General Comments

NBCI (Nanotechnology Business Creation Initiative) is a Japanese institution established in 2003 to launch and expand the nanotechnology business. NBCI is made up of more than 140 Japanese organizations interested in nanotechnology, promoting the collection and sharing of the latest technical and environmental safety information, and networking with industry, academia and government. Furthermore, we are making recommendations on R & D strategies, environmental safety regulations, and standardization activities in the field of nanotechnology.

Basically, we do not agree to evaluate several MWC(N)Ts as a group, because the grouping is not sufficiently justified in the conclusions generalized in the CLH report (Please also see the comment on hazard classes).

Furthermore, we think that the current identity of the substance is unclear and should be clarified to use for regulatory purposes. From the current identity, we cannot identify which substance is in the scope of harmonization, which the company needs to respond to.

- For the numerical values in the report, "a geometric tube diameter range ≥ 30 nm to <3 μm and a length ≥ 5 μm and aspect ratio >3: 1," it is not clear whether these refer to the average values (substance meets the identity of the proposal if the average values are in the range of these values) or the values are for the individual fiber (substance meets the identity of the proposal if one or more fibers is in the range of these values).

Therefore, we propose to include the percentage in the identity of the substance as follows, for example using 80% or more which is the definition of mono-constituent in the REACH and CLP regulations;
"Multi-Walled Carbon Tubes (synthetic graphite in tubular shape), **for 80 % or more of the fibers is in the size range** with a geometric tube diameter range ≥ 30 nm to <3 μm and a length ≥ 5μm and aspect ratio >3:1, including Multi-Walled Carbon Nanotubes, MWC (N)T"

A similar idea is adopted in the definition of nanomaterials, which we believe is a more clear definition.

- The following substances are cited in Table 11 of the CLH Report but are not considered to be “synthetic graphite.” Synthetic graphite is defined by IUPAC[*1] 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.”

- CNT-7 and Short CNT-7: annealed at 1500°C, which are not graphitized (Huaux et al., 2016).
- MWCNT A, MWCNT B, MWCNT C, and MWCNT D: synthesis at the temperature of 850–1150°C, which are not graphitized (Rittinghausen et al., 2014).

As detailed above, the substances are clearly not in the scope of the substance identification 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.” Therefore, the study data generated with those substances cannot be considered in the determination of classifications in the Proposal for Harmonised Classification and Labelling. Each reference in the CLH Report should be re-evaluated based on the production process (i.e., graphite or not), and the identity of the substance should be address appropriately.

In conclusion, we cannot agree to evaluate several MWC(N)Ts as a group. Furthermore, the current substance identity is not appropriate to gather comments from companies that may have concerns.

[*1] IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"). Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997). Online version (2019-) created by S. J. Chalk. ISBN 0-9678550-9-8. https://doi.org/10.1351/goldbook.

Comments on the open hazard classes: Carcinogenicity

a) IARC evaluation

The 11 studies are cited in the CLH Report Table 11, but these reports do not clearly support the classification of MWC(N)T as Carc. 1B

The IARC evaluated MWCNTs and classified MWNT-7 under the carcinogenic category 2B and other MWCNTs under the carcinogenic category 3. In the CLH report, there are new studies for MWNT-7 that show carcinogenicity in animals, which strengthen the classification for MWNT-7 as a carcinogen. For other MWC(N)Ts, some materials show carcinogenicity in animals but there is only one experimental data for each material, thus the evidence is not sufficient for the classification. Therefore, the newly evaluated studies in the CLH report do strengthen the classification for MWNT-7 as a carcinogen, but these do not provide sufficient evidence for extending the classification to other MWC(N)Ts with WHO fiber dimensions.

In conclusion, the current situation (evidence of carcinogenicity) is the same as the situation where IARC made the conclusion separately for MWNT-7 and other MWC(N)Ts. We strongly support the IARC's conclusion that MWNT-7 has sufficient evidence and other MWC(N)Ts have limited evidence for carcinogenicity, which in the CLP criteria, would be Carc. 1B for MWNT-7 and not Carc. 1B for other MWC(N)Ts.

b) Classification of MWC(N)T as Carc. 1B

The CLH report proposed grouping several MWC(N)Ts into one group on the assumption that they have the same hazard. However, there is insufficient justification to group substances of different manufacturing methods or sizes (diameter/length) under the same hazard group.

In "Appendix for nanoforms applicable to the Guidance on Registration and substance identification," the document states that justification shall be provided for the "set of similar nanoforms" as follows;

"*According to Annex VI of REACH: A 'set of similar nanoforms' is a group of nanoforms characterised in accordance with section 2.4 where the clearly defined boundaries in the parameters in the points 2.4.2 to 2.4.5 of the individual nanoforms*

within the set still allow to conclude that the hazard assessment, exposure assessment and risk assessment of these nanoforms can be performed jointly. ***A justification shall be provided to demonstrate that a variation within these boundaries does not affect the hazard assessment, exposure assessment and risk assessment of the similar nanoforms in the set.*** *A nanoform can only belong to one set of similar nanoforms."*

Although this is the guidance for the registrants, we think that the same approach should be applied for the CLH proposal. For example, the above guidance states the minimum justification that registrants should include in their reports:

- *How does the particle size of the different nanoforms impact the* ***dissolution rate and solubility*** *of the set members?*
- *How does the particle size of the different nanoforms within the set impact the t****oxicokinetic behaviour*** *as well as fate and (bio)availability of the set members?*
- *How does the particle size of the different nanoforms within the set impact the (eco)****toxicity*** *of the set members? Is there a direct* relationship between the particle size and the (eco)toxicity*?*

The guidance also states as follows for elongated nanoforms;

- *The width, together with length, is considered as a critical parameter that can be used as an indication of the rigidity of these nanoforms. Consideration on rigidity is therefore linked to the requirement on particle size distribution in point 2.4.2 of Annex VI of REACH and the* ***registrant must justify how the variation in width of the particles of the different forms will affect the rigidity of the particles and consequently the (eco)toxicological profile of the different nanoforms****. When there is a variability in the width of the particles constituting the nanoforms covered by the set, the* ***registrant must provide a justification demonstrating that this variation does not affect the joint hazard assessment*** *of these nanoforms.*
- *The registrant must also take into account variations in the length and aspect ratio of elongated particles when building the set of nanoforms. When there is a variation in length and/or aspect ratio of the particles of the nanoforms covered by the set, the* ***registrant must provide a justification demonstrating that this variation does not affect the joint hazard assessment*** *of these nanoforms.*

As previously mentioned above, most of the data in the current CLH report is for MWNT-7, and we think that the current CLH report critically lacks the description for the justification of the grouping. For example, the following literature shows that the grouping is not appropriate.

- Results published by Nagai et al. (2011) demonstrate that the geometric tube diameter is an important parameter for inducing injury to human mesothelial cells. The ability of MWCNTs to pierce cell membranes is inversely proportional to its diameter, i.e., the thinner the MWCNTs, the more likely they are to penetrate cell membranes and develop mesotheliomas (see table below). Thus, it is inappropriate to assume that several MWC(N)Ts are of the same hazard, given the evidence that the degree of carcinogenicity varies with size (diameter).

	NT50a	NT115	NT145	NTtngl
Diameter [nm]	49.95	116.2	143.5	N.D.
Piercing mesothelial cell membranes	Yes	Low	Very low	None
Carcinogenicity to rats	High	N.D.	Low	None

N.D.: Not determined

From the above, we believe that each MWC(N)T should be evaluated separately. When evaluating each material separately, we agree that MWNT-7 meets the carcinogenicity Category 1B of the CLP criteria, since there is clear evidence obtained by the inhalation study (OECD 451 with CLP compliance) and several supporting studies. On the other hand, for other MWC(N)Ts, there is only one study each that shows carcinogenicity. In addition, these studies have several substantial deviations from the standard test guideline used in regulatory purposes;

- the route of exposure is intraperitoneal, transtracheal, or intrascrotal instillation whereas inhalation is the preferred route in the guideline for inhalable test materials,
- the dosing regime (only one or several instillations in the early part of the study) does not satisfy the provision of the guideline that states that the exposure should cover the major part of the life span of the test animals,
- the non-physiological dosing with a single treatment or several treatments results in a local bolus dose leading to excess evaluation.

Therefore, we believe that a single study with several substantial deviations should not be treated as “sufficient evidence” of carcinogenicity.

In conclusion, since there is a lack of justification to group the substance in one category, we think the materials should be evaluated separately. It can be agreed that MWNT-7 is classified as Carc. 1B, but other MWC(N)Ts should not be classified as Carc. 1B.