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TITANIUM DIOXIDE: SUMMARY OF THE DOSSIER

Series on the Safety of Manufactured Nanomaterials
No. 73

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- ENV/JM/MONO(2015)17/PART1
- ENV/JM/MONO(2015)17/PART2
- ENV/JM/MONO(2015)17/PART3
- ENV/JM/MONO(2015)17/PART4
- ENV/JM/MONO(2015)17/PART5
- ENV/JM/MONO(2015)17/PART6
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Series on the Safety of Manufactured Nanomaterials

No. 73

TITANIUM DIOXIDE: SUMMARY OF THE DOSSIER

IOMC
INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT
Paris, 2016

Also published in the Series on the Safety of Manufactured Nanomaterials:

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No. 24, *Preliminary Guidance Notes on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials (2010)*

No. 25, *Guidance Manual for the Testing of Manufactured Nanomaterials: OECD Sponsorship Programme: First Revision (2010)*

No. 26, *Current Development/ Activities on the Safety of Manufactured Nanomaterials: Tour de table at the 7th Meeting of the Working Party on Manufactured Nanomaterials (2010)*

No. 27, *List of Manufactured Nanomaterials and List of Endpoints for Phase One of the Sponsorship Programme for the Testing Manufactured Nanomaterials: Revised (2010)*

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No. 29, *Current Development/ Activities on the Safety of Manufactured Nanomaterials: Tour de table at the 8th Meeting of the Working Party on Manufactured Nanomaterials (2011)*

No. 30, *Regulated Nanomaterials: 2006-2009(2011)*

No. 31, *Information Gathering Schemes on Nanomaterials: Lessons Learned and Reported Information (2011)*

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No. 33, *Important Issues on Risk Assessment of Manufactured Nanomaterials (2012)*

No. 34, *Current Development/ Activities on the Safety of Manufactured Nanomaterials: Tour de table at the 9th Meeting of the Working Party on Manufactured Nanomaterials (2012)*

No. 35, *Inhalation Toxicity Testing: Expert Meeting on Potential Revisions to OECD Test Guidelines and Guidance Document (2012)*

No. 36, *Guidance on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials (2012)*

No.37, *Current Developments in Delegations on the Safety of Manufactured Nanomaterials - Tour de Table at the 10th Meeting of the WPMN (2012)*

No.38, *Co-Operation on Risk Assessment: Prioritisation of Important Issues on Risk Assessment of Manufactured Nanomaterials - Final Report (2013)*

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No.42, *Report of the questionnaire on regulatory regimes for manufactured nanomaterials 2010-2011 (2014)*

No.43, *Genotoxicity of Manufactured Nanomaterials: Report of the OECD expert meeting (2014)*

Nos. 44-54, These items are the dossiers derived from the Testing Programme on Manufactured Nanomaterials which are located at:
http://www.oecd.org/chemicalsafety/nanosafety/testing-programme-manufactured-nanomaterials.htm

No.55, *Harmonized Tiered Approach to Measure and Assess the Potential Exposure to Airbone Emissions of Engineered Nano-objects and their Agglomerates and Aggregates at Workplaces. (2015)*

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No.70, *Single walled carbon nanotubes (SWCNTs): summary of the dossier (2016)*

No.71, *Silicon dioxide: summary of the dossier (2016)*

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ABOUT THE OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 34 industrialised countries in North and South America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

The Environment, Health and Safety Division publishes free-of-charge documents in eleven different series: **Testing and Assessment**; **Good Laboratory Practice and Compliance Monitoring; Pesticides; Biocides; Risk Management; Harmonisation of Regulatory Oversight in Biotechnology; Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents;** and **Safety of Manufactured Nanomaterials.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/chemicalsafety/).

This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organizations.

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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SIDS Initial Assessment Report

1. IDENTITY

1.1. Identification of the Substance

CAS Number:	13463-67-7, anatase: 1317-70-0, rutile: 1317-80-2
IUPAC Name:	Titanium dioxide, Titanium(IV) oxide
Molecular Formula:	TiO2
Structural Formula:	
Molecular Weight:	79,90 kg/kmol
Synonyms:	Titania

As materials tested in the framework in the Sponsorship Programme following materials were chosen and agreed within the group:

Principle material

Aeroxide®P 25 (P25) was chosen as principle material, meaning all endpoints will be addressed for this material, because of its widespread use on the market and within the scientific community to perform comprehensive investigations

- Aeroxide®P 25
  - provided and delivered by Degussa/Evonik, Lot-Nr.: 4168112198
  - provided and delivered by EC/JRC, Lot-Nr.: 4168031098 (called NM105)
  - US-NIST used in addition the certified material SRM 1898 which were synthesised by NIST with the P25 same properties

Other materials used in tests which were in progress, provided by TDMA and EC/JRC:

Since the TiO_2 placed on the market presents high variability in its composition and modification a choice of additional material to be tested based on the following: firstly to cover all the exposure to human and environment scenario, and secondly to test a broad range of material characteristics. For these additional materials it is considered not to address all endpoints but a number of endpoints for comparison.

- PC105 (JRC no. NM102)
  - provided by Cristal Global and delivered EC/JRC, Lot-Nr.: 6292000312
- Hombikat UV 100 (Sachtleben) identified as NM-101 Titanium Dioxide
  - provided and delivered by EC/JRC, Lot-Nr.: 10780048
- UV TITAN M212 (Sachtleben) (JRC no. NM104)
  - provided and delivered by EC/JRC, Lot-Nr.:808001
- UV TITAN M262 (Sachtleben) (JRC no. NM103)
  - provided by EC/JRC, Lot-Nr.:933002
- Tiona AT-1 (non-nano reference) (JRC no. NM100)
  - provided by Cristal Global and delivered EC/JRC, Lot-Nr.: 6111007957

Beside the above listed materials it was agreed that also such materials could be added to the DDP which were comprehensive characterized and employed for broad tests which could lead thereby to a good comparison to the agreed materials.

The materials provided from the manufactures were delivered to the participating laboratories directly with product information, certification of analysis, storage conditions and Safety Data Sheet. Degussa provided a SOP for P25 suspension preparation used by the NanoCare Project.

Materials provided by EC/JRC were bought from the market or provided by the manufacturer e.g. Cristal Global, that handed over its material to EC/JRC at a later stage of the test programme. To assure the traceability, the materials delivered by the EC/JRC were homogenised, sub-sampled and kept under inert atmosphere according §42 of the Guidance Manual for Sponsors before the delivering to the participating laboratories.

The present document summarizes the information that was delivered by participating countries and stakeholder until the deadline for the dossier compilation of the TiO_2 dossier of the OECD WPMN Sponsorship Programme. Within that programme also a literature review in 2012-2013 delivered input to the chosen OECD materials (but not necessarily to the particular batches) by available information on environmental and human health effects as well as environmental behavior.

The ± values within the tables are, depending on the case, standard errors, standard deviations or systematic errors. For more details are available in the dossier.

Composition of nanomaterial being tested:

JRC-no.	***Name***	***Lot.-nr.***	***Producer***	***Method***	***Composition***
-	P25	4168112198	Evonik	ICP, AAS	99,9% TiO_2, 0,138% HCl
NM105	P25	4168031098	Evonik		>99% TiO_2
NM101	Hombikat UV 100	10780048	Sachtleben		91,7% TiO_2, 0,3% SO_4
NM102	PC105	6292000312	Cristal Global	Calculation, S analyser, XRF, AAS	95,4% TiO_2, ≤ 0.3% SO_3, 41mg/kg K_2O, 0.04% P_2O_5, 28mg/kg Fe, 35mg/kg Na_2O
NM103	UV TITAN M262	933002	Sachtleben		89.0% TiO_2, 6.2%Al_2O_3
NM104	UV TITAN M212	808001	Sachtleben		89.0% TiO_2, 6.2%Al_2O_3
NM100	Tiona AT-1	6111007957	Cristal Global	Calculation, S analyser, XRF, AAS	98,7% TiO_2, ≤ 0.05% SO_3, 0,28% K_2O, 0.35% P_2O_5, 38mg/kg Fe

Production method, Basic morphology, description of surface chemistry (e.g. coating or modification), known catalytic activity, and major commercial use

Material	***Production method***	***Morphology***	***Surface coating***	***Catalytic activity***	***Commercial Use***
P25	Flame hydrolysis	spherical	-	photocatalytic, catalytic	photocatalyst, catalyst carrier, heat stabilizer for silicone rubber, also in cosmetics but without Evonik's agreement
NM105	Flame hydrolysis	spherical	-	photocatalytic, catalytic	photocatalyst, catalyst carrier, heat stabilizer for silicone

					rubber, also in cosmetics but without Evonik's agreement
NM101		essentially spherical	-	photocatalytic, catalytic	photocatalytic effects
NM102	precipitation	essentially spherical	-	photocatalytic, catalytic	photocatalytic effects, Denox
NM103	precipitation	essentially spherical	Al_2O_3, dimethicone (hydrophobic)	-	cosmetics
NM104	precipitation	spherical	Al_2O_3, glycerin (hydrophilic)	-	cosmetics
NN100	precipitation	essentially spherical	-	photocatalytic, catalytic	Multiple uses: inc. pigment for paint, paper, ceramics…

1.2. Purity/Impurities/Additives

1.3. Physico-Chemical properties

1.3.1. Agglomeration/aggregation

Summary from scientific literature

Reference	**Material**	**Method**	**Main findings**
Producer information	P25	665/0939 acc to ISO13320	D50=52.2µm
Ottofuelling et al. 2011	P25	multi-dimensional testing	Strong influence of dissolved organic compounds (DOC), mono-and divalent ions, and pH
von der Kammer et al. 2010	P25	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by natural organic matter (NOM), pH
Ottofuelling et al. 2011	NM101	multi-dimensional testing	Strong influence of DOC, mono-and divalent ions, and pH

von der Kammer et al. 2010	NM101	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH

Summary of NANOhub entries for Agglomeration/aggregation (OECD Materials**)**

Material	***Method***	***Result***	***Laboratory***
P25	Transmission electron microscopy (TEM), dynamic light scattering (DLS)	agglomeration depends on pH of media (179-2540nm), stable up to 30day at pH 3, 7.5 and 10, distilled water: 276 nm ± 26 nm	Ministry of KR
P25	Ultrasonic spectroscopy	0,052 µm (+42 mV, pH4.5, IEP 6.9) 0,05 µm (-33.5 mV, pH7.5, IEP 3.6) with 1-3wt%CE64	BAM (GER)
P25	SPMPS	158 nm±10 nm STDEV 0.51 (fluidized bed generator), 184 nm ±10 nm STDEV 0.51 (electrospray)	BAM (GER)
P25	DLS, sonication	Mean 220 nm , stable over 24h (pH 5)	IUTA (GER)
P25	DLS, stirring, centrifugation, filtered	HDD 198 nm (not centrifuged), 132 nm (3000 rpm), 72 nm (6000 rpm) at pH3-4	Ministry of KR
P25	DLS, stirring	Stability influenced by concentration 0.01-10 mg/l: approx. 200-600 nm; 50-100 mg/l: approx. 1200-1400 nm	INIA (ESP)
P25	DLS	852 nm±164 nm	NRC (CAN)
P25	DLS	400 nm PDI 0.39, 200 mg/l in serum containing culture media (sonication)	NRC (CAN)
P25	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH; clear differences between OECD TiO_2-materials	University Vienna (AT)
P25	DLS, stirring, ultrasonic	Ultrapure water: 253-718 nm (2-60 mg/l); M9-test media: 292-1162 nm (1-30 mg/l)	HAW Hamburg (GER)
NM 105	DLS, stirring	Stability influenced by concentration 0.01-1mg/l: approx. 200-400 nm; 10-100 mg/l: approx. 1000-1700 nm	INIA (ESP)
NM 105	Photo correlation spectroscopy (PCS),	depends on sonication method, surface treatment and media	University Graz

	different sonication methods		(AT)
NM 105	DLS	Mean 125 ± 4 nm, acidic conditions; 155 ± 1 nm in BSA 0.05 %	CEA (F) Nanogenotox
NM 105	Small angle x-ray scattering (SAXS)	130 nm, acidic conditions	CEA (F) Nanogenotox
NM 101	DLS, stirring	approx. 200-600 nm (0.01-100mg/l); increasing with increasing concentration	INIA (ESP)
NM 101	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH; clear differences between OECD TiO_2-materials	University Vienna (AT)
NM 102	DLS, sonication	D50=1µm	Producer information
NM 102	DLS	Mean 560 nm, stable over 24h (pH 5)	IUTA (GER)
NM 102	PCS, different sonication methods	depends on sonication method, surface treatment and media	University Graz (AT)
NM 102	multi-dimensional testing	not dispersible	University Vienna (AT)
NM 103	PCS, different sonication methods	depends on sonication method, surface treatment and media	University Graz (AT)
NM 102	DLS	Mean 423 ± 59 nm, acidic conditions; 545 ± 14 nm in BSA 0.05 %	CEA (F) Nanogenotox
NM 102	SAXS	560 nm, acidic conditions	CEA (F) Nanogenotox
NM 103	DLS	Mean 180 nm, stable over 24h (pH 5)	IUTA (GER)
NM 103	DLS	Mean 245.5 nm, stable over 24h (pH 5); loss of hydrophobic behavior after wetted with water and suspending	IUTA (GER)
NM 103	DLS, stirring	approx. 200-600 nm (0.01-100 mg/l); increasing with increasing concentration	INIA (ESP)

NM 103	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH; clear differences between OECD TiO_2-materials	University Vienna (AT)
NM 103	DLS	Mean 113 ± 3 nm, acidic conditions; 194 ± 2 nm in BSA 0.05 %	CEA (F) Nanogenotox
NM 103	SAXS	140 nm, acidic conditions	CEA (F) Nanogenotox
NM 104	PCS, different sonication methods	depends on sonication method, surface treatment and media	University Graz (AT)
NM 104	DLS, stirring	approx. 400-600 nm (0.01-100 mg/l); increasing with increasing concentration; stable only 3days	INIA (ESP)
NM 104	DLS	mean 205.6 nm, stable over 24h (pH 5)	IUTA (GER)
NM 104	DLS	mean 205 nm, stable over 24h (pH 5), loss of hydrophilic behavior after wetted with water and suspending	IUTA (GER)
NM 104	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH; clear differences between OECD TiO_2-materials	University Vienna (AT)
NM 100	PCS, different sonication methods	depends on sonication method, surface treatment and media	University Graz (AT)
NM 100	multi-dimensional testing	not dispersible	University Vienna (AT)
NM 100	DLS, stirring, ultrasonic	Ultrapure water: 296-357 nm (2-200 mg/l); M9-test media: 306-1509 nm (1-100 mg/l)	HAW Hamburg (GER)

Summary of NANOhub entries for Agglomeration/aggregation (other TiO_2 materials)

Material	***Method***	***Result***	***Laboratory***
Sukgyung	DLS	276 nm	Ministry of KR
MTI5, MTI	DLS	881 nm±137 nm	NRC (CAN)
MTI5, MTI	DLS	460 nm PDI 0.26, 200 mg/l in serum containing culture media (sonication)	NRC (CAN)

MTI30, MTI	DLS	1317±151nm	NRC (CAN)
NAM5, NanoAmor	DLS	975±269 nm	NRC (CAN)
NAM10; NanoAmor	DLS	928±75 nm	NRC (CAN)
NAM30, NanoAmor	DLS	729±186 nm	NRC (CAN)
NAM10x40; NanoAmour	DLS	243 nm±5 nm	NRC (CAN)
NAM10x40, NanoAmor	DLS	420 nm PDI 0.38, 200 mg/l in serum containing culture media (sonication)	NRC (CAN)
Hombitan LW-S, Sachtleben	DLS	340±8 nm	NRC (CAN)
Hombitan LW-S, Sachtleben	DLS	365nm PDI 0.14, 200mg/l in serum containing culture media (sonication)	NRC (CAN)
Bulk rutile	DLS	1262 nm±525 nm	NRC (CAN)
Vive nano (coated)	DLS	600 nm PDI 0.5, 200 mg/l in serum containing culture media (sonication)	NRC (CAN)

1.3.2. Crystalline phase

Summary from scientific literature

Reference	Material	Method	Results
Producer information	P25	x-ray diffraction (XRD)	Anatase (88%) and rutile (12%)
Producer information	NM 102	XRD	95% anatase
Producer information	NM 100	XRD	98.7% anatase

Summary of NANOhub entries for Crystalline phase (OECD Materials)

Material	***Method***	***Result***	***Laboratory***
P25	XRD	Anatase (87%) and rutile (13%)	Ministry of KR
P25	XRD	Anatase (83%) and rutile (17%)	NRC (CAN)
NM 105	XRD	Anatase (84 %) and rutile (16 %)	Nanogenotox

Summary of NANOhub entries for Crystalline phase (other TiO_2 materials)

Material	***Method***	***Result***	***Laboratory***
MTI5	XRD	anatase	NRC (CAN)
MTI30	XRD	rutile	NRC (CAN)
NAM5	XRD	anatase	NRC (CAN)
NAM10	XRD	anatase	NRC (CAN)
NAM30	XRD	rutile	NRC (CAN)
NAM10x40	XRD	rutile	NRC (CAN)
Hombitan LW-S	XRD	anatase	NRC (CAN)
Bulk rutile	XRD	rutile	NRC (CAN)

1.3.3. Dustiness

Summary of NANOhub entries for Dustiness (OECD Materials)

Material	***Method***	***Result***	***Laboratory***
NM 100	Vortex shaker dustiness	Respirable dustiness index: 1500 mg/kg	INRS (F) Nanogenotox
NM 101	Rotating drum dustiness	Inhalable dustiness index: 728 ± 10 mg/kg Respirable dustiness index: 24 ± 9 mg/kg	NRCWE (DK) Nanogenotox
NM 101	Vortex shaker dustiness	Respirable dustiness index: 5600 mg/kg	INRS (F) Nanogenotox
NM 102	Rotating drum dustiness	Inhalable dustiness index: 268 ± 39 mg/kg Respirable dustiness index: 15 ± 2 mg/kg	NRCWE (DK) Nanogenotox
NM 102	Vortex shaker dustiness	Respirable dustiness index: 9200 mg/kg	INRS (F) Nanogenotox
NM 104	Rotating drum dustiness	Inhalable dustiness index: 3911 ± 235 mg/kg Respirable dustiness index: 38 ± 7 mg/kg	NRCWE (DK) Nanogenotox
NM 104	Vortex shaker dustiness	Respirable dustiness index: 6400 mg/kg	INRS (F) Nanogenotox
NM 105	Rotating drum dustiness	Inhalable dustiness index: 1020 ± 20 mg/kg Respirable dustiness index: 28 ± 10 mg/kg	NRCWE (DK) Nanogenotox
NM 105	Vortex shaker dustiness	Respirable dustiness index: 11000 mg/kg	INRS (F) Nanogenotox

1.3.4. Average crystallite size

Summary from scientific literature

Reference	Material	Method	Results
Producer information	P25	TEM	19.8nm

Summary of NANOhub entries for Average crystallite size (OECD Materials)

Material	*Method*	*Result*	*Laboratory*
P25	TEM	10.3-41.9 nm (95%), average 26 nm	Ministry of KR
P25	TEM	15 nm	INIA (ESP)
P25	XRD	34.1nm	NRC (CAN)
NM105	TEM	16 nm	INIA (ESP)
NM 105	XRD	Anatase 23.3 ± 19.3 nm/ Rutile 56.9 ± 69.3 nm	NRCWE (DK), IMC-BAS (BG) Nanogenotox
NM 101	TEM	<10 nm	INIA (ESP)
NM 101	XRD	6.9 ± 5.8 nm	NRCWE (DK), IMC-BAS (BG) Nanogenotox
NM 102	XRD	22.5 ± 18.3 nm	NRCWE (DK), IMC-BAS (BG) Nanogenotox
NM 103	TEM	mean 25 nm	INIA (ESP)
NM 103	XRD	22.3 ± 21.5 nm	NRCWE (DK), IMC-BAS (BG)

			Nanogenotox
NM 104	TEM	mean 22 nm	INIA (ESP)
NM 104	XRD	22.9 ± 21.1 nm	NRCWE (DK), IMC-BAS (BG) Nanogenotox
NM 100	TEM	two peaks: 33.5 nm and 148.25 nm	University Graz (AT)
NM 100	SEM	90-230 nm	HAW Hamburg (GER)
NM 100	XRD	56.7 to 100 nm	NRCWE (DK), IMC-BAS (BG) Nanogenotox

Summary of NANOhub entries for Average crystallite size (other TiO_2 materials)

Material	***Method***	***Result***	***Laboratory***
MT-150AW	XRD	17 nm	AIST (JP)
MP-1133	XRD	20 nm	AIST (JP)
MT-100TV	XRD	17 nm	AIST (JP)
JMT 150IB	XRD	17 nm	AIST (JP)
MTI5	XRD	5.9 nm	NRC (CAN)
MTI30	XRD	163.7 nm	NRC (CAN)
NAM5	XRD	13.2 nm	NRC (CAN)
NAM10	XRD	16.2 nm	NRC (CAN)

NAM30	XRD	68.9 nm	NRC (CAN)
NAM10x40	XRD	Needle like; 12.6 nm	NRC (CAN)
Hombitan LW-S	XRD	169.4 nm	NRC (CAN)
Bulk rutile	XRD	185.2 nm	NRC (CAN)
Vive nano (coated)	XRD	1-10 nm	NRC (CAN)

1.3.5. Representative TEM picture(s)

Summary of NANOhub entries for TEM picture (OECD Materials)

Material	***Method***	***Result***	***Laboratory***
P25	High resolution TEM (HRTEM)/TEM	available	BAM (GER)
P25	TEM	available	University Vienna (AT)
P25	TEM	available	INIA (ESP)
NM 105	TEM	available	University Graz (AT)
NM 105	TEM	available	INIA (ESP)
NM 105	TEM	available	IMC-BAS (BG); CODA-CERVA (B) Nanogenotox
NM 101	TEM	available	University Graz

			(AT)
NM 101	TEM	available	University Vienna (AT)
NM 101	TEM	available	INIA (ESP)
NM 101	TEM	available	IMC-BAS (BG); CODA-CERVA (B) Nanogenotox
NM 102	TEM	available	University Graz (AT)
NM 102	TEM	available	IUTA (GER)
NM 102	TEM	available	IMC-BAS (BG); CODA-CERVA (B) Nanogenotox
NM 103	TEM	available	University Graz (AT)
NM 103	TEM	available	IUTA (GER)
NM 103	TEM	available	INIA (ESP)
NM 103	TEM	available	IMC-BAS (BG); CODA-CERVA (B) Nanogenotox
NM 104	TEM	available	University Graz (AT)
NM 104	TEM	available	INIA (ESP)
NM 104	TEM	available	IMC-BAS (BG); CODA-CERVA (B) Nanogenotox

NM 100	TEM	available	University Graz (AT)
NM 100	TEM	available	IMC-BAS (BG); CODA-CERVA (B) Nanogenotox

1.3.6. Particle size distribution – dry and in relevant media

Summary from scientific literature

Reference	**Material**	**Method**	**Results**
Producer information	P25	665/0939 acc to ISO13320	D50=52.2 µm
Producer information	NM 102	DLS, sonication	D50=1 µm

Summary of NANOhub entries for PDF (OECD Materials)

Material	***Method***	***Result***	***Laboratory***
P25	SMPS	Mean: long DMA: 21.3 nm±1 nm STDEV 0.71; nanoDMA: 22.6±1 nm STDEV 0.72; FMPS: 20.5 nm±2.5 nm STDEV 0.75 (atomizer), 158 nm±10 nm STDEV 0.51 (fluidized bed generator), 184 nm ±10 nm STDEV 0.51 (electrospray)	BAM (GER)
P25	TEM	26.1 nm±1.3 nm	Ministry of KR
NM 105	TEM	21 nm±9 nm (CODA-CERVA); 24 nm±5 nm (INRS); 20.5 nm±8.6 nm (IMC-BAS)	IMC-BAS (BG); CODA-CERVA (B) Nanogenotox

1.3.7. Specific surface area

Summary from scientific literature

Reference	Material	Method	Results
Producer information	P25	665/T100 acc to ISO 9277	57 m^2/g (range 35-65 m^2/g)
Producer information	NM 102	BET	85 m^2/g

Summary of NANOhub entries for specific surface area (OECD Materials)

Material	*Method*	*Result*	*Laboratory*
P25	Brunauer-Emmett-Teller-Methode (BET)	55.72 m^2/g	AIST (JP)
P25	BET	57.02 m^2/g	Ministry of KR
P25	BET	60 m^2/g	INIA (ESP)
P25	BET	48.9 m^2/g	NRC (CAN)
NM 105	BET	55 m^2/g	INIA (ESP)
NM 105	BET	46 m^2/g	IMC-BAS (BG) Nanogenotox
NM 105	SAXS	47 ± 2 m^2/g	CEA (F) Nanogenotox
NM 101	BET	289 m^2/g	INIA (ESP)

NM 101	BET	316 m^2/g	IMC-BAS (BG) Nanogenotox
NM 101	SAXS	170 ± 9 m^2/g	CEA (F) Nanogenotox
NM 102	BET	78 m^2/g	IMC-BAS (BG) Nanogenotox
NM 102	SAXS	66 ± 3 m^2/g	CEA (F) Nanogenotox
NM 103	BET	54 m^2/g	INIA (ESP)
NM 103	BET	51 m^2/g	IMC-BAS (BG) Nanogenotox
NM 103	SAXS	51 ± 2 m^2/g	CEA (F) Nanogenotox
NM 104	BET	59 m^2/g	INIA (ESP)
NM 104	BET	56 m^2/g	IMC-BAS (BG) Nanogenotox
NM 104	SAXS	52 ± 2 m^2/g	CEA (F) Nanogenotox
NM 100	BET	9 m^2/g	IMC-BAS (BG) Nanogenotox

Summary of NANOhub entries for specific surface area (other TiO_2 materials)

Material	***Method***	***Result***	***Laboratory***
MT-150AW	ISO 9277	122.9 m^2/g	AIST (JP)
MP-1133	ISO 9277	10.47 m^2/g	AIST (JP)
MT-100TV	ISO 9277	55.98 m^2/g	AIST (JP)
JMT 150IB	ISO 9277	75.63 m^2/g	AIST (JP)
MTI5	BET	280.8 m^2/g	NRC (CAN)
MTI30	BET	10.2 m^2/g	NRC (CAN)
NAM5	BET	125.9 m^2/g	NRC (CAN)
NAM10	BET	102.7 m^2/g	NRC (CAN)
NAM30	BET	24.2 m^2/g	NRC (CAN)
NAM10x40	BET	132.2 m^2/g	NRC (CAN)
Hombitan LW-S	BET	9.87 m^2/g	NRC (CAN)
Bulk rutile	BET	9.0 m^2/g	NRC (CAN)

1.3.8. Zeta potential (surface charge)

Summary from scientific literature

Reference	Material	Method	Main findings
Producer information	P25	665/T200 acc to ISO787-9	pH3.6, pH value of aqueous suspension
Ottofuelling et al. 2011	P25	multi-dimensional testing	Strong influence of DOC, mono-and divalent ions, and pH
von der Kammer et al. 2010	P25	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH
Ottofuelling et al. 2011	NM 101	multi-dimensional testing	Strong influence of DOC, mono-and divalent ions, and pH
von der Kammer et al. 2010	NM 101	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH
Producer information	NM 102		10% aqueous dispersion pH5.8, pH value of aqueous suspension

Summary of NANOhub entries for zeta potential (OECD Materials)

Material	*Method*	*Result*	*Laboratory*
P25	DLS	> +20 mV at pH 5	IUTA (GER)
P25	DLS	IEP at pH 6	Ministry of KR
P25	DLS	-16.3 mV to -25.3 mV (0.01-100mg/l)	INIA (ESP)
P25	ultrasonic spectroscopy	+42 at pH 4.5 IEP 6.9; with 1-3wt%CE64: -33.5mV at pH 7.5 IEP 3.6	BAM (GER)
P25	DLS	-2.7 mV ± 11.6 mV	NRC (CAN)
P25	DLS	-12 mV, 200mg/l in serum containing culture media (sonication)	NRC (CAN)
P25	multi-dimensional	Strong influence of mono-and divalent ions, stabilizing by NOM, pH; clear differences	University Vienna (AT)

	testing	between OECD TiO_2-materials	
P25	DLS	-27 ± 7.8 mV (H2O, pH6.75), -28.7 ± 6.7 mV (M9 Media)	HAW Hamburg (GER)
NM 105	DLS	-31.04 mV to 5.3 mV (0.01-100mg/l)	INIA (ESP)
NM 105	PCS	depends on sonication method, surface treatment and media	University Graz (AT)
NM 105	DLS	Stable suspensions at acidic pH (below pH 4), positive charge, exceeding 30 mV. Negative zeta potentials,lower than -30 mV, observed at high pH values. IEP= 6.6	CEA (F) Nanogenotox
NM 101	DLS	-19.7 mV to -28.3 mV (0.1-100 mg/l)	INIA (ESP)
NM 101	PCS	depends on sonication method, surface treatment and media	University Graz (AT)
NM 101	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH; clear differences between OECD TiO_2-materials	University Vienna (AT)
NM 102	PCS	depends on sonication method, surface treatment and media	University Graz (AT)
NM 102	DLS	> +25 mV at pH 5	IUTA (GER)
NM 102	multi-dimensional testing	not dispersible	University Vienna (AT)
NM 102	DLS	Stable suspensions at acidic pH (below pH 4), positive charge, exceeding 30 mV. Negative zeta potentials, lower than -30 mV, observed at high pH values. IEP= 6	CEA (F) Nanogenotox
NM 103	DLS	-10.2 mV to 18 mV (0.01-50 mg/l)	INIA (ESP)
NM 103	PCS	depends on sonication method, surface treatment and media	University Graz (AT)
NM 103	DLS	> +25 mV at pH 5	IUTA (GER)
NM 103	micro-electrophoresis	>+38 mV at pH 5, IEP 8-9, zeta potential hysteresis depending on pH was determined	IUTA (GER)
NM 103	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH; clear differences between OECD TiO_2-materials	University Vienna (AT)

NM 103	DLS	Stable suspensions at acidic pH (below pH 4), positive charge, exceeding 30 mV. Negative zeta potentials, lower than -30 mV, observed at high pH values. IEP= 8.2	CEA (F) Nanogenotox
NM 104	DLS	-24.7 mV to 10.6 mV (0.01-100mg/l)	INIA (ESP)
NM 104	PCS	depends on sonication method, surface treatment and media	University Graz (AT)
NM 104	micro-electrophoresis	>+38 mV at pH 5, IEP 8-9, zeta potential hysteresis depending on pH was determined	IUTA (GER)
NM 104	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH; clear differences between OECD TiO_2-materials	University Vienna (AT)
NM 104	DLS	Stable suspensions at acidic pH (below pH 4), positive charge, exceeding 30 mV. Negative zeta potentials, lower than -30 mV, observed at high pH values. IEP= 8.2	CEA (F) Nanogenotox
NM 100	PCS	depends on sonication method, surface treatment and media	University Graz (AT)
NM 100	multi-dimensional testing	not dispersible	University Vienna (AT)
NM 100	DLS	-48.42 ± 2.2 mV (H_2O), -28.54 ± 3.4 mV (M9 Media)	HAW Hamburg (GER)

Summary of NANOhub entries for zeta potential (other TiO_2 materials)

Material	***Method***	***Result***	***Laboratory***
Sukgyung	DLS	DW -30.6 ± 5.0 mV; pH6 +acetate ions 3.2 ± 5.8 mV, +phosphate ions -42.6 ± 5.7 mV	Ministry of KR
MTI5	DLS	-8.7 mV ± 8.7 mV	NRC (CAN)
MTI5	DLS	-12 mV, 200 mg/l in serum containing culture media (sonication)	NRC (CAN)
MTI30	DLS	-14.7 mV ± 5.4 mV	NRC (CAN)
NAM5	DLS	-10.1 mV ± 15.3 mV	NRC (CAN)
NAM10	DLS	-10.5 mV ± 11.6 mV	NRC (CAN)

NAM30	DLS	-29.3 mV ±13.8 mV	NRC (CAN)
NAM10x40	DLS	-42.6 mV ±1.5 mV	NRC (CAN)
Hombitan LW-S	DLS	-45.7 mV ±2.2 mV	NRC (CAN)
Hombitan LW-S	DLS	-13mV, 200 mg/l in serum containing culture media (sonication)	NRC (CAN)
Bulk rutile	DLS	-26.7 mV ±10.2 mV	NRC (CAN)
Vive nano (coated)	DLS	-19 mV, 200 mg/l in serum containing culture media (sonication)	NRC (CAN)

1.3.9. Surface chemistry (where appropriate)

Summary of NANOhub entries for surface chemistry (OECD materials)

Material	***Method***	***Result***	***Laboratory***
NM 105	Energy-dispersive X-ray spectroscopy (EDS)	Minor coating of Si (0.07 wt %), Al (0.04 wt %),	IMC-BAS (BG) Nanogenotox
NM 101	EDS	Minor coating of Si (0.29 wt %), Al (0.09 wt %),	IMC-BAS (BG) Nanogenotox
NM 102	EDS	Minor coating of Si (0.08 wt %), Fe (0.07 wt %), Al (0.05 wt %),	IMC-BAS (BG) Nanogenotox
NM 103	Rose Bengal adsorption method	lower hydrophilic surface with a binding constant of K=0.092 ml/mg ± SD 0.020	University Graz (AT)
NM 103	Scanning electron microscopy with Energy-dispersive X-ray spectroscopy (SEM EDX), inductively coupled plasma optical emission spectrometry (ICP-OES)	covered by hydrophobic layer of dimethicone (C2H6OSi)n	IUTA (GER)

NM 103	EDS	Minor coating of, Al (3.43 wt %), Si (0.68 wt %), Fe (0.06 wt %)	IMC-BAS (BG) Nanogenotox
NM 104	Rose Bengal adsorption method	high hydrophilic surface with a binding constant of K=0.045 ml/mg ± SD 0.003	University Graz (AT)
NM 104	SEM EDX	EDX scans of the agglomerates reveal the presence of titanium and aluminium	IUTA (GER)
NM 104	EDS	Minor coating of Al (3.22 wt %), Si (0.18 wt %),	IMC-BAS (BG) Nanogenotox
NM 100	Rose Bengal adsorption method	0.099 ml/mg	University Graz (AT)
NM 100	EDS	Minor coating of Fe (0.49 wt %), Si (0.28 wt %), Al (0.09 wt %)	IMC-BAS (BG) Nanogenotox

1.3.10. Photo-catalytic activity

Summary of NANOhub entries for Photocatalytic activity (OECD materials)

Material	***Method***	***Result***	***Laboratory***
P25	UV-Vis spectr.	Orange II degradation in combination with UV-B exposure	Ministry of KR
P25	HCHO degradation	Degradation of HCHO over time, depending on TiO_2 concentration	Naresuan University (TH)
P25	Electron paramagnetic resonance spectroscopy (EPR)	P25 showed a hydroxyl radical generation with UV irradiation	IUTA (GER)
NM 103	EPR	No hydroxyl radical generation was detected with or without UV irradiation, independent of preparation method	IUTA (GER)
NM 104	EPR	No hydroxyl radical generation was detected with or without UV irradiation, independent of preparation method	IUTA (GER)

Summary of NANOhub entries for Photocatalytic activity (other TiO_2 materials)

Material	*Method*	*Result*	*Laboratory*
Sukgyung	NADH monitoring	Depending on pH, NP-concentration, ion buffer concentration; minimum at pH7	Ministry of KR

1.3.11. Pour density

Summary from scientific literature

Reference	Material	Method	Main findings
Producer information	P25	665/T701 acc to ISO787-11; 665/0702	Tamped density 141g/l; bulk density 107 g/l

Summary of NANOhub entries for pour density (OECD materials)

Material	*Method*	*Result*	*Laboratory*
NM 100	BET	Total pore volume: 0.0324 ml/g	IMC-BAS (BG) Nanogenotox
NM 101	BET	Total pore volume: 0.3190 ml/g	IMC-BAS (BG) Nanogenotox
NM 102	BET	Total pore volume: 0.2996 ml/g	IMC-BAS (BG) Nanogenotox
NM 103	BET	Total pore volume: 0.2616 ml/g	IMC-BAS (BG) Nanogenotox
NM 104	BET	Total pore volume: 0.1935 ml/g	IMC-BAS (BG) Nanogenotox
NM 105	BET	Total pore volume: 0.1937 ml/g	IMC-BAS (BG) Nanogenotox

1.3.12. Porosity

Summary of NANOhub entries for Porosity (OECD materials)

Material	***Method***	***Result***	***Laboratory***
NM 100	BET	Micropore volume: 0.0 ml/g	IMC-BAS (BG) Nanogenotox
NM 101	BET	Micropore volume: 0.00179 ml/g	IMC-BAS (BG) Nanogenotox
NM 102	BET	Micropore volume: 0.00034 ml/g	IMC-BAS (BG) Nanogenotox
NM 103	BET	Micropore volume: 0.0 ml/g	IMC-BAS (BG) Nanogenotox
NM 104	BET	Micropore volume: 0.0 ml/g	IMC-BAS (BG) Nanogenotox
NM 105	BET	Micropore volume: 0.0 ml/g	IMC-BAS (BG) Nanogenotox

1.3.13. Redox potential

Summary of NANOhub entries for Redox potential (OECD materials)

Material	***Method***	***Result***	***Laboratory***
NM 100	OxoDish fluorescent sensor plate for O_2 detection	Drecrease in dO_2 value in Gambles solution and Caco 2 media, The maximum O_2 changes observed for NM-are in the order of 40 µmol/ml, which suggests that the particle reactivity can exceed 1µmol/mg.	NRCWE (DK) Nanogenotox
NM 101	OxoDish fluorescent sensor plate for O_2 detection	Increase in dO_2 in Caco 2 medium only. The maximum O_2 changes observed for NM-are in the order of 40 µmol/ml, which suggests that the particle reactivity can exceed 1µmol/mg.	NRCWE (DK) Nanogenotox
NM 102	OxoDish fluorescent sensor plate for O_2 detection	Increase in dO_2 value in Gambles solution and Caco 2 medium The maximum O_2 changes observed for NM-are in the order of 40 µmol/ml, which suggests that the particle reactivity can exceed 1µmol/mg.	NRCWE (DK) Nanogenotox

NM 103	OxoDish fluorescent sensor plate for O_2 detection	Drecrease in dO_2 value in Gambles solution and Caco 2 medium. No notable reactivity in BSA medium The maximum O_2 changes observed for NM-are in the order of 40 µmol/ml, which suggests that the particle reactivity can exceed 1µmol/mg.	NRCWE (DK) Nanogenotox
NM 104	OxoDish fluorescent sensor plate for O_2 detection	No notable reactivity in BSA medium, low reactivity in Gambles solution and Caco-2 medium. The maximum O_2 changes observed for NM-are in the order of 40 µmol/ml, which suggests that the particle reactivity can exceed 1µmol/mg.	NRCWE (DK) Nanogenotox
NM 105	OxoDish fluorescent sensor plate for O_2 detection	No notable reactivity in BSA medium, low reactivity in Gambles solution and Caco-2 medium The maximum O_2 changes observed for NM-are in the order of 40 µmol/ml, which suggests that the particle reactivity can exceed 1µmol/mg.	NRCWE (DK) Nanogenotox

1.3.14. Radical formation potential (including surface properties)

Summary of NANOhub entries for Radical formation potential (OECD materials)

Material	***Method***	***Result***	***Laboratory***
P25	EPR	hydroxyl radical generation with UV irradiation	IUTA (GER)
NM 103	EPR	no hydroxyl radical generation without UV, no surface reactivity	IUTA (GER)
NM 104	EPR	no hydroxyl radical generation without UV, but a preparation dependent surface reactivity, with no reactivity for low energy and reactivity for a higher energy input	IUTA (GER)

1.3.15. Flammability

Summary of NANOhub entries for Flammability (OECD materials)

Material	***Method***	***Result***	***Laboratory***
P25	EN 14034 Part 1-4. VDI 2263-1	no ignition could be observed, not dust explosible, Burning Class 1	BAM (GER)

1.3.16. Explosiveness

Summary of NANOhub entries for Explosiveness (OECD materials)

Material	*Method*	*Result*	*Laboratory*
P25	EN 14034 Part 1-4, VDI 2263-1	no ignition could be observed, not dust explosible, Burning Class 1	BAM (GER)

1.4. Environmental Fate and Behaviour

1.4.1. Photodegradation

1.4.2. Stability in Water

Summary from scientific literature

Reference	Material	Method	Main findings
Ottofuelling et al. 2011	P25	multi-dimensional testing	Strong influence of DOC, mono-and divalent ions, and pH
von der Kammer et al. 2010	P25	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH
Taurozzi et al. 2011	P25	dispersion protocol	Literature review supporting NIST dispersion protocol
Taurossi et al. 2013	P25	dispersion protocol	Ultrasonic Preparation Protocol
Guiot et al. 2012	NM 105	dispersion protocol	pH Adjusted-BSA Optimized Dispersion Protocol
Ottofuelling et al. 2011	NM 101	multi-dimensional testing	Strong influence of DOC, mono-and divalent ions, and pH
von der Kammer et al. 2010	NM 101	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH
Guiot et al. 2012	NM 102	dispersion protocol	pH Adjusted-BSA Optimized Dispersion Protocol

Guiot et al. 2012	NM 103	dispersion protocol	pH Adjusted-BSA Optimized Dispersion Protocol
Guiot et al. 2012	NM 104	dispersion protocol	pH Adjusted-BSA Optimized Dispersion Protocol

Summary of NANOhub entries for Stability in water (OECD materials)

Material	***Method***	***Results***	***Laboratory***
P25	monitoring HHD	Moderately hard water: no increase or decrease of HHD within 55h	Ministry of KR
P25	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH; clear differences between OECD TiO_2-materials	University Vienna (AT)
P25	dispersion protocol	Ultrasonic Preparation Protocol	US NIST
P25	dispersion protocol	Preparation of TiO_2 dispersion in biological test media for tox assessment	US NIST
P25	literature review	Literature review supporting NIST dispersion protocol	US NIST
P25	dispersion protocol	OECD dispersion protocol	US NIST
P25	dispersion protocol	Preparation of TiO_2 dispersion for tox and env testing	US NIST
P25	dispersion protocol	Preparation of TiO_2 dispersion for testing of environmental fate	IUTA (GER)
P25	Inter-laboratory testing (DLS)	Comparable results between different laboratories, 179-234nm, high reproducibility, low variance	IUTA (GER)
NM 101	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH; clear differences between OECD TiO_2-materials	University Vienna (AT)
NM 102	multi-dimensional testing	not dispersible	University Vienna (AT)
NM 103	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH; clear differences between OECD TiO_2-materials	University Vienna (AT)
NM 103	SEM EDX, ICP-OES	loss of hydrophobic behaviour after wetting with water and after suspension preparation; nearly all of the Dimethicon from the surface was released; 87 % detected in the supernatant; Al_2O_3 coating was not significantly affected; IEP pH 8 – 9 according to Al_2O_3	IUTA (GER)
NM 104	multi-dimensional testing	Strong influence of mono-and divalent ions, stabilizing by NOM, pH; clear differences between OECD TiO_2-materials	University Vienna (AT)
NM 104	SEM EDX, LC MS,	glycerol was released completely; Al_2O_3 coating was not affected; IEP pH 8 – 9 according to Al_2O_3	IUTA (GER)

	enzymatic UV test		
NM 100	multi-dimensional testing	not dispersible	University Vienna (AT)

Summary of NANOhub entries for Stability in water (other TiO_2 materials)

Material	***Method***	***Result***	***Laboratory***
15nm, rutile, polymorph, $Al(OH)_3$ surface layer (Prespers Inc.)	SEM–EDS	45 min of treatment with swimming pool and seawater significantly induced the redistribution of Al/Ti (%), which changed the surface characteristics of particles.	US-EPA Virkutyte et al. 2012

1.4.3. Transport between Environmental Compartments

Summary from scientific literature

Reference	**Material**	**Method**	**Main findings**
Boncagni et al. 2009	P25	Transport in model plume with sediment, column and batch experiment with sediment, 48-72h	High aggregation and deposition of P25 compared to other TiO_2 materials; increased aggregation at acidic pH, partially resuspension at pH 11 or increased flow velocity.
Godinez et al 2011	P25	Aggregation and transport behavior in saturated porous media, 3 h	Less aggregation at pH9 compared to pH7; surfactant reduce aggregate size; retention in column by deposition as key process; surfactant increases mobility in soil column
Battin et al. 2009	P25	Modeling of transport in river; Transportation in model plume, 48h	Travel distance in pure water 10 km downstream; biofilm reduces travel distance by an factor of 2.7; deposition induce accumulation in biofilm
Battin et al. 2009	NM 101	Modeling of transport in river; Transportation in model plume, 48 h	Travel distance in pure water 12 km downstream; biofilm reduces travel distance by an factor of 2.3; deposition induce accumulation in biofilm

Summary of NANOhub entries for Transport between env. compartments (OECD materials)

Material	Method	Results	Laboratory
P25	OECD 106	Not applicable, differentiation between agglomerated and adsorbed particles not possible	IUTA (GER)
P25	OECD 106	absorption increases with increasing TiO_2 concentration	Ministry of KR
P25	OECD 106	Not applicable, differentiation between agglomerated and adsorbed particles not possible	Naresuan University (TH)
P25	OECD 312	pH as dominant parameter; at increasing pH an increasing mobility observed	Ministry of KR
P25	OECD 312	no significant mobility deeper than the upper few cm was determined; with SEM / EDX a transport of isolated agglomerates of the material was detected in nearly all segments.	IUTA (GER)
NM 102	OECD 312	no significant mobility deeper than the upper few cm was determined; with SEM / EDX a transport of isolated agglomerates of the material was detected in nearly all segments.	IUTA (GER)
NM 103	OECD 106	Not applicable, differentiation between agglomerated and adsorbed particles not possible	IUTA (GER)
NM 103	OECD 312	no significant mobility deeper than the upper few cm was determined; with SEM / EDX a transport of isolated agglomerates of the material was detected in nearly all segments.	IUTA (GER)

Summary of NANOhub entries for Transport between env. compartments (other TiO_2 materials)

Material	*Method*	*Result*	*Laboratory*
5 nm bare, polymer-coated	Transport in porous media	bare $nTiO_2$ deposition onto sand surfaces is generally high, it can also be dynamic, with changes in elution behavior over time observed for selected conditions. Experiments could not be conducted with bare $nTiO_2$ in $CaCl_2$ solutions Polymer-coated $nTiO_2$: nearly all of the polymer-coated NPs eluting from the sand packed columns ($NaNO_3$ 100-300 mM) , moderate mobile at low $CaCl_2$ concentration	McGill University (CAN) Petosa et al. 2012

1.4.4. Biodegradation

Summary from scientific literature

Reference	Material	Method	Main findings
Kiser et al. 2009	NM101	Batch absorption 3 h; WWTP-simulation	Increasing sorption at increasing biomass concentration, no linear sorption

		6 d	isotherm, surfactants interfere with elimination; NM observed in effluent
Wang et al. 2012	NM 101	WWTP-simulation 6 d	NM aggregation in feeding solution due to divalent cations, 97% elimination; accumulation in biomass

Summary of NANOhub entries for Biodegradation (OECD materials)

Material	***Method***	***Results***	***Laboratory***
P25	OECD 303A	>95% adsorbed to the activated sludge; 4% in water; overall balance showed gap of 18%	IUTA (GER)
P25	OECD 303	The fate was affected by the exposure time and synthetic sewage. 10 mg/L NP released 0.05 mg/L NP to the effluent in the synthetic sewage condition for 8 h exposure time. The effluent COD was affected by Evonik TiO_2 exposure after 24 hrs.	Ministry of KR

1.4.5. Bioaccumulation

Summary from scientific literature

Reference	**Material**	**Organisms**	**Method**	**Main findings**
Sun et al. 2007	P25	C. carpio	25 d, 10 mg/l	Significant adsorption capacity of TiO_2 nanoparticles for As(V); equilibrium established within 30 min; Freundlich isotherm; As accumulation in fish enhanced by the presence of TiO_2 nanoparticles (BCF 55.6 versus 22.7); high accumulation of As and TiO_2 in intestine, stomach and gills; low accumulation in muscle
Zhu et al. 2010	P25	D. magna, D. rerio	Fish: 14 d uptake contaminated daphnia, 7 d depuration (clean daphnia); feeding:2 h/d	evidence that $nTiO_2$ can transfer from D. magna to D. rerio by dietary exposure; BMF=0.024/0.009 (dietary); BCF(d. rerio)=25.38 (0.1 mg/l); 181.38 (1 mg/l) (water exposure); body burden dietary>water exposure

1.4.6. Other Information on Environmental Fate

2. HUMAN HEALTH HAZARDS

2.1. Effects on Human Health

2.1.1. Toxicokinetics, Metabolism and Distribution

- ***Studies in Animals***

In vitro Studies

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In vivo Studies

Inhalation route

Summary from scientific literature

Reference	Material/ Size	Test Organism (Strain)/ Test System	Method	Exposure/ dose	Main findings
Inhalation route					
Ferin et al. 1992	a. P25 b. 250 nm (Fisher)	Rat (Fisher 344) (male)	1. Inhalation 2. intratracheal instillation	1. ~23 mg/m^3, 6 h/d, 5d/wk for 12 wks 2. 75-1000 µg or 500 µg	Nanoparticles retained longer in lung ($t_{1/2}$ = 501 days vs. $t_{1/2}$ = 174 days) and translocated to interstitium at a higher rate than fine particles.
Bermudez et al. 2004	P25 Mean mass median aerodynamic diameter (MMAD): 1.4 µm)	Rat (CDF (F344)/CrlBR) (female) mouse (B3C3F1/CrlB	Inhalation	0.5, 2.0, 10 mg/m^3 6 h/d, 5h /wk, for 13 wks + 4, 13, 26, 52 weeks p.e. (hamster: 46 weeks)	Alveolar clearance of nanoparticles strongly retarded at highest concentration in rats, less in mice and only marginally in hamsters during postexposure. Post-exposure retention half-times in rats at low, mid and high dose levels were 63, 132, and 395 days, respectively

		R) (female) hamster (Lak: LVG (SYR) BR) (female)			
van Ravenzwaay et al. 2009	a. P25 b. 200 nm (Kronos)	Rat (Wistar) (male)	Short-term inhalation test	a. 100 mg/m^3 b. 250 mg/ m^3 6h/d, for 5d	Particles only detected in lungs and mediastinal lymph nodes. No particles detected in liver, kidney, spleen and basal brain with olfactory bulb (detection limit for Ti 0.5 µg/tissue). 200 nm particles translocated more efficiently, possibly because of massive agglomeration of the nanomaterial.
Creutzenberg et al. 2012	a. P25 (hydrophilic, 21 nm; Evonik) b. T805 (hydrophobic, 21 nm; Evonik)	Rat (Wistar) (male and female)	Intratracheal instillation	0.3 mg/rat (single dose)	Calculated lung burden was 1238 µg/lung (near overload) for P25 and 5760 µg/lung (massive overload) for Bayertitan. Agglomerate size was measured following exposure in the alveolar space and in BAL. Either particle type showed a tendency to increasingly agglomerate over time (1h-28d p.e.) and being internalized, predominantly by alveolar macrophages (AM). P25 agglomerates formed larger and more rapidly agglomerates than T805 after uptake in lungs. De-agglomeration and particle entry into epithelial cells played no significant role under exposure conditions applied.
Eydner et al. 2012	a. P25 (anatase/rutile, pps: 21 nm, MMAD: 0.7 µm) b. Bayertitan (rutile, pps: 0.3 µm, MMAD: 1.1 µm)	Rat (Wistar) (female)	Inhalation (OECD 412, GLP)	6h/d (nose-only) for 21 d a. 10 mg/m^3 b. 45 mg/m^3) Recovery time points: 3, 28, 90 d p.e.	No significant difference in particle deposition at near-overload inhalation conditions in the lung between fine and nanoparticles. The main compartment for particles (agglomerates in case of nanoparticles) in TEM analysis proved to be intracellular in AM, followed by pneumocyte I type cells. Particles were absent from mitochondria or nuclei. A relevant difference in translocation to connective tissue in the lung was not found. However, a single nanoparticle-laden granulocyte was found in the capillary, indicating focal translocation.

Summary of NANOhub entries for Toxikokinetics (Inhalation route)

Material	Test Organism/ System	Method	Exposure/ dose	Main findings	Laboratory
P25	Rat (male)	Intravenously administered (single injection)	1 mg/kg	At 6 h, 94%, 2.0%, 0.17%, 0.023%, 0.014%, and 0.026% of administered TiO_2 was found in the liver, spleen, lung, kidney, heart, and blood, respectively. No translocation to the brain was confirmed at a lower detection limit. In the liver and spleen did not change over 30 days, while that in the lung, kidney, and blood decreased with time. Bioaccumulation potential cannot be judged based on study results.	AIST (JP)
NM 105	Rat (male)	OECD 412, 28 days (6 h/d, 5d/wk); Recovery time points: 3/45/94d post-exposure	3,12, and 48 mg/m^3	Deposition of particle-laden macrophages in the respiratory tract, in lungs mainly in the alveoli with a minor portion in the bronchus associated lymphoid tissue and in the interstitium. Time-dependent translocation of particle-laden macrophages or particles. Dose depending clearance (physiological lung clearance, partial clearance, no clearance). In liver, the detected amounts were generally below the detection limit. However, in some individuals considerable masses were detectable: approx. 16 µg/liver at day 45 and 67 µg/liver at day 94 (both high dose). In brain, the detected amounts of TiO_2 were generally below the detection limit.	Fh-ITEM (GER)
NM 103 (see remark technical dossier)	Rat (male)	OECD 412, 28 days (6 h/d, 5d/wk); Recovery time points: 3/45/94 d post-exposure	3,12, and 48 mg/m^3	Deposition of particle-laden macrophages in the respiratory tract, in lungs mainly in the alveoli with a minor portion in the bronchus associated lymphoid tissue and in the interstitium. Time-dependent translocation of particle-laden macrophages or particles. Dose depending clearance (physiological lung clearance, partial clearance, no clearance). In liver, the detected amounts were generally below the detection limit. In brain, the detected amounts of TiO_2 were generally below the detection limit.	Fh-ITEM (GER)
NM 104 (see remark technical dossier)	Rat (male)	OECD 412, 28 days (6 h/d, 5d/wk); Recovery time points: 3/45/94 d post-exposure	3,12, and 48 mg/m^3	Deposition of particle-laden macrophages in the respiratory tract, in lungs mainly in the alveoli with a minor portion in the bronchus associated lymphoid tissue and in the interstitium. Time-dependent translocation of particle-laden macrophages or particles. Dose depending clearance (physiological lung clearance, partial clearance, no clearance). In liver, the detected amounts were generally below the detection limit. However, in some individuals considerable masses of particulate test items were detectable: approx. 14 µg/liver (the mid dose) and 206 µg/liver (high dose) at day 94. In brain, the detected amounts of TiO_2 test items were generally below the limit of detection.	Fh-ITEM (GER)

Oral route

Summary of NANOhub entries for Toxikokinetics (oral route)

Material	Test Organism / System	Method	Exposure/ dose	Main findings	Laboratory
NM 101	Rat (Wistar) (male and female)	Oral (gavage)	5 consecutive days 10.2-11.4 mg/kg bw (male) and 13.1-15.2 mg/kg bw (female). 5 day cumulative dose: 51-57 mg/kg bw (male) and 65.5-76 mg/kg bw (female)	No evidence for uptake of NM-101. Marginally higher concentrations of Ti in the GI tract compared to control.	NRCWE (DK) Nanogenotox
NM 102	Rat (Wistar) (male and female)	Oral (gavage)	5 consecutive days 10.2-11.4 mg/kg bw (male) and 13.1-15.2 mg/kg bw (female). 5 day cumulative dose: 51-57 mg/kg bw (male) and 65.5-76 mg/kg bw (female)	No evidence for uptake of NM 102. Marginally higher concentrations of Ti in the GI tract compared to control	NRCWE (DK) Nanogenotox
NM 103	Rat (Wistar) (male and female)	Oral (gavage)	5 consecutive days 10.2-11.4 mg/kg bw (male) and 13.1-15.2 mg/kg bw (female). 5 day cumulative dose: 51-57 mg/kg bw (male) and 65.5-76 mg/kg bw (female)	No evidence for uptake of NM-103.	NRCWE (DK) Nanogenotox

NM 104	Rat (Wistar) (male and female)	Oral (gavage)	5 consecutive days 10.2-11.4 mg/kg bw (male) and 13.1-15.2 mg/kg bw (female). 5 day cumulative dose: 51-57 mg/kg bw (male) and 65.5-76 mg/kg bw (female)	No evidence for uptake of NM-104.	NRCWE (DK) Nanogenotox
NM 105	Rat (Wistar) (male and female)	Oral (gavage)	5 consecutive days 10.2-11.4 mg/kg bw (male) and 13.1-15.2 mg/kg bw (female). 5 day cumulative dose: 51-57 mg/kg bw (male) and 65.5-76 mg/kg bw (female)	No evidence for uptake of NM-105.	NRCWE (DK) Nanogenotox

Dermal route

Summary from scientific literature

Reference	Material/ Size	Test Organism (Strain)/ Test System	Method	Exposure/ dose	Main findings
Dermal route					
Gontier et al. 2008	a. P25 b. Eurosolex T-2000 c. Anthelios® XL SPF60	Skin specimens obtained from healthy Human Human grafted skin samples in SCID mouse (Severe Combined Immune-Deficient) Pig (domestic) (gender unspecified)	Topical	2 mg/cm^2 of 5% formulation for 2 h	No penetration of either particle formulation in any skin type beyond stratum corneum as evidenced by high resolution electron and ion microscopy
Wu et al. 2009	a. P25 b. 4, 10, 25,60 90 nm commercial particles varying in crystallinity and surface charge	Mouse (BALB/c, *nu/nu*) (male and female) Pig (domestic) (male)	Topical (semi-occluded) Franz cell	400 µg/cm^2 per day for 60 d (mouse) 30 d exposure (pig ear (5% formulations)	Detection (AAS/TEM) of nanoparticles in a variety of secondary organs in mice including brain (P25 only) implied penetration of viable skin layers and dermal absorption. TiO_2 nanoparticles were detected in the epidermis of porcine skin after 30 d of exposure *in vivo*, whereas diffusion *in vitro* through porcine skin was negative.
Sadrieh et al. 2010	a. P25 b. T-Lite SF (coated; Bayer) c. Tipaque CR-50	Minipig (Yucatan) (female)	Topical (High resolution imaging analysis)	2 mg cream (~ 30 mg/g Ti) /cm^2, 4x per d, 5d/wk for 4 wks	No significant penetration through the intact normal epidermis at prolonged exposure as evidenced by inductively coupled plasma mass spectroscopy and electron microscopy-energy dispersive x-ray analysis.

	(~400 nm; Ishihara)				

Other route

Summary from scientific literature

Reference	**Material/ Size**	**Test Organism (Strain)/ Test System**	**Method**	**Exposure/ dose**	**Main findings**
Other route					
Fabian et al. 2008	P25	Rat (Wistar) (male)	OECD 417 (Intravenous injection)	5 mg/kg	Rapid clearance from blood and even 28 d p.e. detection in liver > spleen > lung > kidney but not in blood, plasma, brain or lymph node by ICP-AES.

Summary of NANOhub entries for Toxikokinetics (other route)

Material	**Test Organism/ System**	**Method**	**Exposure/ dose**	**Main findings**	**Laboratory**
NM 100	Rat (Wistar) (male and female)	Intravenous	Single (day 1) or repeated (on 5 consecutive days) 8.7-9.7 mg/kg bw (male) and 12.4-13.7 mg/kg bw (female) 5 day cumulative dose: 43.5-48.5 mg/kg bw (male) and 62-68.5 mg/kg bw (female	NM 100 is rapidly distributed from the bloodstream to the organs with liver > spleen lung >kidney and remains stored in the body for a period of at least 90 days.	RIVM (NL) Nanogenotox

NM 102	Rat (Wistar) (male and female)	Intravenous	Single (day 1) or repeated (on 5 consecutive days) 8.7-9.7 mg/kg bw (male) and 12.4-13.7 mg/kg bw (female) 5 day cumulative dose: 43.5-48.5 mg/kg bw (male) and 62-68.5 mg/kg bw (female)	NM 102 is rapidly distributed from the bloodstream to the organs with liver > spleen lung >kidney and remains stored in the body for a period of 90 at least.	RIVM (NL) Nanogenotox
NM 103	Rat (Wistar) (male and female)	Intravenous	Single (day 1) or 5 consecutive days 10.2-11.4 mg/kg bw (male) and 13.1-15.2 mg/kg bw (female). 5 day cumulative dose: 51-57 mg/kg bw (male) and 65.5-76 mg/kg bw (female)	NM 103 is rapidly distributed from the bloodstream to the organs with liver > spleen lung >kidney and remains stored in the body for a period of 90 at least.	RIVM (NL) Nanogenotox
NM 104	Rat (Wistar) (male and female)	Intravenous	Single (day 1) or 5 consecutive days 10.2-11.4 mg/kg bw (male) and 13.1-15.2 mg/kg bw (female). 5 day cumulative dose: 51-57 mg/kg bw (male) and 65.5-76 mg/kg bw (female)	NM 104 is rapidly distributed from the bloodstream to the organs with liver > spleen lung >kidney and remains stored in the body for a period of 90 at least.	RIVM (NL) Nanogenotox

NM 105	Rat (Wistar) (male and female)	Intravenous	10.5 mg/kg bw. 5 day cumulative dose: 52.5 mg/kg bw	NM 105 is rapidly distributed from the bloodstream to the organs with liver > spleen >lung > kidney to a lesser extent Its concentration declines between day 6 and 90 after administration in all the organs although level of Ti remains above the control liver and spleen.	IMB-BAS (BG) Nanogenotox

2.1.2. Acute Toxicity

Inhalation

Summary from scientific literature

Reference	**Material/ Size**	**Test Organism (Strain)/ Test System**	**Method**	**Exposure/ dose**	**Main findings**
Acute toxicity					
Besov et al. 2010	8 nm anatase (Hombikat UV 100)	Mouse (Tomsk State University, outbred) (male)	Inhalation	~ 4 g/15 min.	Disturbed and aggressive behavior until 5 h after exposure.

Intratracheal Instillation

Summary from scientific literature

Reference	Material/ Size	Test Organism/ System	Method	Exposure/ dose	Main findings
intracheal instillation					
Driscoll and Maurer 1991	a. 0.02 µm (Degussa; P25?) b. 0.3 µm, Fisher Scientific)	Rat (Fisher 344) (male)	Intratracheal instillation	10 mg/kg	Elevated neutrophil numbers and fibrosis correlated with increased release of TNF-alpha and fibronectin in case of ultrafine TiO_2. In contrast to fine TiO_2, no IL-1 release which was in line with absence of granulamatous response.
Oberdörster et al. 1992	a. P25 b. 250 nm (Fisher)	Rat (Fisher 344) (male)	Intratracheal instillation	65, 107, 200, 500, 1000 µg	P25 showed similar PMN response at much lower mass levels compared to 250 nm particles. Increase in PMN numbers observed at the lowest P25 dose level tested. No correlation with other adverse effects was reported in this experiment.
Ferin et al. 1992	TiO_2 of various sizes (12, 21, 230, and 250 nm) including P25	Rat (Fisher 344) (male)	Intratracheal instillation	500 µg	Increased lung burden with decreasing size accompanied by a transient acute inflammatory response.
Osier et al. 1997	a. P25 b. 250 nm (Fisher)	Rat (Fisher 344) (male)	1. Intratracheal instillation 2. Intratracheal inhalation	1. 500 µg (a) and 750 µg (b) 2. 125 mg/m^3 for 2 h	P25 showed slightly higher acute inflammatory response as indicated by a number of BALF parameters and a major role of MIP-2 (chemotactic factor for PMN). No correlation with other adverse effects was reported. Instillation elicited a higher inflammatory response than inhalation.
Rehn et al. 2003	a. P25 b. T805 (20 nm, hydro-phobic)	Rat (Wistar) (female)	Intratracheal instillation	0.15, 0.3, 0.6, and 1.2 mg (single administration / 3 sampling times at	Low dose instillation with nano-TiO_2 resulted in transient pulmonary inflammation with increased PMN numbers in BALF being the most sensitive parameter.

				days 3, 21, and 90 after instillation)	
Renwick et al. 2004	a. P25 (?) Tioxide)	Rat (Wistar) (male)	Intratracheal instillation	125 or 500 µg	Elevated inflammatory BALF parameters only at high dose and more pronounced in case of P25 together with epithelial damage. An increased chemotactic behaviour of AM isolated from P25-treated rats.
Chen et al. 2006	P25 (?)	Mouse (ICR) (male)	Intratracheal instillation	0.1 or 0.5 mg	Induction of pulmonary emphysema, possibly caused by placenta growth factor PIGF and related inflammatory pathways.
Warheit et al. 2007a	a. P25 ("uf TiO_2") b. "uf-A" (136 nm, rutile) c. "uf-B" (150 nm, rutile) d. fine TiO_2 (380 nm, coated rutile)	Rat (DuPont Haskell Laboratory) (male)	Intratracheal instillation	1 or 5 mg/kg	P25 induced pulmonary inflammation, cytotoxicity cell proliferation and adverse lung effects (not specified further): Ranking of inflammatory response: P25 > fine-sized TiO_2 = uf-A = uf-B. Differences possibly due to crystal structure, inherent pH of the particles, or surface chemical reactivity.
Warheit et al. 2007b	a. P25 ("uf-3") b. "uf-1" (136 nm, rutile) c. "uf-2" (150 nm, rutile) d. "F1" (380 nm, coated rutile)	Rat (Crl:CD (SD) IGS BR) (male)	Intratracheal instillation	1 or 5 mg/kg	Ranking of toxicity: uf-3 > F-1 = uf-1 = uf-2. P25 produced sustainable pulmonary inflammation, cytotoxicity and adverse lung tissue effects. Differences possibly due to crystal structure, inherent pH of the particles, or surface chemical reactivity.
Li et al. 2007	a. 3 nm (synthesized) b. 20 nm (P25?, Shanghai Huijing)	Mouse (Kunming) (male)	Intratracheal instillation	0.4, 4 and 40 mg/kg	3 nm particles did not produce more pulmonary toxicity than the 20 nm particles at any dose level. The pH was identified as an important toxicity trigger.
Grassian et al.	a. 5 nm (anatase)	Mouse (C57Bl/6)	Intranasal	a. 0.1, 0.4, 0.6	Several BALF parameters and histopathology revealed that larger

2007a	b. P25 (?) (anatase/ rutile)	(male)	instillation	mg/ml b. 0.5, 2.0, 3.0 mg/ml	particles were only slightly more toxic.
Sager et al. 2008	a. P25 ("UFTiO_2) b. Fine TiO_2 ("FTiO_2") (rutile, 1 µm, Sigma)	Rat (Fisher 344) (male)	Intratracheal instillation	0.0313, 0.0625 and 0.125 cm^2/cm^2 (0.26, 0.52, 1.04 mg UF TiO_2 and 5.35, 10.7 and 21.41 mg for FTiO_2)	P25 was at least 41 fold more potent than fine TiO2 on a mass dose basis with regard to pulmonary inflammation and lung damage. Normalization to surface area doses revealed the major role of surface area in bringing about toxicity.
Oberdörster 2001	a. P25 b. Fine TiO_2 (250 nm)	Rat (Fisher 344) (gender unspecified)	Intratracheal Instillation (+ LPS priming)	50 µg Priming : 70 endotoxin units LPS	P25 higher inflammatory response (PMN in BALF) compared to fine particles, both in the absence and presence (synergistic effect!) of LPS.
Ahn et al. 2005	0.29 µm (DuPont)	Rat (Sprague-Dawley) (male)	Intratracheal Instillation	4 mg/kg	Induction of goblet hyperplasia, mucin gene expression, and increased IL-13 production in mast cells.
Park et al. (2009)	P25	Mouse (ICR) (gender unspecified)	Intratracheal Instillation	5, 20, 50 mg/kg	Induction of pro-inflammatory cytokines in BALF and blood. Granuloma formation in lung tissue and other elevated pro-inflammatory parameters implied induction of chronic inflammation

Dermal

Oral

Other Routes of Exposure

Summary from scientific literature

Reference	Material/ Size	Test Organism / System	Method	Exposure/ dose	Main findings
Other routes					
Fabian et al. 2008	P25	Rat (wistar) (male)	- Intravenous injection	5 mg/kg	No obvious toxic or adverse health effects. No detectable inflammation or organ toxicity up to 28 d p.e., based on 67 different biomarkers in blood
Moon et al. 2010	P25	Mouse (BALB/c) (male)	Intraperitoneal injection (± LPS priming)	40 mg/kg (Priming: 5mg/kg LPS, i.p.)	P25 induced acute pulmonary inflammatory effects: Increased influx of neutrophils and ROS activity; elevation of proinflammatory cytokines and activation of NF-kappaB pathway. P25 acted synergistically with LPS.

Summary of NANOhub entries for Acute Toxicity

Material	Test Organism/ System	Method	Exposure/ dose	Main findings	Laboratory
Acute toxicity oral					
"Sukgyung" Material identity unclear No characterisatio	Rat (6 f)	OECD 423 / GLP (ATC)	300 and 2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	NIER/ MoE KR (2010)

n; No OECD material					
Acute toxicity inhalative					
"Sukgyung" Material identity unclear No characterisation; No OECD material	Rat (5 m/5f)	OECD 403/GLP	6 h Dosing regimen missing Dose not readable	LC_{50} > 9.93 mg/m^3	NIER/ MoE KR (2011)
NM 105	Rat (male)	Intratracheal installation, 4 wk	1.5 mg/lung	Significant changes in BALF parameter in comparison to control	Fh-ITEM (GER)
NM 101	Rat (male)	Intracheal installation, 4wk	1.5 mg/lung	No significant changes in BALF parameter in comparison to control	Fh-ITEM (GER)
NM 102	Rat (male)	Intratracheal installation, 4 wk	1.5 mg/lung	No significant changes in BALF parameter in comparison to control	Fh-ITEM (GER)
NM 103	Rat (male)	Intratracheal installation, 4 wk	1.5 mg/lung	Significant changes in BALF parameter in comparison to control	Fh-ITEM (GER)
NM 104	Rat (male)	Intratracheal installation, 4 wk	1.5 mg/lung	Significant changes in BALF parameter in comparison to control	Fh-ITEM (GER)
NM 100	Rat (male)	Intratracheal installation, 4 wk	1.5 mg/lung	No significant changes in BALF parameter in comparison to control	Fh-ITEM (GER)
P25	Rat (20 m)	Intratracheal instillation (13 wk follow-up)	1 and 5 mg/kg	Signs of mild inflammatory changes in lung from 3d after instillation (BALF parameters) at 5 mg/kg. The inflammatory response gradually decreased over time, and no granulation or fibril formation was observed.	AIST, JP (2011)
JMT-150IB No OECD material	Rat (20 m)	Intratracheal instillation (13 wk follow-up)	1 and 5 mg/kg	Inflammatory changes observed in rats treated with 5 mg/kg were milder than those observed in the rats treated with the positive control (P25) and gradually decreased over time.	AIST, JP (2011)

MP-1133 No OECD material	Rat (20 m)	Intratracheal instillation (13 wk follow-up)	1 and 5 mg/kg	Inflammatory changes observed in rats treated with 5 mg/kg were comparable to positive control (P25) Low dose effects similar to vehicle control but alveolar macrophages were present even 13 wk post-instillation	AIST, JP (2011)
MT-100TV No OECD material	Rat (20 m)	Intratracheal instillation (13 wk follow-up)	1 and 5 mg/kg	Inflammatory changes observed in rats treated with 5 mg/kg were comparable to positive control (P25). Decrease over time.	AIST, JP (2011)
MT-150AW No OECD material	Rat (20 m)	Intratracheal instillation (13 wk follow-up)	1 and 5 mg/kg	Inflammatory changes observed in rats treated with 5 mg/kg were milder than those observed in the rats treated with the positive control (P25). Low dose effects similar to vehicle control but alveolar macrophages were present even 13 wk post-instillation	AIST, JP (2011)
Acute toxicity dermal					
"Sukgyung" Material identity unclear No material characterisation; No OECD material	Rat (5 m/5f)	OECD 402/GLP	2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	NIER/ MoE KR (2010)

2.1.3. Irritation

- *Skin Irritation*

Studies in Animals

- *Eye Irritation*

Studies in Animals

Summary of NANOhub entries for irritation

Material	**Test Organism/ System**	**Method**	**Exposure/ dose**	**Main findings**	**Laboratory**
Skin irritation					
"Sukgyung" Material identity unclear No material characterisation; No OECD material	Rabbit (3)	OECD 404/GLP	patch No dosing information	Primary dermal irritation index (PDII) 0.0. Neither erythema and eschar formation nor oedema formation. → Not irritating	NIER/ MoE KR (2011)
P25	Rabbit (3 m)	OECD 404/non-GLP	0.5 g, up to 240 h (observation up to 72 h)	Not irritating not corrosive (OECD scoring, PPI; Draize criteria)	AIST, JP (2011)
JMT-150IB	Rabbit	OECD	0.5 g, up to 240 h	Not irritating	AIST, JP (2011)

No OECD material	(3 m)	404/non-GLP	(observation up to 72 h)		
MP-1133 No OECD material	Rabbit (3 m)	OECD 404/non-GLP	0.5 g, up to 240 h (observation up to 72 h)	Not irritating	AIST, JP (2011)
MT-100TV No OECD material	Rabbit (3 m)	OECD 404/non-GLP	0.5 g, up to 240 h (observation up to 72 h)	Not irritating	AIST, JP (2011)
MT-150AW No OECD material	Rabbit (3 m)	OECD 404/non-GLP	0.5 g, up to 240 h (observation up to 72 h)	Not irritating	AIST, JP (2011)
Eye irritation					
"Sukgyung" Material identity unclear No material characterisation; No OECD material	Rabbit (3)	OECD 405/GLP	No dosing information	cornea score 0 → non-irritant	NIER/ MoE KR (2011)
P25	Rabbit (3 m)	OECD 405/non-GLP	0.1 g (1 24 and 72 h)	Minimally irritating : M1 (Kay & Calandra classification)	AIST, JP (2011)
JMT-150IB No OECD material	Rabbit (3 m)	OECD 405/non-GLP	0.1 g (1 24, 48 and 72 h)	Non-irritating: N (Kay & Calandra classification)	AIST, JP (2011)
MP-1133 No OECD material	Rabbit (3 m)	OECD 405/non-GLP	0.1 g (1 24, 48 and 72 h)	Practically non-irritating: PN (Kay & Calandra classification)	AIST, JP (2011)

MT-100TV No OECD material	Rabbit (3 m)	OECD 405/non-GLP	0.1 g (1 24, 48 and 72 h)	Practically non-irritating: PN (Kay & Calandra classification)	AIST, JP (2011)
MT-150AW No OECD material	Rabbit (3 m)	OECD 405/non-GLP	0.1 g (1 24, 48 and 72 h)	Minimally irritating : M1 (Kay & Calandra classification)	AIST, JP (2011)

Respiratory Tract Irritation

Studies in Animals

Studies in Humans

2.1.4. Sensitisation

Skin

Respiratory Tract

Summary of NANOhub entries for sensitisation

Material	**Test Organism/ System**	**Method**	**Exposure/ dose**	**Main findings**	**Laboratory**
Skin irritation					
"Sukgyung" Material identity unclear No characterisation; No OECD material	Guinea pig (20 m)	OECD 406/GLP	Percutaneous, occlusive No dosing information	1/17 exhibited grade 1 erythema → weak sensitizer	NIER/ MoE KR (2011)

Studies in Humans

Skin

Respiratory Tract

2.1.5. Repeated Dose Toxicity

Studies in Animals

Inhalation

Short-term Studies

Summary from scientific literature

Reference	Material/ Size	Test Organism (Strain)/ Test System	Exposure/ dose	Main findings
Short-term exposure				
Ferin et al. 1991	a. ultrafine P25 (20 nm) b. fine 250 nm (Fisher)	Rat (Fisher 344) (male)	a. 25.5 mg/m^3 b. 21.8 mg/m^3 (6 h/d for 10 d)	At comparable mass lung burden, only P25 induced an inflammatory response with increased PMN numbers, which, however, was milder than in case of bolus administration. In contrast to intratracheal instillation there was no enhanced translocation in case of smaller particles even at three times higher final total lung burden in case of inhalation. This was attributed to the effective removal by AM as long as the lungs are not overwhelmed.
van Ravenzwaay et al. 2009	a. P25 b. pigmentary TiO_2 (rutile, 200 nm, Kronos)	Rat (Wistar (strain Crl:WI (Han)) (male)	a. 100 mg/m^3 b. 250 mg/m^3 (6 h/d for 5 d)	Mild and reversible neutrophilic inflammation. Partially reversible activation of lung macrophages according to BAL parameters and histological examination after 14 d post-exposure. Nanoparticle effects were slightly more pronounced.
Ma-Hock et al. 2009	P25	Rat (Wistar (strain Crl:WI (Han)) (male)	0, 2, 10 and 50 mg/m^3 (6 h/d for 5 d)	Dose-dependent inflammatory effects in a number of BAL parameters and cell counts. Lung cell proliferation by BrdU labeling already at 2 mg/cm^3 with incomplete recovery 16 d p.e. Histopathological changes in the lung at 10 mg/cm^3 and above but no systemic effects.
Creutzenberg et al. 2009 [abstract]	a. P25 (anatase/rutile, pps: 21 nm, MMAD: 0.7 µm) b. Bayertitan (rutile, pps: 0.3 µm, MMAD: 1.1 µm)	Rat (Wistar) (gender unspecified)	21 d (6 h/d) nose-only a. 2 and 10 mg/m3 b. 9 and 45 mg/m3) Recovery time points: 3, 28, 90 d p.e.	White blood cells decreased in the high-dose (overload) groups at days 28 and 90 for either particle type and on day 3 for P25 only. TiO_2-inhalation even at overload did not alter levels of PMN in BAL.

Eydner et al. 2012	a. P25 (anatase/rutile, pps: 21 nm, MMAD: 0.7 µm) b. Bayertitan (rutile, pps: 0.3 µm, MMAD: 1.1 µm)	Rat (Wistar) (female)	21 d (6h/d) nose-only a. 10 mg/m3 b. 45 mg/m3) Recovery time points: 3, 28, 90 d p.e. (OECD 412, GLP)	No significant change in BAL cells was found for either particle type. The only BAL parameter altered was β-glucoronidase (used as a marker for phagocytic activity) for both nano and bulk particles.
Creutzenberg et al., 2012	P25 Average primary particle size: 21 nm (MMAD approx. 0.8 µm, GSD: 1.8 µm)	Rat (Wistar) (male and female)	21 d (10 mg/m^3 for 6 h/d (nose-only)	Under exposure conditions used, approx. 1.4 mg P25/lung was retained. Histopathology and BAL resulted in insignificant inflammation after 3 d p.e.
Creutzenberg , 2013	1. UV-Titan M 212 (JRC, NM-103; rutile, silicon-treated, hydrophobic; ppd 20 nm) 2. UV-Titan M 262 (JRC, NM-104, rutile, glycerol-treated, hydrophilic; ppd 20 nm) 3. P25 (JRC, NM-105, anatase/rutile 80:20; untreated, hydrophilic; ppd 22 nm)	Rat (Wistar Crl:WI (Han) male	0, 3, 12, 48 mg/m3(nose-only) for 28 d (6h/d, 5d/wk. Recovery time points :3, 45 and 94 d of recovery) (n=12) (partial OECD TG 412)	No pronounced differences in toxicity between particle types related to histopathology and BAL parameters (LDH, β-glucoronidase, total protein, PMN counts). PMN influx ranking NM-104 > NM 103, NM 105 based on relative strength and incomplete recovery of the inflammatory response of the former compared to NM-105. NOAEL: 3 and 5 mg/m3. Solubility and translocation potential was minimal. Particles were detected primarily in intraalveolar macrophages, in low/mid dose groups also in pneumocytes type I, in high dose groups also as intra-alveolar free particles.

Summary of NANOhub entries for RDT (intratracheal instillation, short-term)

Material	**Test Organism/ System**	**Method**	**Exposure/ dose**	**Main findings**	**Laboratory**
NM 101	Rat (Sprague Dawley) (male)	Intratracheal instillation	3 administrations at 0, 24 and 45 h 1.15; 2.3; 4.6 mg/kg bw/d	Dose-dependent increase in the number of neutrophils in BAL	NRCWE (DK) Nanogenotox
NM 102	Rat (Sprague Dawley) (male)	Intratracheal instillation	3 administrations at 0, 24 and 45 h 1.15; 2.3; 4.6 mg/kg bw/d	Dose-dependent increase in the number of neutrophils in BAL	NRCWE (DK) Nanogenotox
NM 103	Rat (Sprague Dawley) (male)	Intratracheal instillation	3 administrations at 0, 24 and 45 h 1.15; 2.3; 4.6 mg/kg bw/d	Dose-dependent increase in the number of neutrophils in BAL	NRCWE (DK) Nanogenotox
NM 104	Rat (Sprague Dawley) (male)	Intratracheal instillation	3 administrations at 0, 24 and 45 h 1.15; 2.3; 4.6 mg/kg bw/d	Dose-dependent increase in the number of neutrophils in BAL	NRCWE (DK) Nanogenotox
NM 105	Rat (Sprague Dawley) (male)	Intratracheal instillation	3 administrations at 0, 24 and 45 h 1.15; 2.3; 4.6 mg/kg bw/d	Dose-dependent increase in the number of neutrophils in BAL	NRCWE (DK) Nanogenotox

Subacute Studies

Summary of NANOhub entries for RDT (inhalation, subacute)

Material	**Test Organism/ System**	**Method**	**Exposure/ dose**	**Main findings**	**Laboratory**
NM 105	Rat (male)	OECD412, 28days (6 h/d, 5d/wk); Recovery time point at 90 d post-exposure	3,12, and 48 mg/m^3	Dose-dependent increase of lung weight; After recovery the mid dose groups had returned to control levels whereas lungs weights in the high groups were still statistically significant increased; PMN at low dose similar to clean air control but statistically significant at mid and high dose; changes in biochemical parameters of BAL (high dose) in comparison to control	Fh-ITEM (GER)
NM 103	Rat (male)	OECD412, 28days (6 h/d, 5 d/wk); Recovery time point at 90 d post-exposure	3,12, and 48 mg/m^3	Dose-dependent increase of lung weight; After recovery the mid dose groups had returned to control levels whereas lungs weights in the high groups were still statistically significant increased; slight inflammation (10%PMN) at low dose, returned to normal after recovery; mid and high dose: strong and severe PMN levels; changes in biochemical parameters of BAL (mid and high dose) in comparison to control	Fh-ITEM (GER)
NM 104	Rat (male)	OECD412, 28days (6 h/d, 5 d/wk); Recovery time point at 90 d post-exposure	3,12, and 48 mg/m^3	Dose-dependent increase of lung weight; After recovery the mid dose groups had returned to control levels whereas lungs weights in the high groups were still statistically significant increased; slight inflammation (10% PMN) at low dose, remain after recovery (5-8%); mid and high dose: strong and severe PMN levels; changes in biochemical parameters of BAL (mid and high dose) in comparison to control	Fh-ITEM (GER)

Subchronic Studies

Summary from scientific literature

Reference	Material/ Size	Test Organism/ System	Method	Exposure/ dose	Main findings
RDT – inhalation (subchronic)					
Ferin et al. 1992	a. P25 b. 250 nm (Fisher)	Rat (Fisher 344) (male)	Inhalation	~23 mg/m^3, (6 h/d, 5d/wk for 90 d)	The more efficient interstitial translocation of P25 was accompanied by an acute transient inflammatory response as revealed by increased PMN cell numbers in BALF.
Oberdörster et al. 1994a	a. P25 b. 250 nm (Fisher)	Rat (Fisher 344) (male)	Inhalation	a. 23.5 mg/m^3 b. 22.3 mg/m^3 (6 h/d, 5 d/wk for 12 wks)	P25 induced a progressive increase in total cell and PMN numbers (and lavageable protein), which persisted almost a year p.e. Retained (for 7 months) impairment test particle clearance function of alveolar macrophages in case of P25. Histology revealed early fibrotic reactions (reversible) and type II cell hyperplasia in case of P25. Altogether, nanoparticles had a higher pulmonary inflammatory potency than pigment particles which was attributed rather to their relatively larger surface area than to particle volume.
Oberdörster et al. 1994b	a. P25 b. 250 nm (Fisher)	Rat (Fisher 344) (male)	Inhalation	a. 23.5 mg/m^3 b. 22.3 mg/m^3 (6 h/d, 5 d/wk for 12 wks)	At comparable volumetric loading, P25 particles caused greater pulmonary inflammation, penetrated more readily into the interstitium (accumulation in lymph nodes), and led to greater impairment of particle clearance and a higher degree of (mild) fibrosis than pigment particles. An additional surface area-based effector mechanism was hypothesised to the volumetric impairment of AM clearance function.
Baggs et al. 1997	a. P25 b. 250 nm (Fisher)	Rat (Fisher 344) (male)	Inhalation	a. 23.5 mg/m^3 b. 22.3 mg/m^3 (6 h/d, 5 d/wk for 12 wks)	Development of interstitial fibrosis within 6 months (more pronounced in case of P25) that largely returned to control levels after 1 yr p.e.

Bermudez et al. 2004	P25	Rat (CDF (F344)/CrlBR) (female) Mouse (B3C3F1/CrlBR) (female)Hamster (Lak: LVG (SYR) BR) (female)	Inhalation	0.5, 2.0, 10 mg/m^3 (6h/d, 5h /wk, for 13 wks)	Markedly impaired particle clearance from lung and pulmonary inflammatory response in mice and - more severe - in rats but not in hamsters. Only rats showed progressive epithelial changes including metaplasia in the high dose group. Alveolar cell proliferation and histopathological lesions already evident at mid dose level.

Chronic Studies

Summary from scientific literature

Reference	**Material/ Size**	**Test Organism/ System**	**Method**	**Exposure/ dose**	**Main findings**
RDT –inhalation (chronic)					
Creutzenberg et al. 1990;	P25	Rat (Wistar) (female)	Inhalation (whole-body exposure chambers)	7.5 mg/m^3 for 4 months (19 h/d, 5 d/wk), followed by 15 mg/m^3 for 4 months (19 h/d, 5 d/wk), and 10 mg/m^3 for 14 months (19h/d, 5d/wk)	Substantial increase in lung weight over time (peaking at 18 months of exposure) and histopathology indicated pronounced proliferative response of lung tissue. Lung burden after 2 yrs was 39.3 mg indicating massive overload. Tracer (^{85}Sr polystyrene) half-time of ~ 500d indicated collapse of clearance functions.
Muhle et al. 1990	P25	Rat (Wistar) (male and female)	OECD 453 Inhalation	7.2 mg/m^3 for 4.5 months, followed by 14.8 mg/m^3 for the 4 following months and 9.4	Interstitial fibrosis at 12 and 18 months. Lung burden increased by a factor of 4.25 after 22 months of exposure accompanied by disturbed lung function, shallower breathing and altered particle deposition pattern.

				mg/m^3 after 8 months (for a total of 24 months) (95h/wk)	

Dermal

Summary from scientific literature

Reference	Material/ Size	Test Organism/ System	Method	Exposure/ dose	Main findings
RDT – dermal route					
Wu et al. 2009	P25	Mouse (BALB/c, *nu/nu*) (male and female)	Topical (semi-occluded)	400 µg/cm^2 per day, for 60 d	Induction of various tissue damage, most notably in skin and liver accompanied by signs of oxidative stress (elevated superoxide dismutase and malondialdehyde as well as reduced hydroxyproline levels).

Oral

Summary from scientific literature

Reference	Material/ Size	Test Organism/ System	Method	Exposure/ dose	Main findings
RDT – oral route					
Trouiller et al. 2009	P25	Mouse (C57Bl/6Jp^{un}/p^{un}) (males and pregnant	Oral (drinking	500 mg/kg, for 5 d	P25 induced a proinflammatory response in peripheral blood as revealed by altered cytokine mRNA levels.

		dams for *in utero* exposure)	water)		

Summary of NANOhub entries for RDT toxicity (oral)

Material	**Test Organism/ System**	**Method**	**Exposure/ dose**	**Main findings**	**Laboratory**
RDT oral					
"Sukgyung" Material identity unclear No characterisation; no OECD material	Rat (10 m, 10 w per dose)	OECD 408/GLP (90 d RDT)	Dosing information unspecified	NOEL > 1000 mg/kg bw/d (nominal) "Histopathology:" was "yes". Rated as "done" instead of "positive".	NIER/ MoE KR (2012)
NM 105	Rat (male)	Non standard test	1, and 100 µg µg/kg bw/d (once a day for 15 days)	Increased epithelial permeability in jejunum and colon at 1 and 100 µg/ml Enhanced bacterial translocation from gut to mesenteric lymphnode at 100 µg/kg	E Houdeau, F Pierre (INRA Toulouse) M Carrière (CEA Grenoble) (FR)

Other Route

Studies in Humans

Inhalation

Dermal

Oral

2.1.6. Mutagenicity

Studies in Animals

In vitro Studies

Reference	Material/ Size	Test Organism/ System	Method	Exposure/ dose	Main findings
Genotoxicity – in vitro					
Rahman et al. 2002	a. Ultrafine TiO_2 (20 nm, P25?) b. fine TiO_2 (200 nm)	Syrian hamster embryo cell line (SHE cells)	Micronucleus test	1.0 µg/cm^2 for 12 to 72 h	Ultrafine TiO_2 induced weak but significant induction of micronuclei, possibly by disturbed chromosome segregation in mitosis, and apoptosis
Kang et al. 2008b	P25	Human peripheral lymphocytes	1. Alkaline comet assay 2. CBMN	20, 50, or 100 mg/ml (1. for 24 h 2. for 72 h)	Significantly increased micronucleus formation and DNA breakage in a dose-dependent manner. Evidence that ROS activation of specific p53 signalling pathway is involved in apoptosis.
Shi et al. 2009	P25	Human fetal hepatocyte cell line (L-02 cells)	1. Comet assay (alkaline and neutral) 2. Micronucleus test 3. 8-OHdG	0 – 1 µg/ml (for 24h)	P25 was negative in the comet and micronucleus assay but produced 8-OHdG adducts. However, it synergistically increased DDP-induced formation of 8-OHdG adducts, DNA breaks and chromosomal damage.
Barillet et al. 2010	a. P25 b. "TiO_2-CEA" (95% anatase, 12 nm PPS)	Rat kidney proximal cell line (NRK-52E cells)	γ-H2AX foci (immunostaining)	20-200 µg/ml (for 24 h)	P25 did not induce double strand breaks in the H2AX assay. TiO_2-CEA proved positive in the Comet assay showing dose-dependence but no

			Comet assay		clear correlation to ROS production.
Jugan et al. 2012	P25 and other nanoparticles (size range 12 – 140 nm, anatase or rutile).	Human lung carcinoma cell line (A549 cells)	1. Comet assay 2. Micronucleus assays 3. γ -H2AX immunostaining, 4. 8- OHdG analysis, 5. H2-DCFDA, 6. glutathione content, antioxidant enzymes activities	50-200 µg/ml up to 48 h (depending on test)	positive (small and spherical NP) ROS generation Oxidative DNA damage, including single-strand breaks and 8-OHdG, but not double-strand breaks or chromosomal breaks or losses. NPs impaired cell ability to repair damage to DNA.
Gurr et al. 2005	a. HOMBIKAT UV 100 (10 nm, anatase) b. Millenium PC500 (20 nm, anatase) c. Rutile (200 nm) d. Anatase (200 nm)	Human bronchial epithelial cell line (BEAS-2B cells)	1. comet assay (+ enzyme digestion) 2. Micronucleus test	10 µg/ml (for 24 h)	Nano-sized anatase TiO_2 nduced oxidative DNA damage and micronuclei formation in BEAS-2B cells in the absence of photoactivation. However, the treatment with non-nano anatase particles did not induce oxidative stress in the absence of light irradiation. Rutile non-nano sized particles induced hydrogen peroxide and oxidative DNA damage in the absence of light but the non-nano anatase particles did not."

Summary of NANOhub entries for genotoxicity in vitro

Material	**Test Organism/System**	**Method**	**Exposure/dose**	**Main findings**	**Laboratory**
Genotoxicity in vitro					
P25 Sukgyung; Material identity unclear	Salmonella typhimurium TA 1535, TA 1537, TA 98 and TA 100 Escherichia coli	OECD 471 (Ames)	0, 313, 625, 1250, 2500 and 5000 µg/plate (+/- S9)	Negative (precipitation at 5000 µg/plate)	NIER/ MoE KR (2009)

No characterisation	WP2uvrA				
P25 Sukgyung; Material identity unclear No characterisation	Chinese hamster ovary cell line (CHO-K1 cells)	OECD 473 (chromosome aberration)	0, 39.06, 78.13, 156.25 µg/mL for 24 hrs 0, 19.53, 39.06, 78.13 µg/mL for 6 h treatment and 18 h recovery (+S9)	Negative (precipitation >312.5 µg/ml)	NIER/ MoE KR (2011)
P25	Salmonella typhimurium TA 1535, TA 1537, TA 98 and TA 100 Escherichia coli WP2 (+/- S9 mix)	Ames Assay (compatible with OECD 471)	5000, 2500, 1250, 625, and 312.5 µg/plate (+/- S9 mix)	Negative (precipitation > 1250 µg/plate)	AIST, JP (2011)
P25	Chinese hamster Lung fibroblasts (V79 cells)	comet Assay	1, 10, 100 mg/L for 24 and 48h	Positive at 100 mg/L after 24 h	Univ Alberta CA (2012)
Homitan LW-S No OECD material	Chinese hamster Lung fibroblasts (V79 cells)	comet Assay	1, 10, 100 mg/L for 24 and 48 h	Slightly positive at 100 mg/L (not significant compared to control)	Univ Alberta CA (2019
MTI5 No OECD material	Chinese hamster Lung fibroblasts (V79 cells)	comet Assay	1, 10, 100 mg/L for 24 and 48 h	Positive at 100 mg/L after 24 h	Univ Alberta CA (2019
JMT-150IB No OECD	Salmonella typhimurium TA	Ames Assay (compatible	5000, 2500, 1250, 625, and 312.5 µg/plate	Negative	AIST, JP (2011)

material	1535, TA 1537, TA 98 and TA 100 Escherichia coli WP2 (+/- S9 mix)	with OECD 471)	(+/- S9 mix)	(precipitation > 625 µg/plate –S9, > 1250 µg/plate +S9)	
MP-1133 No OECD material	Salmonella typhimurium TA 1535, TA 1537, TA 98 and TA 100 Escherichia coli WP2 (+/- S9 mix)	Ames Assay (compatible with OECD 471)	5000, 2500, 1250, 625, and 312.5 µg/plate (+/- S9 mix)	Negative (precipitation > 625 µg/plate –S9, > 1250 µg/plate +S9)	AIST, JP (2011)
MT-100TV No OECD material	Salmonella typhimurium TA 1535, TA 1537, TA 98 and TA 100 Escherichia coli WP2 (+/- S9 mix)	Ames Assay (compatible with OECD 471)	5000, 2500, 1250, 625, and 312.5 µg/plate (+/- S9 mix)	Negative (precipitation > 625 µg/plate)	AIST, JP (2011)
MT-150AW No OECD material	Salmonella typhimurium TA 1535, TA 1537, TA 98 and TA 100 Escherichia coli WP2 (+/- S9 mix)	Ames Assay (compatible with OECD 471)	5000, 2500, 1250, 625, and 312.5 µg/plate (+/- S9 mix)	Negative (precipitation > 625 µg/plate)	AIST, JP (2011)
NM 100	Human bronchial epithelial cell line (16-HBE cells)	Comet assay	2; 8; 32; 128; 512 µg/ml for 3 h and 24 h	Negative at 3 h Negative at 24 h	BfR (GE) Nanogenotox
NM 102	Human bronchial epithelial cell line (16-HBE cells)	Comet assay	2; 8; 32; 128; 512 µg/ml (0.42 ; 1.67 ; 6.67 ; 26.7 ; 107 µg/cm²) for 3 h and 24 h	Positive at 3 h: dose-dependent increase in the % Tail DNA Negative at 24 h	BfR (GE) Nanogenotox
NM 102	Human bronchial	Micronucleus	41; 51.2; 64 µg/ml for 41	Negative	IPL (F)

	epithelial cell line (16-HBE cells)	assay (OECD guideline 487)	h		Nanogenotox
NM 102	Human bronchial cell line (BEAS-2B cells)	Comet assay	50; 100; 256 µg/ml (10.42 ; 20.83 ; 53.33 µg/cm²) for 3 h and 24 h	Negative at 3 h Negative at 24 h	NIOM (PL) Nanogenotox
NM 102	Human bronchial cell line (BEAS-2B cells)	Comet assay	64; 128; 256 µg/ml (32; 64; 128 µg/cm²) for 24 h	Positive in 5 out 6 experiments	Round robin test Nanogenotox
NM 102	Human bronchial cell line (BEAS-2B cells)	Micronucleus assay (OECD guideline 487	32; 64; 128; 256 µg/ml (16; 32; 64; 128 µg/cm²) for 48 h	Negative	FIOH (FI) Nanogenotox
NM 102	Human bronchial cell line (BEAS-2B cells)	Micronucleus assay (OECD guideline 487	64; 128; 256 µg/ml (32; 64; 128 µg/cm²) for 48 h	Negative in 4 out 6 experiments Equivocal in one experiments Positive in one experiment	Round robin test Nanogenotox
NM 102	Human pulmonary cell line (A549)	Comet assay	50; 100; 256 µg/ml (10.42 ; 20.83 ; 53.33 µg/cm²) for 3 h and 24 h	Positive at 3h: dose-dependent increase in the % Tail DNA significant increase at the 256 µg/ml Negative at 24h:	NIOM (PL) Nanogenotox
NM 102	Human pulmonary cell line (A549 cells)	Micronucleus assay (OECD guideline 487	2; 4; 8; 16; 32; 64; 128; 256; 512 µg/ml (0.4 ; 0.8 ; 1.6 ; 3.2 ; 6.4 ; 12.8 ; 25.6 ; 51.2 ; 102.4 µg/cm²) for 24 h	Negative	RIVM (NL) Nanogenotox
NM 102	Human intestinal cell line (Caco-2 cells)	Comet assay	50; 100; 256 µg/ml (10.42 ; 20.83 ; 53.33 µg/cm²) for 3 h and 24 h	Negative at 3h Positive at 24 h: at 100 and 256 µg/ml	NIOM (PL) Nanogenotox
NM 102	Human intestinal cell line (Caco-2	Comet assay	64; 128; 256 µg/ml (32; 64; 128 µg/cm²) for 24 h	Negative in 3 experiments	Round robin test

	cells)			Positive in 2 experiments	Nanogenotox
NM 102	Human intestinal cell line (Caco-2 cells)	Micronucleus assay (OECD guideline 487	9.5; 28; 85; 128; 256 µg/ml (2.5 ; 7.5 ; 22 ; 34 ; 67 µg/cm²) for 52 h	Negative	Anses (F) Nanogenotox
NM 102	Human intestinal cell line (Caco-2 cells)	Micronucleus assay (OECD guideline 487	64; 128; 256 µg/ml (32; 64; 128 µg/cm²) for 48 h	Negative in 2 experiments Positive in one experiment	Round robin test Nanogenotox
NM 102	Human primary peripheral blood lymphocytes	Micronucleus assay (OECD guideline 487	5; 15; 45; 125; 250 µg/ml for 30 h	Equivocal: increase in the % Tail DNA at one dose	INSA (PT) Nanogenotox
NM 102	Mouse lymphoma cell line (L5178Y TK $^{+/-}$ cells)	In vitro mammalian cell gene mutation tests (OECD Guideline 476)	32; 64; 128; 256/ 312.5; 625; 1250; 2500 µg/ml for 24 h	Negative	IPL (F) Nanogenotox
NM 102	Human keratinocytes cells (NHEK)	Comet assay	15; 33; 65 µg/ml (5; 10; 20 µg/cm²) for 3 h and 24 h	Equivocal at 3 h and 24 h: increase in the % Tail DNA at one dose	IMB-BAS (BG) Nanogenotox
NM 102	Human keratinocytes cells (NHEK)	Micronucleus assay (OECD guideline 487	7.5; 37.5; 75 µg/ml (2.3; 11,5; 23 µg/cm²) for 54 h	Positive at all doses: dose-dependent increase	IMB-BAS (BG) Nanogenotox
NM 102	3D human skin	Comet assay	82; 164; 246 µg/cm² for 3 h and 24 h	Negative at 3 h and 24	BfR (GE) Nanogenotox
NM 103	Human bronchial epithelial cell line (16-HBE cells)	Comet assay	2; 8; 32; 128; 512 µg/ml (0.42 ; 1.67 ; 6.67 ; 26.7 ; 107 µg/cm²) for 3 h and 24 h	Negative at 3 h and 24	BfR (GE) Nanogenotox
NM 103	Human bronchial epithelial cell line	Micronucleus assay (OECD	64; 128; 256 µg/ml for 41 h	Negative	IPL (F) Nanogenotox

	(16-HBE cells)	guideline 487)			
NM 103	Human bronchial cell line (BEAS-2B cells)	Comet assay	50; 100; 256 µg/ml (10.42; 20.83; 53.33 µg/cm²) for 3 h and 24 h	Negative at 3 h and 24	NIOM (PL) Nanogenotox
NM 103	Human bronchial cell line (BEAS-2B cells)	Micronucleus assay (OECD guideline 487)	32; 64; 128; 256 µg/ml (16; 32; 64; 128 µg/cm²) for 48 h	Negative	FIOH (FI) Nanogenotox
NM 103	Human pulmonary cell line (A549 cells)	Comet assay	50; 100; 256 µg/ml (10.42; 20.83; 53.33 µg/cm²) for 3 h and 24 h	Negative at 3 h and 24 h	NIOM (PL) Nanogenotox
NM 103	Human pulmonary cell line (A549 cells)	Micronucleus assay (OECD guideline 487	2; 4; 8; 16; 32; 64; 128; 256; 512 µg/ml 0.4 (0.8; 1.6; 3.2; 6.4; 12.8; 25.6; 51.2; 102.4 µg/cm²) for 24 h	Negative	RIVM (NL) Nanogenotox
NM 103	Human intestinal cell line (Caco-2 cells)	Comet assay	50; 100; 256 µg/ml (10.42; 20.83; 53.33 µg/cm²) for 3 h and 24 h	Negative at 3 h Equivocal at 24 h: Increase at one dose only	NIOM (PL) Nanogenotox
NM 103	Human intestinal cell line (Caco-2 cells)	Micronucleus assay (OECD guideline 487	9.5; 28; 85; 128; 256 µg/ml (2.5; 7.5; 22; 34; 67 µg/cm²) for 52 h	Negative	Anses (F) Nanogenotox
NM 103	Human primary peripheral blood lymphocytes	Micronucleus assay (OECD guideline 487	5; 15; 45; 125; 250 µg/ml for 30 h	Positive: Increase at 5 and 45 µg/ml	INSA (PT) Nanogenotox
NM 103	Mouse lymphoma cell line (L5178Y TK $^{+/-}$ cells)	In vitro mammalian cell gene mutation tests (OECD Guideline 476)	32; 64; 128; 256/ 312.5; 625; 1250; 2500 µg/ml for 24 h	Negative	IPL (F) Nanogenotox
NM 103	Human	Comet assay	15; 33; 65 µg/ml (5; 10;	Equivocal at 3 h and 24 h: increase at one dose only	IMB-BAS

	keratinocytes cells (NHEK cells)		20 µg/cm²) for 3 h and 24 h		(BG) Nanogenotox
NM 103	Human keratinocytes cells (NHEK cells)	Micronucleus assay (OECD guideline 487	7.5; 37.5; 75 µg/ml (2.3; 11.5; 23 µg/cm²) for 54 h	Positive; increase at all doses. Dose-dependent increase	IMB-BAS (BG) Nanogenotox
NM 103	3D human skin	Comet assay	82; 164; 246 µg/cm² for 72 h	Negative	BfR (GE) Nanogenotox
NM 104	Human bronchial epithelial cell line (16-HBE cells)	Comet assay	2; 8; 32; 128; 512 µg/ml (0.42 ; 1.67 ; 6.67 ; 26.7 ; 107 µg/cm²) for 3 h and 24 h	Negative	BfR (GE) Nanogenotox
NM 104	Human bronchial epithelial cell line (16-HBE cells)	Micronucleus assay (OECD guideline 487)	64; 128; 256 µg/ml for 41 h	Negative	IPL (F) Nanogenotox
NM 104	Human bronchial cell line (BEAS-2B cells)	Comet assay	50; 100; 256 µg/ml (10.42; 20.83; 53.33 µg/cm²) for 3 h and 24 h	Negative	NIOM (PL) Nanogenotox
NM 104	Human bronchial cell line (BEAS-2B cells)	Micronucleus assay (OECD guideline 487)	32; 64; 128; 256 µg/ml (16; 32; 64; 128 µg/cm²) for 48 h	Negative	FIOH (FI) Nanogenotox
NM 104	Human pulmonary cell line (A549 cells)	Comet assay	50; 100; 256 µg/ml (10.42; 20.83; 53.33 µg/cm²) for 3 h and 24 h	Negative	NIOM (PL) Nanogenotox
NM 104	Human pulmonary cell line (A549 cells)	Micronucleus assay (OECD guideline 487	2; 4; 8; 16; 32; 64; 128; 256; 512 µg/ml 0.4 (0.8; 1.6; 3.2; 6.4; 12.8; 25.6; 51.2; 102.4 µg/cm²) for 24 h	Negative	RIVM (NL) Nanogenotox
NM 104	Human intestinal cell line (Caco-2 cells)	Comet assay	50; 100; 256 µg/ml (10.42; 20.83; 53.33 µg/cm²) for 3 h and 24 h	Negative at 3 h and 24 h	NIOM (PL) Nanogenotox

NM 104	Human intestinal cell line (Caco-2 cells)	Micronucleus assay (OECD guideline 487	9.5; 28; 85; 128; 256 µg/ml (2.5; 7.5; 22; 34; 67 µg/cm²) for 52 h	Negative	Anses (F) Nanogenotox
NM 104	Human primary peripheral blood lymphocytes	Micronucleus assay (OECD guideline 487	5; 15; 45; 125; 250 µg/ml for 30 h	Positive: Increase at 15 and 45 µg/ml	INSA (PT) Nanogenotox
NM 104	Mouse lymphoma cell line (L5178Y TK $^{+/-}$ cells)	In vitro mammalian cell gene mutation tests (OECD Guideline 476)	32; 64; 128; 256/ 625; 1250; 2500; 5000 µg/ml for 24 h	Negative	IPL (F) Nanogenotox
NM 104	Human keratinocytes cells (NHEK cells)	Comet assay	40; 80; 160 µg/ml (12.5; 25; 50 µg/cm²) for 3 h and 24 h	Equivocal at 3 h and 24 h: increase at one dose only	IMB-BAS (BG) Nanogenotox
NM 104	Human keratinocytes cells (NHEK cells)	Micronucleus assay (OECD guideline 487	17.3; 36.5; 173 µg/ml (5.4; 27; 54 µg/cm²) for 54 h	Positive; increase at all doses. Dose-dependent increase	IMB-BAS (BG) Nanogenotox
NM 104	3D human skin	Comet assay	82; 164; 246 µg/cm² for 72 h	Negative	BfR (GE) Nanogenotox
NM 105	Human bronchial epithelial cell line (16-HBE cells)	Comet assay	2; 8; 32; 128; 512 µg/ml (0.42 ; 1.67 ; 6.67 ; 26.7 ; 107 µg/cm²) for 3 h and 24 h	Negative at 3 h Positive at 24 h increase in % Tail DNA at the highest dose. Dose-dependent increase	BfR (GE) Nanogenotox
NM 105	Human bronchial epithelial cell line (16-HBE cells)	Micronucleus assay (OECD guideline 487)	8; 12; 16 µg/ml for 41 h	Negative	IPL (F) Nanogenotox
NM 105	Human bronchial cell line (BEAS-2B cells)	Comet assay	50; 100; 256 µg/ml (10.42; 20.83; 53.33 µg/cm²) for 3 h and 24 h	Negative	NIOM (PL) Nanogenotox

NM 105	Human bronchial cell line (BEAS-2B cells)	Micronucleus assay (OECD guideline 487)	32; 64; 128; 256 µg/ml (16; 32; 64; 128 µg/cm²) for 48 h	Negative	FIOH (FI) Nanogenotox
NM 105	Human pulmonary cell line (A549 cells)	Comet assay	50; 100; 256 µg/ml (10.42; 20.83; 53.33 µg/cm²) for 3 h and 24 h	Negative	NIOM (PL) Nanogenotox
NM 105	Human pulmonary cell line (A549 cells)	Micronucleus assay (OECD guideline 487	2; 4; 8; 16; 32; 64; 128; 256; 512 µg/ml 0.4 (0.8; 1.6; 3.2; 6.4; 12.8; 25.6; 51.2; 102.4 µg/cm²) for 24 h	Negative	RIVM (NL) Nanogenotox
NM 105	Human intestinal cell line (Caco-2 cells)	Comet assay	50; 100; 256 µg/ml (10.42; 20.83; 53.33 µg/cm²) for 3 h and 24 h	Negative at 3 h Positive at 24 h: increase in % Tail DNA at 100 and 256 µg/ml. Dose-dependent increase	NIOM (PL) Nanogenotox
NM 105	Human intestinal cell line (Caco-2 cells)	Micronucleus assay (OECD guideline 487	9.5; 28; 85; 128; 256 µg/ml (2.5; 7.5; 22; 34; 67 µg/cm²) for 52 h	Negative	Anses (F) Nanogenotox
NM 105	Human primary peripheral blood lymphocytes	Micronucleus assay (OECD guideline 487	5; 15; 45; 125; 250 µg/ml for 30 h	Negative	INSA (PT) Nanogenotox
NM 105	Mouse lymphoma cell line (L5178Y TK $^{+/-}$ cells)	In vitro mammalian cell gene mutation tests (OECD Guideline 476)	32; 64; 128; 256/ 625; 1250; 2500; 5000 µg/ml for 24 h	Negative	IPL (F) Nanogenotox
NM 105	Human keratinocytes cells (NHEK cells)	Comet assay	15; 33; 65 µg/ml (5; 10; 20 µg/cm²) for 3 h and 24 h	Equivocal at 3 h and 24 h: increase at one dose only	IMB-BAS (BG) Nanogenotox
NM 105	Human keratinocytes cells	Micronucleus assay (OECD	6.7; 33.5; 67 µg/ml for 54 h	Positive; increase at all doses. Dose-dependent increase	IMB-BAS (BG)

	(NHEK cells)	guideline 487			Nanogenotox
NM 105	3D human skin	Comet assay	82; 164; 246 µg/cm² for 72 h	Negative	BfR (GE) Nanogenotox

Photogenotoxicity

Summary from scientific literature

Reference	**Material/ Size**	**Test Organism/ System**	**Method**	**Exposure/ dose**	**Main findings**
Photogenotoxicity					
Linnainmaa et al. 1997	1. P25 2. UV Titan M160 (20 nm, rutile, coated) 3. Pigmentary TiO_2 (anatase, 170 nm, Kemira)	Rat Liver immortal Epithelial cells (RLE cells)	CBMN	5, 10 and 20 µg/cm^2 for 20 h	Negative for single or combined treatment, irrespective of absence or presence of UV irradiation (366 nm, 5 min).
Nakagawa et al. 1997	P25	1. and 2. Mouse lymphoma cell line (L5178Y TK $^{+/-}$ cells) 3. Chinese hamster lung cell line (CHL/IU cells) 4. Salmonella typhimurium	1. Alkaline comet assay (SCG assay) 2. Mammalian cell mutation assay 3. Chromosome aberration assay 4. Ames test	1. 3.1 - 800 µg/ml for 24h 2. 250 – 2000 µg/ml 3. 0.78 – 50 µg/ml (-UV/vis) and 25 – 800 µg/ml (+UV/vis) (for 24h) 3. 5000 - 40000 µg/ml (for 48h)	No or only weak genotoxicity in the dark but significant chromosome aberrations upon UV/vis irradiation following industry standard protocol. The mutagenic assays were negative, indicating that photogenotoxic potential is rather clastogenic.
Theogaraj et	P25 (?) plus 7 other	Chinese hamster ovary cell	Chromosome	800 – 5000 µg/ml (for	UV-irradiated cells (750mJ/cm^2)

al. 2007	different TiO_2 particle types of different shape, modification and crystallinity	line (CHO cells)	aberration assay	3h + 17 h recovery, - S9 mix)	showed no photogenotoxicity with either particle type at any concentration.
Gerloff et al. 2009	a. P25 b. Anatase, modified, < 10 nm (Sigma) c. Anatase, 40-300 nm (Aldrich)	Human intestinal cell line (Caco-2 cells)	Fpg-comet assay	20 µg/cm^2	Increased DNA damage as well as significant oxidative damage only upon ambient light irradiation. No relationship between particle surface area and DNA damage.
SCCNFP 2000	UV TITAN M 212, rutile, 20 nm, coated (Kemira)	Salmonella typhimurium and Escherichia coli	Ames test	Doses unspecified	negative
SCCNFP 2000	UV TITAN M 262, rutile, 20 nm, coated (Kemira)	Salmonella typhimurium and Escherichia coli	Ames test	Doses unspecified	negative
Rehn et al. 2003	a.. P25 b. T805, 20 nm surface-silanised (Degussa)	Rat (Wistar) (female)	Intratracheal instillation (8-OHdG) (single administration / 3 sampling times at days 3, 21, and 90 after instillation)	1.25 mg/rat	Immunohistochemistry of lung tissue did not reveal ROS-dependent 8-OHdG adduct formation 90 d p.e.

In vivo Studies

Summary from scientific literature

Reference	**Material/ Size**	**Test Organism/ System**	**Method**	**Exposure/ dose**	**Main findings**
Genotoxicity – in vivo					
Gallagher et al. 1994	P 25	Rat (Wistar) (female)	Inhalation (^{32}P-post-labelling	10.4 mg/m^3 (2 mo, 6 mo, for 2 yrs)	Formation of a specific (putative I-compound) adduct in peripheral lung tissue DNA after 2 yrs of exposure.

			assay)		
Rehn et al. 2003	a. P25 b. T805, 20 nm surface-silanised (Degussa)	Rat (Wistar) (female)	Intratracheal instillation (8-OHdG) (single administration / 3 sampling times at days 3, 21, and 90 after instillation)	1.25 mg/rat	Immunohistochemistry of lung tissue did not reveal ROS-dependent 8-OHdG adduct formation 90 d p.e.
Trouiller et al. 2009	P25	Mouse (C57Bl/6Jp^{un}/p^{un}) (males and pregnant dams for *in utero* exposure)	Oral administration 1. In vivo DNA deletion transgenic mouse system 2. Alkaline comet assay (peripheral blood) 3. γ-H2AX assay (bone marrow cells) 4. Micronucleus assay) 5. 8-OHdG frequency (liver)	0-500 mg/kg (5 d)	P25 induced 8-OHdG, micronuclei, DNA deletions, and γ-H2AX foci. Most assays positive at 500 mg/kg only. γ-H2AX foci increased dose-dependently. Systemic oxidative genotoxicity was assumed as underlying mechanism (but bioavailability of Ti not measured). No positive control.

Summary of NANOhub entries for genotoxicity in vivo

Material	**Test Organism/System**	**Method**	**Exposure/dose**	**Main findings**	**Laboratory**
P25?	Mouse (6m/dose)	OECD 474 (RBC micronucleus)	500, 1000 and 2000 mg/kg body weight	negative	NIER/ MoE KR (2011)
NM 101	Rat (Sprague Dawley) (male)	Intratracheal instillation 1- Comet	1 administration at 0, 24 and 45 h 1.15, 2.3,	1- Negative in Lung, BAL fluid, Liver, Kidney, Spleen 2- Negative	NRCWE (DK) Nanogenotox

		assay 2- Micronucleus assay in bone marrow (OECD guideline 474)	4.6 mg/kg bw		
NM 102	Rat (Sprague Dawley) (male)	Intratracheal instillation 1- Comet assay 2- Micronucleus assay in bone marrow (OECD guideline 474)	1 administration at 0, 24 and 45 h 1.15, 2.3, 4.6 mg/kg bw	1- Negative in Lung, BAL fluid, Liver, Kidney, Spleen 2- Negative	NRCWE (DK) Nanogenotox
NM 102	Rat (Wistar) (male)	Oral 1- Comet assay 2- Micronucleus assay in bone marrow (OECD guideline 474)	1 administration at 0, 24 and 45 h 6.5, 13.5, 26 mg/kg bw	1- Negative in Intestine, Blood, Bone marrow, Liver, Kidney - Positive in Spleen and Colon 2- Negative	IMB-BAS (BG) Nanogenotox
NM 102	Mouse (C57Bl/6 pUR288 transgenic) (male)	Intravenous 1- Comet assay 2- Micronucleus assay in bone marrow (OECD	10 and 15 mg/kg bw 1 administration per day for 2 days Sacrifice 28 days later	1- Negative in liver and spleen 2- Negative 3- Negative	INSA (PT) Nanogenotox

		guideline 474) 3- Transgenic Rodent Gene Mutation Assays (OECD Guideline 488)			
NM 103	Rat (Sprague Dawley) (male)	Intratracheal instillation 1- Comet assay 2- Micronucleus assay in bone marrow (OECD guideline 474)	1 administration at 0, 24 and 45 h 1.15, 2.3, 4.6 mg/kg	1- Negative in Lung, BAL fluid, Liver, Kidney, Spleen 2- Negative	NRCWE (DK) Nanogenotox
NM 103	Rat (Wistar) (male)	Oral 1- Comet assay 2- Micronucleus assay in bone marrow (OECD guideline 474)	1 administration at 0, 24 and 45 h 6.5, 13.5, 26 mg/kg bw	1- Negative in colon, blood, bone marrow, spleen, liver, kidney - Equivocal in spleen - Positive in intestine 2- Negative	IMB-BAS (BG) Nanogenotox
NM 103	Rat (Wistar) (male and female)	Intravenous Micronucleus assay in bone marrow (OECD guideline 474)	1 administration per day for 5 days 8.7-9.7 mg/kg bw (Male); 12.4-13.7 mg/kg bw (Female)	Negative	IMB-BAS (BG) Nanogenotox

NM 104	Rat (Sprague Dawley) (male)	Intratracheal instillation 1- Comet assay 2- Micronucleus assay in bone marrow (OECD guideline 474)	1 administration at 0, 24 and 45 h 1.15, 2.3, 4.6 mg/kg	1- Negative in Lung, BAL fluid, Liver, Kidney, Spleen 2- Negative	NRCWE (DK) Nanogenotox
NM 104	Rat (Wistar) (male)	Oral 1- Comet assay 2- Micronucleus assay in bone marrow (OECD guideline 474)	1 administration at 0, 24 and 45 h 6.5, 13.5, 26 mg/kg bw	1- Negative in intestine, colon, blood, liver, kidney - Positive in spleen and bone marrow 2- Negative	IMB-BAS (BG) Nanogenotox
NM 104	Rat (Wistar) (male and female)	Intravenous Micronucleus assay in bone marrow (OECD guideline 474)	1 administration per day for 5 days 8.7-9.7 mg/kg bw (Male); 12.4-13.7 mg/kg bw (Female)	Negative	IMB-BAS (BG) Nanogenotox
NM 105	Rat (Sprague Dawley) (male)	Intratracheal instillation 1- Comet assay 2- Micronucleus assay in bone marrow (OECD	1 administration at 0, 24 and 45 h 1.15, 2.3, 4.6 mg/kg	1- Negative in Lung, BAL fluid, Liver, Kidney, Spleen 2- Negative	NRCWE (DK) Nanogenotox

		guideline 474)			
NM 105	Rat (Wistar) (male)	Oral 1- Comet assay 2- Micronucleus assay in bone marrow (OECD guideline 474)	1 administration at 0, 24 and 45 h 6.5, 13.5, 26 mg/kg bw	1- Negative in intestine, blood, bone marrow, liver, kidney - Positive in colon and spleen	IMB-BAS (BG) Nanogenotox

2.1.7. Carcinogenicity

In vitro Studies

In vivo Studies in Animals

Summary from scientific literature

Reference	**Material/ Size**	**Test Organism/ System**	**Method**	**Exposure/ dose**	**Main findings**
Heinrich et al., 1995	P25	Rat (Wistar) (female) Mouse (NMRI and C57BL/6N) (female)		7.2 mg/m^3 for 4 months, 14.8 mg/m^3 for 8 mo, 9.4 mg/m^3 for 16 (5.5) mo.	Rats but not mice showed increased P25-induced tumor incidence after 18/24 months and accumulating pulmonary overload. Histopathology revealed a spectrum of benign and malignant (squamous cell carcinomas and adenocarcinomas) tumors.
Pott and Roller 2005	1. P25 2. Anatase, 0.2 µm (Sigma)	Rat (Wistar) (female)	Multiple intratracheal instillations	1. 5 x 3 mg 2. 5 x 6 mg 3. 10 x 6 mg (each regime over a	Tumor incidences for P25 (1. 52%, 2. 67%, 3. 70%) were significantly higher than for micron-sized TiO_2. Rapid development of broad spectrum of benign and malignant tumors at instant overload conditions. Authors postulated a linear dose-response relationship.

				period of 30 mo)	

2.1.8. Toxicity for Reproduction

Studies in Animals

Effects on Fertility

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Developmental Toxicity

Summary from scientific literature

Reference	**Material/ Size**	**Test Organism/ System**	**Method**	**Exposure/ dose**	**Main findings**
Development					
Scuri et al. 2010	P25	Rat (Fischer 344) (female)	Inhalation	12 mg/m^3; 5.6 h/d for 3 d	Age-dependent upregulation in the expression of lung neurotrophins associated with increased airway responsiveness in neonates and weanlings but not in adults.

2.1.9. Specific Investigations

Immunotoxicity

Summary from scientific literature

Reference	**Material / Size**	**Test Organism/ System**	**Method**	**Exposure/ dose**	**Main findings**
Park et al. 2009	P25	Mouse (ICR) (gender unspecified)	Intratracheal Instillation	5, 20, 50 mg/kg	Dose-dependent induction of proinflammatory as well as Th1-type and Th2-type cytokine. B-cell proliferation in spleen and blood and increased IgE in BALF. Granuloma formation and expression of MIP-2 and MCP-1 in alveolar tissue. Microarray analysis revealed increased expression of MHC-1 class genes. It was concluded that P25 induced chronic inflammation in mice
Gustafsson et al. 2011	P25	Rat (Dark Agouti) (male)	Intratracheal instillation	1, 5, and 7.5 mg/kg	Induction of long-lasting lymphocyte response after a transient innate immune activation of eosinophils, neutrophils, dendritic cells, and NK cells

Neurotoxicity

Summary from scientific literature

Reference	Material/ Size	Test Organism/ System	Method	Exposure/ dose	Main findings
Wang et al. 2007c	a. rutile, 25 nm (Dayang) b. rutile, 80 nm (Dayang) c. fine anatase, 155 nm (Zhonglian)	Mouse (CD-1 (ICR)) (gender unspecified)	Nasal inhalation (instillation?)	10 µl TiO_2 suspension (0.1 g/ml) every 2 d for 1 mo.	Microbeam SRXRF mapping techniques revealed that TiO_2 particles of different size and crystallinity translocated to the olfactory bulb via primary olfactory neurons, fine-sized particles showing wider distribution. The presence of particles affected the micro-distribution of Fe, Cu, and Zn in the olfactory bulb.
Shin et al. 2010	a. P25 b. Rutile, 1 µm (Sigma)	Mouse (C57BL/6) (male)	Intraperitoneal injection	1 mg/mouse (Pre-treament with 5mg/kg LPS, i.p.)	Elevated expression of proinflammatory cytokines (IL-1beta, TNF-alpha), increased ROS levels and activated microglia 24 h after LPS challenge in TiO_2-treated mouse brains. P25 had no effect w/o LPS pre-treatment. The cytokine response was lower for fine TiO_2.

Cardiovascular Toxicity

Summary from scientific literature

Reference	Material/ Size	Test Organism/ System	Method	Exposure/ dose	Main findings
Nurkiewicz et al., 2008	a. P25 b. 1 µm (Sigma)	Rat (Sprague_Dawley) (male)	Short-term inhalation	1.5 – 16 mg/m^3 (240 – 720 min)	Intravital analysis of the exteriorized spinotrapezius muscle together with functional tests and histopathology revealed that brief inhalative exposure to sub-inflammatory doses of P25 produced dose-dependent effects on vasodilation of systemic arterioles. These were more pronounced than with fine particles at equivalent pulmonary loads.

Nurkiewicz et al., 2009	a. P25 b. <5 µm (Sigma)	Rat (Sprague_Dawley) (male)	Short-term inhalation	1.5 – 16 mg/m^3 (240 – 720 min)	Nanoparticle exposure at doses which induce microvascular dysfunction also decreases NO bioavailability by at least two functionally distinct mechanisms. The mechanisms involved appeared to be similar between fine- and nanosized particles but the effective dose for nanoparticles was more than six times lower.
LeBlanc et al. 2009	P25	Rat (Sprague_Dawley) (male)	Short-term inhalation	6 mg/m^3 for 240 min	P25 inhalation also interfered with coronary microvascular function: spontaneous tone was increased and endothelium-dependent vasodilation in subepicardial arterioles was impaired, likely involving altered microvascular permeability.
LeBlanc et al. 2010	P25	Rat (Sprague_Dawley) (male)	Short-term inhalation	6 mg/m^3 for 240 min	Impaired endothelium-dependent vasoreactivity in coronary arterioles induced by P25 exposure is associated with ROS increases in the microvascular wall and an altered prostanoid formation.

Phototoxicity

Summary from scientific literature

Reference	Material/ Size	Test Organism/ System	Method	Exposure/ dose	Main findings
Cai et al. 1992	P25	Human Cervix carcinoma cell line (HeLa cells)	1. Cytotoxicity (Colony forming assay) 2. Antitumor effect in vivo	12–120 µg/ml UV irradiation: 10 min (500 W Hg lamp)	Dose-dependent cytotoxicity in the presence of UV-light, involving ROS that possibly interfere with mitochondrial electron transport chain. Photoexcited particles also suppressed the growth of HeLa cells implanted in nude mice
Sakai et al. 1994	P25	Human Bladder tumor cell line (T24 cells)	Cytotoxicity (Colony forming assay)	100 µg/ml UV irradiation: 4-6 min (150 W Xenon lamp)	Fluorescence indicator studies suggested that cell death induced by photo-excited P25 is associated with prior increase in cell membrane permeability for Ca^{2+}.

Lu et al. 2008	a. P25 (Degussa, ~21 nm) b. anatase ("HR3", 5-10 nm; Zhejiang Hongsheng) c. rutile ("DJ3", 50 nm; Zhejiang Hongsheng)	1. cell-free 2. Mouse skin homogenates	Western blotting	Reaction mixture: BSA (0.5 mg/ml), $NaNO_2$ (0.25–1.0 mM), and suspended TiO_2 (0.2–3.0 mg/ml) were mixed sufficiently in 0.1 M phosphate buffered saline (PBS) at pH 7.0. UV light illumination using a GYZ220-230V 250 W lamp (Philips) in a distance of 30 cm for 8 h.	P25 and anatase showed a high photocatalytic activity regarding to protein tyrosine phosphorylation, both in a reaction mixture and in skin homogenate, whereas rutile photocatalytic activity was low.
Sanders et al. 2011	22 nm anatase/rutile 25 nm anatase 31 nm anatase/rutile (P25) 59 nm anatase/rutile 142 nm anatase 214 nm rutile	Human retinal pigment epithelial cell line (ARPE-19 cells)	Cell viability (PI) Flow cytometry (ROS: mitosox fluorescence) Thiobarbituric acid reactive substance (TBARS) assay (nanoparticle reactivity)	0, 0.3, 1, 3, 10, 30, or 100 µg/ml for 24 UVA: 2 hrs, 7.53 J/cm^2	UVA lowered cell viability and increased ROS generation. The 25 nm anatase and 31 nm anatase/rutile were the most phototoxic (LC_{50} with UVA < 5 µg/ml), while the 142 nm anatase and 214 nm rutile were the least phototoxic. Relative potency of the six samples: smaller particles being more toxic; larger surface areas being more toxic; particles generating more ROS being more toxic.

Toxicity in vitro

Summary from scientific literature

Reference	Material/ Size	Test Organism/ System	Method	Exposure/ dose	Main findings
Renwick et al. 2001	a. "UTiO$_2$", 29 nm (Degussa) (P25?) b. fine TiO$_2$, 250 nm (Tioxide)	Mouse alveolar macrophage cell line (J774.2,MΦ cells)	Phagocytic activity	0.0975– 0.78 µg/mm^2 for 8 h	Dose-dependent impairment of indicator bead phagocytosis. Nanoparticles had a slightly more inhibitory effect.
Xia et al. 2006	P25	Mouse macrophage cell line (RAW 264.7 cells)	ROS production (fluorescence analysis)	10 µg/ml (4 h-16 h)	P25 was capable of ROS generation in a cell-free system but incapable of doing so in RAW 264.7 cells, despite effective particle uptake.
Kang et al. 2008a	a. P25 b. Fine TiO$_2$, 1 µm (Sigma)	Mouse macrophage cell line (RAW 264.7 cells)	ROS production (fluorescence analysis)	0.5–100 µg/ml (4-24 h)	P25 enhanced intracellular ROS generation to a greater extent than fine TiO$_2$. P25 induced ERK1/2 activation, and enhanced secretion of proinflammatory TNF-∝ and MIP-2 in a concentration-dependent manner.
Han et al. 2008	1. P25	Mouse fibroblastic cell line (L929 cells)	1. Cell proliferation (MTT assay) 2. Apoptosis (Propidium iodide)	50, 100, 200 µg/ml (24-72 h)	P25 (as well as several other TiO$_2$ anatase or rutile nanoparticles of 20-100 nm) had no effect on cell proliferation or apoptosis.
Komatsu et al. 2008	Anatase TiO$_2$, 25-70 nm (Aldrich)	Mouse Leydig cell line (TM3 cells)	Cell proliferation and function	100 µg/ml (24 h)	Inhibition of viability and a transiently reduced proliferation but no direct effect on the induction of oxidative stress or synthesis of testosterone.
Gerloff et al. 2009	P25	Human intestinal cell line (Caco-2 cells)	Cytotoxicity (LDH and WST-1 assay)	1.25, 5, 20 and 80 mg/cm^2 (4 and 24 h)	Dose-dependent cytotoxicity observed with LDH (disturbed membrane integrity) and WST-1 (disturbed metabolic activity).

VanWinkle et al. 2009	nano-TiO_2, ~ 25 nm (Degussa; P25?)	Rat Type I-like alveolar epithelial cells (R3-1 cells)	1. Cellular uptake (TEM/EDS) 2. ROS generation (Amplex Red assay)	1. 1.2 µg/cm^2 (24 /48h) 2. 0.4 µg/cm^2 (20 min)	Particle uptake and subsequent localisation in cytoplasm, mitochondria and lysosomes but no increased intracellular H_2O_2 production or ROS-induced cell death.
Zhao et al. 2009	a. P25 b. Rutile, > 5 µm (Sigma)	Mouse epidermal cell line (JB6 cells)	Apoptosis (MTT assay, YOPRO-1 iodide staining, Western blot analysis)	0.1-20 µg/cm^2 (24 h)	P25 more potent in inducing apoptosis than fine particles. Evidence was presented that the apoptotic pathway involved caspase-8/Bid and intrinsic mitochondrial pathways as well as mitochondrial membrane injury.
Barillet et al. 2010	P25	Rat kidney cell line (NRK-52E cells)	1. Cell viability (MTT and LDH assay) 2. ROS production (FDA fluorescence assay)	1. 0.25-100 µg/ml (48 h) 2. 50, 100, 200 µg/ml (24 h)	Dose-dependent increase of cell mortality and intracellular ROS generation.
Simon et al. 2010	P25 (fluorescent dye-modified and native)	Human Primary foreskin keratinocytes	1. Cell proliferation 2. Cytotoxicity (apoptosis) 3. Intracellular Ca^{2+}-homeostasis (high-resolution imaging analysis)	1. 0.2, 2, 20 µg/cm^2 (8d) 2. 2 µg/cm^2 (24 h)	Internalization of P25 induced an increase in intracellular Ca^{2+}, as well as a dose-dependent decrease in cell proliferation, actin reorganization and keratinocyte differentiation, but no cytotoxicity. Fluorescence-labelled particles were less toxic than unlabelled particles.
Long et al. 2006	P25	Mouse microglia cell line (BV2 cells)	1. ROS production (luminescence probing) 2. Cell viability (intracellular ATP levels)	1. 2.5-120 ppm (5-120 min) 2. 2.5-120 ppm (6 and 18 h)	P25 induced a rapid, sustainable ROS release by oxidative burst and by interference with mitochondrial electron transport chain without seriously affecting cell viability.

Long et al. 2007	P25	Mouse microglia cell line (BV2 cells) Rat dopaminergic neural cell line (N27 cells) Rat Primary embryonic striatum cells	1. Microarray analysis 2.Cell viability (intracellular ATP levels) 3. Apoptosis	2.5–120 ppm (24-72 h, depending on cell culture type)	Whereas P25 was not cytotoxic for isolated N 27 neurons, it rapidly damaged neurons at low concentrations in complex brain cultures, possibly through ROS generated by microglia.
Liu et al. 2010	P25	Rat pheochromo-cytoma nerve cell line (PC12 cells)	1. Cell viability (MTT assay) 2. Intracellular ROS production (fluorometry 3. Apoptosis (PI flow cytometry)	1-100 µg/ml (6 – 48 h)	P25 elicited a dose- and time-dependent decrease in cell viability associated with intracellular accumulation of ROS and apoptosis.
Shin et al. 2010	P25	Mouse microglia cell line (BV2 cells)	TNF-alpha (ELISA) NF-kappaB binding (EMSA)	100 ng/ml LPS or P25 alone or in combination for 24 h	P25 induced ROS generation and activated LPS-stimulated microglia leading to enhanced TNF-alpha production and elevated NF-kappaB binding activity.
Liu et al 2010a	P25	Rat Primary alveolar macrophages	Assays on Nitric oxide, cytokines, Neutral red uptake, chemotactic migration, F_c receptor-mediated rosette formation MHC II cytometry	18.75, 37.5, 75, 150, 300 µg/ml (24 h)	TiO_2 induced inflammatory response (as indicated by NO and TNF-alpha level increases) and inhibited immune functions of alveolar macrophages, e. g. phagocytosis, chemoattraction, F_c- and MHC-receptor expression, TNF-alpha and NO synthesis.

Winter et al. 2010	a. P25 (PPD range: 20-80 nm; Evonik) b. DQ 12 (PPD range: 40-300 nm, Sigma Aldrich)	Mouse Bone marrow-derived dendritic cells	Particle uptake, stimulation and inflammasome activation of dendritic cells in vitro; IL-1 beta determination in supernatant (ELISA) and apoptosis (annexin V staining)	1. 5–50 µg/cm^2 for18 h for stimulation. 2. 20 or 40 µg/cm^2 (2h) for inflammasome activation after 6h pre-stimulation with LPS (0.1 µg/ml) ± incubation with cytochalasin D (1.5 µg/ml, 30 min.) to block actin polymerization after pre-stimulation with LPS.	P25 induced upregulation of MHC-II, CD80, and CD86 on dendritic cells, and activated the inflammasome, leading to significant secretion of IL-1beta- in wild-type but not Caspase-1- or NLRP3-deficient mice. P25 also led to enhanced ROS production.

Summary of NANOhub entries for in vitro toxicity

Material	**Test Organism/System**	**Method**	**Exposure/dose**	**Main findings**	**Laboratory**
P25	Chinese hamster lung fibroblasts (V79 cells)	Comet Assay 24h; MTT assay 24, 48h Hamzeh et al. 2013	1,10,100 mg/l	The apoptosis/necrosis rate:100 mg/L 30.6 ± 2.1% (control 0.9 ± 0.2%), 10 mg/l 9.6 ± 0.3%; significant changes in cell viability in comparison to control; significant changes in DNA strand break (OTM and % Tail DNA) in comparison to control	University Alberta (CAN)
MTI5 No OECD Material	Chinese hamster lung fibroblasts (V79 cells)	Comet Assay 24h; MTT assay 24, 48h Hamzeh et al. 2013	1,10,100 mg/l	The apoptosis/necrosis rate:100 mg/L 20.6 ± 2.0% (control 0.9 ± 0.2%), 10 mg/l 10.5 ± 1.4%; significant changes in cell viability in comparison to control; significant changes in DNA strand break (OTM and % Tail DNA) in comparison to control	University Alberta (CAN)

MTI10x40 No OECD Material	Chinese hamster lung fibroblasts (V79 cells)	Comet Assay 24h; MTT assay 24, 48h Hamzeh et al. 2013	1,10,100 mg/l	The apoptosis/necrosis rate:100 mg/L 26.2 ± 1.6% (control 0.9 ± 0.2%), 10 mg/l 9.6 ± 0.5%; significant changes in cell viability in comparison to control; significant changes in DNA strand break (OTM and % Tail DNA) in comparison to control	University Alberta (CAN)
Hombitan LW-S No OECD Material	Chinese hamster lung fibroblasts (V79 cells)	Comet Assay 24h; MTT assay 24, 48h Hamzeh et al. 2013	1,10,100 mg/l	The apoptosis/necrosis rate:100 mg/L 12.3 ± 2.1% (control 0.9 ± 0.2%), 10 mg/l 7.1 ± 0.8%; significant changes in cell viability in comparison to control; significant changes in DNA strand break (OTM but not % Tail DNA) in comparison to control	University Alberta (CAN)
Vive Nano No OECD Material	Chinese hamster lung fibroblasts (V79 cells)	Comet Assay 24h; MTT assay 24, 48h Hamzeh et al. 2013	1,10,100 mg/l	The apoptosis/necrosis rate:100 mg/L 8.6 ± 12% (control 0.9 ± 0.2%); No significant differences to control	University Alberta (CAN)
NM 105	Human buccal squamous epithelial cell line (TR 146 cells)	Roblegg et al. 2012, 4h, permeability	100 µg/ml	Localization in the stratum superficial and deeper parts of the epithelium	University Graz (AT)
NM 105	Human buccal squamous epithelial cell line (TR 146 cells)	Roblegg et al. 2012, 4h and 24h, cyto-toxicity	1-200 µg/ml	mitochondrial activity/viability was not reduced; At a particle concentration of 80 µg/ml and higher significant increased metabolic activity after 4 h, returned to the level of untreated cells after 24 h exposure; no significant influence on the membrane integrity	University Graz (AT)
NM 101	Human buccal squamous epithelial cell line (TR 146 cells)	Roblegg et al. 2012, 4h, permeability	100 µg/ml	Permeability across the buccal mucosa with a thickness of approximately 700 µm was determined; penetration into epithelium; no detection in basal lamina	University Graz (AT)
NM 101	Human buccal squamous epithelial cell line (TR 146 cells)	Roblegg et al. 2012, 4h and 24h, cyto-toxicity	1-200 µg/ml	Negligible reduced mitochondrial activity/viability, indicating no cytotoxic effects. After 4 and 24 h incubation time, more than 90 % viability was maintained. no significant influence on the membrane integrity.	University Graz (AT)
NM 100	Human buccal	Roblegg et al.	100 µg/ml	permeability into the mucus layer, the epithelium. and basal lamina	University

	squamous epithelial cell line (TR 146 cells)	2012, 4 h, permeability			Graz (AT)
NM 100	Human buccal squamous epithelial TR 146 cells	Roblegg et al. 2012, 4 h and 24 h, cyto-toxicity	1-200 µg/ml	negligible reduced mitochondrial activity/viability, indicating no cytotoxic effects. After 4 and 24h incubation time, more than 90 % viability was maintained. No significant influence on the membrane integrity.	University Graz (AT)
NM 103	Rat hepatoma cell line (H4IIE cells)	MTT NRU LDH, 24 h and 72 h	100- 0.003 µg/mL	Absence of toxicity at the tested doses	INIA (SP)
NM 104	Rat hepatoma cell line (H4IIE cells)	MTT NRU LDH; 24 h and 72 h	24 h and 72 h 100-0.003 µg/mL	Absence of toxicity at the tested doses	INIA (SP)

3. HAZARDS TO THE ENVIRONMENT

3.1. Aquatic Effects

Acute Toxicity Test Results

Fish

Summary from scientific literature

Reference	Material	Organism/	Method	NOEC	LOEC	LC50	EC50	others
Griffit et al. 2008	P25	D. rerio	ASTM 2002, 48 h			>10 mg/l		
Ramsden et al. 2013	P25	D. rerio	14 d exposure, 21d post exposure					Sub lethal effects, lower cumulative number of viable embryos
Bar-Ilan et al. 2012	P25	D. rerio	120 hpf			>1000 µg/ml; 300 µg/ml (SSR)		uptake by embryos, uniform distribution with no tissue-specificity, uptake and location photo-independent; with SSR stunted growth, craniofacial, mal-formations, pericardial oedema, tail malfor-mations, <10% appeared normal; prior illumination of TiO_2 do not increase toxicity but produces photosensitivity; 8-OHdG levels toTiO_2NPs +SSR were much higher than TiO_2NPs –SSR
Bar-Ilan et al. 2013	P25	D. rerio	23d, from embryogenesis to juvenile metamorphosis; 14hSSR/day			1 ng/mL		stunted growth, malformation, reduction in overall size, failure to progress through metamorphosis, and specific defects; body burden: dose depending, as aggregates in all tissues sampled and at all concentrations tested; most commonly intestinal tract, gills, liver; 8-OHdG-formation dose and illumination dependent
Yang et al. 2013	P25	D. rerio	from embryonic stage until the larval stage,			290 mg/L; 159 mg/L (with HA and lower		Without SSR: HA reduced TiO_2NP uptake; TiO_2NP exposure in the presence of HA resulted in higher mortality and higher

			5d			body burden)		TBARS concentration (lipid peroxidation); with SSR: Decomposition of HA molecules on the TiO_2NP surfaces, LC50=, 8-OHdG levels 2.8 higher with HA
Federici et al. 2007	P25	O. mykiss	14 d exposure					0.1-1.0mg/l exposure causes some pathology
Ramsden et al. 2009	P25	O. mykiss	8 weeks dietary exposure					This study demonstrates that fish can accumulate Ti from a dietary TiO_2 NP exposure, and that a number of subtle physiological and biochemical disturbances occur.
Warheit et al. 2007	P25	O. mykiss	OECD 203			>100 mg/l		
Al-Jubory et al. 2012	P25	O. mykiss	4h, uptake experiments isolated perfused intestine, 1mg/l					Bulk/ nano: elevation of total Ti metal concentrations in the tissue, and the appearance of total Ti metal in the serosal, remains uncertain whether result of particle uptake, dissolved Ti ion uptake or both; much faster net uptake of Ti from exposures to the NP; nystatin-sensitive and vanadate-sensitive Ti uptake associated with TiO_2 exposures; suggesting that both particulate and dissolved metals components are involved in the overall uptake.
Boyle et al. 2013	P25	O. mykiss	14 d exposure; 1 mg/l					Bulk/nano: increases in the Ti concentrations of gill tissue, no measurable increases of Ti in the internal organs, gill pathologies; nano: Time of spenting swimming at high speed was significantly decreased, compared to controls, but not fish exposed to bulk TiO_2, associated with decreased area of red pulp in the spleen, increases in haematocrit and whole blood haemoglobin, all consistent with a compensation for respiratory hypoxia without the accumulation of plasma lactate, retaining competitive, no effect on duration of competitive contests, the level of aggression, and contest outcome, no neurological injury but some apparent enlargement of the blood vessels on the brain, whole brain homogenates showed a statistically significant increase in ROS defences.

Chen et al. 2011	P25	D. rerio	larvae development until 120hpf	≥10mg/l (Hatchability, survival,malformation rate)	0.1mg/l (swimming behaviour)			

Summary of research contribution for Fish acute (OECD materials)

Material	Organism	Method	NOEC	LOEC	LC50	EC50	others	Laboratory
P25	D. rerio	OECD 212, 8 d		1000 mg/l (body length)				INIA (ESP)
P25	medaka	early life stage 17d exposure, 5d post exposure					premature hatch of a greater number of medaka embryos; exhibited moribund swimming behaviour and greater mortality at 15 days post hatch	Trent University (CAN) Paterson et al. 2011
P25	medaka	96-h acute toxicity assay			155 mg/l; 2.2 mg/l (SSR)			US-EPA Ma et al. 2012
NM 105	D. rerio	OECD 212, 8 d		1000 mg/l (body length)				INIA (ESP)
NM 101	D. rerio	OECD 212, 8 d		100 mg/l (body length)			no effect on hatching and mortality	INIA (ESP)
NM 101	D. rerio	OECD 236, 72 h	≥100 mg/l	>100 mg/l				RWTH Aachen (GER)
NM 102	D. rerio	OECD 236, 72 h	≥100 mg/l	>100 mg/l				RWTH Aachen (GER)
NM 103	D. rerio	OECD 212, 8 d		1000 mg/l (body length)			no effect on hatching and mortality	INIA (ESP)
NM 104	D. rerio	OECD 212, 8 d		1000 mg/l			no effect on hatching and	INIA (ESP)

				(body length)			mortality	
NM 100	D. rerio	OECD 212, 8 d		100 mg/l (body length)			no effect on hatching and mortality	INIA (ESP)
NM 100	D. rerio	OECD 236, 72 h	≥100 mg/ l	>100 mg/l				RWTH Aachen (GER)

Summary of research contribution for Fish acute (other TiO_2 materials)

Material	Organism	Method	NOEC	LOEC	LC50	EC50	others	Laboratory
Sigma Aldrich Cat# 634662.25g, rrutil/anatase <100nm, no OECD material	P. promelas	EPS 1/RM/22,7 d					mortality <12.5% (1-16 g/l)	HydroQual (CAN)
Polyacrylate coated (Vive Nano Inc.), no OECD material	D. rerio	OECD FET draft, 72h			>2000 mg/l		mortality < 18% (1 - 200 mg/L)	University Alberta (CAN)

Invertebrates

Summary from scientific literature

Reference	Material	Organism	Method	NOEC	LOEC	LC50	EC50	others
Griffit et al. 2008	P25	D. magna, C. dubia	ASTM, 48h			>10 mg/l		
Marcone et al. 2012	P25	S. similis	OECD 202, 48 h UVA	>100 mg/l			7.8 mg/l (UV)	
Wahrheit et al. 2007	P25	D. magna	OECD 202				>100 mg/l	
Li et al. 2011	P25	C. dubia	Growth assay 48 h	>100 mg/l				

Windeatt & Handy 2012	P25	C. maenas	Ex vitro nerv stimulation Shanes 1951;					The study concludes that there were no effects of the materials at the concentrations (1mg/l) tested on the compound action potential of the shore crab in physiological saline.

Summary of research contribution for Invertebrates acute (OECD materials)

Material	Organism	Method	NOEC	LOEC	LC50	EC50	others	Laboratory
P25	D. magna,	EPA-821-R-02-2012, 48 h				130.5 mg/l (70 nm); 108.1 mg/l (128 nm); 97.9 mg/l (154 nm)	With UV: low survival rate between 1.06-5.3 mg/l	Ministry of KR
	M. macrocopa					1.9 mg/l (70 nm); 2.8 mg/l (128 nm); 3.6 mg/l (154 nm)	With UV: low survival rate between 1.06-5.3 mg/l	Ministry of KR
P25	D. magna	OECD 202, 48 h					mortality <10% for all test conc. (100-1500 mg/l)	INIA (ESP)
P25	D. magna	OECD 202, 96 h				52.3 mg/l	EC10=11 mg/l;	University Frankfurt (GER)
P25	D. magna	48 h, SSR (16 h:8 h)					wavelength depending ROS; Intracellular ROS production occurs over the entire surface of the organism	US-EPA Ma et al. 2012
P25	D. magna	48h, SSR (16 h:8 h)			500 mg/l; 29,8 µg/L (SSR)			US-EPA Ma et al. 2012
P25	C. elegans	ISO 10872; 4 d		10 mg/l (reproduction); 30 mg/l (growth rate)			SSR increases the inhibition of reproduction and growth rate by a factor of approx. 2 (100 mg/l); accumulation and agglomeration (130 µm) in the gut with inhibition of feeding by blocking the defecation	HAW Hamburg (GER)
NM 105	D. magna	OECD					mortality <10% for all test conc. (100-	INIA (ESP)

		202, 48 h					1500 mg/l)	
NM 101	D. magna	OECD 202; 48 h, SSR (16 h:8 h)	18.5 mg /l; 0.25 mg /l (SSR)	33.3 mg /l; 0.69 mg /l (SSR)		79.52 mg/l; 1.28 mg/l (SSR)		RWTH Aachen (GER)
NM 101	D. magna	OECD 202, 48 h					mortality <10% for all test conc. (100-1500 mg/l)	INIA (ESP)
NM 102	D. magna	OECD 202; 48 h, SSR (16 h:8 h)	>50 mg/l; 0.08 mg/l (SSR)	0.25 mg /l (SSR)		0.53 mg/l (SSR)		RWTH Aachen (GER)
NM 103	D. magna	OECD 202, 48 h					mortality <10% for all test conc. (100-1500 mg/l)	INIA (ESP)
NM 104	D. magna	OECD 202, 48 h					mortality <10% for all test conc. (100-1500 mg/l)	INIA (ESP)
NM 100	D. magna	OECD 202; 48 h, SSR (16 h:8 h)	>50 mg/l; 1.85 mg/l (SSR)	5.56 mg /l (SSR)		3.88 mg/l (SSR)		RWTH Aachen (GER)
NM 100	C. elegans	ISO 10872; 4 d	>100 m g/l				accumulation and fine agglomeration in the gut with inhibition of feeding by blocking the defecation	HAW Hamburg (GER)

Summary of research contribution for Invertebrates acute (other TiO_2 materials)

Material	Organism	Method	NOEC	LOEC	LC50	EC50	Results	Laboratory
Vive Nano, no OECD material	D. magna, Hydra	OECD 202, 48 h; Trottier et al. 1997, 9 6h			11.5 mg/l		d. magna: UCL=15.9 mg/l (mortality)	Wilfrid Laurier University (CAN)
							hydra morphology: IC50=20.1 mg/l, UCL=21.3 mg/l, LCL=18.5 mg/l	Wilfrid Laurier University (CAN)

Algea and cyanobacteria

Summary from scientific literature

Reference	Material	Organism	Method	NOEC	LOEC	LC50	EC50	others
Hartmann et al. 2010	P25	P. subcapitata	ISO 8692, 72h				71.1 mg/l	EC10=15.5 mg/l, EC20=26.2 mg/l,
Metzler et al. 2011	P25	P. subcapitata	4d exposure (13 d old algae)				113 mg/l	Yield; EC50 was 6.5particles cell−1 (log), or (3.3±0.0)×106 particles cell−1
Hartmann et al. 2012	P25	P. subcapitata	OECD 201 48 h/72 h				220 mg/l/200 mg/l (48 h), 160 mg/l (72 h)	Fluorescence: EC10= 10 mg/l/11mg/l; Haemocytometer 72h: EC10=38 mg/l
Hund-Rinke 2006	P25	D. subcapitata	72 h exposure				44 mg/l	
Wang et al. 2008	P25	C. reinhartii	72 h exposure				10 mg/l (growth)	
Hartmann et al. 2010	NM 101	P. subcapitata	ISO 8692, 72 h				241 mg/l	EC10=3.3 mg/l, EC20=14.5 mg/l, (EC50 not reliable due to large confidence interval)
Hund-Rinke 2006	NM 101	D. subcapitata	72 h exposure				>50 mg/l	

Summary of research contribution for Algea & cyanobacteria (OECD materials)

Material	Organism	Method	NOEC	LOEC	LC50	EC50	others	Laboratory
P25	P. subcapitata	OECD 201 72 h				28.35 mg/l	cell number; EC10=2.01mg/l, EC90=400.45mg/l	DTU (DK)
P25	P. subcapitata	EPS1/RM/25 96 h	0.6 mg/l	1.1 mg/l		16.36±6.64 mg/l	particle agglomerations/aggregations were observed with algae sedimentation	NRC (CAN) Hamzeh et al. 2014
P25	P. Capricornutum	OECD 201 72 h					IC50 = 8.27mg/l (300nm); IC50 = 15.58mg/l (70nm)	Ministry of KR

Summary of research contribution for Algea & cyanobacteria (other TiO_2 materials)

Material	Organism	Method	NOEC	LOEC	LC50	EC50	others	Laboratory
NAM5 no OECD material	P. subcapitata	EPS1/RM/25, 96 h	5.68 mg/l	11.36 mg/l	4.79±1.02 mg/l		particle agglomerations/aggregations were observed with algae sedimentation	NRC (CAN) Hamzeh et al. 2014
NAM10 no OECD material	P. subcapitata	EPS1/RM/25, 96 h	2.84 mg/l	5.68 mg/l	7.27 ± 1.55 mg/l		particle agglomerations/aggregations were observed with algae sedimentation	NRC (CAN) Hamzeh et al. 2014
NAM30 no OECD material	P. subcapitata	EPS1/RM/25, 96 h	0.09 mg/l	0.45 mg/l	1.77 mg/l (0.29-6.77 mg/l)		particle agglomerations/aggregations were observed with algae sedimentation	NRC (CAN)
NAM10x40 no OECD material	P. subcapitata	EPS1/RM/25, 96 h	0.009 mg/l	0.09 mg/l	0.49 mg/l (0.07-1.58 mg/l)		particle agglomerations/aggregations were observed with algae sedimentation	NRC (CAN)
MTI-5 no OECD material	P. subcapitata	EPS1/RM/25, 96 h	0.71 mg/l	1.42 mg/l	2.41±0.48 mg/l		particle agglomerations/aggregations were observed with algae sedimentation	NRC (CAN) Hamzeh et al. 2014

MTI30 no OECD material	P. subcapitata	EPS1/RM/25, 96 h	5.68 mg/l	11.36 mg/l	57.3 mg/l (22.5-1389 mg/l)		particle agglomerations/aggregations were observed with algae sedimentation	NRC (CAN)
Hombikat LW-S no OECD material	P. subcapitata	EPS1/RM/25, 96 h	0.2 mg/l	0.4 mg/l	2.7 mg/l (0.6-3.8 mg/l)		particle agglomerations/aggregations were observed with algae sedimentation	NRC (CAN)
Sig-Bulk1, Sigma Aldrich no OECD material	P. subcapitata	EPS1/RM/25, 96 h	2.84 mg/l	5.68 mg/l	62.8 mg/l		particle agglomerations/aggregations were observed with algae sedimentation	NRC (CAN)
Sig-Bulk2, Sigma Aldrich no OECD material	P. subcapitata	EPS1/RM/25, 96 h	22.72 mg/l	45.45 mg/l	57.19±23.28 mg/l		particle agglomerations/aggregations were observed with algae sedimentation	NRC (CAN)
Sig-10x40, Sigma Aldrich no OECD material	P. subcapitata	EPS1/RM/25, 96 h	0.45 mg/l	0.91 mg/l	3.6 mg/l (0.7-6.7 mg/l)		particle agglomerations/aggregations were observed with algae sedimentation	NRC (CAN)

Others

Summary from scientific literature

Reference	Material	Organism	Method	NOEC	LOEC	LC50	EC50	others
Bundschuh et al. 2011	P25	G. fossarum	Feeding activity 7 d, UV 12 h/d; food choice trial, 24 h		≤0.2 mg/l			Feeding activity: adverse sub lethal effects even at 0.2 mg/l lowest test conc. with/without UV; food choice: no effect
Canesi et al. 2010a	P25	M. gallopopvinicialis	24 h					Concentration depending sub lethal effects
Canesi et al .2010b	P25	M. gallopopvinicialis	24 h					Concentration depending sub lethal effects
Battin et al. 2009	P25	planktonic and biofilm comm.	Cell membrane integrity, ROS , 48 h					Cell membrane damage more pronounced in free-living cells than biofilm; intracellular ROS generation
Miller et al. 2010	P25	T. pseudonana, S. Marinoi, D. Tertiolecta, I. galbana	96 h growth test	≥1000 µg/l				
Ververs et al. 2008	P25	O. mykiss	NRR assay 24 h, comet assay 4 h, SEM 4 h, MN assay 48 h					Several effects were observed
Battin et al. 2009	NM 101	planktonic and biofilm comm..	Cell membrane integrity, ROS, 48 h					Cell membrane damage more pronounced in free-living cells than biofilm; intracellular ROS generation

Summary of research contribution for other acute aquatic toxicity (OECD materials)

Material	Organism	Method	NOEC	LOEC	LC50	EC50	others	Laboratory
P25	Tadpole	C-fin Assay, 48 h					no introducing of endocrine disruption effects, but TiO_2 was not inert with regards to causing cellular stress by crystalline structure	University of Victoria (CAN)
NM 103	Tadpole	C-fin Assay, 48 h					no introducing of endocrine disruption effects, but TiO_2 was not inert with regards to causing	University of Victoria (CAN)

							cellular stress by crystalline structure	
NM 104	Tadpole	C-fin Assay, 48 h					no introducing of endocrine disruption effects, but TiO_2 was not inert with regards to causing cellular stress by crystalline structure	University of Victoria (CAN)
NM 100	Tadpole	C-fin Assay, 48 h					no introducing of endocrine disruption effects, but TiO_2 was not inert with regards to causing cellular stress by crystalline structure	University of Victoria (CAN)

Chronic Toxicity Test Results

Fish

Invertebrates

Summary from scientific literature

Reference	Material	Organism	Method	NOEC	LOEC	LC50	EC50	others
Bundschuh et al. 2012	P25	D. magna	F0: OECD 211, 5th brood: OECD 202, 96 h	≤0.2 mg/l (F0)			5th brood: approx. 8mg/l (adults no exposure), 5 mg/l (adults 0.02 mg/l), 3,5 mg/l (adults 2 mg/l)	
Li et al 2011	P25	C. dubia	growth assay EPA Method 1002, 48 h				42 mg/l (reproduction), >100 mg/l (growth)	Results indicated that NP could disrupt the assimilation and consumption of energy in C. dubia dramatically.

Summary of research contribution for Invertebrates chronic (OECD materials)

Material	Organism	Method	NOEC	LOEC	LC50	EC50	others	Laboratory
P25	D. magna	OECD 211, 21 d	≥5 mg/L				growth, reproduction, mortality	Fh-IME (GER)
P25	D. magna	OECD 211, 21 d	3 mg/l	10 mg/l			reproduction and growth rate	INIA (ESP)
P25	D. magna	OECD 211, 21 d	1.78 mg/l	2.67 mg/l		12.1 mg/l	Reproduction; EC10=0.34 mg/l	University Frankfurt (GER)

P25	D. magna	multi-generation study, all generations acc. OECD 211, 5 generations each 96h				12.1 mg/l (F0), 1.70 mg/l (F4)	F5: population collapse at 1.78 mg/l	University Frankfurt (GER)
P25	H. azteca	EPS/11RM/33 28 d					dry weight: IC20=6.3 mg/l IC50=23.4 mg/l (measured conc.) NM105: dry weight: IC20=4.3 mg/l IC50=14.5 mg/l (measured conc.)	Wilfrid Laurier University (CAN)
P25	C. riparius	OECD 219, 28 d	≥100 mg/l				Emergence rate/development rate/sexes	Fh-IME
P25	L. variegatus	OECD 225, 28 d	≥100 mg/l				Reproduction biomass	Fh-IME
NM 105	D. magna	OECD 211, 21 d	3 mg/l	10mg/l			reproduction and growth rate	INIA (ESP)
NM 101	D. magna	OECD 211, 21 d	1 mg/l	3mg/l			reproduction and population growth rate	INIA (ESP)
NM 101	H. azteca	EPS/11RM/33 28 d					growth (dry weight): IC20=8.8 mg/l, IC50=15.98 mg/l (measured conc.)	Wilfrid Laurier University (CAN)
NM 101	C. riparius	OECD 219, 28 d	≥100 mg/l				Emergence rate/development rate/sexes	Fh-IME
NM 102	H. azteca	EPS/11RM/33 28 d					growth (dry weight): IC20=11.8 mg/l, IC50=31.2 mg/l (measured conc.)	Wilfrid Laurier University (CAN)
NM 103	D. magna	OECD 211, 21 d	>10 mg/l (reproduction), 3 mg/l (population growth rate)	>10 mg/l (reproduction), 3 mg/l (population growth rate)				INIA (ESP)
NM 103	H. azteca	EPS/11RM					growth (dry weight): IC20=5.5 mg/l,	Wilfrid Laurier

		/33 28 d					IC50=36.4 mg/l (measured conc.)	University (CAN)
NM 104	D. magna	OECD 211, 21 d	>10 mg/l	>10 mg/l			Reproduction/population growth rate	INIA (ESP)
NM 104	H. azteca	EPS/11RM /33 28 d					growth (dry weight): IC20=1.9 mg/l, IC50=6.5 mg/l (measured conc.)	Wilfrid Laurier University (CAN)

Summary of research contribution for Invertebrates chronic (other TiO_2materials)

Material	Organism	Method	NOEC	LOEC	LC50	EC50	others	Laboratory
anatas nano powder S. aldrich	H. azteca	EPS/11RM/33 28 d			66.3 mg/l		LC25=21.4 mg/l	Wilfrid Laurier University (CAN)

- ***Toxicity to Microorganisms***

Summary from scientific literature

Reference	Material	Organism	Method	NOEC	LOEC	LC50	EC50	others
Ge et al. 2011	P25	Natural soil microbial community	15d/60d		≤ 500 mg/kg (15d/60d)			P25 reduced both microbial biomass as indicated by declines in both SIR (substrate induced respiration acitivy) and DNA and diversity (by T-RFLP).

Summary of research contribution for Microorganisms (OECD materials)

Material	Organism	Method	NOEC	LOEC	LC50	EC50	others	Laboratory
P25	S. meliloti	48h	???	???	???	???	???	NRC (CAN)
P25	Natural soil bacteria	OECD 216, 28 d	via powder: 3h: 9.3 mg/kg, 28 d: 45 mg/kg; via disper.: 3h/28d: ≥21 mg/kg				via powder: 3h: EC10=23.6mg/kg EC25=108.3mg/kg	Fh-IME (GER)
P25	Natural soil	OECD 217,	≥100 g/kg (via powder),				respiration rate	Fh-IME (GER)

	bacteria	28d	≥21 mg/kg (via disper.)					
NM 101	Activ.sludge microorg. domestic WWT	OECD 209, 3 h	≥1000 mg/l	>1000 mg/l			Respiration rate, nitrification	RWTH Aachen
NM 102	Activ.sludge microorg. domestic WWT	OECD 209, 3 h	≥1000 mg/l	>1000 mg/l			Respiration rate, nitrification	RWTH Aachen
NM 100	Activ.sludge microorg. domestic WWT	OECD 209, 3 h	≥1000 mg/l	>1000 mg/l			Respiration rate, nitrification	RWTH Aachen

3.2. Terrestrial Effects

- ***Acute Toxicity Test Results***

Summary from scientific literature

Reference	**Material**	**Organism**	**Method**	**NOEC**	**LOEC**	**LC50**	**EC50**	**others**
McShane et al. 2011	P25	E. fedita, E.andrei	ISO 17512-1 48 h					avoidance: no dose response effects, 45 % avoidance (1.000 mg/kg), 37 % avoidance (10.000 mg/kg
Larue et al.2011	P25	T. aestivum	7 d growth camper	≥2000mg/l				
McShane et al. 2011	NM 101	E. fedita, E.andrei	OECD 207 14 d, ISO 17512-1 48 h	≥10000mg/kg (mortality)				avoidance observed but no concentration relationship

Summary of research contribution for acute Terrestrial Effects (OECD materials)

Material	Organism	Method	NOEC	LOEC	LC50	EC50	others	Laboratory
P25	E. fedita	OECD 207, 14 d					No significant mortality was observed for 50~200 mg/kg, however significant mortality was only detected when E. fetida were exposed to 400 mg/kg.	Ministry of KR
P25	C. elegans	24 h			7.88 mg /l (K-media); 6.36mg/ l (EPA-water)		K-media: LC10=4.7mg/L LC90=13.22mg/L; EPA water LC10=3.73 LC90=10.84mg/l	Ministry of KR
P25	C. elegans	ASTM E2172-01, 24 h					To identify sensitive strain for TiO_2 monitoring, the response of C.elegans to TiO_2 exposure was screened using potentially stress response mutants. Among tested strains, pmk-1(km25) was identified as the most sensitive strain to TiO_2 exposure.	Ministry of KR
P25	A. sativa S. alba Ph. aureus	OECD 208, 14 d; application via powder	≥100 mg/kg; 44mg/kg (growth Ph. aureus)	100 mg/ kg (growth Ph. aureus)			seeding emergence, growth and root length	Fh-IME (GER)
P25	L. esculentum, Ph. Vulgaris, L. Stativa, B. campestris var. Chinensis	OECD 208; USEPA Ecological Effect Test; 48 h	5000 mg/k g	L. sativa: 5000 mg/kg (root length)			germination and root growth	Ministry of KR
P25	L. esculentum, Ph. Vulgaris, L. Stativa, B. campestris var. Chinensis	OECD 208; EPA OPPTS 850.4150, 7 d					no significant effects on antioxidant enzyme activities for every species. Plants were not under more stressful conditions in P25 containing media. And though SOD values would be more sensitive to TiO_2, TiO_2 did not affect plant conditions. Chlorophyll contents were one of the basic and easy	Ministry of KR

							methods to check plant conditions, but did not show any difference between P25 treatments.	
NM 101	E. fedita	OECD 207, 14d	≥1000 mg/kg					RWTH Aachen (GER)
NM 102	E. fedita	OECD 207, 14 d	≥1000 mg/kg					RWTH Aachen (GER)
NM 100	E. fedita	OECD 207, 14 d	≥1000 mg/ kg					RWTH Aachen (GER)

Summary of research contribution for acute Terrestrial Effects (other TiO_2 materials)

Material	Organism	Method	NOEC	LOEC	LC50	EC50	others	Laboratory
not specified	Lettuce	ASTM E1963-02 Section A2					root length EC50 was not possible to determine; some seeds have two roots, some seeds turned filer paper pink	??? (CAN)

- ***Chronic Toxicity Test Results***

Summary from scientific literature

Reference	Material	Organism	Method	NOEC	LOEC	LC50	EC50	others
Heckmann et al. 2011	P25	E. andrei	OECD222, 56 d; limit test 1000 mg/kg					survival: 97.5 ± 2.5 %;cocoon production: 80.7 ± 7.3 %; reproduction hatchability: 74.6 ± 5.7 % (significant); juvenile production: 50.7 ± 7.7 % (significant); biomass: 169 ± 64.0 % (mean increment/loss in wet weight per surviving adult)
McShane et al. 2011	P25	E. fedita, E.andrei	OECD 222, 28 d	≥10.000 mg/kg (repro., mort.)				
Mc Shane et al. 2011	NM 101	E. fedita	OECD 222, 28 d	≥10000 m g/kg				

Summary of research contribution for chronic Terrestrial Effects (OECD materials)

Material	Organism	Method	NOEC	LOEC	LC50	EC50	others	Laboratory
P25	E. andrei	OECD 222, 56 d	Powder on feed: ≥200 mg/kg (mort.), 50 mg/kg (repro.); dispersion on feed: ≥20 mg/k (mort.), ≥10 mg/k (repro.); dispersion in soil: ≥20 mg/kg (mort.), 10 mg/kg (repro.); 3x powder in soils: ≥200 mg/kg, ≥1000 mg/kg, ≥1000 mg/kg (mort.); <50 mg/kg, <10 mg/kg, <50 mg/kg(repro)				powder in soils tested at 3 different times, stimulation of repro. in winter soil	Fh-IME (GER)
P25	C. elegans	Microarray, qRT-PCR; repro. test					preliminary results; 5 mg/L =14%, 10 mg/l=42%, 20 mg/l=32% juveniles compared to negative control	University Alberta (CAN)
P25	H. aculeifer	OECD 226, 14 d	≥1000 mg/kg (first test)				Second test: significant effects at reproduction at 1 and 1000 mg/kg;	Fh-IME (GER)
NM 101	E. fedita	OECD 222, 56 d	repro.: 200 mg/kg soil (powder on feed) 100 mg/kg soil (powder on soil)≥200 mg/kg soil (dispersion on feed)≥400 mg/kg soil; growth: 10 mg/kg soil (dispersion on feed) <10 mg/kg soil (dispersion on soil) 200 mg/kg soil (powder on soil)				stimulation of reproduction in winter soil	Fh-IME (GER)
NM 101	E. fedita	OECD 222, 56 d	≥1000 mg/kg (reproduction)					RWTH Aachen (GER)
NM 102	E. fedita	OECD 222, 56 d	≥1000 mg/kg (reproduction)					RWTH Aachen (GER)
NM 103	E. fedita	OECD 222, 56 d	≥400 mg/kg (reproduction)					Fh-IME (GER)
NM 100	E. fedita	OECD 222, 56 d	≥1000 mg/kg (reproduction)					RWTH Aachen (GER)

Summary of research contribution for chronic Terrestrial Effects (other TiO_2 materials)

Material	Organism	Method	NOEC	LOEC	LC50	EC50	others	Laboratory
NAM5, No OECD material	C.elegans	Microarray, qRT-PCR; repro. test				8.3 mg/l	preliminary results; EC20=2.6 mg/l; 5mg/L =20%, 10mg/l=70%, 20mg/l=17% juveniles compared to negative control	University Alberta (CAN)
NAM10 No OECD material	C.elegans	Microarray, qRT-PCR; repro. test				32.1 mg/l	preliminary results; EC20=7.9mg/l; 5 mg/L =23%, 10mg/l=56%, 20mg/l=25% juveniles compared to negative control	University Alberta (CAN)
NAM30, No OECD material	C.elegans	Microarray, qRT-PCR; repro. test				10.6 mg/l	preliminary results; EC20=2.6mg/l; 5mg/L =14%, 10mg/l=39%, 20mg/l=12% juveniles compared to negative control	University Alberta (CAN)
NAM10x40 No OECD material	C.elegans	Microarray, qRT-PCR; repro. test				3.6 mg/l	preliminary results, EC20=1.5 mg/l; 5 mg/L =20%, 10 mg/l=42%, 20 mg/l=32% juveniles compared to negative control	University Alberta (CAN)
MTI-5 No OECD material	C.elegans	Microarray, qRT-PCR; repro. test				25 mg/l	preliminary results, EC20=1.9 mg/l; 5 mg/L =18%, 10mg/l=59%, 20 mg/l=12% juveniles compared to negative control	University Alberta (CAN)
MTI30 No OECD material	C.elegans	Microarray, qRT-PCR; repro. test				10.1 mg/l	preliminary results; EC20=2.0mg/l; 5 mg/L =32%, 10 mg/l=65%, 20 mg/l=64% juveniles compared to negative control	University Alberta (CAN)
Hombitab LW-S No OECD material	C.elegans	Microarray, qRT-PCR; repro. test				9.7 mg/l	preliminary results; EC20=3.4 mg/l; 5 mg/L =17%, 10 mg/l=21%, 20 mg/l=11% juveniles compared to negative control	University Alberta (CAN)
Bulk rutil No OECD material	C.elegans	Microarray, qRT-PCR; repro. test				15.7 mg/l	preliminary results; EC20=3.4 mg/l; 5 mg/L =36%, 10 mg/l=72%, 20 mg/l=51% juveniles compared to negative control	University Alberta (CAN)

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ANNEX 1

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