Attachment to the responses to comments on the CLH report on titanium dioxide received during public consultation

514 comments have been received as a result of the public consultation. Eight comments were from 5 Member-States (Germany, Sweden, Finland, Netherlands and Belgium), 38 from individuals and the remaining from organizations. Among them:

- 176 are related to identity and scope of the dossier (in particular linked to TiO_2 in a matrix),
- 338 are related to carcinogenicity (human and/or animal data),
- 67 are related to hazard endpoints other than carcinogenicity,
- 226 are related to exposure and risk assessment,
- 294 are related to economic impact of the proposed classification.

It can also be noted that similar comments appeared more than once under different headings/endpoints in the RCOM table and 132 comments referred to comments from Titanium Dioxide Manufacturers Association (TDMA), Titanium Dioxide Industry Consortium (TDIC) or Verbrand Der Chemischen Industrie (VCI).

Some comments also provided new references which were not included in the CLH report. These references have been taken into account in the present attachment to RCOM. However, references related to other PSPs (poorly soluble particles) (such as carbon black) have not been specifically assessed since the CLH report is based on specific data with TiO_2 and other PSPs were only used as supportive data for the hypothesized carcinogenic mode of action. Overall, references submitted during public consultation do not constitute new data and do not impact the CLH proposal.

Finally, the aim of the present attachment to RCOM is to bring further arguments compared to the CLH report in response to the comments received during the public consultation. Please note that points that have already been addressed in the CLH report are not discussed again in this document. In addition, for some unique and particular comments, a specific response was included directly in the RCOM table and not reported hereafter.

RAC's response to the introduction of the RCOM Annex

RAC supports the DS's approach to group the comments received during public consultation and to respond to these comments in a structured approach.

RAC's response relates to this attachment to RCOM. Based on the structure of the DS's comments RAC has only responded to individual stakeholder's comments where specific responses to comments have been given by the DS.

RAC takes note of the DS's decision to base the CLH report on specific data with TiO2 and to use data from poorly soluble particles (PSP) only as supportive data for MOA considerations. RAC is aware that the CLH report and the Opinion concentrates on TiO2 and does not fully consider the data for other poorly soluble, low toxicity (PSLT) substances. RAC acknowledges that the carcinogenicity profile described for TiO2 may also apply to members of a group of chemicals with similar toxicity profile referred to as "poorly soluble low toxicity particles".

1. Comments on Substance identity and scope of the dossier

In the CLH report proposed for public consultation, the scope of the entry for inclusion in Annex VI was "**Titanium dioxide in all phases and phase combinations; particles in all sizes/morphologies**". This proposal is based on both carcinogenicity data and mode of action with a specific assessment of the impact of the size, crystallinity, coating and shape on this endpoint. Considering that the proposed classification is specific to the inhalation route and taking into account the comments received, we propose to refine the scope to **"particles of titanium dioxide in all phases, phase combinations and morphologies with at least one dimension below 10µm".** The combination of the general CAS number 13463-67-7 and the above specific entry allow to sufficiently define the scope of the dossier. Therefore, we are of the opinion that an exhaustive list of all corresponding phases, sizes and morphologies (including coating type) is not warranted. Indeed, our proposal follows a global approach for which we believe that, from the available data, all forms of TiO_2 should be classified as

carcinogenic via inhalation. If new and relevant data is provided for some specific morphologies of TiO_2, it would be possible to submit a dossier for exclusion of such forms from the general entry.

Route of exposure relevant for classification:

The classification proposal is based on effects occurring after inhalation exposure, not by other routes. Therefore, we understand the questions raised relating to the relevance of the classification proposal when TiO_2 is incorporated into matrix/mixtures (e.g. incorporated in printed ink or painting). We agree with the hypothesis that embedded TiO_2 will be less or no more available to be inhaled. In this context, the occurrence of pulmonary overload may be questionable. Nevertheless, dust overload condition may occur as a result of prolonged occupational exposures, even at relatively low levels, due to a low clearance of particles in humans. Currently there is no data to characterize (as free or bound TiO_2) and quantify the release fraction of TiO_2 from matrix/mixtures in representative exposure situations of the life cycle (production, application, abrasive processes etc). Some studies on the release of TiO_2 from solids exist in the literature (see comments 27, 31 and 426). These data focused on nanosized TiO_2 and included other nanomaterials (e.g. carbon black). The recent review of Froggett *et al*., (2014) concluded that "*the robust nanorelease evaluations conducted to date do not indicate a high propensity for discreet nanomaterial release, but rather composite particles of matrix with partially or fully embedded nanomaterials*". They also highlight that more researches as well as harmonization of the instrumentation methods that determine the release are needed. Although not directly relevant to the CLH process, we would like to indicate that submission of data on the release of manufactured TiO_2 that model commercial uses in the substance registration dossier is highly recommended. Moreover, we also agree with the Member State Germany proposal (Comment 54) to specify in the scope that the classification proposal would apply to respirable particles **below 10µm**.

Scope of CLH report versus registration dossier: comparison of physicochemical properties

The data taken from the lead registration dossier for "titanium dioxide" under CAS no. 13463-67-7 is given as additional information to support the scope of the dossier. The registrant concluded in their dossier that all entities considered as "titanium dioxide" are hazard equivalent and can be registered as one substance and have the same classification. They also considered that surface-treatment on titanium dioxide particles does not impact hazard properties. Despite this statement, the FR-MSCA assessed the impact of physicochemical properties (size, crystallinity, coating, shape) on the carcinogenicity endpoint only. The data

available do not show any significant impact of the assessed physicochemical parameters on the carcinogenicity of TiO_2. However, this does not predict any conclusion on other endpoints.

- Characterization of tested materials

Carcinogenicity is observed with different forms of non-treated TiO_2 (micro- and nano-sized rutile and nanosized mixed anatase/rutile). These results fully support the classification proposal for all combinations of titanium dioxide whatever crystalline phase and size. Even if these physicochemical properties can have an impact on respiratory hazard, i.e nanosized and anatase forms seem to be associated to a higher reactivity, the positive results in the different studies do not suggest a significant difference in carcinogenicity potential. Regarding a difference in potency between nano and microforms, the apparent higher potency of nanosized compared to microsized TiO_2 may be due to the mass metrics used. Indeed, this metrics is the subject of ongoing debate on the relevant dose metrics to apply for PSPs and in particular for nanomaterials. Other metrics are currently identified such as surface area, particle number, particle void volume etc. In this context, Gebel (2012) compared carcinogenicity after inhalation to nano and microforms of PSP including TiO_2, using 6 different metrics and concluded that carcinogenic potency of TiO_2 nanomaterials was 1-3 order of magnitude higher than carcinogenic potency of TiO_2 micromaterials. However, the difference in potency between nano and bulk TiO_2 requires further investigation. Since crystalline phase and size do not have a significant impact on carcinogenicity, no separate classification proposal of nanosized versus microsized and anatase versus rutile titanium dioxide is considered justified for carcinogenicity.

- Extrapolation from tested TiO_2 to other morphologies

The extrapolation of the results observed with micro- and nano-sized rutile and nanosized mixed anatase/rutile to all other surface chemistries (non-treated or surface-treated) is supported by the proposed major mode of action linked to inflammatory process which is influenced by biopersistence and poor solubility of TiO_2. Therefore, if the surface treatment is believed to be rapidly removed within the organism, it can be hypothesized that the coated form would also induce lung tumours. In addition, mechanisms of action other than inflammatory process cannot be excluded, in the absence of adequate investigation. Depending on the nature of the coating, some surface-treated particles may be more reactive and induce a higher lung inflammatory response than the equivalent non-surface treated leading to more potent effects. In conclusion, there is no evidence that some forms of TiO_2 would not lead to carcinogenicity at even lower dose levels than those studied in the carcinogenicity studies. Some types of coating used for

common grades of titanium dioxide are available in the substance identity part of the CLH dossier (from IARC monograph 93).

With regard to morphologies, different shapes such as spheres, nanorods, needles, tubes, fibers-like, etc have been identified in the literature. Characterization of the TiO_2 shape was not always available in literature data and thus do not allow to propose a restriction of the classification proposal to specific morphologies. Experimental studies showing carcinogenicity are performed with granular forms of TiO_2. Nevertheless, for TiO_2 with fiber-like shapes, other types of mechanisms of action may be involved in tumour induction, such as "asbestos-like action" identified with other types of fibers. Therefore, there is no justification to exclude these forms from the scope of the dossier as tumours are also expected to occur. For less common morphologies that can be found on the market, there is insufficient evidence to enable a conclusion on non-carcinogenicity. It should be noted that all shapes of TiO_2 have been registered together meaning that their registrants do not anticipate major differences in properties between the shapes.

Overall, since one of the main goals of classification process is to protect human from an identified health concern, limiting the scope of this dossier only to the TiO_2 tested in the experimental studies would not be acceptable, bearing in mind that the available information do not show differences in carcinogenic properties between the grades identified.

Conclusion:

The current scientific knowledge on TiO_2 does not suggest a significant impact of the physicochemical parameters on carcinogenicity and shows that the tested TiO_2 are susceptible to be carcinogenic to humans. However, it would be possible to exclude such forms with specific physicochemical parameters from the general entry if adequate data become available in the future (to be specified in accordance with scientific knowledge). Since it is not fully known what physicochemical parameters could significantly impact carcinogenicity, a broad entry is proposed in this dossier without exclusion of specific well-characterized grades. In conclusion, the refined scope for classification proposal is: "**particles of titanium dioxide in all phases, phase combinations and morphologies with at least one dimension below 10 µm**".

RAC's response to comments on substance identity and scope of the dossier

RAC takes note of the comments on the consequences of incorporation of TiO2 into matrixes/mixtures. RAC emphasises that the toxicity profile described for TiO2 is related to inhalation of respirable dust/particles.

RAC is conscious of the issue of substance identity and the scope of an entry in Annex VI of CLP. The Opinion addresses and discusses the various aspects of different forms of TiO2. Possible differences of micro- and nano-sized TiO2 particles are addressed. RAC considers it important to adequately account for the knowledge that toxicity profiles and potencies are different for poorly soluble low toxicity substances and WHO fibres. RAC proposes to use "titanium dioxide" (without a further physico-chemical description) as the chemical name and to recommend that a Note be added addressing the presumably different toxicity profile of TiO2 WHO fibres. RAC is aware of stakeholder's comments indicating that the titanium dioxide industry does not manufacture any fibrous products.

2. Comments on Carcinogenicity endpoint

The CLH report concludes that TiO_2 is not carcinogenic after oral and dermal contact but is presumed to have carcinogenic potential for humans by inhalation. In this context, a classification as carcinogenic category 1B – H350i, largely based on animal evidence has been proposed (see Appendix 1 of this document on comparison between observed effects and classification criteria).

a. Human data

In the comments received, individuals (e.g medical doctors) or industrial organizations stated that no health issue has been found in their organizations. However, the comments were not sufficiently detailed to be taken into account in our assessment. Indeed, human data considered

in the CLH report are all based on scientific peer-reviewed open literature. It can be noted that human data on TiO_2 presented in the CLH report have already been assessed by IARC in 2006 and 2010. IARC is an international recognized organization and we concur with their conclusions.

We acknowledge that the following studies were not summarized in the CLH report and should be taken into account. The following conclusions are provided to supplement the information.

Ellis *et al*. (2010) evaluated the mortality among workers employed in three DuPont titanium dioxide plants in the United States. It could be noticed that workers at one of the plants were already included in the Chen *et al*. (1988) study. Among the identified 8359 workers, 5054 met the criteria for inclusion in the Ellis *et al*. (2010) study. SMRs were calculated combined and stratified by plants for workers employed at least for 6 months between 1935 and 2005. The average length of follow-up was 29 years. When compared to the US general population, the gender specific standardized mortality ratio (SMRs) for all causes of death were not statistically significantly increased but even statistically significantly decreased in the exposed workers. Concerning the specific concern of cancers of the respiratory system, the same trend was observed with SMRs of 1.03 (95%CI=0.85-1.22) in the first plant, 0.60 (95%CI=0.37-0.92) in the second plant and 0.17 (95%CI=0.01-0.74) in the third plant. No information on TiO_2 exposure has been reported in this study (job description, characterization of TiO_2 (size, crystallinity, shape, coating…), quantification of exposure…).

Using the same plants, the SMR analysis was expanded with DuPont company-wide mortality rates as the referent and the relationships between mortality and cumulative exposure to TiO_2 and $TiCl_4$. The results are reported in Ellis *et al.* (2013) publication. Among the identified 8359 workers, 3607 were included in this new analysis compared to 5054 in Ellis *et al.* (2010) study, in particular due to the exclusion of workers with unknown exposure to TiO_2 or $TiCl_4$ for more than 5 years or greater than 25% of the employment period. Industrial hygiene-monitoring data included area and personal samples taken for various periods ranging from a few minutes to full shift periods and were collected from 1974 through 2002. Five levels of exposure were defined for TiO_2 from none (0-1 mg/m^3 TWA) to very high exposure level (> 20 mg/m^3 TWA). SMRs for all causes of death, all malignant neoplasms, cancer of lung, non-malignant respiratory disease and all heart disease were calculated. For all the five outcomes of interest, SMRs were not statistically significantly increased when compared to US population. However,

when compared to other DuPont workers, three outcomes had statistically significantly increased mortality: all causes (SMR = 1.23; 95% CI = 1.15-1.32), all malignant neoplasms (SMR = 1.17; 95% CI = 1.02-1.33) and lung cancer (SMR = 1.35; 95% CI = 1.07-1.33). Considering each plant individually compared to the regional DuPont employee population, only one of the three plants was associated with statistically significantly increased SMR for all outcomes except "non-malignant respiratory diseases". However, there was no evidence of an increase in the relative ratio (RR) with increasing TiO_2 exposure for any outcome. The only indication of a positive relationship between risk and exposure was non-malignant respiratory disease with exposure lagged 10 years but without statistically significantly elevated RR estimates.

From these publications, a significant increased mortality by lung cancer was found only when workers exposed to TiO_2 were compared to other DuPont workers. However, a link with concentration or duration of exposure to TiO_2 was not found impairing the significance of this result. This is consistent with results of other studies on TiO_2 workers. However, some limitations were reported in these publications including the lack of smoking history data and difficulties to obtain some personal and work history records, in particular for years until 1991.

Recently, Thompson *et al*. (2016) reviewed, among others, epidemiological studies performed with TiO_2. As described in the figure below, two of these studies reported that lung cancer risk was significantly elevated among the workers (Boffetta *et al.*, 2004 and Ellis *et al.*, 2013). However, exposure-response relationships were not observed for the exposure metrics evaluated (e.g duration of employment, cumulative exposure).

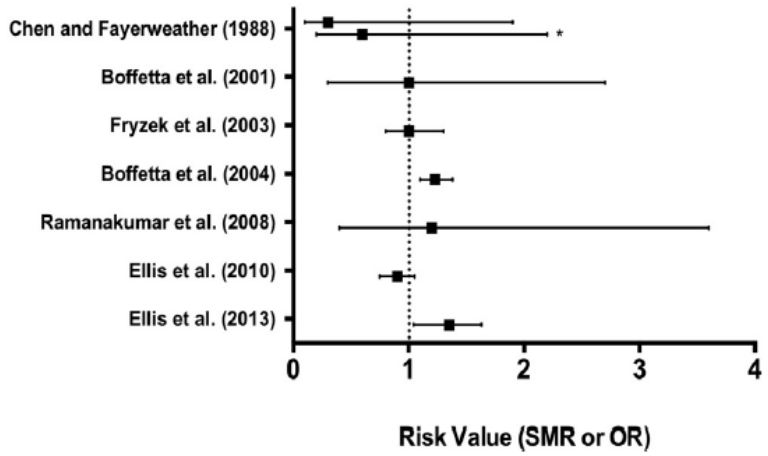

Fig. 2. A summary of lung cancer risk estimates from epidemiologic studies of TiO_2 pigment production workers. Standardized mortality ratio (SMR) or odds ratio (OR) for lung cancer. The 90% or 95% confidence interval for each risk estimate is also presented. In most cases, risk estimates were extracted for the highest exposure groups as identified by the study authors. All studies except Chen and Fayerweather (1998) reported SMRs for lung cancer or ORs based on lung cancer cases. Chen and Fayerweather (1998) reported ORs for lung cancer mortality and lung cancer incidence (indicated with an asterisk).

Figure 1. A summary of lung cancer risk estimates from epidemiologic studies of TiO_2 pigment production workers (extracted from Thompson *et al.*, 2016)

Based on quality elements presented below, they consider that the human data with TiO_2 exposure support a moderate level of confidence for the human evidence of carcinogenicity. Exposure characterization and confounding factors are the main limitations associated with epidemiological data as reflected in the table below where scores for these elements are lower than other.

(A)

Study	External Validity (Indirectness)	Internal Validity (Risk of Bias)					
		Study participants (Q3)	*Confounding (Q4)*	*Data completeness (Q7)*	*Exposure characterization (Q8)*	*Outcome assessment (Q9)*	*Reporting (Q10)*
Boffetta et al (2001)	Low	++	++	++	-	++	++
Boffetta et al (2004)	Low	--	-	-	+	++	++
Chen et al (1988)	Low	+	+	+	+	++	+
Ellis et al (2010)	Low	--	-	+	-	++	++
Ellis et al (2013)	Low	++	-	+	+	++	+
Fryzek et al (2003)	Low	++	--	++	++	++	++
Ramanakumar et al (2008)	Low	++	++	++	-	++	++

Fig. 3. Internal and external validity assessment results of human (A) and animal (B) TiO_2 data. External validity based on the level (very low [dark green] to very high [dark red]) of indirectness (Guyatt et al., 2011); internal validity (definitively low [dark green; ++] to definitely high [dark red–]) based on risk of bias per NTP OHAT (2015). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Figure 2. Internal and external validity assessment results of human data (extracted from Thompson *et al.*, 2016)

They concluded that "*evidence of increased lung cancer risk among TiO_2 production workers is equivocal, and no data exist to assess health effects from environmental exposure*". This conclusion is in line with previous IARC review (2010).

In conclusion, although human data do not demonstrate a link between respiratory cancer and occupational exposure to TiO_2, the evidence is not sufficient to disregard the effects observed in rats based on the methodological limitations of the human studies already reported in the CLH report. In addition, health effects resulting from exposure to dust become obvious only after long-term exposure. It may happen that effects appear even after exposure has ceased, thus being more easily overlooked or mistakenly attributed to non-occupational conditions. For example, mesothelioma resulting from exposure to crocidolite has appeared after latency periods of 40 years or more after beginning of exposure. Therefore, the fact that studies do not report any symptoms in workers can be due to an insufficient duration of exposure and/or follow-up. The establishment of cause-effect between chemicals in the work environment and cancer is complicated by factors such as lapse of time between exposure and disease (latency period), exposure to multiple agents and the fact that cancers from occupational and non-occupational causes are often pathologically identical. In summary, unequivocal demonstration that a substance is not a human carcinogen based on negative human data is difficult since epidemiological data are often limited by a significant level of uncertainty on identification of the substance, confounding factors, measurement of exposure and adequate intensity and duration of exposure, sufficient follow-up time etc.

Finally, with regard to the classification criteria, Category 1B for carcinogenicity is largely based on animal data. We consider that the human data available for TiO_2 do not support a classification as carcinogenic of category 1A as the weight of evidence from human data does not demonstrate a reproducible causal link between exposure and carcinogenesis. However, they are not sufficient to rule out the classification proposal Carc. 1B since epidemiological studies may fail to confirm the carcinogenic properties identified in rat studies because of uncertainties described above.

RAC response to comments on carcinogenicity (human data)

RAC independently assessed all the epidemiological studies available up to now, including four studies initially not assessed by DS, but mentioned during PC (Ellis *et al*., 2010, Ellis *et al*., 2013, Hext *et al*., 2005 and Thompson *et al*., 2016). RAC agreed with the general assessment made by Thompson *et al*. that epidemiological data support a moderate level of confidence for the human evidence and therefore can be used for carcinogenicity risk evaluation. RAC considers that human data do not consistently suggest an association between occupational exposure to TiO2 and risk for lung cancer as far as no specific TiO2 micro and nano particle sizes and/or specific physical forms are regarded. However, one cohort study by Boffetta *et al*. (2004) deals specifically with the respirable fraction of TiO2 dust (calculated from total dust) and suggests that there is no clear dose – response relationship expressed as RR for lung cancer; generally we do not have sufficient amount of relevant studies. In addition, Boffetta *et al*. (2004) indicated in their paper and Hext *et al*. (2005) repeated in their summary paper that the investigated TiO2 concentrations in the occupational environment generally could be too low to cause lung cancer. Therefore RAC concludes that the animal carcinogenicity studies cannot be overruled.

b. <u>Animal data</u>

Classification proposal is largely based on animal studies. However, several comments challenge the extrapolation of carcinogenic effects observed in rats to humans and thus the relevance of the proposed classification.

- Regarding the claim for inadequacy of available animal studies

Lung tumours are reported in two inhalation studies (Lee *et al*., 1985 and Heinrich *et al*., 1995). FR-MSCA recognized the limitations of these studies. Indeed, as clearly reported in the CLH report, the Heinrich *et al.* (1995) study is associated with a reliability of 3 based on the lack of

full characterization of the substance tested and on the exposure protocol (only one concentration varying during the experiment, only female treated). In contrast, the protocol of the Lee *et al.* (1985) study is considered comparable to current guideline and the results therefore more reliable (reliability 2).

Comments related to the tested concentrations:

Even if it is acknowledged that the highest concentration level of 250 mg/m^3 (which was associated with a tumourigenic effect) is substantially higher than current inhalation toxicology practice, it should be noticed that an upper threshold of concentration to be tested is not defined in the OECD guideline n°451. Instead, the highest concentration level must be chosen in order to elicit toxicity, as evidenced by, for example, depression of body weight gain (approximately 10% representing the maximal tolerated dose) but not to alter the animal's normal longevity (OECD guidelines n°451 & guidance on the application of the CLP criteria, 2015). In addition, in the OECD guidance document 116 on the conduct and design of chronic toxicity and carcinogenicity studies, supporting test guidelines 451, 452 and 453 (ENV/JM/MONO(2011)47), it is noted that "*for substances likely to accumulate in the lung over time due to poor solubility or other properties, the degree of lung-overload and delay in clearance needs to be estimated based on adequately designed pre-studies; ideally a 90-day study with postexposure periods long enough to encompass at least one elimination half-time. The use of concentrations exceeding an elimination half-time of approximately 1 year due to lung-overload at the end of study is discouraged*" and that "*the highest dose level should be chosen to identify toxic effects including the principal target organs while avoiding severe toxicity, morbidity, or death*". It can be noted that this guidance does not extend to the testing of nanoparticles.

With regard to the Lee *et al.* (1985) study, the authors considered that clearance mechanisms were overwhelmed by 12 months at the high concentration of 250 mg/m^3 even if elimination half-time has not been reported. However, no marked systemic general toxicity was observed since this concentration did not induce a significant decrease of body weight (-5% in males and -8.7% in females) and was not associated with any excessive mortality (no further details in the publication) when compared to the control group. Thus, the dose selection including the maximal tested concentration of 250 mg/m^3 follows OECD and ECHA recommendations. Moreover, due to faster clearance in rats than in humans, doses inducing overload in rats are required to achieve lung burdens similar to those observed in workers in dusty jobs (IARC

2010; NIOSH, 2011). Consistent with this, Schultz *et al*., (1996) considers that a concentration 100-fold greater than expected human exposures is recommended. Finally, in the Lee *et al.* (1985) study, interval between the tested concentrations is very wide, in particular between the mid concentration of 50 mg/m^3 and the high concentration of 250 mg/m^3. Therefore, it is not known if tumours can occur at a "more realistic" concentration between 50 and 250 mg/m^3. In this context, the significance of the effects observed at the high concentration of 250 mg/m^3 should not be ruled out.

Comments related to the route of exposure:

Lung tumours were also observed in intra-tracheal studies (Pott *et al*., 2005 and Xu *et al*., 2010). FR-MSCA agrees that this route of exposure is not realistic to characterize human risk but is still informative on the hazard point of view and that's why these studies are only used as supporting data for the classification proposal. This is consistent with recommendations from guidance on the application of the CLP criteria (2015): "*Sometimes other non-physiological routes are used, such as intra-muscular, sub-cutaneous, intra-peritoneal and intra-tracheal injections or instillations. Findings from studies using these routes may provide useful information but should be considered with caution. Usually dosing via these routes provides a high bolus dose which gives different toxicokinetics to normal routes and can lead to atypical indication of carcinogenicity. For instance, the high local concentration can lead to local tumours at the site of injection. These would not normally be considered reliable indications of carcinogenicity as they most likely arose from the abnormally high local concentration of the test substance and would lead to a lower category classification or no classification. Where findings are available from studies using standard routes and non-physiological routes, the former will generally take precedence. Usually studies using non-standard routes provide supporting evidence only*." Accordingly, these studies were only used in a weight of evidence approach since they fully support results from inhalation studies.

In conclusion, we recognize that carcinogenicity studies with TiO_2 are either old inhalation studies or performed *via* intra-tracheal route. When assessed, two studies (one by inhalation and one by intra-tracheal route) were assigned with a reliability of 2 (Lee *et al*., 1995 and Pott et *al*., 2005), both demonstrating lung tumours. The two other positive studies (Heinrich *et al*., 1995 and Xu *et al*., 2010) are considered of lower quality but since the effects are consistent with those of Lee *et al.* (1995) and Pott *et al.* (2005), the weight of evidence is judged sufficient to demonstrate that TiO_2 has a carcinogenic potential in rats.

- Regarding the comments on inter-species differences: overload concept, types of tumours and relevance to human situations

It has been argued in many comments that, based on the negative epidemiological studies and on species differences in lung anatomy between rats and humans, lung tumours would not occur in humans in normal condition of use. However, the following elements should be taken into account:

Inter-species differences and overload

TiO_2 induces lung cancer probably due to a chronic inflammation secondary to dust overload in the alveolar region of the lung. Overload condition was also found in mice exposed to TiO_2 without developing cancer. Hamster seems to be not sensitive to overload. These results suggest that the rat is particularly sensitive to lung toxicity of particles among other rodents. However, mice and hamsters are known for not being relevant species to identify human particulate carcinogens (see page 61 of the CLH report). The relevance of rat to predict human particulate lung carcinogenicity is supported by data obtained with crystalline silica or diesel engine emissions (substances known as human carcinogens) for which negative results were found with mice or hamsters although rats developed lung tumours. Thus, from these results, it cannot be concluded that the rat is an inadequate species for the assessment of dust carcinogenicity (Gebel, 2012).

The precise mechanisms underlying particle overload are not known, making difficult the interpretation of species-differences. In this context, any judgment on extrapolation or not of particle overload among different species cannot be fully established. Nevertheless, differences observed between rats, mice and hamsters may be explained, at least partially by biological diversity of detoxification systems, such as anti-oxidant defenses. In addition, differences in term of particle deposition between rodents and humans or non-human primates have been demonstrated. The below overview of inter-species difference is originated from ECETOC technical report No. 122 (2013).

Table 2: Interspecies lung responses[a] following long-term or chronic inhalation exposure to PSPs

Species			
Rat	**Mouse**	**Hamster**	**Primate/Human**
Likelihood for developing particle overload (slow lung clearance)			
+++	+++	+	Not determined
Alveolar macrophage participation			
Active (accumulation in alveolar ducts)	Active (accumulation in alveolar ducts)	Extensive (rapid clearance)	Not as extensive (translocation to interstitial sites)
Pulmonary (neutrophilic) inflammation			
+++	+++	+	+
Epithelial and interstitial cell proliferation			
+++	+	(+)	(+)
Septal fibrosis			
+++	+	(+)	(+)
Anatomical location of retained particulates			
Primarily alveolar (some increased translocation at overload)	Primarily alveolar (some translocation at overload)	Rapid clearance	Primarily interstitial
Lung tumours following chronic exposure			
Yes	No	No	No

[a] Severity low +, moderate ++, high +++, or questionable (+)

Table 1. Interspecies lung responses following long-term or chronic inhalation exposure to PSPs (extracted from ECETOC, 2013)

This table indicates that inter-species differences exist in the lung response to chronic inhalation of PSPs (poorly soluble particles) and that rat could be more sensitive than other species. However, specific mechanistic data are still lacking to adequately compare humans to rats. In the absence of such data, overload must be considered as potentially relevant for humans. Furthermore, behind the above species differences, qualitatively similar lung responses to dust were reported with rats and humans (see pages 61 and 62 of the CLH report). In addition, differences in particle retention do not necessarily raise questions concerning the relevance of lung tumours since accumulation of particles was found in all these species, with a slower clearance reported in humans. Concerning monkey data, the observation reported in the table cannot be linked directly to carcinogenesis, since the exposure (24-month, no lifetime studies) may be not sufficient to detect a carcinogenic potential. Concerning humans, data come from very few case reports or epidemiological studies with limitations already detailed in the CLH report and in point 2a of this document.

The relevance of lung tumour observed in overload condition in rats to humans has been discussed in many publications or meetings. In 1998 in a workshop organized by the

International Life Sciences Institute (ILSI)[1], the consensus views of the participants is the following: "*Because it is not known with certainty whether high lung burdens of PSPs can lead to lung cancer in humans via mechanisms similar to those of rat, in the absence of mechanistic data to the contrary it must be assumed that the rat model can identify potential carcinogenic hazards to humans*". In 2000, a workshop was held in Germany on behalf of the MAK Commission to present the state of the art of fiber and particle toxicity (Greim et al., 2000). In regard to the question "*considering antioxidant, DNA repair and other defense mechanisms, what is the most appropriate model for risk assessment for human exposure* […], *the participants agreed that at present there is no better animal model than the rat for assessing lung cancer risk for poorly soluble particles (PSP). The rat appears to be the only laboratory animal species that develops lung tumors in response to PSP and therefore is the most sensitive species for this endpoint*". The relevance of lung overload mechanism to humans was also considered by the IARC (2010). Species differences, such as respiratory tract structure, differences in particle-induced impairment of clearance, which can result in different lung burdens, were considered and similarly pulmonary inflammation has been reported to be a consequence of exposures to poorly soluble particles in both experimental animals and humans. By analogy, the IARC Working Group took into account the high retained mass lung burdens and decrease of lung clearance observed in coal miners to conclude that animal cancer data obtained under conditions of impaired lung clearance are relevant to humans. In 2011, the MAK Commission "*assumed that the data obtained in test animals on the potential carcinogenicity of particles can be applied to humans if species-specific conditions (anatomy and histology of the respiratory tract) are taken into account. In humans and test animals, the form of tumour and its location in the respiratory tract mainly depend on the dose retained in the most sensitive target*." Relevance of rat data to humans is also supported by Kuempel (2014) based on qualitative similar response to high lung burdens of PSLTs (poorly-soluble low toxicity particles) in both rats and humans and on slower clearance in humans suggesting that particles can build up in the lungs at exposure below those that would cause overloading in rats. In contrast, ECETOC (2013) concluded that humans are considered less sensitive to lung overload than rats based on epidemiological studies and on species-differences in detoxification system and toxicokinetics. In this context, they consider that the rat is a unique model with regard to lung neoplastic responses under conditions of lung overload. A similar conclusion was reached

[1] Nonprofit corporation composed solely by member companies primarily from the food, beverage, pharmaceutical, and chemical industries. Members are all companies; no individual or trade association is eligible for membership in ILSI or its branches.

by Morfeld *et al*. (2015) who commented on the MAK Commission conclusions on general threshold limit value for dust (2011).

In addition, many comments received stated that "*all relevant guidance documents by ECHA, OECD and ECETOC unanimously observe that results from "lung overload" studies in rats should not be transferred to humans.*" This is a subjective interpretation of ECHA and OECD documents. Indeed, in the guidance on the application of the CLP criteria (ECHA, 2015), it is noted that "*the relevance of lung overload in animals to humans is currently not clear and is subject to continued scientific debate*". In addition, according to ECHA Guidance on information requirements on Chemical Safety Assessment Appendix R7-1 (Recommendations for nanomaterials applicable to Chapters R7a and R7c (Human health endpoints); chapter 3.1.1. Consideration of rat lung overload within inhalation toxicity assessment), "[…] *the data obtained from rats may still be useful to predict the effects in humans*" based on a significant relationship between coal mine dust exposure and lung cancer mortality reported by Graber *et al.* (2014) (as cited in the ECHA guidance) and "[…] *studies pointed out that the lung responses to high lung burdens of PSP of low toxicity can be qualitatively similar in rats and humans and that studies in mice and hamsters were also negative for some particles that have been classified as known human carcinogens*" (ECHA, 2016). OECD guidance document 116 on the conduct and design of chronic toxicity and carcinogenicity studies, supporting test guidelines 451, 452 and 453 (ENV/JM/MONO(2011)47) only states that "*the use of concentrations exceeding an elimination half-time of approximately 1 year due to lung-overload at the end of study is discouraged*". In conclusion, all these publications highlight that there is still vigorous scientific debate on this topic. At this time, there is no agreement concluding that pulmonary tumours found in an overload context in rats are not transferrable to humans.

Finally, we can also quote the arguments reported in comment 445 from Member State Germany:

- *A clear-cut threshold for overload cannot be derived as particle clearance from the lung decreases in a linear fashion with increasing dust load also below the Morrow threshold of overload (Morrow PE. Fundam Appl Toxicol. 1988 10(3):369-84; Roller M (2003) Eur J Oncol 8(4), 277-293). Thus, there is no established consensus in the scientific community that titanium dioxide is a threshold carcinogen.* This hypothesis is also reported by Gebel *et al.* (2012) who stated "*that there is no detectable threshold below which lung clearance is not impaired. Already low amounts of dust deposited in the*

terminal airways lead to an increase in clearance half-life. This could indicate that at low and realistic exposure situations, inflammation is evidence and that tumour induction is not only relevant in the overload condition that at least raises questions on a threshold-like mechanism of GBP carcinogenicity."

- *Lung carcinogenicity by titanium dioxide is a consequence of chronic inflammation which was assumed by some researchers to be species-specific for the rat as hamsters and mice did not show lung tumors after granular biodurable particle exposure. Counterarguments are that the latter species may not be adequate indicators for human lung carcinogenicity. For instance, benzoapyrene and vinyl chloride were negative after inhalation in hamsters and mice were negative after crystalline silica exposure, respectively. Moreover, hamsters and mice were studied more rarely for lung carcinogenicity of particles. The negative monkey data after granular biodurable particle can be explained by the fact that only few animals were studied and only one dose was used for only 2 years.*

Inter-species differences and type of lung tumours

Thompson *et al*. (2016) proposes the following Adverse Outcome Pathway (AOP) for pulmonary cancer induced by TiO_2.

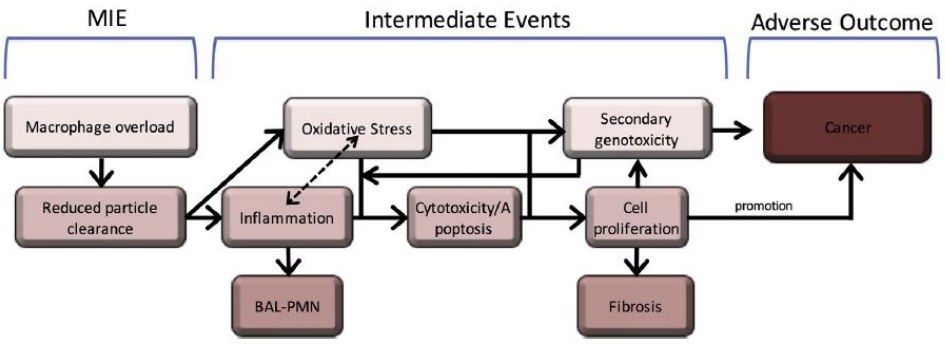

Fig. 4. AOP diagram for TiO_2-induced lung cancer. This AOP was adapted from ECETOC (2013) and placed in a format informed by Adverse Outcome Pathway Knowledge Base (aopkb.org). Note: darker colors represent higher levels of organization (e.g. molecular, cellular/tissue, organ, individual). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Figure 3. AOP diagram for TiO_2-induced lung cancer (extracted from Thompson *et al*., 2016)

Many of the steps presented in the above AOP diagram have been observed in humans with increased particle lung retention (deposits in lung tissues and lymph nodes) and pulmonary inflammation (including decline in lung function, pleural disease with plaques and pleural

thickening, mild fibrotic changes) in workers exposed to PSPs, including TiO_2 (IARC, 2010). Fibrosis and/or inflammation processes (supposed to be early steps in tumour formation according to above AOP) may be considered preneoplastic conditions. Since these effects are reported in humans exposed to PSPs, including TiO_2, it can be hypothesized that lung tumours may also occur in humans. In this context, the lack of demonstration of a link between respiratory cancer and occupational exposure to TiO_2 may be partially explained by a too short follow-up period.

Moreover, particle size, airway anatomy and site of particle deposition are thought to influence the type and location of lung cancers between species. The anatomo-typology of human lung cancers are derived from studies of cigarette-smoke induced lung cancer since cancer data with PSPs are rather limited. The major cell types of cancers are adenocarcinomas, squamous-cell carcinomas, small-cell anaplastic carcinomas and large-cell anaplastic carcinomas. Adenoma/adenocarcinoma and squamous cell carcinomas were found in both rats and humans. Thus, lung tumours found in rats cannot be dismissed as being irrelevant to humans. In addition, it should be reminded that human lung cancers described above are induced by tobacco and may not be comparable to lung cancers induced by TiO_2 in the rats. Therefore, the significance of TiO_2 induced rodent lung tumours should not be diminished simply because they can differ from tobacco-smoke induced lung tumours seen in humans.

Other mechanisms of carcinogenicity

It is generally recognized that particle overload is not sufficient to explain alone carcinogenic effect. Other mechanisms can be expected, in particular for some specific forms of TiO_2 such as nanoforms or "complex" shapes (i.e coated). This hypothesis is mainly led by knowledge on nanoforms. First, overload condition can occur at lower concentration for the following reasons 1) high airborne concentration can be easily reached due to a higher volatility; 2) phagocytic clearance of nanoparticles is less efficient than clearance of fine particles of the same material. Furthermore, contribution of direct cytotoxic effects resulting from greater surface area and higher reactivity can also decrease the threshold for carcinogenic effect. The same argumentation is also applicable for "complex" shapes of TiO_2 but cannot be clearly anticipated due to uncertainties linked to the lack of a well-performed characterization and toxicological studies. In addition, it may also be anticipated that TiO_2 with fiber-like shape would have carcinogenicity potential comparable to other fibers with development of mesothelioma without

significant role of overload. Overall, the threshold for carcinogenic effect may be lower for some undefined forms of TiO_2 than that anticipated with the TiO_2 tested in carcinogenicity studies.

Overall conclusion on animal data

In conclusion, although it can be suggested that rats are more sensitive than humans, it is not known to what extent humans are less susceptible to particle-induced cancer. Due to the lack of quantitative data relating TiO_2 (or other PSP)-associated pathogenesis across species, it cannot be concluded that the rat is not relevant for human hazard identification. Despite the lack of evidence of an increase of lung cancers in workers, the results are not adequate to conclude that effects observed in rats would not occur in humans due to the limitations associated with epidemiological studies (detailed in section 2a of this attachment to RCOM). Therefore, rat remains an appropriate model for predicting neoplastic and non-neoplastic responses to particulates and data from this species are considered relevant for human.

RAC's response on comments on carcinogenicity (animal data)

RAC thoroughly discussed the reliability of the available TiO2 inhalation studies. RAC in the end concluded that the Heinrich *et al.* (1995) study, supported by the results of inhalation studies with other PSLTs, is of adequate quality for classification purposes. Because of excessive exposure conditions RAC considered the Lee *et al.* (1985) study less adequate. For a more detailed discussion of the adequacy of the animal studies, please refer to the Opinion.

RAC takes note of the many stakeholder comments questioning whether experimental inhalation exposure levels tested are relevant for classification purposes. RAC discussed the consequences of high inhalation exposure on particle loading of alveolar macrophages and on TiO2 lung burden in experimental animals and humans. A more detailed discussion of overload issues is included in the Opinion.

RAC discussed the relative importance of inhalation studies and studies conducted by intratracheal instillation. Both types of studies indicate a consistent carcinogenicity profile. As outlined in the Opinion, RAC is of the view that reaching a conclusion on classification for TiO2 is a rather complex process and has to involve a weight-of-evidence approach analysing the dose response relationship in experimental animals, the mode of action and possible differences between experimental animals and humans. This TiO2-related weight-of-evidence approach is outlined in the Opinion.

Many stakeholders argued that the carcinogenicity profile in the rat is unique to the rat. Stakeholders claimed that the adverse outcome pathways in the rat and in humans are different. The Opinion addresses this issue in detail. RAC holds the view that a sufficiently detailed and specific adverse outcome pathway for humans has not yet been described. In the opinion of RAC, the experimental and human evidence so far available supports a lower human sensitivity but does not conclusively exclude a carcinogenic potential or hazard of TiO2 in humans.

RAC considers marked loading of alveolar macrophages as an essential trigger and mechanism of the observed TiO2 carcinogenicity by inhalation. Carcinogenic potency of nano-sized PSLTs is somewhat higher than that of micro-sized PSLTs. RAC however does not recognise relevant differences in the qualitative carcinogenicity profile of micro- and nano-sized TiO2. For TiO2 with WHO fibre shape RAC anticipates a different mode of action and a markedly higher carcinogenic potency.

RAC carefully considered whether the lack of evidence of an increase of lung cancers in humans outweighs the positive experimental animal data. Based on considerations of possible exposure-risk relationships in humans, RAC is of the opinion that the TiO2 related epidemiological studies are not sufficient reasoning to exclude a classification of TiO2.

RAC concludes that the carcinogenic profile of TiO2 in the rat is only related to the inhalation route of exposure. The reported experimental evidence does not indicate carcinogenic potential of TiO2 by the oral or dermal route.

c. Carcinogenicity as a substance-specific effect

Some comments question the rationale of the proposed classification judging the effects as not substance-specific although CLP is based on intrinsic hazard of a substance. Based on inhalation data with various dusts showing lung carcinogenicity, the hypothesis of a non-specific mode of action is raised. In particular, the mechanisms underlying overload and lung formation are likely similar for all PSPs. However, the relative contribution of a particular mechanism may vary for particles with different physicochemical properties. According to ILSI (2010), data suggest that specific PSPs exhibit different potencies for causing overload due to differences in inhaled deposition and subsequent clearance due to differences in aerodynamic and physicochemical properties. Indeed, various physico-chemical parameters like particle size, density and surface area or particle volume may influence establishment of overload of alveolar macrophages. Biosolubility can also be considered to be a major determinant in pulmonary response to particles. Thus, although a similar mechanism of action is reported with different PSPs, this does not invalidate the assumption of specific-substance carcinogenicity. In conclusion, PSPs induce a similar profile of carcinogenicity after inhalation in rats, with differences in potency explained by the specific chemistry of the particles. In this context, the potency of carcinogenic effects observed after TiO_2 inhalation is influenced by intrinsic physicochemical parameters, that is consistent with CLP criteria.

RAC's response on carcinogenicity as a substance-specific effect

Referring to many comments during public consultation RAC acknowledges that the mode of action for the rat lung carcinogenicity can not be considered "intrinsic toxicity" in a classical sense: the deposited particles but not solutes of TiO2 molecules can be assumed to be responsible for the observed toxicity. Nevertheless this mode of action results in relevant toxicity and carcinogenicity. The CLP regulation does not exclude a health hazard classification based on physico-chemical characteristics of a chemical.

Overall conclusion on carcinogenicity endpoint:

Lung tumours were found after TiO_2 exposure in rats under overload conditions. Rats are recognized as particularly sensitive among other species. Mechanisms underlying lung carcinogenicity is not fully known making difficult the interpretation of inter-species differences. At this time, extrapolation to lung overload and subsequent carcinogenicity to humans is still under scientific debate but the discussions reported above show that they should be considered relevant for human. Under CLP regulation, effects observed in the most sensitive species should be considered for classification purposes, except if it can be clearly demonstrated that the species is not adequate. Thus, in the absence of quantitative data allowing conclusions on what extent humans would be less sensitive to rats, rats remain the adequate model for human hazard identification.

In regard to the above-mentioned uncertainties relating to the methodological deficiencies of experimental and human studies and to mode of action hypothesis (overload), we understand that TiO_2 can be a borderline case between category 1 or 2 carcinogenicity classification. This is also reflected by the self-classifications reported on ECHA website, with 9 notifications for Carc 1B and 124 for Carc 2 (including notifiers for the general entry of TiO_2 and the specific entries for anatase and rutile) (see page 10 of the CLH report). However, uncertainties related to lung overload in humans are not a sufficient reason for supporting no classification action. In addition, mechanisms other than "pulmonary overload" can be involved in tumour production suggesting the possibility of a lower or a no threshold carcinogenic effect for some existing grades of TiO_2 compared to that observed in experimental studies. In conclusion, TiO_2 is judged as a "presumed carcinogen", as reflected by the Carc. 1B proposal based on sufficient evidence in animal.

We consider that this proposed classification as carcinogen is in line with recent reviews on TiO_2 performed by scientific and regulatory bodies. In 2010, IARC concluded that TiO_2 "*is possible carcinogenic to humans (Group 2B) based on sufficient evidence in experimental animals and inadequate evidence from epidemiological studies*". In 2011, NIOSH "*has determined that ultrafine TiO_2 is a potential occupational carcinogen*". Although they consider that there is insufficient data for fine TiO_2, they concluded that tumour-response data with fine TiO_2 are consistent with that observed for ultrafine TiO_2. Also in 2011, the MAK classified

TiO_2 as biopersistent granular dust in carcinogenicity of category 4 (carcinogen known to act typically by non-genotoxic mechanisms). Again in 2011, the California Office of Environmental Health Hazard Assessment (OEHHA) listed titanium dioxide (airborne, unbound particles of respirable size) as carcinogen under Proposition 65 using the Labor Code mechanism. In 2015, the SCCS does not recommend "*the use of nano titanium dioxide in spray applications that could lead to exposure of the consumer's lungs to nano titanium dioxide by inhalation*" due to potential carcinogenicity.

RAC response to overall conclusion
The dossier submitter and most of the stakeholders commenting during public consultation disagree as to their respective interpretation of available TiO2-related carcinogenicity data. Most of the stakeholders express the view that rat lung carcinogenicity is only expressed under conditions of excessive exposure and that the knowledge on adverse outcome pathways allows for considering the rat as unique in relation to the carcinogenicity profile described. The dossier submitter holds the opinion that the available evidence supports the conclusion that TiO2 should be considered a presumed human carcinogen. As outlined in detail in the Opinion, RAC is of the opinion that the evidence available is not sufficient for the carcinogenic hazard category 1B. In relation to the various arguments for no classification, RAC had an extensive discussion on whether category 2 or no classification was more appropriate. As outlined and justified in the Opinion in detail, RAC in the end decided that the criteria for category 2 carcinogenicity (by inhalation) are considered to be fulfilled. RAC considers TiO2 a *suspected* rather than a *presumed* human carcinogen. The classification is solely based on the hazardous properties of the substance, it does not address the likelihood of exposure and therefore does not address the risks of exposure.

3. Comments on hazard endpoints other than carcinogenicity

In the current CLH report, the FR-MSCA proposes a general entry for classification of TiO_2 for Carcinogenicity 1B – H350i by inhalation. In that purpose, only studies dealing with carcinogenicity were analysed and reviewed. Any other endpoints were not considered in the present report and are not subject for commenting in this public consultation. Concerning genotoxicity, this endpoint has been filled in the CLH report since it was initially foreseen to

propose a classification for this endpoint. However, since the genotoxic results are not conclusive enough to propose a classification, data had only been presented as supporting information for carcinogenicity endpoint, in particular to investigate the carcinogenic mode of action. In this context, the genotoxicity data reported in the CLH report do not intent to be exhaustive. In contrast, it was preferred to select studies based on chosen criteria to keep only the most reliable data. The restriction in the date of publication (2010-2015) is considered particularly relevant for nanoforms of TiO_2. Indeed, older studies were generally not performed in adequate conditions to take into account the specificity of the size. From the assessed studies, the results indicate that oxidative stress seems to be the main pathway for carcinogenicity. However, some data suggest that nanoparticles of TiO_2 can also interact with DNA. This hypothesis is based on some studies reporting the presence of TiO_2 nanoparticles inside nucleus. At this time, it is difficult to put in perspective this result since accumulation in the nucleus was not systematically investigated in the studies and was not quantified when reported. Because the mechanism of penetration inside the nucleus is unclear and observation techniques are still under debate, the direct genotoxicity of TiO_2 needs to be confirmed. Nevertheless, since the exact mechanism for carcinogenicity of TiO_2 is not currently totally known, the role of direct genotoxicity, even if minor, cannot be excluded. Further research is thus necessary to consolidate the existing scientific literature on mutagenicity/genotoxicity or other hazard classes to propose any other classifications. In conclusion, only carcinogenicity data are judged sufficient to propose a classification at this time.

RAC response to comments on hazard endpoints other than carcinogenicity

RAC acknowledges the various comments by stakeholders on the dossier submitter's considerations on genotoxicity. RAC emphasizes that the dossier does not contain a final conclusion on TiO2 genotoxicity. RAC refers in particular to the EFSA (2016) evaluation on genotoxicity of TiO2 indicating that the genotoxicity of TiO2 is mediated mainly through the generation of oxidative stress in cells. In this EFSA evaluation, much emphasis was laid on a study-specific discussion of the reliability and relevance of the data, including the possible mechanism of genotoxic action. Based on the overall evidence, RAC considers it plausible to assume that inflammatory reactions and reactive oxygen species play a central role in TiO2 genotoxicity and carcinogenicity. In the opinion of RAC, the mode-of-action proposed for the rat is consistent with the assumption of a practical threshold.

4. Comments on exposure and risk assessment

Dosimetry approaches have been proposed in some comments to predict human equivalent doses. In particular, one comment (comment 15) predict the deposition and clearance of inhaled particles in the rat and human respiratory tract from Lee *et al*. (1985) study using MPPD (Multiple Path Particle Dosimetry) model. The approach is adapted for the derivation of human occupational exposure limit value (OEL) e.g. by estimating the working lifetime dose of TiO_2 in the alveolar region of the lungs that was equivalent to a POD (point of departure) estimated from rat data. However, details of the calculations and some options used in the program were not provided and therefore cannot be verified. This is of particular importance since differences were found when using different models for dosimetric adjustments. Moreover, predicted and measured concentrations in the Lee *et al.* (1985) study were not in the same range (124 mg/lung measured in the study versus 19 mg/lung predicted by the model at 50 mg/m^3). These differences suggest that clearance and retention of TiO_2 may not be well predicted by the MPPD model in rat. Extrapolation to human is also questionable as only normal human clearance is taken into account in the model although clearance rates are found to be slower in workers than that in healthy adults without occupational dust exposure. In addition, independently of retained dose, possible heterogeneity of the particles deposition in lung of rats/humans (hotspots) and its influence on cancer development should be discussed. Finally, since MPPD model uses some general physicochemical parameters, field data are necessary to validate the hypothesis that it can be adapted to TiO_2. Overall, dosimetry approaches are used to improve accuracy and reduce uncertainty of internal dose estimates for the derivation of OELs and thus are not judged appropriate for classification purpose only dealing with hazard characterization.

Many comments rely on risk management at workplace, including personal protective equipment and collective measures such as generic dust limit value. In addition, some comments suggest the setting of a specific OEL (Occupational Exposure Limit) for TiO_2 and/or to include workers activities with TiO_2 in Annex I of the Cancer Directive 2004/37/EU as the appropriate way to control possible risk associated with TiO_2. These considerations do not impact the CLH proposal but could be considered in a further risk management option analysis. Although TiO_2 is listed in CoRAP for substance evaluation process that should have been initiated in 2015, the dossier is currently on stand-by due to SID (substance identity) issues. A more logical strategy would have been to proceed to the substance evaluation first and then

submit a CLH report. However, it is not known when the SID issue will be solved in an acceptable way allowing assessing specific risks linked to different forms of TiO_2. Awaiting the update of the registration dossier, FR-MSCA reviewed the existing scientific literature for genotoxicity and carcinogenicity endpoints. Based on these data, it was decided to submit a CLH report to protect human health from a "presumed carcinogen" without waiting the start of the substance evaluation process. This is considered justified since no significant impact of the physicochemical parameters was found for carcinogenicity endpoint. Although not directly relevant to the CLH process, we would like to indicate that regarding the multiple and vast scenarios of handling/preparation/uses and the different protection tools/equipment's in place in each case and facilities, the submission of data in the substance registration dossier explaining how the risks are adequately controlled for each uses with specific forms of TiO_2 during the foreseen substance evaluation process is highly recommended.

RAC response to comments on exposure and risk assessment
Dosimetry models are very much relevant in the context of deriving dose response relationships. RAC took note of corresponding overall results in the context of interpretation of results of epidemiological studies, but did not discuss these models in detail.

5. Comments on economic impact of the proposed classification

The FR-MSCA notices the importance of this chemical for industries in the formulation of many end-use products, and especially the difficulty or the lack of adequate substitution for some uses. These considerations are not taken into account under the CLP regulation but under other processes of REACh regulation. Although not directly relevant to the CLH process, we would like to indicate that the FR-MSCA highly recommends the registrants to bring information on this point in the registration dossier and obtain data in the case of an alternative to TiO_2 is needed.

The FR-MSCA recognises that risk management arising from classification does not take into account the specificity of exposure route. Indeed, as commented, many laws do not distinguish between products containing carcinogens and such products utilizing a "potential carcinogen by inhalation" even when no exposure by inhalation is expected. Discussions on how to deal

with this issue is needed at European Union level. Moreover, several comments reported "disproportionate" impact of the proposed classification on TiO_2 for many products with consumer exposure (such as food additives, cosmetics, biocidal products, pharmaceutics, etc.) considering the withdrawal of CMR 1B substances from the market. However, it should be reminded that for the majority of these cited products, a specific regulation (other than REACh) exists that can overrule the impact of the classification based on risk characterization or other criteria.

With regard to the comments on the impact of this classification proposal on other PSPs, this has not been addressed in this dossier. Indeed, the classification proposal is based on specific data on TiO_2. PSP data were only used as supportive data for the hypothesized carcinogenic mode of action. The relevance of any classification for other PSP should be considered specifically in dedicated CLH reports.

Finally, although not directly relevant to the CLH process, we would like to indicate that, due to the importance of this chemical in the industry and the resulting products, we urge all the registrants to fully improve and complete their registration dossier in order to generate qualitative and/or quantitative data (especially regarding the uses and resulting exposure/characterization assessment related to each form of TiO_2 which should be properly characterized) to facilitate and speeding up the "Substance Evaluation" process under REACh regulation.

RAC's response to comments on economic impact of proposed classification As noted by the dossier submitter, consideration of the economic impact of a proposed classification for a substance is not within the scope of RAC.

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Appendix 1: Comparison to CLP criteria

Toxicological results	CLP criteria	
Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence.		
Strength of evidence		
Sufficient evidence of carcinogenicity Benign tumours in both sexes in rats exposed by inhalation (Lee *et al.*, 1985). Benign and malignant tumours in female rats exposed by inhalation (Heinrich *et al.*, 1995). Benign and malignant tumours in female rats exposed by instillation (Pott *et al.*, 2005). Sufficient evidence in experimental animals supported by IARC conclusions (2010)	Carcinogenicity in experimental animals — sufficient evidence of carcinogenicity: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.	
Additional considerations		
Benign lung tumours: Lee *et al.* (1985) study: bronchioalveolar adenomas: 16% in males and 17% in females at 250 mg/m^3 (rutile TiO_2) versus 3% in males and 0% in females in control group. Pott *et al.* (2005) study: benign tumours: • 21.4%, 17.4% and 23.9% lungs with tumours in females exposed to nano-TiO_2 (P25) (at 5 instillations of 3 mg, 5	(a) tumour type and background incidence	

instillations of 6 mg and 10 instillations of 6 mg, respectively) versus 0% in control group. • 15.9% and 38.6% lungs with tumours in females exposed to fine TiO_2 (at 10 instillations of 6 mg and 20 instillations of 6 mg, respectively) versus 0% in control group. Heinrich *et al.* (1995) study: keratinizing cystic squamous cell tumours: 10% at 18 months, 22% at 24 months, 20% at 30 months (24 months-exposure + 6 months of recovery) in females after inhalation to at 88.1g/m^3xh cumulative exposure (nano-TiO_2 (P25)) versus 0% in controls. **<u>Malignant lung tumours:</u>** Heinrich *et al.* (1995) study: • Squamous cell carcinomas: 15% at 18 months, 22% at 24 months, 3% at 30 months (24 months-exposure + 6 months of recovery) in females after inhalation to 88.1g/m^3xh cumulative exposure (nano-TiO_2 (P25)) versus 0% in controls. • Adenocarcinomas: 10% at 18 months, 11% at 24 months, 13% at 30 months (24 months-exposure + 6 months of recovery) in females after inhalation to 88.1g/m^3xh cumulative exposure (nano-TiO_2 (P25)) versus 0.5% in controls. Pott *et al.* (2005) study: malignant tumours: • 31%, 50% and 45.7% lungs with tumours in females exposed to nano-TiO_2 (P25) (at 5 instillations of 3 mg, 5 instillations of 6 mg and 10 instillations of 6 mg, respectively) versus 0% in control group.		

• 13.6% and 25.0% lungs with tumours in females exposed to fine TiO_2 (at 10 instillations of 6 mg and 20 instillations of 6 mg, respectively) versus 0% in control group. No concurrent historical control data were described in these publications. However, from historical control data found in the literature, lung tumours generally occur at incidences less than 4% in rats.		
Tumours occurred in the lung. The major proposed mode of action is linked to inflammatory process. However, mechanisms of action other than inflammatory process cannot be excluded in the absence of adequate investigation. This is of particular relevance for some specific forms of TiO_2 (such as nanoparticles or fiber-like) that can translocate to other organs after inhalation. However, organs other than lungs were poorly or not examined in the studies performed by inhalation or instillation. Thus, occurrence of tumours in organs other than lungs cannot be assessed.	(b) multi-site responses	
Evidence of malignancy is observed with TiO_2 since lung carcinomas have been reported in one inhalation study and in one instillation study.	(c) progression of lesions to malignancy	
No conclusion on tumour latency is possible from Lee *et al.* (1985) and Pott *et al.* (2005) publications. In Heinrich *et al.* (1995) studies, benign and malignant tumours appeared from 18-month exposure in treated animals.	(d) reduced tumour latency	

Benign effects were reported in both males and females (Lee *et al.* (1985), Heinrich *et al.* (1995) and Pott *et al.* (2005)). Malignant effects were only reported in females but males were not tested in the studies where malignant effects were observed (Heinrich *et al.* (1995) and Pott *et al.* (2005)). Lung tumours are not expected to be gender-specific. This is supported by the fact that benign effects were reported in both sexes.	(e) whether responses are in single or both sexes	
Tumours were only found in rats. No tumours were observed in mice (Heinrich *et al.* (1995)). However, high background tumour response in the control group might have limited the ability to detect any carcinogenicity effect in this study. Furthermore, mice seem to be not an adequate species to assess dust toxicity based on data with crystalline silica or diesel engine emissions.	(f) whether responses are in a single species or several species	
Lung tumours were also reported with several PSPs (ex. diesel exhaust, crystalline silica…)	(g) structural similarity to a substance(s) for which there is good evidence of carcinogenicity	
Tumours occurred after inhalation and instillation.	(h) routes of exposure	
Interspecies differences were reported regarding lung response following inhalation to PSPs. In the absence of specific mechanistic data, lung tumours reported in rats must be considered as potentially relevant to humans. See point 2b of this Appendix to RCOM for details	(i) comparison of absorption, distribution, metabolism and excretion between test animals and humans	
Lung tumours were reported in an overload context in rats.	(j) the possibility of a confounding effect of excessive toxicity at test doses	

Extrapolation of lung overload and subsequent carcinogenicity to humans is still under scientific debate but observations reported under point 2 of this Appendix to RCOM show that it should be considered relevant to humans.		
Lung tumours seem to be mainly due to secondary genotoxicity after inflammation and induction of oxidative lesions. However, it is generally recognized that particle overload is not sufficient to explain alone carcinogenic effect. Other mechanisms can also be expected, in particular for some specific forms of TiO_2 such as nanoforms or "complex" shapes (i.e coated, fiber-like). For example, a direct genotoxic mechanism cannot be ruled out.	(k) mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity	