Background

ECHA recently classified Co metal (CAS# 7440-48-4) as a Category 1B carcinogen, Category 1B reproductive hazard, and Category 2 mutagen and is a trace residual in many stainless steel grades.

Per the MDR 2017/745 Annex I clause 10.4.1 “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,

— (re)administer medicines, body liquids or other substances, including gases, to/from the body, or

— transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the 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:

(a) 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 (1), or

(b) substances having endocrine-disrupting properties for which there is scientific evidence of probable serious effects to human health and which are identified either in accordance with the procedure set out in Article 59 of Regulation (EC) No 1907/2006 of the European Parliament and of the Council (2) or, once a delegated act has been adopted by the Commission pursuant to the first subparagraph of Article 5(3) of Regulation (EU) No 528/2012 of the European Parliament and the Council (3), in accordance with the criteria that are relevant to human health amongst the criteria established therein.”

Per 10993-18:2020, information from the material supplier can be used for “quantitative risk assessment”. Furthermore:

“e) material manufacturer's specification, including, for example, purity, impurity identities and levels, quality, molecular weight, molecular weight distribution, thermal properties, tensile strength, Rockwell hardness, bending modulus, conduction of electricity, and others in addition to the general parameters described in 5.2;

f) details of material composition and formulation (see 5.2) such as Chemical Abstracts Service (CAS) numbers (see B.5.2), mass fraction in percent (%) of each chemical in the formulation, function of each chemical constituent, and structure and formula of each chemical”

Discussion

Surgistar has utilized 304 stainless steel for over 20 years for all of its Needles, Cannulas, and Cystotomes. In fact, 304 stainless steel is the gold standard for all major manufacturers of needle products.

All Surgistar Needles, Cannulas, and Cystotomes are limited exposure devices. The exposure of the patient to cobalt is extremely small. Justification of this potential exposure is found in the article "An integrated benefit-risk assessment of cobalt-containing alloys used in medical devices: Implications for regulatory requirements in the European Union" found in the journal Regulatory Toxicology and Pharmacology 125 (2021) 105004. On page 4 of the article, the authors divide devices into 5 categories. For our devices, the category is "Stainless Steel (Limited Exposure Devices)".

"In the risk assessment presented in this publication, exposure duration has been defined in accordance with the ISO 10993-1 device classifications to align the risk characterization process and terminology to that used globally. Medical devices are classified as limited exposure devices (contact up to 24 h), prolonged exposure devices (contact for > 24 h to 30 days), and long-term contact devices (contact 31–25,000 days) (ISO 10993-1). Differences in the medical device classification under Annex VIII of the MDR which includes transient (<60 min) and short-term (60 min–30 days) categories are not considered to have a significant impact on the overall evaluation described herein."

"The EU Medical Device Regulation (EU, 2017/745) requires an evaluation of the "positive impact of a device on the health of an individual" (EU MDR, 2017: p. 19) versus the "probability of occurrence of direct or indirect harm and the severity of that harm" (EU MDR, 2017: p. 75) as part of a medical device benefit-risk determination. In general, the MDR requires that products remain fit for their intended purpose during normal use conditions with a "high level of protection of health and safety", and that the determination of acceptable risks should consider possible hazards in the context of the "generally acknowledged state of the art" (EU MDR, 2017: p. 94). Medical interventions providing patient benefits such as improved quality of life and/or decreased pain are inherently associated with the possibility of an adverse outcome, and thus devices need to be engineered to reduce risks "as far as possible without adversely affecting the benefit-risk ratio" (EU MDR, 2017: p. 94)."

"Biomaterials have gained broad support as an interface to biological systems used to replace or augment tissues, organs, and/or function due to their material properties and related patient benefits even when weighed against patient risks (potential harm, severity of potential harm, and frequency of occurrence) (Agrawal et al., 2014; O'brien, 2011)."

"Stainless steel has an extensive use in medical devices. Stainless steels in these devices were produced from the extracting and refining of ores that have Co present as a trace element or residual impurity often present at a level of less than 1% w/w (Shetty et al., 2018; Wang et al., 2019) … Stainless steel materials are also used in many limited exposure devices including blades/lancets, actuators, tunnelers, stylets, guide wires, balloon catheters, vessel closure devices, hemostasis clips, implant tools, needles, metal wedges, clevis, surgical hooks, forceps, cutting and drill guides, electrode spatulas, actuating rods, graspers, and knot pushers."

Table 4
CoCA specific device exposure and risk assessment.

Exposure[a]	Device	Co Content (%)	Relative device wear (Group)	Estimated Serum Co Concentration[b]	Hematological, Endocrine, Neurological or Cardiac Effects	Identified Cancer/ Reproductive Risks
Stainless Steel						
Long-term	Head and stem components in hip arthroplasty, acetabular shells	<1[c]	A[c]	(background)	None	None
	Osteosynthesis plate implants	<1[c]	A	(background)	None	None
	External fixator components	<1[c]	A	(background)	None	None
	Occluders, heart valves	<1[c]	A	(background)	None	None
Limited	Wires, stylets, blades/lancets, actuators, tunneler, stylets, guidewires, implant tools, needles, clevis, surgical hook, forceps	<1[c]	A	(background)	None	None
	Cutting and drill guides, invasive tools (e.g., cutting, drilling, reaming, rasping tools)	<1[c]	A	(background)	None	None
	Electrode spatula, actuating rod, grasper, knot pusher	<0.5	A	(background)	None	None

The article concluded that “Collectively, there is overwhelming evidence that the vast majority of Co-containing hip implants, which represent the higher end or an upper bound in terms of Co-exposure compared to other Co-containing implants, do not represent an appreciable risk for systemic Co (or CoCA) toxicity (Bradberry et al., 2014; Kovochich et al., 2018; Zywiel et al., 2016).”

“Most serum Co concentrations associated with the use of CoCA in medical devices will not measurably increase baseline serum concentrations (0.1–0.5 μg Co/L) with the exception of devices with fully articulating surfaces where concentrations in well-functioning devices of 0.5–10 μg Co/L have typically been reported (Alimonti et al., 2005; Coric et al., 2018; Di Santo et al., 2018; Fortmann et al., 2017; Fung et al., 2017; Hartmann et al., 2013; Jantzen et al., 2013; Lützner et al., 2013; Minoia et al., 1990; Mu˜niz et al., 2001; Reiner et al., 2019, 2020). The assessment found that a margin of safety for systemic effects is maintained even in cases of Co sensitivity such as renal failure (which prevents clearance of freely filterable Co) or hypoalbuminemia (which disrupts the sequestration of Co in serum proteins); however, patients with articulating devices and impaired health status should be carefully monitored for Co-related toxicity with suspicion of device failure or when serum Co concentrations exceed 10–100 μg/L (Bradberry et al., 2014; Fung et al., 2017; Kovochich et al., 2018; Packer, 2016; Paustenbach et al., 2013; Tvermoes et al., 2015; Unice et al., 2014; Zywiel et al., 2016).”

“The assessments support that Co alloys and stainless steels used in medical devices are unlikely to reach exposure levels that will elicit toxicity (polycythemia, thyroid changes, or myocardial damage), carcinogenicity, or reproductive toxicity. A comprehensive review of benefit-risk profile and an assessment of alternative materials strongly support the continued use of CoCA in medical devices. These materials have provided a positive impact on the health of a broad and diverse patient population with minimal risk of Co-related health effects associated with intended use and function. Thus, CoCA provide health benefits to broad and diverse patient populations due to their unique properties that make them critical components of medical devices and provide a safe and important option for patients.”

Conclusion

The analysis of available toxicologic information of the materials of construction of Surgistar’s Needles, Cannulas, and Cystotomes has been presented in BER-91-02. Cobalt was identified as the only carcinogenic, mutagenic, or toxic to reproduction (‘CMR’) substance with a threshold above 0.1% W/W. However, the overall toxic and biological risk is considered acceptable. Surgistar will label all of its Needles, Cannulas, and Cystotomes with the ISO symbol for CMR containing devices and the universal symbol for Cobalt.