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Review

Toxicological risk assessment of elemental gold following oral exposure to sheets and nanoparticles – A review

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ABSTRACT

Elemental gold is used as a food coloring agent and in dental fillings. In addition, gold nanoparticles are gaining increasing attention due to their potential use as inert carriers for medical purposes. Although elemental gold is considered to be inert, there is evidence to suggest the release of gold ions from its surface. Elemental gold, or the released ions, is, to some extent, absorbed in the gastrointestinal tract. Gold is distributed to organs such as the liver, heart, kidneys and lungs. The main excretion route of absorbed gold is through urine. Data on the oral toxicity of elemental gold is limited. The acute toxicity of elemental gold seems to be low, as rats were unaffected by a single dose of 2000 mg nanoparticles/kg of body weight. Information on repeated dose toxicity is very limited. Skin rashes have been reported in humans following the ingestion of liquors containing gold. In addition, gold released from dental restorations has been reported to increase the risk of developing gold hypersensitivity. Regarding genotoxicity, *in vitro* studies indicate that gold nanoparticles induce DNA damage in mammalian cells. *In vivo*, gold nanoparticles induce genotoxic effects in *Drosophila melanogaster*; however, genotoxicity studies in mammals are lacking. Overall, based on the literature and taking low human exposure into account, elemental gold via the oral route is not considered to pose a health concern to humans in general.

Contents

1. Human exposure to elemental gold

Elemental gold is important from a safety point of view because of its use as a food coloring agent, its use in dental fillings, and because gold nanoparticles have increasingly been investigated as inert carriers for medical purposes. Humans are exposed to gold from various sources. Non-oral sources include jewelry and during the manufacturing of gold containing products (Brune et al., 1980; Hamilton and de Gannes, 2011; Hewitt, 1988; Rapson, 1985). Oral sources include food, dental fillings, tobacco and pharmaceuticals (Ahnlide et al., 2002; Iyengar et al., 2000; Krachler et al., 2000;

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Nada et al., 1999; Wittsiepe et al., 2003; Ysart et al., 1999). The forms of gold that are relevant for oral exposure are nanoparticles and larger particles, e.g., in the form of thin sheets, as well as gold ions leaking from the surface of particles and from dental fillings. The human intake of dietary gold has been reported to be 10–14 ng/kg bw/day for small children (Wittsiepe et al., 2003; Ysart et al., 1999) and 10 ng/kg bw/day for people consuming a typical American diet (Iyengar et al., 2000). Gold complexes have also been used as antirheumatic pharmaceuticals. These complexes, e.g., sodium aurothiomalate and auranofin, can be converted to other gold complexes in the mammalian body. Thus, this type of gold formulation seems to not be relevant for assessing the toxicology of elemental gold or gold ions released from the surface of elemental gold (Tepperman et al., 1984; Zhao et al., 1992).

2. Absorption, distribution, metabolism and excretion

The body burden of gold in humans has been reported to range from undetectable to 3 μg/kg bw (Brune et al., 1966, 1980; Elmsley, 1998; Parr and Taylor, 1963). Studies with different age groups indicate that gold is not accumulated to a large extent in humans because older individuals do not have higher body burdens of gold than younger individuals (Masiak et al., 1981; Parr and Taylor, 1963).

There are several lines of evidence that show that elemental gold or gold ions released from its surfaces are, to some extent, bioavailable in humans following oral exposure. Russell et al. found that a man who regularly ingested gold-flake-containing liquor over a one-year period had an elevated gold serum level. The liquor was estimated to contain 11–23 mg gold/L. The metallic flakes were 75% gold by weight, with 280 μg of gold per deciliter dissolved in the liquid portion. It was estimated that the individual drank 200–300 mL of the liquor per week, and thus, the intake of elemental gold ranged from 1.7 mg/week (3.3 μg/kg bw/day) to 5.2 mg/week (11 μg/kg bw/day). For gold ions, the intake ranged from 0.56 mg/week (1.1 μg/kg bw/day) to 0.84 mg/week (1.7 μg/kg bw/day). Three months after discontinuing this drinking behavior, the individual had a gold serum concentration of 0.4 mg/L (the normal range was reported to be 0–0.1 mg/L). A urinary gold level of 86 μg/24 h specimen was observed three months after the consumption of the gold-flake containing liquor (the normal range was reported to be 0–1.0 μg/24 h urine). Six months after the last consumption, both serum and urine gold levels were normal (Russell et al., 1996). The release of gold from dental fillings, leading to elevated gold concentrations in the plasma and urine, has also been reported (Ahnlide et al., 2002; Becker et al., 2003; Drasch et al., 2000; Komaromy-Hiller et al., 2000).

Regarding distribution in humans, gold has been found in a range of tissues, including the blood, liver, lung, kidney, heart, spleen, brain, bladder and endometrium (Botzvadze et al., 1969; Brune et al., 1966; Cornelis and Speecke, 1971; Frustaci et al., 1999; Hagenfeldt et al., 1977; Kasperek et al., 1979; Kauf et al., 1984; Parr and Taylor, 1963; Tjioe et al., 1984). In human milk, gold has been reported in the range of 0.1–2.1 μg/L (Krachler et al., 2000; Prohaska et al., 2000).

Regarding animal studies, Hillyer and Albrecht have published a bioavailability study of four sizes of gold nanoparticles (4, 10, 28 and 58 nm) administered to mice for 7 days. The concentration of each particle size was 200 mg/L of drinking water, estimated to be equivalent to 36 mg/kg bw/day.[1] The investigators found that the smaller particles (4 and 10 nm) crossed the gastrointestinal membrane more readily than the larger particles (28 and 58 nm) and that uptake occurred in the small intestine by what was described as: "persorption through single, degrading enterocytes in the process of being extruded from a villus". This resulted in the distribution of gold to the blood, brain, lungs, heart, kidneys, spleen, liver, small intestine and stomach (Hillyer and Albrecht, 2001). Zhang et al. reported that the administration of 2.2 mg/kg bw/day gold nanoparticles (13.5 nm) by oral gavage for 14 days to mice resulted in gold nanoparticles occurring in the blood and in bone marrow cells. Schleh et al. investigated radiolabeled gold nanoparticles with sizes ranging from 1.4 to 200 nm that were either stabilized with mono-sulfonated triphenylphosphine or citrate. The nanoparticles were administered by oral gavage at doses in the range of 4–108 μg/kg bw. After 24 h, the absorption of gold was reported to be in the range of 0.02–0.4% of the administered gold. Gold was found in the liver, kidneys, blood, lungs, heart, brain and spleen. In addition, Schleh et al. found approximately 0.05% of the administered gold in 24 h urine, suggesting this as a route of elimination (Schleh et al., 2012). It is noted by the present authors that the absorbed gold reported by Schleh et al. was not verified in the particle form. The presence of gold nanoparticles in the mammalian body after oral exposure to gold nanoparticles may reflect that gold can be taken up as particles. However, as has been observed for silver nanoparticles, gold nanoparticles may be dissolved in the gastrointestinal tract, taken up as ions and then deposited as particles that form in tissues (Loeschner et al., 2011; van der Zande et al., 2012; Aaseth et al., 1981). It should be noted that when nanoparticles are formulated, the particles are often stabilized with some type of coating. This should be taken into account when evaluating the gold nanoparticle absorption data, as the coating may alter bioavailability (Das et al., 2012; Smith et al., 2013).

3. General toxicity

Gold nanoparticles (10–50 nm) stabilized with a bioadhesive polymer, chitosan, did not cause any signs of toxicity when administered as a single oral gavage dose of 2000 mg/kg bw[2] to rats (Pokharkar et al., 2009). Abraham and Himmel investigated the use of colloidal gold for the treatment of rheumatoid arthritis and found no adverse effects following oral administration of 0.5 mg/kg bw/day for 28 days (Abraham and Himmel, 1997). Zhang et al. administered gold nanoparticles (13.5 nm) to mice at oral gavage doses in the range of 0.14–2.2 mg/kg bw/day for 14 days and found that doses of 0.55–2.2 mg/kg bw reduced body weight compared to the controls (Zhang et al., 2010).

Russell et al. found that a man who ingested gold-flake containing liquor regularly during a one-year period developed a skin rash in the form of lichenoid dermatitis and pruritus. The authors noted that ingredients other than gold could also induce these effects. After the intake stopped, the symptoms gradually cleared within four months, although with residual post-inflammatory hyperpigmentation. It was estimated that the intake of elemental gold was in the range of 3.3–11 μg/kg bw/day. The intake of accompanying dissolved gold was in the range of 1.1–1.7 μg/kg bw/day. Skin rashes were also reported for two other individuals that had ingested the same brand of gold-flake containing liquor: a 47-year old woman drank 100–200 mL of the same liquor for seven months and a 58-year old woman had sporadically consumed 400 mL of this liquor. The skin of these individuals cleared within months after discontinuation of this drinking behavior (Russell et al., 1996, 1997). In addition, Guenthner et al. reported an allergy in the form of erythematous and pruritic rash in a 31-year old woman

[1] This was estimated by the present authors by use of an EFSA default factor for converting the concentration in drinking water to a dose. EFSA (2012) guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data, vol. 10(3). European Food Safety Authority (EFSA), Parma, Italy, EFSA Journal 10 (3) 2579, p. 2579. Available from: http://www.efsa.europa.eu/en/efsajournal/doc/2579.pdf.

[2] The authors of the article did not specifically state that this is per kg bw.