Petition to Toxics Use Reduction Act Administrative Council

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Name/Chemical Abstract Service Number: Single-Walled Carbon Nano-Tubes, Multi-Walled Carbon Nanotubes, Carbon Nanofibers.

Petition: With this petition, Clean Water Action and Public Employees for Environmental Responsibility (PEER) ask the Toxic Use Reduction Institute's (TURI's) Administrative Council to add carbon nanotubes (single-walled and multi-walled) and carbon nanofibers to the Toxic Use Reduction Act Toxic or Hazardous Substance List and to lower the reporting threshold to 100g. We further ask the Administrative Council to list CNTs and CNFs as higher hazard substances.

Chemical Abstracts Service (CAS) Number: There are hundreds of chemical abstract numbers for carbon nanotubes and carbon fibers. We recommend that TURA add carbon nanotubes (CNTs) and nanofibers (CNFs) as a group to the TURA Toxic or Hazardous Substances List, because CNTs and CNFs are best defined by basic physicochemical properties, similar to the "generic" description that EPA has used in its Significant New Use Rules for nano-materials and CNTs.

MassDEP Code: Not found

Summary Rationale: Carbon nanotubes and carbon nanofibers have a wide range of potential applications in medicine, electronics, construction, and consumer products, among others. There are dozens of facilities in Massachusetts either producing or using these materials--and the market is expected to continue to grow. To ensure the safety of workers and the public, Clean Water Action and PEER ask the Toxic Use Reduction Institute's Science Advisory Board to:

- List CNTs (single-walled and multi-walled) and CNFs as higher hazard substances in the List of TURA Chemicals, with a reporting threshold of 100g;
- Categorize these substances as a group, rather than individually.

Justification for this petition is based on evidence regarding pulmonary toxicity and carcinogenicity. Authoritative bodies, including the National Institute for Occupational Safety and Health (NIOSH) and the World Health Organization's International Agency for Research on Cancer (IARC), have reviewed the evidence for pulmonary toxicity and carcinogenicity. NIOSH set a low Recommended Exposure Level (REL) of $< 1\ \mu/m^3$ for both single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) based on pulmonary toxicity concern.[1] This level was set based on technical feasibility to measure in the field, not levels that were considered fully protective and NIOSH advised that facilities using carbon nanotubes should make sure that all workers also receive medical monitoring.[2] IARC classified MWCNT-7, a batch of MWCNTs used in numerous rodent studies, as a Group 2B carcinogen, "possibly carcinogenic" to humans.[3] More recent studies only add to this evidence-base, reinforcing concerns about these health effects as well as additional endpoints.

Given the unique physicochemical properties, de minimis thresholds do not apply to nanomaterials. Both Belgium and France have set a threshold of 100g for nano-materials, while Denmark, Sweden and Norway have no minimum threshold for required reporting.

Overview: What are Carbon Nanotubes and Nanofibers?

Carbon nanotubes are tiny tubes formed from graphene sheets composed of a carbon atom linked with three other carbons to form a hexagonal ring. Carbon nanotubes may be single-walled , double-walled, or multi-walled, with diameters varying from 1-3 nm (for SWCNT) to 10-100 nm (for MWCNT). Lengths vary widely and are often in the tens of micrometres. SWCNTs tend to form aggregates or agglomerates by clumping together with other carbon tubes. Carbon nanofibers can be produced intentionally or as byproducts of CNT formation. A nanofibre is described by the International Standards Organization as a

> "nano-object with two similar external dimensions in the nanoscale and the third dimension significantly larger. A nanofibre can be flexible or rigid. The two similar external dimensions are considered to differ in size by less than three times and the significantly larger external dimension is considered to differ from the other two by more than three times. The largest external dimension is not necessarily in nanoscale."[4]

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[1] United States Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health, *Current Intelligence Bulletin 65: Occupational Exposure to Carbon Nanotubes and NanoFibers*, April 2013. P. iv.

[2] Ibid., p. vi.

[3] International Agency for Research on Cancer, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Some Nanomaterials and Some Fibers* (vol 111), 2014, p. 192.

[4] ISO TS 80004 (2008)

According to NIOSH: "There is no single type of carbon nanotube or nanofiber."[5] These materials differ from each other in terms of their shape and size. Chemical composition may also vary. Two factors influencing chemistry are:

- residual metal catalysts (e.g., iron, nickel, cobalt or molybdenum) which may remain after production and
- functionalization of the CNT and CNFs, which is the addition of other molecules to CNT or CNF surface.

In addition, organic molecules and various forms of carbon, including soot, graphene and fullerenes, may also accompany batches of nanotubes, depending on production methodology.[6] Residual metals, functionalization and presence/absence of other organic molecules or forms of carbon all affect the inherent hazards of a specific carbon nanotube or fiber. As described by Jacobs et al., there are up to 50,000 potential combinations of SWCNTs and inevitably many more MWCNTs.[7]

Uses

CNT and CNF are currently used in commercial, industrial and biomedical applications. They are valued because of their high tensile strength, electrical conductivity, ability to hold an electrical charge, and ability to store gas and energy, among other properties. Current uses include:

Sporting goods: Sportswear and sporting equipment including sneakers,tennis rackets,bicycles, golf clubs, ice hockey sticks, and skis. In sporting equipment, CNTs impart strength while reducing weight. CNTs may be up to 10% of the mass of these items according to IARC.[8]
Building components: paints, composite materials, reinforced concrete
Automobile components, car tires and rubber crumb: CNTs are replacing carbon black in tires, and are therefore also in tire mulch and artificial turf infill made from tires.
Energy/electronics: Wind turbines, solar cells, batteries, biosensors
Computer/telecommunications: Lithium ion batteries in mobile phones and laptops, disk drives
Textiles: Fabrics including polymers that may have antistatic, thermal conductive, flame retardant or tear proof properties.
Paints
Plastics and rubbers
Water filters
Cosmetics: Anti aging cosmetics and sunscreens[9]

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[5] NIOSH, April 2013, p. 1.
[6] Donaldson, Ken, et. al, *Carbon Nanotubes: A Review of their Properties in Relation to Pulmonary Toxicity and Workplace Safety*, Toxicological Sciences, vol 92(1), 2006, p 7.
[7]Jacobs, Molly, et al, *Precarious Promise: A Case Study of Engineered Carbon Nanotubes*, Lowell Center for Sustainable Production, Massachusetts Toxics Use Reduction Institute, March 2014, p. 3.
[8] IARC,(2014), p. 16.
[9] He, Hua et al. *Carbon Nanotube Applications in Pharmacy and Medicine,* BioMed Research International, 2013: 578290.

Medical and pharmaceutical applications: Finally, carbon nanotubes have a wide range of medical and pharmaceutical uses. Because CNTs can be functionalized and can penetrate cytoplastic and nuclear membranes, they have been used in cancer therapy to target cancer cells without toxicity to surrounding cells. Other applications include immunotherapy, gene therapy, and therapies targeting brain diseases, because CNTs can cross the blood brain barrier. Tissue regeneration on CNT scaffolds is another area of research, and CNTS can be used as biosensors and even for delivery of anti-bacterial and antiviral drugs.

According to Jacobs et al,

> "With such extraordinary chemical and physical properties, many believe that CNTs have sparked the next industrial revolution...In just over two decades since the discovery of carbon nanotubes, technologies relying on engineered CNTs have developed at warp speed. Current and anticipated uses of engineered CNTs are numerous and diverse: sporting equipment, solar cells, wind turbines, disk drives, batteries, antifouling paints for boats, flame retardants, life-saving medical devices, drug delivery technologies, and many more. Some have suggested that every feature of life as we know it is or will be impacted by the discovery and use of CNTs."[10]

Production

Massachusetts is one of the nation's leading centers for nanotech. According to the Woodrow Wilson Center's Project on Emerging Nanotechnologies, Massachusetts is fourth in the nation among states with the most nano-technology businesses and research labs, eclipsed only by California, Ohio and Texas. Over 40 Massachusetts cities and towns have one or more nano-facility, with activity concentrated in Worcester, Boston, Cambridge MetroWest, and the North Shore, An estimated 158 companies and another 67 hospital, government and school-based research labs manufacture or use nano-materials, based on data gathered by the Woodrow Wilson Center, Nanowerk, and Standard and Poors. These three entities each have their own databases of nan-technology companies, although the Wilson Center stopped updating its list approximately ten years ago. These lists don't fully overlap. In fact, only 7 companies appear on all three databases, and the sector is dynamic, so it is possible that some entities are no longer operational. However, a quick google search reveals additional nano-technology businesses that do not appear on any of the lists.

Massachusetts also appears to be a significant player in the global CNT market. Nanowerk lists 65 businesses producing carbon nanotubes and nanofibers world-wide, with four located in Massachusetts: Hyperion Catalysis (Cambridge, MA), Nanolab (Waltham, MA), Nano-C (Westwood, MA), and Chasm (Canton, MA). From simple google searches, Clean Water Action found other

[10] Jacobs et al, p. 1.

companies using carbon nanotubes including: Eikos (Franklin, MA), Busek (Natick, MA), and Veeco/CNT (Waltham, MA). Production volumes are unknown as this information has not been collected or made publicly available. However, **trade magazines routlinely list Hyperion Catalysis as the top or one of the top three producers of carbon nanotubes in the world and often list Nanolab and Arkema (which has one facility in Middleton) in the top ten.**

Massachusetts has limited information about these businesses. Clean Water Action was a signatory to a 2017 letter asking the Executive Office of Environmental Affairs to take steps to understand the state of nanomaterial use in the Commonwealth. In response, the Office of Technical Assistance and Technology (OTA) of the TURA program launched a state-wide survey, with the stated purpose of identifying where Massachusetts companies were manufacturing/using nano-materials, determining best practices, including approaches to environmental and worker protections, and understanding how companies were controlling risk and addressing disposal. However, response rates were so minimal that OTA could not even develop an accurate list of companies using nano-materials. Thirty six companies responded to the survey, with 14 responding that they either manufactured/used nano-materials (9) or were engaged in research and development (5). Five had risk management programs. OTA was unable to get full answers from most respondents, and, of course, only a handful of facilities responded.

This leaves Massachusetts without basic information about the manufacture, use, disposal, and release of nano-materials.

Other Governmental Entities Requiring Reporting

Other countries and some states with strong nano-material sectors have taken steps to learn about materials being developed within their geography. The European Union, Canada, and Japan have all taken more action than Massachusetts to address the potential health and environmental risks of nano-materials.

European Union: Many Member States in the European Union have established nano registries. These registries collect general information from engineered nanomaterial manufacturers, importers and distributors about quantities and uses -- similar to reporting elements in the TURA program. A summary of some of these programs is here: https://euon.echa.europa.eu/national-reporting-schemes

France, Belgium, Sweden, Norway and Denmark all require reporting on nano-materials. These registries require reporting by nano-material manufacturers, importers, and distributors. Each country varies slightly but typical metrics include: identification of material, physico-chemical data, eco-toxicological properties, and identity of purchasers or users of nanomaterials.

In addition, the European Union collects detailed chemical information on nano-materials. In 2012 and 2013, the European Union affirmed that Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) covers nano-materials. On December 3, 2018, the European Commission adopted Regulation EU 2018/1880, which sets additional requirements for nano-materials. As of January 1, 2020, the EU requires chemical users to report on nano-materials separate from bulk counterparts, providing data on volume and use, chemical safety assessment, potential routes of exposure and specific physical and chemical properties

Separately. Europe's Regulation 1271/2008 (Classification, Labelling, Packaging regulation or CLP) sets criteria for the classification of materials as hazardous and establishes labelling and packaging requirements for hazardous materials including nanomaterials. In 2011, entities using hazardous nanomaterials were required to submit data to the European Commission. The EU has established an inventory of nanomaterials based on information submitted in compliance with REACH and CLP.

The European Chemicals Agency (ECHA) has a Nano-materials Expert Group to address scientific and technical issues related to the implementation of requirements for nano-materials in accordance with REACH and CLP. ECHA has developed three-year work plans to improve data quality, address nano-materials of concern (identified by member countries), improve transparency around risk and safe use of nano-materials, and foster synergies with international community and research projects.

Canada: Canada's Environmental Protection Act of 1999 requires all importers or manufacturers of chemicals that are "New Substances" to provide notification to Health Canada. All chemicals not on Health Canada's substance list are new substances. Health Canada must complete an assessment of toxicity before a new substance can be manufactured or imported. Health Canada requires certain nano-specific data, including particle size for substances that are nano-materials and particularly for substances that fall into the following five classes, all of which have been shown to behave differently at the nano-scale: carbon nanotubes, inorganic carbon (e.g. fullerenes, graphene graphitic sheets), metal oxides, metals, metal salts and metalloids, and semiconductor quantum dots.

United States: In 2017, the Environmental Protection Agency put in place a one-time reporting requirement for manufacturers of nano-materials. Under the Toxic Substance Control Act, EPA requires manufacturers to report on nano-materials existing in 2017, and any new ones created after 2017, before proceeding with manufacture or processing.

California: As part of California Health and Safety Code 699, S57018-57020, California may require manufacturers and importers of chemicals of concern to provide data on chemicals, including nano-materials, including analytic test method, and fate and transport in the environment. California's Department of Toxic Substances Control exercises this authority through "chemical call ins," through

which the agency requires manufacturers and users of designated chemicals to submit data. In 2008, California issued its first call-in on carbon nanotubes.

In addition, the Berkeley Engineered Nanomaterials Disclosure Ordinance, passed in 2006, requires facilities that manufacture or use engineered nanomaterials to disclose toxicological, pollution and exposure prevention information on an annual basis. City officials established BENDO, because the City was concerned that the lack of environmental health and safety information on nano-materials posed a hazard to first responders.

Exposure

As described in TURI's factsheet on engineered nanomaterials, unbound nanoparticles and nanofibers are a concern for human health and the environment because of the potential for exposure, especially if nanomaterials are in loose powder form, or suspended in liquids and therefore dispersive.[11] Concerns about CNTs and CNFs have largely focused on inhalation exposure, with a particular focus on workers. IARC notes that dermal exposures may also occur as well as ingestion.[12]

Several authoritative bodies have established CNT and CNF recommended exposure limits that are specific to the occupational setting.

- NIOSH set a recommended exposure limit (REL) at < 1 μ/m^3.
- British Standards Institute (BSI) recommended a "benchmark" CNT Occupational Exposure Limit (OEL) of 0.01 fibers/cm^3
- Swiss Accident Insurance Fund for the Swiss occupational exposure limit list (SUVA) set a limit at .01 fibers/cm^3 for both CNT and CNF.

Ellenbecker et al. (2018) argue that an OEL based on fibers/cm^3 is more appropriate and more protective than OELs based on μ/m^3.[13] The BSI OEL and the Swiss Accident Insurance Fund for CNTs is set at the same exposure level as that for asbestos fibers after remediation. This is also the limit used by the U.S. EPA for asbestos remediation.

No regulatory exposure limits that have been for non-occupational exposures. Medical uses represent one type of exposure that must be fully understood. While CNTs can precisely deliver medicine to

[11] University of Massachusetts Lowell, Toxics Use Reduction Institute Massachusetts Chemicals and Materials Fact Sheet: Engineered Nanomaterials, at: https://www.turi.org/TURI_Publications/TURI_Chemical_Fact_Sheets/Nanomaterials_Fact_Sheet
[12] IARC, (2014).
[13] M. Ellenbecker, et al. The Difficulties in Establishing an Occupational Exposure Limit for Carbon Nanotubes. *J Nanoparticle Res.* 2018; 20(5):131.

previously unreachable locations in the human body, the same innate features which make CNTs valuable may present risk.

In consumer products, CNTs are often bound within a product. Over time, erosion through normal wear and tear, may release CNTs.[14] These releases may be low, but may increase during end of product life, for example, if a product is incinerated. CNTs may also be released from a facility to air or waterways or waste streams, entering the environment. Moreover, there is concern that dust rising from artificial turf fields containing rubber infill, and rubber mulch playgrounds, will get into the lungs of athletes and children. (See: https://www.pitchcare.com/news-media/is-artificial-turf-hiding-an-800-pound-gorilla.html)

Health Hazards

Shortly after carbon nanotubes were first synthesized in 1991, evidence emerged of potential toxicity. The main impacts of concern are pulmonary toxicity, including inflammation, granuloma, and fibrosis, and cancer, particularly mesothelioma and other lung cancers. However, research has also linked carbon nanotubes to adverse impacts on other systems including heart, brain, skin and blood, while raising questions about genotoxicity, as well as developmental and reproductive impacts.

A. Pulmonary Toxicity

In 2013, the National Institute for Occupational Safety and Health (NIOSH) issued a *Current Intelligence Brief,* which found that, **at very low doses, carbon nanotubes and carbon nanofibers cause early and persistent lung effects in animals.** NIOSH based its conclusions on a review of 54 studies of mice and rats exposed to carbon nanotubes and nanofibers. NIOSH concluded that the majority of studies found pulmonary harm, including **inflammation (reported in 44 of 54 studies), granulomas (27 of 54 studies), and pulmonary fibrosis (25 of 54 studies).** NIOSH observed, "Various types of laboratory animal studies have been conducted with CNT and CNF using different routes of exposure to evaluate potential toxicity; these studies have shown a consistent toxicological response (e.g., pulmonary inflammation, fibrosis) independent of the study design (i.e., intratracheal, aspiration, and inhalation)."[15]

NIOSH found:

- **Inflammation, granulomas at deposited sites, and early and persistent pulmonary fibrosis at low doses.**"The fibrotic lung effects in the animal studies developed early (within a few

[14] Petersen E,et al. Potential release pathways, environmental fate, and ecological risks of carbon nanotubes. *Env Sci Technol.* 2011;45(23):9837–9856.
[15] NIOSH (20130), p. 13.

weeks) after exposure to CNT or CNF, at relatively low-mass lung doses, and persisted or progressed during the post-exposure follow-up (~1–6 months)"[16]

- **In studies that compared CNTs to materials known to cause lung damage (asbestos, carbon black, silica) , the CNTs were of similar or greater potency.** [17]

- **Reduced lung clearance** Animal studies also showed reduced lung clearance in mice or rats exposed to relatively low-mass concentrations of CNT [18]

- **Migration to intrapleural space** Mice studies showed migration of MWCNT from pulmonary alveoli to intrapleural space, the area where mesothelioma forms in cases of asbestos exposure There was also evidence of MWCNTs migrating to lymphatics.[19]

In subsequent analyses, NIOSH reviewed studies of workers in plants manufacturing MWCNT. These studies found both inflammatory and fibrotic biomarkers in worker biofluids.[20] NIOSH also noted research that documented changes in messenger RNA and non-coding RNA expression in MWCNT-exposed humans. This research also identified miRNAs and target genes and clarified pathways through which MWCNT could trigger cardiac, pulmonary and carcinogenic impacts similar to those seen in rodents.[21]

NIOSH used seven studies to establish a Recommended Exposure Limit (REL) for workers. Two were subchronic (90-day) inhalation studies (Ma-Hock et al. 2009; Pauluhn 2010a), and five were conducted by other routes and with other durations (Lam et al. 2004; Muller et al. 2005; Shvedova et al. 2005,2008; Mercer et al. 2011).

Conducting Benchmark Dose analysis of the inhalation studies, NIOSH estimated that a working lifetime exposure of 0.2-2 mcg/m^3 (8 hour TWA concentration) was associated with a 10% early risk of adverse lung impacts. NIOSH found human equivalent working Lowest Observable Adverse Effect Level (LOAEL) lifetime concentration was between 4–18 μg/$m^{3,}$ and No Observable Adverse Effect

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[16] Ibid., p. viii.
[17] Ibid., p iv, 33, 39.
[18] Ibid, p vii.
[19] Ibid.
[20] Fatkhudinova, Lilya et al, "Fibrosis Biomarkers in workers exposed to MWCNT," Toxicology and Applied Pharmacology, vol 299, May 15, 2016 at https://www.sciencedirect.com/science/article/pii/S0041008X16300382
[21] Shvedova AA, Yanamala N, Kisin ER, Khailullin Birch ME, Fatkhutdinova LM (2016) Integrated Analysis of Dysregulated ncRNA and mRNA Expression Profiles in Humans Exposed to Carbon Nanotubes. PLoS ONE 11(3): e0150628. https://doi.org/10.1371/journal.pone.0150628

Level (NOAEL) between 1–4 µg/m^3.m NIOSH divided these numbers by uncertainty factors to derive the estimated zero risk levels of <1 µg/m3 for working lifetime 8-hr TWA concentrations.[22]

While NIOSH studied only some of the CNTs and CNFs potentially available, researchers concluded,

> "Until the results from animal research studies can fully explain the mechanisms (e.g., shape, size, chemistry, functionalized) that potentially increase or decrease their toxic**i**ty, **all types of CNT and CNF should be considered a respiratory hazard and occupational exposures controlled at the REL of 1 µg/m^3."**[23]

Moreover, NIOSH stated that the animal studies were relevant for humans because "There are well established correlations between results of animal studies and adverse effects in workers exposed to particulates and other air contaminants (NIOSH 2002, 2006, 2011a, b)."[24]

Subsequent to this NIOSH analysis, a 2018 concluded that inhalable, rather than respirable CNT/CNF, was more consistently associated with fibrosis, inflammation, oxidative stress, and cardiovascular biomarkers in humans[25]

In addition to associations between MWCNT exposure and early effects on lung health in humans as observed in other studies, research from 2017 also observed early effects on the immune system.[26]

B. Carcinogenicity

The 2013 NIOSH report also raised questions about the possible carcinogenic and genotoxic effects of carbon nanotubes. Since the report, additional evidence of MWCNT carcinogenicity has emerged with specific concern about long, rigid carbon nanotubes. Studies suggest that multiple mechanisms work together to induce carcinogenesis in rats and mice, including incomplete phagocytosis, aggregation of carbon nanofibers within macrophages, and resultant release of reactive oxygen species cytokines, and DNA damage.[27]

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[22] Ibid., p. 37-48.
[23] Ibid., p. vii.
[24] Ibid., p. v.
[25] Beard, John, et al,.Carbon nanotube and nanofiber exposure and sputum and blood biomarkers of early effect among US workers, *Environment International*, July 2018, pp. 214-228 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5970999/
[26]Vlaanderen, Jelle et al. A Cross-Sectional Study of Changes in Markers of Immunological Effects and Lung Health Due to Exposure to Multi-Walled Carbon Nano-tubes. *Nanotoxicology,* April 2017, 11(3):395-404 at https://www.ncbi.nlm.nih.gov/pubmed/28301273
[27]World Health Organization, International Agency for Research on Cancer, Monograph 111: Some Nanomaterials and Some Fibers: Carbon Nanotubes and Carbon Fibers, 2017, p. 192, https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Some-Nanomaterials-And-Some-Fibres-2017.

In 2017, the International Agency for Research on Cancer (IARC) released ***Monograph 111: Carbon Nanotubes and Carbon Fibers***. **IARC classified MWCNT-7, a batch of multi-walled carbon nanotubes used in many rodent studies, as Class 2B Possible Carcinogen.** MWCNT-7 was associated with both mesothelioma and bronchiolo-alveolar carcinoma.

IARC did **not find adequate evidence to make a classification for SWCNT or other MWCNTs,** although it did note that two MWCNTs with properties similar to MWCNT-7 (long, rigid) also showed some evidence of carcinogenicity. There was no human epidemiological data to assist in review. In making its designation, IARC looked at the following research:

- In 2014, mice who were exposed to MWCNT-7, after inhalation exposure to the known carcinogen methylcholanthrene (3-MC), were significantly more likely to develop cancer. Thirty eight out of 42 mice developed bronchiolo-alveolar adenoma and carcinoma lesions when exposed to both MWCNT-7 and 3-MC. By comparison, 28 of 54 developed cancer when exposed to 3-MC alone. Mice exposed to just MWCNT-7 developed tumors at the same rate as mice in a control group, except tumors were significantly larger.[28]

- In 2008, mice with a single peritoneal injection of MWCNT-7 were significantly more likely to develop peritoneal mesothelioma (14/16) than a control group (0/19).[29]

- In a 2012 study, four groups of mice received peritoneal injection (0, 3, 30, 300 micrograms) of MWCNT-7 and were observed for 365 days. No control mice developed cancer, but 5/20, 7/20 and 19/20 of the MWCNT recipients developed peritoneal mesothelioma, often lethal, with dose dependent increases in effects.[30]

- In a 2009 study, rats given single intrascrotal injection (0.24 μg/L and 0.5 μg/L) of MWCNT-7 had significant increases in mesothelial cell hyperplasia and mesothelioma. No control rats had impacts, while those exposed to MWCNT-7 developed mesothelial cell hyperplasia (6/7) and peritoneal mesothelioma (7/7).[31]

In 2019, IARC released ***IARC Monographs on the Identification of Carcinogenic Hazards to Humans: Report of the Advisory Group to Recommend Priorities for the IARC Monographs for 2020-2024.***[32] According to this 2019 report:

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[28] Ibid., p 66.
[29] Ibid., p. 33-35.
[30] Ibid.
[31] Ibid., p 72.
[32] World Health Organization, International Agency for Research on Cancer, IARC Monographs on the Identification of Carcinogenic Hazards to Humans: Report of the Advisory Group to Recommend Priorities for the IARC Monographs

- Additional research has shown that inhalation of MWCNT-7 causes lung cancer in rats . Specifically, male and female rats were exposed to MWCNT-7 at concentrations of 0, 0.02, 0.2 and 2 mg/m^3 via inhalation for 6 hours/day, 5 days/week for 104 weeks. Both sexes had increased rates of bronchiolo-alveolar carcinoma at 2 mg/m^3 and males at 0.2 mg/m^3 with significantly increased benign and malignant tumors.

  The research found that MWCNT-7 were retained in the lung, with greater doses resulting in more retention. This study set the LOAEL at 0.2 and 2 mg/m^3 and, using the NOAEL approach, calculated OEL for a human worker at 0.15/μg/m^3.

  These researchers also found that CNT fibers retained in the lung formed dense, cocoon-like masses, between 10-20 μm in length, in alveolar macrophages. Inadequate phagocytosis of longer fibers and complete phagocytosis of fibers that subsequently formed these masses both caused release of ROS and cytokines, leading to extended inflammation and hyperplasia. They found an increase in 8 OHdg formation in males exposed to the highest dose.

- Other types of MWCNTs are also showing evidence of carcinogenicity. A 2016 study examined the carcinogenicity of **MWCNT-N** and found that intratracheal administration of MWCNT N, with a diameter of 30-80 nm and length of 4.2 μ/m^3 induced mesothelioma and bronchiolo-alveolar adenoma and carcinomas in rats with 3/38 and 14/38 rats forming cancers after exposure over 125 mcg of MWCNT-N delivered 8 times over weeks. None of the 56 control rats developed cancers.[33]

- A 2014 study demonstrated that, when administered through intraperitoneal injection, **MWCNT-A, B, C,** and **D** (each having a fiber length of at least 5 μm and a fiber diameter of less than 3 μm with an aspect ratio of at least 3:1) caused mesothelioma in rats. The researchers found that the straight, thicker MWCNT caused mesothelioma to appear sooner than the thin rigid fibers, and that thin curved MWCNT were associated with lowest rates of cancer. The researchers hypothesized that aspect ratio and curvature of CNTs impacted carcinogenicity.[34]

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during 2020-2024 at https://monographs.iarc.fr/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf, p. 142.

[33] Suzui et al, Mutliwalled carbon nanotubes intratracheally instilled into the rat lung induce development of pleural malignant mesothelioma and lung tumors, Cancer Science, vol 107. Issue 7, April 2016, p. 24.

[34] Rittinghausen, S, et al, The carcinogenic effect of various multi-walled carbon nanotubes (MWCNTs) after intraperitoneal injection in rats, *Particle and Fiber Toxicology*, 2014, 11:59 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4243371/.

IARC specifically notes that, "Since the previous evaluation, some evidence of oxidative stress, chronic inflammation, and lung fibrosis was reported in exposed humans."[35]

In addition to those studies cited by IARC:
Research completed in 2018 on MWCNT-7 found that intraperitoneal administration caused peritoneal mesothelioma in mice and rats, while intrascrotal injection caused peritoneal mesothelioma in rats only. Whole body inhalation caused lung carcinoma in rats and promoted lung cancer development in mice exposed to 3-MC. They concluded that phagocytosis of MWCNT was a leading cause of cancer and using NOEAL approach, set 0.15 ng/m^3 as protective level for humans.[36]

A 2017 meta-analysis reviewed 26 studies, completed between 2005 and 2013.[37] Of these, 23 found that MWCNT or SWCNT caused advanced persistent inflammation, fibrosis, and increase in inflammatory markers (BALF, cytokines) in rats or mice exposed to low levels of CNTs via inhalation or intratracheal instillation. Data on lung injury was not consistent. Some showed changes in epithelial cells, others did not. However, a large number of studies showed that carbon nanotubes, particularly longer tubes, remained in the lung. The researchers concluded that CNT are biopersistent fibers that cause inflammation, fibrosis, lung cancer, and, with long term exposure, gene damage, and suggested that the impacts were interrelated.[38]

In December 2019, the US National Toxicology Program published a technical report based on studies of another MWCNT, 1020 long. The NTP set NOAELfor exposure to these long, thin nanotubes at .3/mg/m^3.[39]

Physical and chemical properties that affect carcinogenicity
According to NIOSH's review of studies, "Pulmonary responses were qualitatively similar across the various types of CNT and CNF, purified or unpurified with various metal content and different dimensions."[40] But NIOSH also noted that various studies indicate that functionalization can change lung retention and biological response.

In addition, NIOSH found that physical form did affect toxicity. Long (> 5 micrometer) MWCNTs, but not short or tangled CNTs, caused inflammation in mice, and long, thin rigid MWCNT were linked

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[35] Ibid.
[36] Fukushima et al, "Carcinogenicity of multi-walled carbon nanotubes: challenging issue on hazard assessment," Journal of Occupational Health, v 60 (1), Jan 20, 2018, pp 10-30 at:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5799097/
[37] Koboyashi et al, "Review of toxicity studies of carbon nanotubes," *Journal of Occupational Health*, v. 59 (5), Sept 20, 2017, pp. 394-407 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5635148/
[38] Ibid.
[39]National Toxicology Project, NTP Technical Report on the Toxicity Studies of 1020 Multi-walled Carbon Nanotubes Administered by Inhalation to Sprague Dawley Rats and B6C3F1/N Mice, November 2019, at https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox094_508.pdf.
[40] NIOSH, p. vi.

to inflammation and mesothelioma in rats, where thicker or tangled MWCNT were less likely to cause harm, even with high doses.[41]

C. Genotoxicity

NIOSH, IARC and independent researchers have linked SWCNT and MWCNT to genotoxicity. In its 2013 report, NIOSH described three in vitro studies with human cells that showed SWNCT interfering with mitosis, causing genotoxicity and abnormal chromosome number. NIOSH also reviewed research, some of which showed MWCNTs having no genotoxic effect, and others linking MWCNT to "DNA damage, micronuclei formation, disruption of the mitotic spindle, and induction of polyploidy"[42] NIOSH noted that metal residues on CNTs promoted reactive oxygen species, increasing the possibility of DNA damage.

One study found, "Most CNT studies showed the results of genotoxicity in an acute phase following exposure and induced the formation of DNA breakage, micronuclei, and mutations in the lungs after inhalation and intratracheal instillation"[43] They questioned whether the damage seen in the acute phase could be repaired, and suggested that genetic damage in chronic studies may be the result of damage during acute phases of exposure.

These researchers also found that SWCNT and CNF were linked to genotoxicity. In one study, "SWCNTs induced DNA breakage, micronuclei formation, and ROS production in human peripheral bool lymphocytes."[44] In another, "the pharyngeal aspiration of SWCNTs and CNFs in mice increased the incidence of K-ras oncogene mutations in the lungs at 1 year post exposure. Four day inhalation of SWCNTs also increased the incidence of K-ras and micronuclei positive cells in the lungs at 1 year post exposure."[45]

D. Other Impacts

While this petition asks for listing of CNTs and CNFs based on lung toxicity, potential for carcinogenesis, and genotoxicity, there are other potential concerns.

Researchers identified 13 studies of reproductive and developmental impacts of SWCNT and MWCNT on mice and rats, with 9 of 13 studies showing harm, including teratogenic and embryo-lethal effects.[46]

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[41] Ibid. p. viii.
[42] Ibid., p. 14.
[43] Koyabishi et al, p.399.

[44] Ibid., p. 400.
[45] Ibid.
[46] Kobayashi, Table II.

In 2013, NIOSH researchers raised concerns about systemic cardiac response, writing, "Pulmonary exposure to CNT has also produced systemic responses including an increase in inflammatory mediators in the blood, as well as oxidant stress in aortic tissue and increase plaque formation in an atherosclerotic mouse model.[47] Pulmonary exposure to MWCNT also depresses the ability of coronary arterioles to respond to dilators."[48]

A 2019 comprehensive review of research linking MWCNTs to carcinogenicity, cardiac impacts, and genotoxicity, but also hepatotoxic, dermatoxic, nephrotoxic, and neurotoxic outcomes was published.[49] Carbon nanotubes have the potential to improve cancer treatment, because nanomaterials can cross the blood brain barrier, but this review raises questions about neurotoxicity. Researchers found in vitro research linked both pristine and functionalized MWCNT to DNA damage and ROS production, resulting in increased inflammation of neuronal cells.[50] They also described research on rat brains which showed both pristine and functionalized CNTs led to significant decrease in viability of mixed glial cells from the brain striatum.[51] They concluded that the potential for benefit and harm must be weighed together. While CNTs can help deliver treatments, these nano-materials "can also have destructive effects on human health."

Summary

Massachusetts is one of the country's centers for the development of nano-materials. There are available methodologies to ensure that workers are protected from the inherent dangers of CNTs and CNFs, but Massachusetts officials do not know if industries are putting appropriate protections into place. There may be environmental releases, but Massachusetts officials do not know where those releases occur, or in what quantity. There may be applications for which the risks presented by CNTs outweigh the benefits. Alternatively, there may be applications which require the modification of CNTs to reduce risk of harm. As the scale of CNT production continues to grow, Massachusetts should have an understanding of where CNTs and CNFs are being produced, manufactured and released within the Commonwealth in order to weigh the risks and benefits and make informed regulatory decisions. Therefore, we urge you to list CNTs and CNFs as higher hazard substances in the TURA Toxic or Hazardous Substances List, with a reporting threshold of 100g, and categorize these substances as a group, rather than individually.

[47] NIOSH, p. 34.
[48] NIOSH, p. vii.
[49] Madennajad, R et al,. Toxicity of carbon-based nanomaterials: Reviewing recent reports in medical and biological systems, Chemico-biological interactions, July 2019,307 at: https://pubmed.ncbi.nlm.nih.gov/31054282/
[50] Ibid.
[51] Ibid.

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