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Nickel release and surface characteristics of fine powders of nickel metal and nickel oxide in media of relevance for inhalation and dermal contact

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ABSTRACT

Differences in surface oxide characteristics and extent of nickel release have been investigated in two thoroughly characterized micron-sized (mainly <4 μm) nickel metal powders and a nickel oxide bulk powder when immersed in two different synthetic fluids, artificial sweat (ASW-pH 6.5) and artificial lysosomal fluid (ALF-pH 4.5) for time periods up to 24 h. The investigation shows significantly more nickel released from the nickel metal powders (<88%) compared to the NiO powder (<0.1%), attributed to differences in surface properties. Significantly more nickel was released from the nickel metal powder with a thin surface oxide predominantly composed of non-stoichiometric nickel oxide (probably Ni_2O_3), compared to the release from the nickel metal powder with a thicker surface oxide predominantly composed of NiO and to a lesser extent Ni_2O_3 (88% and 25% release after 24 h in ALF, respectively). Significantly lower amounts of nickel were released from the nickel metal powders in ASW (2.2% and <1%, respectively). The importance of particle and surface characteristics for any reliable risk assessment is discussed, and generated data compared with literature findings on bioaccessibility (released fraction) of nickel from powders of nickel metal and nickel oxide, and massive forms of nickel metal and nickel-containing alloys.

1. Introduction

As it is often the case for metals, the physicochemical properties (particle size and size distribution, agglomeration, surface properties) of different nickel-containing substances will influence their toxicological behavior. Water soluble compounds like nickel sulfate or nickel chloride are usually expected to have different toxicities compared to sparingly soluble nickel compounds (Henderson et al., 2012). For those nickel-containing substances that release limited amounts of nickel in aqueous solutions, the surface properties may be decisive to deliver nickel ions at target cellular sites and to be absorbed and/or excreted. The current work hence focuses to assess differences in physicochemical surface properties (i.e., thickness, crystallinity and composition of surface oxides) between samples of nickel metal powders (nickel in elemental state of oxidation) which are naturally covered by a thin nickel oxide (shell) and nickel(II) oxide (green) powders.

Nickel metal is currently classified for human health endpoints: as a skin sensitizer (Category 1, "may cause an allergic skin reaction"), for causing specific target organ toxicity, STOT RE 1 (STOT Repeated Exposure 1: H372: "causes damage to organs through prolonged or repeated exposure"; "route of exposure: inhalation"), and as a suspected carcinogen (Category 2, "suspected of causing cancer") (EC, 2009), while nickel oxide (NiO) is classified as Category 1Ai carcinogen ("may cause cancer by inhalation"), STOT RE 1, and skin sensitizer (Category 1) (EC, 2009).

Human exposure to nickel metal and/or nickel oxide may occur via the main exposure routes (inhalation, ingestion or dermal contact) at occupational settings. Exposure to nickel metal or nickel-containing alloys can also occur via coins (Kasprzak et al., 2003; Lidén and Carter, 2001; Lidén et al., 2008). Cutaneous nickel absorption may result from wearing or handling of jewelries, coins, or utensils fabricated from nickel alloys or nickel coatings (Flint, 1998; Lidén and Carter, 2001; Lidén et al., 2008), although dermal absorption of nickel from nickel metal and Ni-containing alloys is very low (approximately 0.2%, (Hostynek et al., 2001)). Nickel in fly-ash from coal-fired power plants and petroleum, and smoking are examples of sources that may increase the inhaled nickel dose (Sunderman and Oskarsson, 1991; Denkhaus and Salnikow, 2002). Nickel in fly ash is not present as metallic nickel but rather as nickel sulfate and complex Ni oxides (Huggins et al., 2011). Increased incidence of respiratory cancer has been observed among some groups of nickel refinery workers exposed to sulfidic, oxidic and water soluble nickel compounds, e.g. review by Goodman et al. (2011). Only respiratory tumors have been consistently associated with exposure to nickel-containing compounds (Goodman et al., 2011). While the positive association between increased respiratory cancer mortality and overexposures to nickel oxide observed in epidemiological studies was confirmed in animal inhalation

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studies, both animal and human studies show that nickel metal powders are not expected to increase the risk of respiratory cancer (Goodman et al., 2011; Oller et al., 2008). Prior to 2008, when the classification of nickel metal as a Category 2 carcinogen took place, no animal inhalation carcinogenicity study with nickel metal powder was available.

Skin irritation induced by nickel metal and nickel oxide particles seem to be solely related to released soluble nickel species, such as nickel ions, i.e. the *bioaccessible fraction* (the fraction of the sample that has been released or has been solubilized and available for uptake or absorption by humans). Due to the known relationship between the release of nickel ions and skin sensitization (Flint, 1998; Lidén and Carter, 2001; Lidén et al., 2008; Midander et al., 2007), any nickel-containing articles in direct and prolonged contact with the skin are classified as skin sensitizers when exceeding a release rate of 0.5 μg Ni/cm^2/week, as measured by the European Standard reference test method EN 1811 (EN, 2011; EC, 2009). For piercing assemblies, the nickel release limit allowed for the materials to remain in commerce is set to 0.2 μg Ni/cm^2/week (EN, 2011). Many investigations have therefore focused on assessing the bioaccessibility of different nickel compounds, alloys, powders and/or massive material in artificial sweat (Hedberg et al., 2010b; Lidén and Carter, 2001; Lidén et al., 2008; Midander et al., 2007). Nickel-induced allergies are the most frequent reasons for contact dermatitis in the industrialized part of the world, affecting 15% of females and a few% of males (Lidén and Carter, 2001). The ability of nickel ions to cause a dermal reaction in sensitized individuals depends on their concentration, the exposed skin area and the exposure duration (Flint, 1998). Generally, a concentration exceeding 1.5 μg Ni chloride per cm^2 of skin in an open application is required to elicit dermatitis in sensitized individuals (Menné and Calvin, 1993). However, lower concentrations may also induce an allergic reaction if other irritants or allergens are present in parallel (Pedersen et al., 2004).

Due to non-stoichiometric composition of nickel oxides, their physico-chemical properties (i.e., impurities, oxygen content, crystallinity, phases, and water solubility) are not constant and have therefore yielded considerably variable results in cytotoxicity and carcinogenicity studies (Takahashi et al., 1999). The only reasonably well-characterized surface oxide formed on pure nickel metal at room temperature is NiO (Greenwood and Earnshaw, 1997; Kitakatsu et al., 1998; Mitchell et al., 1976), covered by a nearly saturated layer of hydroxyl groups (OH^-) (Kitakatsu et al., 1998). However, claims for the existence of many other oxides (Ni_2O_3, NiO_2) have been made (Barrientos et al., 2009; Greenwood and Earnshaw, 1997). Green nickel oxide (tested in this study) has a rock-salt stoichiometric structure (face cubic centered) (Greenwood and Earnshaw, 1997), poor solubility, and to some extent lower respiratory toxicity than other nickel compounds when compared by acute or subchronic effects (Oller et al., 1997; Takahashi et al., 1999). A study comparing ten different NiO powders reports significant differences in, e.g., solubility (in water, rat serum, and renal cytosol), phagocytosis, morphological transformation and cytotoxicity, and stimulation of erythropoiesis (Sunderman et al., 1987). From that study it was concluded that a high specific surface area and the presence of Ni(III) were associated with the largest biological effects.

Different physical, chemical, or electrochemical processes or their combinations can induce the release of nickel from nickel metal or nickel oxide. For example, nickel metal can be dissolved via corrosion processes in contrast to nickel oxide, which is in its thermodynamically stable form in oxygen environments. For complexing media such as artificial lysosomal fluid (ALF, pH 4.5), which simulates intracellular inflammatory conditions in lung cells following phagocytosis (de Meringo et al., 1994), adsorption of the complexing agents on the particle surface and subsequent complexation to the metal oxide is important (Hedberg et al., 2011). While dissolution of nickel oxide particles in non-complexing media is mainly due to the proton adsorption (pH), showing increasing dissolution with decreasing pH (Ludwig and Casey, 1996), dissolution is significantly enhanced by complexing agents such as oxalate (Ludwig et al., 1996).

The objective of this study was to investigate differences in particle and surface oxide characteristics and the extent of nickel release from micron-sized (<1–50 μm, mainly <4 μm) nickel metal powders compared with a nickel oxide bulk powder to assess whether these differences could explain differences in reported toxicological behavior of such powders. Bioaccessibility studies have been conducted in synthetic fluids of relevance for the two main exposure routes where the release of nickel ions are important for nickel toxicity including artificial sweat, ASW (skin sensitization) and artificial lysosomal fluid, ALF (respiration). This was accomplished via (i) detailed particle characterization in terms of surface area, particle size distribution, particle morphology, and compositional analysis of the surface oxide, and (ii) the assessment of the amount and kinetics of released nickel from the different powders immersed in ASW, pH 6.5, and ALF, pH 4.5, after four different time periods up to 24 h. Generated release data is compared to in vivo respiratory toxicity and carcinogenicity data on the same or similar samples of nickel metal and nickel oxide powders, powder and massive forms of nickel metal and nickel-containing alloys.

2. Materials and methods

2.1. Materials

A nickel oxide powder, denoted "NiO (N46)", and two nickel metal powders of different particle size distribution, denoted "Ni (N13)" and "Ni (N36)", were supplied by the Nickel Producers Environmental Research Association (NiPERA). The nickel metal powder sample (N36) used in the animal studies (Oller et al., 2008) was not ground and therefore the powder tested in vitro is the same as the one the animals were exposed to, allowing comparisons between the in vitro and in vivo results to be made.

2.2. Particle characterization

2.2.1. BET - specific surface area

The specific surface area per mass (m^2/g), BET-analysis (Brunauer–Emmet–Teller method, (Brunauer et al., 1938)) was determined via adsorption of nitrogen at cryogenic condition using a Micromeritics Gemini V instrument. Nitrogen adsorption was measured at five different partial pressures (p/p_0 0.10–0.25). The cross-sectional diameter of nitrogen (0.162 nm^2) was used as input parameter. The powders were dried with nitrogen and flushed in a tube for 30 min at 150 °C. The measured mass was adjusted to correspond to an approximate total surface of 1 m^2. The results are presented in Table 1.

2.2.2. Particle size distribution

Differences in particle size distribution between the different powders were measured in artificial sweat, ASW, with a relatively

Table 1
Measured BET area (m^2/g) of the NiO and Ni metal powders, with a standard deviation of less than 1%.

Powders	BET area
NiO (N46)	0.25
Ni (N13)	1.05
Ni (N36)	2.15