COMPILED COMMENTS ON CLH CONSULTATION

Comments provided during consultation are made available in the table below as submitted through the web form. Please note that the comments displayed below may have been accompanied by attachments which are listed in this table and included in a zip file if non-confidential. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Last data extracted on 24.08.2023

Substance name: Talc (Mg3H2(SiO3)4)
CAS number: 14807-96-6
EC number: 238-877-9
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
07.08.2023	Belgium	EUROTALC	Industry or trade association	1

Comment received

EUROTALC disagrees with the proposed harmonised classification and labelling ("CLH") of talc (Mg3H2(SiO3)4) ("talc" or "the Substance") as suspected human carcinogen in category 2 ("Carcinogen 2") and as specific target organ (lungs) toxicant after repeated exposure in category 1 ("STOT RE 1") for the reasons described below.

EUROTALC has provided a non-exhaustive list of some of the major scientific and legal flaws that were identified in CLH Report prepared by the by the National Institute for Public Health and the Environment of the Netherlands (the "RIVM's CLH Report") with the support of external consultants.

1. Substance ID
Before providing specific comments on the identified scientific and legal flaws for each of the proposed hazard classes, EUROTALC would like to comment on the insufficient identification of the talc, as described in the CLH Report's assessment the of the inhalation route. In particular, such an assessment should take into account that only the respirable fraction of talc particles could reach the deep lungs (alveoli) in a way to possibly produce effects. Therefore, the assessment of the inhalation route and CLH Report should explicitly refer to the relevant form of the Substance, namely "respirable talc", i.e. talc containing 1% or more of particles with aerodynamic diameter ≤ 10 µm. This description is fully consistent with the characteristics of the test material used in the NTP study, i.e. MMAD 2.7 and 3.2 µm, resp.; GSD 1.9 µm (CLH Report, page 14).

2. Physico-chemical properties
The CLH Report (page 8) provides a single set of values for granulometry. For sake of clarity, these particle size distribution ("PSD") values are measured by laser scattering and are only valid for the measured talc product. The granulometry of the product is an important parameter of the product specifications and varies according to the intended uses of the talc products. The representative range of granulometry for talc products placed on the EU market based on our regular measurements (internal quality controls) would be as follow:

D10 = 1.0 - 5.0 µm
D50 = 3.5 - 17.0 µm
D90 = 7.0 - 40.0 µm

3. Data sources
According to the CLH Report (page 6) "[t]he REACH registration dossier for talc (ECHA Dissemination, 2022; last modified: 1 June 2022), has been analysed for study references, which then have been considered as data sources for this CLH report."
The member companies of EUROTALC representing the main EU talc producers however emphasise that talc, naturally occurring and not chemically modified, is exempted from REACH registration and evaluation (REACH Regulation, Annex V.7) and therefore, they have not submitted a REACH registration dossier for their talc.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Attachments 1 and 2.zip

Date	Country	Organisation	Type of Organisation	Comment number
07.08.2023	Belgium	EFPIA (OT Task Force)	Industry or trade association	2

Comment received

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the innovative pharmaceutical sector in Europe. We welcome the opportunity to comment on the ECHA Proposal for Harmonised Classification and Labelling for Talc (Mg3H2(SiO3)4), CAS 14807-96-6. In summary our views are:
• For discussing the association of talc with cancer, it is essential to differentiate between asbestos-containing talc, and pharmaceutical or pharmacopeial-grade talc which is tested for the detection of asbestos. Detectable asbestos in talc warrants the talc to be "not pharmaceutical grade", and it is outside the scope of this current assessment report. Respective toxicity data with pharmaceutical grade talc should be facilitated for the assessment and to conclude any potential carcinogenic effects of talc. As done partially in the ECHA report, the particle size and purity of talc used in each study is crucial to evaluate the study outcome and have reliable conclusions.
• With no sufficient evidence for carcinogenic effects and the identified weaknesses of animal test system after inhalation, classification by the inhalation route is not warranted.
• With no sufficient evidence for carcinogenic effects after oral ingestion, classification by the oral route is not warranted.
• With not sufficient evidence for ovarian cancer association after perineal/vaginal use, classification is not warranted.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Occ Tox TF Talc 07-August 2023_Comments_final.pdf

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	United States of America	Essential Minerals Association	Industry or trade association	3

Comment received

please see the attached comments

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments of the Essential Minerals Association.pdf

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	Belgium	<confidential>	Industry or trade association	4

Comment received

Dear Sir or Madam,

Members of the <confidential> have reviewed comments on the subject document prepared by the Scientific Association of European Talc Industry A.I.S.B.L. (Eurotalc).

As a global organisation consisting of over 250 national and multi-national excipient manufacturers, distributors and finished drug product makers, the <confidential> provides a unified voice to promote the best use of excipients in medicines as a means of improving patient treatment and safety. Dedicated to working closely with regulatory authorities, industry organizations and scientific bodies (globally) to advance public health on matters relating to the quality, safety, manufacture, distribution, use and functionality of excipients, <confidential> is the sole association, globally, representing excipients.
As talc is widely used in the manufacture of medicinal products, the <confidential> has a strong interest in the appropriate classification of excipients as there is a significant crossover in their use across several industrial sectors. The <confidential> supports the application of sound scientific principles to determine suitable requirements for the safe handling of excipients in their production and when used in medical products. Accordingly, the <confidential> fully supports and endorses the comments made by Eurotalc and respectfully requests their consideration as REACH- RIVM / ECHA assess feedback from the consultation process.

Respectfully,
<confidential> President

ECHA note – An attachment was submitted with the comment above. Refer to public attachment EUROTALC comments on the public consultation on the CLH Report on TALC final.zip

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	Belgium	<confidential>	Industry or trade association	5

Comment received

Brussels, 18 August 2023

Comments on Proposal for Harmonised Classification and Labelling- on Talc (EC 238-877-9, CAS number 14807-96-6), version 2.0 (April 2023) by bureau REACH- RIVM (NL)

Dear Sir or Madam,
Members of the <confidential> have reviewed comments on the subject document prepared by the Scientific Association of European Talc Industry A.I.S.B.L. (Eurotalc). These comments are submitted in the two attachments.
As an association, <confidential> brings together producers, distributors, and users of (pharmaceutical) excipients. <confidential> is a member of IPEC Federation whose global membership extends to more than 200 companies. <confidential> offers a unique forum for members to exchange good practices and to develop harmonised standards for pharmaceutical excipients. It strives to continuously promote and achieve worldwide

acceptance and use of <confidential> developed guidelines as a means of improving and ensuring quality, safety, and functionality of excipients.
As talc is widely used in the manufacture of medicinal products, <confidential> has a strong interest in the appropriate classification of excipients as there is a significant crossover in their use across several industrial sectors. <confidential> supports the application of sound scientific principles to determine suitable requirements for the safe handling of excipients in their production and when used in medical products. Accordingly, <confidential> fully supports and endorses the comments made by Eurotalc and respectfully requests their consideration as REACH- RIVM assesses feedback from the consultation process.

Yours faithfully,
<confidential>
<confidential> Chair

ECHA note – An attachment was submitted with the comment above. Refer to public attachment EUROTALC comments on the public consultation on the CLH Report on TALC final.zip

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	Germany	<confidential>	Company-Downstream user	6
Comment received				
The material as placed on the market has a much coarser particle size distribution and has to be artificially dispersed in order to comply with the demands of the corresponding OECD guidelines (eg OECD 413). Comparison of particle size distributions on safety/technical data sheets and OECD test results might be helpful here. Therefore, the material tested is not representative of the material as it is sold and can reasonably expected to be used. We disagree with any classification derived from the assumption that material sold and material tested (after artificially high shear / impact dispersion) are the same. Also, with future REACH revisions coming up, questionable regulation and classification of general dust effects as "substance" effects should be re-considered seriously. Last but not least, the regulatory process of non-warranted classification of one particulate material after the other (TiO2, Talc, ...) based on general dust effects is higly questionable from a fair competition point of view, creating a non-level playing field between competitors.				

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	Germany	Evonik Industries AG	Company-Downstream user	7
Comment received				
Taking the upcoming REACH revision, including GRA and consumer use impact into account, Evonik Industries is questioning whether the STOT RE classification of another particulate material (e.g; Talc, TiO2) under CLP is the right regulatory instrument to protect human health.				

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	Germany	German Social Accident Insurance	National Authority	8
Comment received				

Talc schwer nachvollziehbar erscheint. Die Daten zeigen sowohl unterschiedliche Effekte und beruhen teilweise auch auf nicht vergleichbaren Grundlagen.
Zudem werden in vielen Studien Nebenfaktoren wie eine Belastung durch andere Gefahrstoffe (besonders Asbest) unzureichend berücksichtigt. Insofern andere Gefahrstoffe wie Asbest in den Studien Berücksichtigung fanden, stellt sich dennoch grundsätzlich die Frage, inwieweit bei den Humandaten mögliche Asbestgehalte von Talkumpudern nach dem heutigen Stand der Technik ermittelt wurden. Die in Studien gemachte Angabe „asbestfrei", sollte spezifisch geprüft werden, da sich die Analyseverfahren doch gravierend geändert haben. Somit ist eine in den Studien gemachte Angabe „asbestfrei" nicht zwingend kokkekt, da ggf. der Nachweis nur nicht geführt werden konnte (u.a. Röntgendiffraktion als Analysenmethode, die mit ca. 0,5 Masse-% eine völlig unzureichende Nachweisgrenze für Asbestminerale darstellt). Eine unterschiedliche Definition von Asbest in verschiedenen Ländern, u.a. im Vergleich USA und Deutschland, weißt dabei auf weitere Schwierigkeiten bei der Auswertung von Studien hin.
Generell ist bezüglich einer Einstufung von Talc eine Differenzierung zwischen Talc (in Plättchen-Form) und Talc-Fasern notwendig, sowie der Ausschluss von zusätzlichen Gefahrstoffen wie Asbest in Talc.
Durch die geplante Einstufung wären die Regelungen im Jugendarbeitsschutz betroffen.

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	United States of America	<confidential>	Company-Downstream user	9
Comment received				
see attached document ECHA note – An attachment was submitted with the comment above. Refer to public attachment Talc letter_Final 17Aug2023.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
17.08.2023	Belgium	Cosmetics Europe	Industry or trade association	10
Comment received				
Two references (p.112; Egli& Newton, 196 and De Boer, 1972) cited in the parenthesis do not relate to talc. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cons Talc comments on Talc CLH report_CE-Talc-23-0010_final.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
14.08.2023	Germany	<confidential>	Company-Downstream user	11
Comment received				
Talc is frequently used in the coatings and printing inks industry as a filler, pigment and rheology modifier, but also in primer and filler systems. Talc increases both the opacity and the weather resistance of the end products. It is then firmly bound into the binder matrix -				

and thus cannot be inhaled. In principle, it poses no risk to humans, either in the workplace or when using products containing talc.
From the point of view of the coatings and printing inks industry, the proposed classification and labelling is neither justified nor appropriate. Classifying talc as a suspected carcinogen would have serious consequences for consumers and industry without increasing health protection.
In many regulations, such as those on plant safety, environmental and consumer protection, or in special legislation on biocidal products or cosmetic products, classification and labelling auto-matically creates extensive obligations as well as far-reaching prohibitions and restrictions with-out any further review of whether the use of the substance poses risks. Thus, the proposed classification of talc can be expected to have serious effects on disposal and recycling, considerable restrictions on exports, loss of competitiveness of products containing talc (e.g. in Germany, H 372 in the ChemVerbotsV will require a permit to be issued and the identity to be established), as well as the loss of quality features - such as environmental labels.

Date	Country	Organisation	Type of Organisation	Comment number
13.08.2023	Bulgaria	REACH 2008 Ltd.	Company-Importer	12

Comment received

Dear Sir/Madam,

As Lead registrant and on behalf of all co-registrants of substance Talc (Mg3H2(SiO3)4) CAS Number: 14807-96-6 we support EUROTALC comments and we do not support assessment leading to classification for STOT RE 1 and carcinogen 2 proposed by The Netherlands (Dutch National Institute for Public Health and the Environment).
None of the endpoints of all relevant studies, which we have do not confirm classification criteria for STOT RE 1 and carcinogen 2.

As EUROTALC has prepared substantial comments on this proposed classification with the support of renowned scientific and legal experts we join and support this comments of renowned scientific and legal experts.

The conclusion of renowned scientific and legal experts as well as their report, which we attach as an attachment is the following:
- That there are unsubstantiated overstatements of the carcinogenicity of talc in humans, Specific target organ toxicity — repeated exposure and the proposed CLH classification of talc as CARC 2 and STOT RE 1.

see the attachment

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Final <confidential>_Combined Comments on Proposed CLH_25072023.pdf

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2023	Germany	Epple Druckfarben AG	Company-Downstream user	13

Comment received

Talc is an essential filler and rheology additive in offset printing inks. It is completely dispersed within the binder matrix during the manufacture. Exposure to talc is therefore not

possible in the ready-to-use ink and in the final print product.

Date	Country	Organisation	Type of Organisation	Comment number
10.08.2023	Germany	German Paint and Coatings Association (VdL)	Industry or trade association	14
Comment received				
Use in the coatings and printing inks industry: Talc is frequently used in the coatings and printing inks industry as a filler, pigment and rheology modifier, but also in primer and filler systems. Talc increases both the opacity and the weather resistance of the end products. It is then firmly bound into the binder matrix - and thus cannot be inhaled. In principle, it poses no risk to humans, either in the workplace or when using products containing talc. From the point of view of the coatings and printing inks industry, the proposed classification and labelling is neither justified nor appropriate. Classifying talc as a suspected carcinogen would have serious consequences for consumers and industry without increasing health protection. Protection against particle effects is ensured by national occupational health and safety regulations Inhalation exposure to talc is only expected in workplaces. Most EU member states have intro-duced dust limits in the workplace (between 1.25 and 10 mg/m3). Germany is an international pioneer with a limit value of 1.25 mg/m³. The general dust limit value applies to poorly soluble or insoluble dusts that are not regulated elsewhere. TRGS 900 contains a non-exhaustive list of substances to which the ASGW applies (Chapter 2.5, entry 10 "Talc"). Compliance with the gen-eral dust limit value is mandatory. If the existing protective measures are not sufficient to comply with the occupational exposure limit value, additional protective measures up to and including the wearing of personal protective equipment must be taken (Section 9 (3) GefStoffV). In addition to the ASGW, several other regulations exist in Germany for more extensive protective measures to minimize an exposure. In Germany, this ensures a high level of protection for workers during ac-tivities involving dusts. Effects of harmonized classification on downstream regulations In many regulations, such as those on plant safety, environmental and consumer protection, or in special legislation on biocidal products or cosmetic products, classification and labelling automat-ically creates extensive obligations as well as far-reaching prohibitions and restrictions without any further review of whether the use of the substance poses risks. Thus, the proposed classifi-cation of talc can be expected to have serious effects on disposal and recycling, considerable restrictions on exports, loss of competitiveness of products containing talc (e.g. in Germany, H 372 in the ChemVerbotsV will require a permit to be issued and the identity to be established), as well as the loss of quality features - such as environmental labels. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2023-08-10_VdL-Position Talk_eng_final.pdf				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
07.08.2023	Belgium	EUROTALC	Industry or trade association	15
Comment received				

A. General comments

Carcinogen 2 (ovarian) classification
The Carcinogen 2 (ovarian) endpoint was not part of the RMOA conducted by the Netherlands in 2021 and should therefore be evaluated regarding the various regulatory options provided by the different pieces of chemical legislation.

Carcinogen 2 (lung) classification
In the CLH Report, the NTP study is presented as the most adequate study for Carcinogen 2 classification – the RIVM says this is the only well-conducted rat study which is similar to GLP. However, EUROTALC want to highlight that RIVM erred by disregarding the Oberdorster critical appraisal of the NTP study when interpreting the results in that study by not considering the real lung burden data.
The observed health effects are not related to intrinsic properties of talc, as it is further explained in our legal comments (below and in Attachment 2). These effects resulted from excessive lung overload, impairment of the lung clearing mechanism and subsequent sustained inflammation over time.
In the same time, a large number of valid human epidemiology studies demonstrate the absence of excess cancer risks in representative human cohorts. In particular, the recently updated Italian miner study (Ciocan, 2022) concluded that talc does not pose additional risk for lung cancer based on human monitoring data from more than 1000 miners over a timespan of up to 74 years. These results question both the outcome and relevance of animal data on talc inhalation to humans.
IARC monograph (volume 93) assessed all available studies (including NTP 1993 and Oberdorster 1995) in 2010 and provided the following evaluation and rationale:
• Cancer in humans: "There is inadequate evidence in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibres."
• Cancer in experimental animals:" There is limited evidence in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibres."
• Overall evaluation: "Inhaled talc not containing asbestos or asbestiform fibres is not classifiable as to its carcinogenicity (Group 3)"
IARC's conclusions should be better be taken into account, in particular because no new data has been generated since 2010, except the Italian epidemiology study (Ciocan, 2022) showing no association between exposure to talc and lung cancer and mesothelioma.
IARC will be re-evaluating the talc monograph (volume 93) in June 2024, and it may provide an additional scientific source for the CLH dossier and should be considered for drafting the final RAC opinion.

B. Scientific comments
A team of scientific experts (<confidential>) have been mandated by EUROTALC to review the RIVM's CLH Report. Their conclusions are detailed in the Attachment 1 and can be summarised as follows:
The CLH Report proposes the following:
"Classification in Category 2 is based on limited evidence from human and/or animal studies and considered applicable for talc. Limited evidence of carcinogenicity (ovarian cancer) upon perineal use of talc in humans and limited evidence of lung tumours in one animal study (female rats; NTP carcinogenicity study) are available. Therefore, a classification in Category 2 is warranted" (p. 124).
This proposed classification mixes two sites – lung and ovary – and two different exposure routes, inhalation and perineal respectively.
☐ The lung tumors in rodents were observed after inhalation exposure; however, the NTP study (1993) used very high concentrations of micronized talc that caused excessive lung overload, and therefore are not considered relevant to carcinogenic hazard to humans (Oberdorster, 1995) as the clearance mechanism has been significantly impaired. More so,

the observed effects are triggered by a so-called particle related effect rather than an intrinsic property of talc.
No excess in lung cancer or mesothelioma was found in 5 human epidemiological studies among 4,200 occupationally exposed talc workers during more than 70 years follow -up (See Appendix B in Attachment 1).
☐ The only available animal study pertaining to the potential risk of ovarian cancer after perineal application (Keskin et al., 2009), while not a full two-year bioassay study, found no evidence that perineal application could lead to reproductive tumors in rats.
None of the four cohort studies available on perineal use of talc and ovarian cancer demonstrated any clear or consistent increased risk of ovarian cancer, regardless of the possible (and some irrelevant) claimed study weaknesses.
The experts mandated by EUROTALC conclude that the RIVM's CLH report's summary fails to support its proposed classification of a suspected human carcinogen. Given:
• the lack of carcinogenicity induced by talc in mice (or other animal species than female rats) or via other exposure routes;
• no evidence of lung cancer is demonstrated in epidemiological studies in talc workers and;
• there is little if any reliable evidence for affirmatively and validly classifying talc as a human carcinogen based on epidemiological studies investigating ovarian cancer with any level of confidence. The arguments raised to discount the strong negative findings from the four cohort studies – combined with the thin and uneven scrutiny of the case-control studies, including the nearly universal dismissal of recall bias as a key threat to validity – combine to suggest that this unstructured RIVM review is unreliable and possibly biased.

C. Legal comments
A legal opinion has been sought from Mayer Brown Europe-Brussels LLP (see Attachment 2) which concludes that the RIVM's CLH report fails to establish that the proposed CLH of talc as Carcinogen 2 (by inhalation) meets the applicable CLP classification criteria provided in Article 36(1)(c) and Section 3.6 of Annex I on carcinogenicity.
First, the CLH Report does not demonstrate that talc "has "an intrinsic property to cause cancer" as required for its classification as Carcinogen pursuant to, in particular, Section 3.6.1.1 and Section 3.6.2.2.1 of Annex I to the CLP. The EU Court has recently clarified the scope and meaning of the term "intrinsic property" in the TiO2 Judgement (Joined Cases T-279/20, T-283/20, T-288/20) – which annulled the CLH of TiO2 as Carcinogen 2 - saying that it "must be interpreted in its literal sense as referring to the "properties which a substance has in and of itself" (para138). Strong analogy can be drawn between the findings in the TiO2 Judgment and the proposed CLH for talc.
The EU Court made few additional rulings and bought further clarifications that are all also very relevant for the analysis of the proposed CLH for talc. In particular:
For the carcinogenicity hazard class in particular, the Court found that the CLH of a substance as carcinogenic "can be based only on intrinsic properties of the substance which determine its intrinsic capacity to cause cancer, that is to say, the specific properties of the substance which determine its capacity to cause cancer on its own" (para 142, emphasis added).
According to the Court, the interpretation of "intrinsic property" is consistent with the aim and objectives of the CLH process in general, which is to determine the intrinsic properties of substances and communicate the hazards identified, and also with the Globally Harmonised System for the Classification and Labelling of Chemicals ("GHS") criteria. The GHS criteria distinguish between intrinsic properties that relate to the CLH process and properties that are not specific to the substance. This means that not any property would be "intrinsic" and could justify its classification as carcinogen based on Section 3.6.1.1 of Annex I.
Moreover, the Court specified that the intrinsic property of a substance should be assessed "regardless of […] the possible levels of exposure to the substance" and the "specific circumstances of use" of the substance (para 141, emphasis added).

The RIVM's CLH Report fails to demonstrate that talc has the "intrinsic property" to cause cancer "on its own". It identifies a few animal studies (among which only the NTP 1993 Study being considered as well conducted and similar to guidelines), where some carcinogenic effects were observed, but does not establish a causal link between these effects with the specific chemistry of talc. In other words, it fails to demonstrate that the carcinogenic effects result from the intrinsic properties of talc (particles), i.e. properties that talc (particles) has "in and of itself", and are not merely the result of other properties or external circumstances that are not "specific" to talc, such as the accumulation of poorly soluble particles in the lungs and the related sustained lungs inflammation.
Second, an additional argument in support of the lack of the intrinsic property of talc to cause cancer is based on the identified mode of action (MoA), which is based on the accumulation of talc particles, oxidative stress, inflammation and enhanced cell proliferation that eventually caused cancer.
That MoA is the same as the one described for TiO2.n the TiO2 Judgement the Court has analysed the RAC Opinion on TiO2 (https://echa.europa.eu/documents/10162/682fac9f-5b01-86d3-2f70-3d40277a53c2) – according to which the identified MoA of TiO2 "cannot be considered "intrinsic toxicity" in a classical sense [as] the deposited particles, but not solutes of TiO2 molecules can be assumed to be responsible for the observed toxicity" ¬- to say that this MoA "does not point to an intrinsic property of titanium dioxide particles to cause cancer" (par.157). The RIVM CLH Report repeatedly refers to the same MoA as was used in the TiO2 case, which further supports the contention that talc does not have the "intrinsic property" to cause cancer "on its own".
Therefore, in light of the TiO2 Judgement, the identified MoA further supports the contention that talc does not have the "intrinsic property to cause cancer" on its own but, instead, could result as toxic effect that is merely due to the accumulation of dust. This type of risks is not covered by CLP.
Finally, the RIVM CLH Report seeks to justify the acceptability of the main animal study used in support of the proposed CLH of talc (the NTP Study 1993) - despite of the lung overload and lungs clearance impairment observed in it - based on the so-called Morrow calculation. However, RIVM fails to identify and discuss the main elements and parameters that should be taken into account when applying the Morrow calculation, including, in particular, the specifics of the talc particles tested in the NTP Study 1993, their individual density that allow to calculate the related lungs burdens, etc.
This has also been analysed and confirmed in the TiO2 Judgment according to which "(i)t follows that particle density was an essential factor for the Morrow overload calculation adopted by the RAC and that that density could not, at the obvious risk of discrediting the results of that calculation, be presumed to be the density of the particles, whereas it was known that the nano-sized particles at issue formed agglomerates, that the agglomerate density was lower and that, consequently, the volume occupied by particles in the lungs was greater." (para 102).

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Attachments 1 and 2.zip

Date	Country	Organisation	Type of Organisation	Comment number
07.08.2023	Belgium	EFPIA (OT Task Force)	Industry or trade association	16
Comment received				
(1) Pheochromocytomas are known to be related to chronic pulmonary lesions (fibrosis and inflammation) and hypoxemia in inhalation studies with particulate compounds in rats (Ozaki et al. 2002). Pheochromocytoma is a rat-typical tumour observed in long-term				

animal experiments, with questionable relevance for human exposure (Greim et al., 2009). An extrapolation for human relevance cannot be as clearly supported, making the suggested classification a very precautionary assumption. It is unclear if the lung damage observed in the rat study as primary cause led to the formation of such cancers. Only female, not male rats were affected, and studies in mice and hamster were negative for tumour formation. Inhalation studies in rodents can overestimate carcinogenic potency (Borm & Driscoll, 2019) and there should be sufficient evidence for human relevance to warrant a classification as carcinogen.
(2) Lung tumour in female rats observed, may be considered particle related and not compound-related. Histopathological findings indicative of particle-related overload was observed in lungs (e.g. granulomatous inflammation, hyperplasia, interstitial fibrosis). Even though phagocytic activity of macrophages was not affected, this is not sufficient to exclude the overload phenomena.
(3) Any inhaled dust-and most substances for that matter, may cause inflammation and cell proliferation in the lung, possibly leading to tumor formation if the challenge is sufficiently strong and persistent to overcome the natural defenses of the animals under test. This condition implies the presence of a no-effect threshold at levels below which natural defenses remain functional to prevent tumor formation. In the NTP inhalation bioassays of talc invariably created lung overloads, thus making the interpretation of results quite problematic. Based on thorough review of the toxicologic literature on talc, it was concluded that there is no reason for concern for low-level uses of cosmetic talc (Carr, 1995). Thus, the lung tumor is due to lung overload and physical nature of talc rather than a chemically induced tumor through an intrinsic property.
(4) Further, there have been several studies of thousands of people who were exposed to talc on a daily basis—through their work mining and milling talc powder. These studies demonstrate that exposure to high levels of talc does not increase a person's risk of developing mesothelioma (https://www.factsabouttalc.com/studies). In addition, long term studies of hundreds of patients who have undergone pleurodesis showed no cases of mesothelioma.
(5) No other tumours were observed in rats, indicating that particles swallowed after inhalation and potential solutes of talc did not lead to further malignancies. It is therefore proposed, that for talc, similar to the EU opinion on titanium dioxide (EU Commission REGULATION (EU) 2020/217) deposited particles, but not solutes of talc, are assumed to be responsible for the observed toxicity in the lung and subsequent tumour development (chemical mechanism of action, see comment 13).
(6) Genotoxicity data indicated in the IARC, 2010 monograph (sister chromatid exchanges and DNA repair assay by Endo-Capron et al. 1993), gave negative results in vitro. Some studies listed in the ECHA report, summarize a possible inflammation and oxidative stress pathway in vitro leading to the carcinogenic action of talc, with haemolytic effects on cells demonstrated only at very high concentrations (compared to e.g., asbestos). In the Rodent Dominant Lethal Test (OECD 478) mentioned in the ECHA registration dossier for Talc, doses of 30 to 5000 mg talc/kg body weight showed no chromosome aberrations in the bone marrow and no dominant lethal mutations (ECHA, https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/18727/7/7/1). Lynch et al., 2022 concluded in their systematic review of animal and human data no mechanistic evidence of talc inducing pulmonary carcinogenesis (Lynch et al., 2022).
(7) Pharmaceutical or cosmetic grade talc when used appropriately in medicinal or cosmetic products does not cause cancer. With the mentioned animal studies with the oral route (ingestion), a classification seems unreasonable. It can be argued that the available animal data is not as reliable (only one dose tested, one study with 101 days duration), but overall, no evidence or hint for potential carcinogenic effects were found after oral administration up to 100 mg/day or 50 mg/kg/day. The current data set is not strong enough for a direct classification of carcinogenicity for the oral route.

(8) Epidemiology studies after oral exposure (Chang et al., 2019) could not establish a causal relation and a dose-response relationship between increased hazard ratio for stomach cancer and oral intake of talc preparations (Chinese Herbal medicine prescriptions since 2005 in Taiwan). Their results revealed significant findings at the medium dose group (6-21g talc intake), but not at the highest dose group (+21g talc intake). In addition, the confidence intervals (CI) were large and investigated population exposed to talc was small.
(9) The weight of scientific evidence does not support a causal association between talc for cosmetic use and ovarian cancer. In the area of ovarian cancer the most reliable data come from prospective cohort studies. Multiple prospective cohort studies show no association between perineal use of cosmetic talc and ovarian cancer. (Gertig, 2000; Houghton, 2014; Gonzalez, 2016 and O'Brien, 2020). While some case-control studies showed a statistically significant association between perineal talc use and ovarian cancer, the associations were weak (odds ratios or relative risks of approximately 1.3 based upon meta-analyses and pooled studies). The difference in results between the prospective cohort studies and the case-control studies may be due to known issues with case-control studies including recall bias, selection bias and confounding factors. Further, Goodman et al., 2020 concluded no evidence to support a causal association between perineal talc use and ovarian cancer (Goodman et al., 2020), based on weight-of-evidence from animal and human studies.
(10) Berge et al., 2018 showed the summary relative risk (RR) for use of genital talc and ovarian cancer was 1.22 [95% confidence interval (CI): 1.13-1.30]. The RR for case-control studies was 1.26 (95% CI: 1.17-1.35) and for cohort studies was 1.02 (95% CI: 0.85-1.20, Pheterogeneity=0.007). Serous carcinoma was the only histologic type for which an association was detected (RR: 1.24; 95% CI: 1.15-1.34). The authors clearly state in their conclusion that the ~20% increase in RR is only due to case-control studies and the serous histologic type of cancer. Prospective cohort studies are the preferred studies to minimize recall bias in case-control studies. Limitations of the cohort studies are the general minimal observations of ovarian cancer (ovarian cancer is not a common type of cancer), making it hard to determine an overall increased risk, if any. Similar findings and limitations were stated in Penninkilampi and Eslick, 2019: An association with ever use of talc was found in case–control studies (OR = 1.35; 95% CI = 1.27, 1.43), but not cohort studies (OR = 1.06; 95% CI = 0.90, 1.25). Overall, it can be concluded that additional and independent evaluation of experimental study quality and relevance is needed (e.g., study design, selection, recall, proxy response, health-worker effect, healthy worker survivor effect, confounding, misclassification), as well as evaluation of study methods (e.g., biases, statistical power) and how to extrapolate the findings in the epidemiology studies for each exposure route for classification.
(11) Pharmacopeial grade Talc complies with USP standards that (will) require strict testing for asbestos impurities via both X-ray diffraction (XRD) and Polarized Light Microscopy (PLM) method, achieving a limit of detection for asbestos fibers of 0.01% (update of USP-NF-1901 in Dec-2023). Detectable amounts of Asbestos warrant the talc to be "not pharmaceutical grade" and hence, are not in the scope of this assessment report. Additionally, ECHA defines the characteristics of Talc as "non-asbestiform talc", though study data with relevant impurities (e.g., asbestos) were evaluated in the data set. The purity and particle size of the used talc per study should always be available/mentioned for a reliable assessment and conclusion.
(12) Talc as food additive – E553b – underwent extensive assessments and regulatory approvals (e.g., EFSA, FDA). As antiacid, magnesium trisilicate, is used in daily oral doses of 4g/person per day (EFSA, 2018). Definitive data on carcinogenicity for talc was lacking, but subacute toxicity, genotoxicity and developmental toxicity studies showed no adverse effects for talc (studies in mice and rats, highest dose tested up to 1,600 mg/kg bw per day) (EFSA, 2018).
(13) Chemical crystalline structure of talc/talcum vs. fine powder of magnesium trisilicate; secondary carcinogenicity mechanism due to pro-inflammatory effects (oxidative stress) due to physical features of talc.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Occ Tox TF Talc 07-August 2023_Comments_final.pdf

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	United States of America	Essential Minerals Association	Industry or trade association	17

Comment received

please see the attached comments

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments of the Essential Minerals Association.pdf

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	Germany	<confidential>	Company-Downstream user	18

Comment received

We disagree with the classification. The effects seen upon repeated exposition of rats to talc are similar to the effects seen with TiO2. These effects have been already addressed by court ruling on TiO2 and identified as non-intrinsic and non-substance specific. It is generally known since a long time that persistant exposition to high dust levels can lead to cancer, if the dust levels are so high that lung inflammation cannot restitute but gets chronic (coal mine and quarry workers, farmers, millers, etc.) Therefore, the effects seen with talc are no "talc" effects, but could result from any high, persistant exposure to dust (like e.g. cellulose/hay dust in agriculture!)

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	Germany	Evonik Industries AG	Company-Downstream user	19

Comment received

Talc also does not “have an intrinsic property to cause cancer” as required for its classification as Carc. 2. Evonik industries is supportive of the “Eurotalc” comment laid out under the ‘hazard class carcinogenicity’ paragraph.

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	Germany	German Social Accident Insurance	National Authority	20

Comment received

Hinweise auf ein Krebsrisiko durch reine Talc-Expositionen in Konzentrationen, wie sie an Arbeitsplatz vorkommen, sind aus unserer Sicht nicht zu erkennen.
Eine rein formale Einstufung als Carcinogen 2, basierend auf einer tierexperimentellen Studie, bei der weibliche Ratten nach Exposition gegenüber sehr hohen Konzentrationen in wenigen Fällen Lungenkarzinome entwickelten, ist aus unserer Sicht nicht schlüssig. Die Relevanz dieser Beobachtung für den Menschen aufgrund gleichzeitiger systemisch toxischer Effekte ist bei den außergewöhnlich hohen Konzentrationen zu hinterfragen.
Beim Menschen wurden insgesamt keine vermehrten Lungentumore oder Mesotheliome nach reiner Talc-Exposition beobachtet. Ob Ovarialkarzinome, die in einigen Studien vermehrt nach perinealer / genitaler Anwendung Talc-haltigen Puders beschrieben wurden,

tatsächlich kausal mit Talc an sich zusammenhängen, ist ebenfalls fraglich. Mechanistisch gibt es keine klaren Hinweise auf eine genotoxische, aber auf eine mögliche inflammatorische Wirkung von Talc.

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	United States of America	<confidential>	Company-Downstream user	21

Comment received

see attached document

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Talc letter_Final 17Aug2023.pdf

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	Germany	KRAIBURG TPE GmbH & Co KG	Company-Downstream user	22

Comment received

Identification of the substance (page 1, table 1): The identification of talc resulted in a misclassification of the substance. Asbestos is not talc. The classification of the materials used is based on the fact that the materials do not consist of pure talc but of a mixture of talc and other materials (page 2 table 2). Here it can be assumed that the talc is additionally contaminated with asbestos, which leads to the significantly higher classification of the pure talc.
Asbestos is not listed as an impurity in talc, resulting in a misclassification (page 2 Table 3).

Toxicokinetic data taken into account are based on severely outdated data and additionally rely in part on tested material of which the purity is unknown. Therefore, it is difficult to assess whether the toxicological effects observed are actually attributable on talc or are present due to an impurity (page 8 following, table 8).
The studies regarding the carcinogenicity of talc are based on equally outdated studies (page 13 following) In addition, it is evident that talc contamination in these studies is partly of known and partly of unknown origin. Therefore, it cannot be safely assumed that the results of the studies are attributable on talc. Based on the recent United States court ruling against Johnson & Johnson for asbestos-contaminated baby powder and the related investigations, in this case cancer is attributed to asbestos contamination of talc rather than to talc itself. As it is believed to be the case for another ~38.000 cases. The same rationale cannot be excluded and should therefore be taken into account for the studies cited in the present proposition of a harmonized classification of talc as suspected to causing cancer.
Animal studies show that the main exposure is via inhalation, so differentiation in use must be made. Cosmetic products and their application differ fundamentally from industrial applications and their routes of exposure.
In addition, many of the studies cited are based on health data collected from mine workers. It should be borne in mind that at the time of exposure of the workers concerned, no or only minor occupational health and safety measures were in force. Therefore other factors that contribute significantly to the health status of the workers, should have been taken into account in the studies cited, but were not.
A clear differentiation between talc and asbestos must be made in order to classify talc correctly, and this is not sufficiently possible on the basis of the available data.

Therefore, KRAIBURG TPE GmbH & Co KG does question the rationale and the proposition

for harmonized classification of talc as a suspected carcinogen in whole. Placing the harmonized classification in the way proposed is seen to be over exaggerated.

Date	Country	Organisation	Type of Organisation	Comment number
17.08.2023	Belgium	Cosmetics Europe	Industry or trade association	23

Comment received

Talc particles were found in the uterus and the ovaries upon perineal application in multiple studies.

The references cited in the CLH (p.14; Wehner 2002; Whysner and Mohan, 2000) that claim retrograde transport of talc do not support the allegation. The contents of the references are either counter to the allegation or they are irrelevant to it.

In relation to the mentioned report, we have identified critical points that we would like to highlight and discuss in detail (page reference indicated in parentheses).

In particular, based on the following elements, we believe that the classification of talc as a Category 2 carcinogen by inhalation is not justified.

The most impactful evidence, which weighs in the proposal for classification, is derived from animal studies.

1. Animal Studies: Key Factor in Suspecting Carcinogenicity and Classification. Conclusions of the CLH Report for Category 2 Classification (p.113).
The CLH report highlights that the Category 2 classification is based on the NTP study, which provided evidence of carcinogenicity in female rats.

"Classification in Category 2 is based on limited evidence from human and/or animal studies and considered applicable for talc. Limited evidence of carcinogenicity (ovarian cancer) upon perineal use of talc in humans and limited evidence of lung tumours in one animal study (female rats; NTP carcinogenicity study) are available. Therefore, a classification in Category 2 is warranted."

In summary, animal studies are crucial for the classification of talc as a Category 2 carcinogen by inhalation, with the pivotal study being the 1993 study conducted by NTP (National Toxicology Program).

2. Summary of the study-NTP (1993)- 1.1.1.1 for rats and 1.1.1.2 for mice [https://ntp.niehs.nih.gov/publications/reports/tr/400s/tr421]

1. Groups of 49 or 50 male and 50 F344/N female rats were exposed to aerosols of 0, 6, or 18 mg/m3 talc until mortality in any exposure group reached 80% (113 weeks for males and 122 weeks for females)
2. Groups of 47 to 49 male and 48 to 50 female B6C3F1 mice were exposed to aerosols containing 0, 6, or 18 mg/m3 talc for up to 104 weeks.

Under the conditions of these 2 inhalation studies, there was some evidence of carcinogenic activity of talc in male F344/N rats based on an increased incidence of benign or malignant pheochromocytomas of the adrenal gland. There was clear evidence of carcinogenic activity of talc in female F344/N rats based on increased incidences of alveolar/bronchiolar

adenomas and carcinomas of the lung and benign or malignant pheochromocytomas of the adrenal gland. There was no evidence of carcinogenic activity of talc in male or female B6C3F1 mice exposed to 6 or 18 mg/m3.

Regarding the rat model, certain concerns have been raised by the NTP scientists, as documented in the review written by <confidential> and colleagues, who worked at the National Institute of Environmental Health Sciences and the National Toxicology Program until 2007 [Maronpot RR, Nyska A, Foreman JE, Ramot Y. The legacy of the F344 rat as a cancer bioassay model (a retrospective summary of three common F344 rat neoplasms). Crit Rev Toxicol. 2016 Sep;46(8):641-75. doi: 10.1080/10408444.2016.1174669. Epub 2016 Jun 9. PMID: 27278595; PMCID: PMC5020328.]

This review explains the reasons behind the NTP's decision, after five decades of studies that led to the creation of the world's largest cancer bioassay database, to change the rat model used in their toxicity and carcinogenicity studies, transitioning from F344 rats to Wistar rats and ultimately to Sprague–Dawley rats (King-Herbert & Thayer 2006; King-Herbert et al. 2010). Since NTP's toxicity and carcinogenicity testing practices have often set the standard for other investigators, it is unlikely that the F344 rat will be widely used in future carcinogenesis bioassays.
Regrettably, the NTP's experience over time revealed significant health challenges within the F344/N rat strain, affecting the integrity of certain organs and the animals' lifespan. Due to these and other health issues, the NTP made the decision to transition to a more suitable rat strain for their toxicity and carcinogenicity studies (King-Herbert et al. 2010).
Specifically, we draw attention to three cancers that are notably prevalent in the F344/N rat strain: mononuclear cell leukemia (MNCL) and Leydig cell tumours (LCTs) exhibit high background incidence, with MNCL's incidence varying considerably. The exceptionally high spontaneous incidence of LCT renders this strain unsuitable for reliably predicting potential testicular carcinogenic effects. tunica vaginalis mesothelioma (TVM) is infrequently observed in rat carcinogenicity studies but is unique to the F344 rat, showing a biologically plausible connection to the elevated background incidence of LCT.

Cited from the review:
“Given their high spontaneous background incidence and species-specific biology, we contend that MNCL and LCT, along with TVM responses, in F344 rat carcinogenicity studies are inappropriate tumour types for human health risk assessment and lack relevance in predicting human carcinogenicity.”

In the NCT 1993 study on talc, it was observed that talc caused tumours of a different type compared to the ones that led to the decision of abandoning the F344 rat model. Nonetheless, it is noteworthy that this fact of changing the model raises a reasonable doubt about the reliability and consistency of the data obtained from this particular rat strain. It is essential to consider that the NTP, which has operated the largest and most comprehensive cancer bioassay database in the world, made a drastic decision to transition from using F344 rats to Wistar rats and subsequently to Sprague–Dawley rats in their toxicity and carcinogenicity studies (King-Herbert & Thayer 2006; King-Herbert et al. 2010). Such a profound shift in their experimental model highlights the uncertainty surrounding the tumour responses observed in the F344 rat strain, which had been previously regarded as a standard model for carcinogenesis studies.

The decision to change the rat strain after five decades of extensive research brings into question the suitability and generalizability of the findings obtained from the F344 rats in other carcinogenesis bioassays. Researchers and investigators may now question whether the observed tumour responses in F344 rats can reliably represent potential human health risks associated with various substances. As a result, the confidence in the data obtained

from this rat strain may be diminished, leading to potential implications for future research and risk assessments.

It is essential for scientific investigations to prioritize data reliability and consistency, especially when making significant decisions based on experimental outcomes. The NTP's shift to alternative rat strains for their studies indicates that the reliability of F344 rat data for predicting human health risks may have become less assured. This warrants a careful re-evaluation of the data obtained from the F344 rats and highlights the need for further research and consideration of alternative animal models to ensure robust and accurate toxicological and carcinogenicity assessments.

Considering that the reason for discontinuation of the F344/N rat model was the abnormal development of tumours other than mesothelioma, specifically mononuclear cell leukemia (MNCL) and Leydig cell tumours (LCTs), we conducted further investigation to confirm the unreliability of the portion of the study conducted using the F344/N model. Our objective was to examine whether specific gene mutation patterns underlying the development of LCTs and MNCL could serve as potential indicators of "false positives" related to mesothelioma.

To determine the suitability of F344 rats as a model for lung mesothelioma, we undertook an investigation into shared mutated genes between lung mesothelioma, Leydig cell tumours (LCTs), and mononuclear cell leukemia (MNCL), commonly known as large granular lymphocytic (LGL) leukemia.

Our methodology involved referencing mutated genes linked to lung mesothelioma and Leydig cell tumours (LCTs), as well as mononuclear cell leukemia (LGL), with an emphasis on identifying overlapping genetic mutations. The comprehensive mutation dataset for mesothelioma was sourced from COSMIC, the Catalogue of Somatic Mutations in Cancer, renowned as the most expansive repository of curated somatic mutation information pertaining to human cancers. The aim of the COSMIC was to provide an overview of the data's structure, content, and breadth, facilitating your navigation of COSMIC and optimizing its utility for your research requirements (https://cancer.sanger.ac.uk/cosmic).

Initiating our exploration, we conducted a review of key mutated genes in LCTs (DOI: 10.3389/fonc.2020.00152) and LGLs (http://dx.doi.org/10.1634/theoncologist.2020-0110). This endeavour revealed a subset of genes that exhibited mutations in both mesothelioma (detailed in Table 1) and either LCT or LGL. Specifically, the implicated genes for LGL encompass PTPRT and PTPN14, while DICER1 and CDC27 were identified for LCT. Notably, DICER1 (the predominant gene found mutated in LCT) emerged as one of the top 20 most frequently mutated genes in lung mesothelioma, as illustrated in Figure 1.

By identifying overlapping patterns of mutations in LCTs, LGL leukemia, and lung mesothelioma, our findings strongly suggest that F344 rats are an unsuitable model for this particular cancer.

Figure 1. the top 20 most frequently mutated genes in lung mesothelioma
[see the figure in the enclosed pdf]

3. Conclusions

In light of the aforementioned information, we believe that the study considered pivotal for the classification of talc as a Category 2 carcinogen by inhalation is neither reliable nor relevant. This is because the same authoritative source (NTP) has identified significant limitations arising from the use of a specific rat strain (F344N), which has since been replaced. These limitations may explain the apparent contradictions within the study itself

(where no effects are observed in other mouse strains) and the more significant contradiction with clear and reassuring epidemiological data that exclude any correlation between talc inhalation and the development of mesothelioma.

Therefore, we consider the proposal to classify talc as a Category 2 carcinogen by inhalation to be unsubstantiated and not supported by the available evidence.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cons Talc comments on Talc CLH report_CE-Talc-23-0010_final.pdf

Date	Country	Organisation	Type of Organisation	Comment number
17.08.2023	Sweden	KTF Organisation	Industry or trade association	24

Comment received

Talc is used in many types of chemical products such as paint and plasters. A Carc cat. 2 and STOT RE 1 classification will have a considerable effect on the continued use of talc due to market requirements and expected future regulation aimed at restricting substances on a hazard-based approach. Considering this we as an industry want to stress the importance of a sufficiently well-grounded decision regarding the classification. We are concerned that an important part of the evidence relies of the same principle as in the case of titanium dioxide where the issue of "intrinsic properties" are now under scrutiny in a legal process.

We are also concerned that the form of the substance has not been taken into account as the proposed classification is not likely to be relevant when used in wet paint.

Date	Country	Organisation	Type of Organisation	Comment number
15.08.2023	Germany	Eurocolour e.V.	Industry or trade association	25

Comment received

The shown evidence is no enough to justify a Carc. 2 classification. Valid human epidemiology studies which show that talc is not cancerogen are not respected.
IARC and EPA concluded that Talc is no carcinogen but contaminants like silica or asbestos are.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Position Talc.pdf

Date	Country	Organisation	Type of Organisation	Comment number
14.08.2023	Germany	<confidential>	Company-Downstream user	26

Comment received

Talc does not have an "intrinsic property causing cancer" as required for classification as a carcinogen under section 3.6.2.2.1 of Annex I to CLP. In the titanium dioxide judgment, the term "intrinsic property" was clarified to mean "to be interpreted in its literal sense, in the sense that it refers to the 'properties that a substance has in and of itself'" (para. 138). An intrinsic property is one that can be specifically attributed to a substance and does not apply, for example, to a whole group of substances. The judgment also explained that "the harmonized classification and labelling of a substance as carcinogenic can only be based on

intrinsic properties of the substance that determine its ability to cause cancer, i.e., on the specific properties of the substance that determine its ability to cause cancer by itself" (para. 142). The CLH report does not demonstrate that talc has the intrinsic property of causing cancer on its own. The submitter of the dossier, RIVM, cites some animal studies in which evidence of carcinogenic effects was observed, but does not establish a causal relationship with the specific chemistry of talc. Thus, there is insufficient evidence to support a suspicion (level of evidence required for carcinogen Cat. 2) that talc in and of itself has such a property.

Date	Country	Organisation	Type of Organisation	Comment number
14.08.2023	Germany		MemberState	27
Comment received				

The DE CA supports the proposed classification of Talc as Carc. 2 (H351).

Nevertheless, the DE CA notes that the mode-of-action leading to carcinogenesis remains uncertain and further, more reliable data are needed for a stricter classification (i.e. Carc. 1B). Based on the available data, the mode of action cannot unambiguously be determined, as an overload mechanism cannot fully be excluded. However, in weight of evidence of the observed carcinogenic effects in the rat lungs and the additional indications from epidemiological data regarding the induction of ovary cancer, it is concluded that classification of talc as Carc. 2 (H351) is warranted.
Based on both, the effects observed in rats after inhalation exposure and in humans after perineal exposure, limiting the classification to a specific route of exposure is not indicated. The DS proposes, together with the classification of talc, the inclusion of a specific note (modified Note V) for the endpoint carcinogenicity. It is proposed that if the substance is placed on the market in asbestiform (according to the WHO criteria for fibres), the hazardous properties should be assessed according to Title II of the CLP Regulation to determine whether a higher category should be applied. This is generally supported. However, it may be considered to set a concentration limit (as it was proposed by RAC for other substances, e.g. MWC(N)T), for the amount of fibres that are contained in talc not containing asbestos or asbestiform fibres, as it cannot be excluded that minimal amounts of asbestiform talc will be present along with other morphologies of talc.

With respect to the alleged association between the perineal use of talc and ovarian cancer, the strengths and weaknesses of the available epidemiological studies are well presented and support limited evidence of a carcinogenic potential. However, the discussion of the potential mode(s) of action concerning the formation of ovarian cancer could be elaborated a bit more instead of just mentioning inflammation, oxidative stress and increased cell replication. The dossier submitter might consider to further expand on the mode of action for ovarian cancer by e.g. considering studies on talc/particle migration in the genital tract or on the availability of talc particles in ovarian tissues after perineal talc use as has been presented by CIR in 2013 (CIR, 2013: Safety assessment of Talc as used in Cosmetics, Final Report April 12, 2013, available at https://www.cir-safety.org/supplementaldoc/safety-assessment-talc-used-cosmetics-0; apparently the basis for the publication by Fiume et al., 2015). Limiting biological plausibility to inflammation, oxidative stress and increased cell replication only is considered as weak argumentation.

Date	Country	Organisation	Type of Organisation	Comment number
13.08.2023	Bulgaria	REACH 2008 Ltd.	Company-Importer	28
Comment received				

Comparison with the CLP criteria
The April 2023 CLH Report proposes the following: "Classification in Category 2 is based on limited evidence from human and/or animal studies and considered applicable for talc. Limited evidence of carcinogenicity (ovarian cancer) upon perineal use of talc in humans and limited evidence of lung tumours in one animal study (female rats; NTP carcinogenicity study) are available. Therefore, a classification in Category 2 is warranted" (p. 113).
This classification mixes two sites – lung and ovarian – and two different exposure routes. The lung tumors in rodents were observed after inhalation exposure; however, as stated in Section 3, the NTP study used very high concentrations of micronized talc that caused lung overload and therefore are not considered relevant to carcinogenic hazard to humans(Oberdorster, 1995). The only available animal study pertaining to the potential risk of ovarian or endometrial cancer after perineal application (Keskin et al., 2009), while not a full two-year bioassay study, found no evidence that perineal application could lead to ovarian or endometrial tumors in rats.
It is debatable whether in fact there is "Limited evidence of carcinogenicity (ovarian cancer) upon perineal use of talc in humans" as the epidemiological studies highlighted to support this notion are highly susceptible to post-diagnosis rumination, recall and reporting bias, among other potential biases (e.g., selection bias, which can work in tandem with the former biases, i.e., those that truly believe that talc caused their ovarian cancer are more likely both to volunteer to participate in a study and to more fully or even exaggeratedly report historical exposures relative to control participants reached by random phone dialing. Several case-control studies examine the potential for this bias with some evidence of it occurring, despite the IARC Monograph 93 committee discounting the possibility of bias due to public awareness of the 'hypothesis' – at least up to the time of that evaluation. The CLH report should have acknowledged that the IARC Committee recognized the potential for the bias to increase over time, yet they give no serious consideration to this probability (for which there is clear evidence).
That a robust body of cohort studies is available that eliminates reliance on post-diagnosis recall of historical talc exposures, and that this body of evidence paints a different picture cannot be dismissed (or downplayed with gratuitous criticisms). Had these studies never existed, one might have been on firmer ground to speculate regarding "limited" human evidence. However, now that robust systematic review methods and guidance are readily available, it is not necessary to address every weak statistical association (i.e., "noise") form a diverse body of studies as a "real possibility" when scientifically stronger signals (i.e., good-quality, negative studies) are available.
Ultimately, integrating quality epidemiological evidence demonstrating no causal associations with that from animal studies failing to demonstrate carcinogenicity – other than at overload doses (and possibly particle size distributions smaller than found in industrial and cosmetic talcs) – and weak hypotheses regarding MOA, consistently demonstrates the lack of talc carcinogenicity at human-relevant doses (including those sustained by talc miners and millers).
Conclusions
Overall, Dutch National Institute for Public Health and the Environment (RIVM) did not conduct a transparent, objective and comprehensive review of the body of epidemiological, animal, or mechanistic evidence on talc and carcinogenicity. There is no formal or consistent assessment of methodological quality of individual studies, nor any sound integration of the evidence that appropriately considers the impact of study biases (especially rumination and recall bias in some case-control studies) and other methodological limitations. Recent reviews by Borm (2023), Lynch 24 et al. (2022) and Lynch et al. (2023) all indicate that the CLH report deviates from standard critical review and synthesis methods leading to unsubstantiated overstatements of the carcinogenicity of talc in humans and the proposed CLH classification of talc as CARC 2.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Final <confidential>_Combined Comments on Proposed CLH_25072023.pdf

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2023	Belgium	EUROTALC	Industry or trade association	29
Comment received				
To complement our previous comments, we provide - in attachment - the agglomerate density study reports for 9 talc samples ECHA note – An attachment was submitted with the comment above. Refer to public attachment Agglomerate density study reports_public.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Agglomerate density study reports_Confidential.zip				

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2023	Belgium	EUROTALC	Industry or trade association	30
Comment received				
In their proposal for harmonised classification and labelling of talc from November 2022, the Dossier Submitter (DS) states: "No evidence of lung overload was thus found" with reference to both dose groups of 6 and 18 mg talc/m³ (RIVM, 2022), respectively, in the NTP (1993) study." Based on talc lung burdens after 23 - 24 months, the DS calculated an alveolar macrophage (AM) loading of approximately 50 % for rats exposed to 18 mg/m3, thereby erroneously applying the relative density of talc of 2.7 instead of the agglomerate density. The attachment named 'Final Report Talc AM Overload Calculation EBRC August 2023' provides the correct calculations for the AM loading by considering a range of experimentally determined agglomerate densities for 9 different commercial grades of talc, assumed to represent the range of talc products as placed on the market. In addition, inconsistencies in the NTP study are described and some potential consequences on the overall study outcome are discussed. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Final Report Talc AM Overload Calculations EBRC August 2023.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2023	Germany	Epple Druckfarben AG	Company-Downstream user	31
Comment received				
The CLH report does not demonstrate that talc has the intrinsic property of causing cancer on its own. The cited animal studies show evidence of carcinogenic effects, but do not relate it to the specific chemistry of talc. This situation is comparable to the titanium dioxide case.				

Date	Country	Organisation	Type of Organisation	Comment number
10.08.2023	Germany	German Paint and Coatings Association	Industry or trade association	32

		(VdL)		
Comment received				
Proposed classification is not based on an intrinsic property of the substance: Talc does not have an "intrinsic property causing cancer" as required for classification as a car-cinogen under section 3.6.2.2.1 of Annex I to CLP. In the titanium dioxide judgment, the term "in-trinsic property" was clarified to mean "to be interpreted in its literal sense, in the sense that it refers to the 'properties that a substance has in and of itself'" (para. 138). An intrinsic property is one that can be specifically attributed to a substance and does not apply, for example, to a whole group of substances. The judgment also explained that "the harmonized classification and label-ling of a substance as carcinogenic can only be based on intrinsic properties of the substance that determine its ability to cause cancer, i.e., on the specific properties of the substance that determine its ability to cause cancer by itself" (para. 142). The CLH report does not demonstrate that talc has the intrinsic property of causing cancer on its own. The submitter of the dossier, RIVM, cites some animal studies in which evidence of carcinogenic effects was observed, but does not establish a causal relationship with the specific chemistry of talc. Thus, there is insuffi-cient evidence to support a suspicion (level of evidence required for carcinogen Cat. 2) that talc in and of itself has such a property. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2023-08-10_VdL-Position Talk_eng_final.pdf				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
07.08.2023	Belgium	EUROTALC	Industry or trade association	33
Comment received				
III. HAZARD CLASS STOT-RE 1 A. Scientific comments A team of scientific experts (<confidential>) have been mandated by EUROTALC to review the RIVM's CLH Report. Their conclusions are detailed in the Attachment 1 and can be summarised as follow: While the review concluded that pulmonary effects may at first glance appear sufficient for a STOT-RE1 classification, the Dossier Submitter has not established that these effects are specific to talc. The observed health effects are likely to be non-specific particle effects that could be common to any poorly soluble low toxicity particles (also called PSLTs) rather than a specific effect resulting from the intrinsic properties talc's particles. The TiO2 Judgement is also relevant in the context of a STOT RE classification, as it is explained in the legal comments (below and in Attachment 2). B. Legal comments A legal opinion has been sought from Mayer Brown Europe-Brussels LLP (see Attachment 2) which concludes that the RIVM's CLH report fails to establish that the proposed classification of talc as STOT-RE1 (lung) meets the CLP requirements. In particular, Section 3.9.1.1 of Annex I to the CLP defines STOT RE as "specific toxic effects on target organs occurring after repeated exposure to a substances or mixture". Taking into account the literal interpretation of the word "specific" and the context and purpose of the relevant rules, "specific toxic effects" must be understood as effects are distinctive and characterizing of the classified substance (talc). In other words, that the toxic effects are "specific" in the sense that are the result of (or are sufficiently related to)				

the particular individual chemistry of the classified substance.
More specifically, in light of the TiO2 Judgement, "specific effects" could be regarded as those resulting from the substance's "intrinsic property". Although the wording "intrinsic property" does not explicitly appear as such in the STOT RE hazard class – unlike in the carcinogenicity hazard class – this concept is still relevant for a STOT RE classification.
As the EU Court held in the TiO2 Judgement, the interpretation of the concept of "intrinsic property" is consistent with the aim and objective of the CLH in general, which is to determine the intrinsic properties of substances that must lead to their classification as hazardous products (paras 28,33, 135 and 139) and the GHS criteria that distinguish between intrinsic properties to which the CLH process relates and other properties not specific to the substance (para 140). Therefore, the Court's findings in relation to the concept of "intrinsic properties" are relevant to the CLH process in general, including the STOT RE hazard class, and are not limited to (some) hazard class(es).
The RIVM's CLH Report fails to characterise a "specific" target organ toxicity and demonstrate that the toxic effects observed are "specific" to talc It In particular, it fails to (sufficiently) characterise the talc particles (form, size, shape, etc.) and their particular chemistry to establish a relationship between them and the (alleged) toxic effects produced. It fails therefore to demonstrate how the alleged toxic effects produced are related specifically to talc (particles), and are not, for example, only the common result of the accumulation of an excessive load of particles in the lungs, a phenomenon that would be common to, and shared by, any poorly soluble low toxicity substance with the potential to accumulate in the lungs.
Finally, the NTP 1993 study that is used to support the STOT RE 1 classification cannot justify a classification in category 1. In particular, the CLH Reports notes that in that study effects were observed in female rates at the highest dose level that was "possibly above the maximum tolerable dose". Similarly, impaired lung function in both sexes was observed at this highest dose. Therefore, these effects observed at concentrations above the maximum tolerable level cannot support a classification in category 1 that requires effects at "generally low exposure concentrations" (Table 3.9.1 of Annex I to the CLP). This is further indicated by the guidance values that point to a classification in category 2 (CLH Report, page 154).
The dose/concentration at which effects are produced must be considered in the context of a STOT RE classification, because "all substances are potentially toxic, and what determines the toxicity is a function of the dose/concentration and the duration of exposure", (Section 3.9.2.9.1 of Annex I to the CLP) and repeated dose animal studies are precisely "designed to produce toxicity at the highest dose used" (Section 3.9.2.9.2 of Annex I to the CLP).

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Attachments 1 and 2.zip

Date	Country	Organisation	Type of Organisation	Comment number
07.08.2023	Belgium	EFPIA (OT Task Force)	Industry or trade association	34

Comment received

(1) Observed health effects after inhalation exposure to talc, arise from non-specific particle effects rather than intrinsic compound-specific (chemical) toxicity.
(2) CLP criteria and classification should be based on the intrinsic, hazardous and toxic properties of a substance.
(3) The classification proposal is rather based on the resulting exposure to talc as dust (respirable particles, lung overload) than a specifically characterised target organ toxicity. Such effects can be observed with multiple, dusty and poorly soluble compounds (Study in

rats showed lung tumor in female rats at the highest tested doses, possibly above a maximal tolerable dose, see comments 2 and 3 in the carcinogenicity section).

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Occ Tox TF Talc 07-August 2023_Comments_final.pdf

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	United States of America	Essential Minerals Association	Industry or trade association	35

Comment received

please see the attached comments

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments of the Essential Minerals Association.pdf

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	Germany	<confidential>	Company-Downstream user	36

Comment received

We disagree with the classification. As mentioned above, material tested does not compare to material as placed and handled on the market. The effect level for the proposed classification is strongly dependent on the alveolar mass fraction of the talc and will be much higher in case of artificial aerosol dispersion (OECD 413) compared to normal use. Classification of such non-substance specific (but actually alveolar fraction dependent) effect is believed not possible according to the legal spirit of CLP regulation.

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	Germany	Evonik Industries AG	Company-Downstream user	37

Comment received

Repeated dose studies, in particular 90-day inhalation studies (OECD TG 413), are the basis for the determination of Specific-Target-Organ-Toxicity Repeated Exposure (STOT RE). Based on the results of these studies, a classification and labelling with STOT RE can be derived depending on the NOAEC (inhalation) derived for adverse effects on vital organs. For 90-day inhalation studies, the guidance values to assists experts in a classification process are 20 mg/m³ (STOT RE 1) and 200 mg/m³ (STOT RE 2). If adverse effects in inhalation studies occur, maintain or progress in the vital target organs below these concentrations, a classification with STOT RE 1 or 2 can be derived based on expert judgement.
The CLP Regulation (ECHA, 2017) requires particulate materials to be tested, i.e., the test '…shall be carried out on the substance…° as it "…is placed on the market and in which it can reasonably be expected to be used…' (Art. 8.6 CLP Regulation). Inhalation toxicity testing for regulatory purposes, however, is usually performed following OECD TG 413 (90-day subchronic inhalation toxicity study) (OECD, 2018). The actual guideline requires inhalation exposure of rats to particles with MMAD ≤ 2 µm. Therefore, against the regulatory requirement by CLP (ECHA, 2017), for aerosol generation in the inhalation studies, shear forces need to be applied to reduce the size of the particles as placed on the market to guideline required MMAD range. The reason is simply that only particles with a MMAD in the low µm range in a size of 1-4 µm are respirable for rats and deposited in the

alveoli at a considerable efficiency. Inflammatory changes can only occur when the particulate material reaches and is deposited in the alveoli. Only these deposited particles of respirable size trigger macrophage influx and inflammation to remove the foreign materials. This cleaning process is a non-specific to a certain substance (e.g., Talc) and is activated as soon as a foreign body (particle) has entered the lung.
It should be noted that, in accordance with Article 1(1) of Regulation No 1272/2008, the purpose of the CLP regulation is to ensure a high level of protection of human health and the environment as well as the free movement of chemical substances, mixtures and certain specific articles on the EU market. As stated in the Regulation, the objective of the CLP is to determine the intrinsic properties of the substances, which must lead to their classification as hazardous, so that the hazards posed by those substances (and mixtures containing such substances) can be correctly identified and notified.
Since the classification according to CLP is to be based on intrinsic hazards of a substance, the CLP is not an appropriate tool for the regulation of non-specific local lung effects caused by the physical properties of artificially generated respirable particulate materials. Based on the specific conditions of the OECD TG 413 test, a result, which triggers a STOT RE classification, can be generated for any particulate material, deposited as foreign bodies in the deeper parts of test animal (rat) lungs. Considering the above, Evonik Industries is convinced that a STOT RE 1 classification is not warranted.

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	United States of America	<confidential>	Company-Downstream user	38
Comment received				
see attached document ECHA note – An attachment was submitted with the comment above. Refer to public attachment Talc letter_Final 17Aug2023.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
18.08.2023	Germany	KRAIBURG TPE GmbH & Co KG	Company-Downstream user	39
Comment received				
none				

Date	Country	Organisation	Type of Organisation	Comment number
17.08.2023	Belgium	Cosmetics Europe	Industry or trade association	40
Comment received				
Throughout the CLH, there are non-clinical and epidemiology studies cited for which the purity of the talc is unknown. For those studies, the relationship of the adversity and/or severity to non-asbestos talc is in question. This is an inherent challenge with any case-control epidemiology study (and the many cited in the CLH) but was also noted for two non-clinical studies (Keskin et al., 2009; Hamilton et al., 1984) alleging adversity from "talc" exposure. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cons Talc comments on Talc CLH report_CE-Talc-23-0010_final.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
15.08.2023	Germany	Eurocolour e.V.	Industry or trade association	41
Comment received				
There is no evidence that the effect is specific for talc or not just particle related. The same wrong prinicple as for TiO2 is applied. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Position Talc.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
14.08.2023	Germany		MemberState	42
Comment received				
The DE CA supports the proposed classification of Talc for STOT RE 1 H372 (lungs) (inhalation). In accordance with the DS, the criteria for classification as STOT RE 1 H372, (lungs)(inhalation) are considered fulfilled based on the clear evidence of dose related effects in the lung observed in animal experimental studies. Effects included granulomatous inflammatory reactions leading to morphological changes (hyperplasia), fibrotic and proliferative lesions, and consequent impairment of lung function. In addition, a large data set of epidemiological studies demonstrating increased mortality due to non-malignant respiratory diseases (NMRDs), significant lung damage (pneumoconiosis and impaired lung function) and formation of fibrosis and granuloma (pleural abnormalities and) in the lungs is available, further supporting the proposed classification. The limitation of the classification to the inhalation route and the proposed GCL are supported as well.				

Date	Country	Organisation	Type of Organisation	Comment number
13.08.2023	Bulgaria	REACH 2008 Ltd.	Company-Importer	43
Comment received				
A. Scientific comments: A team of scientific experts (<confidential>) review the CLH report submitted by the Netherlands. Their conclusions are detailed in the Attachment and can be summarised as follow: While the review concluded that pulmonary effects were consistent with a STOT-RE1 classification, the TiO2 judgement of the General Court issued in November 2022 raised a strong awareness and debate that the STOT-RE classification in its current form is not adequate for low-toxicity particles (also called PSLTs). Observed health effects are likely to be non-specific particle effects rather than a specific intrinsic particle effect. In this evolving regulatory context, the STOT-RE classification should take into account the new interpretation of the legal criteria. B. Legal comments A legal opinion has been sought from Mayer Brown Europe-Brussels LLP which concludes that there is considerable doubt that the proposed classification of talc as STOT-RE1 (lung) meets the CLP requirements, especially in light of the interpretation of the General Court in the TiO2 Judgement				

The STOT RE hazard also requires that the substance has an "intrinsic property" to produce the alleged toxicity.
The Court in the TiO2 Judgement stated: "it should be noted, first of all, that it follows from [the CLP] that the aim of harmonized classification and labelling is to determine the intrinsic properties of the substances which must lead to their classification as hazardous products, so that the hazards of these substances (and of the mixtures containing them) can be correctly identified and notified" (par.135). Therefore, the intrinsic property concept underpins any classification for any hazard pursuant to the CLP.
Second, the talc CLH proposal does not characterise a "specific" target organ toxicity. Rather it merely refers to the effects resulting from the exposure to talc as a dust. The effects would be observed with any dust and/or by all the PSLT (poorly soluble low toxicity) particles - and are not specific to talc. The Dutch National Institute for Public Health and the Environment (RIVM) CLH report does not (sufficiently) identify and/or characterise the individual talc 'particles' in theavailable positive animal studies that produce the alleged toxicity. Therefore, Dutch National Institute for Public Health and the Environment (RIVM) does not establish a relation between the talc particles form, size, shape, etc. and the specific chemistry of talc – in a way to identify a toxicity that is "specific" to talc.
Finally, Section 3.9.2.9.1 of CLP states that "all substances are potentially toxic, and what determines the toxicity is a function of the dose/concentration and the duration of exposure". Results obtained in the conditions of (excessive) lung overload cannot be used for classification as STOT RE1 as they are above the appropriate levels of exposure one can take into account for this hazard class. In this respect, we note some contradictions in the talc CLH Report: according to RIVM, the NTP 1993 Study was not conducted in the conditions of excessive overload. However, the CLH report also says that the "lung tumours in female rats were observed at the highest dose level […] which was possibly above the maximum tolerable dose"

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Final <confidential>_Combined Comments on Proposed CLH_25072023.pdf

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2023	Belgium	EUROTALC	Industry or trade association	44
Comment received				
When using the right density, we demonstrate that the NTP study has been conducted in overload conditions for the high doses contrary to what the Dossier Submitter wrote in the CLH proposal. See attachment for details. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Final Report Talc AM Overload Calculations EBRC August 2023.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2023	Germany	Epple Druckfarben AG	Company-Downstream user	45
Comment received				
Again, the CLH report does not show that the toxicological effects are an intrinsic property of talc. Risk of inhalation at the manufacturing site is covered by mandatory dust limits at the workplaces.				

PUBLIC ATTACHMENTS

1. Comments of the Essential Minerals Association.pdf [Please refer to comment No. 3, 17, 35]
2. EUROTALC comments on the public consultation on the CLH Report on TALC final.zip [Please refer to comment No. 4]
3. EUROTALC comments on the public consultation on the CLH Report on TALC final.zip [Please refer to comment No. 5]
4. Talc letter_Final 17Aug2023.pdf [Please refer to comment No. 9, 21, 38]
5. Cons Talc comments on Talc CLH report_CE-Talc-23-0010_final.pdf [Please refer to comment No. 10, 23, 40]
6. Position Talc.pdf [Please refer to comment No. 25, 41]
7. Final confidential_Combined Comments on Proposed CLH_25072023.pdf [Please refer to comment No. 12, 28, 43]
8. Agglomerate density study reports_public.zip [Please refer to comment No. 29]
9. Final Report Talc AM Overload Calculations EBRC August 2023.pdf [Please refer to comment No. 30, 44]
10. 2023-08-10_VdL-Position Talk_eng_final.pdf [Please refer to comment No. 14, 32]
11. Attachments 1 and 2.zip [Please refer to comment No. 1, 15, 33]
12. Occ Tox TF Talc 07-August 2023_Comments_final.pdf [Please refer to comment No. 2, 16, 34]

CONFIDENTIAL ATTACHMENTS
1. Agglomerate density study reports_Confidential.zip [Please refer to comment No. 29]