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Nano-C, Inc.
33 Southwest Park
Westwood, MA 02090
Tel 781.407.9417
Fax 781.407.9419
www.nano-c.com

September 8, 2023

Ms. Heather Tenney
TURI Program Manager
The Offices at Boott Mills West
126 John Street, Suite 14
Lowell, MA 01852

SENT BY: e-mail to Heather_Tenney@uml.edu

RE: Petition to add single-walled and multi-walled carbon nanotubes (CNTs), and carbon nanofibers (CNFs) to the Toxic Use Reduction Act Toxic or Hazardous Substance List - TURA Science Advisory Board Call for Information

Dear Ms. Tenney:

We understand the Toxic Use Reduction Institute's (TURI's) Administrative Council has received a petition to add single-walled and multi-walled carbon nanotubes (CNTs), and carbon nanofibers (CNFs) to the Toxic Use Reduction Act Toxic or Hazardous Substance List. The petitioners have requested the reporting threshold be reduced to 100 grams, and CNTs and CNFs be listed as higher hazard substances.[1]

As a manufacturer of single-walled carbon nanotubes (SWCNTs) in Massachusetts, Nano-C respectfully has submitted information on May 13, 2022, June 15, 2022, September 5, 2022 and November 22, 2022 in response to the above referenced "call for information." On May 26, 2022, June 29, 2022, September 16, 2022 and December 8, 2022, the Science Advisory Board (SAB) met to review and discuss scientific research conducted on SWCNTs. During its December 8, 2022 meeting, the SAB voted to recommend the listing of SWCNTs to the Toxic Use Reduction Act Toxic or Hazardous Substance List "*based on evidence of pulmonary toxicity and environmental persistence. Additional concerns for reactive oxygen species (ROS) production and DNA damage were noted*."[2]

[1] *Petition to Toxics Use Reduction Act Administrative Council*, from Clean Water Action & Public Employees for Environmental Responsibility, to Toxic Use Reduction Institute's (TURI's) Administrative Council, June 24, 2020. https://www.turi.org/content/download/13331/204352/file/Petition_to_Toxics_Use_Reduction_Act_Administrative_Council__4_.pdf

[2] Draft Minutes of the February 10, 2023 SAB Meeting
https://www.turi.org/content/download/14378/223290/file/DRAFT_February_Meeting_Minutes.pdf

During the February 10, 2023, March 10, 2023, and May 12, 2023 meetings, the SAB turned its attention to determine if a recommendation should be made to the Administrative Council to designate CNTs/CNFs "higher hazard substances (HHS)" thereby reducing their reporting threshold. The SAB discussed the HHS designation process employed in 2016 by the then members of the TURI SAB, as well as the 1999 US Environmental Protection Agency's "*rationale for setting very low thresholds for persistent, bioaccumulative and toxic chemicals (PBTs) and chemicals of special concern."*[3] With these determination processes in mind, the SAB evaluated the following criteria for consideration in the HHS designation:

- associated with a severe chronic effect(s), specifically carcinogenicity [e.g., mesothelioma, & carcinogenicity classification by the International Agency for Research on Cancer (IARC)]
- occupational exposure limit(s) (e.g., OSHA PEL, ACGIH TLV®, US NIOSH)[4]
- acute toxicity
- bioaccumulative and/or environmentally persistent/very persistent
- other factor (e.g., effects demonstrated at low doses/concentrations)

With review of the data supporting the criteria listed above, Nano-C concludes SWCNTs do not fulfill the criteria being considered by the SAB for a "higher hazard substance" recommendation. Our analyses follow.

Association with a severe chronic effect(s)

Nano-C's determination: SWCNTs are not classified as a carcinogen by Authoritative Bodies. Existing data do not demonstrate an association between exposure to SWCNTs and an increased risk of any form of cancer. A "higher hazard substance" recommendation for SWCNTs based on the criterion of carcinogenicity/association with a severe chronic effect(s) is not merited.

Per the US OSHA Hazard Communication Standard of 2012 (HCS), classification as a carcinogen is made on the basis of evidence from reliable and acceptable methods, and is intended to be used for substances which have an intrinsic property to produce such toxic effects.[5]

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[3] Draft Minutes of the March 10, 2023 SAB Meeting https://www.turi.org/content/download/14416/223696/file/DRAFT_March_Meeting_Minutes_for_Board_Review%20.pdf

[4] US Occupational Safety & Health Administration Permissible Exposure Limits; American Conference of Governmental Industrial Hygienists Threshold Limit Values®; US National Institute for Occupational Safety and Health

[5] *Hazard Communication, Hazard Classification Guidance for Manufacturers, Importers, and Employers*, Occupational Safety and Health Administration, U.S. Department of Labor, 2016, pp. 151.

If a substance has been designated by OSHA as a carcinogen per 29 CFR part 1910, Subpart Z, Toxic and Hazardous Substances, the OSHA HCS 2012 requires the substance to be classified as a carcinogen.[6] In addition, under OSHA HCS 2012, the following sources may be treated as establishing that a substance is a carcinogen or potential carcinogen for hazard communication:

- National Toxicology Program (NTP), "Report on Carcinogens" (latest edition)
- International Agency for Research on Cancer (IARC) "Monographs on the Evaluation of Carcinogenic Risks to Humans" (latest editions).[7]

OSHA HCS 2012 guidance also suggests consultation of the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs) hazard determination list.[8]

A summary of the carcinogenicity classification of SWCNTs/CNTs by Authoritative Bodies is provided below along with a comprehensive discussion of the IARC's determination for SWCNTs:

AUTHORITATIVE BODY	**STATUS**
U.S. OSHA - 29 CFR part 1910, Subpart Z, Toxic and Hazardous Substances[9]	Single-walled carbon nanotubes not designated as a carcinogen
National Toxicology Program (NTP), *Report on Carcinogens*, Fifteenth Edition[10]	Single-walled carbon nanotubes not listed
International Agency for Research on Cancer (IARC)[11]	Single-walled carbon nanotubes 'not classifiable' as to their carcinogenicity to humans (Group 3)[12] *Additional information provided below*

[6] Ibid., pp. 152.

[7] *Hazard Communication, Hazard Classification Guidance for Manufacturers, Importers, and Employers*, pp. 152.

[8] Ibid., pp. 11.

[9] *Hazard Communication, Hazard Classification Guidance for Manufacturers, Importers, and Employers*, pp. 419.

[10] *15th Report on Carcinogens*, U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, 2021
https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc

[11] *Some Nanomaterials and Some Fibres, Volume 111*, IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, International Agency for Research on Cancer, Lyon, France, 2017, pp. 33-214.

[12] Ibid., pp. 192.
The 2014 IARC Working Group evaluation also states: *MWCNT-7 multiwalled carbon nanotubes are 'possibly carcinogenic to humans' (Group 2B); Multiwalled carbon nanotubes other than MWCNT-7 are 'not classifiable' as to their carcinogenicity to humans (Group 3).*

AUTHORITATIVE BODY	STATUS
American Conference of Governmental Industrial Hygienists (ACGIH®) Threshold Limit Values for Chemical Substances (TLV®-CS) Committee	Single-walled carbon nanotubes not designated as a carcinogen *Additional information provided below*

IARC Classification

A principal objective of the World Health Organization's International Agency for Research on Cancer (IARC) is the "identification of carcinogenic hazards." This identification process … *has evolved over several decades, involves the engagement of international, interdisciplinary Working Groups of expert scientists, the transparent synthesis of different streams of evidence (exposure characterization, cancer in humans, cancer in experimental animals, and mechanisms of carcinogenesis), and the integration of these streams of evidence into an overall evaluation and classification according to criteria developed and refined by IARC."*[13]

In its determination of an agent's carcinogenic hazard, the Working Group evaluates and integrates the body of human and animal evidence, and the mechanistic data. The Working Group then classifies the agent into one of four categories:

- carcinogenic to humans (Group 1)
- probably carcinogenic to humans (Group 2A)
- possibly carcinogenic to humans (Group 2B)
- not classifiable as to its carcinogenicity to humans (Group 3)

In the Fall of 2014, the IARC Working Group met to review the carcinogenicity hazard of carbon nanotubes (CNTs) – SWCNTs and MWCNTs - and other substances. The Working Group noted:

> "[n]*o human cancer data were available to the Working Group, indicating inadequate evidence for the carcinogenicity of CNTs in humans."*

The Working Group reviewed research studies conducted on rodents and in cultured human lung and mesothelial cells. The two laboratory rat studies conducted with SWCNTs were determined to be inconclusive.[14] Examining the mechanistic data, the Working Group stated,

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[13] World Health Organization, International Agency for the Research on Cancer, IARC Monographs on the *Identification of Carcinogenic Hazards to Humans – Preamble*, Lyon, France, Amended January 2019, pp. 1-2. https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf

[14] IARC/WHO Secretariat L Benbrahim-Tallaa; N Guha; V Bouvard; R Carel; F El Ghissassi; Y Grosse; K Z Guyton; B Lauby-Secretan; D Loomis; H Mattock; C Scoccianti; K Strait, *Carcinogenicity of fluoro-edenite, silicon carbide fibres and whiskers, and carbon nanotubes,* The Lancet, Vol 15 December 2014, pp. 1427-1428.

> *As a whole, the Working Group acknowledged that the … mechanisms are all relevant to humans. However, a majority* [of the Working Group] *did not consider the mechanistic evidence for carcinogenicity—especially concerning chronic endpoints—to be strong for any specific CNT. Furthermore, the lack of coherent evidence across the various distinct CNTs precluded generalization to other types of CNTs. Thus, MWCNT-7 was classified as possibly carcinogenic to humans (Group 2B); and SWCNTs and MWCNTs excluding MWCNT-7 were categorised as not classifiable as to their carcinogenicity to humans (Group 3).*[15]

The majority of the 2014 IARC Working Group considered that the lack of coherent evidence among the various CNTs precluded the prediction of carcinogenicity for specific CNTs based on mechanistic evidence alone[16]

IARC has not conducted another comprehensive review of CNTs. However, post the 2014 IARC review, several years later, as an independent endeavor, the members of the Mechanisms Subgroup of the original Working Group conducted *an extended, in-depth examination of the in vivo and in vitro experimental studies according to current hypotheses on the carcinogenicity of inhaled particles and fibers.* [The Mechanisms Subgroup evaluated] *additional studies of CNTs that were not available at the time of the IARC meeting in October 2014.*[17] The post-2014 Mechanisms Subgroup evaluated research data available through 2016, including the 2016 paper by authors Giulia Vietti, et al. titled, *Mechanisms of lung fibrosis induced by carbon nanotubes: towards an Adverse Outcome Pathway*[18] which the SAB considered key information in its recommendation to list SWCNTs to the Toxic Use Reduction Act - Toxic or Hazardous Substance List.

The findings of the post-2014 Mechanisms Subgroup review, "*in general, affirm those of the original evaluation on the inadequate or limited evidence of carcinogenicity for most types of CNTs and CNFs at this time, and possible carcinogenicity of one type of CNT (MWCNT-7)* [Emphasis added]"***.***[19]

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https://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(14)71109-X.pdf

[15] Ibid., pp. 1428.

[16] Kuempel, ED., Jaurand, MC., Møller, P., Morimoto, Y., Kobayashi N., Pinkerton, KE., Sargent, LM., Vermeulen, RCH., Fubini, B., and Kane, AB, *Evaluating the mechanistic evidence and key data gaps in assessing the potential carcinogenicity of carbon nanotubes and nanofibers in humans,* Crit Rev Toxicol., 2017 January; 47(1): 1–58. doi:10.1080/10408444.2016.1206061.

[17] Ibid., pp. 1–58.

[18] Vietti G, Lison D, van den Brule S., *Mechanisms of lung fibrosis induced by carbon nanotubes: towards an adverse outcome pathway (AOP),* Particle and Fibre Toxicology, Vol. 13, 2016. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772332/

[19] Kuempel, ED, et al., pp. 1–58.

The post-2014 Mechanisms Subgroup noted, "*although a considerable body of experimental data on CNTs and CNFs exists, significant data gaps remain in the key steps related to the hypothesized carcinogenic mechanisms of specific types of CNTs and CNFs.*"[20]

In conclusion, the evaluations conducted by the above-mentioned Authoritative Bodies and the weight of evidence do not support the carcinogenicity of SWCNTs.

Occupational exposure limit(s) for SWCNTs

Nano-C's conclusion: No occupational exposure limit established by US OSHA or ACGIH for SWCNTs. The NIOSH Recommended Exposure Limit for CNTs is not a substance specific exposure limit for SWCNTs. The evaluated SWCNT toxicology data for the determination of the NIOSH REL for CNTs are inadequate for the recommendation of SWCNTs a "higher hazard substance."

US employer and employees are informed by occupational exposure limits and guidance developed and issued by three main authoritative bodies: the US Occupational Safety and Health Administration (OSHA); the American Conference of Governmental Industrial Hygienists (ACGIH); and, the National Institute for Occupational Safety and Health (NIOSH).

US *OSHA sets permissible exposure limits (PELs) to protect workers against the health effects of exposure to hazardous substances. PELs are* [enforceable] *regulatory limits on the amount or concentration of a substance in the air.*[21] **OSHA has <u>not</u> developed/issued a permissible exposure limit (PEL) for SWCNTs or for CNTs.**

In 2018, the American Conference of Governmental Industrial Hygienists (ACGIH®) Threshold Limit Values for Chemical Substances (TLV®-CS) Committee selected carbon nanotubes for development of a threshold limit value (TLV®) by including carbon nanotubes on its list of chemical substances and other issues under study. The inclusion of CNTs on the Under Study List signified ACGIH's intention to review the CNT research data to determine if an occupational exposure limit and/or hazard determination is/are warranted. Carbon nanotubes remained on the Under Study List until 2021 when the TLV®-CS Committee moved it to its Tier 2 List indicating the Committee will **not** move forward with the development of a TLV®.[22] In summary, **no AGCIH TLV® has been established for SWCNTs/CNTs; the AGCIH has no plans to establish a TLV in the near future**.

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[20] <u>Ibid</u>., pp. 1–58.

[21] 1988 OSHA PEL Project Documentation
https://www.cdc.gov/niosh/pel88/pelstart.html

[22] Bergeson, L, and Campbell, C., *ACGIH® Will Not Proceed with TLV® for Carbon Nanotubes in 2022, August 4, 2021*
https://nanotech.lawbc.com/2021/08/acgih-will-not-proceed-with-tlv-for-carbon-nanotubes-in-2022/

In 2013, NIOSH published *Current Intelligence Bulletin 65* recommending that exposures to CNT and CNF be kept below the recommended exposure limit (REL) of 1 μg/m^3 of respirable elemental carbon as an 8-hr TWA.[23]

Of note, **a substance-specific occupational exposure limit for SWCNTs was not recommended by NIOSH**.

Limitations of the NIOSH REL for application of SWCNT exposure include:

- the majority of the research data evaluated by NIOSH were conducted on MWCNTs, as limited data evaluating the pulmonary effects of SWCNT exposures in rodents were available to NIOSH during the time of the NIOSH review. No human morbidity data were available for review

- only short-term inhalation studies conducted with SWCNTs were available for consideration. Short-term intratracheal instillation and pharyngeal aspiration studies and one short-term inhalation study conducted with SWCNTs were reviewed by NIOSH; no long-term pulmonary studies were available for review.

  No lethal outcomes were observed in these short-term pulmonary studies, although clear signs of pulmonary toxicity were noted. The limitations of short-term instillation and aspiration studies must be considered when evaluating these pulmonary toxicity results:

  - The delivered dose to the animal, within a fraction of a second, far **exceeds the per unit alveolar surface area in humans exposed to occupational exposure levels over a 40-yr working life**. These bolus dose administration methods ignore completely the effect of dose rate[24]
  - *A high dose rate and high doses may overwhelm normal defense mechanisms and thus result in significant initial pulmonary inflammation, and may also affect disposition of the administered material to secondary organs*[25]

[23] Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, *Current Intelligence Bulletin 65 – Occupational Exposure to Carbon Nanotubes and Nanofibers*, DHHS (NIOSH) Publication No. 2013–145, April 2013, pp. vi.

[24]Oberdorster, G., Castranova, V., Asgharian B., & Sayre, P., *Inhalation Exposure to Carbon Nanotubes (CNT) and Carbon Nanofibers (CNF): Methodology and Dosimetry*, J. Toxicol Environ Health – Part B Crit Review, Vol. 18, No. 0, 2015, pp. 121-212.
doi:10.1080/10937404.2015.1051611.

[25] Ibid., pp. 123.

– Pulmonary toxicology experts agree intratracheal instillation studies *can be problematic as it results in the focal deposition of material*[26,27]

When assessing potential effects of airborne CNT and CNF in animal studies, ***equivalent human exposure conditions ideally need to be mimicked*** *[*Emphasis added*] by considering exposure methods and mode and dosimetric aspects*[28] This was not the case for the sole short-term inhalation study considered by NIOSH. The Shvedova, et al. 2008 study administered a dose of 5 mg/m^3 to mice for 5 hrs/day for 4 days.[29] Oberdorster et al., note *the single inhalation study with SWCNT involved a relatively high aerosol concentration (5 mg/m3) … (Shvedova et al. 2008).*[30,31]

The Shvedova et al. research dose of 5 mg/m^3 is five thousand times (5,000x) the NIOSH REL equaling 730 years of worker exposures at 8 hrs/day for 250 working days per year.[32]

- the REL is ten years old thereby consideration of the well-designed Morimoto et al. inhalation study was not possible

  The Morimoto et al. rat inhalation study found no increases of total cell or neutrophil counts in the bronchoalveolar lavage fluid, or the concentration of cytokine-induced neutrophil chemoattractant in the lungs or bronchoalveolar lavage fluid ninety-days after exposure[33] The

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[26] Driscoll, KE. and Borm, PJA., *Expert workshop on the hazards and risks of poorly soluble low toxicity particles,* Inhalation Toxicology, Vol. 32, No. 2, 2020, pp. 53-62. https://pubmed.ncbi.nlm.nih.gov/32149535/

[27] Driscoll, KE., Costa, DL., Hatch, G., Henderson, R., Oberdorster, G., Salem, H., and Schlesinger, RB., *Forum; Intratracheal Instillation as an Exposure Technique for the Evaluation of Respiratory Tract Toxicity: Uses and Limitations,* Toxicological Sciences, Vol. 55, 2000, pp. 24 –35.

[28] Oberdorster, G., et al., pp. 123.

[29] Shvedova Shvedova AA, Kisin E, Murray AR, Johnson VJ, Gorelik O, Arepalli S, Hubbs AF, Mercer RR, Keohavong P, Sussman N, Jin J, Stone S, Chen B, Deye G, Maynard A, Castranova V, Baron PA, Kagan V., *Inhalation versus aspiration of single walled carbon nanotubes in C57BL/6 mice: inflammation, fibrosis, oxidative stress and mutagenesis*, Am J Physiol Lung Cell Mol Physiol, 2008, Vol. 295, No. 4, pp. L552−L565.

[30] Oberdorster, G., et al., pp. 128.

[31] US OSHA standard of 250 working days per year

[32] At 5,000 µg/m^3, equivalent to 190,000 eight-hour work days at 1 µg/m^3 equaling 730 yrs of exposure

[33] Morimoto, et. al, *Pulmonary toxicity of well-dispersed single-wall carbon nanotubes after inhalation,* Nanotoxicology, November 2012; 6(7), pp. 766–775. doi: 10.3109/17435390.2011.620719

exposure doses of 0.03 mg/m^3 and 0.13 mg/m^3 administered to the experimental animals **are below the concentration** at which lung clearance is retarded[34]

The Morimoto et al. exposure dose of 0.03 mg/m^3 is equivalent to 4 yrs of occupational exposure at the NIOSH REL; the exposure dose of 0.13 mg/m^3 is equivalent to 16 yrs of occupational exposure at the NIOSH REL. Both doses more aptly mimic equivalent human exposure conditions.

In summary, the US OSHA and the ACGIH have not issued an occupational exposure limit for SWCNTs. The NIOSH REL for CNTs is not a substance specific exposure limit for SWCNTs. Few studies conducted on SWCNTs were available during the time of the NIOSH review. The limitations of the short-term studies reviewed render the SWCNT toxicology data inadequate for the determination of a substance specific exposure limit and for the recommendation of SWCNTs a "higher hazard substance."

Acute oral toxicity

Nano-C's conclusion: Ascertainment of a specific median lethal dose by acute oral exposure (LD 50) for SWCNTs is not possible due to the limitations of the guideline studies. Existing SWCNT data are insufficient for a "high hazard substance" recommendation based on the acute oral toxicity criterion.

Matsumoto, et al., conducted an oral acute and a repeat-dose toxicology studies in laboratory rats.[35] ***No deaths occurred, and no abnormalities were observed in the clinical condition during the observation period in any animals [Emphasis added]****. The [oral] LD50 of Nikkiso SWCNT was considered to be greater than 50 mg/kg bw.*[36]

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[34] [L]*ung clearance is retarded by chronic exposure to respirable particles at concentrations of 3 mg/m^3 or higher (Muhle et al, 1988) … the threshold dose leading to impaired alveolar macrophage mediated lung clearance, which is equivalent to approximately 1 mg per gram lung tissue (Morrow, 1988) or 1 µl per gram of lung (Oberdörster, 1995)*

Quotation from: Oberdorster, G., Castranova, V., Asgharian B., & Sayre, P., *Inhalation Exposure to Carbon Nanotubes (CNT) and Carbon Nanofibers (CNF): Methodology and Dosimetry*, J. Toxicol Environ Health – Part B Crit Review, Vol. 18(0), 2015, pp. 123.
doi:10.1080/10937404.2015.1051611.

[35] Matsumoto M, Serizawa H, Sunaga M, Kato H, Takahashi M, Hirata-Koizumi M, Ono A, Kamata E and Hiroseet A, *No toxicological effects on acute and repeated oral gavage doses of single-wall or multi-wall carbon nanotube in rats,* J. Toxicol Sci. Vol. 37, No. 3, 2012, pp. 463-474.
https://pubmed.ncbi.nlm.nih.gov/22687986/

[36] Environment Directorate, Organisation for Economic Co-operation and Development, *Single Walled Carbon Nanotubes (SWCNTs): Summary of the Dossier, Series on the Safety of Manufactured Nanomaterials, No. 70,* Paris, 2016, pp. 25-26.
https://one.oecd.org/document/env/jm/mono(2016)22/en/pdf

Matsumoto, et al. concluded the very high specific volume of SWCNTs does not enable the determination of a specific median lethal dose for oral exposure (LD50); administration of the maximum dose of *2000 mg/kg* as required by the OECD guideline studies for acute and repeated oral dose toxicity was "i*mpracticable*".[37] Guidance for testing voluminous nanomaterials is not available.

In addition to the findings of Matsumoto, et al., the EU registrant manufacturer of SWCNTs determined it was not technically feasible to conduct an acute oral and inhalation toxicity studies on Tuball™ SWCNTs as *"the test item was found to be impossible to formulate satisfactorily in a suitable vehicle for oral or inhalation dosing."*[38]

In their review of the existing data, the Nordic Council of Ministers note, *"[o]nly oral acute toxicity data according to OECD TG 423 are available for Nikkiso SWCNT. Data on additional and different qualities of SWCNT would be needed for a proper assessment of the potential for oral acute toxicity of SWCNTs. Data are too limited for a conclusion on acute oral toxicity of SWCNTs."*[39]

In conclusion, this significant limitation of the testing protocols must be recognized when considering the LD50 > 50 mg/kg bw for SWCNTs as a basis for a "higher hazard substance" recommendation.

Bioaccumulation and environmental persistence

Nano-C's conclusion: The existing evidence is insufficient for a "high hazard substance" recommendation for SWCNTs based on environmental bioaccumulation and persistence.

Bioaccumulation

"Bioaccumulation, … occurs when the chemical concentration in an organism exceeds that in its environmental matrix. The propensity for a chemical to accumulate in tissues could increase the probability of transfer up the food chain from prey to predators, thus creating increasingly larger exposures for upper-level predators, including human beings."[40]

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[37] Ibid., pp. 25.

[38]European Chemicals Agency (ECHA) REACH Registration Dossier for Single Wall Carbon Nanotubes (SWCNT) EC number 943-098-9.
https://echa.europa.eu/registration-dossier/-/registered-dossier/18023/

[39] Larsen PB, Daniel Vest Christophersen VD, and Andersen DN, Nordic Council of Ministers, *Nordic Working Papers - The applicability of the GHS classification criteria to nanomaterials*, Nordic Council of Ministers, 2019, pp. 9.
http://norden.diva-portal.org/smash/get/diva2:1315194/FULLTEXT02.pdf

[40] Bjorkland R, Tobias D,[2] and Petersen EJ, *Increasing evidence indicates low bioaccumulation of carbon nanotubes,* Environmental Science Nanotechnology, Vol. 4, No. 3, pp. 747–766.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5500871/

US EPA grant recipients from the University of South Carolina at Columbia, developed, validated, and applied a new method for detecting SWNT in the aquatic environment, based on near infrared fluorescence (NIRF) spectroscopy.

> *"Application of both the newly developed NIRF spectroscopy technique as well as custom-synthesized radiolabeled SWNT materials to assess the toxicity, fate, and biological uptake of SWNT in the aquatic environment revealed that SWNT associate strongly with particulate phases after entering aquatic systems. Benthic communities appear to be the most important sink for SWNT after entry into the aquatic environment, as these materials become incorporated in bedded sediment.* ***Detailed studies with meiobenthic and macrobenthic estuarine invertebrates revealed that SWNT are practically non-toxic to these organisms and that they may be ingested but not bioaccumulated in tissues to a high level*** [Emphasis added]. *There also was little or no evidence of SWNT trophic transfer within simple benthic food webs as assessed by feeding studies.*[41]

The investigators concluded*, "[t]aken together, our results indicate that SWNT may persist* in the aquatic environment (particularly in sediments)* ***but that they may pose minimal risk to aquatic life*** [Emphasis added].[42]

> (*NOTE, environmental persistence is discussed below.)

A review of the scientific literature from 2005 to mid-2016 supports the findings of the University of South Carolina researchers. Bjorkland et al. reviewed and summarized the literature on CNT[43] bioaccumulation and bioconcentration by invertebrates and non-mammalian vertebrates concluding …

> *"[a] growing body of work finds a low potential for bioaccumulation for CNTs due to the absence of material being absorbed across the gut tract. The findings of bioaccumulation studies are robust across multiple organisms and multiple quantification methods, and the lines of evidence show a lack of CNT transport across epithelial layers at detectable concentrations."*[44]

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[41] Ferguson, P. Lee, Chandler, G. Thomas, *Final Report: Analysis and Fate of Single-Walled Carbon Nanotubes and Their Manufacturing Byproducts in Estuarine Sediments and Benthic Organisms*, EPA Grant Number: R833859, 2011
https://cfpub.epa.gov/ncer_abstracts/INDEX.cfm/fuseaction/display.abstractDetail/abstract_id/8795/report/F

[42] Ibid.

[43] Both SWCNTs and MWCNTs

[44] Bjorkland, R, et al., pp. 747–766.
doi:10.1039/C6EN00389C.

Environmental persistence

Under Section 313 of the US Emergency Planning and Community Right-to-Know Act (EPCRA), EPA uses a half-life criterion of **two months** for water, sediment, and soil and a half-life of two days for air, for the purposes of determining whether a chemical is "persistent" in the environment.[45]

As a definition for "very persistent" could not be identified under US EPCRA, the Stockholm Convention on Persistent Organic Pollutants and the EU REACH Regulation were consulted. Per the Stockholm Convention and the EU REACH Regulation, a substance fulfils the "very persistent" criterion (vP) in any of the following situations:

- the degradation half-life in marine, fresh or estuarine water is higher than 60 days;
- the degradation half-life in marine, fresh or estuarine water sediment is higher than 180 days; or
- the degradation half-life in soil is higher than 180 days.[46]

However, it is important to noted that under the EU REACH Regulation the "persistent" and "very persistent" criteria are not applicable to inorganic substances.[47] SWCNTs is an inorganic substance.

The National Institute of Advanced Industrial Science and Technology (AIST) conducted a series of short-term OECD biodegradation studies evaluating two types of SWCNTs. Biodegradation by biochemical oxygen demand (BOD) after the 28-day cultivation period was 0%.[48] Evidence for the environmental persistence of SWCNTs is suggested by these short-term OECD biodegradation studies. However, the durations of these studies do not meet the timelines of the Stockholm Convention and the EU REACH Regulation criteria.

In conclusion, sufficient evidence that SWCNTs do not bioaccumulate in evaluated environmental organisms. Limited evidence for the environmental persistence of SWCNTs. However, insufficient data for the definitive determination of SWCNTs as an environmentally "persistent" or "very persistent" chemical as per the US EPCRA, EU REACH Regulation and the Stockholm Convention definitions. Thus, insufficient SWCNT evidence for a "higher hazard substance" recommendation based on environmental bioaccumulation and persistence.

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[45] US EPCRA, Federal Register, Vol. 64, No. 209, Friday, October 29, 1999, pp. 58681."
https://www.govinfo.gov/content/pkg/FR-1999-10-29/pdf/99-28169.pdf

[46] Stockholm Convention and EU REACH Regulation Annex XIII definition:
https://reachonline.eu/reach/en/annex-xiii-1-1.2-1.2.1.html
https://www.lawinsider.com/dictionary/very-persistent

[47] ECHA, *Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.11: PBT/vPvB assessment,* 2017, pp. 14
https://echa.europa.eu/documents/10162/13632/information_requirements_r11_en.pdf/a8cce23f-a65a-46d2-ac68-92fee1f9e54f

[48] Environment Directorate, pp. 12.

Other factor - effects demonstrated at low doses/concentrations

Nano-C's conclusion: A definitive laboratory rat study demonstrates no adverse effects after exposure to lower doses of SWCNTs. A "higher hazard chemical" recommendation for SWCNTs is not supported based on this criterion.

The SAB has been interested in determining if SWCNTs may be reasonably anticipated to cause serious or irreversible chronic human health effects at relatively low doses. No epidemiology data are available to provide insight, however the Morimoto et al. inhalation study in rats provides informative evidence.

> "*Wistar rats were exposed to the well-dispersed SWCNT … for 4 weeks. The low and high mass concentrations of SWCNTs were 0.03 ± 0.003 and 0.13 ± 0.03 mg/m^3, respectively. The rats were sacrificed at 3 days, 1 month, and 3 months after the end of exposure. There were no increases of total cell or neutrophil counts in the bronchoalveolar lavage fluid (BALF), or the concentration of cytokine-induced neutrophil chemoattractant in the lungs or BALF in both the high and low concentration-exposed groups. Pulmonary infiltration of neutrophils was not observed in either exposed group throughout the observation period.*"

The authors concluded, *[w]ell-dispersed SWCNT did not induce neutrophil inflammation in the lung under the conditions in the present study*."

The exposure doses of 0.03 mg/m^3 and 0.13 mg/m^3 administered to the experimental animals are below the concentration at which lung clearance is retarded.

> *"It is now well established that lung effects following chronic inhalation to PSPs* [poorly soluble particles] *of low toxicity occur only at exposures which are concurrently leading to an accumulation of particles in the deep lung as a result of significant impairment of pulmonary particle clearance … Analysing results from various lung clearance tests in rats and hamsters … led to the conclusion that lung clearance is retarded by chronic exposure to respirable particles at concentrations of 3 mg/m^3 or higher (Muhle et al, 1988)."*[49]

The Morimoto et al. study is a definitive study for the determination of the effects of exposure to SWCNTs at lower doses demonstrating that serious, irreversible chronic human health effects at relatively low doses **cannot** be reasonably anticipated. This endpoint does not support a "higher hazard chemical" recommendation for SWCNTs.

Conclusion

In closing, based on the above discussion SWCNTs **do not fulfill** the criteria being considered by the SAB for a "higher hazard substance" recommendation:

[49] ECETOC, 2013, pp. 4.

- SWCNTs are not classified as a carcinogen by three key Authoritative Bodies. Existing data do not demonstrate an association between exposure to SWCNTs and an increased risk of any form of cancer

- No occupational exposure limit established by US OSHA or ACGIH for SWCNTs/CNTs. The NIOSH Recommended Exposure Limit for CNTs is not a substance specific exposure limit for SWCNTs. The evaluated SWCNT toxicology data for the determination of the NIOSH REL for CNTs are inadequate for the recommendation of SWCNTs as a "higher hazard substance"

- Ascertainment of a specific median lethal dose by acute oral exposure (LD 50) for SWCNTs is not possible due to the limitations of the guideline studies. Existing SWCNT data are insufficient for a "high hazard substance" recommendation based on the acute oral toxicity criterion

- Sufficient evidence that SWCNTs do not bioaccumulate in evaluated environmental organisms. Limited evidence for the environmental persistence of SWCNTs. However, insufficient data for the definitive determination of SWCNTs as an environmentally "persistent" or "very persistent" chemical as per the US EPCRA, EU REACH Regulation and the Stockholm Convention definitions. The existing evidence is insufficient for a "high hazard substance" recommendation for SWCNTs based on environmental bioaccumulation and persistence

- A definitive laboratory rat study demonstrates **no** adverse effects after exposure to lower doses of SWCNTs.

We thank you again for the opportunity to provide information for this important process.

Respectfully,

Viktor Vejins
President & CEO
Nano-C

Thomas Lada
Vice President of Operations
Nano-C

Jerome Lang
Safety, Health & Environmental
Manager, Nano-C