

Fifth draft statement on the safety of Titanium Dioxide (E171) as a Food Additive- Annex D

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Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment.

Third draft statement on the safety of Titanium Dioxide (E171) as a Food Additive - Annex D

Summary table of studies

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

TiO₂	Quality of Reference characterisation study e.g., OECD/GLP	Method and duration of dosing	Study methodology to include species, numbers, controls,	Results
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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 concentrations in the liver (0.94 ± 0.57 $\mu\text{g/g}$ tissue) and large intestine (1.07 ± 0.38 $\mu\text{g/g}$ tissue) were significantly higher in treated mice compared to controls.

Ti concentrations in the brain, kidney, and testes were below the quantification limit (0.03 $\mu\text{g/g}$).

Ti concentrations in lungs, spleen, stomach, and small intestine were not statistically significant between treated and control mice.

No evidence of gross alteration of immune-cell physiology or inflammation at doses up to 100 mg/kg bw/d via the diet.

Authors demonstrate E171 uptake by Peyer's patches, validating the delivery model.

Presence of E171 particles detected by reflectance confocal microscopy (no quantification of particles completed).

Weak signals observed at the base of Peyer's patches at low and mid-doses. Higher signals

Mice were divided into 4 groups of 18 and given 0,

Mice were exposed to 6.25, 62.5, or 625 mg/kg 0, 1, 10, or 100 mg/kg bw/d E171 via the diet for 6, 12 and 18 weeks.

(equivalent to approximately 0, 1, 10, or 100 mg/kg bw). Then 6 mice per group were euthanized at 6, 12 and 18 weeks.

Riedle et al., 2020 E171, anatase, 119 nm.

Allergenicity

<p>Phue et al., (2022)</p> <p>Food grade titanium dioxide nanoparticles and E171.</p>	<p>Used ELISA to study the alterations of the IgG binding, and mast cell degranulation assay to study allergenicity of milk and individual milk proteins (β-lactoglobulin and casein) in the presence of E171.</p>	<p>For ELISA, primary antibody for casein (Anti-casein rabbit antibody-cat # ab166596), primary antibody for β-lactoglobulin (Anti-LGB rabbit antibody-cat # ab112893) and secondary anti-rabbit antibody (cat # 6721) were used.</p> <p>Quebon skimmed milk was used.</p>	<p>Significant enhancement in the allergenicity of milk proteins/ skimmed milk interacted with both E171 and food grade titanium dioxide nanoparticles.</p> <p>The presence of E171 showed the highest level of LAD2 degranulation (a proxy for allergenicity), followed by food grade titanium dioxide nanoparticles.</p>
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Inflammation and Immunotoxicity

Reference	TiO2 characterisation	Quality of study e.g., OECD/GLP	Method and duration of dosing	Study methodology to include species, numbers, controls,	Results
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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 concentrations in the liver (0.94 ± 0.38 $\mu\text{g/g}$ tissue) and large intestine (0.94 ± 0.38 $\mu\text{g/g}$ tissue) were significantly higher in treated mice compared to controls.

Ti concentrations in the brain, kidney, and testes were below the quantification limit (0.03 $\mu\text{g/g}$).

Ti concentrations in lungs, spleen, stomach, small intestine were not statistically significant between treated and control mice.

	<p>Male C67BL/6J Ausb 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).</p>	<p>At the high dose tested, TiO₂ had minimal impact on the composition of the gut microbiota. Alteration of bacterial metabolites were observed from 10 mg bw/d.</p>
<p>E171, anatase,</p>	<p>Mice were exposed 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.</p>	<p>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). Impact of TiO₂ on colonic epithelial function was determined by comparison of gene expression</p> <p>Doses of 2 and 50 µg TiO₂ significantly promoted biofilm formation of commensal bacteria. There was reduced expression</p>

Riedle et al., 2020

E171, anatase, 119 nm.

Mice were exposed to 0, 1, 10, or 100 mg/kg bw/d E171 via the diet for 6, 12 and 18 weeks.

E171 was formulated into diet.

6-week-old male and female C57BL/6 mice (6/sex/group) were exposed to E171 daily via 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.

No evidence of gross alteration of immune-physiology or inflammation at doses up to 100 mg/kg bw/d via diet.

Authors demonstrated E171 uptake by Peyer's patches, validating delivery model.

Presence of E171 particles detected by reflectance confocal microscopy (no quantification of particles completed).

Weak signals observed at the base of Peyer's patches and mid-intestine at high doses. High signals

This is a review,
and is only
mentioned once
Liu *et al.*, in the TiO₂
2020 statement in a
quote from the
Health Canada
report.

Statistical
significant
decreases
GM-CSF
plasma le
(~30% in
females)
plasma Ig
(~12% in
females a
9% in ma
were obse
at the hig
dose
comparec
controls.

E171
accumula
in the
stomach w
of severa
administe
1,000 mg
E171 for 9
days.

Ti
concentra
increased
the colons
both sexe
administe
1,000 mg
E171
comparec
with the
control, w
colonic,
superoxid
limit

E171 suspended Sprague-Dawley
in distilled rats
water, sonicated (10/sex/group)
for at least 10 were
minutes. administered

E171
administered by 1,000 mg/kg
E171 by oral
gavage at doses
of 0, 10, 100 or
1,000 mg/kg

Studies used to review the toxicokinetic and absorption of the nanoparticle form of TiO₂

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

In the high dose treatment group, significant increases in testicular Ti tissue levels were found in spleen (0.036 ± 0.009 vs. 0.008 µg/g fresh weight; p ≤ 0.05) and ovaries (0.04 ± 0.07 vs. 0.004 µg/g fresh weight; p ≤ 0.05).

Sex-related histological alterations were observed at high dose levels in thyroid, adrenal medulla, adrenal cortex (female) and ovarian granulosa, with general toxic effects.

Altered thyroid function was indicated by reduced T3 (males).

Testosterone levels increased in high-dose males and decreased in females.

Tassinari et al., 2014

TiO₂ nanoparticles (anatase, primary size 25 nm, BET surface area 45-55 m²/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)).

<p>Warheit et al., 2015</p>	<p>1. anatase/rutile (89/11%) (uf-1), d50=43 nm d50=23 nm</p> <p>Methods: XSDC and TEM respectively</p> <p>Shape: Irregular</p> <p>2. anatase (100% nano) (uf-2) d50=42 nm d50=19 nm</p> <p>Methods: XSDC and TEM respectively</p> <p>Shape: Irregular</p> <p>3. rutile (100% nano) (uf-3), d50=47 nm d50=22 nm</p> <p>Methods: XSDC and TEM respectively</p> <p>Shape: rod-like</p> <p>4. anatase (27% nano) (pg-1), d50=153 nm d50=120 nm</p> <p>Methods:</p>	<p>OECD Guideline 414</p>	<p>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.</p> <p>Dose levels: 0, 100, 300 or 1,000 mg/kg bw per day</p> <p>Dosage</p>	<p>Three studies (Group size n=22): Time-mated pregnant Sprague-Dawley rats, (CrI:CD(SD)) exposed to TiO₂ (uf-1, uf-3 and pg-1) by gavage on Gestational Days 6-20.</p> <p>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.</p> <p>Necropsy:</p> <ul style="list-style-type: none"> • gross examination of the dam • counting of corpora lutea • implantation sites • resorptions • live and dead fetuses 	<p>At 1,000 mg/1/kg per day, mean fetal sex ratio and the means for male and female fetuses per litter were statistically significantly different from control group means.</p> <p>Mean male fetuses: 7.2</p> <p>Mean male fetuses control group: 5.5</p> <p>Test facility historical control group data range: 5.2 to 7.4.</p> <p>Mean female fetuses: 4.8</p> <p>Mean female fetuses control group: 6.7</p> <p>Test facility historical control group data range: 5.8 to 8.3.</p> <p>Mean fetal sex ratio of the 1 mguf-1/kg bw per day group: 6.2</p>
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<p>Bettini et al., 2017</p>	<p>1) E 171, anatase, 20–340 nm (118 nm) (TEM); 44.7% particles 100 nm;</p> <p>2) TiO₂ NPs (NM-105), anatase/rutile, 15–24 nm.</p>	<p>OECD?</p>	<p>Series One Dosage: 200 μ L with TiO₂ NM-105, E171 (10 mg/kg of BW/day) or water for 7 days by gavage.</p> <p>Series Two Dosage: E-171 at 200 μ g or 10 mg/kg of BW/day via drinking water for 100 day (with or without DMH treatment)</p>	<p>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.</p> <p>Tissue imaging, flow cytometry and cytokine assays, tissue inflammation and gut permeability measurements were conducted.</p> <p>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.</p>	<p>Titanium was detected in the immune cells of Peyer's patches. Dendritic cell percentage was increased, observed days after exposure. no effect at 100 days.</p> <p>No effects in spleen.</p> <p>Regulatory T and T-helper cells were significantly decreased days after exposure and at 100 days for rats exposed to E 171.</p> <p>Stimulation in vitro of immune cells isolated from Peyer's patches had a decreased T-helper (Th) IFN-γ secretion and splenic Th1/Th17 inflammatory responses increased</p>
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Karimpour TiO₂ NPs,
et al., anatase, 10–25
2018 nm

One dose of
TiO₂ NP (100
mg/kg per
day) or the
test vehicle
(control
group) daily
for 5 weeks

NMRI = Naval
Medical
Research
Institute

54 ten week old
(25±2 g) adult
female NMRI mice
were divided into
a control group
which received
vehicle (saline
solution) orally
and TiO₂ NP
group which
received 100
mg/kg per day
TiO₂ NP solution
orally.

Pregnancy and in
vitro
fertilization rates,
histological
changes in
ovaries,
malondyaldehyde
and estrogen
hormone

levels in the blood
serum were
assessed after
five weeks.

24 hours post last
administration of
test item: 3
control or test
female mice were
housed with 3
male mice

for 11 days. The
percentage of

There was a
significantly
decreased
pregnancy rate
(70% vs. 100%
the control group)
a 20% decrease
litter size and
increases in
circulating
oestrogen (25%)
and MDA (25%)

Degeneration
reduction of
follicles, cyst
formation and
impairment of
follicular
development
the ovaries were
observed in the
TiO₂ NPs group
but no
quantitative
was provided

Additionally a
lower number
oocytes was
isolated from
TiO₂ NP group
well as a high
percentage of
development
arrest before
blastocyst stage
after in vitro
fertilisation. The
authors proposed
that this could
have been an
indirect effect
TiO₂ NPs through

Khorsandi
et al.,
 2016

TiO₂ NPs 30 nm

Test item: NTiO ₂ nanopowder (TNP, Sigma) made with 100 ml	32 adult 6-8 weeks old male NMRI mice (25-30 g)	Body weight unaffected by treatment.
BSA (bovine serum albumin) solution dissolve in Milli-Q water.	Four groups of 8 mice with a dosage of 75, 100 and 300 mg/kg TNP for 35 consecutive days respectively for each of the test groups and the control group received saline orally for 35 consecutive days.	Dose-depend decreases in weight were observed from dose of 100 m bw per day. Mid- and high dose groups showed decre in serum and testicular testosterone levels, the diameter and volume of seminiferous tubules, the height of the spermatogen epithelium and total Leydig c numbers how the total volu of the interst tissue increas
Oral Dosage Groups:		
TNP-1: 75 mg/kg TNP		
TNP-2: 100 mg/kg TNP	Testicular testosterone levels, testis weight, total volumes of testis, seminiferous tubules, interstitial tissue and total Leydig cell numbers were measured.	
TNP-3: 300 mg/kg TNP		
Control: saline solution		

Lee *et al.*, TiO₂ NPs P25
2019 (15–24 nm)

OECD
Guideline
414 (Pre-
natal
Toxicity
Study)

Test item:

Nanoparticles
in deionised
water.

80/20 Sprague–Dawley
anatase/rutile. rats (12 females
per group)

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

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 statistical
significant
differences in
general clinic
signs, body
weight, organ
weights (abs
and relative t
body weight)
macroscopic
findings exce
statistically
significant
decrease in f
intake but no
correlated
decreased bo
weight or bod
weight gain o
the study per
of the female
the high-dose
group.

No statistical
significant
differences in
caesarean se
parameters a
fetal externa
visceral
examination.

A small but
statistically
significant
increase (4%
observed in t
number of
ossification

Aberrant Crypt Foci (ACF) as a marker for carcinogenicity

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

E-171

consumption of
not alter T-cell
mediated
mechanisms of
immune contr

Dietary E-171
did not induce
inflammation
peripherally of
the GI tract.

Six-week-old male
Wistar Han IGS
(CrI:WI (Han))
rats.

An increase w
observed in th
relative spleen
weight in 22.4
mg E-171/kg b
per day + DMH
compared to n
initiated anim
and an increas
in IL-17A in co
(22.4 mg E
171/kg bw per
day + DMH) a
IL-12p70 in
plasma (3.5 m
E 171/kg bw p

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.

day + DMH),
with no dose-
related effects

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.

No changes w
observed in
spleen
cellularity.

Akagi et al.,
2023 - 28 Day Study

6 nm TiO₂ nanoparticles

5 female and 5 male F344/DuCrIj rats

TiO₂ NPs with a crystallite size of 6 nm were examined in male and female F344/DuCrIj rats by repeated oral administration of 10, 100, and 1000 mg/kg bw/day (5/sex/group) for 28 days

No mortality was observed in any group, and no treatment-related adverse

effects were observed in body weight, urinalysis, haematology, serum biochemistry, organ weight. Histopathological examination revealed TiO₂ particles as depositions of yellowish-brown material. The

particles observed in the gastrointestinal lumen were also found in the nasal cavity, epithelium, and stromal tissue the 28-day study.

Overall, No effects were observed after repeated oral administration of TiO₂ with a crystallite size of 6 nm at up to 1000 mg/kg bw/day regarding general toxic

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
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Results:

F0 - Dose-dependent marginal increase in TiC blood and urine concentration rats dosed with 1000 mg/kg bw/day

No test item-related effects on sexual function or fertility in males or females. No test item-related pre- or postnatal loss observed

No test item-related thyroid hormone or haematological effects..

No test item-related differences in splenic lymphocyte subpopulation distribution

No test item

No test item-related effects on behaviour or external appearance.

No test item-related thyroid hormone effects.

No test item-related effects on body weight, food consumption and water consumption.

No test item-related effects on haematology and

biochemical parameters or urinalysis.

No test item-related effects on thyroid and sexual hormones or sperm.

No test item-related changes in bone marrow

CD® (Sprague Dawley) IGS Rat (CrI:CD(SD))

F0 satellite group - 30 male, 30 female per group + additional 40 (20 male, 20 female) for use

Test substance: Anatase E-171, 51% of particles 100 nm.

F0 satellite group: 0, 100, 300, and 1000 mg/kg bw/day over 10 weeks (prior to

OECD Test Guideline

Immunotoxicity

Reference	TiO2 characterisation	Quality of study e.g., OECD/GLP	Method and duration of dosing	Study methodology to include species, numbers, controls,	Results
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Han <i>et al.</i> , 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.	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 concentration increased in the colons of both sexes administered 1,000 mg/kg E171 compared with the control while colonic, superoxide dismutases (SOD)-1 (male and female) and SOD-2 (female) protein levels were down-
					Statistically significant decreases in GM-CSF plasma levels (~30% in females) and plasma IgM (~12% in females and 9% in males) were observed at the highest dose compared to controls.
					E171 accumulation in the stomach was observed in several rats administered 1,000 mg/kg E171 for 90 days.

[TR-097: Titanium Dioxide \(CASRN 13463-67-7\) \(nih.gov\)](#)

NCI, 1979
- see link
->

Titanium dioxide anatase

Purity: 98%

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 and female mice, no tumours occurred in dosed groups and incidences that were significantly higher than those for corresponding control groups. It is concluded that under the conditions of the bioassay, titanium dioxide was not carcinogenic by the oral route for Fischer 344 rats or B6C3F1 mice.

Akagi et al.,
2023 - 28 Day Study

6 nm TiO₂ nanoparticles

5 female and 5 male F344/DuCrIjCrIj rats

TiO₂ NPs with a crystallite size of 6 nm were examined in male and female F344/DuCrIjCrIj rats by repeated oral administration of 10, 100, and 1000 mg/kg bw/day (5/sex/group) for 28 days

No mortality was observed in any group, and no treatment-related adverse

effects were observed in body weight, urinalysis, haematology, serum biochemistry, or organ weight. Histopathologic examination revealed TiO₂ particles as depositions of yellowish-brown material. The particles observed in the gastrointestinal lumen were also found in the nasal cavity, epithelium, and stromal tissue in the 28-day study.

Overall, No effects were observed after repeated oral administration of TiO₂ with a crystallite size of 6 nm at up to 1000 mg/kg bw/day regarding general toxicit

Akagi et al., 2023
- 90 Day Study
6 nm TiO₂ nanoparticles

10 female and
10 male
F344/DuCrIj
rats

TiO₂ NPs with a
crystallite size of
6 nm were
examined in
male and female
F344/DuCrIj
rats by repeated
oral
administration of
100, 300, and
1000 mg/kg
bw/day
(10/sex/group)
for 90 days

Neurotoxicity

Reference	TiO2 characterisation	Quality of study e.g., OECD/GLP	Method and duration of dosing	Study methodology to include species, numbers, controls,	Results
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*Sofranko
et al.,
2021*

10 mg/g TiO₂, 2
mg/g
polyvinylpyrrolidone-
coated Ag

OECD 424
Neurotoxicity
study in the
rodents

10 female and 10
male C57BL/6J
mice

The mice
ad libitum
pellets of
10 mg/g
mg/g
polyvinyl
coated
pellets f

Grissa et al. (2016)

TiO₂ NPs, anatase, 5-12 nm (TEM, XRD).

Internal exposure: quantitative in male Wistar rat tissues; methodology with important flaws.

There w
statistic
significa
related
the leve
100 and
bw per c
groups c
and a st
significa
related
brain TM
mg/kg b
TiO₂ NP

Gerber et al., 2022

TiO₂ NPs, average primary particle size of 26.2 ± 10.7 nm

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.

Acute and

sub-chronic exposure to TiO₂ NP is without effects, whereas chronic exposure only modestly reduces neuronal

function without affecting morphology.

Ciu et al.,
2021

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).

TiO₂ NPs exposure
during the
adolescent period
induced
anxiety-like
behaviour,
cognitive
impairment,
neuroinflammation
and oxidative
damage in
hippocampus, and
BEO treatment
could significantly
ameliorate the
neurotoxicity
induced by TiO₂
NPs exposure.

Naima et
al., 2021

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.

Acute intravenous
injection of TiO₂-
NPs impaired
behaviour
performances
through brain
biochemical and
structural changes
and precautions
should be taken to
their usage in food
additive and
medical
applications.