Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Multi-Walled Carbon Tubes (synthetic graphite in tubular shape) with a geometric tube diameter range ≥ 30 nm to < 3 µm and a length ≥ 5 µm and aspect ratio ≥ 3:1, including Multi-Walled Carbon Nanotubes, MWC(N)T

EC Number: -
CAS Number: -

CLH-O-0000007108-75-01/F

Adopted

18 March 2022

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON MULTI-WALLED CARBON TUBES (SYNTHETIC GRAPHITE IN TUBULAR SHAPE) WITH A GEOMETRIC TUBE DIAMETER RANGE ≥ 30 NM TO < 3 MM AND A LENGTH ≥ 5 MM AND ASPECT RATIO > 3:1, INCLUDING MULTI-WALLED CARBON NANOTUBES, MWC(N)T

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: Multi-Walled Carbon Tubes (synthetic graphite in tubular shape) with a geometric tube diameter range ≥ 30 nm to < 3 µm and a length ≥ 5 µm and aspect ratio > 3:1, including Multi-Walled Carbon Nanotubes, MWC(N)T
EC number: -
CAS number: -
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Netherlands		MemberState	1
Comment received				
The similarity of certain types of MW-C(N)T to asbestos, both in terms of physicochemical properties (e.g., diameter, length, aspect ratio, rigidity, persistence) and adverse effects observed (i.e., mesothelioma and lung cancer) is cause for concern.				
Dossier Submitter's Response				
The applicability of the asbestos-like pathogenicity paradigm to certain MWCNT and the wealth of respective experimental evidence motivated this CLH proposal				
RAC's response				
RAC agrees with the DS, this is also clearly explained in the opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
02.09.2021	Belgium	Japan Business Council in Europe	Industry or trade association	2
Comment received				
Plese kindly refer our comment in the attachement. ECHA note – An attachment was submitted with the comment above. Refer to public attachment JBCE Input to Registry of CLH intention(MWCNT)-Final.pdf				
Dossier Submitter's Response				
We fully agree that "not every low diameter MWC(N)T is tangled and not every high diameter MWC(N)T is straight". However, this is not the argumentation presented in the				

report. The described mode of action in the report is not dependant on how tangled or straight a tube is. It is triggered by the rigidity of a tube, which by itself can be tangled or straight. The diameter of a tube is used here as a pragmatic surrogate parameter for fibre rigidity.

We also agree that synthesis conditions can influence the shape of a CNT. Arc discharge synthesis, being a high-temperature process, generally leads to highly ordered tubular graphene structures with low numbers of defects that exhibit straight tube geometries, whereas CVD processes at lower temperature and processes with irregular precursor supply tend to result in more defective tubular graphene structures. Such structural defects can lead to intrinsically curled or bent tubes.

Furthermore, we agree that entanglement is possible both for thin and thick CNTs, since thin and flexible CNTs may spontaneously entangle upon mutual contact in order to save surface energy during growth or processing. For thick and rigid CNTs, entanglement may occur under dense growth conditions either already during synthesis or by interlocking of intrinsically bent tubes upon mutual contact.

The distinction between tubes of smaller diameter (≤ 30 nm) and larger diameter (> 30 nm) was however not proposed to discriminate between straight and curled or bent morphologies as is assumed in the comment, but to distinguish between flexible and rigid fibres, as there is strong experimental evidence that mesothelioma induction is governed by respirability, length, biopersistence and last, not least, flexural rigidity of fibres. Tubes of larger diameter were observed to be more rigid and to induce asbestos like carcinogenicity, see Rittinghausen et al. (2014)[1].

The CLH proposal states that tube diameter is used as pragmatic surrogate for fibre rigidity, as a precise and reproducible method is not yet available. To date, evidence is lacking showing that low-diameter MWCNT, i) induce mesothelioma induction, ii) are able to pierce mesothelial cells, iii) are not completely phagocytised by alveolar macrophages, iv) are detected in the pleural region after lung exposure. For several high-diameter MWCNT this has been independently demonstrated. Likewise, SWCNT have not been demontstrated to exhibit a mesotheliomatogenic potential. However, if reliable evidence would become available that low-diameter MWCNT (or SWCNT) would do so, extension of the classification should be considered.

Regarding the aspect of "group of substances" we would like to highlight that different MWC(N)Ts are <u>not</u> different substances, but only different forms of a single substance.

Because of the lack of sufficient evidence, SWCNT were rightly deemed not classifiable. However, after the publication of the IARC monograph evidence amounted that fibre pathogenicity is not limited to MWNT-7 but applies to other rigid (high-diameter) MWCNT as well, thus justifying the regulatory scope beyond one specific nanomaterial.

Proper classification based on scientific evidence
The DS internally discussed the introduction of exemption criteria similar to Note Q for the classification of mineral wool. This note requires either in vivo biopersistence testing or intraperitoneal injection, or long-term inhalation testing. Since any pristine MWCNT is known to be quite bioresistant, this is an ambigious criterion when proving fibre pathogenicity. Instead, the intraperitoneal injection (IP) test is deemed highly informative

but would likely need long-term follow-up. Therefore, note Q was dropped entirely. However, since the industry requests scientific evidence, a negative IP test may be reconsidered as valid exemption criterion.

[1] Rittinghausen, S., Hackbarth, A., Creutzenberg, O., Ernst, H., Heinrich, U., Leonhardt, A. and Schaudien, D. (2014): The carcinogenic effect of various multi-walled carbon nanotubes (MWCNTs) after intraperitoneal injection in rats. Particle and Fibre Toxicology 11

RAC's response

RAC agrees with the response of the DS, this is clearly reflected in the opinion.

Date	Country	Organisation	Type of Organisation	Comment number
02.09.2021	France		MemberState	3

Comment received

France wants to thank the German CA for the submitted CLH report and supports the proposed classifications.

However, we question the scope of the proposed entry i.e: Multi-Walled Carbon Tubes (synthetic graphite in tubular shape) with a geometric tube diameter range equals or higher than 30 nm to lower than 3 µm and a length equals or higher than 5 µm and aspect ratio equals or higher than 3:1, including Multi-Walled Carbon Nanotubes, MWC(N)T.

Regarding the lower band of the proposal (equals or higher than 30 nm for the diameter of the fiber), it seems that there is a data/regulatory gap for MWCT with a diameter comprised between 15 nm to 30 nm in term of carcinogenicity data. Indeed, positive results were obtained with MWCT with diameter equals or higher than 30 nm and negative results were reported with MWCT having a diameter of about 10-15 nm. In contrast, mutagenicity studies show some positive effects (in vitro and/or in vivo) with MWCT having diameter lower than 30 nm. If rigidity is the main rationale to propose the entry's scope for the classification of MWCT, there is a data gap for fiber with diameter comprised between 15 and 30 nm, as no validated methodology is currently available to ascertain rigidity measurement. Moreover, it was demonstrated for fiber with a diameter equals or lower than 15 nm that the rigidity paradigm is not followed but this was not demonstrated for several types of MWCT and it has to be confirmed to clearly exclude the fraction of fiber with a diameter of 15 to 30 nm from the proposal. Finally, it can be noted that WHO definition for fibre dimensions do not set a lower ban for diameter (length: equals or higher than 5 µm, diameter: lower than 3 µm, aspect ratio equals or higher than 3:1).

Overall, considering all these elements, France considers that setting the lowest value of the boundary at 15 nm (instead of 30 nm) can be more appropriate.

Dossier Submitter's Response

A possible regulatory gap was already addressed in the report. Apart from this uncertainty in length determination, the available data for carcinogenicity based on an asbestos-like fibre pathogenicity mechanism provide experimental evidence for induction of mesothelioma by MWCNT with mean carbon tube diameters as thin as 37 nm but no induction by MWCNT of ~ 15 nm in diameter. For MWCNT with diameters in-between evidence for mesothelioma induction is lacking. Therefore, a threshold of 30 nm was assigned, including a safety margin. The respective evidence regarding lower diameter MWC(N)T was deemed insufficient at the time of editorial finalisation of the CLH report. A

new publication (Saleh et al., 2020) reports some experimental evidence for a carcinogenic potential of tangled MWCNT of 7.4/19 nm in diameter but is assumed to depend on other pathogenicity mechanisms (see response to comment no. 10 below). Nevertheless, as soon as a solid scientific evidence for the set mode of action is given also for tubes having a diameter less than 30 nm we will assess to re-open the classification for MWC(N)Ts with the aim to lower the diameter of the tubes covered.

RAC's response

RAC agrees with the response of the DS. The publication of Saleh *et al*. 2020 and the potential effects of the lower range diameter MWC(N)T are clearly described in the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
02.09.2021	Japan	Nanotechnology Business Creation Initiative	Industry or trade association	4

Comment received

Because of the error message "Do not use characters", our comment is attached as PDF file in the Public attachment. The characters are used as substance identiy in our comment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment NBCI_Comment on CLH report_20210902.pdf

Dossier Submitter's Response

a) SID, threshold

A harmonized classification is in general proposed for "ideal substances". Meaning as soon as the substance, as defined in Annex VI of the CLP regulation (EG) 1272/2008, is present on its own, as a constituent/impurity or in a mixture in the threshold defined in the CLP regulation for the specified hazard the substance or the mixture need to be classified. Thus, setting any other threshold is not required and not meaningful in this context.

b) *Several of the substances tested in key studies are not "synthetic graphite" and IARC evaluation*

The CLH dossier proposal aims at a harmonised classification of engineered, i.e. synthesized, substances of graphitic structure in tubular shape. Whereas the IUPAC term "synthetic graphite" was introduced as a nomenclature for bulk graphite and not as a legally binding definition for the use of the term "synthetic". IUPAC, which aims at providing tools for communication of chemical knowledge, is still working on a nomenclature for carbon nanotubes and related materials (Project 2013-056-1-800). In our CLP proposal, we did not rely on the IUPAC definition of "synthetic graphite". Thus, we are not limited or restricted to the criteria laid down by IUPAC.

The referred temperature of 2500 K and above relates to the synthesis of bulk graphite by the Acheson or a standard high-temperature graphitization processes of carbonaceous precursors. Such high temperatures are required both for purifying the precursor and for establishing long-ranged graphitic order. Principally, non-bulk structures as carbon nanotubes and graphene can be synthesised at lower temperatures as the formation of crystalline order in nanotube walls growing from a catalyst particle is energetically

favoured and requires far fewer carbon bond rearrangements than basal plane formation in three-dimensional bulk carbons. Contemporary chemical vapour deposition processes use high-purity precursors and catalytic effects to further lower the temperatures required for (MW)C(N)T synthesis. All (MW)C(N)T materials referred to in the draft dossier are of synthetic origin and of at least partially graphitic structure as transmission electron microscopy or Raman spectroscopy have shown. The term "synthetic graphite in tubular shape" is therefore technically correct. Regarding the grouping: We did not apply the concept of grouping. All different forms of MWC(N)T are covered by the same substance identity. Not all tubes falling under our assessment are nanoforms due to having a diameter of >100 nm. Rather, the CLH report provides sufficient causal endpoint-specific evidence from a number of animal studies that the evaluated substance is presumed to have a carcinogenic potential for humans in analogy to the classification of asbestos or other MMMF. The publication of Nagai et al. (2011): The CLH report discussed this study as it provided relevant evidence corroborating the importance of fibre dimensions and morphology of MWCNT as determinants of mesothelioma induction by providing evidence for a mechanism for direct mesothelial injury (as the title of the study implies). In essence, long, thin nanoforms were found to be able to pierce the plasma membrane of mesothelial cells in vitro, whereas short thick nanoforms were not. However, it is important to refer to the morphological differences as well: while long, thin (~ 50 nm, MWNT-7) MWCNT that pierced were described as "needle-like", short ones were not. Similarly, long, very thin MWCNT (15 nm) with an entangled morphology, neither pierced mesothelial cells. The latter material was demonstrated in a follow up study to be unable to induce mesothelioma by intraperitoneal injection (Nagai et al., 2013). It should also be taken into account that mesothelial piercing is a late adverse event requiring pleural migration.
RAC's response
RAC concurs with the response of the DS.

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Germany	TSafeE GmbH	Company-Importer	5
Comment received				
Opting-out registrant TSafeE GmbH, only representative on behalf of JEIO Registered substance Multi-Walled Carbon Nanotubes (MWCNT), synthetic graphite in tubular shape (EC no. 936-414-1) We carefully compared the substance definition of the CLH proposal with our registered substance ID. We understand that our registered MWCNTs do not fall under the substance definition of the current CLH proposal. This is due to the fiber-like shape in contrast to a rigid type characterized in the CLH proposal. Therefore, we conclude that our registration will not be affected by a harmonized classification.				
Dossier Submitter's Response				
It is in the responsibility of the manufacturer, importer or downstream user to conclude whether their substance is covered by a harmonised classification.				

RAC's response to
RAC agrees with the DS, this is outside the scope and responsibility of RAC.

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Germany	<confidential>	Company-Importer	6

Comment received

As a subsidiary of a non-EU producer of Multi-Walled Carbon Tubes, we would like to take the opportunity to comment on this CLH report submitted by BAuA within the public consultation phase.
In summary, we consider that the evaluation of several MWC(N)Ts under the substance identity of Multi-Walled Carbon Tubes (synthetic graphite in tubular shape) with a geometric tube diameter range ≥ 30 nm to less than 3 µm and a length ≥ 5 µm and aspect ratio ≥ 3:1, including Multi-Walled Carbon Nanotubes, MWC(N)T is not sufficiently justified for the reasons explained below, notably in terms of lack of sufficient data to warrant classification of MWCNT substances, excluding MWNT-7, as Carc. 1B according to the CLP Regulation, and lack of sufficient proof for selection of the parameters of the substance identity.

1) The CLH report identifies the substance addressed by this proposed harmonised classification and labelling as Multi-Walled Carbon Tubes (synthetic graphite in tubular shape) with a geometric tube diameter range ≥ 30 nm to less than 3 µm and a length ≥ 5 µm and aspect ratio ≥ 3:1, including Multi-Walled Carbon Nanotubes, MWC(N)T. It is our opinion that this substance identity is not appropriate.
The substances, whose study data were evaluated in the CLH report and used for the assessment on classification, highly differ in the dimensions of their carbon tubes. Both length and diameter differed widely and aspect ratios showed high variability. The study results show that the effects in regard to carcinogenetic potential elicited by individual substances also present significant divergence from one substance to another. For example the impact of different diameters on carcinogenicity was demonstrated by Nagai et al. (2011). The study showed that an increase in thickness reduced the ability of the MWCNTs to pierce mesothelial cell membranes, thereby reducing the risk for mesothelioma development. A diameter of ca. 143 nm already reduced the capability for tumour induction significantly. Those findings regarding the influence of differing values for the dimensions are not sufficiently taken into account by the broad ranges for all dimensions set in the substance identity of the CLH report.
In addition, the substance identity lacks definition of thresholds. It is not clear whether a substance has to be regarded as in scope of the CLH report if one fibre meets the criteria or if the average values of the fibres of the substance have to meet the criteria. Further specification of the substance identity by inclusion of a percentage value of fibres that have to fulfil the criteria for diameter and length has to be considered. Such definition was already done for nanoforms. As detailed in Annex VI of the REACH Regulation a nanoform is identified, among other criteria, if "for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm". Using a similar approach the substance identity should be reconsidered to "Multi-Walled Carbon Tubes (synthetic graphite in tubular shape) with 50 % or more of the fibres having a geometric tube diameter […]".

2) The substances affected by the CLH report are identified as "Multi-Walled Carbon Tubes (synthetic graphite in tubular shape) […]". Due to the identification of the

substances as "synthetic graphite" only data generated with substances of such specification should be taken into account for deduction of classification and labelling in the CLH report. Synthetic graphite is defined by IUPAC as "A material consisting of graphitic carbon which has been obtained by graphitizing of non-graphitic carbon by chemical vapour deposition (CVD) from hydrocarbons at temperatures above 2500 K, by decomposition of thermally unstable carbides or by crystallizing from metal melts supersaturated with carbon."
Rittinghausen et al. (2014) provide details on the synthesis process for the substances MWCNT A- D used in their study. The substances are produced by means of the chemical vapour deposition method using high temperatures during synthesis, namely 850–900 °C for cyclohexane and acetonitrile and 1100–1150°C for benzene. The temperatures used are well below the 2500 K (= 2226.85 °C) required for production of synthetic graphite. Therefore, the substances are no synthetic graphites per IUPAC definition and data generated using these substances should not be taken into account for the derivation of classification and labelling for Multi-Walled Carbon Tubes (synthetic graphite in tubular shape) with a geometric tube diameter range ≥ 30 nm to less than 3 µm and a length ≥ 5 µm and aspect ratio ≥ 3:1, including Multi-Walled Carbon Nanotubes, MWC(N)T.

Dossier Submitter's Response

1) The SID was extrapolated beyond a diameter in nanosize in order to cover MWCNT slightly larger than 100 nm (the nano-definition threshold) in diameter, which were found to have a mesotheliomagenic potential but also to align the applicability domain to the WHO fibre criteria with regard to length, diameter and aspect ratio.

   The CLH report rated the publication of Nagai et al (2011) as a key study, as it provided relevant evidence corroborating the importance of fibre dimensions and morphology of MWCNT as determinants of mesothelioma induction by providing evidence for a mechanism for direct mesothelial injury (as the title of the study implies). In essence, long, thin nanoforms were found to be able to pierce the plasma membrane of mesothelial cells in vitro, whereas short, thick nanoforms were not. However, it is important to refer to the morphological differences as well: while the long thin (~ 50 nm, MWNT-7) MWCNT that pierced were described as "needle-like", short ones were not. Similarly, long, very thin MWCNT (~ 15 nm) with an entangled morphology neither pierced mesothelial cells. The latter material was demonstrated in a follow up study to be unable to induce mesothelioma by intraperitoneal injection (Nagai et al., 2013). It should also be taken into account that mesothelial piercing is a late adverse event requiring pleural migration. Regarding the point of defining a threshold: A harmonized classification is in general proposed for "ideal substances". Meaning as soon as the substance, as defined in Annex VI of the CLP regulation (EG) 1272/2008, is present on its own, as a constituent/impurity or in a mixture in the threshold defined in the CLP regulation for the specified hazard the substance or the mixture need to be classified. Thus, setting any other however received or set threshold is not required and not meaningful in this context.

2) The CLH dossier proposal aims at a harmonised classification of engineered, i.e. synthesized, substances of graphitic structure in tubular shape. Whereas the IUPAC term "synthetic graphite" was introduced as a nomenclature for bulk graphite and not as a legally binding definition for the use of the term "synthetic". IUPAC, which

aims at providing tools for communication of chemical knowledge, is still working on a nomenclature for carbon nanotubes and related materials (Project 2013-056-1-800). In our CLP proposal, we did not rely on the IUPAC definition of "synthetic graphite". Thus, we are not limited or restricted to the criteria laid down by IUPAC. The referred temperature of 2500 K and above relates to the synthesis of bulk graphite by the Acheson or a standard high-temperature graphitization processes of carbonaceous precursors. Such high temperatures are required both for purifying the precursor and for establishing long-ranged graphitic order. Principally, non-bulk structures as carbon nanotubes and graphene can be synthesised at lower temperatures as the formation of crystalline order in nanotube walls growing from a catalyst particle is energetically favoured and requires far fewer carbon bond rearrangements than basal plane formation in three-dimensional bulk carbons. Contemporary chemical vapour deposition processes use high-purity precursors and catalytic effects to further lower the temperatures required for (MW)C(N)T synthesis. All (MW)C(N)T materials referred to in the draft dossier are of synthetic origin and of at least partially graphitic structure as transmission electron microscopy or Raman spectroscopy have shown. The term "synthetic graphite in tubular shape" is therefore technically correct.
RAC's response
RAC concurs with the DS response.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Germany	<confidential>	Company-Importer	7
Comment received				
The CLH report states that its conclusion on classification for carcinogenicity is different from the previous conclusion on categorization by the International Agency for Research on Cancer (IARC) for carbon nanotubes (IARC 2017) as the "the IARC categorisation not yet considered highly relevant findings, in particular those by Kasai et al. (2016), Suzui et al. 2016 and Rittinghausen et al. (2014) which not only strengthen the classification for MWNT-7 as a human carcinogen but also provide sufficient evidence for extending the classification to other MWCNT with WHO fibre dimensions.". Suzui et al. (2016) used MWCNT-N with the length of 4.2 µm or 2.6 µm and a diameter range of 30-80 nm. Considering the lengths of MWCNT-N the substance doesn't fall within the dimension boundaries of the substance identity provided in the CLH report and is outside the WHO fibre dimensions (length: ≥ 5 µm, diameter: less than 3 µm, aspect ratio ≥ 3:1). Therefore, these data cannot be taken into account for conclusions on carcinogenicity of MWCNT with WHO fibre dimensions and for the substance identity provided in the CLH report. MWCNT A-D produced by Rittinghausen et al. and used in the respective study don't meet the definition of synthetic graphite by IUPAC as they were synthesized at temperatures well below 2500 K. Therefore, data generated using these substances cannot provide sufficient evidence for carcinogenicity of Multi-Walled Carbon Tubes (synthetic graphite in tubular shape) with a geometric tube diameter range ≥ 30 nm to less than 3 µm and a length ≥ 5 µm and aspect ratio ≥ 3:1, including Multi-Walled Carbon Nanotubes, MWC(N)T. Kasai et al. (2016) conducted their study using MWNT-7, thereby generating data				

supporting the classification of MWNT-7 only. This study does not provide evidence for classification on carcinogenicity of MWCNTs in general.
Taking into consideration that the findings of the particularly relevant publications either were derived from MWCNTs of different substance identities than the substance identity addressed in the CLH report or from MWNT-7 only, the data provide no evidence for carcinogenicity of MWCNT with WHO fibre dimensions. Therefore, the IARC categorisation assessment for MWCNTs in general in Group 3 (not classifiable) still applies. Only the highly relevant finding for carcinogenicity of MWNT-7 was not yet considered during the IARC categorisation assessment and the applicability of classification as Carc. 1B according to CLP Regulation for MWNT-7 is supported.

Furthermore, the test materials from the different studies presented in the CLH report were judged for their potential for carcinogenicity/preneoplasia. These judgements are presented in Table 13a of the CLH report. In most studies conducted and concluded on a judgment of "Yes"for carcinogenicity, MWNT-7 was used as test material. Further studies considered to show evidence of carcinogenetic potential were conducted with test material not meeting the WHO fibre dimensions or not meeting the definition of synthetic graphite. Only two test materials (MWCNT-L and NTlong2), besides MWNT-7, meet all criteria for the substance identity of the CLH report and show a potential for carcinogenicity. For each material only one study with limited reliability is presented, thereby not providing sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen) and classification for Carc. 1B for other MWCNT with WHO fibre dimensions. Even for test materials not in scope of the substance identity of the CLH report, but assessed as showing potential for carcinogenicity in Table 13a, the data is highly limited as different test materials were used in one study only, the studies were conducted mostly in rats, seldom in mice, but never in non-rodent species and the exposure route was mostly non-physiological.

Taken together sufficient evidence for a classification of MWNT-7 as Carc. 1B under CLP is provided in the CLH report and is therefore supported by us. However, the evidence presented in the CLH report is not sufficient to justify a classification of other MWCNTs as Carc. 1B according to the CLP Regulation. Therefore, we consider that grouping of other MWCNTs together with MWNT-7 for assessment of carcinogenicity is not appropriate.

Dossier Submitter's Response

Deviating from sharp boundaries is always a matter of discussion, in particular when different studies provide divergent measures and/or refer to average values only. A 5 µm threshold length was assigned and justified in the CLH report as follows (note the difference of mean length vs. length range with regard to the study of Suzui et al., 2016, which explains why the study indeed strengthens the classification):

"*The smallest mean tube length of MWCNT materials inducing both malignant mesothelioma and lung tumours was 2.6 ± 1.6 µm as administered as the "unfiltered fraction" and 2.0 ± 0.4 µm as measured in tumour tissue areas (Suzui et al., 2016) following intrapulmonary spraying. However, a large size range between 1-10 µm in the unfiltered fraction was reported, making it impossible to determine a critical size form this data. Nagai et al. (2011) identified a tube length of 4-5 µm and a needle-like shape as important tumour-inducing factors in vivo. This was supported by a number of in vitro studies which reported that long (> 5 µm) but not short tubes are more cytotoxic for mesothelial and epithelial cells (Nagai and Toyokuni, 2012; Nymark et al., 2014) and more cytotoxic and inflammogenic for (alveolar) macrophages (Sweeney et al.; 2014, 2015; Boyles et al., 2015). Schinwald et al. (2012) and Poland et al. (2012) proposed a generic threshold or minimum length of 4 to 5 µm for fibre-induced acute pleural inflammation, based on intrapleural injections and intraperitoneal injection or pharyngeal aspiration, respectively, into mice of fibrous high aspect ratio nanomaterials of definite lengths, such*

as silver or nickel nanowires. The size limit is explained with the trapping of larger fibres at the stomata in the parietal pleura (the size of which ranges from 4-10 μm in rodents), where they accumulate and less by the incapability of alveolar macrophages to cope with these longer objects known as frustrated phagocytosis."

The CLH dossier proposal aims at a harmonised classification of engineered, i.e. synthesised, substances of graphitic structure in tubular shape. Whereas the IUPAC term "synthetic graphite" was introduced as a nomenclature for bulk graphite and not as a legally binding definition for the use of the term "synthetic". IUPAC, which aims at providing tools for communication of chemical knowledge, is still working on a nomenclature for carbon nanotubes and related materials (Project 2013-056-1-800).

The referred temperature of 2500 K and above relates to the synthesis of bulk graphite by the Acheson or a standard high-temperature graphitisation processes of carbonaceous precursors. Such high temperatures are required both for purifying the precursor and for establishing long-range graphitic order. Principally, non-bulk structures as carbon nanotubes and graphene can be synthesised at lower temperatures as the formation of crystalline order in nanotube walls growing from a catalyst particle is energetically favoured and requires far fewer carbon bond rearrangements than basal plane formation in three-dimensional bulk carbons. Contemporary chemical vapour deposition processes use high-purity precursors and catalytic effects to further lower the temperatures required for (MW)C(N)T synthesis.

All (MW)C(N)T materials referred to in the draft dossier are of synthetic origin and of at least partially graphitic structure as transmission electron microscopy or Raman spectroscopy have shown. The term "synthetic graphite in tubular shape" is therefore technically correct.

However, even if the addition ("synthetic graphite in tubular shape") would be deleted from the substance identity it would not affect the content and applicability domain of the CLH proposal.

Irrespective of the production process, the study of Rittinghausen et al. (2014) clearly showed that the mesothelioma-inducing potency was correlated to the rigidity of the tested MWCNT, measured as curvature, which in turn was dependent of the fibre thickness. It therefore strongly supports the asbestos-related pathogenicity mode of action for rigid MWCNT and thus justifies the extension of classifiable MWCNT beyond MWNT-7. Rather, MWNT-7 is to be seen as a data-rich reference material.

The DS is of the opinion that the provided data from a variety of independent animal studies (including both toxicokinetic and toxicological evidence) is exhaustively discussed in the CLH report, as is the applicability of Cat. 1B classification by addressing factors a-k individually according to section 3.6.2.3.2 *Additional considerations for classification* of the CLP Guidance. Altogether, the provided weight-of-evidence justifies harmonised classification in Cat. 1B of the substance as such with certain dimensional specifications, as appropriate risk management measure to meet the carcinogenicity concern of fibre pathogenicity following inhalation.

RAC's response

RAC concurs with the DS response.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON MULTI-WALLED CARBON TUBES (SYNTHETIC GRAPHITE IN TUBULAR SHAPE) WITH A GEOMETRIC TUBE DIAMETER RANGE ≥ 30 NM TO < 3 MM AND A LENGTH ≥ 5 MM AND ASPECT RATIO > 3:1, INCLUDING MULTI-WALLED CARBON NANOTUBES, MWC(N)T

Date	Country	Organisation	Type of Organisation	Comment number
02.09.2021	Japan	Nanotechnology Business Creation Initiative	Industry or trade association	8
Comment received				
Because of the error message "Do not use characters", our comment is attached as PDF file in the Publuc attachment. The characters are used as substance identiy in our comment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment NBCI_Comment on CLH report_20210902.pdf				
Dossier Submitter's Response				
See above				
RAC's response				
See previous responses.				

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Japan	Zeon Corporation	Company-Manufacturer	9
Comment received				
carc.1B in the CLP annex ECHA note – An attachment was submitted with the comment above. Refer to public attachment CommentByZeonOnCLHReportFigs.pdf				
Dossier Submitter's Response				
We agree that synthesis conditions can influence the shape of a CNT. Arc discharge synthesis, being a high-temperature process, generally leads to highly ordered tubular graphene structures with low numbers of defects that exhibit straight tube geometries, whereas CVD processes at lower temperature and processes of irregular precursor supply tend to result in more defective tubular graphene structures. Such structural defects can lead to intrinsically curled or bent tubes. We also agree that entanglement is possible both for thin and thick CNTs since thin and flexible CNTs may spontaneously entangle upon mutual contact in order to save surface energy during growth or processing. For thick and rigid CNTs, entanglement may occur either under dense growth conditions already during synthesis or by interlocking of intrinsically bent tubes upon mutual contact. The distinction between tubes of smaller diameter (≤ 30 nm) and larger diameter (> 30 nm) was however not proposed to discriminate between straight and curled or bent morphologies as is assumed in the comment, but to distinguish between flexible and rigid fibres as there is strong experimental evidence that the toxicity of fibres is governed by respirability, length, biopersistence and last, not least flexural rigidity. Tubes of larger diameter were observed to be more rigid and to induce asbestos-like carcinogenicity, see Rittinghausen et al. (2014)[1].				

[1] Rittinghausen, S., Hackbarth, A., Creutzenberg, O., Ernst, H., Heinrich, U., Leonhardt, A. and Schaudien, D. (2014): The carcinogenic effect of various multi-walled carbon nanotubes (MWCNTs) after intraperitoneal injection in rats. Particle and Fibre Toxicology 11

As was pointed out above, CNT entanglement state is not a sufficient proxy for flexural rigidity, therefore CNT diameter was chosen for rigidity scales with the 4th power of diameter.

To date, evidence is lacking that low-diameter MWCNT, i) induce mesothelioma induction, ii) are able to pierce mesothelial cells, iii) are not completely phagocytosed by alveolar macrophages, iv) are detected in the pleural region after lung exposure, whereas for several high diameter MWCNT this has been independently shown.

Referring to the IARC classification, several thin CNT (including SWCNT) were rightly deemed not classifiable. However, evidence amounted after the publication of the IARC monograph that fibre pathogenicity is not limited to MWNT-7 but applies to other rigid (high diameter) MWCNT as well, thus justifying broadening the regulatory scope beyond one specific nanomaterial. If new information would become available demonstrating that low-diameter CNT may also induce fibre-like pathogenicity, extension and re-adjustment of the classification should be considered.

The rationale of the CLH proposal follows the classification of other man-made fibres, which are also classified as substance with or without certain specifications. The DS agrees that the fibre paradigm is not universally applicable. However, the weight-of-evidence approach justifies harmonised classification in Cat. 1B of the substance as such with certain dimensional specifications as appropriate risk management measure to meet the carcinogenicity concern of fibre pathogenicity following inhalation.

The SID reflects alignment to the applicability domain of the WHO fibre criteria with regard to length, diameter and aspect ratio. Accordingly, only a lower length threshold (5 µm) has been assigned. Extra-long MWCNT, e.g. in the cm range, are not directly affected by the classification as these are generally not respirable. However, this requires that it can be demonstrated that no respirable fibres are released during the life cycle of the material (including e.g. incomplete degradation by chlorine bleach).

RAC's response

RAC agrees with the DS response.

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Netherlands		MemberState	10

Comment received

Thank you for this proposal and the extensive work performed so far.

Regarding the international chemical identification; genotoxicity (e.g. DNA strand breakage, DNA oxidation, micronucleus formation, mutations) has been observed for MWCNT with a length below 5 µm in mice and rats (e.g., Cao et al., 2014; Pothmann et al., 2015; Kato et al., 2013; Poulsen et al., 2015; Kim et al., 2014; Muller et al., 2008; Kato et al., 2013). Also, functionalized or otherwise treated MW-CNT samples have been described to possess a different toxic potential, including their ability to elicit genotoxicity and carcinogenicity (this can be higher or lower) compared to the pristine MWCNT

material; is there sufficient evidence to conclude that they will not induce tumor formation in humans at limited fiber length (i.e., below 5 µm)?
It may be advisable to allow for some flexibility regarding the chemical identification; one can think of a similar adaptive approach to the classification of glass fibers, it could be an option for materials that meet the aspect ratio criterium, but not the length criterium, to demonstrate that they are not genotoxic/carcinogenic. Especially for functionalized MWCNT materials that may have a deviating toxic potency, such an approach could be useful.

The proposal considers there is no or limited evidence of carcinogenicity for MWCNTs with a diameter < 30 nm. However, currently a clear rationale for this diameter limit is missing; it is mentioned on page 4 that this cut-off value is based on tumor induction, which may not be a reliable indicator for rigidity. It is known that thinner fibers are more flexible, i.e. less rigid than thicker fibers. However, others have suggested different diameter cut-off values, such as 20 nm (Meyer-Plath et al., 2020). Moreover, on page 86 where the selection of MWC(N)T characteristics is explained, a value of 15 nm is mentioned for "Tube Diameter". The authors state that no data are available for MW-CNT samples with a diameter of 15-30 nm. However, in a recent study, Saleh et al. showed that 8 administrations over a 7 week period via intratracheal instillation of tangled MWCNT with a diameter of only 19 nm (as measured in the air), were shown to induce pulmonary tumors, including adenoma and adenocarcinoma but not mesothelioma, after a 2-year observation period (Saleh et al., 2020). It is worthwhile to mention here that their carcinogenic potency was larger than both that of more rigid MWCNTs with a diameter of 163 nm and that of the crocidolite asbestos reference material. This provides evidence that 'non-rigid' MWCNT may also be carcinogenic, and adds data on MWCNT of lower diameter. Clarification on this matter would be appreciated.

Considering a broader range of tumor induction for carcinogenicity classification would be recommended, i.e. both mesothelioma induction after pleural translocation (which has been observed for MWC(N)T with a diameter of >30 nm) and lung cancer arising within the broncho-alveolar region (which has been observed for MWC(N)T of lower diameter).

The following three recent references could be considered for further discussion on this classification proposal:
Saleh, D. M., Alexander, W. T., Numano, T., Ahmed, O. H. M., Gunasekaran, S., Alexander, D. B., Abdelgied, M., El-Gazzar, A. M., Takase, H., Xu, J., Naiki-Ito, A., Takahashi, S., Hirose, A., Ohnishi, M., Kanno, J., and Tsuda, H. 2020. 'Comparative carcinogenicity study of a thick, straight-type and a thin, tangled-type multi-walled carbon nanotube administered by intra-tracheal instillation in the rat', Particle and Fibre Toxicology, 17: 48.https://doi.org/10.1186/s12989-020-00382-y.

Meyer-Plath, A., Bäger, D., Dziurowitz, N., Perseke, D., Simonow, B. K., Thim, C., Wenzlaff, D., and Plitzko, S. 2020. 'A Practicable Measurement Strategy for Compliance Checking Number Concentrations of Airborne Nano- and Microscale Fibers', Atmosphere, 11.https://doi.org/10.3390/atmos11111254.

Murphy, F., Dekkers, S., Braakhuis, H., Ma-Hock, L., Johnston, H., Janer, G., di Cristo, L., Sabella, S., Jacobsen, N. R., Oomen, A. G., Haase, A., Fernandes, T., and Stone, V. 2021. 'An integrated approach to testing and assessment of high aspect ratio nanomaterials and its application for grouping based on a common mesothelioma hazard', NanoImpact:

100314.https://doi.org/10.1016/j.impact.2021.100314.
This study presents a proposal for grouping high aspect ratio nanomaterials into mesothelioma-positive and negative HARNS, including cut-offs and tests. Therefore this study may provide useful additional / supporting information.

Other references as cited in our comments, a reaction/discussion on our comments and the references therein would be highly appreciated:
Cao Y, Jacobsen NR, Danielsen PH, Lenz AG, Stoeger T, Loft S, Wallin H, Roursgaard M, Mikkelsen L, Møller P. Vascular effects of multi-walled carbon nanotubes in dyslipidemic ApoE−/− mice and cultured endothelial cells. Toxicol Sci. 2014;138:104–116.

Pothmann D, Simar S, Schuler D, Dony E, Gaering S, Le Net JL, Okazaki Y, Chabagno JM, Bessibes C, Beausoleil J, et al. Lung inflammation and lack of genotoxicity in the comet and micronucleus assays of industrial multiwalled carbon nanotubes Graphistrength(©) C100 after a 90-day nose-only inhalation exposure of rats. Part Fibre Toxicol. 2015;12:21.

Poulsen SS, Saber AT, Williams A, Andersen O, Kobler C, Atluri R, Pozzebon ME, Mucelli SP, Simion M, Rickerby D, et al. MWCNTs of different physicochemical properties cause similar inflammatory responses, but differences in transcriptional and histological markers of fibrosis in mouse lungs. Toxicol Appl Pharmacol. 2015;284:16–32.

Kato T, Totsuka Y, Ishino K, Matsumoto Y, Tada Y, Nakae D, Goto S, Masuda S, Ogo S, Kawanishi M, et al. Genotoxicity of multi-walled carbon nanotubes in both in vitro and in vivo assay systems. Nanotoxicology. 2013;7:452–461.

Kim JS, Sung JH, Choi BG, Ryu HY, Song KS, Shin JH, Lee JS, Hwang JH, Lee JH, Lee GH, et al. In vivo genotoxicity evaluation of lung cells from Fischer 344 rats following 28 days of inhalation exposure to MWCNTs, plus 28 days and 90 days post-exposure. Inhal Toxicol. 2014;26:222–234.

Muller J, Huaux F, Fonseca A, Nagy JB, Moreau N, Delos M, Raymundo-Pinero E, Beguin F, Kirsch-Volders M, Fenoglio I, et al. Structural defects play a major role in the acute lung toxicity of multiwall carbon nanotubes: toxicological aspects. Chem Res Toxicol. 2008b;21:1698–1705.

Dossier Submitter's Response

When considering regulatory activities towards Multi-walled Carbon Nanotubes (MWCNT), Germany pursued a two-fold approach (communicated and presented both on a RIME meeting in 2015 and an NMEG meeting in 2018). A more or less parallel assessment of MWCNT was initiated based on different mechanistic principles due to the high variability of the morphology and geometry of the otherwise highly biodurable nanoforms, which coincided with a different state of toxicological understanding. According to the mode of action, different principles were identified: well documented fibre-like pathogenicity in case of rigid nanoforms on the one hand and granular particle and/or substance-specific toxicity in case of tangled nanoforms, which lacked clear evidence for carcinogenicity. In the opinion of the DS, the available data for the former is sufficient to prepare a CLH proposal. For the latter, the DS decided to start a SEv process[2] first, which might lead to

[2] Meanwhile Germany prepared a conclusion document with regard to the SEv because it was concluded that a CCH is required before the SEv process can be finalised. Therefore, the SEv process is currently halted but not yet completed.

specific study requests thus clarifying the prevailing mode of action for adverse effects following repeated inhalation, including a putative carcinogenic potential. The outcome of the SEv could then result either in an extension of a harmonised classification or different management options. It is noted that this dual approach does not ignore a potential carcinogenicity and/or organ-specific toxicity following repeated inhalation in case of tangled MWCNT. However, they were excluded from the CLH proposal because of limited evidence regarding a mode-of-action which can be sufficiently explained based on fibre morphology.

After the finalisation of the CLH proposal and for the first time at all, a scientific publication by Saleh et al (2020) provided evidence for low-diameter (19 nm in air, 7.4 nm in vehicle) MWCNT inducing lung carcinoma (but no mesothelioma) within 2 years after repeated intratracheal intrapulmonary spraying for 24 weeks. The authors (who tested rigid MWCNT and asbestos fibres in parallel) discussed a variety of modes of carcinogenic action for tangled nanotubes, e.g. based on inflammatory unspecific particle overload, metal contamination, and surface chemistry. Neither of the administered nanoforms induced mesothelioma and none were detected in the pleura, which was assumed to be due to the CNT being "trapped" in lung granulomas preventing translocation and/or migration. In fact, the publication does not diminish the conclusions for the carcinogenic mechanism of the submitted CLH proposal, based on reproducible evidence for fibre morphology as primary if not sufficient driver of pathogenicity. However, it includes important findings and conclusions supporting a re-opening of the SEv process.

It was further suggested to consider more references demonstrating a genotoxic potential of MWCNT. The endpoint genotoxicity of MWC(N)T has been evaluated in the report. It was concluded that there is some evidence for a genotoxic potential of MWCNT, in particular with regard to inducing aneuploidy. However, data was deemed insufficient for a respective classification of high-diameter carbon tubes, since positive findings usually refer to low-diameter MWCNT (addressed in the parallel SEv). Since the fibre mode-of-action considered in the CLH proposal does not necessarily require a direct genotoxic activity (indirect genotoxicity due to an inflammatory ROS response originating from defending leucocytes is plausible as well), more references on genotoxicity do not need to be taken into account to further substantiate the CLH proposal.

RAC's response

RAC agrees with response of the DS. The paper of Saleh *et al* is included in the opinion and the potential effects caused by the lower range diameter MWCNT are described in the opinion.

Date	Country	Organisation	Type of Organisation	Comment number
02.09.2021	Belgium	Japan Business Council in Europe	Industry or trade association	11

Comment received

Plese kindly refer our comment in the attachement.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment JBCE Input to Registry of CLH intention(MWCNT)-Final.pdf

Dossier Submitter's Response
See above
RAC's response
See previous comments.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Germany	<confidential>	Company-Importer	12
Comment received				
No comment.				
Dossier Submitter's Response				
-				
RAC's response				
-				

PUBLIC ATTACHMENTS
1. CommentByZeonOnCLHReportFigs.pdf [Please refer to comment No. 9]
2. JBCE Input to Registry of CLH intention(MWCNT)-Final.pdf [Please refer to comment No. 2, 11]
3. NBCI_Comment on CLH report_20210902.pdf [Please refer to comment No. 4, 8]