
[214]J. P. Thyssen, W. Uter, J. McFadden, T. Menné, R. Spiewak, M. Vigan, A. Gimenez-Arnau, and C. Lidén, Contact Dermatitis **64**, 121 (2011).
[215]L. A. Fischer, J. D. Johansen, and T. Menné, Br. J. Dermatol. **157**, 723 (2007).
[216]G. Burstein and C. Liu, Corros. Sci. **49**, 4296 (2007).