Deliverable Report for Grant Agreement Number 760813

Deliverable 2.1

Critical toxicity data for IVIVE based on existing *in vivo* oral and inhalation toxicity studies

Due date of deliverable: 31/12/2018
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Lead beneficiary for this deliverable: *NRCWE*

Dissemination Level:		
PU	Public	x
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

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1. Description of task

<u>Task 2.1</u> Collecting existing high-quality (un)published data from *in vivo* sub-acute and (sub)chronic inhalation and oral toxicity studies; (NRCWE, LTAP, RIVM, JBRC, KRISS, IUF, BASF); **M1-12**

Existing high-quality *in vivo* data generated following exposure to the selected Tier 1 ENM (Table 1) will be collated, including data on biodistribution, pro- and anti-inflammatory responses, fibrosis and carcinogenicity. The task leader (NRCWE) will collect this information from PATROLS partners involved in this Task (each of whom has been responsible for conducting these studies), the OECD sponsorship program, other EU projects (e.g. NANoREG), and the scientific literature with a strong preference for studies that have been performed according to OECD technical guidelines. This approach minimises the need for new animal testing. Crystalline silica data will be included for benchmarking as for these particles a wealth of data already exists. This *in vivo* data will be evaluated to summarise relevant adverse outcomes, identify data gaps, and to inform the development of *in vitro* assays in **WP3** and **WP4**, including the relevant dose range and endpoints to be tested. The PATROLS consortium has access to data as well as stored tissues from sub-chronic 90-day and 2-year inhalation studies already performed with all the ENM included in the project (as indicated in Table 1). This includes full histopathology examination of the lung (and extra-pulmonary target organs if there were indications of effects), comprehensive clinical chemistry, cytology of blood and investigation of the BALF. These data will be shared with T2.5 and transferred to **WP6** (**Task 6.1**) for curation in the PATROLS database.

**Note the description of the task is from the Grant Agreement. "Table 1" refers to Table1 in the Grant Agreement copied below and reflects the state of knowledge before the project started. Reference numbers in Table 1 refers to the reference list in the Grant Agreement.*

Table 1 from the PATROLS Grant Agreement: ENM selected for PATROLS with associated high-quality in vivo data available within the PATROLS consortium

ENM Major Group[19]	ENM & Supplier	Lung (inhalation)	GIT Exposure	Liver Exposure	Ecotoxicity tests
1: Soluble (release possibly toxic ions)	**ZnO** (NM111; JRC)	STIS & 90days- *Inflammation & Fibrosis*[37]	**No data available**	Pulmonary exposure- *No translocation*	Zebrafish larvae- *Developmental toxicity*[38]; Daphnids- *Accumulation and toxicity*[39]; Algae- *Toxicity*[40] *and trophic transfer*[41]
	Ag (Sigma 576832) (CAS#:7440-22-4)† or (NM300/302; JRC)‡	**No data available**	28days (Feed pellets) *Impact on GIT microbiota*[42]	**No data available**	Soil Microbe Communities *Structure and function toxicity*[43]
2: Biopersistent high aspect ratio ENM (fibre paradigm) ᐞ*LFA will serve as a positive fibre control (WP3 only)*	**MWCNT**[44](Mitsui-7)	Inhalation (2yrs); Pharyngeal aspiration (56days)[44] *Fibrosis & Carcinogenicity*	**No data available**	Pulmonary exposure *Translocation to liver*[45]	**No data available**
	MWCNT (NM402; JRC)	STIS & 90days *Inflammation*[46]	No uptake	**No data available**	**No data available**
3: Passive (no reactivity or toxic potential)	**$BaSO_4$** (NM220; Fraunhofer IME)	STIS, 28days, 90days, 1yr, 2yrs[37,47] *No adverse findings*	28days (gavage) No adverse effects[48].	STIS (28days) *Translocation to liver; no histopathology change*[37]	**No data available**
4: Active (positive, insoluble; promote cellular effects and/or mobility in the organism)	**CeO_2** (NM212; Fraunhofer IME)	STIS, 28 & 90days, 1yr, 2yrs- *Inflammation*[49]	90days (feed pellets)	STIS (28days) *Translocation to liver ; no histopathology*[49]	Algae and Daphnids *Chronic toxicity*[50,51]
	TiO_2 (NM105; JRC)*	STIS, 90days, 2yrs exposures[52] *Inflammation* Carcinogenicity study (currently ongoing by JBRC)	**No data available**	**No data available**	Zebrafish larvae- *Developmental toxicity*[53]; Daphnids-*Toxicity*[54]; Algae- *Toxicity and trophic transfer*[41]
	Amorphous SiO_2 (SAS; IUF)	**No data available**	28 & 84days (mice, feed pellets); 84days (rats, feed) *Fibrosis*[55]	**No data available**	**No data available**
	Crystalline SiO_2# (DQ_{12} quartz; IOM)*	STIS & 2yrs exposures *Inflammation*	**No data available**	**No data available**	**No data available**

STIS: short-term inhalation studies. † Ag NPs sourced from Sigma (CAS#576832) will be used for all mammalian cell analysis based upon previous research and understanding from EU FP7 ENPRA. ‡ NM-300/302 will be used for eco-orientated model approaches due to the already existing literature. ᐞ Long amosite fibre asbestos (LFA) will be used in WP3 (only in specific assays, and at one concentration at the quasi-ALI[56]) as a pathogenic, positive fibre control. * Human data is also available in the literature (International Agency for Research on Cancer (IARC)). # DQ_{12} will act as the positive non-nanosized, (pro)inflammatory and (pro-)fibrotic particle control.

2. Description of work & main achievements

2.1. Introduction

The *in vivo* anchoring of *in vitro* assays depends on two major presumptions; first, that the adverse pathway can be mimicked in cell assays, and second, that the ENM can reach the target tissues and interact with the relevant cell types. Existing high-quality *in vivo* toxicity data generated for the selected ENM after repeated exposures have been collected from PATROLS partners and the scientific literature. Data for crystalline silica (DQ12) have been included for comparison and benchmarking.

2.2. Methodology

Literature search

Literature search and data extraction were distributed among task partners per PATROLS nanomaterial and exposure route. The literature search was based on each partners experience in the field of nanotoxicology. More information on the search strategy can be found in Annex A.

Selection criteria

In vivo toxicity studies with **repeated inhalation or oral exposure** for a **minimum of 90 days** (subchronic and chronic) were selected, since this exposure duration is considered sufficient for obtaining reliable data for regulatory risk assessment.

Data extraction

An Excel data template was made with input from WP2, 3, 4 and 6 on the required parameters concerning nanomaterial physico-chemical characteristics, study design, toxicological outcomes and biodistribution. Data from studies that met the selection criteria were extracted with focus on genotoxicity, carcinogenicity, histopathology, fibrosis, inflammation, and biodistribution. Data were continuously added to the Excel table "PATROLS task 2_1 *in vivo* data" on the PATROLS server to make it available to all partners ahead of the deliverable in December 2018.

Unpublished data

Data from relevant unpublished toxicity studies performed by PATROLS partners have been shared with PATROLS members: a repeated dose 90-day oral toxicity study with TiO_2 performed by KRISS (KRISS, 2018) and a 2-year inhalation study with CeO_2 and $BaSO_4$ performed by BASF (data partly published in conference abstracts (Brunner et al., 2016; Ernst et al., 2017; Ma-Hock et al., 2017; Tenschert, 2018)). Parts of the unpublished data have been removed from this public summary report.

Summary report

A short summary is given for each nanomaterial describing the selected studies, the effects found after exposure, data on biodistribution, and whether any data gaps have been identified. The focus of the summaries is the toxicological effects in lung, liver and gastrointestinal tract. Specific data on nanomaterial physico-chemical characteristics, study design, toxicological outcomes and biodistribution can be found in Annex B. No-observed-adverse-effect-concentration and lowest-observed-adverse-effect-concentration (NOAEC/LOAEC) for inhalation studies are reported as mg/m^3 unless otherwise stated. No-observed-adverse-effect-level and lowest-observed-adverse-effect-level (NOAEL/LOAEL) for oral studies are reported in mg/kg body weight/day unless otherwise stated.

Task partners

NRCWE: Trine Berthing, Alicja Mortensen, LTAP: Sybille van den Brûle, Dominique Lison, RIVM: Ilse Gosens, Minne Heringa, Flemming Cassee, KRISS: Min Beom, IUF: Roel Schins, BASF: Lan Ma-Hock.

2.3. Results and discussion

2.3.1. *In vivo* toxicity data

Extracted *in vivo* data are collected in the Excel table "PATROLS task 2_1 *in vivo* data" available to PATROLS partners via the internal PATROLS server. A public formatted version is included in Annex B. The table consists of three Excel sheets: Abbreviations, Inhalation and Oral. It contains specific data on nanomaterial physico-chemical characteristics, study design, toxicological outcomes and biodistribution for each relevant *in vivo* toxicity study. Note that the abbreviation "nd" (not determined) is used to denote that a given parameter was not analysed or not reported. Data in grey colour are from studies of shorter duration than 90 days that therefore do not meet the selection criteria of task 2.1. Despite this, the data are included since they may be relevant for other tasks in PATROLS.

2.3.2. Summaries of inhalation toxicity

Table 2: Overview of number of (sub)chronic inhalation toxicity studies, reported effects and biodistribution data.

ENM	Number of studies	Pulmonary effects	Liver effects	GI-tract effects	Biodistribution
ZnO	1	Yes	ND	ND	Yes
Ag	1	Yes	Yes	ND	Yes
MWCNT Mitsui-7	2	Yes	No	No	Limited
MWCNT NM-402	1	Yes	No	No	Limited
$BaSO_4$	3	Yes	No*	No*	Limited*
CeO_2	2	Yes	No*	No*	Limited*
TiO_2	3	Yes	No	ND	Limited
Amorphous SiO_2	3	Yes	No	No	Limited
Crystalline SiO_2	3	Yes	No	No	Limited

Yes: effects have been shown/biodistribution has been analysed in several organs.
No: organ has been analysed and no effects found.
ND (not determined): organ was not analysed.
Limited: limited information on biodistribution, e .g only lung burden.
*A 2-year inhalation toxicity study is currently being examined and finalised; results are not yet published.

2.3.2.1. Zinc oxide

Available studies

There is only one study available that qualifies for the 90-day or longer criterion: the 13-week part of the study of Adamcakova-Dodd et al. (Adamcakova-Dodd et al., 2014). Mice were exposed to a single target concentration of 3.5 mg/m^3 ZnO nanoparticles (Meliorum Technologies, Inc. Rochester, NY) during a 2- and 13- week whole body exposure (4 hr/day, 5 days/wk). The aerosol (geometric mean mobility diameter 46 nm for the 2-week and 36 nm for the 13-week exposure respectively, GSD 1.8) was generated from a 1 mg/mL suspension of ZnO nanoparticles (NPs) in water. Effects and total zinc levels (in broncho-alveolar lavage fluid (BALF), lung, blood, heart, brain, liver, spleen and kidney) were assessed immediately after the last exposure and after a recovery period of three weeks.

Effects after exposure

Lung

Moderate lung inflammation was found based on cell differentials after 2 or 13 weeks of exposure. For the 2-week exposure there was an increase in macrophages and neutrophils, while immediately after the cessation of the 13-week exposure only a significant increase in macrophages was found. No cellular damage or lipid peroxidation (reactive oxygen species (ROS) assay) have been detected at these time points. Genotoxicity was not assessed. A significant increase in the number of macrophages in the lungs was related to a moderate increase of pro-inflammatory mediators (IL-12 (p40) and MIP-1α). Histopathology evaluation of lung tissues as well as pulmonary mechanics measurements revealed no significant changes from controls. There were no eosinophils and few neutrophils found in BAL fluid or lung tissue in mice after inhalation exposure to ZnO NPs in sub-acute or sub-chronic exposure. Only a moderate presence of slightly foamy alveolar macrophages in mice exposed to ZnO NPs necropsied immediately post exposure was seen. It is possible that repeated inhalation exposure to ZnO NPs at low exposure concentrations may lead to the attenuation of pulmonary responses by development of pulmonary tolerance. However, the mechanism is not fully understood.

No particles inside macrophages or in lung tissue could be detected by dark-field microscopy and TEM-EDS after 13 weeks of exposure and after 3 weeks recovery period.

Liver

Histopathology was not performed on organs other than the lungs. No effect on the liver was reported.

GIT

Histopathology was not performed on organs other than the lungs. No effect in the GIT was reported

Other

Haematological analysis revealed a statistically significant increase in haematocrit (the volume percentage (vol%) of red blood cells in blood) values in mice exposed for 13 weeks at 3 weeks post-exposure. There was no sign of systemic inflammation based on haematology parameters.

Increased Zn levels were found in the heart.

Histopathology was not performed on organs other than the lungs. No pathological response was reported in other organs.

Overall NOAEC/LOAEC for key effect

It is not possible to identify a NOAEC/LOAEC since the study only includes a single exposure concentration. This study has therefore limited relevance for determining the dose-response relationship. The lung effects can be linked to the Zn lung dose at two time points after a single exposure concentration.

Biodistribution

Zn concentration was measured in BALF, lung, blood, heart, brain, liver, spleen and kidney after 2- or 13-weeks of exposure and after a three week recovery period. Only after 2 weeks of exposure, significantly increased Zn levels were found only in the BALF and lung. After 13 weeks of exposure significantly increased levels were found only in the heart. After a recovery period of three weeks, no significantly increased Zn levels were found in any of the examined organs, suggesting fast clearance. Effects can be explained by the dissolution of Zn ions at low pH: in artificial lysosomal fluid (pH4.5) 100% is dissolved within 24 hrs, whereas in Gamble's buffer (pH7.4) less than 1% of ZnO is dissolved. ZnO can be cleared efficiently from the lung by dissolution. Note that in an *in vitro* air-liquid interface lung system, clearance via dissolution within cells needs to be taken into account.

Data gaps

- A dose-response could not be established due to only one concentration and two time points tested in Adamcakova-Dodd et al. It is important to mention that exposure concentration, exposure mode and time post exposure plays an important role in the toxicity of ZnO NPs. Other studies show that after instilling a bolus dose of ZnO NPs (in rats or mice), a much more marked inflammatory response is observed compared to this inhalation study. Available inhalation studies of shorter duration using multiple exposure concentrations could be evaluated in order to derive a dose-response for the adverse lung effects.
- Systemic and local genotoxicity has not been assessed.

2.3.2.2. Silver

Available studies

One study of adequate duration was identified (described in two separate publications): a 90-day rat study stated to follow TG OECD 413 and to have been performed under GLP, with self-generated Ag NPs of 6-55 nm which do not agglomerate administered by whole-body inhalation at 0, 0.049, 0.13, 0.51 mg/m³ (Sung et al., 2009, 2008).

Effects after exposure

Lung

Chronic alveolar inflammation (defined by alveolitis, granulomatous lesions, and alveolar wall thickening), a mixed cell perivascular infiltrate, and alveolar macrophage accumulation.

Decreased lung function (Tidal volume) (estimated NOAEC/LOAEC: 133/515 µg/m³) (Sung et al., 2008).

Liver

Statistically significantly increased incidence of minimal bile-duct hyperplasia and single-cell hepatocellular necrosis (females only) (NOAEC/LOAEC: 133/515 µg/m^3) (Sung et al., 2009).

GIT

The GIT was not analysed, neither for organ weights nor for histopathology.

Other

No other adverse effects reported.

Overall NOAEC/LOAEC for key effect

Estimated NOAEC/LOAEC: 133/515 µg/m³

Biodistribution

Ag levels were measured in liver, kidneys, olfactory bulb, brain, lungs, and whole blood after 90 days. All organs reported showed dose-dependent increase in Ag content.

Data gaps

- Lung burden over time, lung clearance, and reversibility of effects is unknown because an interim sacrifice or a recovery period was not included in the study.
- Tissue levels of Ag were determined with AAS, thus it remains unknown whether the detected Ag was in the ionized form and/or particle form.
- Particle size range was more than one order of magnitude, so the effects cannot be attributed to one nano-size only. Moreover, these particles were freshly generated and not from powders or suspensions available in the PATROLS Tier 1 ENM panel
- Systemic and local genotoxicity was not assessed.

2.3.2.3. MWCNT Mitsui-7

Available studies

Two inhalation studies of adequate duration with the specific MWCNT Mitsui-7 of adequate duration were identified. One 90-day study was performed as a sub-chronic inhalation toxicity study according to OECD TG 413, with 0.2, 1 and 5 mg/m^3 Mitsui-7 (Kasai et al., 2015). One 2-year study was performed as a carcinogenicity study according to OECD TG 451, with 0.02, 0.2, and 2 mg/m^3 Mitsui-7 with an MMAD of 3-4 µm (Kasai et al., 2016). A description of MWCNT deposition sites in the lung can be found in Fukushima et al. (Fukushima et al., 2018).

Effects after exposure

Lung

- Lung carcinogenicity (NOAEC/LOAEC: 0.02/0.2 mg/m^3 for neoplastic changes, bronchiolo-alveolar carcinoma, adenosquamous carcinoma, poorly differentiated adenocarcinoma, squamous carcinoma, bronchoalveolar adenoma)
- Inflammation in terms of alteration of cellular and biochemical bronchoalveolar lavage fluid composition (NOAEC/LOAEC: 0.02/0.2 mg/m^3) and histopathology (granulomatous change, accumulation of alveolar macrophages and inflammatory infiltration in visceral pleura. NOAEC/LOAEC: 0.02/0.2 mg/m^3 for non-neoplastic changes).
- Localized fibrosis in the alveolar wall (NOAEC/LOAEC: 0.02/0.2 mg/m^3) and pleura (NOAEC/LOAEC: 0.2/2 mg/m^3).

Liver

No effects reported (NOAEC: 5 mg/m^3), besides the observation of translocated MWCNT (Kasai et al., 2016).

GIT

No effects reported (NOAEC: 5 mg/m^3).

Other

The 90-day study indicated systemic inflammation (increasing neutrophil percentages in blood with increasing dose (data not shown, no statistics), however this did not persist in the 2-year study (no change in haematology (NOAEC/LOAEC: 2/nd mg/m^3)).

Overall NOAEC/LOAEC for key effect

Lung carcinogenicity (NOAEC/LOAEC: 0.02/0.2 mg/m^3 for neoplastic changes).

Biodistribution

- Lung burden was measured after tissue digestion for both the 90-day and 2-year studies.
- The number of MWCNTs was counted in pleural and abdominal lavage after 2 years of exposure.

- Single or aggregated MWCNTs were found in the nasal cavity, larynx, trachea, lungs, lymph nodes, spleen, liver, kidneys, olfactory bulb, and brain after 2 years of exposure.
- A description of MWCNT deposition sites and cellular interactions in the lung can be found in Fukushima et al. (Fukushima et al., 2018).

Data gaps

- Systemic and local genotoxicity has not been assessed in these studies.
- There was no post-exposure recovery time in any of the studies, to assess clearance rate of MWCNT Mitsui-7.

2.3.2.4. MWCNT NM-402

Available studies

One inhalation study of adequate duration with the specific MWCNT NM-402 was identified (Pothmann et al., 2015; Régnier et al., 2017). Rats were exposed nose-only for 90 days to target concentrations of 0.05, 0.25 and 5.0 mg/m³ and sacrificed 24 h, 90 days and 1 year after the last exposure. The study was performed according to OECD TG 413.

Effects after exposure

Lung

- Inflammation in terms of alteration of cellular and biochemical bronchoalveolar lavage fluid composition (NOAEC/LOAEC: 0.05/0.25 mg/m^3), and histopathology (alveolar granulocyte infiltration and interstitial inflammation (NOAEC/LOAEC: 0.25/5 mg/m^3)) persisting after 1 year recovery (Pothmann et al., 2015; Régnier et al., 2017).
- Focal collagen depositions in alveolar septa appear 90 days post-exposure, and develop into focal alveolar septal fibrosis 1 year post-exposure (NOAEC/LOAEC: 0.25/5 mg/m^3) (Régnier et al., 2017).

Liver

No effects reported (NOAEC: 5 mg/m^3). A lack of genotoxicity was shown by *in vivo* comet assay in isolated liver, lung and kidney cells, as well as a negative micronucleus test for bone marrow cells) at 24h post-exposure (NOAEC: 5 mg/m^3).

GIT

No effects reported.

Other

Indication of systemic inflammation in terms of significant changes in the differential white blood cells counts 24 hours and 90 days post-exposure (NOAEC/LOAEC: 0.25/5 mg/m^3).

Overall NOAEC/LOAEC for key effect

The authors identified a NOAEC/LOAEC of 0.25/5 mg/m³ for lung inflammation after 90-day exposure.

Biodistribution

There is no quantification of biodistribution in this study. However, deposition of black particles in the lungs and cortex/paracortex of the tracheobronchial lymph nodes were observed in all rats. No MWCNT aggregates were observed in the liver, kidneys, bone marrow or other organs.

After 90 days recovery, the mean severity scores of black particles in the lung decreased at 0.05 and 0.25 mg/m³, indicating partial clearance at these two lower concentrations; however, at 5.0 mg/m³, the mean severity score was overall similar indicating incomplete clearance during this timeframe in lungs at this exposure level of MWCNT NM-402.

After 90 days recovery, the mean severity score of black particle deposition in tracheobronchial lymph nodes was similar at 0.25 mg/m³ and slightly increased at 5.0 mg/m³, consistent with continuous drainage of black particles from the lungs after the end of exposure.

Data gaps

- There is no quantification of biodistribution in this study.
- There is no information on genotoxicity published
- There is no carcinogenicity study for MWCNT NM-402.

2.3.2.5. Barium sulphate

Available studies

$BaSO_4$ NPs have been tested at a single concentration of 50 mg/m³ in a 90-day nose-only study in female Wistar rats (at 6 h/day, 5 days/week with a recovery period up to 90 days) (Schwotzer et al., 2017), in a 90-day whole-body study (6 h/week) (Konduru et al., 2014) and in a 2-yr whole-body study (6 h/d, 5d/week) where $BaSO_4$ NPs were included as a negative control in a CeO_2 NP inhalation study (data partly published in abstracts (Ernst et al., 2017; Ma-Hock et al., 2017)). The analysis of the 2-year study is currently on-going and parts of the results are included in this public deliverable.

Effects after exposure

<u>Lung</u>

Lung inflammation: minimal to slight alveolar/interstitial infiltration of inflammatory cells, statistically significant compared to controls at day 90+1 and day 90+28 with no persistent granulomatous inflammation was found in the 90-day nose-only inhalation study (Schwotzer et al., 2017). In the 90-day whole-body study, slightly increased inflammatory cells were observed in lavage fluid, however histopathology was not performed (Konduru et al., 2014). Exposure to the same concentration of 50 mg/m³

for 2 years led to severe inflammation based on cell differentials in BALF. Histopathological examination revealed squamous metaplasia.
No genotoxicity was found based on γ-H2AX immunohistochemistry of lung tissue in the 90 day nose-only inhalation study and in a pig A gene mutation assay and micronucleus assay in rat blood cells in the 2-yr study.
No (interstitial) fibrosis or tumours were found in the 90-day nose-only study (Schwotzer et al., 2017). Fibrosis was found in the two-year study.

Liver
In the 90-day nose-only inhalation study, no other organs besides the respiratory tract were examined. In the 90-day whole-body inhalation study, no effects in other organs were found. In the 2-year study, effects in other organs beside the lung are currently being examined.

GIT
In the 90-day nose-only inhalation study, no other organs besides the respiratory tract were examined. In the 90-day whole-body inhalation study, no effects in other organs were found. In the 2-year study, effects in other organs beside the lung are currently being examined.

Other
In the 2-year study, urinary, haematological, and blood biochemical analyses revealed no toxicological changes in female rats.

Overall NOAEC/LOAEC for key effect

Key effect is lung inflammation. Only one concentration was tested so no NOAEC/LOAEC could be derived.

Biodistribution

Lung burden has been determined in the 90-day nose-only study, lung and associated lymph node burden has been established in the 90 day whole body study. In the 2-yr study, barium levels in whole blood, liver, kidney, spleen, bone, bone marrow, brain, lung-associated lymph nodes and lung have been measured, but the results are not yet known as the study is on-going.

Data gaps

- There is no dose-response known for the lung inflammatory effects, only information on occurrence at different time-points.
- From the 2-year study, results on effects or barium levels in other organs besides the lung are currently being examined.

2.3.2.6. Cerium oxide

Available studies

There are one published study (Schwotzer et al., 2017) and one partly published study (data published in abstracts (Brunner et al., 2016; Ernst et al., 2017; Ma-Hock et al., 2017; Tenschert, 2018)) and genotoxicity parameters published by Cordelli et al. (Cordelli et al., 2017)) available. The study of Schwotzer et al. is a 90-day (6 hrs/day, 5 days/week) nose-only inhalation study to 0.1, 0.3, 1 and 3 mg/m³ of CeO_2 (NM-212) according to OECD TG 413 (with the exception that only females were tested) with recovery period up to 90 days. The other study (2-year study) used CeO_2 (NM-212) in an extended OECD TG 453 under GLP conditions. Female rats were exposed whole-body to 0.1, 0.3, 1, or 3 mg/m³ for max. 104 weeks (6 h/d, 5d/week) with an interim sacrifice after 52 weeks exposure.

Effects after exposure

Lung

Lung inflammation with a NOAEC below 1.0 mg/m^3 (benchmark dose (lower confidence limit) of 0.41 mg/m^3) was estimated in the 90-day study and a LOAEC of 1.0 mg/m^3 based on the most sensitive marker (polymorphonuclear cells (PMN) in BALF). Total protein levels in BALF confirmed NOAEC and LOAEC. Histological examination of the lungs in the 90-day study was performed only for the highest concentration tested. At 3.0 mg/m^3: minimal to slight alveolar/interstitial infiltration of inflammatory cells that was statistically significant compared to controls at 90+1, 90+28 and 90+90 days was observed. The histological changes in the lung included: *persistent granulomatous inflammation* with syncytial giant cells, accumulation of particle laden macrophages and in alveolar/interstitium, bronchio-alveolar hyperplasia, accumulation of particle laden macrophages in lung associated lymph nodes. No inflammation or cell damage was observed in the nasal cavity.
In the 2-yr study, lung inflammation was observed with a LOAEL at 0.1 mg/m³ (lowest concentration tested) based on histopathology and lung lavage parameters with increased total cell number, neutrophils, eosinophils, lymphocytes, macrophages, LDH, ALP and total protein at 0.1 mg/m^3 and above.

Lung fibrosis: In the 90-day nose-only study, after 1 and 28 days of exposure, there was no sign of interstitial fibrosis (Schwotzer et al., 2017). After 90 days of exposure however, based on histopathology, very slight interstitial fibrosis was seen after 3.0 mg/m^3, which was statistically significantly different from controls at 90+90 days. Authors evaluated fibrosis as adverse as it developed from ongoing alveolar/interstitial granulomatous inflammation. Only one concentration was examined therefore no NOAEC/LOAEC was determined. In the 2-yr study, interstitial fibrosis was found.

Lung genotoxicity: in the 90-day study, at the highest concentration of 3.0 mg/m^3, γ-H2AX immunohistochemistry in the lung was significantly different from clean air

controls at 90+1 90+28 and 90+90 days. In the 2-yr study (Cordelli et al., 2017), no genotoxicity was found in the *pig A* gene mutation and micronucleus assays in rat peripheral blood cells after 3 and 6 months of exposure.

Lung oxidative stress: in the 90-day study, at 3.0 mg/m^3: 8-OHdG as marker of oxidative stress assessed by immunohistochemistry was significantly different from clean air control at 90+1 90+28 and 90+90 days.

Lung cell proliferation: in the 90-day study, at 3.0 mg/m^3: Ki67 as marker of cell proliferation by immunohistochemistry on terminal bronchi and lung parenchyma was significantly different from clean air control at 28, 90+1, 90+28 and 90+90 days.

Liver

In the 90-day study, histopathology was not examined for other organs besides the respiratory tract (left lung lobes including bronchi as well as mediastinal and tracheobronchial lung-associated lymph nodes, trachea, pharynx and nasal cavities including nasal mucosa associated lymphoid tissue). From the 2-yr study, effects in other organs beside the lung are currently being examined.

GIT

In the 90-day study, no other organ besides the respiratory tract was examined. From the 2-yr study, effects in other organs beside the lung are being examined, but the results are not yet available.

Other

In the 90-day study at 90+1 days: 1.0 mg/m^3 and 3.0 mg/m^3 CeO_2 caused an increase in the percentage of blood neutrophils and a decrease in blood lymphocytes. This systemic inflammatory response with NOAEC: 0.3 mg/m^3, LOAEC: 1.0 mg/m^3 was the only effect in haematology and clinical chemistry analyses. From the 2-yr study, effects in other organs beside the lung are being examined, but the results are not yet available.

Overall NOAEC/LOAEC for key effect

Lung inflammation with LOAEC 0.1 mg/m^3 based on BALF and histopathology parameters in the 2-yr study.

Biodistribution

In the 90-day study, only lung burden and lung clearance rate have been determined. Nanomaterial is translocated to lung-associated lymph nodes as expected.
In the 2-yr study, cerium levels after 3, 12 and 24 months in whole blood, liver, kidney, spleen, bone, bone marrow, brain, lung-associated lymph nodes and lung are being examined. The results are not yet available.

Data gaps

- Effects in other organs besides the respiratory tract have not been assessed in the 90-day study.

- From the 2-year study, results on effects or Ce levels in other organs besides the lung are currently being examined.

2.3.2.7. Titanium dioxide

Available studies

Three studies with adequate duration were identified:

- One 90-day study (Bermudez et al., 2004) was performed in rats, mice and hamster with a recovery period of up to 52 weeks. In this study, the animals were whole-body exposed to TiO_2 (Degussa) at 0.5, 2 and 10 mg/m³ (6 h/day).
- The second study was a long-term inhalation study in female mice and rats (Heinrich et al., 1995). In this study, rats (Wistar) and mice (NMRI) were whole body exposed to an average of 10 mg/m³ TiO2 P25 (Degussa) for 18 h/day, 5 days per week for 24 and 13.5 months, respectively.
- The third study (Muhle, Kittel, Ernst, Mohr, & Mermelstein, 1995) was performed in male and female F344 rats with Bayertitan T (rutile) at 5 mg/m³ (6 h/day, 5days/week, 24 month).

Effects after exposure

Lung

In the 90-day inhalation study (Bermudez et al., 2004), rat was the most sensitive species, followed by mice and hamster. In hamster, no adverse effects were found in clinical chemistry of blood, nor were there any in histopathology. In lavage fluid, total number of cells, neutrophils, lymphocytes and macrophages were increased at 10 mg/m³, which was considered not adverse due to missing correlate in histopathology. The NOAEC in hamster was 10 mg/m³. In mice, aggregations of heavily particle-laden macrophages were found (central lobar centriacinar) at 10 mg/m³. With time, heavily particle-laden macrophages moved to interstitial areas, primarily around blood vessels and peribronchiolar interstitium. Perivascular lymphoid proliferation was observed in addition. No fibrosis was diagnosed. NOAEC was 2 mg/m³ for mice based on histopathology and lung lavage. The LOAEC was considered 10 mg/m³. Rats were more susceptible than the other species. At 10 mg/m³ progressive epithelial proliferative changes, including metaplastic changes, were observed in centri-acinar regions (bronchiolization of alveolar epithelium) which were associated with particle-laden macrophages. At this concentration, septal fibrosis was observed in addition. At 2 mg/m³ accumulation of particle-laden macrophages in subpleural regions and centriacinar zones was observed. Moreover, minimal hypertrophy and hyperplasia of type II cells was observed. The NOAEC for nano TiO_2 was 0.5 mg/m³ in rats.

In the long-term study with TiO_2 P25 (Heinrich et al., 1995), the target concentrations changed several times during the exposure period, and the daily exposure duration of 18 hours was higher than the guideline requirement. The strain of mice in this study was considered not appropriate due to high spontaneous lung tumour rates.

Whereas no treatment-related lung tumour was found in mice, benign squamous cell tumour, adenocarcinoma, adenoma and squamous cell carcinoma were diagnosed in rats. Moreover, bronchoalveolar hyperplasia, interstitial fibrosis, and particle-laden macrophages within the alveolar region were observed. Only one high concentration was tested, no statement on potential NOAEC or LOAEC was possible.

In the study with Bayertitan (Muhle et al., 1995), slight fibrosis was found, no increased tumour incidence was recorded. Only one high concentration was tested, no statement on potential NOAEC or LOAEC was possible.

Liver
No effects in the liver were reported, since histopathology on organs other than the lungs has not been performed.

GIT
No effects in the GIT were reported, since histopathology on organs other than the lungs has not been performed.

Other
In the long-term study performed by Heinrich et al. only polycyclic aromatic hydrocarbon-related DNA adducts were examined. No difference was found between TiO_2-exposed groups and the control.

Overall NOAEC/LOAEC for key effect

In the 90-day study, NOAEC in hamster was 10 mg/m³, for mice 2 mg/m³ (LOAEC was 10 mg/m³), and 0.5 mg/m³ for rats (LOAEC 2 mg/m³).
In the long-term study, both Heinrich et al. and Muhle et al. (1995) tested only one concentration, thus a NOAEC or LOAEC was not determined.

Biodistribution

Biodistribution to non-pulmonary organs and tissues was not determined in the available studies. In all cases, lung burden and lung-associated lymph nodes were examined. Moreover, lung clearance half times were determined in several cases.
Only lung and lung-associated lymph nodes were examined for content of Titan (Bermudez et al., 2004). In the rats, lung burden after the 13 weeks exposure period was assessed to be 0.44 (0.5 mg/m³), 1.7 (2 mg/m³) and 11 mg (10 mg/m³) per gram dry lung. These values are approximate readings from figures. No table was available. The lung burden decreased over time while the content in the lymph nodes increased. The lung clearance ($t_{1/2}$) was about 63 days at 0.5 mg/m³, 132 days at 2 mg/m³ and 395 days at 10 mg/m³. In mice, similar lung burdens per gram dry lung were achieved as in rats after 90-day inhalation exposure. The lung clearance half time was 48 and 40 days at 0.5 and 2 mg/m³, respectively. Slow clearance was observed in the group of mice exposed to 10 mg/m³ (319 days). The lung burden in hamsters was low with 0.18 mg (at 0.5 mg/m³), 0.58 mg (at 2 mg/m³) and 2 mg (at 10 mg/m³) per gram dry lung after 13 weeks exposure. The clearance half time was about 33 to 39 days.

In the rat long-term study performed by Heinrich et al. (1995) lung burden were about 5 mg/lung after 3 months exposure and increased steadily with the exposure duration to end up with 40 mg per lung after 2-years exposure. The lung clearance half time was 368 days determined after 18 months exposure and 3 months recovery period. In mice, the lung burden was 0.8 mg after 3 months exposure, 2.5 mg after 6 months and 5.2 mg per lung after 12 months.

In the study with Bayertitan T, lung burden was 2.7 mg per lung. No ex-pulmonary organ burden was determined. Lung clearance was not determined.

Data gaps

- No dose-response relationship in the long-term study in rats (only one concentration tested in each study). NOAEC or LOAEC for rat was not available.
- Examination of systemic toxicity was not reported
- Biodistribution in non-pulmonary organs was not reported.
- Systemic and local genotoxicity has not been assessed.

2.3.2.8. Amorphous silicon dioxide

Available studies

Three inhalation studies with amorphous SiO_2 of adequate duration were identified.

- The first study (Reuzel, Bruijntjes, Feron, & Woutersen, 1991) examined Aerosil 200 at three concentrations (1, 6 and 30 mg/m³), Aerosil R 974 and Sipernat 22S at about 30 mg/m³ and quartz dust at 60 mg/m³. Animals were sacrificed immediately after 13 weeks exposure, 13, 26, 39 and 52 weeks after the exposure. This study examined comprehensively the overall toxicity, including systemic toxicity, of the materials. With exception of particle size distribution measurements, this study was considered scientifically valid and of high quality.
- The second study (Johnston et al., 2000) included 6.5 and 13 weeks inhalation of a high dose of 50 mg/m³ amorphous SiO_2 (12nm diameter) and 3 mg/m³ crystalline SiO_2, including 12- and 32-week post-exposure recovery. This study used a high dose known to induce high pulmonary inflammatory response, and solely examined adverse effects in lung.
- The third study (Sutunkova et al., 2017) included 3 and 6 months inhalation at two concentrations (2.6 and 10.6 mg/m³) of industrial condensation dust (78% SiO_2, mainly amorphous, 90nm diameter). Sutunkova et al. do not report the group size and therefore the validity of the results is uncertain.

Effects after exposure

<u>Lung</u>

Inflammation was observed after exposure to Aerosil 200 in a concentration-related manner (Reuzel et al., 1991). Morphological effects in the lungs comprised accumulation of alveolar macrophages, cellular debris and polymorphonuclear

leucocytes in the alveolar spaces, increased cellularity, seen as an increase in the number of type II pneumocytes and macrophages within the alveolar walls, alveolar broncholization, focal interstitial fibrosis, and cholesterol clefts at 30 mg/m³. At 1 mg/m³ accumulation of alveolar macrophages, increased septal cellularity, polymorphonuclear leucocytes in alveolar spaces were still observed, though less severe. Similar effects were observed in animals exposed to 30 mg/m³ Aerosil R974 or Sipernat 22S. Animals exposed to Sipernat 22S showed the least severe effects. All the effects were greatly resolved after 52 weeks post-exposure recovery period.

Inflammation in terms of histopathology, inflammatory cytokine and alterations in bronchoalveolar lavage fluid composition, after 6.5 and 13 weeks exposure to a high dose of 50 mg/m³ amorphous SiO_2, did not persist 12 and 32 weeks post-exposure (Johnston et al., 2000). No significant sign of inflammation was found with industrial SiO_2 dust in terms of histopathology or haematology (BALF was not analysed) (NOAEC/LOAEC: 10.6/nd) (Sutunkova et al., 2017).

Fibrosis was found in animals exposed to 30 mg/m³ Aerosil 200, but not in those exposed to 30 mg/m³ Aerosil R974 or Sipernat 22S. However, lung collagen contents were increased in all exposed animals in comparison to the concurrent control (Reuzel et al., 1991).
Fibrosis found in alveolar septa after 3-month exposure to a high dose of 50 mg/m³ amorphous SiO_2, did not persist after 8-month post-exposure recovery (Johnston et al., 2000). Indications of pulmonary fibrosis (increase in lung mass and hydroxyproline) after 3-month exposure to industrial dust, did not persist after 6 months of exposure (NOAEC/LOAEC: 10.6/nd) (Sutunkova et al., 2017).

Liver
Liver was examined histologically by Reuzel et al. and no treatment-related lesions were observed. Liver weight was analysed by Sutunkova et al. and no significant change in relative liver weight was found, despite an increase of silicon content. Liver was not analysed by Johnston et al.

GIT
Reuzel et al. examined the GIT and no treatment-related lesions were observed. No effects were reported by Sutunkova et al. and Johnston et al.

Other
Systemic genotoxicity was found ('Random Amplification of Polymorphic DNA' (RAPD) assay in nucleated blood cells and bone marrow cells) at doses of 2.6 and 10.6 mg/m^3 of industrial condensation dust (Sutunkova et al., 2017). However, no mutagenicity (HPRT mutation frequency) was found in isolated alveolar type II epithelial cells at dose 50 mg/m^3 of commercial amorphous SiO_2 (Johnston et al., 2000).

Overall NOAEC/LOAEC for key effect

The results on pulmonary fibrosis and inflammation in the three studies suggested

that different amorphous silicas have varying potency to cause pulmonary effects. Among these three studies, the LOAEC of 1 mg/m³ was determined for Aerosil 200. Aerosil R974 was tested only at 30 mg/m³. Due to the histological findings, no NOAEC or LOAEC could be determined for Aerosil R974. Sipernat 22S showed only mild effects at 30 mg/m³, which may be considered as LOAEL. The NOAEC/LOAEC would be 10.6/50 mg/m³ in the studies by Sutunkova et al. and Johnston et al.

Biodistribution

- Silicon lung burden was determined by Reuzel et al. after 13 weeks exposure, as well as after 13, 26, 39 and 52 weeks post-exposure.
- Silicon organ burden was measured by Sutunkova et al. after 3 and 6 months exposure to two concentrations: Silicon content of the lung, liver, kidney, spleen and blood was higher than controls, and dependent on the level and duration of exposure. Silicon content of urine and feces was higher than controls, and dependent on the level of exposure, but for the high dose it was inversely dependent on duration of exposure. Transmission electron microscopy confirms that silica particles are retained in the lungs, though in a small amount, and are present in the olfactory area of the brain.
- Silicon lung burden was determined by Johnston et al. after 6.5 and 13 weeks exposure, as well as after 12-week and 32-week recovery period. The silicon content in lung decreased during the post-exposure period.

Data gaps

- Genotoxicity is unclear since contradictory results have been found in genotoxicity tests (systemic vs local) in the two subchronic studies.
- Carcinogenicity study is lacking, however no proliferative lesions were found in the subchronic studies.

2.3.2.9. Crystalline silicon dioxide

Available studies

Three studies with adequate duration were identified.

- First study was a 90-day study (Reuzel et al., 1991) performed in Wistar rats with a recovery period of up to 52 weeks. In this study the animals were whole-body exposed to 60 mg/m³ quartz dust (Sikron F300) for 13 weeks (6h/day, 5d/week).
- The second 90-day study (Johnston et al., 2000) was performed in male F344 rats with recovery period up to 32 weeks. In this study, the animals were whole-body exposed to crystalline silica (Degussa) at 3 mg/m³ (6 h/day, 5 days/week) for 6.5 or 13 weeks.
- The third study was a long-term inhalation study in male and female F344 rats (Muhle et al., 1995). In this study, rats were whole body exposed to an average of 1 mg/m³ crystalline silica DQ12 for 6 h/day, 5 days per week for 24 months (the cumulative dose is about 5 mg DQ12/rat).

Effects after exposure

Lung

In the 90-day inhalation study (Reuzel et al., 1991), granuloma like lesions, accumulation of alveolar macrophages, cellular debris, intra-alveolar polymorphonuclear leucocytic infiltration, increased septal cellularity, alveolar bronchiolization, focal interstitial fibrosis, and cholesterol clefts were observed in the lung. The incidence and severity of these findings progressed during the course of the post-exposure period. Consistently lung collagen content was low after the exposure, but increased steadily to more than 4 times of the control males and more than 3 times of the control females.

In the 90-day inhalation study (Johnston et al., 2000), increased numbers of neutrophils and macrophages, progressive inflammation, and greatly thickened alveolar septa were observed. Consistently, increased cell counts, protein concentration and enzyme activities were observed in lung lavage fluid. After 12 weeks post-exposure, polymorphonuclear granulocytes and lactate dehydrogenase in lavage fluid were still significantly higher than in the controls.

In the long-term study with DQ12 several histological changes were found. The non-neoplastic changes comprised multifocal lipo-proteinosis adjacent to fibrotic areas, cholesterol clefts, foamy macrophages containing lipoid substances (98 %), intra-alveolar and interstitial inflammatory cell infiltrates (comprising neutrophils), lung subpleural and peribronchiolar fibrosis. Neoplastic changes comprised adenomas, adenocarcinomas, benign cystic squamous cell tumours, adenosquamous carcinomas, squamous cell carcinomas.

Liver

Reuzel et al. examined many organs and tissues in addition to the respiratory tract. They stated that no adverse effects were observed. In the studies performed by Johnston et al. and Muhle et al. no effects in the liver were reported, since histopathology on organs other than the lungs was not performed.

GIT

Reuzel et al. examined GIT in addition to the respiratory tract. They stated that no adverse effects were observed. In the studies performed by Johnston et al. and Muhle et al. histopathology on organs other than the lungs was not performed.

Other

In the 90-day study by Johnston et al., the HPRT test was performed in isolated alveolar epithelial type II cells, revealing a 4.3 fold increase of mutation frequency.

Overall NOAEC/LOAEC for key effect

In both studies only one concentration was tested with above mentioned adverse effects. Thus, NOAEC or LOAEC was not determined.

Biodistribution

In Johnston et al. and Muhle et al., lung burden and burden in lung-associated lymph

nodes were examined. However, biodistribution to extra-pulmonary organs and tissues was not determined.

Data gaps

- No dose-response relationship in the long-term study for rats as only one concentration was tested in each of the studies. For the same reason NOAEC or LOAEC for rat could not be identified.
- Biodistribution to extra-pulmonary organs was not determined.

2.3.3. Summaries of oral toxicity

No studies of adequate duration were found for oral exposure to MWCNT Mitsui-7 and NM-402, $BaSO_4$, CeO_2 and crystalline SiO_2 DQ12.

Table 3: Overview of number of (sub)chronic oral toxicity studies, reported effects and biodistribution data.

ENM	Number of studies	Pulmonary effects	Liver effects	GI-tract effects	Biodistribution
ZnO	5	No	No	Yes	Yes
Ag	2	No	Yes	No	Yes
MWCNT Mitsui-7	0	ND	ND	ND	ND
MWCNT NM-402	0	ND	ND	ND	ND
$BaSO_4$	0	ND	ND	ND	ND
CeO_2	0	ND	ND	ND	ND
TiO_2	5	No	Yes/No	Yes/No	Limited*
Amorphous SiO_2	7	No	Yes/No	No	Yes
Crystalline SiO_2	0	ND	ND	ND	ND

Yes: effects have been shown/biodistribution has been analysed in several organs.
No: organ has been analysed and no effects found.
Yes/No: effects have been found in some studies and other studies found no effects. ND (not determined): organ was not analysed/biodistribution was not analysed.
*Limited information on biodistribution from the five oral repeated dose studies, but much more information can be found in intravenous studies (single and repeated dose) and single dose oral studies not included here.

2.3.3.1. Zinc oxide

Available studies

Four subchronic toxicity studies in rats with ZnO administered by oral gavage (90 days, performed according to OECD TG 408), and one biodistribution study after 90 days exposure to ZnO were identified. None of the studies used the specific ZnO

NM-111 from JRC.

- Three studies assessed toxicity of 31.25 (only Kim et al.), 125, 250 and 500 mg/kg bw/day of ZnO with negative or positive surface coating, including 2-week recovery at the highest dose (Y.-R. Kim, Park, et al., 2014; Park, Kim, et al., 2014; Park, Shin, et al., 2014).
- One 90-day study with 67.1, 134.2, 268.4, 536.8 mg ZnO /kg bw/day, also included dissolution tests in gastric fluid and water and *in vitro* cytotoxicity tests in a human gastric adenocarcinoma cell line (Seok et al., 2013).
- The biodistribution publication addresses quantitative biodistribution of ZnO in tissues (and TiO_2) at the three highest doses at the end of exposure in the study by Seok et al. (Cho et al., 2013).

Effects after exposure

Liver

NOAEL of 500 mg/kg/day (highest dose tested) is identified from the three studies by Kim et al. and Park et al.

NOAEL of 536.8 mg/kg/day (highest dose tested) is identified in the study by Seok et al.

Lung

NOAEL of 500 mg/kg/day (highest dose tested) is identified from the three studies by Kim et al. and Park et al.

NOAEL of 536.8 mg/kg/day (highest dose tested) is identified in the study by Seok et al.

GIT

Local effects in stomach due to direct contact with ZnO are independent of surface charge: erosion, inflammation and epithelial and mucus cell hyperplasia in the limiting ridge and glandular part of the stomach (lowest NOAEL/LOAEL for the 3 toxicity studies: nd/31.25) (Y.-R. Kim, Park, et al., 2014; Park, Kim, et al., 2014; Park, Shin, et al., 2014). The histopathological changes in stomach were absent after the 2-week recovery period. Similar changes were reported in forestomach (non-glandular stomach). The changes in the non-glandular (forestomach) and glandular stomach are considered as treatment related but not adverse as they can be ascribed to the combination of irritation by gavage (mechanical irritation) and by the test compound given as bolus. This is supported by regression of the changes during the recovery period. In addition, effects in forestomach are not relevant for human risk assessment, since humans do not have a forestomach. No histopathological changes were found in stomach in the study by Seok et al. (NOAEL/LOAEL: 536.8/nd).

Other

- Anemia-related changes in hematological and blood biochemical analysis (lowest NOAEL/LOAEL for the 4 toxicity studies: 125/250) (Y.-R. Kim, Park, et al., 2014; Park, Kim, et al., 2014; Park, Shin, et al., 2014; Seok et al., 2013).

- Inflammation of the pancreas in terms of histopathology, resolves or reduces during 2 weeks post-exposure (lowest NOAEL/LOAEL for the 4 toxicity studies: 31.25/125) (Y.-R. Kim, Park, et al., 2014; Park, Kim, et al., 2014; Park, Shin, et al., 2014; Seok et al., 2013).
- Retinal atrophy in the eyes, persistent in after 2-week recovery (31.25/125) (Y.-R. Kim, Park, et al., 2014; Park, Kim, et al., 2014; Park, Shin, et al., 2014).

Overall NOAEL/LOAEL for key effect

Inflammation of the pancreas and anaemia-related changes in blood (lowest NOAEL/LOAEL for the 4 toxicity studies: 31.5/125. NOAEL/LOAEL for unmodified ZnO NPs in Seok et al.: 268.4/536.8).

Biodistribution

- (Cho et al., 2013): Organ burden and Zn levels in blood, urine and feces measured at 3 doses at the end of 90-days exposure. Significant increase in Zn concentration in liver, kidney, spleen, brain, blood, urine and feces.
- (Park, Kim, et al., 2014; Park, Shin, et al., 2014): Zn concentrations dose-dependently increased in the liver, kidney, intestine, plasma and feces at day 90. For positively charged ZnO, the Zn level was also increased in lung (Park, Kim, et al., 2014). Toxicokinetics for negatively charged ZnO, such as Zn half time (hours) in blood, was measured at 3 doses at day 0, 28 and 90 of exposure (Park, Shin, et al., 2014).

Data gaps

- There is no genotoxicity assessment (systemic or local) included in these subchronic studies.
- The studies are too short to detect development of cancer.

2.3.3.2. Silver

Available studies

For this nanomaterial two studies could be identified that were performed according to GLP and aligning with OECD testing guidelines TG 407 (“Repeated Dose 28-Day Oral Toxicity Study in Rodents”) (Y. S. Kim et al., 2008) and TG 408 (“Repeated Dose 90-Day Oral Toxicity Study in Rodents”) (Y. S. Kim et al., 2010), respectively. Both studies were performed in the same laboratory and included analysis of biodistribution by measuring Ag concentrations at time of sacrifice in various organs and tissues.

Another type of Ag NP was investigated in an independent 90-days study, aligning with OECD TG 408 (Yun et al., 2015).

The 90-day study by Kim et al. (2010) was judged of most appropriate relevance for PATROLS and thus used for NOAEL identification (Y. S. Kim et al., 2010). The study was performed in five weeks old F344 rats using Ag nanoparticles from NAMATECH Ltd. (Daejeon, Korea) with a size of 56 ± 1.46 nm (count median diameter ±

geometric standard deviation) and > 99.98% purity. Particle size was determined by Transmission Electron Microscopy in 0.5% aqueous carboxymethylcellulose (CMC). The Ag was administered by oral gavage at a vehicle dosing volume of 10 ml/kg body weight, using 0.5% CMC as vehicle. The dose levels were selected based on the findings from the preceding 28-day study (Y. S. Kim et al., 2008), and were: vehicle control, 30 mg/kg/day, 125 mg/kg/day, and 500 mg/kg/day.
The 90-day study by Yun et al. was performed in five weeks old Sprague-Dawley rats with, daily gavage treatments of citrate-capped Ag nanoparticles at 257.6, 515.3 and 1030.5 mg/kg, using distilled water as vehicle. The Ag NP had a primary size of 11 nm (determined by TEM), and hydrodynamic size of 19.0 ± 4.6 nm (DLS determined).
The 28-day study by Kim et al. (2008), performed in eight weeks old Sprague-Dawley rats included genotoxicity evaluation using a bone marrow micronucleus test in accordance with OECD TG 474 ("Mammalian Erythrocyte Micronucleus Test"). Dose levels were: vehicle control, 30 mg/kg/day, 300 mg/kg/day, and 1000 mg/kg/day.

Effects after exposure

Liver
Slight liver damage was reported for the highest dose group (500 mg/kg) of the 90-day study by Kim et al. (Y. S. Kim et al., 2010). Effects were indicated by increased levels of ALP and cholesterol in both the male and female rats. Histopathological examination revealed an increased incidence of bile-duct hyperplasia with or without accompanying necrosis, fibrosis, and/or pigmentation, however without statistical significance. On the basis of the combined clinical chemistry and histopathology findings the authors suggested a NOAEL of 30 mg/kg/day and LOAEL of 125 mg/kg/day.
Effects were also observed in the 90-day study by Yun et al. (Yun et al., 2015). The incidence of lymphocyte infiltration in livers of both male and female rats mice in the high-dose group (1030.5 mg/kg) were higher than that in the control group, but the authors also reported that there was no difference in severity of lymphocyte infiltration between the groups. Noteworthy, lymphocyte infiltration was also observed in several control rats of both genders. Biochemical analysis of serum revealed increased levels of ALP in male and female rats exposed to 1030.5 mg/kg Ag nanoparticles. In the female rats, the relative liver weight was significantly decreased after Ag nanoparticle treatment at a dose of 515.3 mg/kg, but not at the higher dose.

Lung
No significant treatment-related change in relative lung weight was observed at sacrifice. No dose related changes in lung histopathology (i.e. inflammation, histocytosis) were found (Y. S. Kim et al., 2010). Lung histopathology was also not observed in the Yun et al. (2015) study.

GIT
No microscopic abnormalities were found in intestine, except for a dose-related increase in the prevalence of villi pigmentation in the male rats (Y. S. Kim et al., 2010). In the study by Yun et al (2015) data on GIT histology were not reported.

Other

There were significant decreases in body weight of the male rats exposed to 500 mg/kg/day at 4, 5 and 7 weeks of exposure as well as at sacrifice (13 weeks) in the absence of significant differences in food consumption and water intake (Y. S. Kim et al., 2010). There were no significant dose-related changes in the body weights of female rats (Y. S. Kim et al., 2010). In study by Yun et al (2015) no effects of Ag were observed regarding body weight or mean daily food and water consumption.

In the 28-day exposure study (Y. S. Kim et al., 2008), genotoxicity was evaluated by bone marrow micronucleus test. No statistically significant treatment-related increase of micronuclei was detected in the male and female rats when compared to the corresponding negative controls (NOAEL = 1000 mg/kg/day).

Some gender specific effects were observed in the Yun et al study (2015). This included increased white blood cell counts (female rats treated with 1030.5 mg/kg Ag), decreased platelet levels (males, 1030.5 mg/kg), serum calcium levels (in female rats of all Ag dose groups compared to controls).

Overall NOAEL/LOAEL for key effect

NOAEL of 30 mg/kg/day is identified from the 90-day study by Kim et al. (Y. S. Kim et al., 2010).

Biodistribution

- In the 90-day study by Kim et al. (2010), silver distribution was determined at sacrifice (13 weeks) by AAS (7300 method, NIOSH 1999) and expressed as µg/g wet weight. Statistically significant dose-dependent increases in silver concentrations were found in all tissues investigated, i.e. in liver, kidneys, brain, lungs, testes and blood. A two-fold higher accumulation of silver was found in the kidneys of female rats when compared with the male rats across all the dose groups.
- Silver concentrations were also determined in the Yun et al study (2015) at 13 weeks sacrifice using ICP-MS. Increased Ag concentrations were found in blood and further organs (blood > spleen > lung > kidney > liver > brain).

Data gaps

- Systemic genotoxicity of the Ag in the 28-day exposure study (Y. S. Kim et al., 2008) was evaluated in bone marrow cells, but not in target tissues of main relevance to PATROLS (i.e. liver, intestine, lung).
- Silver biodistribution was determined by AAS (Y. S. Kim et al., 2010) and ICP-MS (Yun et al., 2015) and thus does not allow insight on its (chemical/particulate) speciation.

2.3.3.3. MWCNT

Available studies

No toxicity studies of adequate duration were found for repeated oral exposure with

the two specific MWCNTs.
One methodological study with 100 days oral exposure to a MWCNT with similar dimensions to NM-402 is published (Shipelin et al., 2017). This methodological paper describes the effect of using surfactant for dispersing MWCNT in drinking water on intestinal permeability, but includes no other toxicological analyses.
For two studies with 90 and 180 days oral exposure to MWCNT similar to NM-402, only the abstracts were available (Ahn et al., n.d.; Khripach et al., 2014) and thus the data were not included here.

Overall NOAEL/LOAEL for key effect

No toxicity studies of adequate duration were found. However, a 28-day study with NM-402-like MWCNT, performed according to OECD TG 423 for testing acute oral toxicity, shows no toxicity (NOAEL: 50 mg/kg bw/day, the highest dose tested) (Matsumoto et al., 2012).

Data gaps

There is a lack of available (sub)chronic oral toxicity studies as well as carcinogenicity studies for MWCNT. The oral route can be relevant for MWCNT since a fraction of airborne MWCNT or MWCNTs cleared from the lungs can be swallowed. Systemic and local genotoxicity has not been assessed.

2.3.3.4. Titanium dioxide

Available studies

Five studies of adequate duration and sufficient characterization of the test material were identified.

- Only one 90-day study was performed as a toxicity study following OECD TG 408 (unpublished) (KRISS, 2018), including a recovery period of 28 days. In this study with oral gavage of 250, 500 or 1000 mg/kg/day AEROXIDE® TiO2 P25, no effects were observed on any of the endpoints investigated, including no effects in lung, liver or GIT (NOAEL of 1000 mg/kg/day, highest dose tested).
- One 26-week study focused on the mechanism of TiO_2-induced endoplasmatic reticulum stress in liver and its effect on plasma glucose level (10, 20, 50, 100, 200 mg/kg/day) (Hu et al., 2018).
- One 100-day study was performed with food grade TiO_2 E171, which contained a nanofraction of 44.7% by number of nanoparticles, with focus on effects in the colon (0.2 and 10 mg/kg/day) (Bettini et al., 2017).
- One 90-day study was only addressing quantitative biodistribution of TiO_2 in tissues (260.4, 520.8, 1041.5 mg/kg/day) (Cho et al., 2013).
- Another 90-day study was only addressing effects on the cardiovascular system which is not the focus of PATROLS (0.2, 10, 50 mg/kg/day) (Chen et al., 2015).

A 90-day and a 2-year oral study in rats and mice with TiO_2 pigment similar to

E171 were excluded, because of insufficient physico-chemical characterization (nanofraction unknown) (National Cancer Institute, 1979).

Effects after exposure

Liver

A NOAEL of 1000 mg/kg/day (highest dose tested) is identified from the study by KRISS (KRISS, 2018, unpublished).

In the mechanistic study by Hu et al. there are indications of liver effects:

- Indication of insulin resistance (IR) (blood glucose was elevated (NOAEL/LOAEL: 20/50 mg/kg bw/d), while insulin was unchanged) (Hu et al., 2018). Liver RNA analysis indicated that TiO_2 NPs affected pathways for controlling plasma glucose homeostasis and xenobiotic biodegradation via cytochrome P450, as well as the generation of ROS and other oxidants, and could induce endoplasmatic reticulum (ER) stress and inflammation. ER stress has been suggested as a potential mechanism involved in IR (Hu et al., 2018).
- Indication of oxidative stress (total superoxide dismutase and GSH consumed at higher rate (NOAEL/LOAEL: 20/50 mg/kg bw/d) in liver and serum, and higher levels of MDA in serum and liver at these doses) (Hu et al., 2018).

Although not included in the database because of the study duration shorter than 90 days, several papers have reported additional or more severe liver effects. Therefore, these effects could be considered as well.

- Liver edema in a 30-d study with young rats (3 weeks old instead of 8) (NOAEL/LOAEL: 10/50 mg/kg bw/d) (Wang et al., 2013).
- Increase in AST, ALP and ALT in plasma of mice exposed 14 d (LOAEL: 10 mg/kg bw/d) (Shukla, Kumar, Vallabani, Pandey, & Dhawan, 2014).
- Increase in AST, ALP and ALT in plasma, increase in MDA, Bax gene expression, necrosis and steatosis in liver, and decrease in GSH, SOD enzyme activity, GPX enzyme activity, and Bcl-2 gene expression in liver at single dose of 100 mg/kg bw/d in rats exposed 60 days. (Morgan, Ibrahim, Galal, Ogaly, & Abd-Elsalam, 2018).

Lung

A NOAEL of 1000 mg/kg/day (highest dose tested) is identified from the study by KRISS (KRISS, 2018, unpublished).

GIT

A NOAEL of 1000 mg/kg/day (highest dose tested) is identified from the study by KRISS (KRISS, 2018, unpublished).

In the mechanistic study by Bettini et al. with food grade TiO_2 there are indications of GIT effects:

- Involvement of food grade TiO_2 in colorectal cancer has been suggested based on an unusual finding of aberrant crypt foci (putative pre-neoplastic lesion) in healthy rats (Bettini et al., 2017).
- Effect on T cell populations in Peyer's Patches (decrease in regulatory T cells (CD4+CD25+FoxP3+) and decrease in CD4+CD25+ T helper cells) (Bettini et al., 2017).
- Low-grade inflammation in the colon (moderate increase in cytokines (TNF-α, IL-8 and IL-10) but no cleaved caspase-1 or its products IL-1β and IL-18 in colonic mucosa) (Bettini et al., 2017).

Other

Two studies indicated systemic inflammation (NOAEL/LOAEL: 10/50 mg/kg bw/d) (increased white blood cells count (WBC) and granulocytes (GRN) in blood (Chen et al., 2015), and increased concentrations of tumour necrosis factor α (TNF α) and interleukin 6 (IL-6) in serum (Hu et al., 2018)).

Overall NOAEL/LOAEL for key effect

NOAEL of 1000 mg/kg/day (highest dose tested) is identified from the study by KRISS. However, some subacute studies report effects in liver and gut at lower doses. This could be due to different types of TiO_2 materials.

Biodistribution

- (Hu et al., 2018): After 28 weeks of exposure there are higher organ levels of Ti than in control found via tissue digestion for liver, pancreas, spleen, kidney and small intestine
- (Cho et al., 2013): After 90 days of exposure, there is increased Ti concentration found via ICP-MS in feces and in blood at the two highest doses (520.8 and 1041.5). There is no significant increase of Ti concentration in urine, liver, spleen, kidney, and brain.
- (Bettini et al., 2017) (qualitative): After 7 days of exposure, particles are found in gut lumen, Peyers patches (PP), colon mucosa and liver. Sub-cellular localization is shown via high-resolution imaging.

It must be considered that feed may add to the background levels of TiO_2 in organs of laboratory animals, and that detection sensitivities and specificity differ among analytical methods applied. This can result in an inability to detect small increases in organ levels after TiO_2 dosage.

Data gaps

- The studies are too short to demonstrate development of cancer. (A 2-year study with uncharacterized TiO_2 pigment did not show any carcinogenicity (National Cancer Institute, 1979))
- Systemic and local genotoxicity assessments were not included in these sub-chronic studies, except for a negative comet assay on Peyer's Patches after 7 days in Bettini et al.. In general, the genotoxicity assays published show

contradictory results according to reviews (Charles et al., 2018; Møller et al., 2017) and some genotoxicity studies are of limited validity and/or cannot be used for regulatory risk assessment (EFSA, 2016).

2.3.3.5. Amorphous silicon dioxide

Available studies

Six studies of adequate duration were identified. In these studies, often more than one amorphous silica was tested. Depending on the production procedure, amorphous silica may exert different toxicity, which was shown by various inhalation studies.

There were three 90-day studies with oral gavage in rats performed according to OECD TG 408, two of them were following GLP regulations.

- In the first study, colloidal silica of 20 or 100 nm particle size were tested in doses of 500, 1000 and 2000 mg/kg body weight for each of the substances (Y.-R. Kim, Lee, et al., 2014) (for comparison the estimated human intake is 2 mg/kg bw/day).
- A second 90-day study tested one type of amorphous silica at doses 245, 490 and 980 mg/kg body weight (Yun et al., 2015).
- The third 90-day study was performed with two types of precipitated amorphous silica, one with about 26 nm and one with 1088 nm primary particle size (Liang et al., 2018). The doses were 167, 500 and 1500 mg/kg body weight for each of the substances.

There were three studies with dietary exposure of silica.

- One feeding study in rats testing two types of pyrogenic synthetic amorphous silica: SAS, a commercially available food additive (similar to E551, primary particle size of 7nm) and NM-202 (primary particle size between 10 and 25 nm) (van der Zande et al., 2014). The food additive SAS was administered in the diet at doses of 100, 1000 and 2500 mg/kg body weight/day and NM-202 at doses of 100, 500 and 1000 mg/kg bw/day for 28 days and doses of 2500mg SAS/kg bw/day or 1000 mg NM-202/kg bw day for 84 days. The study examined transcriptomics and biodistribution in selected extra-pulmonary organs, clinical chemistry parameters and histopathology.
- One 28-week feeding study was performed with perlite powder (containing 72 % silica) in mice (Sakai & Nagao, 1985). The highest dose was 20 % in feed.
- One long-term feeding study was performed with colloidal silica Syloid (Takizawa et al., 1988) in mice and rats. The highest tested dose was 6100 mg/kg body weight per day for mice (93 weeks), and 2100 mg/kg body weight per day for rats (103 weeks).

In addition, one 28-day oral gavage study is included because it was performed by a PATROLS partner and thus provides first-hand data (Buesen et al., 2014). This study tested Levasil©200 and 3 surface-modified Levasil©200, each at doses of 1000

mg/kg body weight.

Effects after exposure

Liver

In the study with 28-day oral gavage, the NOAEL was 1000 mg/kg body weight for Levasil 200 and its surface-modified forms (Buesen et al. 2014). In the 84-day study with dietary exposure in rats, the NOAEL of food-grade hydrophilic pyrogenic synthetic amorphous silica was the highest tested dose 2500 mg/kg body weight per day (van der Zande et al., 2014). Fibrosis was observed at this dose, but the incidence did not reach statistical significance. In the same study, NM-202 was tested at 1000 mg/kg body weight which showed a significantly increased incidence of mild fibrosis in the liver, which was accompanied by increased expression of fibrosis-related genes (LOAEL: 1000 mg/kg body weight) (van der Zande et al., 2014).
In the 90-day studies with oral gavage of different types of amorphous silica performed according to OECD TG 408, no adverse effects were observed at either of the tested doses (Y.-R. Kim, Lee, et al., 2014; Liang et al., 2018; Yun et al., 2015). The highest NOAEL from these studies was 2000 mg/kg body weight per day. In the long-term study with mice and rats, the NOAEL was 5 % in feed for both species, corresponding to 6100 mg/kg body weight per day for mice, and 2100 mg/kg body weight per day for rats (Takizawa et al. 1988). Perlite administered to mice in the diet for 28 weeks did not cause adverse effects in the liver (NOAEL: 20% perlite in feed) (Sakai & Nagao, 1985).

Lung

In the study with 28-day oral gavage, the NOAEL was 1000 mg/kg body weight per day for Levasil 200 and its surface-modified forms (Buesen et al., 2014). In the 84-day study in rats, the NOAELs for dietary exposure to two types of pyrogenic synthetic amorphous silica were the highest doses tested of 2500 mg SAS/kg bw per day and 1000 mg NM-202/kg bw per day (van der Zande et al., 2014).
In the 90-day studies with oral gavage of different types of amorphous silica performed according to OECD TG 408, no adverse effects were observed at either of the tested doses (Y.-R. Kim, Lee, et al., 2014; Liang et al., 2018; Yun et al., 2015). The highest NOAEL from these studies was 2000 mg/kg bw per day. Perlite administered to mice in the diet for 28 weeks did not cause adverse effects in the lung (NOAEL: 20% perlite in feed) (Sakai & Nagao, 1985). In the long-term study with mice and rats, NOAEL was 5 % in feed for both species, corresponding to 6100 mg/kg bw per day for mice, and 2100 mg/kg bw per day for rats (Takizawa et al., 1988).

GIT

In the study with 28-day oral gavage, the NOAEL was 1000 mg/kg body weight for Levasil 200 and its surface-modified forms (Buesen et al., 2014). In the 84-day study in rats, the NOAELs for dietary exposure to two types of pyrogenic synthetic amorphous silica were the highest doses tested of 2500 mg SAS/kg bw per day and 1000 mg NM-202/kg bw per day (van der Zande et al., 2014). Transcriptomics

revealed no change in gene expression pattern for jejunum for both types of tested silica (van der Zande et al., 2014).
In the 90-day studies with oral gavage of different types of amorphous silica performed according to OECD TG 408, no adverse effects were observed at either of the tested doses (Y.-R. Kim, Lee, et al., 2014; Liang et al., 2018; Yun et al., 2015). The highest NOAEL from these studies was 2000 mg/kg bw per day. Perlite did not cause adverse effects in the GIT during 28-week dietary administration to mice (NOAEL: 20% perlite in feed) (Sakai & Nagao, 1985). In the long-term study with mice and rats, the NOAEL was 5 % in feed for both species, corresponding to 6100 mg/kg bw per day for mice, and 2100 mg/kg bw per day for rats (Takizawa et al., 1988).

Other
Perlite powder administered in feed to mice reduced growth rates at 20% and 10 % perlite in feed. Based on growth rate, the NOAEL for perlite is 1 % in feed. The studies did not show any adverse effects in other organs with any of the tested amorphous silica after oral administration by gavage or in the diet.

Overall NOAEL/LOAEL for key effect

NOAEL of 5 % colloidal silica in feed (highest dose tested) is identified from Takizawa et al (1988) in a long-term study in rats (2100 mg/kg bw/day), and mice (6100 mg/kg bw/day).
The study by van der Zande et al. (2014) suggests that dietary exposure to 1000 mg NM-202 per kg bw per day for 84 days causes mild liver fibrosis in rats. However, additional studies are needed to evaluate the relevance of the effects reported (EFSA, 2018).

Biodistribution

- (van der Zande et al., 2014): After 28-day exposure via feed to SAS up to 2500 mg/kg bw per day, no difference in Si levels in the examined organs was found (liver, spleen, kidney, brain and testes). In NM-202 exposed groups statistically significantly increased Si levels were found in the liver for the low and mid doses (100 and 500 mg/kg bw per day), and in kidneys and spleen for a low dose only. After 84 days of dietary exposure to SAS (2500 mg/kg bw per day) the Si level in the spleen was statistically significantly higher than in the control group. The levels of Si in other organs (liver, kidneys, brain and testes) were not statistically significantly different from the controls. After 84 days of dietary exposure to NM-202 (1000 mg/kg bw per day), there was no difference in Si levels in all organs examined.
- (Liang et al., 2018): After 90 days of exposure by gavage, there is no increased concentration of Si found in blood, liver, kidney and testis at the highest dose (1500 mg/kg body weight). Bio-dissolution in gastric and intestinal fluid was determined under static condition (10 mg/mL). The dissolved fraction of silica nanoparticles and silica micronparticles were 0.010% ± 0.002% and 0.015% ±

0.006%, respectively, in the simulated gastric solution and 0.420% ± 0.007% and 0.361% ± 0.052%, respectively, in the intestinal solution.

- (Yun et al., 2015): After 90 days of exposure by gavage, there is no increased concentration of Si found in blood, liver, spleen, kidney, lung and brain at the highest dose (980 mg/kg body weight).

Data gaps

Systemic and local genotoxicity was not assessed in these sub-chronic and chronic studies.

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van der Zande, M., Vandebriel, R. J., Groot, M. J., Kramer, E., Herrera Rivera, Z. E., Rasmussen, K., … Bouwmeester, H. (2014). Sub-chronic toxicity study in rats orally exposed to nanostructured silica. *Particle and Fibre Toxicology*, *11*(1), 1–19. https://doi.org/10.1186/1743-8977-11-8

Wang, Y., Chen, Z., Ba, T., Pu, J., Chen, T., Song, Y., … Jia, G. (2013). Susceptibility of Young and Adult Rats to the Oral Toxicity of Titanium Dioxide Nanoparticles. *Small*, *9*(9–10), 1742–1752. https://doi.org/10.1002/smll.201201185

Yun, J.-W., Kim, S.-H., You, J.-R., Kim, W. H., Jang, J.-J., Min, S.-K., … Che, J.-H. (2015). Comparative toxicity of silicon dioxide, silver and iron oxide nanoparticles after repeated oral administration to rats. *Journal of Applied Toxicology*, *35*(6), 681–693. https://doi.org/10.1002/jat.3125

3. Deviations from the Workplan

There have been no deviations from the workplan.

4. Performance of the partners

The report and data table was drafted by NRCWE with input from LTAP, RIVM, KRISS, IUF and BASF. The report was reviewed by the PATROLS Steering Board for input, comments and amendments. All partners contributed to the task as requested and fulfilled their requirements in a satisfactory time period.

5. Conclusions

The Steering Board deems this deliverable to be fulfilled satisfactory.

6. Annex

6.1. A: Search strategy

The search for relevant studies was distributed among partners and based on each partners experience in nanotoxicology. This deliverable should not be considered as a complete or systematic review.

Inhalation

Relevant (sub)chronic inhalation studies had already been identified in the grant agreement for all PATROLS Tier1 nanomaterials.

Silver, oral

Database: Pubmed

Keyword searches:
“silver” AND “oral” AND “repeated” AND “toxicity” resulted in 20 hits
“silver” and “oral” and “OECD” resulted in 5 hits.

Studies that were retrieved included 21- and 28- Day repeated oral exposure studies, studies focusing on specific effects including microbiome, developmental toxicity. Out of all studies, two 90-days studies were identified that were performed in alignment with OECD and GLP criteria.

Retrieved papers (doi (if available and PMID)
doi: 10.1016/j.fct.2018.01.056. PMID: 29408364
doi: n.a. PMID: 26155640
doi: 10.1186/1743-8977-8-18. PMID: 21631937
doi: n.a. PMID: 20379688
doi: n.a. PMID: 17963127
doi: n.a. PMID: 16327720

doi: n.a. PMID: 15111684
doi: n.a. PMID: 12571677
doi: n.a. PMID: 12539035
doi: n.a. PMID: 10367344
doi: 10.4103/0973-1296.197642. PMID: 28216905
doi: n.a. PMID: 21712637
doi: 10.1186/1743-8977-7-20. PMID: 20691052
doi: 10.1002/tox.22263. PMID: 26996539
doi: 10.1002/jat.3125. PMID: 25752675
doi: 10.1080/08958370701874663 PMID: 18444010
doi: 10.1186/s12951-014-0042-8. PMID: 25311086
doi: 10.1016/j.etap.2010.05.004. PMID: 21787647
doi: 10.1016/j.ntt.2015.08.006. PMID: 26340819
doi: 10.1016/j.fct.2016.09.026. PMID: 27658324
doi: 10.1016/j.jchemneu.2017.09.001. PMID: 28890110
doi: 10.3109/17435390.2015.1078854. PMID: 26525505
doi: 10.3109/17435390.2013.857734. PMID: 24266865
doi: 10.3109/15376516.2013.764950. PMID: 23301827
doi: 10.3109/17435390.2012.676099. PMID: 22417112

MWCNT, oral

Database: Google Scholar

Search term: search word	**No. Hits**	**Relevant references**
allintitle: oral MWCNT	1	(Ahn et al., n.d.) 13-week oral MWCNT and SWCNT *(full text not available)*
allintitle: nanotube oral	13	1 relevant: (Matsumoto et al., 2012) *Only 28-days exposure*
allintitle: nanotubes oral	36	4 relevant: (Christophersen et al., 2016) 10 weeks (*only 1 exposure per week*) oral MWCNT (Shipelin et al., 2017) MWCNT 100d oral (*only methodological, no toxicity)* (Khripach et al., 2014) chronic per-oral MWCNT (*full text in Russian not available*) (Gerencsér, Varjas, Szendi, & Varga, 2016) MWCNT 90d oral (*only 1 exposure per week*)
allintitle: nanofiber oral	11	none relevant
allintitle: nanofibre oral	0	

allintitle: CNT oral	1	none relevant

Ahn, T.-H., Han, Z.-Z., Xu, H.-D., Gil, K.-H., Lee, J.-Y., Kim, K.-H., … Song, S.-W. (n.d.). 2 and 13-Week Repeated Dose Oral Toxicity Studies of SWCNT and MWCNT in ICR Mice. *Korean Journal of Veterinary Science*, *50*(1), 105. Retrieved from http://210.101.116.28/W_files/kiss6/06904155_pv.pdf

Christophersen, D. V, Jacobsen, N. R., Andersen, M. H. G., Connell, S. P., Barfod, K. K., Thomsen, M. B., … Møller, P. (2016). Cardiovascular health effects of oral and pulmonary exposure to multi-walled carbon nanotubes in ApoE-deficient mice. *Toxicology*, *371*, 29–40. https://doi.org/10.1016/j.tox.2016.10.003

Gerencsér, G., Varjas, T., Szendi, K., & Varga, C. (2016). In vivo induction of primary DNA lesions upon subchronic oral exposure to multi-walled carbon nanotubes. *In Vivo*, *30*(6), 863–867. https://doi.org/10.21873/invivo.11006

Khripach, L. V, Rakhmanin, I. A., Mikhajlova, R. I., Knyazeva, T. D., Koganova, Z. I., Zhelezniak, E. V, … Revazova, T. L. (2014). Biochemical effects of chronic peroral administration of carbon nanotubes and activated charcoal in drinking water in rats. *Gigiena i Sanitariia*, (5), 36–42. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25831926

Matsumoto, M., Serizawa, H., Sunaga, M., Kato, H., Takahashi, M., Hirata-Koizumi, M., … Hirose, A. (2012). No toxicological effects on acute and repeated oral gavage doses of single-wall or multi-wall carbon nanotube in rats. *The Journal of Toxicological Sciences*, *37*(3), 463–474. https://doi.org/10.2131/jts.37.463

Shipelin, V. A., Shumakova, A. A., Masyutin, A. G., Chernov, A. I., Sidorova, Y. S., Gmoshinski, I. V., & Khotimchenko, S. A. (2017). In Vivo Subacute Oral Toxicity Assessment of Multiwalled Carbon Nanotubes: Characteristic of Nanomaterial and Integral Indicators. *Nanotechnologies in Russia*, *12*(9–10), 559–568. https://doi.org/10.1134/S199507801705010X

<u>TiO2, oral</u>

Relevant (sub)chronic studies were found via a literature database collected over the years by RIVM

<u>BaSO4 oral</u>

No relevant sub-chronic oral studies found for BaSO4.

Database: pubmed

Keyword: Barium sulfate + oral + repeated dose: 2 hits, both not relevant
Keyword: barium sulfate + oral: 631 hits (lots of human studies)
Keyword: barium sulfate + oral + toxicity: 13 hits
Keyword: barium + oral + toxicity: 33 hits

In addition, a few reviews about barium toxicity. The majority of the oral studies were performed with BaCl2 and BaCO3. The bioavailability of all Ba salts (including sulfate) was comparable.

SiO2, amorphous, oral

Database: pubmed.

The keywords “amorphous silica” and “oral” and “toxicity” resulted in 16 hits.
The keywords “silica” and “oral” and “toxicity” resulted in 333 hits.

Clay, zeolite, perlite, asbestos and other mineral fibres and all silicates (calcium, magnesium silicates etc.) were excluded. Also mesoporous silica was excluded because they were tested as drug delivery system.

4 relevant 90-day studies were identified by reading abstracts. Reading two of those papers, I think at least two are of acceptable quality. In the reviews there were more relevant studies, but we do not have access to the full reports. Therefore, it was agreed not to include them in the data base. Below are the 16 references concerning oral toxicity of amorphous silica, with the most relevant marked in bold.

1) Bernard, B. K., M. R. Osheroff, A. Hofmann and J. H. Mennear (1990). "Toxicology and carcinogenesis studies of dietary titanium dioxide-coated mica in male and female Fischer 344 rats." J Toxicol Environ Health 29(4): 417-429.
2) Buesen, R., R. Landsiedel, U. G. Sauer, W. Wohlleben, S. Groeters, V. Strauss, H. Kamp and B. van Ravenzwaay (2014). "Effects of SiO(2), ZrO(2), and BaSO(4) nanomaterials with or without surface functionalization upon 28-day oral exposure to rats." Arch Toxicol 88(10): 1881-1906.
3) Desai, C. H., A. Burkman and R. Salisbury (1958). "Chronic oral toxicity of aerated silicagel." J Am Pharm Assoc Am Pharm Assoc 47(8): 589-590.
4) Elmore, A. R. (2003). "Final report on the safety assessment of aluminum silicate, calcium silicate, magnesium aluminum silicate, magnesium silicate, magnesium trisilicate, sodium magnesium silicate, zirconium silicate, attapulgite, bentonite, Fuller's earth, hectorite, kaolin, lithium magnesium silicate, lithium magnesium sodium silicate, montmorillonite, pyrophyllite, and zeolite." Int J Toxicol 22 Suppl 1: 37-102.
5) Fruijtier-Polloth, C. (2016). "The safety of nanostructured synthetic amorphous silica (SAS) as a food additive (E 551)." Arch Toxicol 90(12): 2885-2916.
6) Hassankhani, R., M. Esmaeillou, A. A. Tehrani, K. Nasirzadeh, F. Khadir and H. Maadi (2015). "In vivo toxicity of orally administrated silicon dioxide nanoparticles in healthy adult mice." Environ Sci Pollut Res Int 22(2): 1127-1132.

7) Hofmann, T., S. Schneider, A. Wolterbeek, H. van de Sandt, R. Landsiedel and B. van Ravenzwaay (2015). "Prenatal toxicity of synthetic amorphous silica nanomaterial in rats." Reprod Toxicol 56: 141-146.
8) Kim, Y. R., S. Y. Lee, E. J. Lee, S. H. Park, N. W. Seong, H. S. Seo, S. S. Shin, S. J. Kim, E. H. Meang, M. K. Park, M. S. Kim, C. S. Kim, S. K. Kim, S. W. Son, Y. R. Seo, B. H. Kang, B. S. Han, S. S. An, B. J. Lee and M. K. Kim (2014). "Toxicity of colloidal silica nanoparticles administered orally for 90 days in rats." Int J Nanomedicine 9 Suppl 2: 67-78.
9) Li, L., T. Liu, C. Fu, L. Tan, X. Meng and H. Liu (2015). "Biodistribution, excretion, and toxicity of mesoporous silica nanoparticles after oral administration depend on their shape." Nanomedicine 11(8): 1915-1924.
10) Liang, C. L., Q. Xiang, W. M. Cui, J. Fang, N. N. Sun, X. P. Zhang, Y. N. Li, H. Yang, Z. Yu and X. D. Jia (2018). "Subchronic Oral Toxicity of Silica Nanoparticles and Silica Microparticles in Rats." Biomed Environ Sci 31(3): 197-207.
11) Lin, B., Z. Xi, Y. Zhang and H. Zhang (2008). "[Primary study on the hepatotoxicity and nephrotoxicity of rats induced by three kinds of nanomaterials]." Wei Sheng Yan Jiu 37(6): 651-653.
12) Maisanaba, S., M. Puerto, D. Gutierrez-Praena, M. Llana-Ruiz-Cabello, S. Pichardo, A. Mate, M. Jorda-Beneyto, A. M. Camean, S. Aucejo and A. Jos (2014). "In vivo evaluation of activities and expression of antioxidant enzymes in Wistar rats exposed for 90 days to a modified clay." J Toxicol Environ Health A 77(8): 456-466.
13) Maxim, L. D., R. Niebo and E. E. McConnell (2014). "Perlite toxicology and epidemiology--a review." Inhal Toxicol 26(5): 259-270.
14) Sakai, T. and S. Nagao (1985). "Twenty-eight week toxicity study of perlite powder in mice." J Toxicol Sci 10(2): 83-93.
15) Wolterbeek, A., T. Oosterwijk, S. Schneider, R. Landsiedel, D. de Groot, R. van Ee, M. Wouters and H. van de Sandt (2015). "Oral two-generation reproduction toxicity study with NM-200 synthetic amorphous silica in Wistar rats." Reprod Toxicol 56: 147-154.
16) Yun, J. W., S. H. Kim, J. R. You, W. H. Kim, J. J. Jang, S. K. Min, H. C. Kim, D. H. Chung, J. Jeong, B. C. Kang and J. H. Che (2015). "Comparative toxicity of silicon dioxide, silver and iron oxide nanoparticles after repeated oral administration to rats." J Appl Toxicol 35(6): 681-693.

<u>SiO2, crystalline quartz or DQ12, oral</u>

Database: Pubmed

1. “Crystalline silica” + toxicity: 384 hits (among the hits, the majority were instillation or inhalation studies)
2. “Crytalline silica” + “oral toxicity”: 10 hits
3. “DQ 12” and “oral toxicity”: 3 hits

4. Quartz + “oral toxicity”: 10 hits
5. Quartz + “oral study”: 324 hits
6. Quartz + “repeated dose study”:6 hits
7. Quartz + “feeding study”: 13 hits
8. Quartz + “oral exposure”: 68 hits

Most of the studies were done with quartz within resin used for dental treatment. None of them were pure oral feeding or gavage studies.

6.2. B: Public formatted data table “PATROLS task 2_1 *in vivo* data”

Abbreviations

nd	not determined, the parameter was not analyzed or not reported
NM	nanomaterial
NC	No Change
Sig inc	Statistically significant increase
Sig dec	Statistically significant decrease
WBC	White blood cells
MMAD	Mass median aerodynamic diameter
MAD	Median aerodynamic diameter
GSD	Geometric standard deviation
CMAD	Count median aerodynamic diameter
BAL	Bronchoalveolar lavage
NOAEL	No observed adverse effect level
LOAEL	Lowest observed adverse effect level

Notes

Unpublished data have been removed from the public version of this table

Data in grey font are from studies of shorter exposure duration than 90 days

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Ilse Gosens ilse.gosens@rivm.nl	Adamcakova-Dodd 2014 Part Fibre Tox	ZnO	1314-13-2	Meliorum Technologies, Inc. Rochester, NY)	TEM 2 week exposure: 15 ± 4 nm 13 week exposure: 26 ± 11 nm	2 week exposure: 47 ± 1 m^2/g 13 week exposure: 15 ± 4 m^2/g	Surface functionality CO_3^{2-}, OH^-, CH
Minne Heringa Minne.heringa@rivm.nl	Sung 2008 InhalationTox	Ag	(self-generated)	self generated (as in Ji et al., 2007a and 2007b)	TEManalysis: 6-55 nm	(calculated from aerosol conc and aerosol surface area) low dose: 22.1 mid dose: 17.8 high dose: 12.8	Ag (purity not given)

	Nanomaterial		**Aerosol characteristics**	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Adamcakova-Dodd 2014 Part Fibre Tox	ZnO	same crystal structure as that of bulk zincite primary particle size distribution of 15 ± 4 nm and 26 ± 11 nm for the 2 different batches Dissolution of ZnO NPs in simulated biological fluids: less than 1% of ZnO dissolved in Gamble's buffer (pH 7.4) after 2 wks. 100% of the ZnO dissolved within the first 24 hr of mixing in ALF solution.	Geometric mean mobility diameter determined by SMPS 2 week: 46 nm with GSD 1.8 13 week: 36 nm with GSD 1.8	Material density of ZnO 5.61 g/cm^3
Sung 2008 InhalationTox	Ag	spherical	geometric mean diameter ± stdev in chamber: 18.12±1.42 (low dose), 18.33±1.12 (mid dose), 18.93 ±1.59 (high dose)	nd

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Adamcakova-Dodd 2014 Part Fibre Tox	ZnO	yes, particle size distribution with peak below 100 nm measured by SMPS	no	Mice	C57Bl6	male	7	5-6
Sung 2008 InhalationTox	Ag	100% based on DMAS-CPC measurements	no OECD TG reported to have been followed, but other article does say OECD TG 413 and GLP were followed	rat	Sprague Dawley	both	8	10 per sex per dose group, 4 for lung function and BAL cell evaluation

	Nanomaterial				**Toxicological outcomes**	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Adamcakova-Dodd 2014 Part Fibre Tox	ZnO	whole-body	2 and 13 (4h/day, 5d/week) necropsied immediately (0 wk) or 3 weeks (3 wks) post exposure	2 week: 3.6 ± 0.5 mg/m3 13 week: 3.3 ± 0.5 mg/m3	not examined	not examined
Sung 2008 InhalationTox	Ag	inhalation, whole-body	13 (6h/day, 5d/week)	0, 0.049, 0.13, 0.51 (not clear how determined, as only a description is given of the analysis of particle number per cm^3)	nd	nd

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Adamcakova-Dodd 2014 Part Fibre Tox	ZnO	no	not relevant	Lung: Distinct lack of cell injury, fibrosis or eosinophil infiltration in mice from either study. In the few sites with hypercellularity of the alveolar septa, there were occasional granulocytes partially sequestered in the septa composed of both neutrophils and eosinophils, however these were just marginal inside of sticky capillaries due to minor focal activation.	nd (only 1 concentration was tested) after 2 weeks and 13 weeks of exposure
Sung 2008 InhalationTox	Ag	no neoplastic lesions reported	not relevant	Lung: increased incidence of mixed cell infiltrate perivascular and chronic alveolar inflammation, including alveolaritis, granulomatous lesions, and alveolar wall thickening and alveolar macrophage accumulation	I would estimate NOAEL at the mid dose: 0.13 mg/m3

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Adamcakova-Dodd 2014 Part Fibre Tox	ZnO	no fibrosis, based on histopathology of the lung (only 1 c	2 week exposure to 1 concentration %hematocrit in blood air control: 47.7 ± 1.3, 3 week recovery: 52.7 ± 1.1 significant increase significant increase in recruitment of total white blood cells to the lungs that was represented mainly by increased macrophages and a moderate increase of IL-12 (p40) and MIP-1α. None of the other inflammatory pulmonary markers measured in BAL fluid or lungs, histopathology evaluation or changes in pulmonary mechanics after methacholine challenge were significantly different from sham-exposed controls.
Sung 2008 InhalationTox	Ag	not reported	BAL: increased lymphocytes at high dose in males (in females no differences), no further significant differences in cell counts. NOAEL estimated at 0.13 Histology, Lung: significantly increased incidence of mixed cell infiltrate perivascular and chronic alveolar inflammation, including alveolaritis, granulomatous lesions, and alveolar wall thickening and alveolar macrophage accumulation (NOAEL: 0.13)

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Adamcakova-Dodd 2014 Part Fibre Tox	ZnO	only 1 concentration tested after 2 weeks and 13 weeks of exposure	ZnO NPs have very modest inflammatory potency in vivo after repeated inhalation exposures but one time instillation exposure of a bolus dose of NPs caused an inflammatory response. In vitro ZnO NP studies in submersed condition may produce false-positive results due to a higher dissolution of ZnO NPs in media without further translocation and clearance.	blood, liver, kidney, spleen, heart, brain and BAL fluid
Sung 2008 InhalationTox	Ag	increased lymphocytes at high dose in males (in females no differences), no further significant differences in cell counts. NOAEL estimated at 0.13 increased albumin, LDH and total protein at high dose, females (not in males): NOAEL at 0.13	Lung function: All the exposed groups of female rats exhibited decreased minute volumes and peak inspiration flows compared with the control, in males this was only in the high dose group	nd

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Adamcakova-Dodd 2014 Part Fibre Tox	ZnO	directly and 3 weeks after exposure	2 week exposure: BAL fluid air control: 16 ± 2 µg/L, directly 73 ± 9 µg/L= BAL Zn levels back to baseline after 3 weeks recovery lung air control: 123.3 ± 2.6, directly after exposure 144.8 ± 6.9 µg/g (dry wt) Other organs and blood no significant increase compare to air control 13 week exposure: blood air control: 5117 ± 189, after 3 weeks 4950 ± 250 µg/L heart air control: 115.4 ± 4.4 , directly after exposure: 150.9 ± 14.7 µg/g (dry wt)	fast, ZnO dissolves. No rate calculated	not possible to determine since no increase in blood concentration was found
Sung 2008 InhalationTox	Ag	nd	nd	nd	nd

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Adamcakova-Dodd 2014 Part Fibre Tox	ZnO	no significant increase of Zn In blood detected after exposure	important contributor to systemic tissue deposition.	nd	Evaluation of BAL cells and lung tissues using dark field microscopy as well as TEM-EDS did not show a distinct presence of Zn NPs inside the macrophages or lung tissue
Sung 2008 InhalationTox	Ag	nd	nd	no	very minimal tekst

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Minne Heringa Minne.heringa@rivm.nl	Sung 2009 Tox Sci	Ag	(self-generated)	self generated (as in Ji et al., 2007a and 2007b)	TEManalysis: 6-55 nm, mean diameter 18 ±2	(calculated from aerosol conc and aerosol surface area) low dose: 22.1 mid dose: 17.8 high dose: 12.8	Ag by X-ray diffraction not Ag oxides (purity not given) PArticle generator that was used has been shown to generate nanoparticles from 2 to 65 nm in diameter which do not agglomerate in air.

	Nanomaterial		**Aerosol characteristics**	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Sung 2009 Tox Sci	Ag	spherical	geometric mean diameter ± stdev in chamber: 18.12±1.42 (low dose), 18.33±1.12 (mid dose), 18.93 ±1.59 (high dose). Cumulative mean diameter CMD (GSD) 18 (1.5) corresponds well to geometric mean diameter.	nd

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Sung 2009 Tox Sci	Ag	100% based on DMAS-CPC measurements	OECD TG 413 and GLP	rat	Sprague Dawley	both	8	10 per sex per dose group, 4 for lung function and BAL cell evaluation

	Nanomaterial				**Toxicological outcomes**	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Sung 2009 Tox Sci	Ag	inhalation, whole-body	13 (6h/day, 5d/week)	0, 0.049, 0.13, 0.51 (not clear how determined, as only a description is given of the analysis of particle number per cm^3)	nd	nd

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Sung 2009 Tox Sci	Ag	no neoplastic lesions reported	not relevant	In liver: minimal bile-duct hyperplasia (m+f), Single-cell hepatocellular necrosis (f). In lung: chronic alveolar inflammation, a mixed cell perivascular infiltrate, and alveolar macrophage accumulation.	I would estimate NOAEL at the mid dose: 0.13 mg/m3

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Sung 2009 Tox Sci	Ag	only seen in liver of 1 female at high dose: not significant	Histology, Lung: significantly increased incidence of mixed cell infiltrate perivascular and chronic alveolar inflammation, including alveolaritis, granulomatous lesions, and alveolar wall thickening and alveolar macrophage accumulation in lung (NOAEL: 0.13) Hematology and blood biochemistry not changed.

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Sung 2009 Tox Sci	Ag	nd	organ weights unchanged, kidney function unchanged	reported: liver, kidneys, olfacotry bulb, brain, lungs, whole blood

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Sung 2009 Tox Sci	Ag	after 90d	see table 7 in publication: all organs reported showed dose-dependent increase in Ag	nd	nd

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Sung 2009 Tox Sci	Ag	nd	nd	no	same study as above, but other part of results presented.

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Trine Berthing trb@nfa.dk	Kasai 2016 PartFibrTox	MWCNT Mitsui-7		MWNT-7; Lot No. 080126 until 88 weeks, Lot No. 071223 from 89 weeks, from Hodogaya Chemical, Co. Ltd. (Tokyo, Japan).	Bulk lot No. 071223, avg diameter 83.8 nm and length 5.2 µm, with 45.1 % of the tubules being longer than 5 µm. Bulk lot No. 080126, avg diameter 90.7 nm and length 5.7 µm, with 48.7 % of the tubules being longer than 5 µm.	24–28 (info from supplier)	

	Nanomaterial		**Aerosol characteristics**	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Kasai 2016 PartFibrTox	MWCNT Mitsui-7	LA-ICP-MAS: iron, chromium and nickel were 4400, 48, and 17 ppm	MMAD 1.2–1.4, GSD 2.6–3.0, micro-orifice uniform deposit cascade impactor (MOUDI)	nd

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Kasai 2016 PartFibrTox	MWCNT Mitsui-7	nd	OECD Guideline for Testing of Chemicals 451 “Carcinogenicity Studies” and OECD Principles of Good Laboratory Practice	Rat	F344	male female	6	n=50 lung histopathology, n=10+ lung burden, n=5 BALF, n=10 pleural cavity lavage, n=10 abdominal lavage

	Nanomaterial				**Toxicological outcomes**	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Kasai 2016 PartFibrTox	MWCNT Mitsui-7	inhalation, whole-body	104 (6h/day, 5days/week)	0, 0.02, 0.2, and 2	nd	Yes

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Kasai 2016 PartFibrTox	MWCNT Mitsui-7	Lung: Bronchiolo-alveolar carcinoma Adenosquamous carcinoma Poorly differentiated adenocarcinoma Squamous carcinoma Bronchiolo-alveolar adenoma Peritoneum: Malignant mesothelioma.	0.02/0.2	Lung: Bronchiolo-alveolar hyperplasia Atypical hyperplasia Alveolar hyperplasia Bronchiolar hyperplasia Accumulation: alveolar macrophage Focal fibrosis: alveolar wall Granulomatous change Pleura: Simple mesothelial hyperplasia Focal fibrosis: parietal (diaphragm) Focal fibrosis: ventral (lung) Inflammation: mediastinum	0.02/0.2

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Kasai 2016 PartFibrTox	MWCNT Mitsui-7	Histology: Focal fibrosis alveolar wall (0.02/0.2). Focal fibrosis parietal/ventral pleura (0.2/2).	BAL: Sig inc: total cells, neutrophils, eosinophils, lymphocytes, macrophages (0.2/2) Sig inc: ALP, LDH, total protein (0.02/0.2). Histology: Inflammation mediastinum (0.2/2), Inflammation: diaphragm (not significant) Hematology: NC (2/nd) Clinical chemistry: NC (2/nd)

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Kasai 2016 PartFibrTox	MWCNT Mitsui-7	Sig inc: total cells, neutrophils, eosinophils, lymphocytes, macrophages (0.2/2) Sig inc: ALP, LDH, total protein (0.02/0.2).	No exposure-related deaths or clinical signs. No growth retardation based on body weight. Urinary, hematological, and blood biochemical analyses revealed no toxicological changes in either male or female rats. Macroscopic findings: multiple grayish, white areas and nodules were found in the lungs of a large number of male and female rats exposed to 2 mg/m3 MWNT-7. The color tone of the lung surface was darkened in line with the exposure concentration. Absolute and relative lung weights were significantly elevated in male rats exposed to 0.2 and 2 mg/m3 MWNT-7, and they were significantly increased in all exposed female groups. No mesothelioma was detected - Ilse Gosens RIVM: this is due to highly agglomerated aerosol that has been used. This is being filtered by the rats nose, so very little fibers reach the pleura.	Lung, pleural lavage, abdominal lavage. Qualitative by darkfield microscopy: nasal cavity, larynx, trachea, lungs, lymph nodes, pleura (diaphragm), spleen, liver, kidneys, olfactory bulb, and brain

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Kasai 2016 PartFibrTox	MWCNT Mitsui-7	Lung burden via digestion at end of exposure, and of rats that died unexpectedly during exposure. No post-exposure recovery.	Lung burden via digestion at end of exposure: Male 0.02 mg/m3: 10.0 ug/lung, 0.09 × 10^9 fibers/lung, 0.029 ug/g body weight, 0.26 × 10^6 fibers/g body weight 0.2: 152.4, 1.38 × 10^9, 0.434, 3.92 × 10^6 2: 1797.8, 16.2 × 10^9, 4.954, 44.7 × 10^6 Female 0.02: 8.1, 0.07 × 10^9, 0.034, 0.31 × 10^6 0.2: 118.4, 1.07 × 10^9, 0.453, 4.09 × 10^6 2: 1154.1, 10.4 × 10^9, 4.712, 42.5 × 10^6 Pleural lavage at end of exposure: The number of MWNT-7 fibers in the pleural area were 38, 134, and 1468 fibers in the 0.02, 0.2, and 2 mg/m3 exposed males and 23, 240, and 847 fibers in the 0.02, 0.2, and 2 mg/m3 exposed females. Abdominal lavage: The number of MWNT-7 fibers in the abdominal area were 16, 161, and 2429 fibers in the 0.02, 0.2, and 2 mg/m3 exposed males and 34, 294, and 3329 fibers in the 0.02, 0.2, and 2 mg/m3 exposed females.	nd	nd

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Kasai 2016 PartFibrTox	MWCNT Mitsui-7	nd	Number of MWNT-7: 1ug = 9.03 × 10^6 (calculated by scanning electron microscopy). Single or aggregated MWNT-7 s were found in the nasal cavity, larynx, trachea, lungs, lymph nodes, spleen, liver, kidneys, olfactory bulb, and brain of the exposed rats of both sexes. MWNT-7 fibers in the kidney, olfactory bulb, and brain were single and not aggregated. Fukushima2018JOccupHealth: Deposition sites in the lung of MWCNTs are mostly in macrophages, granulomatous lesions, sites of alveolar fibrosis, and BALT, and also non-phagocytosed MWCNTs were observed in the alveolar space.	no	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Trine Berthing trb@nfa.dk	Kasai 2015 Nanotox	MWCNT Mitsui-7		Hodogaya Chemical Co., Ltd. (MWNT-7, Lot No. 071223 and 080126, Tokyo, Japan)	bulk-mean width 90.7 nm and length was 5.7 mm, 48.7% of tubules being longer than 5 mm	24–28 (info from supplier)	nd (supplier info: carbon purity of >99.6% (No. 071223) and >99.8% (No. 080126))

	Nanomaterial		**Aerosol characteristics**	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Kasai 2015 Nanotox	MWCNT Mitsui-7		MMAD 1.4–1.6, GSD 2.3–3.0, micro-orifice uniform deposit cascade impactor (MOUDI). Width of 96.4, 98.0 and 94.1 nm, length of 5.83, 6.19 and 5.53 mm, for 0.2, 1 and 5 mg/m3 groups, respectively.	nd

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Kasai 2015 Nanotox	MWCNT Mitsui-7	nd	OECD Guideline for Testing of Chemicals 413 ''Subchronic Inhalation Toxicity: 90-day Study'' and OECD Principles of Good Laboratory Practice	Rat	F344/DuCrlCrlj	male female	6	n=10 per sex. N=5 (lung burden)

	Nanomaterial				**Toxicological outcomes**	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Kasai 2015 Nanotox	MWCNT Mitsui-7	inhalation, whole-body	13 (6 h/day, 5 days/week)	0.2, 1 and 5	nd	nd

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Kasai 2015 Nanotox	MWCNT Mitsui-7	none	5/nd	Nasal cavity : Goblet cell hyperplasia Eosinophilic globules, olfactory epithelium Eosinophilic globules, respiratory epithelium Nasopharynx: Goblet cell hyperplasia Lung: Granulomatous change Focal fibrosis alveolar wall Visceral pleura: Inflammatory infiltration Deposition of MWCNT: Nasal cavity, respiratory epithelium Larynx, epithelium Trachea, epithelium Bronchus-associated lymphoid tissue Mediastinal lymph nodes Lung: Bronchiolar space Alveolar space Alveolar wall	Nasal cavity, Nasopharynx, Lung : 0.2/1 Visceral pleura: 1/5

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Kasai 2015 Nanotox	MWCNT Mitsui-7	Histology: Lung, Focal fibrosis alveolar wall (0.2/1)	Histology: Lung: Granulomatous change (0.2/1) Visceral pleura: Inflammatory infiltration (1/5) BAL (no statistics): Inc: total cells, neutrophils, lymphocytes (estimated 0.2/1) Sig inc: bi- and multinucleated macrophages (nd/0.2) Sig inc: ALP, LDH, total protein, albumin (nd/0.2). Hematology: Neutrophil percentages in differential white blood cells of 0, 0.2, 1 and 5 mg/m3-exposed female groups were 21%, 24%, 25% and 28% (data not shown, no statistics) Clinica chemistry: NC (5/nd)

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Kasai 2015 Nanotox	MWCNT Mitsui-7	BAL (no statistics): Inc: total cells, neutrophils, lymphocytes (estimated 0.2/1) Sig inc: bi- and multinucleated macrophages (nd/0.2) Sig inc: ALP, LDH, total protein, albumin (nd/0.2).	Lung weights were increased 1.2-fold with 1 mg/m3 and 1.3-fold with 5 mg/m3 in both sexes compared to the controls. In the bronchoalveolar lavage fluid (BALF) analyses, inflammatory parameters were increased concentration-dependently in both sexes from 0.2 mg/m3. Granulomatous changes in the lung were induced at 1 and 5 mg/m3 in females and even at 0.2 mg/m3 in males. Focal fibrosis of the alveolar wall was observed in both sexes at 1 mg/m3 or higher. Inflammatory infiltration in the visceral pleural and subpleural areas was induced only at 5 mg/m3. In conclusion, we determined 0.2 mg/m3 as the low-observed-adverse-effect level (LOAEL) for respiratory tract toxicity.	Quantitative: Lung Qualitative: nasal cavity, larynx, trachea, lungs, lymph nodes, pleura (diaphragm), spleen, liver, kidneys, olfactory bulb, and brain

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Kasai 2015 Nanotox	MWCNT Mitsui-7	Lung burden via digestion at end of exposure	Lung burden via digestion at end of 13-week exposure: 3.23, 21.2 and 120.3 mg/left lung, respectively, for 0.2, 1 and 5 mg/m3 concentration, and in the female groups were 2.30, 13.7 and 80.3 mg/left lung, respectively.	nd	nd

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Kasai 2015 Nanotox	MWCNT Mitsui-7	nd	Histological observation of deposition of MWCNT: Nasal cavity, respiratory epithelium Larynx, epithelium Trachea, epithelium Lung: Bronchiolar space Alveolar space Alveolar wall Bronchus-associated lymphoid tissue Mediastinal lymph nodes	no	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Trine Berthing trb@nfa.dk	Pothmann 2015 PFT	MWCNT NM-402		Graphistrength© C100, Arkema France, (batch no. 110329-018)	External Diameters (nm) (mean ± sd) 12.1 ± 3.5 Internal Diameters (nm) (mean ± sd) 4.4 ± 1.5 Lenght (nm) mean ± sd 1069 ± 1102 D10 209 D50 708 D90 2400 Min. length 90 Max. length 7200 (n≥100)	225.6	%C 92.0, 91.6 (Elementary organic analysis)

	Nanomaterial		**Aerosol characteristics**	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Pothmann 2015 PFT	MWCNT NM-402	Particle Size Distribution (µm) D10 223 D50 418 D90 655 Metal Content Al (% w/w) 3.0 ± 1.5 (n = 4) Fe (% w/w) 2.7 ± 0.6 (n = 4) Co (ppm) <50 Cr (ppm) <50 Mn (ppm) <50 Mo (ppm) <50 Nb (ppm) <50 Ni (ppm) <50 Ti (ppm) <50 V (ppm) <50 W (ppm) <50 Chemical Surface Analysis by XPS C (% w/w) 99.5 ± 0.2 (n = 14) O (% w/w) 0.54 ± 0.20 (n = 14) N (% w/w) < 0.2 (n = 14) Al (% w/w) < 0.2 (n = 14) Fe (% w/w) < 0.2 (n = 14) Diameters External Diameters (nm) (mean ± sd) 12.1 ± 3.5 Internal Diameters (nm) (mean ± sd) 4.4 ± 1.5 Walls number (mean ± sd)I 12 ± 4 Lenght (nm) mean ± sd 1069 ± 1102 D10 209	MMAD: nd, 1.62 ± 0.39, 2.30 ± 0.34. GSD: nd, 4.67 ± 4.81, 2.47 ± 0.26. Mercer cascade impactors (In-Tox Products, Moriarty, USA) using a standard impactor Model 02-005. CMAD (nm): 196.2 ± 54.7, 231.5 ± 65.1, 208.0 ± 62.0 Wide Range Particle Spectrometer© (WRPS, Model 1000XP, MSP Corporation, Shoreview, USA) in the size range of 5 nm to 10 µm to determine CMAD.	0.17, 0.18 *Adapted from ISO 3923/2. Calculated by weighing the mass of 50 cm3 of MWCNT*

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Pothmann 2015 PFT	MWCNT NM-402	nd	OECD test guidelines no. 413, 474 and 489 and OECD Principles of Good Laboratory Practice	Rat	Wistar RccHan: WIST(SPF)	male female	8	n=35 per sex n=10 per sex for histology and BALF n=5 per sex for micronucleus test n=5 males for comet assay

	Nanomaterial				**Toxicological outcomes**	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Pothmann 2015 PFT	MWCNT NM-402	inhalation, nose-only	90 days (6h/day, 5days/week) + 90 days recovery	0.05, 0.25 and 5	Micronucleus test, bone marrow, negative at 24h post-exposure, all doses (0.05, 0.25 and 5). Comet assay, isolated lung, liver and kidney cells, negative at 24h post-exposure, all doses (0.05, 0.25 and 5).	nd

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Pothmann 2015 PFT	MWCNT NM-402	none	5/nd	*No statistical analysis - instead all lesions are listed.* 24h and 90days post-exposure Lung: Black particle deposition Alveolar macrophages Alveolar eosinophilic material (considered to be the result of macrophages membrane cell rupture) Alveolar granulocyte infiltration Interstitial inflammation Bronchiolar cell hypertrophy/hyperplasia (only 24h post-exposure) Focal/multifocal collagen depositions, alveolar septa (only 90days post-exposure) Increased lymphocytes in bronchus associated lymphoid tissue (only 24h post-exposure) Tracheobronchial lymph nodes: Black particle deposition Increased lymphocytes, cortex/paracortex Endothelial vacuolation, high endothelial venule Nasal cavity epithelium, eosinophilic globules Larynx, squamous metaplasia	0.05/0.25 (Lung, Tracheobronchial lymph nodes, Nasal cavity, Larynx, 24h and 90 days after recovery)

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Pothmann 2015 PFT	MWCNT NM-402	Histology: Focal/multifocal collagen depositions, alveolar septa (only 90days post-exposure) (0.25/5)	Histology: Alveolar granulocyte infiltration (0.25/5) Interstitial inflammation (0.25/5) Increased lymphocytes in bronchus associated lymphoid tissue (only 24h post-exposure) (0.25/5) Hematology: Sig inc: neutrophil, Sig dec: lymphocyte (24h and 90 days post-exposure) (0.25/5) (Following statistically significant changes are not considered treatment-related by authors, since they are in the range of historical controls: Sig inc: eosinophil (24h post-exposure, not 90days post-exposure) (0.05/0.25). Sig inc: prothrombin time (24h post-exposure, not 90days post-exposure) (not dose-depedent). Sig inc: platelets (24h post-exposure - only male, not 90days post-exposure) (0.25/5).) Blood chemistry: Sig inc: potassium (nd/0.05) (24h post-exposure, not 90days post-exposure) (According to authors: low magnitude and not treatment related) Sig changes in creatinine, triglycerides, sodium, chloride, calcium, and total proteins (not considered treatment-related by authors, since it is within historical controls)

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Pothmann 2015 PFT	MWCNT NM-402	BAL 24h and 90 days post-exposure Sig inc: total cells, neutrophils, lymphocytes (0.05/0.25) Sig dec: macrophages (0.05/0.25) NC: viability Sig inc: protein, phospholipids, LDH , GGT, ALP (0.05/0.25) Sig inc: TNF-α, IL-1β (0.05/0.25) (IL-5, IL-1 α measured, but no dose-response)	All animals survived the 90-day exposure and recovery periods. There were no test-item related clinical signs in any group. Slightly reduced body weight gains were seen in males and females exposed to 0.25 and 5.0 mg/m3 during several weeks of exposure. However, the mean body weights of these animals remained similar to the control group during the exposure period. Increased body weight gains in males and females and body weights in males were observed during recovery in animals exposed to 5.0 mg/m3. Black brown foci in the lung and black brown discoloration of the bronchial lymph nodes were recorded in all or most animals 24 h and 90 days after 90 days of exposure to 5.0 mg/m3. Twenty-hour hours post-exposure, absolute and relative (to body weight) lung weights were increased in males (+47 and +50 %, respectively) and females (+45 and +50 %, respectively) exposed to 5.0 mg/m3 (Table 7). Lung weight (absolute and relative) were still increased in males (+62 and +53 %, respectively) and females (+45 and +36 %, respectively) exposed to 5.0 mg/m3 after 90 days of recovery.	nd Microscopical examination of black particles in all histology organs.

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Pothmann 2015 PFT	MWCNT NM-402	nd	nd	nd After 90 days of recovery, the mean severity of black particles in the lung decreased at 0.05 and 0.25 mg/m3, indicating partial clearance of the black particles at these two lower concentrations; however, at 5.0 mg/m3, the mean severity score were overall similar indicating incomplete clearance during this timeframe in these lungs overloaded with Graphistrength© C100 particles. After 90 days of recovery, the mean severity score of black particle deposition in tracheobronchial lymph nodes was similar at 0.25 mg/m3 and slightly increased at 5.0 mg/m3, consistent with continuous drainage of black particles from the lungs after the end of the treatment.	nd

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Pothmann 2015 PFT	MWCNT NM-402	nd	Deposition of variably-sized and shaped black particles, localized in the lungs, within the alveolar macrophages, were observed in all rats exposed to 0.05 and 0.25 mg/m3 and within tissue macrophages or free within the alveolar lumen or at the tracheal bifurcation in rats exposed to 5.0 mg/m3. Minimal to marked concentration-related deposition of black particles in cortex/paracortex of the tracheobronchial lymph nodes in rats exposed to 0.25 and 5.0 mg/m3. No deposit of MWCNT aggregate was observed in the liver, kidneys and bone marrow and other organs	no	Data from 52-week post-exposure recovery in Regnier2017JPhysics including Blood pressure, hematology, blood chemistry, urinalysis, BAL, Lung histopathology, sperm analysis. Extensive physchem characterization before and after aerosolization in Additional File available on-line at the Journal.

		Nanomaterial			NM phys-chem characteristics (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017)	BaSO4					
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Kundura et al. 2014 PartFibrTox (only inhalation data of this paper)	BaSO4	7727-43-7	Solvay (batch 8143)	25 nm	41.4	not reported, but it was the same batch as above.
Ilse Gosens ilse.gosens@rivm.nl	Schwotzer 2017 PartFib	$BaSO_4$	7727-43-7	NM-220 JRC	37.5 nm	BET 41.4 m2/g	nd

	Nanomaterial		**Aerosol characteristics**	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017)	BaSO4			
Kundura et al. 2014 PartFibrTox (only inhalation data of this paper)	BaSO4	non-spherical globular with no fibre, rod or platelet impurities. Photocatalytic activity (methylen blue assay) was extremly low. Zeta-Potential at pH 7 was --28 mV	MMAD ranged from 2,0 µm to 2.7 µm, GSD was 2.0 for all measurements	nd
Schwotzer 2017 PartFib	$BaSO_4$	purity > 93.8% water solubility 0.6 x 10^{-3} W-% Ba^{++} More characterisation information is provided by Wohlleben W, Ma-Hock L, Boyko V, Cox G, Egenolf H, Freiberger H, et al. Nanospecific guidance in REACH: a comparative physical-chemical characterization of 15 materials with methodical correlations. J Ceramic Sci Technol. 2013;4:93–104. doi:10.4416/JCST2012-00045.	MMAD 2.95 µm and GSD 2.43 µm By gravimetric analysis using Marple298 Personal Cascade Impactor	nd

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017)	BaSO4							
Kundura et al. 2014 PartFibrTox (only inhalation data of this paper)	BaSO4	yes. SMPS measurement CMDs were between 0.25 to 0.3 µm.	OECD 412, GLP	rat	Wistar Han	female	9 weeks	n=10 histopathology, n=5 lavage
Schwotzer 2017 PartFib	$BaSO_4$	nd, but the high MMAD indicated high agglomeration. Consequently, deposition is predicted in the upper respiratory tract. This is supported by finding major histopathological effects in the nasal cavity and only marginal effects in the alveoli.	OECD TG413	rat	Wister	Female	10	10 rats/dose group for hematological and clinico-chemical examination. 5 rats/dose group for lung burden. 5 rats/ dose group for all 5 time points for BALF. 10 rats/ dose group histology 6 rats/dose group highest exposure for immunohistochemistry 576 rats in total, combined with CeO2.

	Nanomaterial				Toxicological outcomes	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017)	BaSO4					
Kundura et al. 2014 PartFibrTox (only inhalation data of this paper)	BaSO4	whole-body	6 h/week, 4 weeks + 4 weeks recovery (histopath + lavage); 6h/week, 13 weeks (lavage only)	50 mg/m³	nd	nd
Schwotzer 2017 PartFib	$BaSO_4$	inhalation nose-only	90 days (6 h/day, 5 days/week) with recovery period up to 90 days	required: 50 mg/m3 measured: 48.82 +/ 4.52	Negative. 50 mg/m3: g-H2AX immunohistochemistry not significantly different from clean air control	nd

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017)	BaSO4				
Kundura et al. 2014 PartFibrTox (only inhalation data of this paper)	BaSO4	no adverse effects	50 mg/m³ (4 weeks exposure)	no adverse effects	50 mg/m³ (4 weeks exposure)
Schwotzer 2017 PartFib	$BaSO_4$	no	No neoplastic changes at the single concentration tested, 50 mg/m3	Lung: Accumulation of particle laden macrophages and in alveolar/interstitium at 1, 28, 90+1, 90+28 and 90+90 days. Lung-associated lymph nodes: accumulation of particle laden macrophages mediastinal and tracheobronchial significant at 28, 90+1, 90+28 and 90+90 days. Nasal cavity: accumulation of particle laden macrophages at 28, 90+1, 90+28 and 90+90 days. Eosinophilic globules in olfactory and respiratory epithelium at day 90+1, 90+28 and 90+90 days. Mucus cell hyperplasia and inflammation at 90+1 days. Recovers after 90 days.	nd (only 1 concentration was tested, 50) but multiple timepoints

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017)	BaSO4		
Kundura et al. 2014 PartFibrTox (only inhalation data of this paper)	BaSO4	No fibrosis at the single dose, 50 mg/m³	No inflammation observed after 28 day exposure, NOAEL 50 mg/m³ After 90 day exposure, LOAEL 50 mg/m³ due to minimal increased neutrophiles in BAL
Schwotzer 2017 PartFib	$BaSO_4$	No interstitial fibrosis at single dose tested, 50	Very slight alveolar/interstitial infiltration of inflammatory cells significant at 90+1 and 90+28. No persistent granulomatous inflammation.

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017)	BaSO4			
Kundura et al. 2014 PartFibrTox (only inhalation data of this paper)	BaSO4	On day 29: sig inc neutrophile, MCP-1, CINC-1/IL-8 (50 mg/m³)	the marginal effects in the lavage was considered non-adverse, because of the marginality and missing corresponding histopathology finding)	lung, lung associated lymph nodes
Schwotzer 2017 PartFib	$BaSO_4$	only 1 concentration examined but multiple timepoints. PMN significantly different at 90+1 day, but not yet at day 28. Lymphocytes significantly different at 90+28 day and not yet at 90+1 day.	Main aim of the study was to investigte potential health effects of CeO2 NPs after subchronic inhalation to low doses. BaSO4 is classified as inert dust, low concentrations were not tested. A high exposure level was tested to test if there is an upper limit of no effects when administered over longer time spans. 50 mg/m3: Ki67 as marker of cell proliferation immunohistochemistry on terminal bronchi significantly different in terminal bronchi at 90+1 and 90+90 days. and significantly different from controls in lung parenchyma at 28 and 90+1 day.	lung

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017)	BaSO4				
Kundura et al. 2014 PartFibrTox (only inhalation data of this paper)	BaSO4	on day 29 (the day after last exposure), day 30 (two days after the last exposure), day 63 (35 days after the last exposure)	0.84 mg/lung (day 29), 0.90 mg/lung (day 30); 0.04 mg/lung (day 63, after about 4 weeks exposure-free period)	10 days	nd.
Schwotzer 2017 PartFib	$BaSO_4$	day 1 and day 28 during 90 day exposure as well as 1, 28 and 90 days after 90 day exposure	day 1: clean air gives 1.2 +/- 1.0 ug/lung 50mg/m3 gives 143+/-16.3 ug/lung day 28: clean air gives 0.6 +/- 0.2 ug/lung 50 mg/m3 gives 1078+/-197 ug/lung d90+1: clean air gives 1.8 +/- 0.8 ug/lung 50 mg/m3 gives 1591 +/-530 ug/lung d90+28: clean air gives 0.8 +/- 0.5 ug/lung 50 mg/m3 gives 871 +/-322 ug/lung d90+90: clean air gives 1.3 +/- 1.3 ug/lung 50 mg/m3 gives 571 +/-358 ug/lung	50 mg/m3: 56	nd

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017)	BaSO4				
Kundura et al. 2014 PartFibrTox (only inhalation data of this paper)	BaSO4	nd.	fast clearance and IT data indicated bioavailablility, highest amount of Ba was found in bone and bone marrow, as well as in blood	no	
Schwotzer 2017 PartFib	$BaSO_4$	nd	material is cleared to lung-associated lymph nodes as expected	nd	high MMAD indicates agglomeration. Major histopathological effects were found mainly in nasal cavity. Alveolar deposition and inflammatory reactions were low. Blood concentration not measured

		Nanomaterial			NM phys-chem characteristics (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017), gentox parameters published by Cordelli et al. 2016	CeO2					

	Nanomaterial		Aerosol characteristics	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017), gentox parameters published by Cordelli et al. 2016	CeO2			

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017), gentox parameters published by Cordelli et al. 2016	CeO2							

	Nanomaterial				Toxicological outcomes	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017), gentox parameters published by Cordelli et al. 2016	CeO2					

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017), gentox parameters published by Cordelli et al. 2016	CeO2				

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017), gentox parameters published by Cordelli et al. 2016	CeO2		

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017), gentox parameters published by Cordelli et al. 2016	CeO2			

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017), gentox parameters published by Cordelli et al. 2016	CeO2				

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Unpublished data, personal communication, Tenschert et al., Laux et. al. (SOT 2016), Ma-Hock et al., Ernst et al. (Eurotox 2017), gentox parameters published by Cordelli et al. 2016	CeO2				

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Ilse Gosens ilse.gosens@rivm.nl	Schwotzer 2017 PartFib	CeO_2	1306-38-3	NM-212 JRC	28.4 nm +/- 10.4 (mean Ferets diameter from SEM pictures) (partially based on Singh 2014)	BET 27.2 +/- 0.9 m^2/g and BET 27.9 +/- 1.5 m^2/g based on measurements in 2 different laboratoria (Singh 2014)	nd

	Nanomaterial		**Aerosol characteristics**	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Schwotzer 2017 PartFib	CeO_2	purity > 99.5% water solubility < 1 µg/L Detailed characterisation report is available: Singh C, Friedrichs S, Ceccone G, Gibson N, Jensen KA, Levin M, et al. Cerium dioxide NM-211, NM-212, NM-213, characterisation and test item preparation: JRC repository: NM-series of representative manufactured nanomaterials. Luxembourg: Publications Office of the European union; 2014	0.1 mg/m3: MMAD 0.71 µm and GSD 3.59 0.3 mg/m3: MMAD 0.63 µm and GSD 3.83 1.0 mg/m3: MMAD 0.68 µm and GSD 4.23 3.0 mg/m3: MMAD 0.79 µm and GSD 3.50 By gravimetric analysis using Marple298 Personal Cascade Impactor	nd, but powder is highly agglomerated based on SEM pictures presented in Singh 2014. Material density of CeO2 is 7.65 g/cm3. It is estimated that the effective density is between 1.5 - 2.4 g/cm3 (based on DeLoid NatCommun2014).

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Schwotzer 2017 PartFib	CeO_2	nd, but there is dustiness data reported in Singh 2014. Based on the MMAD and GSD, the reported alveolar effects in histopathology, a substantial amount reaches the alveolar compartment and is likely < 500nm.	OECD TG413	rat	Wister	Female	10	10 rats/dose group for hematological and clinico-chemical examination. 5 rats/dose group for lung burden. 5 rats/ dose group for all 5 time points for BALF. 10 rats/ dose group histology 6 rats/dose group highest exposure for immunohistochemistry 576 rats in total, comnied with BaSO4

	Nanomaterial				Toxicological outcomes	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Schwotzer 2017 PartFib	CeO_2	inhalation nose-only	90 (6 h/day, 5 days/week) with recovery period up to 90 days	required: 0.1, 0.3, 1.0 and 3.0 mg/m3 measured: 0.12 +/- 0.04, 0.33 +/- 0.09, 1.06 +/- 0.16 and 3.04 +/- 0.30 mg/m3	positive. 3.0 μg/m3: γ-H2AX immunohistochemistry significantly different from clean air control at 90+1 90+28 and 90+90 days.	nd

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Schwotzer 2017 PartFib	CeO_2	no		Histopathology only examined for 3.0 mg/m3 Lung: Accumulation of particle laden macrophages and in alveolar/interstitium at 1, 28, 90+1, 90+28 and 90+90 days. Bronchio-alveolar hyperplasia signifcantly different at 90+1, 90+28 and 90+90 days. Lung-associated lymph nodes: accumulation of particle laden macrophages mediastinal and tracheobronchial significant at 28, 90+1, 90+28 and 90+90 days. Nasal cavity: accumulation of particle laden macrophages at 28, 90+1, 90+28 and 90+90 days. No inflammation or cell damage.	nd (only 1 concentration was tested) but multiple timepoints. Lung burdens determined, possibility to connect to lung burden.

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Schwotzer 2017 PartFib	CeO_2	yes Histopathology lung: very slight interstitial fibrosis after 3.0 mg/m3 significantly different from control at 90+90 days. Authors rate it as adverse as it follows from ongoing alveolar/interstitial granulomatous inflammation. Only 1 concentration examined. At 1 and 28 days of exposure, no sign of interstitial fibrosis.	yes NOAEL below 1.0 mg/m3 (NOAEL bmdl of 0.41 mg/m3) based on most sensitive marker PMN in BALF. Total protein in BALF confirms NOAEL and LOAEL. LOAEL 1.0 mg/m3 based on PMN in BALF. At 90+1 days: 1.0 mg/m3 and 3.0 mg/m3 CeO2 caused an increase in blood neutrophils at the cost of blood lymphocytes. NOAEL: 0.3 mg/m3, LOAEL: 1.0 mg/m3. Only 1 concentration examined in histology. At 3.0 mg/m3: very slight alveolar/interstitial infiltration of inflammatory cells significant at 90+1, 90+28 and 90+90 days. Persistent granulomatous inflammation with syncytial giant cells.

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Schwotzer 2017 PartFib	CeO_2	NOAEL PMN BALF: 0.3 mg/m3 LOAEL PMN BALF: 1.0 mg/m3 NOAEL lymphocytes BALF: 0.3 mg/3 LOAEL lymphocytes BALF: 1.0 mg/m3	3.0 mg/m3: 8-OHDG as marker of oxidative stress immunohistochemistry significantly different from clean air control at 90+1 90+28 and 90+90 days. 3.0 mg/m3: Ki67 as marker of cell proliferation immunohistochemistry on terminal bronchi and lung parenchym significantly different from clean air control at 28, 90+1, 90+28 and 90+90 days. Exposure to 0.1 and 0.3 mg/3 did not lead to lung inflammation or lung overload. Exposure to 1.0 mg/m3 start to increase the clearance rate and also inflammation is seen. Exposure to 3.0 mg/m3 for 90 days leads to lung overload and inflammation.	lung

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Schwotzer 2017 PartFib	CeO_2	day 1 and day 28 during 90 day exposure as well as 1, 28 and 90 days after 90 day exposure	day 1: clean air gives 1.2 +/- 1.0 ug/lung 0.1 mg/m3 gives 2.5+/-0.8 ug/lung 0.3 mg/m3 gives 5.4 +/- 1.9 ug/lung 1.0 mg/m3 gives 19.6 +/- 5.6 ug/lung 3.0 mg/m3 gives 21.0 +/- 1.0 ug/lung day 28: clean air gives 0.6 +/- 0.2 ug/lung 0.1 mg/m3 gives 12.0 +/-2.9 ug/lung 0.3 mg/m3 gives 33.5 +/- 2.8 ug/lung 1.0 mg/m3 gives 152 +/- 37.4 ug/lung 3.0 mg/m3 gives 391 +/- 92.3 ug/lung d90+1: clean air gives 1.8 +/- 0.8 ug/lung 0.1 mg/m3 gives 33.1 +/-1.4 ug/lung 0.3 mg/m3 gives 99.2 +/- 10.1 ug/lung 1.0 mg/m3 gives 476 +/- 74.0 ug/lung 3.0 mg/m3 gives 1280 +/- 82.5 ug/lung d90+28: clean air gives 0.8 +/- 0.5 ug/lung 0.1 mg/m3 gives 24.7 +/-6.1 ug/lung 0.3 mg/m3 gives 85.1 +/- 18.2 ug/lung 1.0 mg/m3 gives 366 +/- 24.7 ug/lung 3.0 mg/m3 gives 1285 +/- 69.9 ug/lung d90+90: clean air gives 1.3 +/- 1.3 ug/lung 0.1 mg/m3 gives 13.2 +/-3.2 ug/lung 0.3 mg/m3 gives 41.9 +/- 8.8 ug/lung 1.0 mg/m3 gives 263 +/- 15.4 ug/lung 3.0 mg/m3 gives 1013 +/- 243 ug/lung	0.1 mg/m3: 67 0.3 mg.m3: 69 1.0 mg/m3: 108 3.0 mg/m3: 224	nd

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Schwotzer 2017 PartFib	CeO_2	nd	material is cleared to lung-associated lymph nodes as expected	nd	blood concentration not measured

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Keller et al 2014	CeO2	1306-38-4	UmiCore, IPDS Code: 73567919	28.4 nm (SEM)	27,2	

	Nanomaterial		Aerosol characteristics	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Keller et al 2014	CeO2		MMAD 0.9 µm to 2.2 µm and GSD between 2.4 to 2.9	calculated agglomerate density

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Keller et al 2014	CeO2	yes. SMPS measurement CMDs were between 0.25 to 0.3 µm.	OECD 412	rat	Wistar Han	female	9	n=10 histopathology, n=5 lavage

	Nanomaterial				Toxicological outcomes	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Keller et al 2014	CeO2	whole-body	4 weeks	0.5, 5 and 25 mg/m³	nd	nd

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Keller et al 2014	CeO2	no	not applicable	Lung:alveolar histiocytosis, eosinophilic granular materials, BALT:macrophage aggregated particles, BALT: occurance of particles, granulomatous inflammation, particles within histiocytes. Lung-associated lymph nodes: macrophage aggregates, occurence of particles, lympho-reticulocellular hyperplasia	0.5 mg/m³

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Keller et al 2014	CeO2	no	BAL: Sig inc: total cells, neutrophils, eosinophils, lymphocytes, macrophages (0.5/nd) Sig inc: ALP, LDH, total protein (0.5/nd). Histology: Inflammation granulomatous (0.5/nd) Hematology: NC (2/nd) Clinical chemistry: NC (2/nd)

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Keller et al 2014	CeO2	immediately after 4 weeks exposure, and after 4 weeks exposure-free observation period: Sig inc: total cells, neutrophils, eosinophils, lymphocytes, macrophages (0.5/nd) Sig inc: ALP, LDH, total protein (0.5/nd)	No clinical signs of toxicity observed, no growth retardation based on body weight. Hematological, clinical chemistry examinations in blood did not reveal any adverse effects. Nor were there any changes of acute phase proteins.	lung, lung associated lymph nodes

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Keller et al 2014	CeO2	after 28 day exposure on day 28, post-exposure on study days 30, 31, 37, 63, 93, 157	lung burden determined by ICP-MS at end of exposure: 0.5 mg/m³: 41 µg/lung (day 29); 55 µg/lung (day 30), 39 µg/lung (day 31); 40 µg/lung (day 37); 23 µg/lung (day 63); 17 µg/lung (day 93); 9 µg/lung (day 157). 5 mg/m³: 0.52 mg/lung (day 29); 0.59 mg/lung (day 30); 0.56 mg/lung (day 63) 25 mg/m³: 2.62 mg/lung (day 29); 3.14 mg/lung (day 30); 2.21 mg/lung (day 31); 2.54 mg/lung (day 37); 2.47 mg/lung (day 63); 2.46 mg/lung (day 93); 1.8 mg/lung (day 157)	0.5 mg/m³: 70 days; 5 mg/m³: > 200 days; 25 mg/m³: >> 200 days	nd

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Keller et al 2014	CeO2	nd	detected in lung-associated lymph nodes	no	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Ilse Gosens ilse.gosens@rivm.nl	Gosens 2014 Nanotoxicology	3 types of CeO2	1306-38-3	nanosized NM-211, NM-212 and micron sized NM-213	NM-211: 5-10 nm NM-212: 40 nm NM-213: < 5000 nm	NM-211: 63.95 NM-212: 27.15 NM-213: 3.73	nd

	Nanomaterial		**Aerosol characteristics**	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Gosens 2014 Nanotoxicology	3 types of CeO2	NM-211: purity 99.5% NM-212: purity 99.95% NM-213: purity 99.5% Solubility of the particles was negligible in water at neutral pH	MMAD determined by APS NM-211: 1.02 and GSD 1.82 NM212: 1.17 and GSD 2.07 NM-213: 1.40 and GSD 1.64 MMD determined by SMPS NM-211: 0.276 and CMD 1.48 NM-212: 0.366 and CMD 1.56 NM-213: 0.464 and CMD 1.32	Material density of CeO_2 is 7.65 g/cm^3.

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Gosens 2014 Nanotoxicology	3 types of CeO2	CMD (scanning mobility particle sizer) NM-211: 0.21 and SD 1.76 NM-212: 0.25 and SD 1.78 NM-213: 0.34 and SD 1.52	OECD412 with the exception that the different dosing is aplied by varying the exposure time. This considered similar to exposure to different concentrations during 6 h for an insoluble test material such as CeO_2. A dose-equivalent is derived by multiplying the duration of exposure with the exposure concentration.	rat	Wistar	male and female	7-9	5 per group

	Nanomaterial				**Toxicological outcomes**	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Gosens 2014 Nanotoxicology	3 types of CeO2	nose-only	4 (40 minutes, 2 hours or 6 hours per day) with recovery period up to 28 days only for the highest dose group and air controls	NM-211: 10.79 mg/m^3 NM-212: 19.95 mg/m^3 NM-213: 55 mg/m^3	nd	nd

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Gosens 2014 Nanotoxicology	3 types of CeO2	no		Aggregates of brown/green particles and/ or macrophages containing these particles in the lungs and the draining (tracheobronchial) lymph nodes. After recovery period, macrophages with brown/greenish particles/aggregates persisted in the alveoli and in the tracheobronchial lymph nodes. In addition, increased septal cellularity was observed in NM-212 and NM-211 exposed animals, indicating that a tissue reaction was ongoing.	persists after recovery period NM-211 NOAEL: 3.5, LOAEL: 10.9 mg/m3 NM-212: NOAEL: 6.7, LOAEL: 19.9 mg/m3 NM-213: NOAEL: 18.4, LOAEL: 55 mg/m3

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Gosens 2014 Nanotoxicology	3 types of CeO2	nd	blood hematology NM-213: increase in neutrophils in the high dose male group. NOAEL: 18.4 mg/m3, LOAEL: 55 mg/m3 NM-212 : slight dose-related increase in the number of neutrophils. This increase was still observed in males at the end of the recovery period. NOAEL: 6.7 mg/m3, LOAEL: 19.9 mg/m3 NM-211: increase in the number of neutrophils for females that subsided at the end of the recovery period. NOAEL: 3.5 mg/m3, LOAEL 10.8 mg/m3 lung weight An increase in lung weight was observed after exposure to NM-211 and NM-212 in the mid and high dose group and persisted after the recovery period in the high dose group (only dose group assessed) NM-211 NOAEL: 1.2 mg/m3, LOAEL: 3.5 mg/m3 NM-212 NOAEL: 2.5 mg/m3, LOAEL: 6.7 mg/m3

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Gosens 2014 Nanotoxicology	3 types of CeO2	PMN and macrophage BALF NM-211 NOAEL: -, LOAEL: 1.2 mg/m3 NM-212: NOAEL: -, LOAEL: 2.5 mg/m3 NM-213: NOAEL: -, LOAEL: 5.9 mg/m3 lymphocytes BALF NM-211 NOAEL: -, LOAEL: 1.2 mg/m3 NM-212: NOAEL: 2.5, LOAEL: 6.7 mg/m3 NM-213: NOAEL:5.9, LOAEL: 18.4 mg/m3 ALP NM-211 NOAEL: -, LOAEL: 1.2 mg/m3 NM-212: NOAEL: -, LOAEL: 2.5 mg/m3 NM-213: NOAEL: -, LOAEL: 5.9 mg/m3 GGT NM-211 NOAEL: -, LOAEL: 1.2 mg/m3 NM-212: NOAEL: 2.5, LOAEL: 6.7 mg/m3 NM-213: NOAEL: -, LOAEL: 5.9 mg/m3 LDH NM-211 NOAEL: -, LOAEL: 1.2 mg/m3 NM-212: NOAEL: 6.7, LOAEL: 19.9 mg/m3 NM-213: NOAEL: -, LOAEL: 5.9 mg/m3 NAG NM-211 NOAEL: -, LOAEL: 1.2 mg/m3 NM-212: NOAEL: 6.7, LOAEL: 19.9 mg/m3 NM-213: NOAEL: 18.4, LOAEL: 55 mg/m3 protein NM-211 NOAEL: -, LOAEL: 1.2 mg/m3 NM-212: NOAEL: 2.5, LOAEL: 6.7 mg/m3 NM-213: NOAEL: -, LOAEL: 5.9 mg/m3		see next entry

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Gosens 2014 Nanotoxicology	3 types of CeO2				

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Gosens 2014 Nanotoxicology	3 types of CeO2			nd	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Ilse Gosens ilse.gosens@rivm.nl	Geraets ToxicolSci 2012	3 types of CeO_2	1306-38-3	nanosized NM-211, NM-212 and micron sized NM-213	NM-211: 5-10 nm NM-212: 40 nm NM-213: < 5000 nm	NM-211: 63.95 NM-212: 27.15 NM-213: 3.73	nd
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Muhle et al. 1995 ScanJWorkEnvHealth	TiO2 (Bayertitan T)		Bayer AG, Krefeld, Germany			99.5 % Rutil

	Nanomaterial		**Aerosol characteristics**	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Geraets ToxicolSci 2012	3 types of CeO_2	NM-211: purity 99.5% NM-212: purity 99.95% NM-213: purity 99.5% Solubility of the particles was negligible in water at neutral pH	MMAD determined by APS NM-211: 1.02 and GSD 1.82 NM-212: 1.17 and GSD 2.07 NM-213: 1.40 and GSD 1.64 MMD determined by SMPS NM-211: and CMD 1.48 NM-212: 0.366 and CMD 1.56 NM-213: 0.464 and CMD 1.32	Material density of CeO_2 is 7.65 g/cm^3.
Muhle et al. 1995 ScanJWorkEnvHealth	TiO2 (Bayertitan T)		MMAD 1.1 µm GSD 1.6, respirable fraction 78 % (according to ACGIH)	

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Geraets ToxicolSci 2012	3 types of CeO_2	CMD (scanning mobility particle sizer) NM-211: 0.21 and SD 1.76 NM-212: 0.25 and SD 1.78 NM-213: 0.34 and SD 1.52	not applicable	rat	Wistar	male	7	3 per group
Muhle et al. 1995 ScanJWorkEnvHealth	TiO2 (Bayertitan T)	no	no	rat	F344	male+female	8	50 males + 50 females

	Nanomaterial				**Toxicological outcomes**	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Geraets ToxicolSci 2012	3 types of CeO_2	nose-only	NM-211: 1 day (sacrifice < 1hr after exposure), 12 days (sacrifice < 1hr after exposure), 20 days (sacrifice < 1hr after exposure) and 20 days (sacrifice 48 hrs after exposure) 6 hours per day NM-212 and NM-213: 1 day (sacrifice < 1hr after exposure), 11 days (sacrifice < 1hr after exposure), 19 days (sacrifi ce < 1hr after exposure) and 19 days (sacrifice 72 hrs after exposure) 6 hours per day	NM-211: 10.79 mg/m^3 NM-212: 19.95 mg/m^3 NM-213: 55 mg/m^3	nd	nd
Muhle et al. 1995 ScanJWorkEnvHealth	TiO2 (Bayertitan T)	whole-body	6 h/day, 5d/week, 24 months	5	nd	no (tumor incidence within concurrent control)

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Geraets ToxicolSci 2012	3 types of CeO_2	not applicable		not applicable	
Muhle et al. 1995 ScanJWorkEnvHealth	TiO2 (Bayertitan T)	adenomas adenocarcinomas (incidence within control range)	NOAEL for neoplastic changes 5 mg/m³	foamy macrophages containing lipoid substances (1%) fibrosis (about 5 %)	LOAEL/NOAEL cannot be determined as only one concentration was tested, NOAEL/LOAEL would be far below the tested concentration 5 mg/m³

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Geraets ToxicolSci 2012	3 types of CeO_2	nd	nd
Muhle et al. 1995 ScanJWorkEnvHealth	TiO2 (Bayertitan T)	lung fibrosis at the single dose tested, 5 (low incidence, but significantly increased)	Histology: No inflammation observed at 5 mg/m³

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Geraets ToxicolSci 2012	3 types of CeO_2	nd	focus on biodistribution. Toxicity parameters were described in parallel group as published in Gosens et al 2014 Nanotoxicology	lung, blood, liver, spleen, kidney, testis, epididymis, and brain
Muhle et al. 1995 ScanJWorkEnvHealth	TiO2 (Bayertitan T)	no BAL		

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Geraets ToxicolSci 2012	3 types of CeO_2	NM-211: 1 day (sacrifice < 1hr after exposure), 12 days (sacrifice < 1hr after exposure), 20 days (sacrifice < 1hr after exposure) and 20 days (sacrifice 48 hrs after exposure) 6 hours per day NM-212 and NM-213: 1 day (sacrifice < 1hr after exposure), 11 days (sacrifice < 1hr after exposure), 19 days (sacrifi ce < 1hr after exposure) and 19 days (sacrifice 72 hrs after exposure) 6 hours per day	excel file with all tissue burden at all timepoints measured is available.	elimination half-life could not be reliably determined. At 48 and 72 h exposure, there was no significant reduction of cerium oxide in either lung tissue or other investigated tissues, indicating a long elimination halflife	nd
Muhle et al. 1995 ScanJWorkEnvHealth	TiO2 (Bayertitan T)	24 months	2.72 mg(lung	nd	nd

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Geraets ToxicolSci 2012	3 types of CeO_2	elimination half-life could not be reliably determined. At 48 and 72 h exposure, there was no significant reduction of cerium oxide in either lung tissue or other investigated tissues, indicating a long elimination halflife	The deposition model used in this work estimated that the deposition of cerium oxide in the head region. This suggests that oral exposurev following mucociliary clearance might be an important contributor to systemic tissue deposition	nd	
Muhle et al. 1995 ScanJWorkEnvHealth	TiO2 (Bayertitan T)	nd	no number was reported	no	

		Nanomaterial			NM phys-chem characteristics (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Heinrich et al. 1995 InhalTox	TiO2 P25	13463-67-7	Degussa, Germany	15-40 nm	48 ± 2 m^2/g	80% anatase and -20% rutile
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Heinrich et al. 1995 InhalTox	TiO2 P25	13463-67-7	Degussa, Germany	15-40 nm	48 ± 2 m^2/g	80% anatase and -20% rutile

	Nanomaterial		**Aerosol characteristics**	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Heinrich et al. 1995 InhalTox	TiO2 P25		MMAD 0.8 µm GSD 1.8 (n=24, Berner Impactor measurement range from 15 nm to 16 µm)	
Heinrich et al. 1995 InhalTox	TiO2 P25		MMAD 0.8 µm GSD 1.8 (n=24, Berner Impactor measurement range from 15 nm to 16 µm)	

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Heinrich et al. 1995 InhalTox	TiO2 P25	no	no	rat	Wistar (CrL:(WI)BR)	female		100 for carcinogenicity 80 for histology (serial sacrifice), 14 for DNA adducts, 66 for lung burden (serial sacrifice), 28 for lung clearance
Heinrich et al. 1995 InhalTox	TiO2 P25	no	no	mice	NMRI (Crl:NMRI BR)	female		80 for carcinogenicity, 40 for histology, 40 for lung burden (serial sacrifice)

	Nanomaterial				**Toxicological outcomes**	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Heinrich et al. 1995 InhalTox	TiO2 P25	whole-body	18 h/day, 5 d/week, 24 months Carcinogenicity group was sacrificed 6 mon after termination of the exposure	7.2 mg/m³ for 4 months 14.8 mg/m³ for 4 months 9.4 mg/m³ for 16 months average of 24 months was 10 mg/m³	No increased incidence of PAH-derived DNA adducts in lung at 10 mg/m³ (no positive control was reported.)	Yes
Heinrich et al. 1995 InhalTox	TiO2 P25	whole-body	18 h/day, 5 d/week, 13.5 months Carcinogenicity group was sacrificed 6 mon after termination of the exposure	7.2 mg/m³ for 4 months 14.8 mg/m³ for 4 months 9.4 mg/m³ for 5.5 months average of 13.5 months was 10 mg/m³	No increased incidence of PAH-derived DNA adducts in lung at 10 mg/m³ (no positive control was reported.)	no

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Heinrich et al. 1995 InhalTox	TiO2 P25	Benign squamous cell tumor, Adenocarcinoma, Adenoma, Squamous cell carcinoma	average concentration of 10 mg/m³ caused high incidence of tumor. NOAEL/LOAEL cannot be established in rats.	bronchioloalveolar hyperplasia, interstitial fibrosis, particle-laden macrophages within alveolar region	cannot be determined. Considering incidence and serverity of the findings, the average concentration of 10 mg/m³ over 24 months was mach higher than the potential LOAEL.
Heinrich et al. 1995 InhalTox	TiO2 P25	Adenocarcinoma, Adenoma (This strain has high incidence of spontaneous lung tumors. The observations were considered not treatment-related!)	average concentration of 10 mg/m³ NOAEL for neoplastic change was 10 mg/m³ in mice.	not reported	not reported

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Heinrich et al. 1995 InhalTox	TiO2 P25	very slight interstital fibrosis (lung histology) LOAEL 10 mg/m³ for fibrotic changes	histology LOAEL cannot be determined, because only one high concentration was tested. The incidence of the findings were high and severe. It cannot be assessed where the NOAEL or LOAEL might be.
Heinrich et al. 1995 InhalTox	TiO2 P25	not reported	histology, lung weights doubled at the end of the study. LOAEL cannot be determined, because only one high concentration was tested. The incidence of the findings were high and severe. NOAEL or LOAEL would be far below the tested concentration.

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Heinrich et al. 1995 InhalTox	TiO2 P25	stated "published in another paper"	high concentration effects	lungs
Heinrich et al. 1995 InhalTox	TiO2 P25	not determined	high concentration effects	lungs

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Heinrich et al. 1995 InhalTox	TiO2 P25	3, 6, 12, 18, 22 and 24 months	3 month: 5202 ± 544 µg 6 months: 23192 ± 3918 µg 12 months: 34849 ± 10200 µg 18 months: 40050 ± 3491 µg 22 months: 37773 ± 9898 µg 24 months: 39287 ± 7364 µg	3 months: 208 d 12 months: 403 d 18 months: 357 d 18 months (+3 months Rec): 368 d measured with $^{59}Fe_2O_3$ tracer after exposure for 3, 12 and 18 months, as well as 18 months exp and 3 months recovery.	not determined
Heinrich et al. 1995 InhalTox	TiO2 P25	3, 6 and 12 months	3 month: 800 µg 6 months: 2500 µg 12 months: 5200 µg	not reported	not determined

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Heinrich et al. 1995 InhalTox	TiO2 P25	not determined	no information	no	
Heinrich et al. 1995 InhalTox	TiO2 P25	not determined	no information	no	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Bermudez et al. 2004 T	TiO2	13463-67-6	DeGussa- Hüls AG	21 nm	nd	nd

	Nanomaterial		Aerosol characteristics	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Bermudez et al. 2004 T	TiO2	nd	MMAD 1.29±0.30 µm GSD 3.65±1.24 (hamster);	nd

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Bermudez et al. 2004 T	TiO2	no	OECD 413 / non-GLP	hamster	LVG(SYR)BR hamster;	female	7 to 8 weeks	n=5 (histo left lung, burden right lung), addtional animals n=5 for lavage

	Nanomaterial				Toxicological outcomes	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Bermudez et al. 2004 T	TiO2	whole-body	6 h/week, 13 weeks	0.5 mg/m³, 2 mg/m³, 10 mg/m³	not reported	nd

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Bermudez et al. 2004 T	TiO2	no adverse effects	NOAEL for neoplastic change 10 mg/m³ at any time point	no adverse effects	NOAEL 10 mg/m³ at any time points

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Bermudez et al. 2004 T	TiO2	no fibrosis, NOAEL 10 mg/m³	no inflammation NOAEL 10 mg/m³

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Bermudez et al. 2004 T	TiO2	Sig inc: total cells, neutrophiles, lymphocytes, macrophages NOAEL 2 mg/m³	LDH and protein did not change significantly at any time point	lung, lung associated lymph nodes

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Bermudez et al. 2004 T	TiO2	after 13 weeks exposure, 4, 13, 26 and 52 weeks post-exposure	~approximately value, reading from figures after 13 weeks exposure: 10 mg/m³: 2 mg/g dry lung; 2 mg/m³: ~0.58 mg/g drylung 0.5 mg/m³: ~0.18 mg/g dry lung 4 weeks post-exposure: 10 mg/m³: 1.8 mg/g dry lung 2 mg/m³: ~0.3 mg/g dry lung 0.5 mg/m³: ~0.06 mg/g dry lung 13 weeks post-exposure: 10 mg/m³: ~ 0.5 mg/g dry lung 2 mg/m³: ~0.1 mg/g dry lung 0.5 mg/m³: ~0.05 mg/g dry lung 26 weeks post-exposure: 10 mg/m³: + 2 mg/m³: + mg/g dry lung 0.5 mg/m³: nd 52 weeks post-exposure: 10 mg/m³: +; 2 mg/m³: nd 0.5 mg/m³: nd	10 mg/m³: decreased to 3 % of the initial value after 52 weeks post-exposure t1/2 (10 mg/m³): 39 days t1/2 (2 mg/m³): 37 days t1/2 (0.5 mg/m³): 33 days	nd

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Bermudez et al. 2004 T	TiO2	nd		no	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Bermudez et al. 2004 T	TiO2	13463-67-6	DeGussa- Hüls AG	21 nm	nd	nd

	Nanomaterial		Aerosol characteristics	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Bermudez et al. 2004 T	TiO2	nd	MMAD 1.45±0.49 µm GSD 2.46±0.31 (mouse)	nd

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Bermudez et al. 2004 T	TiO2	no	OECD 413 / non-GLP	mouse	B3C3F1/CrlBR mice	female	7 to 8 weeks	n=5 (histo left lung, burden right lung), addtional animals n=5 for lavage

	Nanomaterial				Toxicological outcomes	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Bermudez et al. 2004 T	TiO2	whole-body	6 h/week, 13 weeks	0.5 mg/m³, 2 mg/m³, 10 mg/m³	not reported	nd

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Bermudez et al. 2004 T	TiO2	no neoplastic lesions	NOAEL for neoplastic change 10 mg/m³ at any time point	10 mg/m³: aggregations of heavily particle-laden macrophages, central lobar centriacinar, with the time movement to interstitial areas, primarily around blood vessels and peribronchiolar interstitium, perivascular lymphoid proliferation	2/10

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Bermudez et al. 2004 T	TiO2	NOAEL 10 mg/m³ (no fibrosis)	Histology: 2 mg/m³ /nd Hematology: 10 mg/m³ /nd lavage: 10 mg/m³ /nd

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Bermudez et al. 2004 T	TiO2	sig inc: LDH at 10 mg/m³ directly after 13 weeks exposure, 4 and 13 weeks post-exposure, sig inc: total protein, absolute and relative countes of neutrophile, macrophage and lymphocytes at 10 mg/m³ directly after 13 weeks exposure, 4, 13, 26, 52 weeks post-exposure	inc cell proliferation: terminal bronchol: after exposure at 10 mg/m³ Alveolar region: 13 and 26 weeks post-exposure at 10 mg/m³.	lung, lung associated lymph nodes

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Bermudez et al. 2004 T	TiO2	after 13 weeks exposure, 4, 13, 26 and 52 weeks post-exposure	~approximately value, reading from figures after 13 weeks exposure: 10 mg/m³: ~10.5 mg/g dry lung; 2 mg/m³: ~1.45 mg/g dry lung 0.5 mg/m³: ~0.35 mg/g dry lung 4 weeks post-exposure: 10 mg/m³: ~10.5 mg/g dry lung 2 mg/m³: ~0.7 mg/g dry lung 0.5 mg/m³: ~0.18 mg/g dry lung 13 weeks post-exposure: 10 mg/m³: ~ 9.2 mg/g dry lung 2 mg/m³: ~0.3 mg/g dry lung 0.5 mg/m³: ~0.1 mg/g dry lung 26 weeks post-exposure: 10 mg/m³: ~7.5 mg/g dry lung 2 mg/m³: ~0.18 mg/g dry lung 0.5 mg/m³: 0.09 mg/g dry lung 52 weeks post-exposure: 10 mg/m³: ~6 mg/g dry lung; 2 mg/m³: nd; 0.5 mg/m³: nd	10 mg/m³: decreased to 46 % of the initial value after 52 weeks post-exposure; t1/2 = 319 days 2 mg/m³: decreased to 25 % of the initial value after 52 weeks post-exposure; t1/2=40 days 0.5 mg/m³: decreased to 10 % of the initial value after 52 weeks post-exposure; t1/2 = 48 days	

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Bermudez et al. 2004 T	TiO2				

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Bermudez et al. 2004 T	TiO2	13463-67-6	DeGussa- Hüls AG	21 nm	nd	nd

	Nanomaterial		Aerosol characteristics	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Bermudez et al. 2004 T	TiO2	nd	MMAD 1.44±0.57 µm GSD2.60±0.38 (rat)	nd

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Bermudez et al. 2004 T	TiO2	no	OECD 413 / non-GLP	rat	CDF(F344)/CrlBR rat	female	7 to 8 weeks	n=5 (histo left lung, burden right lung), addtional animals n=5 for lavage

	Nanomaterial				Toxicological outcomes	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Bermudez et al. 2004 T	TiO2	whole-body	6 h/week, 13 weeks	0.5 mg/m³, 2 mg/m³, 10 mg/m³	not reported	nd

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Bermudez et al. 2004 T	TiO2	no neoplastic lesions	NOAEL for neoplastic change 10 mg/m³	0.5 mg/m³: particles within alveolar macrophage, very minimal changes in the patterns of alveolar macrophage accumulation 2 mg/m³: particle-laden macrophage accumulationm, aggregation in subpleural regions and in centriacinar zones, associated with minial hypertrophy and hyperplasia of type II cells, became more focal and could be noted in intersitial area. 10 mg/m³: progressive epithelial proliferative changes including metaplastic changes in centriacinar region (bronchiolization of alveolar epithelium) associated with particle-laden macrophage accumulation.	0.5/2

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Bermudez et al. 2004 T	TiO2	10 mg/m³: minimal to mild particel-induced alveolar septal fibrosis (only at the 52 week final sacrifice)	BAL: 2 mg/m³ / n.d. Blood hematology: 10 mg/m³ / nd Clin Chemistry: 10 mg/m³ / nd Lavage: 2 mg/m³ / nd

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Bermudez et al. 2004 T	TiO2	sig inc: total protein at 10 mg/m³ directly after 13 weeks exposure and 4 weeks post-exposure; sig inc: LDH at 10 mg/m³ directly after 13 weeks exposure, 4 and 13 weeks post-exposure; sig inc: total protein, absolute counts of neutrophile, macrophage and lymphocytes at 10 mg/m³ directly after 13 weeks exposure, 4 and 13 post-exposure, relative counts of neutrophile, macrophage and lymphocytes at all time points including 52 weeks post-exposure	inc cell proliferation: Terminal bronchol: after exposure at 2 and 10 mg/m³ Alveolar region: after exposure at 2 and 10 mg/m³; still increased 4 and 13 weeks post-exposure at 10 mg/m³.	lung, lung associated lymph nodes

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Bermudez et al. 2004 T	TiO2	after 13 weeks exposure, 4, 13, 26 and 52 weeks post-exposure	~approximately value, reading from figures after 13 weeks exposure: 10 mg/m³: 11 mg/g lung; 2 mg/m³: 1.7 mg/g lung 0.5 mg/m³: ~0.44 mg/g lung 4-weeks post-exposure: 10 mg/m³: ~10.1 mg/g lung 2 mg/m³: ~1.5 mg/g lung 0.5 mg/m³: ~0.24 mg/g lung 13 weeks post-exposure: 10 mg/m³: ~9.2 mg/g lung 2 mg/m³: ~0.79 mg/g lung 0.5 mg/m³: ~0.15 mg/g lung 26 weeks post-exposure: 10 mg/m³: ~8 mg/g lung 2 mg/m³: ~0.6 mg/g lung 0.5 mg/m³: ~0.1 mg/g lung 52 weeks post-exposure: 10 mg/m³: ~6.5 mg/g lung 2 mg/m³: ~0.5 mg/g lung 0.5 mg/m³: ~0.05 mg/g lung	10 mg/m³: decreased to 57 % of the initial value after 52 weeks post-exposure; t1/2=395 days 2 mg/m³: decreased to 25 % of the initial value after 52 weeks post-exposure; t1/2=132 days 0.5 mg/m³: decreased to 10 % of the initial value after 52 weeks post-exposure; t1/2=63 days	nd

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Bermudez et al. 2004 T	TiO2	nd		nd	

		Nanomaterial			NM phys-chem characteristics (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Trine Berthing trb@nfa.dk	Sutunkova 2017 Toxicology	SiO2 amorphous		Industrial condensation dust collected in the horizontal section of the flue gas duct from the hood over a silicon smelting ore-thermal furnace and sieved through a<2 µm screen	Diameter 90 ± 30 (SEM)	nd	78% free SiO2: 72% amorphous and 6% crystalline
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Reuzel et al. 1991 FoodChemTox	Aerosil 200		Degussa AG (Frankfurt am Main, Germany)	12	200	99.8 % SiO2

	Nanomaterial		**Aerosol characteristics**	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Sutunkova 2017 Toxicology	SiO2 amorphous	Mainly spherical (with a small number of relatively large solitary particles of an irregular shape). Kinetics of particle dissolution measured in BALF supernatant, Normal saline and Ringer-Locke's solution.	nd	nd
Reuzel et al. 1991 FoodChemTox	Aerosil 200	spherical, hydrophile, pH 3.6 to 4.3	not determined	nd

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Sutunkova 2017 Toxicology	SiO2 amorphous	nd	nd	Rat	outbred white rats from own breeding colony	female	not reported	not reported
Reuzel et al. 1991 FoodChemTox	Aerosil 200	no	not mentioned, study design looks very similar to a guideline study	rat	Wistar (Cpb:Wu)	male and female	7 weeks (6 weeks at delivery)	70 males + 70 females 0 w post-exp: 20 m+20 f /gr 13 w post-exp: 10 m+10 f/gr 26 w post-exp: 10 m+10 f/gr 39 w post-exp: 10 m+10 f/gr 52 w post-exp: 20 m+20 f/gr

	Nanomaterial				**Toxicological outcomes**	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Sutunkova 2017 Toxicology	SiO2 amorphous	inhalation, nose-only	12 and 24 (4h/day, 5days/week)	2.6 ± 0.6 and 10.6 ± 2.1	Positive. RAPD (Random Amplified Polymorphic DNA)(= Comet? Ratio of total radioactivity of all tail to head fractions), nucleated blood cells and bone marrow cells, positive at dose 2.6 and 10.6.	nd
Reuzel et al. 1991 FoodChemTox	Aerosil 200	whole-body	6 h/day, 5d/week, 13 weeks	1.3 ± 0.1 5.9 ± 0.2 31.0 ± 0.9	nd	nd

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Sutunkova 2017 Toxicology	SiO2 amorphous	none	10.6/nd	Lung, after 6 months exposure: Enlarged alveolar septa Solitary clusters of dust particles Round cellular nodules No collagen around/within nodules. Net of thin argyrophilic reticular fibers, early stage of nodular sclerosis. Tracheobronchial lymph nodes, after 6 months exposure: Cellular nodules with early signs of sclerosis. Other organs not analysed.	2.6/10.6
Reuzel et al. 1991 FoodChemTox	Aerosil 200	no	30 mg/m³ (NOAEL)	accumulation of alveolar macrophages, cellular debris and polymorphonuclear leucocytes in the alveolar spaces, increased cellularity, seen as an increase in the number of type II pneumocytes and macrophages within the alveolar walls, aleveolar broncholization, focal interstitial fibrosis, cholesterol clefts	nd/1 mg/m³

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Sutunkova 2017 Toxicology	SiO2 amorphous	Lung: NC: relative lung mass (10.6/nd) (Sig inc: relative lung mass after 3-month exposure). Sig dec: lipid content of lung (no dose-response) NC: Hydroxyproline content in lung (10.6/nd) (Sig inc: hydroxyproline content after 3-month exposure)	Hematology: Sig dec: banded neutrophils (no dose-response). Sig inc: segmented neutrophils (2.6/10.6). Sig dec: AST activity (no dose-response), MDA (nd/2.6) Sig inc: Ceruloplasmin in blood serum (2.6/10.6)
Reuzel et al. 1991 FoodChemTox	Aerosil 200	6 mg/m³ (NOAEL) NOAEL for this endpoint is not determined	histology, blood hematoloy (nd / 1 mg/m³)

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Sutunkova 2017 Toxicology	SiO2 amorphous	nd	Authors: Nano-silica containing aerosol did not display systemic toxicity even at a relatively high concentration and longer exposure period Sig dec: brain mass (nd/2.6) Urinalysis: NC (10.6/nd)	Lung, lung associated lymph nodes, liver, kidney, spleen, brain, blood, urine, feces
Reuzel et al. 1991 FoodChemTox	Aerosil 200	no BAL	particle size distribution was	lungs

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Sutunkova 2017 Toxicology	SiO2 amorphous	Silica content after 3 and 6 months exposure to two concentrations. No post-exposure recovery.	See all organ burdens in table 4 in original publication. Silica content of the lung, liver, kidney, spleen and blood is higher than controls, and being dependent on level and duration of exposure. Silica content of urine and feces is higher than controls, and dependent on level of exposure, but for the high dose is inversely dependent on duration of exposure.	nd	nd
Reuzel et al. 1991 FoodChemTox	Aerosil 200	0, 13, 26, 39 and 52 weeks after exposure (exposure duration 13 weeks), reported only for 30 mg/m³	males (read from a figure): 0 weeks post-exposure: about 0.25 mg 13, 26, 39 and 52 weeks post-exposure: very low females (read from a figure): 0 weeks post-exposure: 0.2 mg 13, 26, 39 and 52 weeks post-exposure: very low	not reported, based on the data between 13 and 26 weeks	nd

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Sutunkova 2017 Toxicology	SiO2 amorphous	nd	The silicon contents was determined by atomic absorption analysis with electrothermal atomization on an atomicabsorption spectrophotometer ContrAA-700 (Analytik Jena AG). Transmission electron microscopy confirms that silica particles are retained in the lungs, though in a small amount, and present in olfactory area of the brain.	no	The silica (mostly amorphous) containing submicron particles with a prevailing proportion of those in the nanoscale range induce, when instilled intratracheally, a pulmonary cell response comparable with that to highly cytotoxic and fibrogenic standard quartz powder DQ12. Nevertheless, in long-term inhalation experiments at realistic concentrations, they proved to be of very low systemic toxicity and negligible pulmonary fibrogenicity. This paradox may be explained by low SiO2 retention in lungs and other organs due to a relatively high solubility of these nanoparticles in relevant biological and model milieus. However, their genotoxic action and transnasal penetration into the brain found in the same inhalation experiment should make one give a cautious overall assessment of this aerosol as an occupational or environmental hazard.
Reuzel et al. 1991 FoodChemTox	Aerosil 200	nd	only lung and lung associated lymph nodes were examined.	nd	brain, liver, kidney, spleen, eyes, salivary gland, whole gastrointestinal tract, skin, skeleton muscle, testes, different lymph nodes (and more)were examined by histopathology. No adverse effects were observed. Lung collagen content increased in a concentration-related manner, no significant increase at 1 mg/m³.

		Nanomaterial			NM phys-chem characteristics (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Reuzel et al. 1991 FoodChemTox	Aerosil R 974		Degussa AG (Frankfurt am Main, Germany)	12	170	>99.8 % SiO2
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Reuzel et al. 1991 FoodChemTox	Sipernat 22S		Degussa AG (Frankfurt am Main, Germany)	18	190	98%
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Johnston et al. 2000 ToxSci	amorphous silica (Aerosil 200)		DeGussa	12	200±25	SiO2

	Nanomaterial		**Aerosol characteristics**	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Reuzel et al. 1991 FoodChemTox	Aerosil R 974	spherical, hydrophobe, pH 3.6 to 4.3 it is a modification of aerosil	not determined	nd
Reuzel et al. 1991 FoodChemTox	Sipernat 22S	spherical, hydrophil, pH 6.3	not determined	nd
Johnston et al. 2000 ToxSci	amorphous silica (Aerosil 200)		0.81 µm	nd

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Reuzel et al. 1991 FoodChemTox	Aerosil R 974	no	not mentioned, study design looks very similar to a guideline study	rat	Wistar (Cpb:Wu)	male and female	7 weeks (6 weeks at delivery)	70 males + 70 females 0 w post-exp: 20 m + 20 f 13 w post-exp: 10 m + 10 f 26 w post-exp: 10 m + 10 f 39 w post-exp: 10 m + 10 f 52 w post-exp: 20 m + 20 f
Reuzel et al. 1991 FoodChemTox	Sipernat 22S	no	not mentioned, study design looks very similar to a guideline study	rat	Wistar (Cpb:Wu)	male and female	7 weeks (6 weeks at delivery)	70 males + 70 females 0 w post-exp: 20 m + 20 f 13 w post-exp: 10 m + 10 f 26 w post-exp: 10 m + 10 f 39 w post-exp: 10 m + 10 f 52 w post-exp: 20 m + 20 f
Johnston et al. 2000 ToxSci	amorphous silica (Aerosil 200)	no	no	rat	F344	male	unkown (weight 200-250 g)	lavage n=4 lung burden n=4 Histpath, RNA expression of MIP-2 and HPRT were performed in lavaged lung

	Nanomaterial				**Toxicological outcomes**	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Reuzel et al. 1991 FoodChemTox	Aerosil R 974	whole-body	8 h/day, 5d/week, 13 weeks	34.7 ± 0.7	nd	nd
Reuzel et al. 1991 FoodChemTox	Sipernat 22S	whole-body	9 h/day, 5d/week, 13 weeks	34.9 ± 0.5	nd	nd
Johnston et al. 2000 ToxSci	amorphous silica (Aerosil 200)	whole-body	6h/day, 5 day/week, for 6.5 weeks or 13 weeks, 12 and 32 weeks post-exposure	50	Negative. HPRT in isolated alveolar epithlial cells, no increase of mutation frequency.	nd

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Reuzel et al. 1991 FoodChemTox	Aerosil R 974	no	30 mg/m³ (NOAEL)	granuloma-like lesions, accumulation of alveolar macrophages, increased cellularity, seen as an increase in the number of type II pneumocytes and macrophages within the alveolar walls	nd. (because only one concentration was examined)
Reuzel et al. 1991 FoodChemTox	Sipernat 22S	no	30 mg/m³ (NOAEL)	accumulation of alveolar macrophages	30 mg/m³
Johnston et al. 2000 ToxSci	amorphous silica (Aerosil 200)	no neoplastic lesions	NOAEL for neoplastic changes 50 mg/m³	increased numbers of neutrophiles and macrophages, thickening of alveolar septa (less severe than those exposed to crystal silica. TUNEL stain positive cells in bronchiols, endothelium of small vessels and parenchyma. More intense than in those exposed to quartz	not applicable, only one concentration was tested. NOAEL/LOAEL would be far below the tested concentration

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Reuzel et al. 1991 FoodChemTox	Aerosil R 974	30 mg/m³ (NOAEL)	histology, blood hematoloy NOAEL could not be determined, as only 1 concentration was tested.
Reuzel et al. 1991 FoodChemTox	Sipernat 22S	30 mg/m³ (NOAEL)	histology, blood hematoloy (nd / 30 mg/m³)
Johnston et al. 2000 ToxSci	amorphous silica (Aerosil 200)	yes	inflammation histology and lavage (NOAEL/LOAEL cannot be assessed, as only one concentration was tested)

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Reuzel et al. 1991 FoodChemTox	Aerosil R 974	no BAL		lungs
Reuzel et al. 1991 FoodChemTox	Sipernat 22S	no BAL		lungs
Johnston et al. 2000 ToxSci	amorphous silica (Aerosil 200)	sig inc: total cell counts and PMN, after 6.5 and 13 weeks exposure. sig dec: macrophages, after 6.5 and 13 weeks exposure sig inc; LDH, protein, ß-glucuronidase after 6.5 and 13 weeks exposure. sign. Inc. PMN and LDH after 12-weeks post-exposure. No changes in BAL after 32-week recovery period.	Histopathology was described very briefly, TUNEL stain was performed, without quantitative data. Intensely stained TUNEL-positive cells were found throughout terminal bronchiolar epithelium and paracyma of rats exposed to amorphous silica. After 8mon recovery, the effect was not observed anymore.	lung

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Reuzel et al. 1991 FoodChemTox	Aerosil R 974	0, 13, 26, 39 and 52 weeks after exposure (exposure duration 13 weeks)	males (read from a figure): 0 weeks post-exposure: about 1.1 mg 13 weeks post-exposure: 0.4 mg 26 weeks post-exposure: 1.1 mg 39, 52 weeks post-exposure: very low females (read from a figure): 0 weeks post-exposure: 0.7 mg 13 weeks post-exposure: 0.2 mg 26 weeks post-exposure: 0.1 mg 39, 52 weeks post-exposure: very low	not reported, based on the data < 39 weeks	nd
Reuzel et al. 1991 FoodChemTox	Sipernat 22S	0, 13, 26, 39 and 52 weeks after exposure (exposure duration 13 weeks)	males (read from a figure): 0 weeks post-exposure: about 0.5 mg 13 weeks post-exposure: 0.1 mg 26 weeks post-exposure: 0.5 mg 39, 52 weeks post-exposure: very low females (read from a figure): 0 weeks post-exposure: 0.4 mg 13 weeks post-exposure: 0.1 mg 26, 39, 52 weeks post-exposure: very low	not reported, based on the data < 39 weeks	nd
Johnston et al. 2000 ToxSci	amorphous silica (Aerosil 200)	6.5 weeks exposure 13 weeks exposure 13 weeks exp + 12 weeks post-exp 12 weeks exp + 32 weeks post-exp	6.5 weeks exposure: 755.9 ± 22.9 13 weeks exposure: 882.7 ± 83.1 13 weeks exp + 12 weeks post-exp: 156.0 ± 38.6 12 weeks exp + 32 weeks post-exp: 92.6 ± 38.6 control group 6.5 weeks exposure: 55.9 ± 40.4 13 weeks exposure: 42.5 ± 16.9 13 weeks exp + 12 weeks post-exp: 28.1 ± 13.0 12 weeks exp + 32 weeks post-exp: 39.8 ± 8.7	nd.	nd.

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Reuzel et al. 1991 FoodChemTox	Aerosil R 974	nd	only lung and lung associated lymph nodes were examined.	nd	no adverse effects in all above mentioned organs and tissues, lung collagen content increased. During post-exposure decreased gradually.
Reuzel et al. 1991 FoodChemTox	Sipernat 22S	nd	only lung and lung associated lymph nodes were examined.	nd	no adverse effects in all above mentioned organs and tissues, lung collagen content increased. During post-exposure decreased gradually.
Johnston et al. 2000 ToxSci	amorphous silica (Aerosil 200)	nd.	nd.	RNA expression of MIP-2 and GAPDH in lavaged lung	MIP-2 RNA expression was increased in lungs of rats exposed to amorphous silica, which resign to the control level during the post-exposure period

		Nanomaterial			NM phys-chem characteristics (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Johnston et al. 2000 ToxSci	crytalline silica (cristobalite, C and E-minerals)		King of Prussia			SiO2
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Muhle et al. 1995 ScanJWorkEnvHealth	crytalline silica (DQ-12)		Bergbauforschung, Essen, Germany			87 % Ŭquartz determined by XRD

	Nanomaterial		**Aerosol characteristics**	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Johnston et al. 2000 ToxSci	crytalline silica (cristobalite, C and E-minerals)		1.3 µm	nd
Muhle et al. 1995 ScanJWorkEnvHealth	crytalline silica (DQ-12)		MMAD 1.3 µm GSD 1.8, respirable fraction 74 % (according to ACGIH)	nd

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Johnston et al. 2000 ToxSci	crytalline silica (cristobalite, C and E-minerals)	no	no	rat	F344	male	unkown (weight 200-250 g)	lavage n=4 lung burden n=4 Histpath, RNA expression of MIP-2 and HPRT were performed in lavaged lung
Muhle et al. 1995 ScanJWorkEnvHealth	crytalline silica (DQ-12)	no	no	rat	F344	male + female	8	50 males + 50 females

	Nanomaterial				Toxicological outcomes	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Johnston et al. 2000 ToxSci	crytalline silica (cristobalite, C and E-minerals)	whole-body	6h/day, 5 day/week, for 6.5 weeks or 13 weeks, 12 and 32 weeks post-exposure	3	Positive. HPRT in isolated alveolar epithlial cells, 4.3 fold increase of mutation frequency	nd
Muhle et al. 1995 ScanJWorkEnvHealth	crytalline silica (DQ-12)	whole-body	6 h/day, 5d/week, 24 months	1	nd	yes

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Johnston et al. 2000 ToxSci	crytalline silica (cristobalite, C and E-minerals)	no neoplastic lesions	NOAEL for neoplastic changes 3 mg/m³	increased numbers of neutrophiles and macrophages, progressive inflammation, greatly thickened alveolar septa. TUNEL-Stain positive cells near cell debries in hypertrophic area of the parencyma.	not applicable, only one concentration was tested. NOAEL/LOAEL would be far below the tested concentration
Muhle et al. 1995 ScanJWorkEnvHealth	crytalline silica (DQ-12)	adenomas adenocarcinomas benign cystic quamous cell tumors adenosquamous carcinoma squamous cell carcinoma	nd. (only 1 concentration was tested, NOAEL/LOAEL would be far below the tested concentration 1 mg/m3)	bronchoalveolar hyperplasia of the alveolar type, at the end of the exposure period also in subpleural areas and in areas of fibrosis and inflammation multifocal lipoproteinosis, adjacent to fibrotic areas cholesterol lefs foamy macrophages containing lipoid substances (98 %) intra-alveolar and interstial inflammatory cell infiltrates consisting PMN (70 %) lung fibrosis, subpleural and peirbronchiolar	(NOAEL cannot be determined, only 1 concentration was tested. NOAEL/LOAEL would be far below the tested concentration)

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Johnston et al. 2000 ToxSci	crytalline silica (cristobalite, C and E-minerals)	yes	inflammation histology and lavage (NOAEL/LOAEL cannot be assessed, as only one concentration was tested)
Muhle et al. 1995 ScanJWorkEnvHealth	crytalline silica (DQ-12)	fibrotic foci at 1 mg/m³, NOAEL or LOAEL cannot be established.	Histology, lung: Intraalveolar and interstitial inflammatory c

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Johnston et al. 2000 ToxSci	crytalline silica (cristobalite, C and E-minerals)	sig inc: total cell counts, PMN, macrophage, after 6.5 and 13 weeks exposure, as well as after 12 and 32 weeks post-exposure period. sig dec: macrophages, after 6.5 and 13 weeks exposure, as well as after 12 and 32 weeks post-exposure period. sig inc; LDH, protein, ß-glucuronidase after 6.5 and 13 weeks exposure, as well as after 12 and 32 weeks post-exposure period.	TUNEL stain was performed, without quantitative data. After the exposure,TUNEL-positive cells were comparible to the air controls. 8 mont after the exposure, TUNEL positive cells were found near cell debris in hypertrophic areas of parenchym. These lungs showed regions of emphysema	lung
Muhle et al. 1995 ScanJWorkEnvHealth	crytalline silica (DQ-12)	no BAL		lung

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Johnston et al. 2000 ToxSci	crytalline silica (cristobalite, C and E-minerals)	6.5 weeks exposure 13 weeks exposure 13 weeks exp + 12 weeks post-exp 12 weeks exp + 32 weeks post-exp	6.5 weeks exposure: 335.6 ± 28.3 13 weeks exposure: 819.0 ± 83.3 13 weeks exp + 12 weeks post-exp: 657.6 ± 28.0 12 weeks exp + 32 weeks post-exp: 743.0 ± 14.5 control group 6.5 weeks exposure: 55.9 ± 40.4 13 weeks exposure: 42.5 ± 16.9 13 weeks exp + 12 weeks post-exp: 28.1 ± 13.0 12 weeks exp + 32 weeks post-exp: 39.8 ± 8.7	nd.	nd.
Muhle et al. 1995 ScanJWorkEnvHealth	crytalline silica (DQ-12)	after 24 months	0.91 mg/lung	nd	nd

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Johnston et al. 2000 ToxSci	crytalline silica (cristobalite, C and E-minerals)	nd.	nd.	RNA expression of MIP-2 and GAPDH in lavaged lung	MIP-2 RNA expression was strongly increased in lungs of rats exposed to crytobalite, which persisted during the post-exposure period
Muhle et al. 1995 ScanJWorkEnvHealth	crytalline silica (DQ-12)	nd	the fraction of the material retained in the lung-associated lymph nodes was much higher than that of the TiO2-exposed group. (no number was reported)	no	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Reuzel et al. 1991 FoodChemTox	quartz dust (Sikron F300)		Quartz Werke (Frechen, Germany)	8000 nm	<1.5 m^2/g	99 % SiO2

	Nanomaterial		Aerosol characteristics	
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Size** Median aerodynamic diameter, standard deviation, applied instrument (MMAD/MAD (µm) and GSD/CMD)	**Density** (g/cm^3)
Reuzel et al. 1991 FoodChemTox	quartz dust (Sikron F300)	corse, irregular, sharp edges, hydrophile, pH 7	MMAD was not measured. Agglomerate size rangeded from 0.1 µm to 25 µm	nd

	Nanomaterial		Study design					
Reference	**NM**	**Characterization of nanosize fraction (<500 nm)?**	**OECD guideline/GLP**	**Species**	**Strain**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)
Reuzel et al. 1991 FoodChemTox	quartz dust (Sikron F300)	no	not mentioned, study design looks very similar to a guideline study	rat	Wistar (Cpb:Wu)	male + female	7 weeks (6 weeks at delivery)	70 males + 70 females 0 w post-exp: 20 m + 20 f 13 w post-exp: 10 m + 10 f 26 w post-exp: 10 m + 10 f 39 w post-exp: 10 m + 10 f 52 w post-exp: 20 m + 20 f

	Nanomaterial				**Toxicological outcomes**	
Reference	**NM**	**Administration route** (whole-body or nose-only)	**Duration of exposure** (weeks) (h/day, days/week)	**Exposure concentrations** (mg/m3)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no
Reuzel et al. 1991 FoodChemTox	quartz dust (Sikron F300)	whole-body	6 h/day, 5d/week, 13 weeks	58.5 ± 0.7	nd	1 squamouse cell carcinoma after 52 weeks recovery

	Nanomaterial				
Reference	**NM**	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/m3)	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**
Reuzel et al. 1991 FoodChemTox	quartz dust (Sikron F300)	1 year after 13 weeks exposure, squamous cell metaplasia in one male, small but unequivocal squamous cell carcinoma in one female.	LOAEL 58.7 mg/m³	granuloma like lesions, accumulation of aveolar macrophages, cellular debris, IPLI, increased septal cellularity, alveolar bronchiolization, focal interstitial fibrosis, cholesterol clefts	LOAEL/NOAEL cannot be determined as only one concentration was tested, NOAEL/LOAEL would be far below the tested concentration

	Nanomaterial		
Reference	**NM**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**
Reuzel et al. 1991 FoodChemTox	quartz dust (Sikron F300)	yes, LOAEL not determined (only 1 group)	histology, blood hematoloy, clinical chemistry NOAEL could not be determined, as only 1 concentration was tested.

	Nanomaterial			Biodistribution
Reference	**NM**	**BAL** Total and differential cell counts, biochemical markers **(NOAEL/LOAEL)**	**Toxicological comments**	**Compartments monitored**
Reuzel et al. 1991 FoodChemTox	quartz dust (Sikron F300)	no BAL	only one concentration was tested, particle size was very large	lungs

	Nanomaterial				
Reference	**NM**	**Sampling regime** (i.e. time of sampling)	**Organ burden** (timepoint, ug/organ)	**Lung clearance/ post-exposure retention half-time** (days)	**Systemic absorption fraction or rate** (&unit)
Reuzel et al. 1991 FoodChemTox	quartz dust (Sikron F300)	0, 13, 26, 39 and 52 weeks after exposure (exposure duration 13 weeks)	Males (read from a figure): 0 weeks post-exposure: about 4.6 mg 13 weeks post-exposure: 1.4 mg 26 weeks post-exposure: 2 mg 39 weeks post-exposure: 3.4 mg 52 weeks post-exposure: 2.5 mg females (read from a figure): 0 weeks post-exposure: 2.9 mg 13 weeks post-exposure: 1.4 mg 26 weeks post-exposure: 1.6 mg 39 weeks post-exposure: 1.6 mg 52 weeks post-exposure: 1.4 mg	not reported, based on the data longer than 52 weeks	nd

	Nanomaterial				
Reference	**NM**	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)	**General comments**
Reuzel et al. 1991 FoodChemTox	quartz dust (Sikron F300)	nd	only lung and lung associated lymph nodes were examined.	nd	brain, liver, kidney, spleen, eyes, salivary gland, whole gastrointestinal tract, skin, skeleton muscle, testes, different lymph nodes (and more)were examined by histopathology. No adverse effects were observed. Lung collagen content increased progressively duing the post-exposure period

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Trine Berthing trb@nfa.dk	Kim 2014 IntJNanomed	ZnO (negative and positive surface charge)		American Elements (Los Angeles, CA, USA, Lot Number 1871511079–673). The surface charge was modified with coating reagents, citrate (for [–] charge) and L-serine (for [+] charge)	nd They write 100 nm, but it is not measured. They refer to ref 18 Kim 2012 ToxEHS in which 20nm and 70nm ZnO from a different supplier is characterized in PBS, cell media and deionized water.	nd	nd

	Nanomaterial		Exposure-related phys-chem	Study design		
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Exposure-related phys-chem** (size/agglomeration in formulation/vehicle...)	**OECD guideline/GLP**	**Species**	**Strain**
Kim 2014 IntJNanomed	ZnO (negative and positive surface charge)	The surface charge was modified with coating reagents, citrate (for [–] charge) and L-serine (for [+] charge)	nd The gavage solution is prepared once a day and homogenized by vortexing before administration	OECD TG 408/GLP	Rat	Crl:CD(SD) Sprague Dawley

	Nanomaterial						
Reference	**NM**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)	**Administration route and mode** (daily gavage, ad lib. via drinking water or feed...)	**Duration of exposure** (weeks) (days/week)	**Doses** (mg/kg bw/day)
Kim 2014 IntJNanomed	ZnO (negative and positive surface charge)	male female	7 (6 weeks + acclimatization and quarantine)	n=10-15 per sex	oral gavage, daily	90 days (7d/w) + 2 week recovery for highest dose	31.25, 125, 500

	Nanomaterial		Toxicological outcomes			
Reference	**NM**	**Formulation/vehicle** (volume, concentration, composition)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/kg bw)
Kim 2014 IntJNanomed	ZnO (negative and positive surface charge)	10 mL/kg bw, composition not stated directly. ZnO coatings were done in 1 w/v% sodium citrate pH7 (for [–] charge) or L-serine pH6 (for [+] charge) in 20 mM HEPES buffer. Distilled water and a vehicle solution were administered by gavage to the negative control and vehicle control groups, respectively.	nd	nd	none	500/nd

	Nanomaterial			
Reference	**NM**	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**
Kim 2014 IntJNanomed	ZnO (negative and positive surface charge)	*(no statistics, all observed lesions are listed)* Nonglandular stomach: squamous cell hyperplasia vacuolation Glandular stomach: intracytoplasmic hyaline droplet submucosal edema and inflammation eosinophilic chief cell mucous cell hyperplasia (resolved during 2 week recovery) pancreas: Acinar cell apoptosis chronic inflammation (resolved during 2 week recovery) eye: retinal atrophy prostate gland: suppurative inflammation	Stomach, prostate gland (nd/31.25) Eye (31.25/125) Pancreas (125/500)	Histology (500/nd)

	Nanomaterial		
Reference	**NM**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**	**Toxicological comments**
Kim 2014 IntJNanomed	ZnO (negative and positive surface charge)	Histology: Glandular stomach: submucosal edema and inflammation (nd/31.25) Pancreas: chronic inflammation (125/500) Prostate gland: suppurative inflammation (nd/31.25) Hematology (end of exposure, n=10, only effects significantly different from negative AND vehicle control included here): Sig dec: Hb, Ht, MCV, MCH, MCHC, prothrombin time (125/500, ZnOAE100(−) and ZnOAE100(+)). Sig inc: total erythrocyte count, eosinophils (125/500, ZnOAE100(−)). Sig inc: total white blood cell and Platelets/thrombocyte counts (125/500, ZnOAE100(+)) Blood biochemistry (end of exposure, n=10, only effects significantly different from negative AND vehicle control included here): Sig dec: total protein, albumin (125/500, ZnOAE100(-) and ZnOAE100(+)) Sig inc: inorganic phosphorous (125/500, ZnOAE100(-) and ZnOAE100(+)) Sig inc: alkaline phosphatase (125/500, ZnOAE100(+)) Hematology and biochemistry (2 weeks post-exposure, n=5, only highest dose 500): in table 8 and 10	The effects induced by both ZnO NPs included salivation, white feces, statistically significant changes in feed and water consumption and in hematological and blood biochemical analysis, which could correlate with anemia-related parameters, in the 500 mg/kg groups of both sexes. Target organs for the test articles are considered to be the stomach, pancreas, eye, and prostate gland. Significant toxic effects were observed in both sexes at doses greater than 125 mg/kg; therefore, the NOAEL of both test articles, ZnOAE100(−) and ZnOAE100(+), was considered to be 31.5 mg/kg for both sexes. Body weight: No statistically significant differences were observed between the treated rats and their respective control groups in both sexes Urinalysis: No statistically significant changes were observed between the groups treated with ZnOAE100(−) and ZnOAE100(+) and the controls in both sexes

	Nanomaterial	Biodistribution			
Reference	**NM**	**Compartments monitored**	**Sampling regime**	**Organ burden** (timepoint, ug/organ)	**Organ clearance/ post-exposure retention half-time** (days)
Kim 2014 IntJNanomed	ZnO (negative and positive surface charge)	nd	nd	nd	nd

	Nanomaterial				
Reference	**NM**	**Systemic absorption fraction or rate** (&unit)	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)
Kim 2014 IntJNanomed	ZnO (negative and positive surface charge)	nd	nd	White feces were observed in the 500 mg/kg groups of both test articles from day 2 until treatment completion in both sexes	no

	Nanomaterial	
Reference	**NM**	**General comments**
Kim 2014 IntJNanomed	ZnO (negative and positive surface charge)	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Trine Berthing trb@nfa.dk	Park, Shin et al. 2014 IntJNanoMed	ZnO (negative surface charge)		Ultra fine Zinc Oxide ZnO-310 were purchased from Sumitomo Osaka Cement Co., Ltd (Tokyo, Japan)	The average diameter was 29±3 nm in deionized water. They refer to ref 19 Kim 2012 ToxEHS in which 20nm and 70nm ZnO from the same supplier is characterized in PBS, cell media and deionized water.	nd Possibly in ref 19 Kim 2012 ToxEHS	nd Possibly in ref 19 Kim 2012 ToxEHS

	Nanomaterial		Exposure-related phys-chem	Study design		
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Exposure-related phys-chem** (size/agglomeration in formulation/vehicle...)	**OECD guideline/GLP**	**Species**	**Strain**
Park, Shin et al. 2014 IntJNanoMed	ZnO (negative surface charge)	The surface charge was modified with coating reagent citrate (for [–] charge). Wurtzite crystal structure.	nd The modified ZnO and gavage solution is prepared once a day.	OECD/GLP	Rat	Sprague Dawley, specific pathogen-free

	Nanomaterial						
Reference	**NM**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)	**Administration route and mode** (daily gavage, ad lib. via drinking water or feed...)	**Duration of exposure** (weeks) (days/week)	**Doses** (mg/kg bw/day)
Park, Shin et al. 2014 IntJNanoMed	ZnO (negative surface charge)	male female	6 (5weeks + 7 days acclimatization)	n= 10 (90 day tox) n=5 (2 week recovery) n=2 (biodistribution)	oral gavage, daily	90 days (nd days/week) + 2 week recovery at highest dose	125, 250, 500

	Nanomaterial		**Toxicological outcomes**			
Reference	**NM**	**Formulation/vehicle** (volume, concentration, composition)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/kg bw)
Park, Shin et al. 2014 IntJNanoMed	ZnO (negative surface charge)	10 mL/kg bw. 12.5, 25 and 50 mg/mL. Vehicle: HEPES-citrate buffer pH7 (1M Na2CO3 [molecular weight {MW} =105.99], 20 mM HEPES buffer [MW =238.3] and sodium citrate). Negative control with distilled water, vehicle control with HEPES-citrate.	nd	nd	none	500/nd

	Nanomaterial			
Reference	**NM**	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**
Park, Shin et al. 2014 IntJNanoMed	ZnO (negative surface charge)	*(no statistics, all observed lesions are listed)* Forestomach: Epithelial vacuolation Stomach, limiting ridge: basal cell hyperplasia, epithelial hyperplasia, epithelial vacuolation, hyperkeratosis, submucosal inflammatory cell infiltration Glandular stomach: erosive lesions, infiltrating epithelial globule leukocytes, submucosal edema, and inflammation, chief cell-like cells with eosinophilic cytoplasmic granules, reduced number of parietal cells Pancreas: acinar cell apoptosis, ductular hyperplasia, periductular lymphoid cell infiltration, regenerative acinar cells Eye: minimal-to-severe grade retinal atrophy	Stomach (nd/125) Pancreas (250/500) Eye (125/250)	Histology (500/nd)

	Nanomaterial		
Reference	**NM**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**	**Toxicological comments**
Park, Shin et al. 2014 IntJNanoMed	ZnO (negative surface charge)	Histology: Stomach, limiting ridge: submucosal inflammatory cell infiltration. Glandular stomach: infiltrating epithelial globule leukocytes, submucosal edema, and inflammation. (nd/125) Pancreas: periductular lymphoid cell infiltration (250/500). Hematology (at end of exposure, n=10, only effects significantly different from negative AND vehicle control included here): Sig dec: Mean cell hemoglobin (125/250) Sig dec: Mean cell hemoglobin concentration, Mean cell volume (250/500) Sig inc: Total erythrocyte (250/500) Hematology (14 weeks post-exposure, n=5, only for highest dose 500): Sig inc: Total erythrocyte Sig dec: Mean cell hemoglobin Blood biochemistry (n=10, end of exposure, only effects significantly different from negative AND vehicle control included here): Sig dec: Total protein, Albumin (125/250) Sig inc: Creatine kinase (250/500)	No rats died during the test period. However, ZnOSM20(−) NPs (500 mg/kg) induced changes in the levels of anemia-related factors, prompted acinar cell apoptosis and ductular hyperplasia, stimulated periductular lymphoid cell infiltration and excessive salivation, and increased the numbers of regenerative acinar cells in the pancreas. In addition, stomach lesions were seen at 125, 250, and 500 mg/kg, and retinal atrophy was observed at 250 and 500 mg/kg. The Zn concentration was dose-dependently increased in the liver, kidney, intestines, and plasma, but not in other organs investigated. Histopathological findings regarding the ZnOSM20(−) NP-induced lesions in the eye, pancreas, and stomach did not show good correlation with the distribution data.

	Nanomaterial	Biodistribution			
Reference	**NM**	**Compartments monitored**	**Sampling regime**	**Organ burden** (timepoint, ug/organ)	**Organ clearance/ post-exposure retention half-time** (days)
Park, Shin et al. 2014 IntJNanoMed	ZnO (negative surface charge)	Plasma, feces, brain, liver, kidney, testes, ovaries, spleen, lung, stomach, small intestine, and large intestine	Organ burden at day 90: Blood (1 mL) tail vein, stool sample, brain, liver, kidney, testes, ovaries, spleen were collected. For toxicokinetic analysis, blood samples were collected from the tail vein of all rats (negative control, vehicle control, and 125, 250, and 500 mg/kg groups) on the initial day of experimentation, and again on days 28 and 90 (n=3–9 animals per group). On day 1, blood samples were taken at 2 or 10 hours before the initiation of treatment in three animals; at 0.5, 4, or 24 hours after the initiation of treatment in another three animals; and at 1 or 6 hours after the initiation of treatment in the remaining animals. On day 28, blood was taken from 0.5 to 24 hours after the initiation of treatment in all animals; and on day 90, blood was taken at 1, 2, 4, 6, 10, or 24 hours after the initiation of treatment. Inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis	Table 9: organ burden measured by ICP-OES (inductively coupled plasma optical emission spectrometry), unit not reported. No clear differences were observed between the data for the male and female rats (Table 9). However, Zn concentrations dose-dependently increased in the liver, kidney, intestine, and plasma of the experimental compared with the control groups. The ZnOSM20(−) NPs were also dose-dependently excreted into the feces, as evidenced by high Zn levels. On the other hand, little or no increase was found in the Zn concentration in the brain, testis, ovary, spleen, stomach, or lung, with the exception of the stomach in the female 500 mg/kg group (Table 9). Thus, the histopathological findings regarding the ZnOSM20(−) NP-induced lesions in the eye, pancreas, and stomach did not show good correlation with the distribution data.	nd

	Nanomaterial				
Reference	**NM**	**Systemic absorption fraction or rate** (&unit)	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)
Park, Shin et al. 2014 IntJNanoMed	ZnO (negative surface charge)		Table 8: Half time (hours) in blood measured at all 3 doses for male and female at day 0, 28 and 90 of exposure. Tmax was 4–6 hours, regardless of the day of NP administration, and the average T1/2 in the blood was 1–13 hours (Table 8). E.g. at end of 90 day exposure: 125, male female: 2.18 3.31 250: 8.71 7.63 500: 10.36 8.59	Table 8, Toxicokinetic results: AUC, area under the serum concentration time curve; Cmax, maximum observed peak serum concentration; F, female; M, male; MRT, mean residence time; Tmax, time at which was observed; T1/2, half life time Table 9, Tissue distribution. Toxicokinetics: On the first day of ZnOSM20(−) NP administra□on, Cmax values were fairly similar in the male and the female 125, 250, and 500 mg/kg groups (47.38–67.03 μg/mL) (Table 8) and were not dose-dependent. However, they increased in a dose-dependent manner in both sexes on days 28 and 90.20 In general, the AUC values were dose-dependent in males and females on all three days, with the exception of the first day of administration in males (Table 8). Tmax was 4–6 hours, regardless of the day of NP administration, and the average T1/2 in the blood was 1–13 hours (Table 8). Histopathological findings regarding the ZnOSM20(−) NP-induced lesions in the eye, pancreas, and stomach did not show good correlation with the distribution data.	no

	Nanomaterial	
Reference	**NM**	**General comments**
Park, Shin et al. 2014 IntJNanoMed	ZnO (negative surface charge)	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Trine Berthing trb@nfa.dk	Park, Kim et al. 2014 IntJNanoMed	ZnO (positive surface charge)		Ultra fine Zinc Oxide ZnO-310 were purchased from Sumitomo Osaka Cement Co., Ltd (Tokyo, Japan)	The average diameter was 29±3 nm in deionized water. They refer to ref 19 Kim 2012 ToxEHS in which 20nm and 70nm ZnO from the same supplier is characterized in PBS, cell media and deionized water.	nd Possibly in ref Kim 2012 ToxEHS	nd Possibly in ref Kim 2012 ToxEHS

	Nanomaterial		Exposure-related phys-chem	Study design		
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Exposure-related phys-chem** (size/agglomeration in formulation/vehicle...)	**OECD guideline/GLP**	**Species**	**Strain**
Park, Kim et al. 2014 IntJNanoMed	ZnO (positive surface charge)	The surface charge was modified with coating reagent L-serine (for [+] charge). Wurtzite crystal structure.	nd The modified ZnO and gavage solution is prepared once a day.	OECD principles of GLP	Rat	Sprague Dawley, specific pathogen-free

	Nanomaterial						
Reference	**NM**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)	**Administration route and mode** (daily gavage, ad lib. via drinking water or feed...)	**Duration of exposure** (weeks) (days/week)	**Doses** (mg/kg bw/day)
Park, Kim et al. 2014 IntJNanoMed	ZnO (positive surface charge)	male female	6 (5weeks + 7 days acclimatization)	n= 10 (90 day tox) n=5 (2 week recovery) n=2 (biodistribution)	oral gavage, daily	90 days (nd days/week) + 2 week recovery at highest dose	125, 250, 500

	Nanomaterial		Toxicological outcomes			
Reference	**NM**	**Formulation/vehicle** (volume, concentration, composition)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/kg bw)
Park, Kim et al. 2014 IntJNanoMed	ZnO (positive surface charge)	10 mL/kg bw. 12.5, 25 and 50 mg/mL. Vehicle: HEPES-citrate buffer pH7 (1M Na2CO3 [molecular weight {MW} =105.99], 20 mM HEPES buffer [MW =238.3] and sodium citrate). Negative control with distilled water, vehicle control with HEPES-citrate.	nd	nd	none	500/nd

	Nanomaterial			
Reference	**NM**	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**
Park, Kim et al. 2014 IntJNanoMed	ZnO (positive surface charge)	*(only effects significantly different from negative AND vehicle control included here)* Non-glandular stomach: Squamous cell hyperplasia, Squamous cell vacuolation, Subepithelial inflammatory cell infiltration Glandular stomach: Submucosal inflammatory cells infiltration, Superficial epithelial degeneration/regeneration, Intracytoplasmic hyaline droplet, Mucous cell hyperplasia, Eosinophilic chief cells Pancreas: Acinar cell apoptosis Chronic inflammation Eye: retinal atrophy The lesions observed in the pancreas and stomach disappeared in the recovery group. Retinal atrophy was also observed in 2 week	Stomach, Pancreas (nd/125) Eye (250/500)	Histology (500/nd)

	Nanomaterial		
Reference	**NM**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**	**Toxicological comments**
Park, Kim et al. 2014 IntJNanoMed	ZnO (positive surface charge)	Histology: Non-glandular stomach: Subepithelial inflammatory cell infiltration. Glandular stomach: Submucosal inflammatory cells infiltration (nd/125) Pancreas: Chronic inflammation (nd/125) Hematology (at end of exposure, n=10, only effects significantly different from negative AND vehicle control included here): Sig inc: Total leukocyte count, Total erythrocyte (250/500) Sig dec: Hemoglobin concentration, Mean cell hemoglobin concentration (250/500) Sig dec: Mean cell volume, Mean cell hemoglobin (pg) (125/250) Hematology (14 weeks post-exposure, n=5, only for highest dose 500): Sig inc: Total erythrocyte Sig dec: Mean cell volume, Mean cell hemoglobin, Mean cell hemoglobin concentration Blood biochemistry (n=10, end of exposure, only effects significantly different from negative AND vehicle control included here): Sig dec: Total protein, Albumin (125/250) Sig inc: Alkaline phosphatase (250/500)	Target organs were found to be the pancreas, eye, and stomach. No rats died during the test period. There were no significant clinical changes due to the test article during the experimental period in functional assessment, body weight, food and water consumption, ophthalmological testing, urine analysis, necropsy findings, or organ weights, but salivation was observed immediately after administration in both sexes. The total red blood cell count was increased, and hematocrit, albumin, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration were decreased significantly compared with control in both 500 mg/kg groups. Total protein and albumin levels were decreased significantly in both sexes in the 250 and 500 mg/kg groups. Histopathological studies revealed acinar cell apoptosis in the pancreas, inflammation and edema in stomach mucosa, and retinal atrophy of the eye in the 500 mg/kg group.

	Nanomaterial	Biodistribution			
Reference	**NM**	**Compartments monitored**	**Sampling regime**	**Organ burden** (timepoint, ug/organ)	**Organ clearance/ post-exposure retention half-time** (days)
Park, Kim et al. 2014 IntJNanoMed	ZnO (positive surface charge)	Plasma, feces, brain, liver, kidney, testes, ovaries, spleen, lung, stomach, small intestine, and large intestine	Organ burden at day 90: 1 mL blood, tail vein, stod	Table 11: Tissue distribution. ZnO concentration was increased in the liver, kidney, intestine, plasma, and lung. And excreted in the feces	nd

	Nanomaterial				
Reference	**NM**	**Systemic absorption fraction or rate** (&unit)	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)
Park, Kim et al. 2014 IntJNanoMed	ZnO (positive surface charge)	nd	nd		no

	Nanomaterial	
Reference	**NM**	**General comments**
Park, Kim et al. 2014 IntJNanoMed	ZnO (positive surface charge)	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Trine Berthing trb@nfa.dk	Seok 2013 J Appl To	ZnO		Nanostructured & Amorphous Materials, Inc. (TX, USA) in the form of a distilled water dispersion	(40, provided by manufacturer)	(60 ±10, provided by manufacturer)	nd

	Nanomaterial		Exposure-related phys-chem	Study design		
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Exposure-related phys-chem** (size/agglomeration in formulation/vehicle...)	**OECD guideline/GLP**	**Species**	**Strain**
Seok 2013 J Appl To	ZnO	Zeta potential at pH 2-12: ZnO NPs were negatively charged at neutral or basic pH values but positively charged at pH values less than 4. Solubility in artificial gastric fluid (AGF) at pH 1.7 and pH 7.4 and in distilled water pH 7.4. The white, milky-colored ZnO NP solution cleared within a few minutes when added to acidic artificial gastric fluid (AGF, pH 1.7). After 24 h, around 98% of the ZnO NP mass had dissolved in the AGF, whereas ZnO NPs in DW showed minimal dissolution (Fig. 2). After a 24-h incubation of ZnO NPs in AGF, increasing the pH of the solution to 7.4 did not result in reaggregation (Fig. 2). Likewise, ZnO NPs in DW or RPMI-1640 culture medium supplemented with 10% fetal bovine serum (FBS) maintained their morphology and size (Fig. 3). However, ZnO NPs in AGF dissolved fully; only the grid could be observed (Fig. 3C).	The hydrodynamic size of ZnO NPs in distill	OECD TG 408 and GLP	Rat	Sprague Dawley

	Nanomaterial						
Reference	**NM**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)	**Administration route and mode** (daily gavage, ad lib. via drinking water or feed...)	**Duration of exposure** (weeks) (days/week)	**Doses** (mg/kg bw/day)
Seok 2013 J Appl To	ZnO	male female	8	n=11 per sex	oral gavage	13 (nd days/week)	67.1, 134.2, 268.4, 536.8

	Nanomaterial		Toxicological outcomes			
Reference	**NM**	**Formulation/vehicle** (volume, concentration, composition)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/kg bw)
Seok 2013 J Appl To	ZnO	10 mL/kg bw. ZnO in distilled water.	nd	nd	none	536.8/nd

	Nanomaterial			
Reference	**NM**	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**
Seok 2013 J Appl To	ZnO	Pancreas: pancreatitis with focal lymphocyte infiltration and mild acinar apoptosis No significant pathological changes observed in heart, liver, lung, spleen, thymus, kidney, adrenal gland, testes, ovary, brain and pituitary gland, the nasal cavity, eyes with Harderian glands, spinal cord (thoracic portion together with corresponding vertebral bones), salivary glands, stomach, small intestine (duodenum, jejunum and ileum), large intestine (cecum, colon and rectum), pancreas, urinary bladder, skin with mammary glands, mesenteric lymph nodes, trachea, esophagus, thyroid glands, tongue, thigh muscle, sciatic nerve, epididymides, seminal vesicles, prostate (ventral and dorsolateral lobes), uterus, ovaries and vagina	Pancreas (268.4/536.8)	Histology (536.8/nd)

	Nanomaterial		
Reference	**NM**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**	**Toxicological comments**
Seok 2013 J Appl To	ZnO	Histology: Pancreatitis (268.4/536.8) Hematology: Sig dec: mean cell volume (67.1/134.2) Sig dec: hemoglobin, hematocrit, mean corpuscular hemoglobin (268.4/536.8) Sig inc: platelets (268.4/536.8) Serum biochemistry: Sig inc: Na (nd/67.1) TG? Sig inc: Cl (67.1/134.2) Sig dec: total protein (67.1/134.2) Sig inc: alkaline phosphatase, phosphorus (268.4/536.8) Sig dec: albumin (268.4/536.8)	Author conclusion: According to our 13-week repeated oral toxicity study using ZnO NPs, the no observed adverse effect level (NOAEL) of ZnO NPs in SD rats is 268.4. In conclusion, we demonstrated that oral intake of high dose ZnO NPs can cause pancreatitis and anemia, likely as a result of the absorption of ionized Zn owing to the complete dissolution of ZnO NPs in the acidic gastric fluid

	Nanomaterial	Biodistribution			
Reference	**NM**	**Compartments monitored**	**Sampling regime**	**Organ burden** (timepoint, ug/organ)	**Organ clearance/ post-exposure retention half-time** (days)
Seok 2013 J Appl To	ZnO	nd	nd	nd	nd

	Nanomaterial				
Reference	**NM**	**Systemic absorption fraction or rate** (&unit)	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)
Seok 2013 J Appl To	ZnO	nd	nd		no

	Nanomaterial	
Reference	**NM**	**General comments**
Seok 2013 J Appl To	ZnO	Figure 6: in vitro Cell viabilit

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Trine Berthing trb@nfa.dk	Cho 2013 PFT	ZnO (and TiO2)		Nanostructured and Amorphous Materials, Inc. (TX, USA), ZnO nanoparticles at 20 wt% in distilled water (DW)	89.3 ± 44.7 (SEM) 40 (manufacturer)	(60±10, provided by manuf	nd
Roel Schins, IUF roel.schins@uni-duesseldorf.de	Kim 2010 Particle and Fibre Toxicology	Ag	7440-22-4	NAMATECH, Ltd. (Daejeon, Korea), purity > 99.98%	Mean 56 nm (GSD= 1.46) by TEM, determined in 0.5% aq. carboxymethylcellulose	nd	

	Nanomaterial		Exposure-related phys-chem	Study design		
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Exposure-related phys-chem** (size/agglomeration in formulation/vehicle...)	**OECD guideline/GLP**	**Species**	**Strain**
Cho 2013 PFT	ZnO (and TiO2)	hexagonal shape and crystal structure. The zeta potential of ZnO was more negative than TiO2, at 11.7 ± 0.8 mV for pH 2 and -25.1 ± 2.6 mV for pH 8. ZnO dissolved in acidic gastric fluid (AGF) within five minutes. In basic conditions, ZnO showed minimal dissolution after monitoring for up to 24 h.	The hydrodynamic size 201.8 ± 17.2 nm sug	OECD TG 408/GLP	Rat	Sprague Dawley, specific pathogen-free
Kim 2010 Particle and Fibre Toxicology	Ag		Mean 56 nm (GSD= 1.46) by TEM, determined in 0.5% aq. carboxymethylcellulose	OECD TG 408, GLP	rat	Fisher 344, specific-pathogen free

	Nanomaterial						
Reference	**NM**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)	**Administration route and mode** (daily gavage, ad lib. via drinking water or feed...)	**Duration of exposure** (weeks) (days/week)	**Doses** (mg/kg bw/day)
Cho 2013 PFT	ZnO (and TiO2)	male female	7 (6weeks+7d	n=11 per sex n=5 (excretion in feces and urine)	oral gavage, daily	13 (7d/w)	134.2, 268.4, 536.8
Kim 2010 Particle and Fibre Toxicology	Ag	male & female	5	n=10 per sex and dose group	oral gavage, daily	13 (7 days/week)	vehicle, 30, 125 and 500

	Nanomaterial		Toxicological outcomes			
Reference	**NM**	**Formulation/vehicle** (volume, concentration, composition)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/kg bw)
Cho 2013 PFT	ZnO (and TiO2)	10 ml/kg bw.	nd	nd	nd	nd
Kim 2010 Particle and Fibre Toxicology	Ag	0.5% aqueous carboxymethylcellulose; gavage dosing volume of 10 ml/kg	nd	nd	none	500/nd

	Nanomaterial			
Reference	**NM**	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**
Cho 2013 PFT	ZnO (and TiO2)	nd	nd	nd
Kim 2010 Particle and Fibre Toxicology	Ag	Liver: Minimal bile-duct hyperplasia, with or without necrosis, fibrosis, and/or pigmentation (no stats performed)	30/125 Suggested by authors on combined evaluation of clinical chemistry (statistically analysed) and histology (no stats)	Histology (500/nd) (Incidence of fibrosis is similar for all groups including controls)

	Nanomaterial		
Reference	**NM**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**	**Toxicological comments**
Cho 2013 PFT	ZnO (and TiO2)	nd	nd
Kim 2010 Particle and Fibre Toxicology	Ag	Histology (no stats): minimal tubular basophilia in kidneys of males (only observed at the highest dose, 500); Hematology: statistically significant increase in monocytes of females (only observed at the highest dose, 500)	Significant increases in ALP, cholesterol in males and females

	Nanomaterial	Biodistribution			
Reference	**NM**	**Compartments monitored**	**Sampling regime**	**Organ burden** (timepoint, ug/organ)	**Organ clearance/ post-exposure retention half-time** (days)
Cho 2013 PFT	ZnO (and TiO2)	Blood, urine, feces, liv	Ti and Zn content (ICP-MS) in Blood via abdominal	At the end of 13 week exposure. Significant increase in Zn concentration in liver, kidney, spleen and brain in the highest dose group (536.8). Concentration of Zn in liver and kidney was much higher than in the spleen and brain, with a positive, dose-related trend. Figure 5: Tissue concentration (ug/g) of Zn at end of exposure. Additional file 2, figure S2: Organ burden (ug/organ) at end of exposure	nd Figure 6: Excreation in feces and urine at end of exposure.
Kim 2010 Particle and Fibre Toxicology	Ag	liver, kidneys, brain, lu	Ag (elemental) determined in liver, kidneys, brain, lungs, testes and blood at sarcifice (13 weeks) using AAS (NIOSH 7300 method):	Dose dependent increases of Ag in all organs - All values in Table 10 , For lowest treatment dose (i.e. 30 mg/kg/bw/day) in males: Mean values of 6.56 µg/g (testes), 4.20 µg/g (liver), 1.49 µg/g (kidneys), 0.47 µg/g (brain), 1.94 µg/g (lungs) and 0.111 µg/g (blood), and in females: 8.56 µg/g (liver), 7.98 µg/g (kidneys), 0.38 µg/g (brain), 4.97 µg/g (lungs) and 0.087 µg/g (blood).	nd

	Nanomaterial				
Reference	**NM**	**Systemic absorption fraction or rate** (&unit)	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)
Cho 2013 PFT	ZnO (and TiO2)	nd Figure 3: Ti and Zn concentration in blood at the end of exposure.	nd	Absorption: Significantly increased Zn blood concentration at the highest dose (536.8). Clear dose-response relationship. The Zn blood concentration was almost 10-fold higher than the Ti concentration in the TiO2-treatment groups. Distribution: Significant increase in Zn concentration in liver, kidney, spleen and brain in the highest dose group (536.8). Concentration of Zn in liver and kidney was much higher than in the spleen and brain, with a positive, dose-related trend Excretion: Concentration of Zn in the urine of ZnO-treatment groups was significantly increased in the middle- and high-dose groups and showed positive trend dose-responses. Ti or Zn concentrations in the feces were very high compared to concentrations in the urine or tissues, with clear dose responses.	no
Kim 2010 Particle and Fibre Toxicology	Ag	nd	nd		nd

	Nanomaterial	
Reference	**NM**	**General comments**
Cho 2013 PFT	ZnO (and TiO2)	
Kim 2010 Particle and Fibre Toxicology	Ag	Study outcomes may be put into perspective with NOEAL/LOAEL derived from 28 day study findings (Kim et al., 2008)

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Roel Schins, IUF roel.schins@uni-duesseldorf.de	Yun et al. 2015 J Appl Toxicol	Citrate-capped Ag NP at 20 wt% in distilled water		ABC Nanotech Co Ltd. (Daejeon, Korea)	11 nm (determined by TEM)	nd	
Sybille van den Brule sybille.vandenbrule@uclouvain.be	van den Brule et al, 2016 pft	Ag NP, Polyvinylpyrrolidone (PVP)-coated	7440-22-4	Sigma-Aldrich (Silver 576832-5G, Vial # MKBN3581V, MO, USA)	55.17 ± 2.67 nm (TEM, mean area equivalent circular diameter)	5.57 ± 0.08 m^2/g (N2 physisorption)	nd
Trine Berthing trb@nfa.dk	Shipelin 2017 NanotechRussia	MWCNT		Taunit-M® (OOO Nanotekhtsentr, Tambov, Russia)	Supplier info: outer diameter 15–40 nm, diameter of inner cavity 3–8 nm, the average length—2 µm.		Supplier info: impurities including amorphous carbon was less than 1.5%.

	Nanomaterial		Exposure-related phys-chem	Study design		
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Exposure-related phys-chem** (size/agglomeration in formulation/vehicle...)	**OECD guideline/GLP**	**Species**	**Strain**
Yun et al. 2015 J Appl Toxicol	Citrate-capped Ag NP at 20 wt% in distilled water	Spherical (verified by SEM and TEM)	hydrodynamic size of 19.0 ± 4.6 nm (determined by DLS), Zeta-potential: –21.13 mV	OECD TG 408, GLP	rat	Sprague-Dawley (Orient Bio, Seongnam, Korea)
van den Brule et al, 2016 pft	Ag NP, Polyvinylpyrrolidone (PVP)-coated	Purity: 99.5 % Ag; PVP coating: 0.2 %, as stated by the provider; non porous (porosity 0.027 cm^3/g, N2 physisorption)	lab pellets (Carfil, Rats & Mice Maintenance, Oud-Turnhout, Belgium) supplemented with 0, 46, 460 or 4600 ppb Ag NP by the provider during the preparation of the pellets (Food bags were γ-irradiated and stored at room temperature, in dark and dry conditions)	OECD guideline 407 for testing of chemicals (“Repeated dose 28-d oral study in rodents”)	mouse	C57BL/6
Shipelin 2017 NanotechRussia	MWCNT		bimodal aggregate (coil) size distribution of MWCNTs with mean hydrodynamic diameters of 80 and 200 nm	GLP	Rat	Wistar

	Nanomaterial						
Reference	**NM**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)	**Administration route and mode** (daily gavage, ad lib. via drinking water or feed...)	**Duration of exposure** (weeks) (days/week)	**Doses** (mg/kg bw/day)
Yun et al. 2015 J Appl Toxicol	Citrate-capped Ag NP at 20 wt% in distilled water	male & female	5	n=12 per sex and dose group	oral gavage, daily	13 (7 days/week)	vehicle, 257.6, 515.3 and 1030.5
van den Brule et al, 2016 pft	Ag NP, Polyvinylpyrrolidone (PVP)-coated	female	12	n = 3-5	food pellets, daily	28 d	**Target intake**: 0, 11.4, 114 and 1140 µg Ag NP/kg bw/d (0, 0.0114, 0.114 and 1.14 mg Ag NP/kg bw/d), considering a 20 g mouse consuming an average of 5 g pellets per day (0, 46, 460 or 4600 ppb Ag NP (µg Ag NP/kg pellet). **Calculated intake**: 0, 7.75-8.6, 71.1-78.5 and 654.9-800.8 µg Ag NP/kg bw/d (60-75 % of the target intake, based on pellet consumption and bw)
Shipelin 2017 NanotechRussia	MWCNT	male	nd	n=16 n=8 (cognitive tests)	oral via drinking water (dosage adjusted daily to body weight)	14 (100 days)	0.01, 0.1, 1.0, and 10

	Nanomaterial		Toxicological outcomes			
Reference	**NM**	**Formulation/vehicle** (volume, concentration, composition)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/kg bw)
Yun et al. 2015 J Appl Toxicol	Citrate-capped Ag NP at 20 wt% in distilled water	distilled water	nd	nd	nd	1030.5/nd
van den Brule et al, 2016 pft	Ag NP, Polyvinylpyrrolidone (PVP)-coated	0, 46, 460 or 4600 µg Ag NP/kg pellet	nd	nd	nd	nd
Shipelin 2017 NanotechRussia	MWCNT	water with 1 vol % of Tween 20	nd	nd	nd	nd

	Nanomaterial			
Reference	**NM**	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**
Yun et al. 2015 J Appl Toxicol	Citrate-capped Ag NP at 20 wt% in distilled water	Mild Lymphocyte infiltration observed in livers of 8 out of 12 male and 6 out of 12 female rats at 1030.5 mg/kg, but also in considerable number of controls (5 out of 12 and 4 out of 12, respectively). Lymphocyte infiltration in kidneys found in few rats (with increasing dose)	515.3/1030.5 based on combined evaluation of clinical chemistry (statistically analysed) and histology (no stats)	no
van den Brule et al, 2016 pft	Ag NP, Polyvinylpyrrolidone (PVP)-coated	**GIT:** no intestinal damage or structural alterations: ileal villi well conserved, goblet cells unaffected and glycocalyx integrity intact; colonic tissue unaffected.	> 0.8 mg Ag NP/kg bw/d	nd
Shipelin 2017 NanotechRussia	MWCNT	nd	nd	nd

	Nanomaterial		
Reference	**NM**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**	**Toxicological comments**
Yun et al. 2015 J Appl Toxicol	Citrate-capped Ag NP at 20 wt% in distilled water	Hematology: Increased white blood cell count in female rats (nd/1030.5)	Increased serum ALP in males and females (nd/1030.5) and calcium in females (nd/257.6); decreased platelets in males (nd/1030.5); no abnormal daily activity and clinical symptoms observed during exposure. Reduced pituitary gland weight in males (nd/1030.5) and relative liver weight in females (nd/515.3).
van den Brule et al, 2016 pft	Ag NP, Polyvinylpyrrolidone (PVP)-coated	Serum C-Reactive Protein (C-RP): no change (> 0.8 mg Ag NP/kg bw/d)	**Mortality:** no; **bw:** no change; **Gut microbiota** (analyzed by 16S rRNA bacterial sequencing): disturbance of bacterial evenness (α-diversity) and populations (β-diversity) in a dose-dependent manner, increase of the ratio between Firmicutes (F) and Bacteroidetes (B) phyla, effects similar to those reported in metabolic and inflammatory diseases, such as obesity (**LOAEL 7.75-8.6 µg Ag NP/kg bw/d**). Effects probably dependent on Ag NP aging in food (due to sulfidation that limits the release of toxic Ag ions)
Shipelin 2017 NanotechRussia	MWCNT	nd	Assay for Intestinal permeability: Chick ovalbumin (OVA) was administered intragastrically to rats with a dose of 2 g/kg BW through a probe 3 h before euthanasia. % OVA in blood determined. Reduction in thymus weight of all exposed animals by 26–35%, significant increase of 20% in brain mass at highest dose (10) and in adrenal mass by 32% at middle dose (0.1).

	Nanomaterial	Biodistribution			
Reference	**NM**	**Compartments monitored**	**Sampling regime**	**Organ burden** (timepoint, ug/organ)	**Organ clearance/ post-exposure retention half-time** (days)
Yun et al. 2015 J Appl Toxicol	Citrate-capped Ag NP at 20 wt% in distilled water	Blood, liver, kidney, spleen, lung, brain, urine and feces	Analysed in five rats per group by inductively coupled plasma mass spectrometry	At 13 weeks, increased Ag concentration in blood and further organs, orders of magnitude in µg/g are approximately 100-400 (blood), 0.5-2 (liver), 4-15 (kidney), 30-125 (spleen), 2.5-25 (lung), 1-2 (brain)	nd
van den Brule et al, 2016 pft	Ag NP, Polyvinylpyrrolidone (PVP)-coated	nd	nd	nd	nd
Shipelin 2017 NanotechRussia	MWCNT	nd	nd	nd	nd

	Nanomaterial				
Reference	**NM**	**Systemic absorption fraction or rate** (&unit)	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)
Yun et al. 2015 J Appl Toxicol	Citrate-capped Ag NP at 20 wt% in distilled water	nd	nd		no
van den Brule et al, 2016 pft	Ag NP, Polyvinylpyrrolidone (PVP)-coated	nd	nd	nd	available for gut microbiota sequencing (EBI Metagenomics repository, http://www.ebi.ac.uk/ena/data/view/PRJEB14370)
Shipelin 2017 NanotechRussia	MWCNT	nd	nd	nd	no

	Nanomaterial	
Reference	**NM**	**General comments**
Yun et al. 2015 J Appl Toxicol	Citrate-capped Ag NP at 20 wt% in distilled water	
van den Brule et al, 2016 pft	Ag NP, Polyvinylpyrrolidone (PVP)-coated	
Shipelin 2017 NanotechRussia	MWCNT	Methodological paper testing the effect of using surfactant for dispersion of MWCNT in drinking water on intestinal permeability. Perhaps relevant for in vitro models.

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Trine Berthing trb@nfa.dk	Matsumoto 2012 JToxSci	MWCNT (and SWCNT, data not included here)		OECD WPMN MWCNT (Lot No.: 04-12/10#1-(4)) supplied by Nikkiso Co., Ltd. (Shizuoka, Japan)	entangled MWCNTs with a diameter of around 30 nm		
Trine Berthing trb@nfa.dk	Buesen 2014 ArchTox	BaSO4 (NM-220)		Powder from Solvay, Brussels, Belgium			

	Nanomaterial		Exposure-related phys-chem	Study design		
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Exposure-related phys-chem** (size/agglomeration in formulation/vehicle...)	**OECD guideline/GLP**	**Species**	**Strain**
Matsumoto 2012 JToxSci	MWCNT (and SWCNT, data not included here)		Dispersion examined qualitatively with light microscopy	OECD TG 423 and TG 407/ GLP.	Rat	Crl:CD(SD)
Buesen 2014 ArchTox	BaSO4 (NM-220)		285 nm/9, Particle size/dispersability in DMEM/FCS, Analytical ultracentrifugation, D50/average agglomeration number	OECD TG 407 limit test	Rat	Wistar Crl:WI(Han)

	Nanomaterial						
Reference	**NM**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)	**Administration route and mode** (daily gavage, ad lib. via drinking water or feed...)	**Duration of exposure** (weeks) (days/week)	**Doses** (mg/kg bw/day)
Matsumoto 2012 JToxSci	MWCNT (and SWCNT, data not included here)	male female	5	n=6 or 12 per sex	oral gavage, daily	4 + 2 weeks recovery for highest dose	0.5, 5.0 and 50
Buesen 2014 ArchTox	BaSO4 (NM-220)	male female	6	n=5 per sex	oral gavage, daily	4 (7days/week)	1000

	Nanomaterial		Toxicological outcomes			
Reference	**NM**	**Formulation/vehicle** (volume, concentration, composition)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/kg bw)
Matsumoto 2012 JToxSci	MWCNT (and SWCNT, data not included here)	5% gum acacia of aqueous solution	nd	nd	none	nd (histopathology was only done for highest dose of 50, where no neoplastic changes were observed)
Buesen 2014 ArchTox	BaSO4 (NM-220)	6.5 wt% in PBS+BSA	nd	nd	none	1000/nd

	Nanomaterial			
Reference	**NM**	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**
Matsumoto 2012 JToxSci	MWCNT (and SWCNT, data not included here)	none	nd (histopathology was only done for highest dose of 50, where no histopathological changes were observed)	Histology (no fibrosis observed at highest dose 50)
Buesen 2014 ArchTox	BaSO4 (NM-220)	Minimal to slight inflammatory cell infiltrates in the submucosa of the glandular stomach (female group)	nd/1000	Histology (1000/nd)

	Nanomaterial		
Reference	**NM**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**	**Toxicological comments**
Matsumoto 2012 JToxSci	MWCNT (and SWCNT, data not included here)	Hematology: (Sig dec, but within historical controls: eosinophil, end of exposure (2.5/5) and after 2 weeks recovery (5/50)) Clinical chemistry: (Sig dec: γ-globulin (5/50), Gamma-GTP (no dose-response), only observed at end of exposure, not after recovery. Not cosidered treatment related.)	Based on the absence of toxicological effects, the no observed adverse effect levels (NOAELs) of repeated dose toxicity of SWCNT and MWCNT were considered to be 12.5 mg/kg bw/day and 50 mg/kg bw/day in rats (the highest dose tested), respectively.
Buesen 2014 ArchTox	BaSO4 (NM-220)	Histology: Minimal to slight inflammatory cell infiltrates in the submucosa of the glandular stomach, female group (nd/1000) Hematology: NC total WBC and differential count (1000/nd), sig inc Large Unstained Cells (nd/1000) Clinical chemistry, acute phase proteins: sig inc haptoglobin (nd/1000), NC: α2-macroglobulin (1000/nd)	For none of the test groups, recorded changes in hematological parameters were assessed as being related to the treatment with the respective nanomaterials. For none of the test groups, recorded changes in clinical chemistry parameters or the acute phase proteins were assessed as being adverse and related to the NM treatment. Neither in sub-studies A nor B, any treatment-related, adverse changes of any of the urine parameters assessed were recorded. There were no significant increases or decreases of the mean absolute organ weights. At a dose level of 1,000 mg/kg, none of the tested NMs had a biologically relevant impact on the plasma metabolome pattern of rats.

	Nanomaterial	Biodistribution			
Reference	**NM**	**Compartments monitored**	**Sampling regime**	**Organ burden** (timepoint, ug/organ)	**Organ clearance/ post-exposure retention half-time** (days)
Matsumoto 2012 JToxSci	MWCNT (and SWCNT, data not included here)	nd	nd	nd	nd
Buesen 2014 ArchTox	BaSO4 (NM-220)	nd	nd	nd	nd

	Nanomaterial				
Reference	**NM**	**Systemic absorption fraction or rate** (&unit)	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)
Matsumoto 2012 JToxSci	MWCNT (and SWCNT, data not included here)	nd	nd	Black feces were observed in both sexes in all the treatment groups. Grayish green/dark green contents in the cecum, colon and/or rectum were observed in both sexes at 5.0 mg/kg bw/day and higher. Not observed after 2 week recovery.	no
Buesen 2014 ArchTox	BaSO4 (NM-220)	nd	nd		yes, metabolome analysis was performed in plasma samples

	Nanomaterial	
Reference	**NM**	**General comments**
Matsumoto 2012 JToxSci	MWCNT (and SWCNT, data not included here)	
Buesen 2014 ArchTox	BaSO4 (NM-220)	

		Nanomaterial			NM phys-chem characteristics (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Minne Heringa Minne.Heringa@rivm.nl	Hu 2018 Nanotoxicol.	TiO2 (P25)	not provided	P25 from Sigma Co.	26.42 ± 7.73 (SEM and TEM)	not determined	not determined
Minne Heringa Minne.Heringa@rivm.nl	Bettini 2017 Nature Scientific Reports	TiO2 (E171)	not provided	E171 sample obtained from French commercial supplier of food colouring	20-340 (TEM-EDX)	not determined	not determined
Min Beom mbheo@kriss.re.kr	GLP data, unpublished	AEROXIDE® TiO2 P25					
Minne Heringa Minne.Heringa@rivm.nl	Chen 2015 Toxicol. Lett.	TiO2	not provided	Shanghai Aladdin Reagent Co, China	24 ± 5 nm	63.95 m^2/g (BET)	not determined

	Nanomaterial		Exposure-related phys-chem	Study design		
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Exposure-related phys-chem** (size/agglomeration in formulation/vehicle...)	**OECD guideline/GLP**	**Species**	**Strain**
Hu 2018 Nanotoxicol.	TiO2 (P25)	hydroynamic size in PBS: 42.15 ± 6.71nm; anatase/rutile crystal structure	not determined	none	mice	ICR
Bettini 2017 Nature Scientific Reports	TiO2 (E171)	hydrodynamic diameter 373 ±20 nm, zeta potential -23.9±2.4 mV	comparison to the initial bolus, TiO2 particles did not reagglomerate in vivo when transiting along the gut	none	rat	Wistar
GLP data, unpublished	AEROXIDE® TiO2 P25					
Chen 2015 Toxicol. Lett.	TiO2	spherical shape, anatase, purity of 99.90%, zeta potential of 11.1 mV in water, 4.7 mV in artifical gastric juice, and -13.7 in artifical intestinal juice	size of 40.9 ± 0.4 in water, 149±33.9 in artifica=ial gastric juice and 168.1±29.6 in artifical intestinal juice	none	rat	Sprague-Dawley

	Nanomaterial						
Reference	**NM**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)	**Administration route and mode** (daily gavage, ad lib. via drinking water or feed...)	**Duration of exposure** (weeks) (days/week)	**Doses** (mg/kg bw/day)
Hu 2018 Nanotoxicol.	TiO2 (P25)	not reported!	>6 weeks	not reported!	oral, "via a syringe"	26 weeks, (7d/week)	0,10, 20, 50, 100, 200
Bettini 2017 Nature Scientific Reports	TiO2 (E171)	male	(adult)	n=11-12	oral, drinking water	14 weeks, 100 days (and separate experiment of 7 days)	0.2 and 10
GLP data, unpublished	AEROXIDE® TiO2 P25						
Chen 2015 Toxicol. Lett.	TiO2	male and female	4	n=10 per sex per dose	oral, gavage	30 and 90 days, daily	0.2,10,50

	Nanomaterial		Toxicological outcomes			
Reference	**NM**	**Formulation/vehicle** (volume, concentration, composition)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/kg bw)
Hu 2018 Nanotoxicol.	TiO2 (P25)	not reported, seems to be PBS	not determined	not determined	not determined	not determined
Bettini 2017 Nature Scientific Reports	TiO2 (E171)	not reported	(separate 7-d exposure: Peyer's Patch, comet, negative)	not determined	Colon: in healthy rats some increase in aberrant crypt foci (putative pre-neoplastic lesions) (in colon-tumour induced rats: number and size of aberrant crypt foci increased with 10 mg/kg bw/d E171, as pre-neoplastic lesions)	effect seen at only dose of 10 mg/kg BW/day
GLP data, unpublished	AEROXIDE® TiO2 P25					
Chen 2015 Toxicol. Lett.	TiO2	ultrapure water, 1 mL	not determined	not determined	not observed (only heart analyzed)	50/not applicable

	Nanomaterial			
Reference	**NM**	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**
Hu 2018 Nanotoxicol.	TiO2 (P25)	no apoptotic cells in pancreas or liver (not more analyzed)	not applicable (insufficient analyses)	not determined
Bettini 2017 Nature Scientific Reports	TiO2 (E171)	not observed (unclear whether only colon was analyzed)	no effect seen at only dose of 10 mg/kg BW/day	not observed (unclear whether only colon was analyzed)
GLP data, unpublished	AEROXIDE® TiO2 P25			
Chen 2015 Toxicol. Lett.	TiO2	not observed (only heart analyzed)	50/not applicable	not observed (only heart analyzed)

	Nanomaterial		
Reference	**NM**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**	**Toxicological comments**
Hu 2018 Nanotoxicol.	TiO2 (P25)	increased secretions of TNF-α and IL-6 in serum (10/50)	Study focussed on effects on glucose levels and pathways: plasma glucose levels increased after 8 weeks at 50 mg/kg bw /d and higher; total suporoxide dismutase and GSH consumed at higher rate at 50 mg/kg bw/d in liver and serum, and higher levels of MDA in serum and liver at these doses: indicators of oxidative stress. In earlier study (Hu et al., 2016), disconuation fo dosing did not lead to recovery of glucose and ox. stress levels. addition of antioxidants (resveratrol and vitamin E) did keep glucose and ox. stress levels normal.
Bettini 2017 Nature Scientific Reports	TiO2 (E171)	Flow cytometry of cells from Peyer's Patches: decrease in regulatory T cells (Tregs) (CD4+CD25+FoxP3+) and decrease in CD4+CD25+ T helper (Th) cells (results only reported for dose 10). Cytokine assay of colonic mucosa: Moderate increase in TNF-α and IL-10 but no cleaved caspase-1 or its effectors IL-1β and IL-18 in colonic mucosa (results only reported for dose 10). (after 7 d exposure: in mucosa of small and large intestine, no effect on myeloperoxidase (MPO, marker of neutrophilia) or content of basal cytokines)	no effect on gut permeability to EDTA
GLP data, unpublished	AEROXIDE® TiO2 P25		
Chen 2015 Toxicol. Lett.	TiO2	increased WBC and granulocytes in blood females of 50 mg/kg bw/d after 90 days (10/50); cytkines in serum not really chagned (30 d study)	the reported cardiovascular effects are so temporary and slight, I do not consider them of high relevance

	Nanomaterial	Biodistribution			
Reference	**NM**	**Compartments monitored**	**Sampling regime**	**Organ burden** (timepoint, ug/organ)	**Organ clearance/ post-exposure retention half-time** (days)
Hu 2018 Nanotoxicol.	TiO2 (P25)	liver, pancreas, spleen, kidney, small intestine, muscle	tissues digested after sacrifice at 26 weeks	see figure 1C in publication (about 1-6 ug/g)	not determined
Bettini 2017 Nature Scientific Reports	TiO2 (E171)	gut lumen, Peyers patches (PP), colon mucosa, liver	Qualitative high-resolution imaging after 7 days exposure.	not determined	not determined
GLP data, unpublished	AEROXIDE® TiO2 P25				
Chen 2015 Toxicol. Lett.	TiO2	not determined	not determined	not determined	not determined

	Nanomaterial				
Reference	**NM**	**Systemic absorption fraction or rate** (&unit)	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)
Hu 2018 Nanotoxicol.	TiO2 (P25)	not determined	not determined	higher organ levelsthan in control found for liver, pancreas, spleen, kidney and small intestine	yes, RNA sequencing of liver, showing induced endoplasmic reticulum stress and an inflammatory response through MAPK and NF--κB at 50 mg/kg bw/d and higher, and
Bettini 2017 Nature Scientific Reports	TiO2 (E171)	not determined	not determined	After 7 days of exposure: particles found in gut lumen, Peyers patches (PP), colon mucosa, liver. Including high-resolution imaging of subcellular locations.	no
GLP data, unpublished	AEROXIDE® TiO2 P25				
Chen 2015 Toxicol. Lett.	TiO2	not determined	not determined		no

	Nanomaterial	
Reference	**NM**	**General comments**
Hu 2018 Nanotoxicol.	TiO2 (P25)	
Bettini 2017 Nature Scientific Reports	TiO2 (E171)	
GLP data, unpublished	AEROXIDE® TiO2 P25	
Chen 2015 Toxicol. Lett.	TiO2	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Trine Berthing trb@nfa.dk	Cho 2013 PFT	TiO2 (and ZnO)		Powder-form TiO2 nanoparticles from ABC Nanotech Co., Ltd. (Daejeon, Korea)	26.4 ± 6.1 (SEM) 21 (manufacturer)	(50±15, provided by manuf	nd
Minne Heringa Minne.Heringa@rivm.nl	Morgan 2018 Biomedicine & Pharmacotherapy	TiO2	not provided	Sigma Aldrich	10 nm	> 150m2/g	not determined

	Nanomaterial		Exposure-related phys-chem	Study design		
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Exposure-related phys-chem** (size/agglomeration in formulation/vehicle...)	**OECD guideline/GLP**	**Species**	**Strain**
Cho 2013 PFT	TiO2 (and ZnO)	spherical. Anatase 80: 20 Rutile. The zeta potential of TiO2 was 54.4 ± 0.7 mV for pH 2 and 7.9 ± 2.7 mV for pH 8. TiO2 showed minimal dissolution in both acidic gastric fluid (AGF) and at pH 7.4	TiO2 had hydrodynamic sizes (37.8 ± 0.4 nm) in distilled water similar to the primary particle size.	OECD TG 408/GLP	Rat	Sprague Dawley, specific pathogen-free
Morgan 2018 Biomedicine & Pharmacotherapy	TiO2	purity of 99.9%	not determined	none	rat	(albino)

	Nanomaterial						
Reference	**NM**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)	**Administration route and mode** (daily gavage, ad lib. via drinking water or feed...)	**Duration of exposure** (weeks) (days/week)	**Doses** (mg/kg bw/day)
Cho 2013 PFT	TiO2 (and ZnO)	male female	7 (6weeks+7d	n=11 per sex	oral gavage, daily	13 (7d/w)	260.4, 520.8, 1041.5
Morgan 2018 Biomedicine & Pharmacotherapy	TiO2	male	(adult)	n=10	oral, no further details give	60 days	0, 100

	Nanomaterial		**Toxicological outcomes**			
Reference	**NM**	**Formulation/vehicle** (volume, concentration, composition)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/kg bw)
Cho 2013 PFT	TiO2 (and ZnO)	10 ml/kg bw.	nd	nd	nd	nd
Morgan 2018 Biomedicine & Pharmacotherapy	TiO2	PBS	DNA laddering assay (no OECD TG, not common): positive	not determined	not observed (only liver analyzed)	no effects seen at only dose of 100 mg/kg bw/d

	Nanomaterial			
Reference	**NM**	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**
Cho 2013 PFT	TiO2 (and ZnO)	nd	nd	nd
Morgan 2018 Biomedicine & Pharmacotherapy	TiO2	only liver analyzed: hepatocellular necrosis, macro vascular and micro vascular steatosis and disorganization of the hepatic cords	effects seen at only dose of 100 mg/kg bw/d	not observed (only liver analyzed; only dose of 100)

	Nanomaterial		
Reference	**NM**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**	**Toxicological comments**
Cho 2013 PFT	TiO2 (and ZnO)	nd	nd
Morgan 2018 Biomedicine & Pharmacotherapy	TiO2	not determined in blood/ not observed in liver (at only dose of 100)	higher ALT, AST and ALP in serum; no changes in relative liver weights; indications of oxidative stress: increased MDA, decreased GSH, GPx and SOD; (all at only dose of 100)

	Nanomaterial	Biodistribution			
Reference	**NM**	**Compartments monitored**	**Sampling regime**	**Organ burden** (timepoint, ug/organ)	**Organ clearance/ post-exposure retention half-time** (days)
Cho 2013 PFT	TiO2 (and ZnO)	Blood, urine, feces, liv	Ti and Zn content (ICP-MS) in Blood via abdominal	At the end of 13 week exposure. No significant increase of Ti concentrations in liver, spleen, kidney, and brain. Figure 4: Tissue concentration (ug/g) of Ti at end of exposure. Additional file 2, figure S1: Organ burden (ug/organ) at end of exposure	nd Figure 6: Excreation in feces and urine at end of exposure.
Morgan 2018 Biomedicine & Pharmacotherapy	TiO2	not determined	not determined	not determined	not determined

	Nanomaterial				
Reference	**NM**	**Systemic absorption fraction or rate** (&unit)	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)
Cho 2013 PFT	TiO2 (and ZnO)	nd Figure 3: Ti and Zn concentration in blood at the end of exposure.	nd	Absorption: Significantly increased Ti blood concentration at the two highest doses (520.8 and 1041.5). The Zn blood concentration in the ZnOtreatment groups was almost 10-fold higher than the Ti concentration in the TiO2-treatment groups. Distribution: Ti concentrations in liver, spleen, kidney, and brain showed no significant increase. Excretion: No significant increase in Ti concentration in urine. Ti or Zn concentrations in the feces were very high compared to concentrations in the urine or tissues, with clear dose responses.	no
Morgan 2018 Biomedicine & Pharmacotherapy	TiO2	not determined	not determined		mRNA levels of pro-apototic Bax and anti-apoptotic Bcl-2 analyzed: Bax increased and Bcl-2 decreased, confirmed with proetin expression analysis through immunostaining

	Nanomaterial	
Reference	**NM**	**General comments**
Cho 2013 PFT	TiO2 (and ZnO)	
Morgan 2018 Biomedicine & Pharmacotherapy	TiO2	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Minne Heringa Minne.Heringa@rivm.nl	Jia 2014 Arch. Toxicol.	TiO2	not provided	Sigma Aldrich	25 nm, measurements not reported	not determined	not determined
Minne Heringa Minne.Heringa@rivm.nl	Wang 2013 Small	TiO2	not provided	Shanghai Aladdin Reagent Co., Ltd, China.	75 nm average diameter	63.95 m^2/g (BET)	nd
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)		Fuji Davison Chemical Ltd, Japan	no information	no information	no information

	Nanomaterial		Exposure-related phys-chem	Study design		
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Exposure-related phys-chem** (size/agglomeration in formulation/vehicle...)	**OECD guideline/GLP**	**Species**	**Strain**
Jia 2014 Arch. Toxicol.	TiO2	not determined	not determined	none	mouse	Kunming
Wang 2013 Small	TiO2	spherical shape, anatase, purity of 99.90%, zeta potential of -33.46 mV in water, 6.98 mV in artifical gastric juice, and -2.47 in artifical intestinal juice	hydrodynamic diameter of 473.6 nm in water, 1702 nm in artificial gastric juice and 2081 nm in artifical intestinal juice	none	rat	Sprague-Dawley
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	no information	no information	no	rats	Fischer (Funabashifarm Animal Co Ltd. Japan)

	Nanomaterial						
Reference	**NM**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)	**Administration route and mode** (daily gavage, ad lib. via drinking water or feed...)	**Duration of exposure** (weeks) (days/week)	**Doses** (mg/kg bw/day)
Jia 2014 Arch. Toxicol.	TiO2	male	4 (pubertal)	n=15	oral	6 (42 d, daily)	10, 50 or 250
Wang 2013 Small	TiO2	male	3 or 8 weeks	n=7 per age per dose	oral, intragastric	30d	0-10-50-200
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	male and female	5 weeks	as a rule 10 rats/group/sex after 6 months and after 12 rats and 20 rats/dose/sex after 24 months	daily via feed	103 weeks (7d/week)	1.25 % (0.5 g/kg bw/day for male and female); 2.5% (1 g/kg bw/day for male and female), 5 % (2.1 g/kg bw/day for male and female)

	Nanomaterial		Toxicological outcomes			
Reference	**NM**	**Formulation/vehicle** (volume, concentration, composition)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/kg bw)
Jia 2014 Arch. Toxicol.	TiO2	Dispersedin PBS with 0.5 % Tween 80, sonicated	not determined	not determined	not observed (only testes analyzed)	250/not applicable
Wang 2013 Small	TiO2	ultrapure water	not determined	not determined	not observed (liver, kidney, spleen, testis, lung and heart)	200/not applicable
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	in feed	nd	no	none	NOAEL: 5 % in feed

	Nanomaterial			
Reference	**NM**	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**
Jia 2014 Arch. Toxicol.	TiO2	only testes analyzed: vacuoles in seminiferous tubules at 50 and 250 mg/kg/day; decreased layers of spermatogenic cells at 250 mg/kg/day.	10/50	not observed (only testes analyzed) (250/not applicable)
Wang 2013 Small	TiO2	liver edema in young rats (50 and 200 mg/kg bw/day): hepatic cord disarray, perilobular cell swelling, vacuolization, or hydropic degeneration	10/50	not observed (liver, kidney, spleen, testis, lung and heart) (200/not applicable)
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	none	NOAEL: 5 % in feed	no substance-related findings NOAEL: 5 % in feed

	Nanomaterial		
Reference	**NM**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**	**Toxicological comments**
Jia 2014 Arch. Toxicol.	TiO2	not determined in blood/ not observed in testes (250/ not applicable)	250 mg/kg bw/d decreased body weight gain; no effect on absolute and relative wieght of testes and epididymis; increase in % abnormal sperm, at 50 and 250 mg/kg bw/d; no change in sperm numbers; serum testosterone levels decreased at 50 and 250 mg/kg bw/d
Wang 2013 Small	TiO2	infiltration inflammatory cells in liver adult rats at 10 and 50 mg/kg bw/d (not 200). Not sufficient for NOAEL	no effect on body weight at sacrifice, no effect on rel. organ weights; BUN ↑, TBIL ↓ in adult rats, rest biochemistry unchanged --> slight injury liver and kidney; glucose ↑, LDL-C ↑, AST ↓, ALT/AST ↑, TBIL ↑, HBDH ↓, CK ↓ in young rats (50 and/or 200 mg/kg bw/day) --> liver and heart injury
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	blood hematology, clinical chemistry, histology (NOAEL; 5 % in feed, corresponding to 2100 mg/kg bw/day)	

	Nanomaterial	Biodistribution			
Reference	**NM**	**Compartments monitored**	**Sampling regime**	**Organ burden** (timepoint, ug/organ)	**Organ clearance/ post-exposure retention half-time** (days)
Jia 2014 Arch. Toxicol.	TiO2	not determined	not determined	not determined	not determined
Wang 2013 Small	TiO2	liver, kidney, spleen	at sacrfice after 30 d	no sign difference versus control	not determined
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	not examined	not examined	not examined	not examined

	Nanomaterial				
Reference	**NM**	**Systemic absorption fraction or rate** (&unit)	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)
Jia 2014 Arch. Toxicol.	TiO2	not determined	not determined		mRNA level analysis of genes involved in cholesterol transport and testosterone synthesis:StAR, P450scc, 3β-HSD and AR not changed, but P450-17α, 17β-HSD, Cyp19 were changed, all three startign at different dose levels. The latter confirmed with protein expression level analysis.
Wang 2013 Small	TiO2	not determined	not determined		no
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	not examined	not examined		no

	Nanomaterial	
Reference	**NM**	**General comments**
Jia 2014 Arch. Toxicol.	TiO2	
Wang 2013 Small	TiO2	
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)		Fuji Davison Chemical Ltd, Japan	no information	no information	no information
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Sakai et al 1985 J Tox Sci	Perlite, mineral containing 72 % silica		nature source	no information	no information	SiO2 72 %; 15 % Al2O3; 2.5 % Fe2O3; 2.5 % CaO; 7 % Ka2O
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Kim et al. 2014. Intern. J Nanomed.	colloidal silica (100 nm)		E&B Nanotech CoLtd (Gyeonggi-do, Republic of Korea)	100 nm	no information	no information

	Nanomaterial		Exposure-related phys-chem	Study design		
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Exposure-related phys-chem** (size/agglomeration in formulation/vehicle...)	**OECD guideline/GLP**	**Species**	**Strain**
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	no information	no information	no	mice	B6C3F1 (Funabashifarm Animal Co Ltd. Japan)
Sakai et al 1985 J Tox Sci	Perlite, mineral containing 72 % silica	no information	no information	no	mice	ICA mice (Charles River Japan)
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (100 nm)	Zeta potential: -45.2 ±0.1 mV	hydrodynamic diameter: 91.6±0.5 nm	OECD 408	rats	Sprague Dawley Crl:CD (SD) (Orient Bio, Gyeonggi-do, Korea)

	Nanomaterial						
Reference	**NM**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)	**Administration route and mode** (daily gavage, ad lib. via drinking water or feed...)	**Duration of exposure** (weeks) (days/week)	**Doses** (mg/kg bw/day)
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	male and female	5 weeks	as a rule 10 mice/group/sex after 6 months and after 12 months and 20 mice/dose/sex after 21 months	daily via feed	93 weeks (7d/week)	1.25 % (1.4 g/kg bw/day for male and 1.6 g/kg bw/day for female); 2.5% (3.0 g/kg bw/day for male and 2.7 g/kg bw/day for female), 5 % (6.1 g/kg bw/day for male and 6.6 g/kg bw/day for female)
Sakai et al 1985 J Tox Sci	Perlite, mineral containing 72 % silica	male and female	4	n= 21 per sex	oral, feed	28 weeks (7 days/week)	Assuming bw of 30 g, 1 % (1.7 g/kg bw/day); 10 % (16.7g/k bw/day; 20 % (33.3 g/kg bw/day) in feed
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (100 nm)	male and female	7 weeks (?) body weight range 187-205 g for males, 143 to 167 for females at the start	Sacrifaced after 90 day administration: n=10/dose/sex, Recovery period of 2 weeks: control and high dose n=5/dose/sex	daily gavage	14 weeks, 7d/week	500, 1000, 2000 mg/kg bw/day

	Nanomaterial		**Toxicological outcomes**			
Reference	**NM**	**Formulation/vehicle** (volume, concentration, composition)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/kg bw)
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	in feed	nd	no	none	NOAEL: 5 % in feed
Sakai et al 1985 J Tox Sci	Perlite, mineral containing 72 % silica	feed	nd	no	none	NOAEL 20% (40 g/kg bw/day at the intitial time, 20 g/kg bw/day at the end of the study)
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (100 nm)	suspended in distilled water, administration volume 10 mL/kg bw/day	no	nd (90 day study)	none	NOAEL: 2000 mg/kg bw/day

	Nanomaterial			
Reference	**NM**	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	none	NOAEL: 5 % in feed	no substance-related findings NOAEL: 5 % in feed
Sakai et al 1985 J Tox Sci	Perlite, mineral containing 72 % silica	none	NOAEL 20% (40 g/kg bw/day at the intitial time, 20 g/kg bw/day at the end of the study)	Histology (20 to 40g/kg bw/day) not histo findings
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (100 nm)	none	NOAEL: 2000 mg/kg/bw/day	NOAEL: 2000 mg/kg bw/day

	Nanomaterial		
Reference	**NM**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**	**Toxicological comments**
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	blood hematology, clinical chemistry, histology (NOAEL; 5 % in feed, corresponding to 6100 mg/kg bw/day)	
Sakai et al 1985 J Tox Sci	Perlite, mineral containing 72 % silica	Histology (20 to 40g/kg bw/day) Hematology: (20 to 40g/kg bw/day)	no adverse findings in hematology and histopathology. NOEL was determined at 1 % (2 g/kg bw/day at the beginning to 1 g/kg bw/day at the end) due to retarded body weight development.
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (100 nm)	blood hematology, clinical chemistry, histology (NOAEL; 2000 mg/kg bw/day)	no substance-related adverse effects in all examined endpoints

	Nanomaterial	Biodistribution			
Reference	**NM**	**Compartments monitored**	**Sampling regime**	**Organ burden** (timepoint, ug/organ)	**Organ clearance/ post-exposure retention half-time** (days)
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)		not examined	not examined	not examined
Sakai et al 1985 J Tox Sci	Perlite, mineral containing 72 % silica		nd	nd.	not examined
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (100 nm)	no	not applicable	not examined	not examined

	Nanomaterial				
Reference	**NM**	**Systemic absorption fraction or rate** (&unit)	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	not examined	not examined		no
Sakai et al 1985 J Tox Sci	Perlite, mineral containing 72 % silica	not examined	not examined		no
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (100 nm)	not examined	not examined		no

	Nanomaterial	
Reference	**NM**	**General comments**
Takizawa et al. 1988 Acta medica et biologica	colloidal silica (SYLOID 244)	
Sakai et al 1985 J Tox Sci	Perlite, mineral containing 72 % silica	
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (100 nm)	

		Nanomaterial			NM phys-chem characteristics (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Kim et al. 2014. Intern. J Nanomed.	colloidal silica (20 nm)		E&B Nanotech CoLtd (Gyeonggi-do, Republic of Korea)	20 nm	no information	no information
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Yun et al. 2015 J Appl Toxicol	amorphous SiO2		ABC Nanotech Co Ltd. (Daejeon, Korea)	12 nm by SEM, hydrodynamic diameter 33.5 nm, zeta potential -44.37 mV	not determined. The substance was delivered as suspension in water (20 %)	no information
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2		ST-NANO Co Ltd. (Shanghai, China)	about 26 nm	152.2 m^2/g	SiO2 99.2%
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2		Aladdin Industrial Inc. (Shanghai, China)	about 1088 nm	4.4 m^2/g	SiO2 99.6 %
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	van der Zande et al. 2014 Part Fibre Tox	synthetic amorphous silica, E551		Evonik Degussa GmbH (Frankfurt, Germany)	7 nm	380 m^2/g	99.8 % (food grade)

	Nanomaterial		Exposure-related phys-chem	Study design		
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Exposure-related phys-chem** (size/agglomeration in formulation/vehicle...)	**OECD guideline/GLP**	**Species**	**Strain**
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (20 nm)	Zeta potential: -38.3 ±1.2 mV	hydrodynamic diameter: 21.0±0.1 nm	OECD 408	rats	Sprague Dawley Crl:CD (SD) (Orient Bio, Gyeonggi-do, Korea)
Yun et al. 2015 J Appl Toxicol	amorphous SiO2	no information	20 % in destilled water, 33.5 nm hydrodynamic diameter	OECD 408 Limit test	rats	Sprague Dawley (Orient Bio, Seongnam, Korea)
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	precipitated silica without surface coating, purity 99.2 %, Zeta -64.1mV, pH value of the suspension 6.7	25.9 ± 3.4 nm, suspended in deionized water, hydrodynamic diameter was 246.6 ± 47.8 nm	OECD 408, GLP	rats	Sprague Dawley (HFK Bioscience Co Ltd, China)
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	precipitated silica without surface coating, purity 99.6 %, Zeta -63.0mV, pH value of the suspension 6.4	1087.8 ± 389.6 nm, suspended in deionized water, hydrodynamic diameter was	OECD 408, GLP	rats	Sprague Dawley (HFK Bioscience Co Ltd, China)
van der Zande et al. 2014 Part Fibre Tox	synthetic amorphous silica, E551	hydrophilic pyrogenic, 78 % < 100 nm	about 80 mg/g feed (pasted with choclate milk), 40 % between 5 and 200 nm (control feed contains about 1 mg/g feed silica without fraction between 5 and 200 nm)	no guideline, no GLP	rats	Sprague-Dawley, (Harlan, Horst, the netherland)

	Nanomaterial						
Reference	**NM**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)	**Administration route and mode** (daily gavage, ad lib. via drinking water or feed...)	**Duration of exposure** (weeks) (days/week)	**Doses** (mg/kg bw/day)
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (20 nm)	male and female	7 weeks (?) body weight range 187-205 g for males, 143 to 167 for females at the start	Sacrifaced after 90 day administration: n=10/dose/sex, Recovery period of 2 weeks: control and high dose n=5/dose/sex	daily gavage	13 weeks, 7d/week	500, 1000, 2000 mg/kg bw/day
Yun et al. 2015 J Appl Toxicol	amorphous SiO2	male and female	5	n=12 per sex	oral gavage, daily	13 weeks	245, 490 and 980 mg/kg bw/day
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	male and female	not given, weight between 60 to 80 g at delivery	n=10 per sex	oral gavage, daily	13 weeks	167, 500 and 1500 mg/kg bw/day
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	male and female	not given, weight between 60 to 80 g at delivery	n=10 per sex	oral gavage, daily	13 weeks	167, 500 and 1500 mg/kg bw/day
van der Zande et al. 2014 Part Fibre Tox	synthetic amorphous silica, E551	male	9 weeks	n=5 per dose and time point	oral via feed	28 days and 84 days	100, 1000 and 2500 mg/kg boy/day for 28 days and 2500 mg/kg bw/day for 84 days

	Nanomaterial		Toxicological outcomes			
Reference	**NM**	**Formulation/vehicle** (volume, concentration, composition)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/kg bw)
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (20 nm)	suspended in distilled water, administration volume 10 mL/kg bw/day	nd	nd (90 day study)	none	NOAEL: 2000 mg/kg bw/day
Yun et al. 2015 J Appl Toxicol	amorphous SiO2	water	nd	nd (90 day study)	none	NOAEL 980 mg/kg bw/day
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	water	nd	nd (90 day study)	none	NOAEL 1500 mg/kg bw/day
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	water	nd	nd (90 day study)	none	NOAEL 1500 mg/kg bw/day
van der Zande et al. 2014 Part Fibre Tox	synthetic amorphous silica, E551	feed, 80 mg/g feed, clean feed were provided in addition to ensure the daily food requirement of the animals	nd	nd (28 and 84 day study)	none	NOAEL 2500 mg/kg bw/day

	Nanomaterial			
Reference	**NM**	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (20 nm)	none	NOAEL: 2000 mg/kg/bw/day	NOAEL: 2000 mg/kg/bw/day
Yun et al. 2015 J Appl Toxicol	amorphous SiO2	none	NOAEL 980 mg/kg bw/day	no substance-related histological findings, NOAEL 980 mg/kg bw/day
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	none	NOAEL 1500 mg/kg bw/day	no substance-related histological findings, NOAEL 1500 mg/kg bw/day
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	none	NOAEL 1500 mg/kg bw/day	no substance-related histological findings, NOAEL 1500 mg/kg bw/day
van der Zande et al. 2014 Part Fibre Tox	synthetic amorphous silica, E551	none	NOAEL 2500 mg/kg bw/day	no substance-related histological findings, NOAEL 2500 mg/kg bw/day

	Nanomaterial		
Reference	**NM**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**	**Toxicological comments**
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (20 nm)	blood hematology, clinical chemistry, histology	no substance-related adverse effects in all examined endpoints
Yun et al. 2015 J Appl Toxicol	amorphous SiO2	for histology, hematology and clinical chemistry NOAEL 980 mg/kg bw/day	no adverse findings in hematology and histopathology. NOAEL was determined at highest tested dose of 980 mg/kg bw/day.
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	for histology, hematology and clinical chemistry NOAEL 1500 mg/kg bw/day	no adverse findings in hematology and histopathology. NOAEL was determined at highest tested dose of 1500 mg/kg bw/day.
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	for histology, hematology and clinical chemistry NOAEL 1500 mg/kg bw/day	no adverse findings in hematology and histopathology. NOAEL was determined at highest tested dose of 1500 mg/kg bw/day.
van der Zande et al. 2014 Part Fibre Tox	synthetic amorphous silica, E551	only selected clinical chemical parameters were examined (ALP, AST, creatinine, urea after 28 day; some more after 84 days treatment, no systemic toxicity were observed by examining clinical chemical parameters, no immuntoxic effects (IgG, IgM) NOAEL 2500 mg/kg bw/day	

	Nanomaterial	Biodistribution			
Reference	**NM**	**Compartments monitored**	**Sampling regime**	**Organ burden** (timepoint, ug/organ)	**Organ clearance/ post-exposure retention half-time** (days)
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (20 nm)	no	not applicable	not examined	not examined
Yun et al. 2015 J Appl Toxicol	amorphous SiO2	blood, liver, spleen, kidney, lung, brain	once at the end of the dosing period of 13 weeks	no dose-related increase in comparison to the control	no evaluation possible
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	blood, liver, kidney, testis	once at the end of the dosing period of 13 weeks	no dose-related increase in comparison to the control	no evaluation possible
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	blood, liver, kidney, testis	once at the end of the dosing period of 13 weeks	no dose-related increase in comparison to the control	no evaluation possible
van der Zande et al. 2014 Part Fibre Tox	synthetic amorphous silica, E551	liver, kidney, spleen, brain, testis	after 28 days and 84 days feeding	SAS, high dose group (after 84 days): liver: 78± 2 mg/kg tissue weight kidney: 79± 4 mg/kg tissue weight spleen: 248± 81 mg/kg tissue weight brain: 100± 23 mg/kg tissue weight testis: 105± 17 mg/kg tissue weight Detection limit was 75 mg/kg tissue weight. In the organs of other groups, no silica was detected.	not determined

	Nanomaterial				
Reference	**NM**	**Systemic absorption fraction or rate** (&unit)	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (20 nm)	not examined	not examined		no
Yun et al. 2015 J Appl Toxicol	amorphous SiO2	no evaluation possible	no evaluation possible	Blood, liver, kiney, spleen, lungs were examined, no increases in comparison to the control	no
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	no evaluation possible	no evaluation possible	Blood, liver, kiney and testis were examined, no increases in comparison to the control	no
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	no evaluation possible	no evaluation possible	Blood, liver, kiney and testis were examined, no increases in comparison to the control	no
van der Zande et al. 2014 Part Fibre Tox	synthetic amorphous silica, E551	not calculated	no evaluation possible	probably dissolved in digestive fluide and adsorbed by the tissues	transcriptomics for jejunum and liver, no changed gene expression pattern was observed

	Nanomaterial	
Reference	**NM**	**General comments**
Kim et al. 2014. Intern. J Nanomed.	colloidal silica (20 nm)	
Yun et al. 2015 J Appl Toxicol	amorphous SiO2	not clear which type the amorphous SiO2 was tested.
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	hydrophilic precipitated amorphous SiO2
Liang et al. 2018 Biochem. Environ Scie	precipitated amorphous SiO2	hydrophilic precipitated amorphous SiO2
van der Zande et al. 2014 Part Fibre Tox	synthetic amorphous silica, E551	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	van der Zande et al. 2014 Part Fibre Tox	NM 202		Joint research center Nanomaterials reporsitory	10-25 nm	200 m^2/g	99.9%
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Buesen 2014 ArchTox	SiO2 naked (Levasil®200)		AkzoNobel	mean 14 nm according to producer (5-50 nm, determined by REM/TEM)	213 m^2/g (according to producer) 123 m^3/g (determined after drying the sample, the voids between polymers was inaccessible).	SiO2 (about 40 % in water, pH 10.2)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Buesen 2014 ArchTox	SiO2 PEG		BASF research lab	mean 15 nm, ranged from 8 to 45 nm determined by REM/TEM	not determined. Since the functionalization agents only partially covered the surface of the well-dispersed primary particles, the effective specific surface is not expected to cahnge due to surface functionalization	SiO2 functionalized with PEG-500 coating (about 20 % in water)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Buesen 2014 ArchTox	SiO2 Phosphate		BASF research lab		see above	SiO2 functionalized with triphenyl methyl-phosphonium (about 20 % in water)

	Nanomaterial		Exposure-related phys-chem	Study design		
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Exposure-related phys-chem** (size/agglomeration in formulation/vehicle...)	**OECD guideline/GLP**	**Species**	**Strain**
van der Zande et al. 2014 Part Fibre Tox	NM 202	hydrophilic pyrogenic, 61 % < 100 nm	about 80 mg/g feed (pasted with choclate milk), 100 % in nano range (control feed contains about 1 mg/g feed silica without fraction between 5 and 200 nm)	no guideline, no GLP	rats	Sprague-Dawley, (Harlan, Horst, the netherland)
Buesen 2014 ArchTox	SiO2 naked (Levasil®200)	granular particles. Organic inpurities determined by XPS on the surfac, C-C, C-H, C-O, Na2O).	40 nm in water 420/28 in DMEM/FCS, D50/AAN	OECD 407 Limit test	rat	Wistar Crl:WI(Han)
Buesen 2014 ArchTox	SiO2 PEG	Levasil 200 with covalent surface functionalization with low-molar-mass silane having a PEG end group with a molecular weight of 500 g/mol, imparting steric stailization	50 nm in water 3200/213 in DMEM/FCS, D50/AAN	OECD 407 Limit test	rat	Wistar Crl:WI(Han)
Buesen 2014 ArchTox	SiO2 Phosphate	Levasil 200 with covalent surface functionalization with low-molar-mass silane having a nagative charged phosphonate end group on a flexible short C3-linker	40 nm in water 30/2 in DMEM/FCS, D50/AAN	OECD 407 Limit test	rat	Wistar Crl:WI(Han)

	Nanomaterial						
Reference	**NM**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)	**Administration route and mode** (daily gavage, ad lib. via drinking water or feed...)	**Duration of exposure** (weeks) (days/week)	**Doses** (mg/kg bw/day)
van der Zande et al. 2014 Part Fibre Tox	NM 202	male	9 weeks	n=5 per dose and time point	oral via feed	28 days and 84 days	100, 500 and 1000 mg/kg boy/day for 28 days and 1000 mg/kg bw/day for 84 days
Buesen 2014 ArchTox	SiO2 naked (Levasil®200)	male female	6	n=5 per sex	oral gavage, daily	4 (7days/week)	1000
Buesen 2014 ArchTox	SiO2 PEG	male female	6	n=5 per sex	oral gavage, daily	4(7days/week)	1000
Buesen 2014 ArchTox	SiO2 Phosphate	male female	6	n=5 per sex	oral gavage, daily	4 (7 days/week)	1000

	Nanomaterial		Toxicological outcomes			
Reference	**NM**	**Formulation/vehicle** (volume, concentration, composition)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/kg bw)
van der Zande et al. 2014 Part Fibre Tox	NM 202	feed, 80 mg/g feed, clean feed were provided in addition to ensure the daily food requirement of the animals	nd	nd (28 and 84 day study)	none	NOAEL 1000 mg/kg bw/day
Buesen 2014 ArchTox	SiO2 naked (Levasil®200)	9.1 wt% in PBS+BSA	nd	nd (28 day study)	none	1000/nd
Buesen 2014 ArchTox	SiO2 PEG	10.1 wt% in PBS+BSA	nd	nd (28 day study)	none	1000/nd
Buesen 2014 ArchTox	SiO2 Phosphate	10.3 wt% in PBS+BSA	nd	nd (28 day study)	none	1000/nd

	Nanomaterial			
Reference	**NM**	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**
van der Zande et al. 2014 Part Fibre Tox	NM 202	Liver: increased incidence of fibrotic change (LOAEL 1000 mg/kg bw/day)	LOAEL 1000 mg/kg bw/day	Histology, liver: increased incidence of fibrotic change LOAEL 1000 mg/kg bw/day
Buesen 2014 ArchTox	SiO2 naked (Levasil®200)	nd	1000/nd	Histology (1000/nd)
Buesen 2014 ArchTox	SiO2 PEG	nd	1000/nd	Histology (1000/nd)
Buesen 2014 ArchTox	SiO2 Phosphate	nd	1000/nd	Histology (1000/nd)

	Nanomaterial		
Reference	**NM**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**	**Toxicological comments**
van der Zande et al. 2014 Part Fibre Tox	NM 202	only selected clinical chemical parameters were examined (ALP, AST, creatinine, urea after 28 day; some more after 84 days treatment, no systemic toxicity were observed by examining clinical chemical parameters, no immuntoxic effects (IgG, IgM) NOAEL 1000 mg/kg bw/day	
Buesen 2014 ArchTox	SiO2 naked (Levasil®200)	Histology: (1000/nd) Hematology: (1000/nd) Clinical chemistry, acute phas (1000/nd)	see above
Buesen 2014 ArchTox	SiO2 PEG	Histology: (1000/nd) Hematology: (1000/nd) Clinical chemistry, acute phas (1000/nd)	see above
Buesen 2014 ArchTox	SiO2 Phosphate	Histology: (1000/nd) Hematology: (1000/nd) Clinical chemistry, acute phas (1000/nd)	see above

	Nanomaterial	Biodistribution			
Reference	**NM**	**Compartments monitored**	**Sampling regime**	**Organ burden** (timepoint, ug/organ)	**Organ clearance/ post-exposure retention half-time** (days)
van der Zande et al. 2014 Part Fibre Tox	NM 202	liver, kidney, spleen, brain, testis	after 28 days and 84 days feeding	Detection limit was 75 mg/kg tissue weight. no silica was detected.	not determined
Buesen 2014 ArchTox	SiO2 naked (Levasil®200)	nd	nd	nd	nd
Buesen 2014 ArchTox	SiO2 PEG	nd	nd	nd	nd
Buesen 2014 ArchTox	SiO2 Phosphate	nd	nd	nd	nd

	Nanomaterial				
Reference	**NM**	**Systemic absorption fraction or rate** (&unit)	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)
van der Zande et al. 2014 Part Fibre Tox	NM 202	not calculated	no evaluation possible	probably dissolved in digestive fluide and adsorbed by the tissues	transcriptomics for jejunum and liver, significant increase in the expression of fibrosis-related genes at 25 mg/kg bw/day after 84 days
Buesen 2014 ArchTox	SiO2 naked (Levasil®200)	nd	nd		yes, metabolome analysis was performed in plasma samples
Buesen 2014 ArchTox	SiO2 PEG	nd	nd		yes, metabolome analysis was performed in plasma samples
Buesen 2014 ArchTox	SiO2 Phosphate	nd	nd		yes, metabolome analysis was performed in plasma samples

	Nanomaterial	
Reference	**NM**	**General comments**
van der Zande et al. 2014 Part Fibre Tox	NM 202	
Buesen 2014 ArchTox	SiO2 naked (Levasil®200)	
Buesen 2014 ArchTox	SiO2 PEG	
Buesen 2014 ArchTox	SiO2 Phosphate	

		Nanomaterial			**NM phys-chem characteristics** (only for non-JRC materials)		
Who entered information (name and e-mail)	**Reference**	**NM**	**CAS number**	**NM source** (supplier, batch..)	**Primary particle size** (nm)	**Surface area** (m2/g)	**Chemical composition** (e.g. WDXRF)
Lan Ma-Hock, BASF (lan.ma-hock@basf.com)	Buesen 2014 ArchTox	SiO2 amino		BASF research lab		see above	SiO2 functionalized with aminopropyl trimethoxy slilane (about 20 % in water)

	Nanomaterial		Exposure-related phys-chem	Study design		
Reference	**NM**	**Other phys-chem characteristics** (shape, charge, reactivity, surface coating, contaminants e.g. metals, endotoxin...)	**Exposure-related phys-chem** (size/agglomeration in formulation/vehicle...)	**OECD guideline/GLP**	**Species**	**Strain**
Buesen 2014 ArchTox	SiO2 amino	Levasil 200 with covalent surface functionalization with low-molar-mass silane having a positive charged amino end group on the same C3-linker	42 nm in water 1350/90 in DMEM/FCS, D50/AAN	OECD 407 Limit test	rat	Wistar Crl:WI(Han)

	Nanomaterial						
Reference	**NM**	**Sex**	**Age at start of exposure** (weeks)	**Group size** (per endpoint if relevant)	**Administration route and mode** (daily gavage, ad lib. via drinking water or feed...)	**Duration of exposure** (weeks) (days/week)	**Doses** (mg/kg bw/day)
Buesen 2014 ArchTox	SiO2 amino	male female	6	n=5 per sex	oral gavage, daily	4 (7 days/week)	1000

	Nanomaterial		Toxicological outcomes			
Reference	**NM**	**Formulation/vehicle** (volume, concentration, composition)	**Genotoxicity** Assay, negative/positive, at which dose	**Carcinogenicity** Yes/no	**Histopathology neoplastic** All observed types of neoplastic lesions	**Histopathology neoplastic NOAEL/LOAEL** (mg/kg bw)
Buesen 2014 ArchTox	SiO2 amino	10.3 wt% in PBS+BSA	nd	nd (28 day study)	none	

	Nanomaterial			
Reference	**NM**	**Histopathology non-neoplastic** Type of lesion with statistically significant incidence	**Histopathology non-neoplastic NOAEL/LOAEL**	**Fibrosis** Assay/sample **(NOAEL/LOAEL)**
Buesen 2014 ArchTox	SiO2 amino	nd	1000/nd	Histology (1000/nd)

	Nanomaterial		
Reference	**NM**	**Inflammation** Sample: histology, blood hematology, clinical chemistry, lavage... **(NOAEL/LOAEL)**	**Toxicological comments**
Buesen 2014 ArchTox	SiO2 amino	Histology: (1000/nd) Hematology: (1000/nd) Clinical chemistry, acute phas (1000/nd)	see above

	Nanomaterial	Biodistribution			
Reference	**NM**	**Compartments monitored**	**Sampling regime**	**Organ burden** (timepoint, ug/organ)	**Organ clearance/ post-exposure retention half-time** (days)
Buesen 2014 ArchTox	SiO2 amino	nd	nd	nd	nd

	Nanomaterial				
Reference	**NM**	**Systemic absorption fraction or rate** (&unit)	**Elimination rate or half-life from systemic circulation** (&unit)	**Biodistribution comments**	**Omics data available?** (yes/no, GEO or ArrayExpress accession number)
Buesen 2014 ArchTox	SiO2 amino	nd	nd		yes, metabolome analysis was performed in plasma samples

	Nanomaterial	
Reference	**NM**	**General comments**
Buesen 2014 ArchTox	SiO2 amino	