EXECUTIVE SUMMARY

Stainless steels are a group of iron-based alloys containing at least 10.5% chromium and a maximum of 1.2% carbon. Chromium makes stainless steels corrosion resistant.

As stainless steels are composed of several metals, chemical legislation [for example, REACH and CLP (Classification, Labelling and Packaging Regulation) in the EU] and the voluntary GHS (Globally Harmonized System for Classification and Labelling of Chemicals) consider these alloys as preparations or mixtures of substances. However, chromium and other alloying elements limit the release of constituents from the stainless steel matrix, which significantly affects its toxicity when compared to the toxicity of its constituents.

The aim of this report is to assess the toxicological relevance of the available data to human health, draw conclusions about the toxicity of stainless steel, and give recommendations for the classification and labelling of stainless steel according to GHS. Special interest is taken in toxic endpoints like sensitization, respiratory tract toxicity, mutagenicity and carcinogenicity.

STUDIES ON METAL RELEASE FROM STAINLESS STEEL

Metal release from stainless steel sheets and particles, as well as from consumer products and medical devices, has been determined in numerous studies. Studies on the release of chromium and nickel from kitchenware made of stainless steel have provided inconsistent results. In some studies, the chromium or nickel concentration in foods has increased, for example when acidic food had been prepared in new stainless steel pans and bowls, whereas, in other studies, researchers did not observe a remarkable increase. However, in any case, the measured releases have been very low compared to the intake of chromium and nickel via the food. Some studies show that chromium and nickel may be released from stainless steel medical implants or appliances like orthodontic appliances, although the results have been inconsistent. Scientists have observed a large variation in the chromium and nickel concentrations in saliva. However, the ingested amount of chromium or nickel released from orthodontic appliances seems to be well below the daily dietary intake levels. Not much data are available on the metal release from stainless steel prosthetic implants. The conflicting results seen in these studies may be related to analytical challenges. Several *in vitro* studies focus on the release of metallic constituents from stainless steel in different synthetic body fluids. Because of the risk of skin sensitization caused by nickel, previous studies have focused particularly on nickel release from stainless steel in synthetic sweat.

When measuring the nickel release from various stainless steel materials into synthetic sweat, blood and urine, scientists observed that the surface finish of the materials significantly affected the nickel release. From the polished materials, the nickel release into each of the test fluids was generally very low. In the case of stainless steel plates with a matt or mirrored finish, the release of nickel appeared increase and, in some cases, the release of nickel into urine and blood plasma was more than twice as high as into artificial sweat. The metal ion release from stainless steel 316L particles of various sizes and from metal sheets of various grades, into artificial sweat has also been studied. The total release into artificial sweat is generally very low. Scientists have only observed higher release rates with the resulphurated grade 303 steel.

Researchers have also studied the release of metals from stainless steel in other artificial body fluids to mimic inhalation or gastrointestinal exposure scenarios. When the releases of different metal constituents of stainless steel are compared, iron is usually released at higher amounts than chromium and nickel. However, in all cases the release of metal ions is very low. Usually less alloyed ferritic grades release more metals, but the increase is attributed to the release of iron. The differences in release rates between different grades or surface finishes of stainless steel are usually small (for example, twofold).

Significant differences have been seen when the release from stainless steel has been compared to the release from pure metals. In one study, which compared the release from 316 sheets of stainless steel to the release from plain nickel and iron in artificial lysosomal fluid, researchers observed thousand-fold differences in iron and nickel release. The releases of chromium were on the same level both from stainless steel and from pure chromium metal. These *in vitro* studies suggest that, while chromium bioaccessibility from stainless steel is similar to that from metallic chromium, the iron and nickel bioaccessibility from stainless steel is significantly lower than from plain (unalloyed) iron and nickel particles. Thus, stainless steel containing 17.2% chromium and 10.7% nickel behaves as a mixture of chromium with <0.1% iron and nickel. These results strongly support the conclusion that the health effects of stainless steel cannot be estimated solely on the basis of its bulk contents of iron and nickel. This can be explained by the chromium oxide passivation layer, which comprises most of the stainless steel surface. The enrichment of chromium oxide in the surface occurs during *in vitro* incubation in artificial biological fluids and decreases release rates. This most likely also occurs *in vivo*.

TOXICOKINETICS

No studies have been performed to specifically investigate the toxicokinetic parameters of stainless steel. Two studies presenting limited human toxicokinetic data, based on workers in stainless steel production, have been published. However, the data do not provide much information on the toxicokinetic profile of stainless steel.

IN VITRO CYTOTOXICITY

The cytotoxicity of stainless steel has been studied *in vitro* neutral red uptake tests and the toxicity has been low. These tests are currently being validated by ECVAM (European Centre for the Validation of Alternative Methods) for their applicability when establishing the starting dose for acute oral toxicity tests. It is, therefore, not possible to draw conclusions for instance about the oral acute toxicity based on these available test data.

ACUTE TOXICITY

Although there are no data on acute toxicity studies of stainless steels, the long-term use and subacute studies strongly suggest that no acute toxicity via inhalation, dermal or oral exposure is expected. Also, none of the constituent metals is known to be acutely toxic.

IRRITATION AND CORROSION

The low solubility of stainless steel makes it an improbable irritant. There are no reports of skin or eye irritation by stainless steel. We have not found any studies of eye irritation by metallic nickel. Metallic chromium has not been tested for irritation. Chromium always has, however, a coating of Cr_2O_3, which has been found to be non-irritating and non-corrosive to the skin and eyes. Also, the fact that stainless steel has extensively been used in objects which come into contact with the skin, and even with people's eyes, without resulting in any reports of irritation, supports the assumption that stainless steel can be regarded as non-irritant.

SKIN SENSITIZATION

Nickel is a common contact allergen, and therefore the potential of stainless steel to cause sensitization is of interest. Release tests of stainless steel samples into various artificial body fluids generally show low release rates of nickel. EU has restricted the release of nickel into synthetic sweat to 0.5 µg/cm^2/week (0.2 µg/cm^2/week for piercing post assemblies), which is also the limit for sensitization classification according to the CLP.

Study reports on nickel release from different grades of stainless steels clearly show that even in the worst cases, the Ni release from stainless steels is usually clearly below the limit of 0.5 µg/cm^2/week. Only studies with one grade (AISI 303, high sulphur content) have shown release rates above the limit. One current study indicates that from unfinished or unpolished stainless steels twice as much nickel may be released into urine and blood plasma as compared with artificial sweat.

Chromium is released from stainless steel as non-sensitizing trivalent chromium. Chromium(VI) (which is a known sensitizer) has not been detected in release tests.
A clear decrease in frequency of nickel allergy was observed when comparing groups of young women before and after the Ni release restriction came into force. The same results were also obtained when comparing groups who had their ears pierced before/after the restriction was implemented. These studies strongly support the assumption that the limit 0.5 µg/cm^2/week can protect consumers from Ni sensitization.
The potential of stainless steel to elicit reactions in nickel-sensitized persons has been tested in a number of studies. The results clearly show that no allergic reactions occur, and based on this, stainless steels can be regarded as safe even in persons with nickel allergy. The frequency of nickel sensitivity among patients with stainless steel orthopaedic prostheses is not increased, and allergy tests performed before and after implantations do not show any signs of inducing nickel sensitivity.
Studies on patient groups with stainless steel coronary stents indicate that implanting stainless steel stents obviously does not significantly induce nickel sensitivity, but the role of nickel allergy in stent restenosis cannot be excluded.
The amount of available data is insufficient for final conclusions, but, based on the most extensive studies, the use of stainless steel in coronary stents seems to be safe. Based on the low release rates of nickel, sensitization caused by stainless steel can be regarded as unlikely. Also its widespread use and the low number of confirmed cases of nickel allergy, even in persons previously sensitized to nickel, support the conclusion that stainless steel is not a potential sensitizer.

REPEATED DOSE AND LONG-TERM EXPOSURE TOXICITY

A 28-day repeated inhalation study, performed with stainless steel, clearly indicates a lack of toxicity. The doses used in the stainless steel study were markedly higher than those used in the corresponding nickel metal study. In the study researchers saw no adverse effects, even at the highest concentration of stainless steel (1 mg/L), whereas another 28-day study with nickel metal showed that the lowest nickel dose (0.004 mg/L) already resulted in clear signs of toxicity. Available data on animal or human long-term exposure via metallic implants do not indicate any adverse local or systemic effects caused by stainless steel.

MUTAGENICITY

In *in vitro* genotoxicity studies stainless steel has been negative. There is no relevant *in vivo* data on the mutagenicity of stainless steel but the negative data from *in vitro* mutagenicity studies and the lack of clear mutagenicity of the main metallic components of stainless steel support the conclusion that stainless steel is not genotoxic. Regarding nickel, only soluble nickel compounds have been classified at mutagenicity cat 2 within the EU according to the CLP system, whereas nickel metal has not been classified. Although the current data does not warrant a mutagen classification for nickel metal, even if metallic nickel were to be classified, the substantially lower release of nickel from stainless steel compared to nickel metal supports the non-classification of stainless steel.

CARCINOGENICITY

Animal studies on the carcinogenicity of stainless steel include studies evaluating the ability of different stainless steel implants to induce local cancers at the place of implantation. No indication of carcinogenicity has been seen in these studies. Human data on occupational exposure to stainless steel, for example in grinding and polishing tasks, have not raised concerns about the potential carcinogenicity of stainless steel. Although there are few case reports on the stainless steel implants and local tumours near them, analytical epidemiological studies on the carcinogenicity of various implants have not shown any evidence of increased cancer risk. The IARC has concluded that stainless steel implants are *not classifiable as to their carcinogenicity to humans (Group 3).*

Based on older studies of local cancers after local injection/instillation of nickel metal at various sites, metallic nickel has been classified within the EU at CLP cat 2 for its carcinogenicity. However, *in vitro* studies on the release of nickel from stainless steel and a recent *in vivo* repeated-dose inhalation toxicity study show that nickel plays a significantly lower role in the toxicity of stainless steel than can be predicted on the basis of its bulk concentration. This conclusion is strongly supported by negative animal studies evaluating the ability of different stainless steel implants to induce local cancers at the place of implantation. In addition, negative stainless steel genotoxicity data and available human data on, for example, the grinding and polishing of stainless steel and the use of stainless steel implants, do not raise concerns about the carcinogenicity of stainless steel. Thus, the weight of evidence supports the non-carcinogenicity of stainless steel regardless of the possible carcinogenicity of nickel.

REPRODUCTIVE TOXICITY

No data exist on the reproductive or developmental toxicity of stainless steel. None of the main metallic components of stainless steel has shown reproductive toxic properties. Some soluble nickel compounds have been classified at Category 1B for developmental toxicity within the EU according to the CLP system. Recent EU risk assessment on nickel concluded that, since the developmental toxicity of nickel compounds is related to the systemically available nickel, this effect should be considered as relevant for metallic nickel as well, but, because the potential dose of nickel from metallic nickel is substantially lower than from the soluble compounds, it was agreed that metallic nickel should not be classified for this effect. Based on the low nickel release from stainless steel, it is very unlikely that it would cause reproductive or developmental toxicity. Testing of stainless steel for these properties is considered irrelevant and inadvisable.

CONCLUSIONS

One conclusion suggested by the data is that stainless steel is likely to exert very low toxicity. Based on the GHS classification and labelling criteria for mixtures, many stainless steels should be classified as specific target organ toxicants and/or category 2 carcinogens within the EU because of their nickel content. However, available stainless-steel-specific data provides solid evidence that this kind of classification is misleading.

In vitro release tests show that nickel release from stainless steel in artificial lung fluids is substantially lower than from nickel metal due to the chromium(III) oxide enrichment at the surface of stainless steel. A recent 28-day study on stainless steel inhalation toxicity showed low inhalation toxicity from stainless steel compared to nickel powder. Therefore, no classification for target organ toxicity in repeated exposure to stainless steel is proposed. A low dissolution of metallic constituents and available toxicological data do not support classification for mutagenicity or carcinogenicity either.

The small differences in metal release from different grades of stainless steels under various pH conditions are considered negligible when compared to the difference seen in the release of nickel from pure nickel and from stainless steel.

Certain resulphurated stainless steels (for example, AISI 303) may release nickel above 0.5 $\mu g/cm^2$/week in artificial sweat. Although the actual threshold for the induction of nickel allergy is unknown, it has been seen in Europe that the limit set within the EU for nickel containing alloys in direct or prolonged contact with the skin has significantly decreased the prevalence of nickel allergies. In the case of sulphur-rich stainless steels like AISI 303, the risk of sensitization is higher. Therefore, these grades of stainless steel should be considered potentially sensitizing in close and prolonged skin contact.

Nowadays, within Europe, these grades of steel are not recommended for use in continuous contact with the skin. Experts have not found cases of skin sensitization when these grades of steel are used in nuts and bolts, bushings, shafts, aircraft fittings, electrical switchgear components, gears, valve bodies and valve trim. This can be explained by the limited exposure time. The data presented in this review shows that the toxicity of stainless steel cannot be predicted solely from the bulk concentrations of constituents, but their actual release plays an essential role. This must be taken into account in the hazard assessment and classification of stainless steel as indicated above.

The applicability of this same approach to other alloys has to be, however, considered separately, taking into account the specific properties of the alloy. This demands further studies and validation of release tests for different kinds of alloys. We do not propose any further toxicity testing with stainless steels. The main hazards of stainless steels are related to the processing of stainless steel, especially welding, and, therefore, future emphasis should be on the assessment and management of these risks.