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Abstract #695 | Poster or Short Oral Communication

Mice exposed to food-grade titanium dioxide from *in utero* life to adulthood show sex-specific gut microbiota and metabolic disorders which are aggravated under Western-diet

L. Evariste[1], E. Gaultier[1], C. Cartier[1], J. Noireaux[2], B. Chassaing[3], E. Houdeau[1], B. Lamas[1]

[1] *Toxalim UMR1331 (Research Centre in Food Toxicology), Toulouse University, INRAE, ENVT, INP-Purpan, UPS, Toulouse, France*
[2] *Department of biomedical and inorganic chemistry, LNE, Trappes, France*
[3] *INSERM U1016, team "Mucosal microbiota in chronic inflammatory diseases", CNRS UMR 8104, Université de Paris, Paris, France*

Background: Food additives are one major hallmark of ultra-processed food in the Western diet, a food habit often associated with metabolic disorders. Among these additives, the whitener and opacifying agent titanium dioxide (TiO_2, E171 in EU) raises public health issues due to systemic passage, organ accumulation (including placenta) and a maternofetal passage of TiO_2 nanoparticles (found in the meconium) in human, showing early life exposure. In this context, exposure to TiO_2 with biocidal properties could alter the gut colonization by the microbiota that plays a key role in intestinal and metabolic functions, leading to health effects at adulthood. Our aim in mice was to assess the fetal passage of TiO_2 (E171) particles given to dams and the consequences on gut microbiota and metabolic functions of the offspring.

Methods: Female mice (F0) were exposed to a control or E171-enriched normal diet at a human dose level (10 mg/kg bw/day) during pregnancy and lactation. At weaning, part of the descendants (F1) were fed with the same diet as their mother and the other part received a Western diet (WD) supplemented or not with the E171 (10 mg/kg bw/day) until postnatal day (PND) 150. Total fetal titanium (Ti) content was measured by ICP-MS at day 18 of pregnancy, and in the liver of F1 descendants at PND150. Intestinal inflammation and microbiota composition were studied at PND150 using ELISA for cytokines and 16S gene sequencing, respectively. Metabolic status was evaluated using oral glucose tolerance test and fasting insulin.

Results: Compared to controls, high Ti level was detected in fetuses of E171-exposed mothers, while further liver Ti accumulation was evidenced at PND150 in F1 descendants fed with the same E171-enriched diet, regardless of the sex. Under normal diet, chronic E171 exposure starting *in utero* increased production of the pro-inflammatory cytokine IL1β in the colon of adult F1 males. Changes in the gut microbiota composition occurred in males only, showing an increase of β-diversity and Firmicutes/Bacteroidetes ratio. This occurred concomitantly to glucose intolerance and higher fasting insulin levels, while the same E171 treatment fostered WD-induced colon inflammation and glucose intolerance. In contrast, decreased secretion of pro- (IL1β, TNFα, IFNγ, IL17) and anti-(IL10) inflammatory cytokines occurred in the colon of E171-exposed F1 females under normal diet, while the metabolic alterations induced by WD showed no worsening.

Conclusions: These results showed that a long-term exposure to food-grade TiO_2 (E171) starting from *in*

utero life alters intestinal and metabolic homeostasis in a sex-dependent manner, characterized by altered glucose metabolism, gut dysbiosis and worsening of WD-induced metabolic disorders in male mice only. Taken together, these data suggest that a lifespan exposure to TiO_2 from dietary sources could both initiate and promote the development of metabolic disorders in humans.