References - Statement on the safety of Titanium Dioxide (E171) as a Food Additive

In this guide

Akagi, J.I., Mizuta, Y., Akane, H., Toyoda, T., and Ogawa, K. (2023) Oral toxicological study of titanium dioxide nanoparticles with a crystallite diameter of 6 nm in rats. Particle & Fibre Toxicology. 20;20(1): 23. https://doi.org/10.1186/s12989-023-00533-x

Ammendolia, M.G., Iosi, F., Maranghi, F., Tassinari, R., Cubadda, F., Aureli, F., Raggi, A., Superti, F., Mantovani, A., and De Berardis, 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. http://dx.doi.org/10.1016/j.fct.2017.01.031

ANSES (Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail). (2017). Expert Committee (commissioned by ANSES.)

404 | ANSES - French Agency for Food, Environmental and Occupational Health and Safety

Bachler, G., von Goetz, N., & Hungerbuhler, K. (2015). Using physiologically based pharmacokinetic (PBPK) modeling for dietary risk assessment of titanium dioxide (TiO2) nanoparticles. Nanotoxicology, 9(3): 373-380. https://doi.org/10.3109/17435390.2014.940404

Balcaen, L., Bolea-Fernandez, E., Resano, M., and Vanhaecke, F. (2014). Accurate determination of ultra-trace levels of Ti in blood serum using ICP-MS/MS. Analytica chimica acta, 809: 1-8. https://doi.org/10.1016/j.aca.2013.10.017

Bates, B., Collins, D., Jones, K., Page, P., Roberts, C., Steer, T., and Swan, G. (2020). National Diet and Nutrition Survey Results from years 9, 10 and 11 (combined) of the Rolling Programme (2016/2017 to 2018/2019). Available at: NDNS: results from years 9 to 11 (2016 to 2017 and 2018 to 2019) - GOV.UK (www.gov.uk)

Bates, B., Cox, L., Nicholson, S., Page, P., Prentice, A., Steer, T., and Swan, G. (2016). National Diet and Nutrition Survey Results from Years 5 and 6 (combined) of the Rolling Programme (2012/2013 – 2013/2014). Available at: NDNS: results from Years 5 and 6 (combined) - GOV.UK (www.gov.uk)

Bates, B., Lennox, A., Prentice, A., Bates, C., Page, P., Nicholson, S., and Swan, G. (2014). National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009 – 2011/2012). Available at: National Diet and Nutrition Survey: Headline Results from Years 1, 2 and 3 (combined) of the Rolling Programme 2008/09 – 2010/11 - GOV.UK (www.gov.uk)

Bettini, S., Boutet-Robinet, E., Cartier, C., Coméra, C., Gaultier, E., Dupuy, J., Naud, N., Taché, S., Grysan, P., Reguer, S., Thieriet, N., Réfrégiers, M., Thiaudière, D., Cravedi, J-P., Carrière, M., Audinot, J-N., Pierre, F. H., 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. https://doi.org/10.1038/srep40373

Bischoff, N.S., de Kok, T.M., Sijm, D.T.H.M., van Breda, S.G., Briedé, J.J., Castenmiller, J.J.M., Opperhuizen, A., Chirino, Y.I., Dirven, H., Gott, D., Houdeau, E., Oomen, A.G., Poulsen, M., Rogler, G., and 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. https://dx.doi.org/10.3390/ijms22010207

Blevins, L. K., Crawford, R. B., Bach, A., Rizzo, M. D., Zhou, J., Henriquez, J. E., Khan, D. M. I. O., Sermet, S., Arnold, L. L., Karen L. Pennington, K. L., Souza, N. P., Cohen, S. M. and Kaminski, N. E. (2019). Evaluation of immunologic and intestinal effects in rats administered an E171-containing diet, a food grade titanium dioxide (TiO2). Food and Chemical Toxicology: 133: 110793. DOI: 10.1016/j.fct.2019.110793

Böckmann, J., Lahl, H., Eckert, T., and Unterhalt, B. (2000) Titan-blutspiegel vor und nach belastungsversuchen mit titandioxid. [Blood titanium levels before and after oral administration of titanium dioxide.] Pharmazie. 55(2):140–3 (in German).

Canli, E.G., Gumus, C., Canli, M., and Ila, H.B. (2020). The effects of titanium nanoparticles on enzymatic and non-enzymatic biomarkers in female Wistar rats, Drug and Chemical Toxicology, 1–9. https://doi.org/10.1080/01480545.2019.1708925

Chen, Z., Zheng, P., Han, S., Zhang, J., Li, Z., Zhou, S., and Jia, G. (2020). Tissue-specific oxidative stress and element distribution after oral exposure to titanium dioxide nanoparticles in rats. Nanoscale. 12(38): 20033-20046. DOI: 10.1039/d0nr05591c.

Cheng, L., and Lai, M.D. (2003). Aberrant crypt foci as microscopic precursors of colorectal cancer. World Journal of Gastroenterology: 9(12). DOI: 10.3748/wjg.v9.i12.2642

Clapper, M.L., Chang, W.C.L., and Cooper, H.S. (2020). Dysplastic aberrant crypt foci: biomarkers of early colorectal neoplasia and response to preventive intervention. Cancer prevention research: 13(3), pp.229-240. https://doi.org/10.1158/1940-6207.capr-19-0316

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. https://doi.org/10.1186/s12989-020-00357-z

Commission Regulation (EU) 2022/63 of 14 January 2022 amending Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the food additive titanium dioxide (E171). Available at: Publications Office (europa.eu)

Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM). (2024a). Assessment of in vitro studies of TiO2 genotoxicity. (not yet published).

Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM). (2024b). Assessment of in vivo studies of TiO2 genotoxicity. (not yet published)

COT Statement on Fluorine in the 1997 Diet Study. Available at: fluoride.PDF (food.gov.uk)

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT). 2022. Interim position paper on titanium dioxide. Available at: TiO2 COT Interim position paper (food.gov.uk)

Demir, E., Akça, H., Turna, F., Aksakal, S., Burgucu, D., Kaya, B., Tokgün, O., Vales, G., Creus, A., and Marcos, R. (2015). Genotoxic and cell-transforming effects of titanium dioxide nanoparticles. Environmental Research. 136:300-8. https://doi.org/10.1016/j.envres.2014.10.032

Department of Health (2013). Diet and Nutrition Survey of Infants and Young Children (DNSIYC), 2011. Available at: Diet and nutrition survey of infants and young children, 2011 - GOV.UK (www.gov.uk)

Di Bucchianico, S., Cappellini, F., Le Bihanic, F., Zhang, Y., Dreij, K., and Karlsson, H.L. (2017). Genotoxicity of TiO2 nanoparticles assessed by mini-gel comet assay and micronucleus scoring with flow cytometry. Mutagenesis: 32(1): 127-137. https://doi.org/10.1093/mutage/gew030

Disdier, C., Devoy, J., Cosnefroy, A., Chalansonnet, M., Herlin-Boime, N., Brun, E., Lund, A., and Mabondzo, A., (2015). Tissue biodistribution of intravenously administrated titanium dioxide nanoparticles revealed blood-brain barrier clearance and brain inflammation in rat. Particle and Fibre Toxicology, 12, 24. https://doi.org/10.1186/s12989-015-0102-8

Donner, E.M., Myhre, A., Brown, S.C., Boatman, R., and Warheit, D.B. (2016). In vivo micronucleus studies with 6 titanium dioxide materials (3 pigment-grade & 3 nanoscale) in orally-exposed rats. Regul Toxicol Pharmacol. 74:64-74. https://doi.org/10.1016/j.yrtph.2015.11.003

Dudefoi, W., Terrisse, H., Richard-Plouet, M., Gautron, E., Popa, F., Humbert, B., Ropers, M-H. (2017a). Criteria to define a more relevant reference sample of titanium dioxide in the context of food: a multiscale approach. Food Additives and Contaminants: Part A. 34(5):653-665. DOI: 10.1080/19440049.2017.1284346

Dudefoi, W., Moniz, K., Allen-Vercoe, E., Ropers, M.H. and Walker, V.K., (2017b) Impact of food grade and nano-TiO2 particles on a human intestinal community. Food and Chemical Toxicology, 106 pp.242-249. https://doi.org/10.1016/j.fct.2017.05.050

Engineering Biology Research Consortium (EBRC). (2022). Summary Report: Relative oral bioavailability of 5 different TiO2 grades. (Unpublished).

European Commission, Directorate-General for Health and Food Safety, Opinion on titanium dioxide (nano form) coated with cetyl phosphate, manganese dioxide or triethoxycaprylylsilane as UV-filter in dermally applied cosmetic, (2017) Publications Office Link: Opinion on titanium dioxide (nano form) coated with cetyl phosphate, manganese dioxide or triethoxycaprylylsilane as UV-filter in dermally applied cosmetic - Publications Office of the EU (europa.eu)

ECHA (2021) Guide on the classification and labelling of titanium dioxide. Available at: ECHA: Guide on the classification

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrients Sources added to Food). (2016). Re-evaluation of titanium dioxide (E171) as a food additive. EFSA Journal 14(9): 4545, 83. https://doi.org/10.2903/j.efsa.2016.4545

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. https://doi.org/10.2903/j.efsa.2017.5042

EFSA FAF Panel (EFSA Panel on Food Additive and Flavourings), 2019. Scientific opinion on the proposed amendment of the EU specification for titanium dioxide (E171) with respect to the inclusion of additional parameters related to its particle size distribution. EFSA Journal 2019;17(7):5760, 23. https://doi.org/10.2903/j.efsa.2019.5760

EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings) (2021) Scientific Opinion on the safety assessment of titanium dioxide (E171) as a food additive. EFSA Journal 2021;19(5):6585, 130. https://doi.org/10.2903/j.efsa.2021.6585

JECFA (1969) Joint FAO/WHO Expert Committee on Food Additives. Toxicological evaluation of some food colours, emulsifiers, stabilizers, anti-caking agents and certain other substances. FAO Nutrition Meetings Report Series No. 46A WHO/FOOD ADD/70 pp 36. 150. Titanium dioxide (FAO Nutrition Meetings Report Series 46a) (inchem.org)

FAO/WHO (Joint FAO/WHO Expert Committee on Food Additives). (2024). Evaluation of certain food additives: ninety-seventh report of the Joint FAO/WHO Expert Committee on Food Additives. WHO technical report series; 1051. Available at: Evaluation of certain food additives: ninety-seventh report of the

Joint FAO/WHO Expert Committee on Food Additives

Farrell, T.P., and Magnuson, B. (2017). Absorption, Distribution and Excretion of Four Forms of Titanium Dioxide Pigment in the Rat. Journal of Food Science. 82(8):1985-1993. https://doi.org/10.1111/1750-3841.13791

Food Standards Australia New Zealand (FSANZ). (2022). Titanium Dioxide as a Food Additive. Available at: FSANZ_TiO2_Assessment_report.pdf (foodstandards.gov.au)

Gao, Y., Ye, Y., Wang, J., Zhang, H., Wu, Y., Wang, Y., Yan, L., Zhang, Y., Duan, S., Lv, L. and Wang, Y. (2020). Effects of titanium dioxide nanoparticles on nutrient absorption and metabolism in rats: distinguishing the susceptibility of amino acids, metal elements, and glucose. Nanotoxicology. 14(10): 1301-1323. https://doi.org/10.1080/17435390.2020.1817597

Geiss, O., Ponti, J., Senaldi, C., Bianchi, I., Mehn, D., Barrero, J., Gilliland, D., Matissek, R., and Anklam, E. (2020). Characterisation of food grade titania with respect to nanoparticle content in pristine additives and in their related food products. Food Additives & Contaminants: Part A, 37(2) pp.239-253. DOI: 10.1080/19440049.2019.1695067

Geraets, L., Oomen, A.G., Krystek, P., Jacobsen, N.R., Wallin, H., Laurentie, M., Verharen, H.W., Brandon, E.F., and de Jong, W.H. (2014). Tissue distribution and elimination after oral and intravenous administration of different titanium dioxide nanoparticles in rats. Particle Fibre Toxicology. 11:30. https://doi.org/10.1186/1743-8977-11-30

Gore, E.R., Gower, J., Kurali, E., Sui, J.L., Bynum, J., Ennulat, D., and Herzyk, D.J., (2004). Primary antibody response to keyhole limpet hemocyanin in rat as a model for immunotoxicity evaluation. Toxicology, 197, 23–35. https://doi.org/10.1016/j.tox.2003.12.003

Grissa, I., Guezguez, S., Ezzi, L., Chakroun, S., Sallem, A., Kerkeni, E., Elghoul, J., El Mir, L., Mehdi, M., Cheikh, H.B., Haouas, Z. (2016). The effect of titanium dioxide nanoparticles on neuroinflammation response in rat brain. Environmental Science Pollution Research International. (20):20205-20213. https://doi.org/10.1007/s11356-016-7234-8

Grissa, I., ElGhoul, J., Mrimi, R., El Mir, L., Cheikh, H.B. and Horcajada, P., (2020). In deep evaluation of the neurotoxicity of orally administered TiO2 nanoparticles. Brain Research Bulletin. 155: 119-128.

https://doi.org/10.1016/j.brainresbull.2019.10.005

Guillard, A., Gaultier, E., Cartier, C., Devoille, L., Noireaux, J., Chevalier, L., Morin, M., Grandin, F., Lacroix, M.Z., 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. https://doi.org/10.1186/s12989-020-00381-z

Han, H.Y., Yang, M.J., Yoon, C., Lee, G.H., Kim, D.W., Kim, T.W., Kwak, M., Heo, M.B., Lee, T.G., Kim, S. and Oh, J.H. (2020). Toxicity of orally administered food-grade titanium dioxide nanoparticles. Journal of Applied Toxicology. 41 (7): 1127-1147. https://doi.org/10.1002/jat.4099

Han, H.Y., Yang, M.J., Yoon, C., Lee, G.H., Kim, D.W., Kim, T.W., Kwak, M., Heo, M.B., Lee, T.G., Kim, S. and Oh, J.H. (2021). Toxicity of orally administered food-grade titanium dioxide nanoparticles. Journal of Applied Toxicology. 41(7):1127-1147. https://doi.org/10.1002/jat.4099

Health Canada. (2022). State of the Science of Titanium Dioxide (TiO2) as a Food Additive. Available at: H164-341-2022-eng.pdf (publications.gc.ca)

Hendrickson, O.D., Pridvorova, S.M., Zherdev, A.V., Klochkov, S.G., Novikova, O.V., Shevtsova, E.F., Bachurin, S.O., and Dzantiev, B.B. (2016). Size-dependent differences in biodistribution of titanium dioxide nanoparticles after sub-acute intragastric administrations to rats. Current Nanoscience. 12:228–236. http://dx.doi.org/10.2174/1573413711666151008013943

Hendrickson, O.D., Platonova, T.A., Piidvorova, S.M., Zherdev, A.V., Gmoshinsky, I.V., Vasilevskaya, L.S., Shumakova, A.A., Hotimchenko, S.A., and Dzantiev, B.B. (2020). Electron-microscopic investigation of the distribution of titaniumdioxide (rutile) nanoparticles in the rats'small intestine mucosa. Liver, and Spleen. Current Nanoscience. 16: 268–279. http://dx.doi.org/10.2174/1573413715666190328181854

Heringa, M,B, Peters, R.J.B., Bleys, R., van der Lee, M.K., Tromp, P.C., van Kesteren, P.C.E., van Eijkeren, J.C.H., Undas, A.K., Oomen, A.G., and Bouwmeester, H. (2018). Detection of titanium particles in human liver and spleen and possible health implications. Particle and Fibre Toxicology. 15(1): 15. https://doi.org/10.1186/s12989-018-0251-7

Huang, C., Sun, M., Yang, Y., Wang, F., Ma, X., Li, J., Wang, Y., Ding, Q., Ying, H., Song, H., Wu, Y., Jiang, Y., Jia, X., Ba, Q., and Wang, H. (2017). Titanium dioxide nanoparticles prime a specific activation state of macrophages. Nanotoxicology. 11(6): 737-750. https://doi.org/10.1080/17435390.2017.1349202

Hummel, T.Z., Kindermann, A., Stokkers, P.C., Benninga, M.A. and ten Kate, F.J. (2014). Exogenous pigment in Peyer patches of children suspected of having IBD. Journal of pediatric gastroenterology and nutrition. 58(4): 477- 480. https://doi.org/10.1097/mpg.0000000000000221

IARC (International Agency for Research on Cancer)/WHO. (2010). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 93. Carbon Black, Titanium Dioxide, and Talc. Available online: IARC Publications Website - Carbon Black, Titanium Dioxide, and Talc

ISO (International Organization for standardisation). (2023). Nanotechnologies – Vocabulary — Part 1: Core vocabulary. Available at: ISO 80004 - 1: 2023(en), Nanotechnologies – Vocabulary — Part 1: Core vocabulary

Jensen, D.M., Løhr, M., Sheykhzade, M., Lykkesfeldt, J., Wils, R.S., Loft, S., and Møller, P. (2019). Telomere length and genotoxicity in the lung of rats following intragastric exposure to food-grade titanium dioxide and vegetable carbon particles. Mutagenesis. 34(2): 203-214. https://doi.org/10.1093/mutage/gez003

Jones, K., Morton, J., Smith, I., Jurkschat, K., Harding, A.H. and Evans, G., (2015) Human in vivo and in vitro studies on gastrointestinal absorption of titanium dioxide nanoparticles. Toxicology letters. 233(2): 95-101. https://doi.org/10.1016/j.toxlet.2014.12.005

Kämpfer, A.A., Busch, M., Büttner, V., Bredeck, G., Stahlmecke, B., Hellack, B., Masson, I., Sofranko, A., Albrecht, C., and Schins, R.P. (2021). Model Complexity as Determining Factor for In Vitro Nanosafety Studies: Effects of Silver and Titanium Dioxide Nanomaterials in Intestinal Models. Small. 17(15): 2004223. https://doi.org/10.1002/smll.202004223

Karimipour, M., Javanmard, M.Z., 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. 16(6): 397–404. Available at: Oral administration of titanium dioxide nanoparticle through ovarian tissue alterations impairs mice embryonic development - PubMed (nih.gov)

Kreyling, W.G., 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. https://doi.org/10.1080/17435390.2017.1306892

Kreyling, W.G., 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. https://doi.org/10.1080/17435390.2017.1306893

Lee, J., Jeong, J-S., Kim, S. Y., Park, M-K., Choi, S-D., Kim, U-J., Park, K., Jeong, E. J., Nam, S-Y. and Yu, W-J. (2019). Titanium dioxide nanoparticles oral exposure to pregnant rats and its distribution. Particle and Fibre Toxicology. 16:31 https://doi.org/10.1186/s12989-019-0313-5.

Leuschner. (2020). Extended One-Generation Reproductive Toxicity study of titanium dioxide E171 in rats by oral administration via the diet. (Unpublished report).

Lomer, M.C., Grainger, S.L., Ede, R., Catterall, A.P., Greenfield, S.M., Cowan, R.E. et al. (2005). Lack of efficacy of a reduced microparticle diet in a multi-centred trial of patients with active Crohn's disease. European Journal of Gastroenterological Hepatology. 17(3): 377–84. https://doi.org/10.1097/00042737-200503000-00019

Mortensen, N. P., Caffaro, M. M., Aravamudhan, S., Beeravalli, L., Prattipati, S., Snyder, R. W., Watson, S. L., Patel, P. R., Weber, F. X., Montgomery, S. A., Sumner, S. J. and Fennell, T. R. (2021). Simulated Gastric Digestion and In Vivo Intestinal Uptake of Orally Administered CuO Nanoparticles and TiO2 E171 in Male and Female Rat Pups. Nanomaterials. 11: 1487. https://doi.org/10.3390/nano11061487

National Cancer Institute. (1979). Bioassay of Titanium Dioxide for Possible Carcinogenicity. Carcinogenicity. 97, [Online]. Available at: TR-097: Titanium Dioxide (CASRN 13463-67-7) (nih.gov)

OECD Test Guidelines for Chemical Testing OECD Test Guidelines for Chemicals - OECD

Pele, L.C., Thoree, V., Bruggraber, S., Koller, D., Thompson, R.P., Lomer, M.C., and Powell, J.J., (2015). Pharmaceutical/food grade titanium dioxide particles are absorbed into the bloodstream of human volunteers. Particle and Fibre Toxicology. 12: 26. https://doi.org/10.1186/s12989-015-0101-9

Perez, L., Scarcello, E., Ibouraadaten, S., Yakoub, Y., Leinardi, R., Ambroise, J., et al. (2021). Dietary nanoparticles alter the composition and function of the gut microbiota in mice at dose levels relevant for human exposure. Food Chemical Toxicology. 154: 112352. https://doi.org/10.1016/j.fct.2021.112352

Peters, R.J.B., Oomen, A.G., van Bemmel, G., van Vliet, L., Undas, A.K., Munniks, S., Bleys, R.L.A.W., Tromp, P.C., Brand, W., and van der Lee, M. (2020). Silicon dioxide and titanium dioxide particles found in human tissues. Nanotoxicology. 14: 420–432. https://doi.org/10.1080/17435390.2020.1718232

Pinget, G., Tan, J., Janac, B., Kaakoush, N.O., Angelatos, A.S., O'Sullivan, J., Koay, Y.C., Sierro, F., Davis, J., Divakarla, S.K. and Khanal, D. Moore, R. J., Stanley, D., Wojciech Chrzanowski, W. and Macia, L. (2019). Impact of the food additive titanium dioxide (E171) on gut microbiota-host interaction. Frontiers in Nutrition. 6: 57. https://doi.org/10.3389/fnut.2019.00057

Proquin, H., Rodriguez-Ibarra, C., Moonen, C.G., Urrutia Ortega, I,M., Briede, J.J., de Kok, T.M., van Loveren, H., and Chirino, Y.I. (2017). Titanium dioxide food additive (E171) induces ROS formation and genotoxicity: Contribution of micro and nano-sized fractions. Mutagenesis. 32: 139–149. https://doi.org/10.1093/mutage/gew051

Proquin, H., Jetten, M.J., Jonkhout, M.C.M., Garduno-Balderas, L.G., Briedé, J.J., de Kok, T.M. et al. (2018). Gene expression profiling in colon of mice exposed to food additive titanium dioxide (E171). Food Chemical Toxicology. 111: 153–65. https://doi.org/10.1016/j.fct.2017.11.011

Riedle, S., Wills, J. W., Miniter, M., Otter, D. E., Singh, H., Brown, A. P., Micklethwaite, S., Rees, P., Jugdaohsingh, R., Roy, N. C., Hewitt, R. E., and Powell, J. J. (2020). A murine oral-exposure model for nano- and micro-particulates: demonstrating human relevance with food-grade titanium dioxide. Nano-Micro Small. 16(21): e2000486. https://doi.org/10.1002/smll.202000486

Roberts, C.; Steer, T.; Maplethorpe, N.; Cox, L.; Meadows, S.; Page, P.; Nicholson, S.; Swan, G. (2018). National Diet and Nutrition Survey Results from Years 7 and 8 (combined) of the Rolling Programme (2014/2015 – 2015/2016). Available at: National Diet and Nutrition Survey (publishing.service.gov.uk)

Rodríguez-Escamilla, J.C., Medina-Reyes, E.I., Rodríguez-Ibarra, C., Déciga-Alcaraz, A., Flores-Flores, J.O., Ganem- Rondero, A., Rodríguez-Sosa, M., Terrazas, L.I., Delgado-Buenrostro, N.L. and Chirino, Y.I. (2019). Food-grade titanium dioxide (E171) by solid or liquid matrix administration induces inflammation, germ cells sloughing in seminiferous tubules and blood-testis barrier disruption in mice. Journal of Applied Toxicology. 39(11): 1586-1605. https://doi.org/10.1002/jat.3842

Rompelberg, C., Heringa, M.B., van Donkersgoed, G., Drijvers, J., Roos, A., Westenbrink, S., Peters, R., van Bemmel, G., Brand, W. and Oomen, A.G., (2016). Oral intake of added titanium dioxide and its nanofraction from food products, food supplements and toothpaste by the Dutch population. Nanotoxicology. 10(10): 1404-1414. https://doi.org/10.1080/17435390.2016.1222457

Ropers, M.H., Terrisse, H., Mercier-Bonin, M., and Humbert, B. (2017). Titanium dioxide as food additive. InTech. 1-22. DOI: 10.5772/intechopen.68883

Ruiz, P.A., Morón, B., Becker, H.M., Lang, S., Atrott, K., Spalinger, M.R. et al. (2017). Titanium dioxide nanoparticles exacerbate DSS-induced colitis: role of the NLRP3 inflammasome. Gut. 66(7): 1216–24. https://doi.org/10.1136/gutjnl-2015-310297

Sadiq, R,, Bhalli, J.A., Yan, J., Woodruff, R.S., Pearce, M.G., Li, Y., Mustafa, T., Watanabe, F., Pack, L.M., Biris, A.S., Khan, Q.M., and Chen, T. (2012). Genotoxicity of TiO2 anatase nanoparticles in B6C3F1 male mice evaluated using Pig-a and flow cytometric micronucleus assays. Mutation Research. 745(1-2): 65-72. https://doi.org/10.1016/j.mrgentox.2012.02.002

SCCS (Scientific Committee on Consumer Safety), 2020. Opinion on Titanium dioxide (TiO2) used in cosmetic products that lead to exposure by inhalation. Adopted on 6 October 2020. Available online: Opinion on Titanium dioxide (TiO2) used in cosmetic products that lead to exposure by inhalation (europa.eu)

SCF (Scientific Committee for Food) (1977): Reports of the Scientific Committee for Food: Fourth Series, p. 27.

Shelby, M.D., Erexson, G.L., Hook, G.J., and Tice, R.R. (1993). Evaluation of a three-exposure mouse bone marrow micronucleus protocol: results with 49 chemicals. Environmental and Molecular Mutagenesis. 21: 160–179. https://doi.org/10.1002/em.2850210210

Shelby, M.D., and Witt, K.L. (1995). Comparison of results from mouse bone marrow aberration and micronucleus test. Environmental and Molecular Mutagenesis. 25: 302–313. https://doi.org/10.1002/em.2850250407

Shwter, A.N., Abdullah, N.A., Alshawsh, M.A., El-Seedi, H.R., Al-Henhena, N.A., Khalifa, S.A., and Abdulla, M.A. (2016). Chemopreventive effect of Phaleria macrocarpa on colorectal cancer aberrant crypt foci in vivo. Journal of Ethnopharmacology. 193: 195–206. https://doi.org/10.1016/j.jep.2016.08.002

Sofranko, A., Wahle, T., Heusinkveld, H.J., Stahlmecke, B., Dronov, M., Pijnenburg, D., Hilhorst, R., Lamann, K., Albrecht, C. and Schins, R.P. (2021). Evaluation of the neurotoxic effects of engineered nanomaterials in C57BL/6J mice in 28-day oral exposure studies. Neurotoxicology. 84: 155-171. https://doi.org/10.1016/j.neuro.2021.03.005

Stoccoro, A., Di Bucchianico, S., Coppedè, F., Ponti, J., Uboldi, C., Blosi, M., Delpivo, C., Ortelli, S., Costa, A.L., and Migliore, L. (2017). Multiple endpoints to evaluate pristine and remediated titanium dioxide nanoparticles genotoxicity in lung epithelial A549 cells. Toxicology Letters. 276: 48-61. https://doi.org/10.1016/j.toxlet.2017.05.016

Talamini, L., Gimondi, S., Violatto, M.B., Fiordaliso, F., Pedica, F., Tran, N.L., 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(8): 1087-1101. https://doi.org/10.1080/17435390.2019.1640910

Tassinari, R., Cubadda, F., Moracci, G., Aureli, F., D'Amato, M., Valeri, M., De Berardis, B., Raggi, A., Mantovani, A., Passeri, D., Rossi, M., and 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. https://doi.org/10.3109/17435390.2013.822114

TDMA (Titanium Dioxide Manufacturer’s Association). (2022). Comparison of current food grade titanium dioxide (E171) with historical samples of Unitane O-220. Unpublished draft TDMA|1175b dated 12 April 2022 provided to the FSA by the TDMA.

Trakman, G.L., Lin, W.Y.Y., Hamilton, A.L., Wilson-O’Brien, A.L., Stanley, A., Ching, J.Y. et al. (2022). Processed food as a risk factor for the development and perpetuation of Crohn’s disease—the ENIGMA study. Nutrients. 14(17): 3627.

https://doi.org/10.3390/nu14173627

Ünal, F., Demırtaş Korkmaz, F., Suludere, Z., Erol, Ö. (2021). Genotoxicity of Two Nanoparticles: Titanium Dioxide and Zinc Oxide. Gazi University Journal of Science. 34(4): 948-958.

Urrutia-Ortega, I.M., Garduño-Balderas, L.G., Delgado-Buenrostro, N.L., Freyre-Fonseca, V., Flores-Flores, J.O., González-Robles, A., Pedraza-Chaverri, J., Hernández-Pando, R., Rodríguez-Sosa, M., León-Cabrera, S. and Terrazas, L.I. (2016). Food-grade titanium dioxide exposure exacerbates tumor formation in colitis associated cancer model. Food and Chemical Toxicology. 93: 20-31. https://doi.org/10.1016/j.fct.2016.04.014

Verleysen, E., Waegeneers, N., Brassinne, F., De Vos, S., Jimenez, I.O., Mathioudaki, S., Mast, J. (2020). Physico-chemical characterization of the pristine E171 food additive by standardized and validated methods. Nanomaterials. 10: 592. https://doi.org/10.3390/nano10030592

Verleysen, E., Waegeneers, N., De Vos, S., Brassinne, F., Ledecq, M., Van Steen, F., Andjelkovic, M., Janssens, R., Mathioudaki, S., Delfosse, L., Machiels, R., Cheyns, K., and Mast, J. (2021). Physicochemical characterization of nanoparticles in food additives in the context of risk identification. EFSA supporting publication. https://doi.org/10.2903/sp.efsa.2021.EN-6678

Vignard, J., Pettes-Duler, A., Gaultier, E., Cartier, C., Weingarten, L., Biesemeier, A. et al. (2023). Food-grade titanium dioxide translocates across the buccal mucosa in pigs and induces genotoxicity in an in vitro model of human oral epithelium. Nanotoxicology. 17(4): 289–309. https://doi.org/10.1080/17435390.2023.2210664

Warheit, D.B., Boatman, R., and Brown, S.C. (2015). 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. http://dx.doi.org/10.1016/j.yrtph.2015.09.032

Warheit, D.B., Brown, S.C., and Donner, E.M. (2015). Acute and subchronic oral toxicity studies in rats with nanoscale and pigment grade titanium dioxide particles. Food Chemical Toxicolology. 84: 208-24. https://doi.org/10.1016/j.fct.2015.08.026

Weir, A., Westerhoff, P., Fabricius, L., Hristovski, K., and Von Goetz, N. (2012). Titanium dioxide nanoparticles in food and personal care products. Environmental science and technology. 46(4): 2242-2250. https://doi.org/10.1021/es204168d

Winkler, H.C., Notter, T., Meyer, U., Naegeli, H. (2018). Critical review of the safety assessment of titanium dioxide additives in food. J Nanobiotechnology. 16(1): 51. https://doi.org/10.1186/s12951-018-0376-8

Yang, X. H., Fu, H. T., Wang, X. C., Yang, J. L., Jiang, X. C., and Yu, A. B. (2014). Synthesis of silver-titanium dioxide nanocomposites for antimicrobial applications. Journal of nanoparticle research. 16: 1-13.