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Background: Edible gold (Au) is used as a food additive (E175 in EU) with no maximum level (*quantum satis*) for confectionery and cake decorations, coatings and in beverages. Food-grade gold is often composed of thin Au sheets or flakes exhibiting micro- and nanometric dimensions in their thickness. Concerns about the toxicity of mineral particles used as food additives for human health are increasing with respect to the particular physico-chemical properties of nanosized particles, which enable them to cross biological barriers and interact with various body cell compartments. The aim of this study in mice was to explore the fate of the food additive E175 following chronic oral exposure in mice at human relevant levels, and to concomitantly assess the potential impacts on digestive physiology, taking into account a potential sexual dimorphism.

Methods: Female and male mice were exposed to E175 (0.1; 1 and 10µg/kg BW/day) or a 100% nanosized Au nanomaterial (Ref-Au; 10µg/kg BW/day) incorporated into food pellets at human relevant doses for 90 days. Biodistribution of Au particles using confocal microscopy and MET-EDX as well as histomorphological damages were evaluated in liver, spleen and intestine. Cells from intestinal and liver tissues were isolated and stained with an anti-γH2AX antibody for genotixicity. Gut microbiota composition, intestinal permeability and intestinal pro- and anti-inflammatory cytokine production were measured by 16S gene sequencing, Ussing chambers and ELISA, respectively.

Results: A 90-day exposure to E175 or Ref-Au in mice did not induce any histomorphological damage in the liver, spleen or intestine, nor genotoxic effects in the colon and liver despite an apparent higher absorption level of Au particles from the Ref-Au material compared to the E175 food additive. While exposure to Ref-Au did no impact intestinal microbiota, a marked alteration in its bacterial composition characterized by an increased Firmicutes/Bacteroidetes ratio and of the Proteobacteria abundance, as well as a decreased production of short-chain fatty acids were reported after E175 treatment in females compared to males. In the colon, increased production of IL-6, TNFα and IL-1β were also observed in females at the end of the 90-day treatment with E175, while in contrast, decreased IL-6, IL-1β, IL-17 and TGFβ levels were found in males.

Conclusions: These results revealed that a 90-day exposure to E175 added to the diet alters the gut

microbiota and intestinal immune response in a sex-dependent manner in mice. Within the dose range of human dietary exposure to E175, these alterations remained low in both sexes and mostly appeared to be non-toxic. However, at the higher dose, the observed gut dysbiosis and the development of a low-grade inflammation in the female colon could favour the occurrence of metabolic disorders. These data support the need to establish toxic reference values for the safe use of gold as food additive in the human diet.