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

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Absorption, Distribution, Metabolism and Excretion (ADME) – E171 animal studies

Reference	TiO2 characterisation	Quality of study e.g., OECD/GLP	Method and duration of dosing	Study methodology to include species, numbers, controls,	Results

Bettini et al., 2017	1) E 171, anatase, 20–340 nm (118 nm) (TEM); 44.7% particles 100 nm; 2) TiO2 NPs (NM-105), anatase/rutile, 15–24 nm.	OECD	Series One Dosage: 200 µ L with TiO2 NM-105, E171 (10 mg/kg of BW/day) or water for 7 days by gavage. Series Two Dosage: E-171 at 200 µ g or 10 mg/kg of BW/day via drinking water for 100 days (with or without DMH treatment). Series Three Dosage: No	Series One: rats (n = 10 rats/group) dosed daily by intragastric gavage (200 µ L) with TiO2 NM-105, E171 (10 mg/kg of BW/day) or water for 7 days. Tissue imaging, flow cytometry and cytokine assays, tissue inflammation and gut permeability measurements were conducted. Series Two: rats (n = 11 to 12 per group) were treated or not with 1,2-dimethylhydrazine (DMH) to induce colon carcinogenesis and exposed to E-171 at 200 µ g or 10 mg/kg of BW/day via drinking water for 100 days. Control animals (n = 12) received water only. Flow cytometry and cytokine assays were	Titanium w detected i immune c Peyer's pa Dendritic percentag increased observed after expo no effect days. No effects spleen. Regulator and T-help were sign decreased after expo at 100 da rats expos 171. Stimulatio of immun isolated fr Peyer's pa had a dec T-helper (γ secretio splenic Th inflammat responses increased With expo TiO2 NP t an observ increase i percentag

Talamini et al., 2019	E171 (35% nano determined by TEM), 99.3% pure anatase, 201.2 ± 8.5 nm in suspension (NTA). No sonification or deagglomeration to simulate realistic conditions.	This work was reviewed by the Institute for Pharmacological Research Mario Negri IRCCS Animal Care and Used Committee (IACUC) and then approved by the Italian National Institute of Health (code:42/2016-PR).	Treatments were given 3 days per week for 3 weeks for a total of 9 treatments in 21 days. Average daily dose of ~2 mg/kg bw. Treatments were dripped slowly into the mice's mouths, allowing each drop to be swallowed.	NFR male mice (22/group) were administered either water (control) or 5 mg/kg bw E171 suspended in water. Ti concentrations in tissues were determined by single particle ICP-MS analysis.	Ti concen in the live 0.57 µg/g and large (1.07 ± 0. tissue) we significant in treated compared controls. Ti concen in the bra kidney, ar were belo quantifica (0.03 µg/g Ti concen in lungs, s stomach, intestine v statistical significant treated ar mice.

					No eviden gross alte immune-c physiolog inflammat doses up mg/kg bw diet.
Riedle et al., 2020	E171, anatase, 119 nm.	N/A	Mice were exposed to 0, 1, 10, or 100 mg/kg bw/d E171 via the diet for 6, 12 and 18 weeks.	Mice were divided into 4 groups of 18 and given 0, 6.25, 62.5, or 625 mg/kg diet (equivalent to approximately 0, 1, 10, or 100 mg/kg bw). Then 6 mice per group were euthanized at 6, 12 and 18 weeks.	Authors demonstra uptake by patches, v the delive Presence particles c by reflecta confocal microscop quantifica particles completed Weak sign observed base of Pe patches a mid-doses signals ob highest do indicating of dose-re

Comera et al. 2020	Food grade TiO2 (E171) 95% anatase.	European legislation (Council Directive 2010/63/UE) and French Decree 2013–118-compliant.	Mice (4 per group). Dosage: single dose (200 µl) of either E171 at 40 mg/kg of body weight (BW) or 200 µl of vehicle (water) by intragastric gavage. In addition, in some experiments, the gavage solution from sonicated E171 particles was equilibrated in 30% corm oil and vortexed before oral delivery.	Adult C57BL/6 mice (12–18 weeks). Animals were terminated at 2, 4, 8, and 24 hours to recover the intestine.	Small inte TiO2 abso peaked at jejunal an villi and re to basal le h and und at 4 h but present at the jejuna patches. Colon: Low absorption Blood: TiO particles w detected a 8-hours po treatment 30 minute exposure the presen absence o pharmaco inhibitors paracellul junction (T permeabil absorption jejunal vil decreased (p 0.001 v control) in presence triaminop Other inhi had no sig effect. Absorptio goblet cel associated

Dudefoi 2017b	Food-grade TiO2 (E171-1, 17% NPs and 100% anatase and E171-6a).	N/A	Dosage: 100–250 ppm.	Method: A defined model intestinal bacterial community.	At these l concentra impact on productio only a mi on fatty a profiles w observed limited ef bacterial communit
Proquin et al. 2018	E171 in combination with azoxymethane (AOM)/dextran sodium sulphate (DSS) vs E171 only.	N/A	Dosage: 5 mg/kg bw per day of E171 by gavage for 2, 7, 14, and 21 days.	BALB/c mice.	E171 indu downregu genes inv the immu system w indicative impairme Additional signalling involved i variety of cancer inc colorectal were mod and effect observed indicated potential associatio oxidative

Jensen et al. 2019	Vegetable carbon (E153) and food-grade titanium dioxide (E171), mean TiO2 particle size of 270 nm.	N/A	Dosage: 10 weeks by oral gavage once a week.	Rats.	TiO2-only Decreased expressio protein TJ observed rats only e to E171 (5 mg/kg/we shorter lu telomeres This study no oxidati damage in or lung an changes i DNA repa of oxidativ damage in lung.

Farrell TP and Magnuson B. (2017).	4 different food grade TiO2 test items containing a range of particle sizes and morphologies.	GLP-compliant, OECD TG 41.	Dosage: Four grades of TiO2 (200 ppm) or control (0 ppm) via the diet for 7 days followed by a control diet for 1, 24, or 72 hours.	Male and female Sprague-Dawley rats were given TiO2 by the diet equivalent to 30 mg/kg bw/day for 7 days. Animals were then terminated post-feeding at 1, 24 and 72 hours.	Ti in kidne and musc below LOD mg/kg ww Ti in tissu above LO 0.1-0.3 m Ti in blood 0.04 mg/L samples. Ti in urine equal to 2 dose/L an LOQ. Ti in faece found to b main rout excretion. No differe absorption found bet different g TiO2.

Absorption, Distribution, Metabolism and Excretion (ADME) – non-E171/Nanoparticle animal studies

Reference	TiO2 characterisation	Quality of study e.g., OECD/GLP	Method and duration of dosing	Study methodology to include species, numbers, controls,	Results

Warheit, Boatman and Brown, 2015	1) anatase/rutile (89/11%) (uf-1), d50=43 nm d50=23 nm. Methods: XSDC and TEM respectively Shape: Irregular. 2) anatase (100% nano) (uf-2) d50= 42 nm d50=19 nm. Methods: XSDC and TEM respectively. Shape: Irregular. 3) rutile (100% nano) (uf-3), d50=47 nm d50=22 nm Methods: XSDC and TEM respectively. Shape: rod-like. 4) anatase (27% nano) (pg-1), d50=153 nm d50=120 nm Methods: XSDC and TEM	OECD Guideline 414.	Sterile water-based TiO2 sample formulations were administered by oral gavage to time-mated rats from the time of approximate implantation until the day prior to expected parturition. Dose levels: 0, 100, 300 or 1,000 mg/kg bw per day. Dosage volume: 5	Three studies (Group size n=22): Time-mated pregnant Sprague–Dawley rats, (Crl:CD(SD)) exposed to TiO2 (uf-1, uf-3 and pg-1) by gavage on Gestational Days 6–20. Three additional studies (Group size n=22-23) pregnant Wistar rats exposed to TiO2 (uf-2 and pg-2) by gavage from Gestational Days 5 to 19. Necropsy: • Gross examination of the dam, • Counting of corpora lutea, • Implantation sites, • Resorptions, • Live and dead fetuses, • Fetal sex,	At 1,000 1/kg pe mean fe ratio an means f and fem fetuses were statistic significa differen the con group m Mean m fetuses: Mean m fetuses group: 5 Test fac historica group d range: 5 7.4. Mean fe fetuses: Mean fe fetuses group: 6 Test fac historica group d range: 5 8.3. Mean fe ratio of 1,000 m bw per group: 6

Tassinari et al., 2014	TiO2 nanoparticles (anatase, primary size 25 nm, BET surface area 45-55 m^2/g, purity 99%).	All experiments on animals were performed according to the European Community Council Directive 86/609/EEC (EEC 1986).	TiO2 nanoparticles were administered by oral gavage over 5 consecutive days at a dose of 0, 1, 2 mg/kg body weight per day.	Sprague-Dawley rats were divided into 3 treatment groups (7 rats/sex/group). Treatment groups were high dose (2 mg/kg bw), low dose, (1 mg/kg bw), and controls (CTRL) (vehicle only (distilled water)).	In the h treatme group, significa increase total Ti levels w found ir (0.036 ± vs. 0.04 0.008 µ weight; 0.05) ar ovaries 0.07 vs. 0.04 µg weight; 0.01). Sex-rela histolog alteratio observe both do in thyro adrenal medulla adrenal (female ovarian granulo without toxicity. Altered function indicate reduced (males) Testoste levels ir in high- males a decreas

Ammendolia et al. 2017	Nano-sized titanium dioxide (anatase, primary size 25 nm, BET surface area 45–55 m2/g, purity 99%).	N/A	TiO2 NPs at 2 mg/kg bw per day for five days in male and female rats.	N/A	Nanopa deposit intestin and inc serum testoste levels. T was no of oxida stress o alterati concent of TiO2 howeve treatme associat testoste Insulin-l Growth showed increase prolifer

Geraets et al. 2014	TiO2 NPs (sizes NM-100, NM-101, NM-102, NM-103, and NM-104) with differing particle sizes and structure.	N/A	Dosage: Oral and intravenous administration of a single or five repeated doses.	TiO2 nanoparticle kinetics were investigated using intravenous injection and oral dosing in rats. For orally dosed rats, liver, spleen and lymph nodes were targeted for analysis.	Followir exposur levels ir liver an were or occasio above t and was detecte lymph r low leve Followir intraver exposur distribu observe all tissu kidney, spleen, brain, th and reprodu organs liver ide as the r target. Recover hours p exposur 64-95% 108% respecti male ar female The ma relative decreas TiO2 up days po exposur 26%.

Hendrickson et al. 2016	2 test items TiO2 NPs (5-10 nm and 20-25 nm respectively).	N/A	Dosage: Intragastric administration of TiO2 NPs (1 of 2 test items) for 28 days at a dose of 250 mg/kg of body weight per day.	Male rats.	GIT and seconda organ transloc were siz depend Larger nanopa exposur showed deposit liver, ki spleen, small in (0.01– 0 of organ Smaller nanopa exposur resulted deposit brain, lu heart, li kidneys small in testicle blood (0.004– µg/g of

Hendrickson et al. 2020	TiO2 NPs	N/A	Dosage: A single dose suspension of TiO2 NPs (250 mg/kg of body weight).	Model: A Physiological model designed to mimic the intestinal lumen of an experimental animal.	TiO2 NP found ir small in mucosa and spl TiO2 NP resulted differen changes cellular ultrastr in the endopla reticulu mitocho extensi the peri spaces caused like stru to appe The mo sensitiv was not the spl

Kreyling et al. 2017a	TiO2 anatase NPs. Median agglomerate size: 70 nm.	N/A	Dosage: 40–400 µg/kg bw single intravenous dose in aqueous suspension.	Female Wistar rats. Clearance and biokinetics were observed from 1-hour post-dosage to 4 weeks.	Highest accumu occurre liver aft day (95 then the spleen (carcass skeleton and blo (0.4%). NPs wer detecte other or levels lo than the TiO2 NP blood d quickly after ex Organs tissue N were st day-28.

Kreyling et al. 2017b	TiO2 NPs.	N/A	Dosage: Oral dosage of a single dose of an aqueous TiO2 NP suspension at 30–80 µg/kg bw.	Female Wistar-Kyoto rats. Assessed 1 h, 4 h, 24 h and 7 days post-oral exposure.	0.6% of adminis dose pa gastro- intestin after 1 l 0.05% o dose we distribu the bod days dis across t followin organs: liver (0. lungs (0 ng/g), k (0.29 ng brain (0.36 ng spleen (ng/g), u (0.55 ng bone de (0.98 ng Faecal e was cor after 4-5

				6–7-week-old male B6C3F1 mice.		
Sadiq et al. 2012	TiO2 NPs.	N/A	Dosage: 1) Intravenous 0.5, 5.0, and 50 mg/kg TiO2 NPs. 2) Intravenous three daily doses of 50 mg/kg TiO2 NPs Ti levels in bone marrow measured after 4, 24, and 48 hours of the last treatment.	In vivo micronucleus and Pig-a (phosphatidylinositol glycan, class A gene) mutation assays using TiO2 NPs to evaluate genotoxicity. Blood: Samples taken one day before the treatment and on Day 4, and Weeks 1, 2, 4, and 6 after the beginning of the treatment. Pig-a mutant frequencies were determined at Day −1 and Weeks 1, 2, 4 and 6, percent micronucleated-reticulocyte frequencies were measured only on Day 4.	Blood re No incre Pig-a m frequen %MN-RE Tissue r Ti NPs p at 4 hou exposur %RETs reduced treated on Day depend which s cytotox TiO2-NP bone m No evid genotox

Absorption, Distribution, Metabolism and Excretion (ADME) – E171 and non-E171/Nanoparticle Human Studies

Reference	TiO2 characterisation	Quality of study e.g., OECD/GLP	Method and duration of dosing	Study methodology to include species, numbers, controls,	Results
Pele et al. 2015	Pharmaceutical/food grade TiO2, anatase, 50-250nm.	This study was conducted based on ethical approval under EC01/037.	Dosage: A single dose of 100 mg TiO2.	Test subjects: Humans with normal intestinal permeability. Blood samples were collected at between 0.5 to 10 h post-oral exposure. Blood samples were analysed for visual TiO2 reflective particles using dark field microscopy.	Early absorption occurred by 2 hours with a peak maximum at 6 hours. Following oral dosing. This mirrors the results of a previous study by Bockmann et al (2000) which the authors were attempting to replicate.

Guillard et al. 2020	Basal Ti level in human placenta study. TiO2 with 55% NPs, 20 to 440 nm.	N/A	Samples were taken of plancenta and meconium from human babies (n=22) and tested for TiO2 and other metals and trace elements.	TiO2 in human placentas was analysed by ICP-MS and STEM coupled to EDX spectroscopy.	All placenta contained TiO2 at 0.01 to 0.48 mg/kg of tissue with the majority below 100nm in size (over 50%). Meconium samples also contained TiO2 between 0.02-1.5 mg/kg.

Heringa et al. 2018	Post-mortem analysis of human liver and spleen TiO2 analysis.	N/A	N/A	High resolution ICP-MS was used to detect TiO2 in the liver and spleen in 15 deceased humans (9 female and 6 male).	7 of the 15 livers sampled contained TiO2 and 13 of 15 of spleen samples contained the same. Particle sizes respectively for liver and spleen: 85–550nm and 85–720nm with 24% 100 nm in size. Particle mass concentration for liver and spleen respectively: To 0.3 mg t itanium/kg tissue and 0.01 to 0.4 mg titanium/kg tissue. Average concentration in liver and spleen samples: 40 ng/g and 80 ng/g.

Peters et al. 2020	Postmortem tissue analysis of deceased persons for the presence of TiO2. Detected particle sizes were in the range of 50–500 nm, with a mode of 100–160 nm.	15 humans sampled, 8 female and 7 male aged 64-98 years. Postmortem liver, spleen, kidney, jejunum and ileum were sampled.	Findings of between 0.01 to 2.0 mg Total Ti/kg with median values (mg Ti/kg): Liver = 0.02, Spleen = 0.04, Kidney = 0.05, Jejunum = 0.13, Ileum = 0.26. Particulate TiO2 were observed from 0.01 to 1.8 mg Ti/kg with median values (mg Ti/kg): Liver = 0.02, Spleen = 0.02, Kidney = 0.03, Jejunum = 0.08, Ileum = 0.25. Particulate TiO2 accounted for 80% of the

Aberrant Crypt Foci (ACF) as a marker for carcinogenicity

Reference	TiO2 characterisation	Quality of study e.g., OECD/GLP	Method and duration of dosing	Study methodology to include species, numbers, controls,	Results

		E-171 consum not alte mediate mechan immune
Six-week-old male Wistar Han IGS (Crl:WI (Han)) rats. Test material: Food grade sample E-171. DIfferent grades of commercially-available E-171 were averaged to produce the test material supplied. Test material was added to feed. Two feed batches: batch one was fed throughout the 7-day study and through week 10 of the 100-day study. Batch two was fed post-week 10 of the 100-day study. 7-day study: 4 groups of 5 animals (randomised based on weight),		Dietary did not inflamm periphe the GI t An incre observe relative weight mg E-1 per day compar initiated and an in IL-17 (22.4 m 171/kg day + D IL-12p7 plasma E 171/k day + D with no related No char observe spleen cellular No char observe percent CD103- CD4+ T cells or

Akagi et al., 2023 – 28 Day Study	6 nm TiO2 nanoparticles.	N/A	5 female and 5 male F344/DuCrlCrlj rats.	TiO2 NPs with a crystallite size of 6 nm were examined in male and female F344/DuCrlCrlj rats by repeated oral administration of 10, 100, and 1000 mg/kg bw/day (5/sex/group) for 28 days.	No mor observe group, a treatme related effects observe weight, urinalys haemat serum biocher organ w Histopa examin reveale particle deposit yellowis materia particle observe gastroin lumen w found in nasal ca epitheli stromal the 28-d study. Overall, effects observe repeate adminis TiO2 wi crystall 6 nm at 1000 m bw/day regardi general

Donner et al. 2016	One of three pigment-grade or one of three ultrafine /nanoscale anatase and/or rutile TiO2 test materials.	OECD 474 Guidelines.	Dosage: Single oral gavage doses of 500, 1000 or 2000 mg/kg body weight with negative (water) and positive controls (cyclophosphamide).	Male and female rats. Blood samples were collected 48 and 72 h post-exposure.	There w relevan increas micronu RET fre any TiO exposed at eithe point at dose le All tests negativ for in vi genotox effects, significa or liver increas followin exposu highest

Reproductive toxicity

Reference	TiO2 characterisation	Quality of study e.g., OECD/GLP	Method and duration of dosing	Study methodology to include species, numbers, controls,	Results

Results:

F0 - Dose-dependent marginal increase in blood and concentrat rats dosed 1000 mg/k bw/day.

No test ite related eff on sexual function or fertility in or females test item-r pre- or pos loss observ

No test ite related thy hormone o haematolo effects.

No test ite related differences splenic lymphocyt subpopula distributio

No test ite related cha related to histopatho examinatio including t testis and epididymid and intesti

Leuschner, 2020 – Satellite study	Test substance: Anatase E-171, 51% of particles 100 nm. Dietary particle size: 31-43% of particles 100 nm.	OECD Test Guideline 443.	F0 satellite group: 0, 100, 300, and 1000 mg/kg bw/day over 10 weeks (prior to mating and up to the end of weaning periods).	CD® (Sprague Dawley) IGS Rat (Crl:CD(SD)). F0 satellite group – 30 male, 30 female per group + additional 40 (20 male, 20 female) for use as an F1 generation of satellite animals to be used as the positive control group in the KLH-assay (?) Endpoint: ACE	No test ite related eff behaviour external appearanc No test ite related thy hormone e No test ite related eff on body w food consumpti water consumpti No test ite related eff on haemat and biochemica parameter urinalysis. No test ite related eff on thyroid sexual hor or sperm. No test ite related cha in bone ma or organ weights. No test ite related histopatho effects in t high dose

Lee et al., 2019	TiO2 NPs P25 (15–24 nm).	OECD Guideline 414 (Pre-natal Toxicity Study).	Test item: Nanoparticles in deionised water. 80/20 anatase/rutile. Mean diameter of approximately 21 nm (minimum of 100 particle sizes averaged) administered daily by oral gavage. Dosage: Test item was administered from Gestational Days 6 to 19 at dose levels of 0, 100, 300 and 1000 mg/kg with a dose volume of 10 mL/kg.	Sprague–Dawley rats (12 females per group). Quantitative analysis in blood/tissues. Four groups of twelve females per group in the toxicology group (total test animals: 48) and four groups of four females in the tissue distribution group (total test animals: 16).	No statistic significant differences general cli signs, body weight, org weights (absolute a relative to weight), macroscop findings ex statistically significant decrease i intake but correlated decreased weight or b weight gai during the period of t females of high-dose No statistic significant differences caesarean section parameter fetal exter and viscera examinatio A small bu statistically significant increase (4 was observ the numbe ossification centres in metatarsal

Immunotoxicity

Reference	TiO2 characterisation	Quality of study e.g., OECD/GLP	Method and duration of dosing	Study methodology to include species, numbers, controls,	Results

					Statistically significant decreases in CSF plasma levels (~30% females) and plasma IgM (~12% in females and in males) we observed at t highest dose compared to controls. E171 accumulation the stomach of several rat administered 1,000 mg/kg E171 for 90 days.
Han et al. , 2020	E171, anatase, 150 nm, 99.5% purity.	Study conducted according to OECD TG 408.	E171 suspended in distilled water, sonicated for at least 10 minutes. E171 administered by oral gavage at doses of 0, 10, 100 or 1,000 mg/kg bw/d for 90 days. Quantitative analysis in Sprague-Dawley rat's	Sprague–Dawley rats (10/sex/group) were administered E171 by oral gavage at doses of 0, 10, 100 or 1,000 mg/kg bw/d for 90 days. Ti concentrations were measured in the colons, kidneys, and spleens harvested from	Ti concentrat increased in colons of bot sexes administered 1,000 mg/kg E171 compar with the cont while colonic superoxide dismutases (SOD)-1 (mal and female) SOD-2 (fema protein levels were down-regulated. When expose to AGS cells

NCI, 1979	TR-097: Titanium Dioxide (CASRN 13463-67-7) (nih.gov) Titanium dioxide anatase. Purity: 98%.	N/A	Groups of 50 rats of each sex and 50 mice of each sex were administered titanium dioxide in the diet at one of two doses, either 25,000 or 50,000 ppm, for 103 weeks and then observed for 1 additional week. Matched controls consisted of 50 untreated rats of each sex and 50 untreated mice of each sex. All surviving rats and mice were killed at 104 weeks.	Administration of the titanium dioxide had no appreciable effect on the mean body weights of rats or mice of either sex. With the exception of white feces, there was no other clinical sign that was judged to be related to the administration of titanium dioxide. Survival of the rats and the male mice at the end of the bioassay was not affected by the test chemical; mortality in female mice was dose related. Sufficient numbers of dosed and control rats and mice of each sex were at risk for development of late-appearing tumors.	In the male a female mice, tumours occurred in dosed groups incidences th were significantly higher than those for correspondin control group is concluded under the conditions of bioassay, titanium diox was not carcinogenic the oral route Fischer 344 r or B6C3F1 m

Akagi et al., 2023 – 28 Day Study	6 nm TiO2 nanoparticles.	N/A	5 female and 5 male F344/DuCrlCrlj rats.	TiO2 NPs with a crystallite size of 6 nm were examined in male and female F344/DuCrlCrlj rats by repeated oral administration of 10, 100, and 1000 mg/kg bw/day (5/sex/group) for 28 days.	No mortality observed in a group, and n treatment-related adve effects were observed in b weight, urinalysis, haematology serum biochemistry organ weight Histopatholo examination revealed TiO particles as depositions c yellowish-bro material. The particles observed in t gastrointesti lumen were a found in the nasal cavity, epithelium, a stromal tissu the 28-day study. Overall, no effects were observed aft repeated ora administratio TiO2 with a crystallite siz 6 nm at up to 1000 mg/kg bw/day regarding general toxic

Akagi et al., 2023 – 90 Day Study	6 nm TiO2 nanoparticles.	N/A	10 female and 10 male F344/DuCrlCrlj rats.	TiO2 NPs with a crystallite size of 6 nm were examined in male and female F344/DuCrlCrlj rats by repeated oral administration of 100, 300, and 1000 mg/kg bw/day (10/sex/group) for 90 days.	No mortality observed in a group, and n treatment-related adve effects were observed in b weight, urinalysis, haematology serum biochemistry organ weight addition, the were observe Peyer's patch in the ileum, cervical lymp nodes, mediastinal lymph nodes bronchus-associated lymphoid tiss and trachea the 90-day study. Overall, no effects were observed aft repeated ora administratio TiO2 with a crystallite siz 6 nm at up to 1000 mg/kg bw/day regarding general toxic accumulation titanium in th liver, kidneys

					Male C67BL/6JAusb mice were exposed to E171 via drinking water at doses of either 0, 2, 10, or 50 mg TiO2/kg BW/day for 3 weeks to determine impact on colonic microbiota composition and on gut bacterial metabolites (10 mice/group).	At the highes dose tested, TiO2 had minimal impa on the composition the gut microbiota. Alterations in bacterial metabolites were observe from 10 mg/k bw/d.
					Incubated commensal bacteria derived from mouse colons anaerobically for 5 days with dose of 0, 2, 10, 50 µg/ml of TiO2 biofilm formation (6 mice/group).	Doses of 10 a 50 µg/ml TiO significantly promoted bio formation by commensal bacteria.
				Mice were exposure to E171 via drinking water for 4 weeks at doses of 0, 2, 10, 50 mg/kg bw/d. Dose is calculated based on water intake measured per cage.	Impact of TiO2 on colonic epithelial function was determined by comparison of gene expression of key markers Muc2, Tjp1, Defb3, and Gzmb in colonic	There was reduced expression o colonic mucin gene, a key component o the intestina
		N/A	E171, anatase, 30-300 nm.	Microbiota populations in		
Pinget et			E171 was			

Neurotoxicity

Reference	TiO2 characterisation	Quality of study e.g., OECD/GLP	Method and duration of dosing	Study methodology to include species, numbers, controls,	Resu

Sofranko et al., 2021	10 mg/g TiO2, 2 mg/g polyvinylpyrrolidone-coated Ag.	OECD 424 Neurotoxicity study in the rodents.	N/A	10 female and 10 male C57BL/6J mice. The mice were fed ad libitum with food pellets dosed with 10 mg/g TiO2, 2 mg/g polyvinylpyrrolidone-coated Ag or control pellets for 28 days.	The TiO2 appli pelle fema mice expo or w post reco No m neur chan neur biocl imm analy obse beha in ar cogn abse the A mice perfo were the r diffe sexe mice expo 28 d cons moto and corti spec kinas Fema were inves

Grissa et al. (2016)	TiO2 NPs, anatase, 5–12 nm (TEM, XRD).	N/A	Internal exposure: quantitative in male Wistar rat tissues; methodology with important flaws.	N/A	Ther stati signi relat the l and per c grou a sta signi relat brair mg/k TiO2
Gerber et al., 2022	TiO2 NPs, average primary particle size of 26.2 ± 10.7 nm.	N/A	N/A	The aim of the study was to investigate the effects of two common types of NP, Titanium dioxide NP (TiO2 NP) and silver NP (AgNP), on neuronal function following acute (0.5 h), sub-chronic (24 h and 48 h) and chronic (14 days) exposure in vitro rat cortical cells.	Acut chro TiO2 effec chro only redu funct affec morp

Ciu et al., 2021	TiO2 NPs.	N/A	36 male Sprague Dawley rats aged postnatal day 21 (PND 21) were injected intraperitoneally with TiO2 NPs (20 mg/kg) and/or BEO (200 mg/kg).	N/A	TiO2 durin perio anxi beha impa neur and dam hipp BEO signi ame neur by Ti expo
Naima et al., 2021	TiO2 NPs.	N/A	Rats were injected intravenously with a single dose of TiO2-NPs (20 mg/kg body weight) and were subjected to cognitive and emotional tests using Morris water maze and elevated plus maze.	N/A	Acut injec impa perfo throu bioch struc and shou their addi appl

Canli et al., 2020	TiO2 NPs	N/A	Oral administration of TiO2 for 14 days (0, 0.5, 5, and 50 mg/kg bw/day).	Female rats.	Resu brain decr treat ATPa incre Intes ATPa show chan Leve show chan TBAR high show decr TiO2 accu (dos in tis The to be sens agai TiO2