

References - Review of EFSA Opinion

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This is a paper for discussion.

This does not represent the views of the Committee and should not be cited.

Ammendolia MG, Iosi F, Maranghi F, Tassinari R, Cubadda F, Aureli F, Raggi A, Superti F, Mantovani A and DeBerardis B, 2017. Short-term oral exposure to low doses of nano-sized TiO₂ and potential modulatory effects on intestinal cells. Food and Chemical Toxicology, 102, 63–75.

Bettini S, Boutet-Robinet E, Cartier C, Comera C, Gaultier E, Dupuy J, Naud N, Tache S, Grysan P, Reguer S, Thieriet N, Refregiers M, Thiaudiere D, Cravedi JP,

Carriere M, Audinot JN, Pierre FH, Guzylack-Piriou L and Houdeau E., 2017. Food-grade TiO₂ impairs intestinal and systemic immune homeostasis, initiates preneoplastic lesions and promotes aberrant crypt development in the rat colon. *Scientific Reports*, 7, 40373.

Bischoff NS, de Kok TM, Sijm DTHM, van Breda SG, Briedé JJ, Castenmiller JJM, Opperhuizen A, Chirino YI, Dirven H, Gott D, Houdeau E, Oomen AG, Poulsen M, Rogler G, van Loveren H., 2020. Possible Adverse Effects of Food Additive E171 (Titanium Dioxide) Related to Particle Specific Human Toxicity, Including the Immune System. *International Journal of Molecular Science*, 22(1):207.

Blevins LK, Crawford RB, Bach A, Rizzo MD, Zhou J, Henriquez JE, Khan D, Sermet S, Arnold LL, Pennington KL, Souza NP, Cohen SM and Kaminski NE, 2019. Evaluation of immunologic and intestinal effects in rats administered an E 171-containing diet, a food grade titanium dioxide (TiO₂). *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association*, 133.

Chen Z, Zheng P, Han S, Zhang J, Li Z, Zhou S and Jia G, 2020a. Tissue-specific oxidative stress and element distribution after oral exposure to titanium dioxide nanoparticles in rats. *Nanoscale*, 12, 20033–20046.

Chen Z, Han S, Zheng P, Zhou D, Zhou S and Jia G, 2020b. Effect of oral exposure to titanium dioxide nanoparticles on lipid metabolism in Sprague-Dawley rats. *Nanoscale*, 12, 5973–5986.

Comera C, Cartier C, Gaultier E, Catrice O, Panouille Q, El Hamdi S, Tirez K, Nelissen I, Theodorou V and Houdeau E, 2020. Jejunal villus absorption and paracellular tight junction permeability are major routes for early intestinal uptake of food-grade TiO₂ particles: an in vivo and ex vivo study in mice. *Part Fibre Toxicol*, 17, 26.

Disdier C, Devoy J, Cosnefroy A, Chalansonnet M, Herlin-Boime N, Brun E, Lund A and Mabondzo A, 2015. Tissue biodistribution of intravenously administered titanium dioxide nanoparticles revealed blood-brain barrier clearance and brain inflammation in rat. *Particle and Fibre Toxicology*, 12, 24.

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrients Sources added to Food), 2016. Re-evaluation of titanium dioxide (E 171) as a food additive. *EFSA Journal* 2016;14(9):4545, 83 pp.

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrients Sources added to Food), 2017. Approach followed for the refined exposure assessment as part of the safety assessment of food additives under re-evaluation. EFSA Journal 2017;15(10):5042, 9 pp.

EFSA FAF Panel (EFSA Panel on Food Additive and Flavourings), 2019. Scientific opinion on the proposed amendment of the EU specification for titanium dioxide (E 171) with respect to the inclusion of additional parameters related to its particle size distribution. EFSA Journal 2019;17(7):5760, 23 pp.

EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings) (2021): Safety assessment of titanium dioxide (E171) as a food additive, EFSA Journal 2021; 19(5):6585

EFSA Scientific Committee, 2009. Guidance of the scientific Committee on transparency in the scientific aspects of risk assessments carried out by EFSA. Part 2: general principles. EFSA Journal 2009;7(7):1051, 22 pp.

EFSA Scientific Committee, 2011a. Scientific Opinion on Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain. EFSA Journal 2011;9(5):2140, 36 pp.

EFSA Scientific Committee, 2018a. Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: part 1, human and animal health. EFSA Journal 2018;16(7):5327,95 pp.

Geraets L, Oomen AG, Krystek P, Jacobsen NR, Wallin H, Laurentie M, Verharen HW, Brandon EF and de Jong WH, 2014. Tissue distribution and elimination after oral and intravenous administration of different titanium dioxide nanoparticles in rats. Part Fibre Toxicol, 11, 30.

Gore ER, Gower J, Kurali E, Sui JL, Bynum J, Ennulat D and Herzyk DJ, 2004. Primary antibody response to keyhole limpet hemocyanin in rat as a model for immunotoxicity evaluation. Toxicology, 197, 23-35.

Guillard A, Gaultier E, Cartier C, Devoille L, Noireaux J, Chevalier L, Morin M, Grandin F, Lacroix MZ, Comera C, Cazanave A, de Place A, Gayrard V, Bach V, Chardon K, Bekhti N, Adel-Patient K, Vayssiere C, Fisicaro P, Feltin N, de la Farge F, Picard-Hagen N, Lamas B and Houdeau E, 2020. Basal Ti level in the human placenta and meconium and evidence of a materno-foetal transfer of food-grade TiO₂ nanoparticles in an ex vivo placental perfusion model. Part Fibre Toxicol, 17, 51.

Hendrickson OD, Pridvorova SM, Zherdev AV, Klochkov SG, Novikova OV, Shevtsova EF, Bachurin SO and Dzantiev BB, 2016. Size-dependent differences in biodistribution of titanium dioxide nanoparticles after sub-acute intragastric administrations to rats. *Current Nanoscience*, 12, 228–236.

Hendrickson OD, Platonova TA, Pridvorova SM, Zherdev AV, Gmoshinsky IV, Vasilevskaya LS, Shumakova AA, Hotimchenko SA and Dzantiev BB, 2020. Electron-microscopic investigation of the distribution of titanium dioxide (rutile) nanoparticles in the rats' small intestine mucosa. Liver, and Spleen *Current Nanoscience*, 16, 268–279.

Heringa MB, Peters RJB, Bleys R, van der Lee MK, Tromp PC, van Kesteren PCE, van Eijkeren JCH, Undas AK, Oomen AG and Bouwmeester H, 2018. Detection of titanium particles in human liver and spleen and possible health implications. *Particle and Fibre Toxicology*, 15, 15.

Karimi S, Khorsandi L and Nejaddehbashi F, 2019. Protective effects of Curcumin on testicular toxicity induced by titanium dioxide nanoparticles in mice. *JBRA Assisted Reproduction*, 23, 344–351.

Karimipour M, Zirak JM, Ahmadi A and Jafari A, 2018. Oral administration of titanium dioxide nanoparticle through ovarian tissue alterations impairs mice embryonic development. *International Journal of Reproductive Biomedicine (Yazd, Iran)*, 16, 397–404.

Khorsandi L, Orazizadeh M, Mansouri E, Hemadi M and Moradi-Gharibvand N, 2016. Morphometric and stereological assessment of the effects of titanium dioxide nanoparticles on the mouse testicular tissue. *Bratislavske lekarske listy*, 117, 659–664.

Khorsandi L, Orazizadeh M, Moradi-Gharibvand N, Hemadi M and Mansouri E, 2017. Beneficial effects of quercetin on titanium dioxide nanoparticles induced spermatogenesis defects in mice. *Environmental Science and Pollution Research International*, 24, 5595–5606.

Kreyling WG, Holzwarth U, Haberl N, Kozempel J, Hirn S, Wenk A, Schleh C, Schaffler M, Lipka J, Semmler-Behnke M and Gibson N, 2017a. Quantitative biokinetics of titanium dioxide nanoparticles after intravenous injection in rats: part 1. *Nanotoxicology*, 11, 434–442.

Kreyling WG, Holzwarth U, Schleh C, Kozempel J, Wenk A, Haberl N, Hirn S, Schaffler M, Lipka J, Semmler-Behnke M and Gibson N, 2017b. Quantitative

biokinetics of titanium dioxide nanoparticles after oral application in rats: part 2. *Nanotoxicology*, 11, 443–453.

Lee J, Jeong JS, Kim SY, Park MK, Choi SD, Kim UJ, Park K, Jeong EJ, Nam SY and Yu WJ, 2019. Titanium dioxide nanoparticles oral exposure to pregnant rats and its distribution. *Particle and Fibre Toxicology*, 16, 31.

Lu T, Ling C, Hu M, Meng X, Deng Y, An H, Li L, Hu Y, Wang H, Song G and Guo S, 2020. Effect of nano-titanium dioxide on blood-testis barrier and MAPK signaling pathway in male mice. *Biological Trace Element Research*.

Pele LC, Thoree V, Bruggaber S, Koller D, Thompson RP, Lomer MC and Powell JJ, 2015. Pharmaceutical/food grade titanium dioxide particles are absorbed into the bloodstream of human volunteers. *Particle and Fibre Toxicology*, 12, 26.

Peters RJB, Oomen AG, van Bommel G, van Vliet L, Undas AK, Munniks S, Bleys RLAW, Tromp PC, Brand W and van der Lee M, 2020. Silicon dioxide and titanium dioxide particles found in human tissues. *Nanotoxicology*, 14, 420–432.

Riedle S, Wills JW, Minitier M, Otter DE, Singh H, Brown AP, Micklethwaite S, Rees P, Jugdaohsingh R, Roy NC, Hewitt RE and Powell JJ, 2020a. A murine oral-exposure model for nano- and micro-particulates: demonstrating human relevance with food-grade titanium dioxide. *Nano-Micro Small*, 16, 2000486.

Sprong C, Bakker M, Niekerk M and Vennemann F, 2015. Exposure assessment of the food additive titanium dioxide (E 171) based on use levels provided by the industry. RIVM Letter report, 2015-0195.

Talamini L, Gimondi S, Violatto MB, Fiordaliso F, Pedica F, Tran NL, Sitia G, Aureli F, Raggi A, Nelissen I, Cubadda F, Bigini P and Diomede L, 2019. Repeated administration of the food additive E171 to mice results in accumulation in intestine and liver and promotes an inflammatory status. *Nanotoxicology*, 13, 1087–1101.

Tassinari R, Cubadda F, Moracci G, Aureli F, D'Amato M, Mauro Valeri M, De Berardis B, Raggi A, Mantovani A, Passeri D, Rossi M and Francesca Maranghi F, 2014. Oral, short-term exposure to titanium dioxide nanoparticles in Sprague-Dawley rat: focus on reproductive and endocrine systems and spleen. *Nanotoxicology*, 8, 654–662.

Verleysen E, Waegeneers N, Brassinne F, De Vos S, Jimenez IO, Mathioudaki S and Mast J, 2020. Physico-chemical characterization of the pristine E171 food additive

by standardized and validated methods. *Nanomaterials (Basel)*, 10, 592.

Warheit DB, Boatman R and Brown SC, 2015b. Developmental toxicity studies with 6 forms of titanium dioxide test materials (3 pigment-different grade & 3 nanoscale) demonstrate an absence of effects in orally-exposed rats. *Regulatory Toxicology and Pharmacology*, 73, 887–896.

Additional Documents

Annex A: EOGRT Study Data

Annex B: Summary of Papers