VDDI – Statement

Cobalt in Dental Alloys

Contents

Legal, regulatory and normative consideration of cobalt in dental alloys

Cobalt is registered as a substance in the EU under the European Chemicals Regulation REACH (Registration, Evaluation, Authorisation of Chemicals). Under the CLP Regulation (Classification, Labelling and Packaging of Substances and Mixtures) (ATP 14) cobalt is subject to harmonised classification as mutagenic category 2, carcinogenic category 1B, toxic to reproduction category 1B.

According to Annex 1 (General Safety and Performance Requirements), Chapter II (Design and Manufacture Requirements), complying with 10.4 (MDR and Guidance Scientific Committee on Health, Environmental and Emerging Risks SCHEER GUIDELINES on the benefit-risk assessment of the presence of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting (ED) properties) so-called CMR substances category 1A/B may only be used in medical products under the following conditions:

„10.4. Substances

10.4.1. Design and manufacture of devices

Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks posed by substances or particles, including wear debris, degradation products and processing residues, that may be released from the device.

Devices, or those parts thereof or those materials used therein that:

- are invasive and come into direct contact with the human body,

(…)

shall only contain the following substances in a concentration that is above 0,1 % weight by weight (w/w) where justified pursuant to Section 10.4.2:

substances which are carcinogenic, mutagenic or toxic to reproduction (‘CMR’), of category 1A or 1B, in accordance with Part 3 of Annex VI to Regulation (EC) No 1272/2008 of the European Parliament and of the Council,

(…)

10.4.2. Justification regarding the presence of CMR and/or endocrine-disrupting substances

The justification for the presence of such substances shall be based upon:

(a) an analysis and estimation of potential patient or user exposure to the substance;

(b) an analysis of possible alternative substances, materials or designs, including, where available, information about independent research, peer-reviewed studies, scientific opinions from relevant scientific committees and an analysis of the availability of such alternatives;

(c) argumentation as to why possible substance and/ or material substitutes, if available, or design changes, if feasible, are inappropriate in relation to maintaining the functionality, performance and the benefit-risk ratios of the product; including taking into account if the intended use of such devices includes treatment of children or treatment of pregnant or breastfeeding women or treatment of other patient groups considered particularly vulnerable to such substances and/or materials; and

(d) where applicable and available, the latest relevant scientific committee guidelines in accordance with Sections 10.4.3. and 10.4.4.

10.4.3. Guidelines of phthalates

For the purposes of Section 10.4., the Commission shall, as soon as possible and by 26 May 2018, provide the relevant scientific committee with a mandate to prepare guidelines that shall be ready before 26 May 2020. The mandate for the committee shall encompass at least a benefit-risk assessment of the presence of phthalates which belong to either of the groups of substances referred to in points (a) and (b) of Section 10.4.1. The benefit-risk assessment shall take into account the intended purpose and context of the use of the device, as well as any available alternative substances and alternative materials, designs or medical treatments. When deemed appropriate on the basis of the latest scientific evidence, but at least every five years, the guidelines shall be updated.

As they are metal, cobalt-chromium alloys do not contain any organic substances, therefore Section 10.4.3 does not apply.

MDR quote continued: 10.4.4. Guidelines on other CMR and endocrine-disrupting substances

Subsequently, the Commission shall mandate the relevant scientific committee to prepare guidelines as referred to in Section 10.4.3. also for other substances referred to in points (a) and (b) of Section 10.4.1., where appropriate.

Pursuant to SCHEER Guidance the following will explain why the use of cobalt as an alloy component in alloys is justified for dental purposes / indications and the benefit-risk profile is regarded as positive.

Use of cobalt as an alloy component

Cobalt is used as an alloy component in dental medical devices. Concentrations of 30% to 70% are used in alloys. Cobalt concentrations in dental alloys are typically in the range between 55% and 65%. In extremely rare cases cobalt can be a secondary component of precious metal solders.

Cobalt is also used in low concentrations (< 0.1 wt %) in dental ceramics as an inert pigment (e.g. as cobalt silicate/zirconate).

The following product standards are therefore used:

- Dental alloys: ISO 22674 [1]
- Dental solders: ISO 9333 [2]
- Laser welding rods: ISO 28319 [3]

- Dental ceramics ISO 6872 [4]

The biocompatibility of dental cobalt-based alloys is always assessed within the framework of the conformity assessment procedure as a general safety and performance requirement pursuant to ISO 10993 series and ISO 7405 [5].

Use of cobalt-chromium alloys in dentistry

Cobalt-containing alloys have been known in dentistry for a long time [6, 7] and are a proven material group [8]. They are processed in dental laboratories by dental technicians using casting, sintering, additive (SLM: Selective laser melting) or subtractive procedures (milling) to produce custom-made products as customised dental restorations according to a dentist’s prescription. Crown or bridge frameworks are often veneered with ceramics or composites. Cobalt-based solders and laser welding rods (fillers, materials for laser welding) are also used. Hard soldering or laser welding is used in dental technology to overcome problems with the fit, or to repair or extend existing prosthetic restorations.

The corresponding cobalt-content alloys can be used for the intended purpose of dental restorations with the following indications in dentistry due to their physical and chemical properties:

- Crowns (unveneered or veneered with ceramic or composite)
- Bridges (unveneered or veneered with ceramic or composite)
- Denture frameworks (so-called metal denture base alloys)
- Implant prosthetics (e.g. abutments, bars)
- Orthodontics: retainers, orthodontic appliances, wires
- Solders
- Laser welding rods (fillers)

The cobalt content in dental cobalt-based alloys can be between 30% and 70%. In most cases it is between 55% and 65% [6, 7, 9]. As the main component of cobalt-based alloys, cobalt provides the essential mechanical [10, 11] and chemical [11] properties. Cobalt is responsible for the strength and ductility. The strength and ductility are particularly required by large restorations, such as multi-unit bridges and denture frameworks, to withstand occurring masticatory forces.

As the main component, cobalt gives the modulus of elasticity. Apart from nickel-based alloys, only cobalt-based alloys achieve a modulus of elasticity of over 150 Gpa while maintaining a high ductility [9], thus achieving and even greatly surpassing the requirements of Type 5 according to ISO 22674 [1] [9]. The modulus of elasticity is a decisive factor for assessing bridge frameworks, denture frameworks, bars and abutments. The higher this value, the more advantageous it is [6, 7, 12, 13].

The high corrosion resistance of cobalt-based dental alloys is achieved by alloying with chromium and molybdenum, whereby molybdenum can be wholly or partially substituted by tungsten [12, 13].

Substitution possibilities for cobalt in dental alloys

Different substitution possibilities for cobalt in dental alloys can be discussed. The following are basically feasible:

1. Substitution of cobalt in the alloy itself
2. Substitution in clinical indications for cobalt-chromium alloys by other materials

Substitution of cobalt in the alloy itself

As a main component, cobalt is responsible in dental cobalt-chromium alloys for the high corrosion resistance (in combination with chromium and molybdenum/tungsten) and strength [6, 7]. In the past, nickel-chromium alloys were an alternative to cobalt-chromium. Beryllium-content alloys with reduced chromium content were also an alternative. Both metals are viewed very critically due to their considerable allergenic potential [1]. Nickel-based alloys exhibit higher corrosion rates than cobalt-chromium alloys, particularly with reduced chromium contents [14]. Nickel is unsuitable as a substitute for cobalt because of the observed allergenic potential. In dental standards nickel is considered as one of the “hazardous elements” [1].

Precious metal alloys (PM alloys) can release ions to a comparable and also greater extent (compare Tab. 1 with [15, 16]). The mechanical properties of PM alloys are also lower than those of cobalt-chromium alloys [9].

The high precious metal prices also reduce a general acceptance. For example, when using 3g for one crown the cost of purely the precious metal alloy depending on the alloy composition is between €120 to €210 (as at 2021, gram prices between €40 and €70) compared to an equivalent crown fabricated using non-precious metal (cobalt-chromium alloy) with a purely material price of approx. €1 (using 5g to obtain the same volume of crown and a non-precious price of €200/kg, as at 2021). While reimbursement of cobalt-chromium alloys as dental restorations in Germany is covered by statutory health insurance, the high-gold-content alloy must be borne privately by the patient.

Use of elemental titanium and titanium alloys for fabricating dental restorations is well known. However, these metals are clearly inferior to cobalt-chromium alloys with regard to the modulus of elasticity.

The alternatives listed for cobalt are therefore out of the question. Other metals such as rhodium (Rh) or iridium (Ir) (in the same group with cobalt) do not achieve the desired properties of cobalt-chromium alloys. Iron and copper (in the same period as cobalt) as main components in dental alloys would increase corrosion.

The combination of cobalt with chromium is therefore one of the most corrosion resistant combinations in comparison with other metal combinations and substitution of cobalt by another material would generally increase corrosion. Increased corrosion would mean a higher exposure of the patient with metal ions, which can be reduced with the use of cobalt-chromium alloys. Of course the benefits of lower overall exposure with metal ions should not occur by using disproportionate, more toxic metal components. Cobalt-chromium alloys are also the alloys that meet the highest requirements of mechanical properties.

Substitution in clinical indications for dental cobalt-chromium alloys by other materials

The following table lists the possible clinical indications of dental cobalt-chromium alloys in the first column [13]. The adjacent columns list the possible alternative materials with respective pros and cons.

Indication	Alternative	Pros	Cons
Crowns	Other metals/alloys (precious metal alloys, titanium)	• State-of-the-art technology/many years of experience in the clinical area • Durability • Aesthetics (precious metal, veneerable) • Processed using the casting technique (i.e. for every lab), Exception titanium and titanium alloys	• Costs (precious metal)
	Ceramic (glass ceramic, zirconia)	• Aesthetics • Biocompatibility • Chairside process (dentist) possible (costs, treatment duration) • Minimally invasive (zirconia unveneered)	• Chipping • Contraindicated with bruxism (glass ceramic) • Not minimally invasive (glass ceramic) • Costs
	Composite	• Aesthetics • Price • Chairside process possible (treatment duration and treatment costs)	• Durability • High abrasion • Low strength • Biocompatibility (with insufficient polymerisation) • Allergies with dental technicians
Bridges	Other metals/alloys (precious metal	• State-of-the-art technology/many	• Low mechanical strengths

	alloys, titanium)	years of experience • Durability • Aesthetics (veneerable) • Processed using the casting technique (i.e. for every lab), Exception titanium and titanium alloys • Virtually no restriction of indications with regard to span and pontics • Precision attachments etc. possible	• Costs (PM alloys) • Ceramic veneering (titanium & titanium alloys)
	Ceramic (zirconia))	• Aesthetics	• Restricted indication ○ With regard to material ○ Anterior/posterior region ○ Number of pontics ○ Precision attachments etc. not practical ○
	Composite	• /	• To date no permanent material available/approved
Metal denture bases (frameworks)	Other metals/alloys	•	• Low mechanical strength (PM alloys, titanium and titanium alloys) • Higher costs (precious metal alloys)
	Ceramic	• /	• Clasps not possible • Insufficient bending strength • Chipping, fractures
	Acrylic	• Inexpensive • Aesthetics	• Insufficient strengths, according to European doctrine • Discolorations • Solubility • Taste irritations
Orthodontic devices/appliances			
Clasps, retainers und friction-pins.	Other metals/alloys	• Strength	• /
	Ceramic	• /	• Insufficient bending strength
	Acrylic	• Aesthetics	• Insufficient mechanical properties
Wires	Other metals/alloys	• Ductility • Strength	• /
	Ceramic	• /	• Technically impossible
	Acrylic	• /	• Insufficient mechanical properties

Tab. 1 Possible indication and substitution possibilities of cobalt-chromium alloys.

According to Table 1 it is clear that there are no alternatives available to cobalt-chromium alloys in the area of metal denture bases and clasps due to their exceptional mechanical properties (spring-hard, flexible, corrosion resistance, bending strength).

High-gold-content alloys, titanium and titanium alloys, or zirconium dioxide-based ceramics can be considered for use with bridges in principle.

Apart from the costs, high-gold-content alloys do not exhibit the same strength as the corresponding cobalt-chromium alloys, meaning wall thicknesses and connector dimensions must be strengthened. The same applies for titanium and titanium alloys [13]. If titanium-based materials are used, there is the added difficulty that the ceramic veneerability is more problematic for the dental technician [17, 18].

The increased space requirement of ceramics in comparison with metal frameworks means that as a rule more tooth structure is removed, which counteracts the minimally invasive approach and places additional stress on the patient. Shoulderless preparation is contraindicated. Zircon dioxides have a relatively high strength but have a lower failure tolerance (lower Weibull modulus) than corresponding cobalt-chromium alloys due to their brittleness. Spans with more than two pontics are therefore contraindicated with zircon dioxides [19]. Furthermore, zircon dioxides are partly contraindicated if bruxism is present, particularly if they are faced using glass veneering ceramics. In this case, the treating dentist must decide which restoration should be used or is optimum for the patient based on the clinical boundary conditions.

For several decades there have been alternative materials for cobalt-chromium crowns in the indication single crown that are strong and corrosion resistant and exhibit a high standard of aesthetics (glass ceramics, translucent zircon dioxides based on 5Y-TZP or 4Y-TZP zircon dioxides). Strength plays a subordinate role with single crowns. Other alternatives for single crowns include veneered precious metal alloys.

If dental alloys are also intended to meet aesthetic aspects, they must generally be faced with translucent glass ceramics. This is particularly the case with dark-coloured cobalt-chromium alloys. This build-up of layers is performed using several furnace firings to obtain a natural tooth appearance and aesthetics. These glass ceramics have different shades and are applied in layers. First, a thin layer (50 µm to 100 µm) of an opaque glass (so-called opaque porcelain) is fired to effectively mask the dark colour of the formed oxides. Then follows translucent layers (0.3 mm to 2.5 mm, so-called dentine and enamel porcelains) to lend the crown a tooth-like appearance. The high strength of cobalt-chromium alloys allows thinner wall thicknesses with the same strength in comparison with precious metal alloys or titanium materials to be selected. This is particularly advantageous with restricted space availability.

Veneering using low-soluble ceramics protects the cobalt-chromium framework, the core of the restoration, against corrosion. The maximum chemical solubility of veneering ceramics is specified in ISO 5873 and ISO 9693 as 100 µg/cm² following acetic acid attack at 80°C. This protects the relevant cobalt-chromium framework against corrosion orally. By covering the surface of the framework to the oral cavity using an inert veneering ceramic, the exposed surface of the framework on which corrosion can occur and therefore result in exposure of the patient to cobalt, is greatly reduced.

Cobalt intake

Cobalt is a relatively rarely occurring metal in nature [20]. Cobalt is used large scale in the technical sector as an alloying element in steels and in the form of cobalt-chromium-molybdenum alloys (stellites) as well as in tungsten carbide production. It is also often used technically in the form of pigments.

In the medical sector stellite-like alloys are used in endoprosthetics (e.g. for hip joints). In dental technology stellite-like alloys are used for the metal denture base technique. Slightly modified stellites, mainly alloyed with tungsten, are used for the fabrication of veneerable crown and bridge frameworks.

Different sources for cobalt come into consideration for humans, which will be listed and discussed in the following.

Cobalt intake through food

Cobalt is ingested to a certain extent by humans through food. The amount ingested can be subject to strong fluctuations depending on eating habits and where a person lives. Very varied concentrations of cobalt have been determined in different types of food [21]. Consequently, data on the daily intake of cobalt reported by different authors sometimes vary greatly (Tab. 2). HOKIN et al. recommend a cobalt intake of 7 µg/d to 82 µg/d [22].

Daily cobalt intake in µg/d	Source
5 - 45	[23]
5 - 45	[24]
7 - 82	[22]
10	[25]
11	[26]
26	[27]

29	[28]
300	[29]

Tab. 2 Daily amount of daily cobalt ingested through food

Cobalt intake through corrosion

Corrosion is the electrochemical reaction of a metal with its environment that results in the formation of ions, which then go into solution. All dental alloys, solders and laser welding material corrode in the oral cavity according to this process. This is unavoidable and applies to every elemental metal or alloy. The only question is how high the ion formation is. ISO 22674 [1] requires a static immersion test to prove the corrosion resistance. In total there should be no more than 200 µg/cm^2 in 7 days of ions released. This requirement is met by cobalt-chromium alloys. The values listed in Tab. 1 also agree with other investigations [30].

With non-precious metal (NPM) alloys the ion release roughly corresponds to the composition, i.e. the main component goes quantitatively strongest into solution. A prerequisite for this is that there is no strong heterogeneous structure. Generally there is no such structure with cobalt-based alloys.

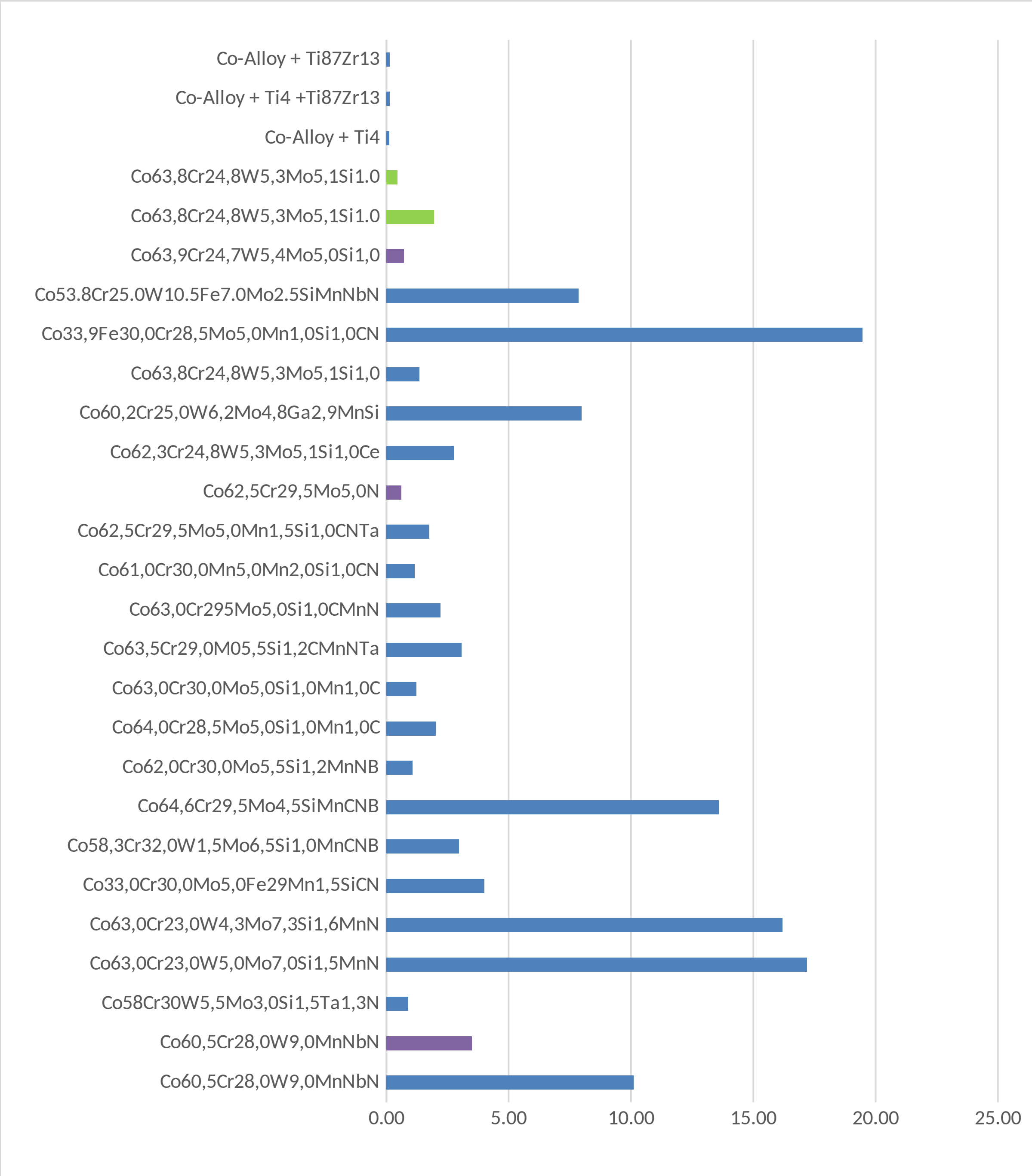
Fig. 1 shows the total ion releases of different cobalt-based dental alloys in the immersion test according to ISO 22674. The total ion release ranges between 0.5 and 20 µg/cm^2 in 7 days. Thereby a maximum daily ion release of less than 3 µg/cm^2 is observed. All alloys analysed therefore fell well below the limiting value of 200 µg/cm^2 in 7 days.

The top three bars in Fig. 1 show a typical material combination consisting of a cobalt-chromium alloy with titanium material. In the immersion tests carried out specimens of cobalt-chromium alloys were tested using Grade 5 titanium screws with specimens of titanium Grade 4, a combination of titanium Grade 4 and a Ti87Zr13 alloy as well as only with a Ti87Zr13 alloy. This formed galvanic elements. It was observed that this did not increase in cobalt release. In contrast, a very low cobalt release was observed. This demonstrates that cobalt-chromium alloys show very stable corrosion behaviour, even under rigorous conditions produced by a low pH value, presence of a complexing agent (lactic acid) and galvanic elements.

If the ion releases of individual compositions (Fig. 1) are taken into consideration, it becomes apparent that some identical compositions result in different ion releases. This cannot be explained by measuring inaccuracies but by different structures and oxide contents, which could result from the processing and manufacture of the semi-finished products (casting ingots, powder, milling discs) [31].

Hereby it should be noted, that the corrosion solution according to ISO 22674 [1] is a very aggressive environment. Not only is the pH value of 2.3 very low and is achieved in extreme cases in the oral cavity for a longer period only with crevice corrosion. Dental cobalt-chromium alloys also have a high corrosion resistance under these conditions [32-34]. A lowering of the pH value by food, e.g. due to acidic drinks [35] or fruit is quickly increased again by saliva [36].

A strong time-lapse effect is therefore to be assumed in the test procedure according to ISO 22674, i.e. the actual daily ion release in the oral cavity should be significantly lower.



Blue: Casting alloys Orange: SLM alloys Green: Milling alloys

Fig. 1 Total ion release (given in µg/cm^2 in 7 days) of different cobalt-based dental alloys in the immersion test pursuant to ISO 22674. The general limiting value for total corrosion given there is 200 µg/cm^2 in 7 days.

The static immersion test pursuant to ISO 22674, where one single measurement is taken after 7 days, can be supplemented by a long-term corrosion test in which measurements can be taken at several intervals, e.g. after 1, 4, 7, 14, 21, 28 and 35 days. This allows a chronological progression of ion release to be obtained. This is shown as an example for a cobalt-based dental alloy (Fig. 2).

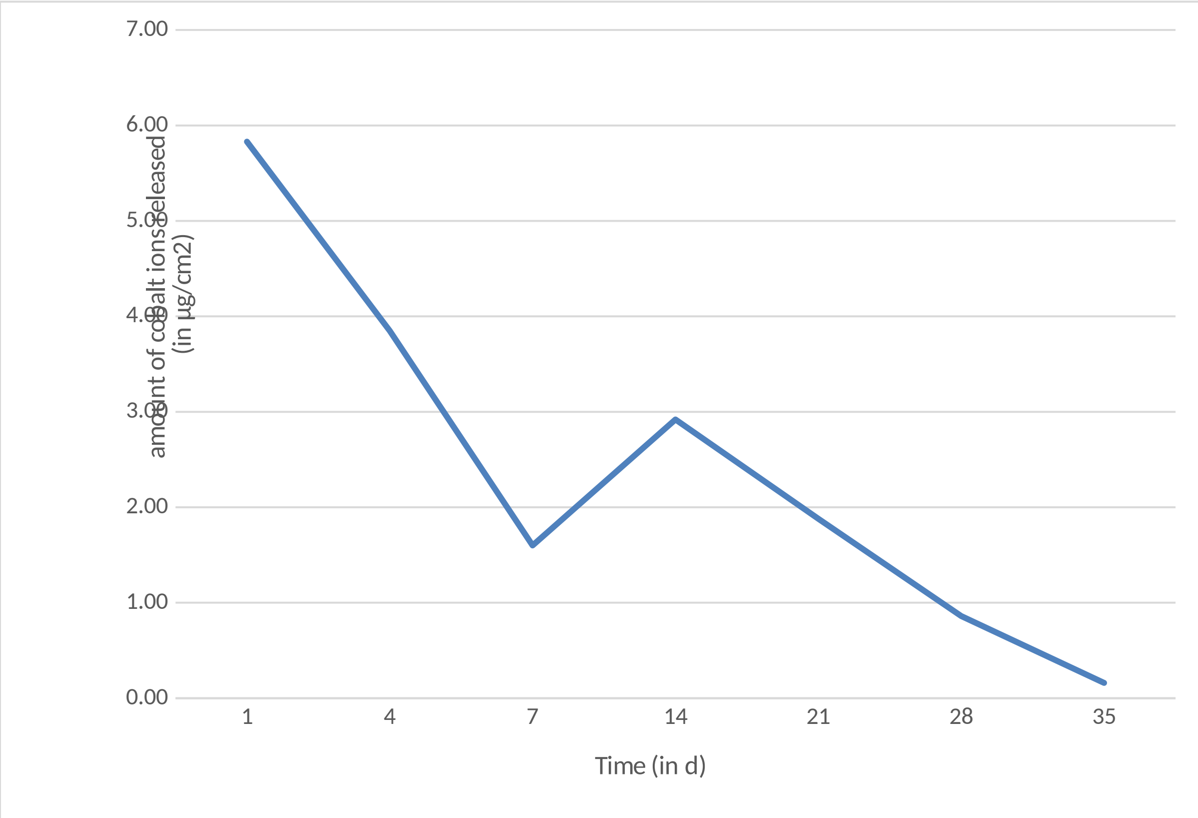


Fig. 2 Chronological progression of the cobalt ion release of a cobalt-based dental alloy in a long-term immersion test

It is evident that the ion releases of dental alloys are highest in the first days, then fall and after approx. 2 to 3 weeks usually approach a much lower corrosion value asymptotically. This does not only apply to the alloy shown (Fig. 2) but for all dental alloys in principle [14].

In assessing the ion release, the surface of the custom-made restoration available for corrosion intraorally must also be included. In this case it must be differentiated between alloys for crowns and bridges and those for denture fabrication.

COLLINS [37] gives the surface of the human oral cavity as 45 cm^2. In a worst-case scenario this would correspond to the total surface of the dental alloy used, if the surface of the custom-made dental laboratory restoration were to cover the entire upper and lower jaws. Such a maximum surface would apply for so-called metal denture base alloys or the total surface of fitted crowns and bridges (alloys for crown and bridge work).

If the surface of a single tooth, for example, is assumed to be 1.4 cm², including representation of any fissures on the occlusal surface, it would correspond to a theoretical surface of 48 cm² with 32 teeth in the adult dentition.

For the example alloys Co63,8Cr24,8W5,1Mo5,3Si1,0 and Co33,9Fe30,0Crs28,5Mo5,0Mn1,0Si1,0CN from Fig. 1, not only the total corrosion values were determined but also the amount of cobalt in the total corrosion. This was between 0.1 µg/cm^2 (min. value) and 3 µg/cm^2 (max. value) cobalt per day.

Compared with the data from Fig. 2 this approximately corresponds to the amount of cobalt (calculated on the proportion of cobalt in the total alloy) that is released from the alloy over the chronological progression:

- Day 1: 5.83 µg/cm² cobalt ions release at the beginning of the test
- Day 35: 0.16 µg/cm² in 7d (total day 28 to 35) cobalt ions release, i.e. on average 0.023 µg/cm² per day

With an assumed maximum surface of 45 cm^2 it would work out as a daily cobalt release of minimum 1.03 µg to maximum 262 µg.

The actual amount of cobalt released is significantly lower, however, as "cumulated" worst-case scenarios were considered in this case.

- The specified total surface of 45 cm^2 (assuming 1.4 cm² per tooth) will not be achieved by dental restorations. Upper dentures are fabricated with a palatal plate. These are usually fabricated using a skeletal design, i.e. the entire upper jaw is not covered. Lower dentures must be fabricated with a sublingual bar for anatomical reasons, the total surface of which is smaller than that of a palatal plate.
- Crowns and bridges involve a maximum of 32 teeth of an adult human. The metal surface of these restorations is less than that of removable dentures. Furthermore, crown and bridge frameworks are usually veneered using ceramic or composite, so that the surface available for ion release is reduced even more. Veneerings can be either full or partial coverage.

The ion releases determined in the immersion test are a worst-case scenario produced by the rigorous conditions.

Cobalt intake through abrasion

In addition to chemical loading due to corrosive processes, dental restorations are also subject to mechanical forces that result in abrasion etc. The particles this releases are transferred to the gastrointestinal tract with the saliva. The particles can be resorbed there via the gastric and intestinal mucosa.

In an experimental study the abrasion behaviour of dental materials was investigated. Different materials were subjected to an abrasion test for the investigation. A sphere made from aluminium oxide, which is the hardest material [38] that is used in dental materials, was used as the antagonist. The following abrasion depths were determined after a specific amount of cycles [39]:

Table 2 Absolute values for vertical substance loss (1 % quantile) in μm

Material	After 100,000 cycles Mean, SD	After 150,000 cycles Mean, SD	After 300,000 cycles Mean, SD
SLM-CoCr (Compartis, Degudent)	−28.7 ± 3.8	−36.3 ± 2.4	−54.4 ± 6.9
Cast CoCr (Remanium star, Dentaurum)	−59.6 ± 23.3	−70.3 ± 16.9	−117.2 ± 18.6
Degudent U (Degudent)	−45.1 ± 24	−59.5 ± 28.1	−74.7 ± 38.3
Degudent G (Degudent)	−47.7 ± 32.7	−55.7 ± 28.5	−65.7 ± 26.8
Degulor M (Degudent)	−52.3 ± 21.6	−62.8 ± 23.8	−79.8 ± 27.7
BiOcclus Inlay (Degudent)	−75.5 ± 38.2	−90.7 ± 45.8	−122.2 ± 59
Enamel	−104.8 ± 45	−107.1 ± 41.7	−128.7 ± 54
Tritan (Dentaurum)	−308.7 ± 46.6	−328.3 ± 45.2	−344.3 ± 27

Fig. 3 Extract (scan) of a publication by SCHWINDLING et al [39] with the final results of the abrasion investigations

In dynamic ageing tests using masticatory loading stimulation an *in vivo* equivalence of 5 years is assumed with 1.2 million cycles as a rule of thumb. A cycle number of 100,000 cycles would thus roughly correspond to an *in vivo* time in situ of 152 days [40, 41].
If one now considers a volume removal of 100 μm * 100 μm * 60 μm with a dental cobalt-chromium alloy (see Fig. 3) at 100,000 cycles and assumes $\rho = 8.5$ g/cm³ as the density, it would give an abrasion value for the cobalt-chromium alloy tested of 0.034 μg/d (total abrasion of the alloy).
If this is extrapolated to 100 such abrasion marks, it gives a value of 3.4 μg/d for the abrasion. This would correspond to a total abrasion surface of 0.1 cm² with a depth of 60 μm. With a total abrasion surface of 1 cm² the abrasion value is 34.0 μg/d.
In considering the abrasion, it must be taken into account that the contact between the teeth is more point loading than surface loading. Aluminium oxide is also not always present as the antagonist. Food is generally softer than cobalt-chromium alloys, which reduces the abrasion of the alloys. Furthermore, it must be taken into consideration, as with corrosion, that in many cases the frameworks are veneered. With metal denture base frameworks the large base plates are not in any contact with antagonists. The assumed contact surfaces of 1 cm^2 and aluminium oxide as the material for the antagonists is therefore a worst-case scenario.

Cobalt intake through dust

It is well known that in some sectors of industry there is a high cobalt exposure of workers employed in the sectors. Mainly the people who work in metallurgy, pigment, steel or tungsten carbide production are affected [42-45].

Dental technicians process a variety of materials by milling and grinding etc. They are therefore exposed to a variety of dusts, aerosols and gases. Health and safety measures such as extraction systems and/or face masks reduce the exposure depending on the level of protection applied.

It is a known fact that the air in dental laboratories among other things also contains cobalt-containing particles [46]. It is therefore recommended in the instructions for use of the respective materials to take the appropriate safety measures such as extraction systems [47-49].

Latest assessments of the maximum workplace concentration (e.g. dental laboratories, production) discussed values of approx. 4-8 µg/cm³, this value is, however, not yet prescribed by law (from "Assessment for the TA Luft [German Clean Air Act] No. 5.2.7.1.1. Carcinogenic Substances" of the UBA [German Environment Agency]). A human breathes approx. 12 to 18 times per minute and inhales approx. 0.5 L of air per breath (https://www.gesundheit.de/krankheiten/lunge/funktion-der-lunge/lebenselixier-luft). If a basic working time of 8 hours is assumed, a dental technician would inhale 4.3 m^3 of air per working day. With such a breathable fraction of cobalt in the air (4-8 µg/cm³) a technician would inhale approx. 25 µg of cobalt.

Further measurements in the dental laboratory (trimming CoCr alloys) produce periodic peak values of 35 µg/cm³ and thus 138 µg of cobalt would be inhaled in 8 hours (worst-case scenario) under constant exposure with this peak value.

Worst-case scenario of cobalt intake of patient with a prosthetic restoration

The corrosion values of cobalt-chromium alloys were determined as between 0.023 µg/cm^2 (min. value) and 5.83 µg/cm^2 (max. value) per day. The assumed maximum surface of a custom-made dental laboratory restoration was determined as 45 cm^2.

The daily cobalt exposure determine under this worst-case scenario was between 1.03 µg to 262 µg per day (Fig. 4). If an average body weight of 60 kg is assumed it would give a dose of 0.017 µg/kg BW (BW = body weight) to 4.4 µg/kg BW.

Exposure to cobalt caused by abrasion is 34 µg per day (Fig. 4), which corresponds to an additional dose of 0.57 µg/kg BW.

The assumed total daily dose of cobalt from a dental restoration added together would be between 0.59 µg / kg BW and 4.97 µg/kg BW

For the assumption that only one single crown with a surface of 1.4 cm² crowned by a cobalt-chromium alloy, the daily exposure is between 0.032 µg and 8.2 µg of cobalt. If an average body weight of 60 kg is assumed, it would give a dose of 0.53 ng/kg BW (corresponding to 0.00053 µg/kg BW) to 0.136 µg/kg BW.

The oral route is presumed as the relevant route for exposure of a patient. Short-term inhalative exposure to dusts, which are created by trimming of the dental restorations intraorally, are regarded as having little relevance for chronic exposure, as only spot grinding is carried out with intraoral repairs.

In 2020 the German Federal Institute for Risk Assessment (BfR) deliberated the released quantity of heavy metals such as lead, cadmium and cobalt from ceramic dishes in a statement [50]:

“Several hazardous effects for humans have been described for the oral intake of cobalt. The most important include cardial effects (cardiomyopathies), effects on erythropoiesis (polycythaemia) as well as on the thyroid gland and immune system (allergic dermatitis). Furthermore, neurological and reprotoxic effects as well as damage to the intestine and kidney occurred in animal studies (ATSDR, 2004; ECHA, 2016; Nielsen et al., 2013)

Uncertainties in the toxicological data situation make it difficult to derive a valid health-based limiting value for chronic exposure to cobalt. Among other things, there are no studies on chronic oral cobalt intake. Available data partly originate from old toxicological (animal) studies that do not correspond with modern requirements and in most cases no NOAEL (the highest dose without observed adverse effects) could be determined.

Various authors identified cobalt-induced cardiomyopathy as one of the most sensitive endpoints.

The majority of committees considers cobalt-induced polycythaemia as the most sensitive parameter for deriving health-based guidelines (AFSSA, 2010; ATSDR, 2004; EFSA, 2009; Nielsen et al., 2013), which was observed with an LOAEL (Lowest Observed Adverse Effect Level) of 1 mg/kg BW/day in a subacute study on six healthy test subjects (Davis and Fields). [50]

In its assessment of cobalt compounds as additives in animal foods the EFSA (European Food Safety Authority, 2009) adopted the MRL (Minimal Risk Level) of the ATSDR (Agency for Toxic Substances and Disease Registry) and estimates a maximum daily intake of 600 µg per person (60 kg, i.e. 10 µg/kg BW/day) as protective compared with the known threshold value-dependent adverse effects.

The French Food Safety Agency (AFSSA, 2010) takes the view that extrapolation of the subacute study on humans can be made to a chronic exposure by an additional factor of 6 in accordance with REACH (Registration, Evaluation, Assessment and restriction of Chemicals) (ECHA, European Chemicals Agency, 2012). This gives a TDI (Tolerable Daily Intake) of 1.6 µg cobalt/kg BW/day based on the MRL of the ATSDR [50].

The BfR considers the TDI of 1.6 µg cobalt/kg BW/day derived by the AFSSA (2010) as the most suitable for assessment of a chronic exposure. (…)

The registration dossier corresponding to REACH regulation for cobalt lists a subacute study on Sprague Dawley rats. A summary of the study was also published recently (Danzeisen et al., 2020). According to this summary the study conformed to GLP (Good Laboratory Practice) in accordance with the OECD (Organisation for Economic Co-operation and Development) guideline 408 [50].

The NOAEL (No-observed-adverse-effect level) was 3 mg $CoCl_2 \cdot 6(H_2O)$/kg BW/day. This corresponds to 0.74 mg cobalt/kg BW/day [50].

Applying an uncertainty factor of 200 (10 each for intra- and inter-species differences, and 2 for extrapolation from a subchronic to a chronic exposure) would give a TDI of 2.9 µg/kg BW/day. The fact that this TDI derived from the animal study virtually corresponds to the TDI from the human study of 1.6 µg/kg BW/day (see above) and also has polycythaemia as an underlying critical effect, can be seen as further evidence for use of the TDI from the human study. It also shows that the uncertainty factors of the AFSSA (2010), which the BfR considers as suitable, have been selected sufficiently conservatively [50].

In addition to its toxicological effect, cobalt in a more complex form is essential for the human body as a component of cobalamin [50].

The D-A-C-H reference value for the recommended daily dose of an adult is 4 µg Vitamin B12 (Ströhle et al., 2019) was published jointly by the German Nutrition Society (DGE), the Austrian Nutrition Society (ÖGE) and the Swiss Society for Nutrition (SSG/SSN). This corresponds to approx. 0.15 µg of cobalt [50].

The Council of Europe guideline on metals and alloys (EDQM, European Directorate for Medicines and Healthcare, 2013) specifies daily intake quantities for cobalt of 0.18 µg/kg BW for adults and 0.31 µg/kg BW for children, which are based on the results of the Total Diet Study (ANSES, 2011) carried out by the French Agency for Food and Occupational Health & Safety ANSES. This corresponds to 11% or 19% of the TDIs of 0.0016 mg/kg BW/day (1.6 µg/kg BW/day) used for deriving the limit value" ---end of BfR quote---

The harmonised ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) guideline on element impurities (Q3D(R1) from March 2019 stipulates a permissible daily exposure by impurities in medicinal products of 50 µg/day. This is in the range of the TDIs derived from the TDI. It should be noted at this stage, that a higher benefit for patients is assumed with medicinal products, whereby a higher risk could be accepted [26].

Exposure assessment of dental cobalt-chromium alloys vs. Derived TDI

The presumed total daily dose of cobalt from dental restorations described above would be between 0.59 µg/kg BW and 4.97 µg/kg BW, and therefore within the range of 1.6 µg/kg BW regarded by BfR as conservative.

The presumed total daily dose includes several worst-case scenarios (surface of the total oral cavity, maximum corrosion values), as a result the presumed values are very high. Safety margins to the conservative, very low TDI are the result of the size of the corrosion surface, the low corrosion values observed over the course of time and veneering of the surfaces.

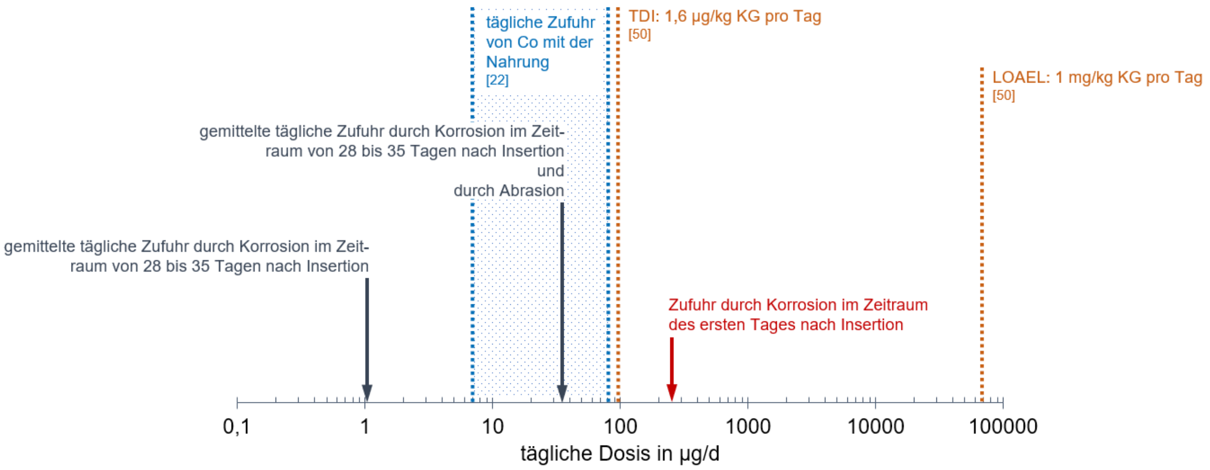
Assuming a potential corrosion surface of 1.4 cm² (single crown), corrosion of 5.83 µg/cm², without abrasion, as the crown is veneered using an inert layer of ceramic, there would be a daily intake of 0.136 µg/kg BW per day. If a daily corrosion of 0.023 µg/cm² is assumed, the daily intake would be 0.53 ng/kg BW (corresponding to 0.00053 µg/kg BW). The daily exposure would therefore be below the TDI of 1.6 µg/kg BW by a factor of 12 to 3019.

The TDI itself is based on conservative assumptions, so that here there is also a certain safety margin to critical intake amounts. Humans ingest cobalt daily from different sources. The main intake route is food. The daily intake amount of cobalt through food according to ANSES is 0.18 µg/kg BW.

Summary consideration of cobalt intake

Fig. 4 shows graphically the LOAEL value (Lowest Observed Adverse Effect Level) of 1000 µg/kg BW per day for cobalt, the derived TDI value of 1.6 µg/kg BW per day, the maximum intake amount of cobalt by corrosion with surfaces of 45 cm² and 1.4 cm² determined in the worst-case scenario, and also the daily intake of cobalt through food.

It should be noted when considering the value in Fig. 4 that the TDI and LOAEL are given in µg/kg BW and mg/kg BW per day. The daily intake marked in red is the absolute amount of cobalt per day (262 µg/d), which could be ingested on the first day due to maximum corrosion. The area marked in blue is absolute values. The daily intake of cobalt marked in red is given in µg/d.



daily intake of Co with food [22]

TDI: 1.6 µg/kg BW per day [50]

LOAL: 1mg/kg BW per day [50]

average daily intake due to corrosion in the period 28 to 35 days after insertion and due to abrasion

average daily intake due to corrosion in the period 28 to 35 days after insertion

Intake due to corrosion in the period of the first day after insertion

0.1 1 10 100 1000 10000 100000

daily dose in µg/d

Fig. 4 Comparison of cobalt intake (given in µg) through food, abrasion and corrosion of one person with a presumed average body weight of 60 kg (worst-case scenario) with the range of optimum daily dose and the LOAEL value (Lowest Observable Adverse Effect Level).

Food intake is the main intake of cobalt for humans, apart from possible occupational exposure. Dental technicians are subjected to a higher cobalt exposure, if they are working with cobalt-containing materials.

Assessment of cobalt in dental alloys

The ECHA classified cobalt as mutagenic category 2, carcinogenic category 1b and toxic to reproduction category 1B. As the risk with these endpoints can never be zero, the BfR derives a TDI value, that is a tolerable exposure value and not a safe dose below which no damage can occur.

In its reasons for classification and in particular not restricting it to a specific exposure route (e.g. only inhalative) the ECHA also considered a possible threshold value (a threshold value can also be regarded as a safe dose):

"As these systemic cancer diseases only occurred near or above the MTD and probably represent a threshold value, it is very likely that high doses are required to indicate systemic cancer diseases via the oral exposure route (if they are indicated at all). Nevertheless, this argumentation cannot be used to exclude the possibility of cancer via other exposure routes and to justify the classification of cobalt as carcinogenic only via the inhalative route. Local carcinogenicity in the gastrointestinal tract after oral exposure also cannot be excluded, particularly taking into consideration that studies with repeated doses of cobalt and cobalt chloride adversely affect the gastrointestinal tract and Kirkland et al. (2015) documented core anomalies (apoptotic changes) in the gastrointestinal tract after oral single-dose exposure (see "RAC evaluation of germ cell mutagenicity"). The RAC (Committee for Risk Assessment) thus recommends classifying cobalt as carcinogenic category 1B (H350), without specifying the exposure route."

Brief assessment of cobalt-containing pigments in dental ceramics and dental acrylics

Consideration of the total exposure of cobalt in dental alloys can also be adopted for cobalt-containing pigments in dental ceramics. With the difference that exposure due to abrasion or solution in the oral cavity is significantly lower for two reasons: on the one hand the weight proportion of cobalt bound in silicates or zirconates is significantly lower than with cobalt-chromium alloys, this is approx. 1 wt% and on the other hand cobalt-containing pigments are always in deeper layers of the veneer ceramic build-up. The two top layers such as enamel or glaze porcelain do not incorporate any cobalt-containing pigments. An exception is the stains, though these are only used selectively on the surface. The acid solubility with veneering ceramics according to ISO 6872 and ISO 9693 is significantly less than 100 µg/cm² (worst case, 80°C with acetic acid, 8 h). In comparison with cobalt-containing dental alloys this therefore gives a “margin of safety” for the TDI which is 10 to 100 times higher.

The same applies for veneering composites.

Conclusion

The potential exposure to the patient due to the amount of cobalt released by dental cobalt alloys or pigments from veneering ceramics and veneering composites is very low. In particular in relation to the amount released over a long period, which is regarded as the toxicological relevant exposure for the relevant endpoint. Consequently, the use of cobalt-containing alloys in dental custom-made restorations, from which the patient benefits, is regarded as acceptable.

Cobalt-based alloys have a high mechanical strength and high corrosion resistance and are technically irreplaceable for specific indications. Moreover, due to the low costs, which are borne by public health systems, they provide the possibility of conservative dental treatment for large sections of the population without the additional costs. Sometimes serious compromises would have to be made with regard to material and/or dental requirements, e.g. teeth would have to be increasingly extracted.

The use of cobalt-based alloys is therefore still a valuable and currently irreplaceable mode of treatment in dentistry.

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Annex 1 Calculations

Corrosion:

Day 1:	5.83 µg/cm² (absolute amount on day 1)
Day 28-35:	0.16 µg/cm² (absolute amount in 7 days) (0.16 / 7) →
Day 28-35 average:	0.023 µg/cm² (absolute amount per day on average)

Calculated worst case on 45 cm² corrosion surface:

Day 1:	262 µg (absolute amount on day 1)
Day 28 – 35 average:	1.03 µg (absolute amount per day in the period day 28-35)

Calculated as dose per kg BW (assuming 60 kg person)

Day 1:	4.4 µg/kg BW per day
Day 28 – 35 average:	0.017 µg/kg BW per day

Plus abrasion (34 µg per day absolute corresponds to 0.57 µg/kg BW per day)

Day 1:	4.97 µg/kg BW per day
Day 28 – 35 average:	0.59 µg/kg BW per day

Margin of Safety:

TDI value of 1.6 µg/kg BW

Day 1:	1.6 µg/kg BW / 4.97 µg/kg BW per day → 0.3
Day 28 – 35 average:	1.6 µg/kg BW / 0. 59 µg/kg BW per day or 0.53 ng/kg BW → 2.7

Calculated on 1.4 cm² corrosion surface:

Day 1:	8.2 µg (absolute amount on day 1)
Day 28 – 35 average:	0.032 µg (absolute amount per day in the period day 28-35)

Calculated as dose per kg BW (assuming 60 kg person)

Day 1:	0.136 µg/kg BW per day
Day 28 – 35 average:	0.00053 µg/kg BW per day or 0.53 ng/kg BW

Margin of Safety:

TDI value of 1.6 µg/kg BW

Day 1:	1.6 µg/kg BW / 0.136 µg/kg BW per day → 12
Day 28 – 35 average:	1.6 µg/kg BW / 0.00053 µg/kg BW per day or 0.53 ng/kg BW → 3091