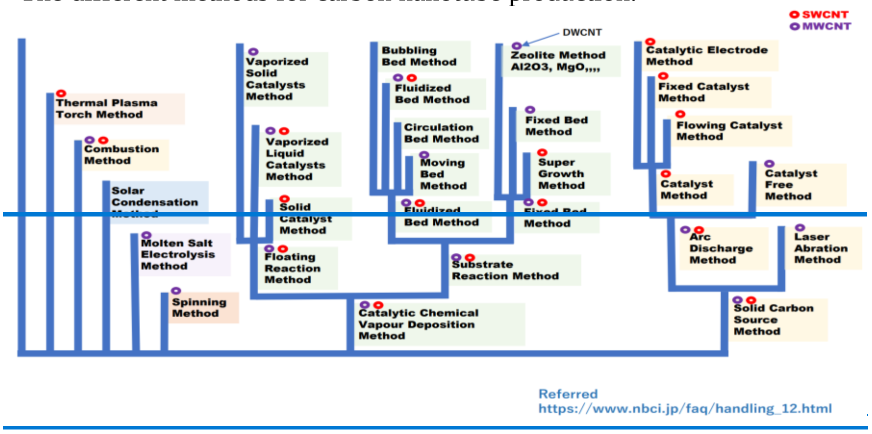
29th, September,2022

Proposal for an objective and consistent hazard classification of MWC(N)T to promote safe innovation

JBCE would like to propose a harmonisation of the classification of MWC(N)T based on the latest knowledge on the effects of carbon nanotubes (CNTs) in organisms. This classification is consistent with the classification of the International Agency for Research on Cancer (IARC).

Indeed, the morphologies, physicochemical properties, and effects on the human organism depend on the different methods for carbon nanotube production[1]. Therefore, from a chemical management perspective, different types of CNTs should be evaluated depending on their characteristics instead of simply grouping them all together under the category "CNTs".

[1] The different methods for carbon nanotube production.



Executive Summary

The classification of carcinogenicity of MWCNT should be harmonised with the authorised international classification since, from the evidence provided, it seems that there is no reason to change it. Hence:

1. MWCNT similar to MWCNT-7 should be classified as suspected human carcinogen (Carc. 2) in the GHS classification. Therefore, straight CNTs, that are neither particularly long nor particularly short, should be considered possibly carcinogenic, as they might have asbestos-like effects in humans even though this has not been scientifically proven yet.
2. MWCNTs other than MWCNT-7 should be classified as non-carcinogenic in the GHS classification.

Details:
The IARC classified the carcinogenicity of asbestos, MWCNT and carbon black as follows:

- *Asbestos* (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite) is classified in Group 1: Carcinogenic to humans.[2]
- *Carbon black and TiO2* are classified in Group 2B: *possibly carcinogenic* to humans.[3]
- *Carbon nanotubes, multiwalled, of type MWCNT-7, carbon black and Nano TiO_2* are classified in Group 2B: *possibly carcinogenic* to humans. [4]
- *Carbon nanotubes, multiwalled,* other *than MWCNT-7*, are classified in Group 3: not classifiable as to its carcinogenicity to humans.

In contrast, in the EU, under the CLP Regulation, as listed in the CLP Annex I, 3.9.2.8.1. (e), *carbon black* and TiO2 are classified as Carc.2.

The proposal by the Federal Institute for Occupational Safety and Health of Germany (BAuA) is *very different* from the IARC classification, as shown in the following table. The CLH report by BAuA proposes *raising* the classification to Carc. 1B, *presumed human carcinogen*, for a large class of MWCNT materials which:

- the IARC group identifies as *not classifiable as carcinogenic*,
- and which are *not inhaled* into the lung.

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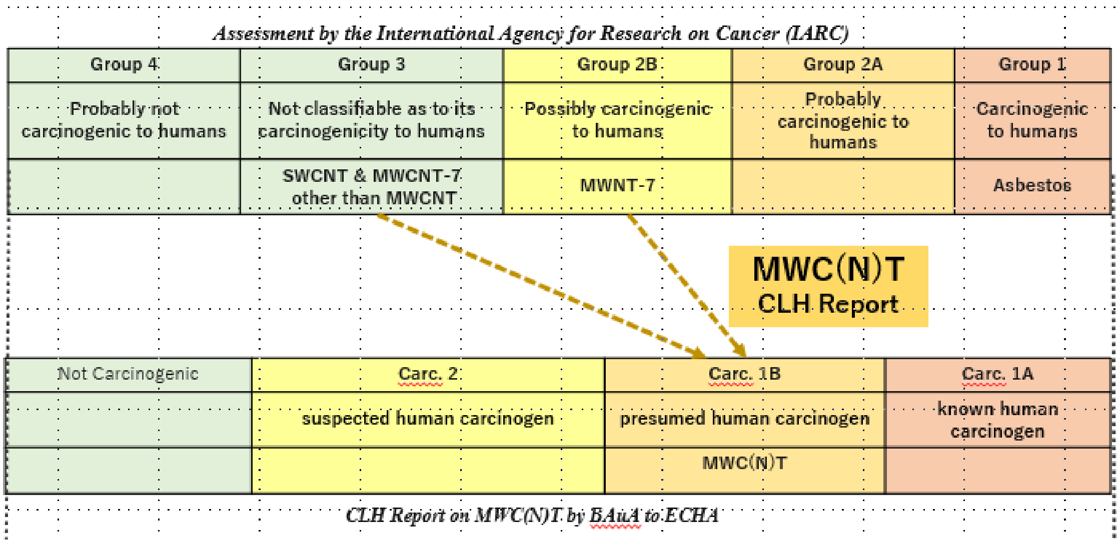
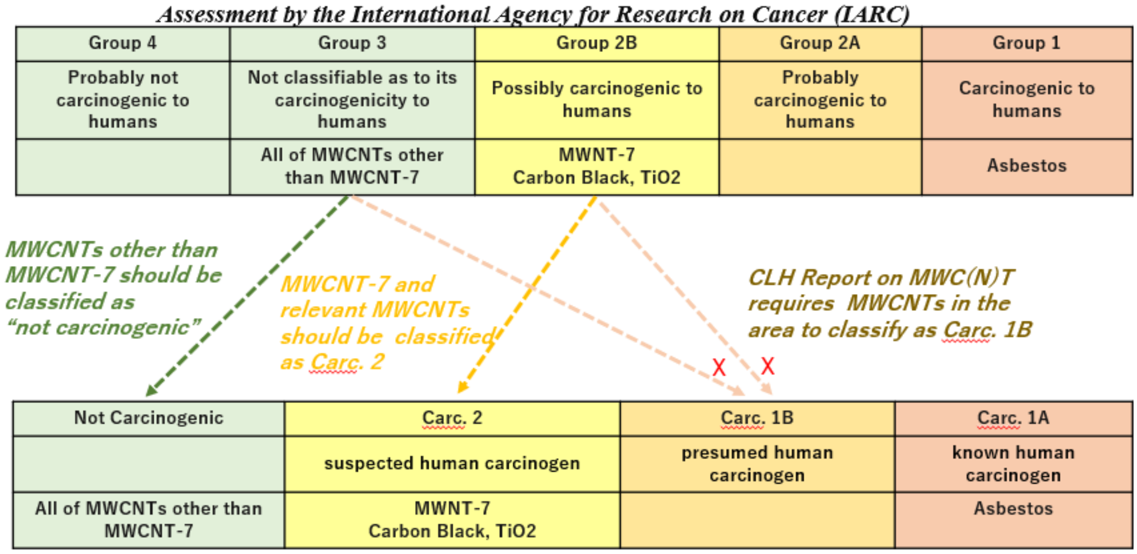
[2] IARC, Asbestos, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man Volume 14. IRAC, 1977
[3] IARAC, Carbon Black, Titanium Dioxide, and Talc, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 93. IARC 2010.
[4] IARC, Some Nanomaterials and Some Fibres, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 111. IARC 2017.



Graph1. Comparison between the IARC assessment and CLH report by BAuA



Graph 2. JBCE suggestion

1. Introduction

For the sake of users and manufacturers of CNTs, JBCE would like to comment on the CLH report on multi-walled carbon tubes and multi-walled carbon nanotubes (MWC(N)Ts), written by BAuA of Germany.

We believe that our knowledge about MWC(N)Ts and our comments on the CLH report could be useful informulating better regulatory measures aiming at facilitating innovation towards the EU Green Deal while ensuring human safety.

2.The classification of CNTs used in the CLH Report by BAuA

Section summary:
The classification of CNTs used in the CLH report makes a few assumptions in contrast with scientific data.

Details:
The CLH report advocates to classify all MWC(N)Ts having a diameter from 30 nm to 3 µm, with a length above 5 µm, and an aspect ratio above 3:1, as presumed or suspected carcinogenic. The proposal is based on the following toxicokinetic characteristics:

1. MWC(N)Ts reach and are retained in the deep lung alveoli by inhalation.
2. Afterwards, the MWC(N)Ts slowly relocate to the alveolar interstitium lung-associated lymph nodes, pleura and other extrapulmonary tissues.
3. MWC(N)T fibres are biopersistent.
4. MWC(N)T fibre retention and deposition depends on time and dose and is related to toxicity.
5. Rigid MWC(N)Ts migrate and penetrate the pleura.
6. Overall, these toxicokinetic properties support an asbestos-like mode of action of rigid MWC(N)T fibers

These points require a few remarks.

1. There is a lot of evidence showing that, in practice, MWC(N)Ts longer than 50 µm don't reach the alveoli of the lung.[5, 6]

2. There is no data supporting relocation for MWC(N)Ts with lengths above 50 µm and for diameters above 150nm.[7]

3. The CLH report is based on the fiber paradigm. In 1997, the WHO called "fiber" all particles that can be observed using an optical microscope – that is, particles longer than 5 µm, with a diameter less than 3 µm, and with an aspect ratio larger than 3:1. Many of these fibers are not biopersistent and are dissolved in organisms after a few weeks. For example, they can be degraded by horse radish peroxidase.

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[5] Y. Taquahashi, An improved dispersion method of multi-wall carbon nanotube for inhalation toxicity studies of experimental animals. *The Journal of Toxicological Sciences (J. Toxicol. Sci.)* Vol.38(4) (2013) 619-628.
[6] T. Kasai, et al., Development of a new multi-walled carbon nanotube (MWCNT) aerosol generation and exposure system and confirmation of suitability for generation and exposure system and confirmation of suitability for conducting a single-exposure inhalation study of MWCNT in rats. *Nanotoxicology*, March 8 (2) (2014) 169-178.
[7] Nagai, et al., Diameter and rigidity of multi-walled carbon nanotubes are critical factors in mesothelial injury and carcinogenesis. *Proc. Natl. Acad. Sci. USA*, 108, E1330-1338(2011).

4. Because many MWC(N)Ts are not biopersistent, this general statement needs to be adjusted.

5. Many MWC(N)Ts are not rigid and, many are not straight. In addition, thick MWC(N)Ts do not migrate as easily as thin MWC(N)Ts.

6. For thick CNTs, for long CNTs, for furballs, microcooils, nanocoils, nanohorns, nanobrushes and for many other types of MWC(N)Ts, there is no asbestos-like mode of action. Also, MWC(N)Ts' chemistry is completely different from that of asbestos.

In short, the CLH report by BAuA makes many sweeping statements that lead to an increased risk assessment with a lack of scientific basis.

3 . On The Relation Between Length, Diameter and Inhalation

Section ssummary:

- Long CNTs, longer than 50 µm, cannot be inhaled and are neither dangerous nor potentially dangerous.
- Thick CNTs, with a diameter above 150 nm, do not induce mesothelioma.

Details:

On the home pages of the Ministry of Health, Labour and Welfare (MHLW) of Japan[8] and of the Environmental Protection Agency of the United States (US EPA)[9], *particulate materials* (PM) smaller than 10µm and smaller than 2.5 µm in diameter are defined as PM10 and PM2.5, respectively. Particulate materials larger than 10 µm can only reach the *upper* respiratory tract, not the deep lung. In contrast, PM10 can be transported to the lower respiratory tract; and only PM2.5 can directly reach the alveoli. For this reason, both the MHLW of Japan and the US EPA do not restrict particulate materials larger than 10µm.[10]

Analogous with the behavior on inhalation of the particulate materials just mentioned, the following properties are expected for MWC(N)Ts in the human body**:**

- MWC(N)Ts longer than 2.5 µm do not reach the deep lung or the alveoli by inhalation.
- MWC(N)Ts in the length range from 2.5 µm to 10 µm can reach the lower respiratory tract of humans by inhalation. Thus, for example, the material MWNT-7 will reach the lower respiratory tract.
- MWC(N)Ts longer than 10 µm do not enter the human respiratory system by inhalation.

In addition, the CLH report refers to the definition of "fiber" by the WHO. Indeed, in 1997, the WHO called "fiber" any particle that can be observed using an optical microscope; that is, particles longer than 5 µm, with a diameter less than 3 µm, and with an aspect ratio larger than 3:1. However, the definition of "fiber" by the WHO has no relation with human health issues. The WHO concept of fiber should *not be used* when discussing carcinogenicity.

The following graph compares the properties of the human respiratory system with the proposed limits by BAuA. The report lists as "suspected carcinogenic" many CNTs that have *no* chance of ever reaching the lungs.[10]

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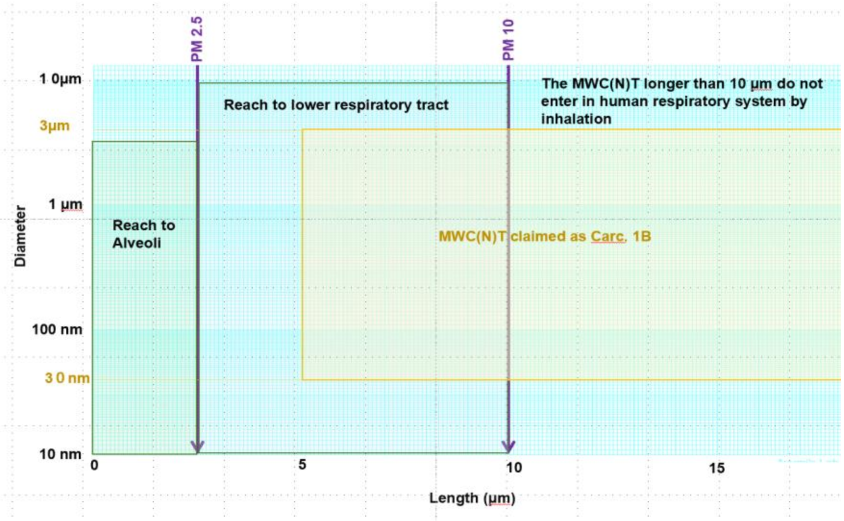
[8] https://www.gov-online.go.jp/useful/article/201303/5.html
[9] https://www.epa.gov/pm-pollution/particulate-matter-pm-basics
[10] L. Yang, et al., The Impact of $PM_{2.5}$ on the Host Defense of Respiratory System, *Front. Cell Dev. Biol.*, 04 March 2020, https://doi.org/10.3389/fcell.2020.00091.



Graph 3. Comparison between the properties of the human respiratory system and the proposed limits by BAuA

The figure compares the size regions of particulate materials deposed in the human respiratory system with the size region proposed in BAuA's report (orange).

In addition, medical research has shown that very thin (below 30 nm) as well as very thick (over 150 nm) MWCNTs are less toxic.[7] The authors specifically propose distinguishing the hazard of MWCNTs by their diameter to distinguish them from asbestos.

In short, we conclude that MWC(N)Ts that are either longer than 50 μm[5, 6] or thicker than 150 nm[7] *cannot* be classified as potential or suspected carcinogens.

4. On The Relation Between Diameter and Shape of CNTs

Section summary:
Different CNT production methods lead to *different CNT shapes*, even for the *same* diameter. Many shapes are not stiff, and thus differ from asbestos, but are curled or tangled balls. In general, CNTs are not fibers, but clusters. For many CNTs, the aspect ratio is hard to measure. **Therefore, the aspect ratio should *not* be used to distinguish or classify CNTs.**

Details:
The study of the growth mechanism of vapor grown carbon fibers indicates:

- All MWC(N)Ts made by CVD initially grow as SWCNTs.
- The morphology and shape of the resulting MWC(N)Ts is the same as the morphology and shape of the initial SWCNTs.
- The thickness of MWC(N)Ts depends on the amount of carbon deposited by thermal pyrolysis of hydrocarbons.

In particular, there is *no* relation between the diameter of MWC(N)Ts and their shape or morphology. The shape of MWC(N)T depends on the shape of the initial SWCNT. For this reason, it is wrong to state, as the CLH report does, that low diameter MWCNTs (< 30 nm) have a more tangled morphology than high diameter materials. In fact, the actual shape depends on the deposition *temperature*: the chemical vapor deposition process under *higher* temperatures results in *straighter*

MWC(N)Ts, due to longer-range ordering of the graphite structure in the tubes.

During the process of production, CNTs often (but not always) form an entangled structure similar to a furball. Such furballs do *not* act like asbestos fibers in the lung. Because furballs and many other structures are *not* asbestos-like, it is therefore *not* possible to call furballs “high aspect ratio materials” (HARM).

Among MWC(N)Ts, there are also coil-shaped structures called “carbon nano coils[11]”, “carbon micro coils[12]”, “carbon nano horns[13]”, and “carbon nano brushes[14]”. When discussing the influence of these materials on human health, it is more important to think about the aspect ratio of the coils and not of the aspect ratio of the nanotubes. Above all the flexibility of the coils must be considered. For such materials, neither length nor aspect ratio are useful or correct parameters to describe them.
Even for MWC(N)Ts having the same diameter and the same length, the materials are quite diverse in *shape and morphology*, such as straight or entangled, in *elasticity,* which depends on the layer number and other properties, in *surface structure,* which depends on the relation between the various graphite structures, and in *surface chemistry*, which depends on the growth method. All these parameters will influence the possible effects on human cells.

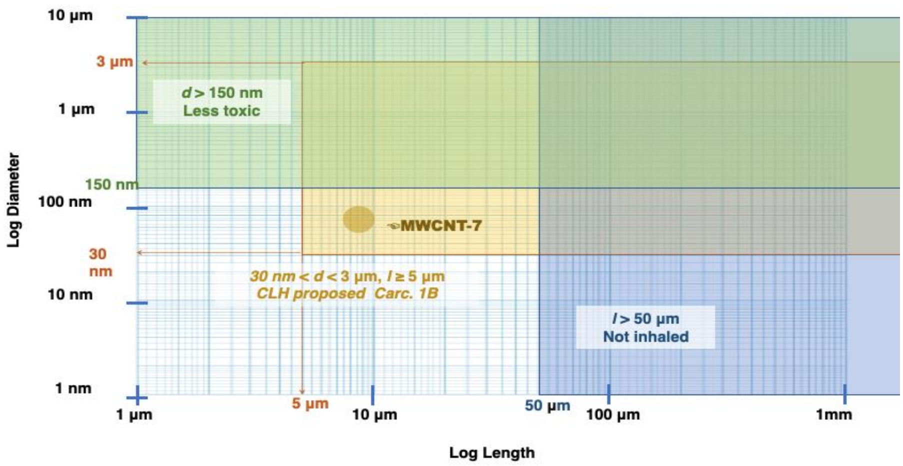
In addition, there is no suitable equipment to reliably determine the diameter of MWC(N)Ts. This is an important technical problem in the estimation of the aspect ratio of MWC(N)Ts.

In short, the aspect ratio is neither a useful nor a practical way to distinguish CNTs from each other or to describe their effects on human cells.

5 . Overall Summary

The above sections have shown that MWCNT hazards correlate with diameter and length, are determined by shape, elasticity and surface chemistry and are not related to aspect ratio. To provide a balanced assessment of the hazards of MW(C)NTs, taking into account the suspected carcinogenic material MWCNT-7, we propose to define the orange region in the following graph as the highest hazard region:

[11] Chengwi Li, et al., A flexible tissue–carbon nanocoil–carbon nanotube-based humidity sensor with high performance and durability, *Nanoscale* 18, 2022.
[12] Microwave absorption properties of carbon fibers with carbon coils of different morphologies (double microcoils and single nanocoils) grown on them
Lei Liu et al. Journal of Materials Science volume 49, pages 4379–4386 (2014)
[13] S. Utsumi, et al., Chapter 13 - Porosity and Adsorption Properties of Single-Wall Carbon Nanohorn, in: J.M.D. Tascón (ed.), *Novel Carbon Adsorbents,* Elsevier, 2012: 401-433(2012).
[14] A. Cao, et al., Multifunctional brushes made from carbon nanotubes. *Nature Materials*, 4, 540–545 (2005).



Graph4. The highest hazard region (in orange region)

1. *Only* MWC(N)Ts with average length between 5µm and 50 µm can be classified as suspected human carcinogen (Carc.2) in the GHS classification, because longer materials are *not* inhaled into the human respiratory system, and only if condition 2 also applies.

2. *Only* MWC(N)Ts with average diameter between 30 nm and 150 nm can be classified as suspected human carcinogen (Carc.2) in the GHS classification, because materials with larger average diameter do not permeate mesothelial cells and are not carcinogenic, and only if condition 1 also applies.

In summary, only materials similar to MWCNT-7 should be classified as suspected human carcinogen (Carc.2) in the GHS classification, in harmony with the monograph on CNTs by the International Agency for Research on Cancer (IARC). For many other CNTs there is no evidence relating to their carcinogenicity and often evidence suggesting the lack of any hazard at all.

CNT has the potential to enable future innovation which will itself accelerate the EU Green Deal. For example, due to its light weight and robustness as a body material in the transportation sector, CNTs will contribute to the reduction of carbon dioxide emissions.

There are many types of CNTs. The CNTs which ensure human safety should be fully utilized for innovation, and hazardous CNTs should be restricted. For this reason, classification based on the latest scientific results will play an important role. We believe that it is possible to minimize risk and promote innovation at the same time in order to bring benefits to the EU.

ABOUT JBCE

Founded in 1999, the Japan Business Council in Europe (JBCE) is a leading European organization representing the interests of about 90 multinational companies of Japanese parentage active in Europe. Our members operate across a wide range of sectors, including information and communication technology, electronics, chemicals, automotive, machinery, wholesale trade, precision instruments, pharmaceutical, textiles and glass products.

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