Human and environmental safety of carbon nanotubes across their life cycle

Mijin Kim[1,&], Dana Goerzen[1,2,&], Prakrit V. Jena[1], Jia (Emma) Zeng[1], Rachel A. Meidl[3,*], Daniel A. Heller[1,2,4*]

[1]Molecular Pharmacology Program, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA.
[2]Department of Physiology, Biophysics, & Systems Biology, Weill Cornell Medicine, Cornell University, New York, NY 10065, USA
[3]Baker Institute for Public Policy, Rice University, Houston, TX 77005, USA.
[4]Department of Pharmacology, Weill Cornell Medicine, Cornell University, New York, NY 10065, USA

[&]These authors contributed equally.
*Corresponding authors: Daniel A. Heller (hellerd@mskcc.org) and Rachel A. Meidl (rachel.a.meidl@rice.edu)

Carbon nanotubes are a large family of carbon-based hollow cylindrical structures with unique physicochemical properties that have motivated research for diverse applications; some have reached commercialization. Recent actions in the European Union that propose to ban this entire class of materials highlight an unmet need to precisely define carbon nanotubes, to better understand their toxicological risk effects on human health and the environment throughout their life cycle, and to communicate science-based policy-driving information regarding their taxonomy, safe sourcing, processing, production, manufacturing, handling, use, transportation, and disposal. In this review, we discuss current information and knowledge gaps regarding these issues. We highlight the significance of life cycle assessments of carbon nanotubes and provide a framework to inform policy decisions.

Carbon nanotubes (CNTs) are a family of sp^2-hybridized carbon-based hollow cylindrical nanostructures. CNTs were first discovered in 1991[1] and quickly garnered international interest among researchers and industries in diverse fields on account of their unique mechanical, physicochemical, and electronic properties.[2-5] They exhibit outstanding mechanical properties due to a combination of stiffness and tensile strength.[3] CNTs can exhibit high conductivity and tunable semiconducting properties.[6,7] The thermal conductivity of CNTs is greater than that of natural diamond and the basal plane of graphite.[3,5] Single-walled carbon nanotubes (SWCNTs) exhibit unique optical properties such as stable fluoresce in the near-infrared (NIR) region.[8] Multi-walled carbon nanotubes (MWCNTs) consist of multiple, nested SWCNTs, resulting in high mechanical strength[9]. Owing to their unique electronic and mechanical properties and physicochemical diversity, CNTs have been extensively investigated for applications in energy storage[10], optoelectronics[11], light sources[11], environmental remediation[12], biological research[13], diagnostics[14], therapeutics[15], functional textiles[16], wearable devices[17], and construction[18]. Industrial applications of CNTs are rapidly expanding, and current markets for CNTs include light-weight, high strength composite materials,[18,19] high performance electronics,[20] and energy storage.[21]

Several thousand tons of CNTs are produced annually for use in research labs and industry.[21] Recent advances in CNT characterization and processing methods have brought CNTs to the forefront of nanomaterial research and applications, substantiating the need to precisely classify and define the various types of CNTs and identify relevant toxicological and environmental risks when making evidence-based policy decisions regarding CNTs at each stage of their life cycle (**Figure 1**). These stages include R&D, sourcing, processing, production, primary and secondary manufacturing, usage, transportation, and end-of-life pathways, such as recycling and disposal. This task is complicated by the diversity of CNT forms and preparations (**Figure 2**), and the wide array of their uses and applications. Emerging evidence paints a nuanced picture of the toxicological risks of CNTs, and policymakers must consider a context-dependent approach to ensure that risks are minimized to industry workers and the public while also minimizing the regulatory burden on industry and research. As applications of CNTs expand, safety, environmental, societal, economic, and other potential impacts and externalities should be assessed across all stages of the life cycle. This review is timely due to rising concerns and limited information regarding CNT toxicity and environmental persistence[22], proposed CNT restrictions in the EU by the International Chemical Secretariat **[G]** correspondences[23-26] and the EU Observatory for Nanomaterials **[G]**,[27] and ongoing CNT-related regulations and research by governmental agencies[28-32].

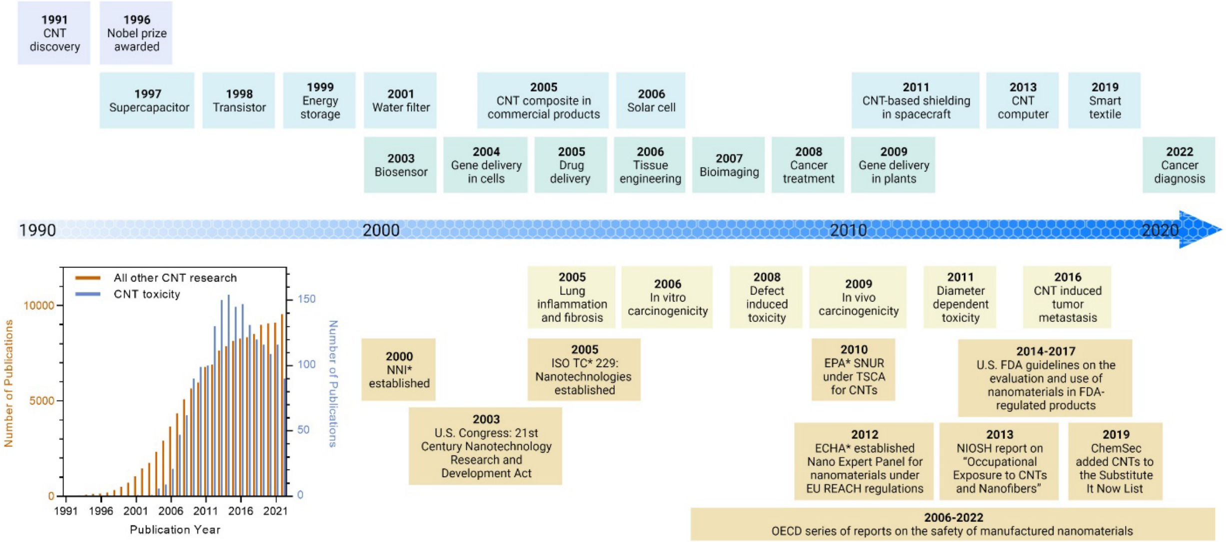


Figure 1 | Progression in CNT research, applications, toxicity assessment, and policies. Timeline of milestone in CNT research (blue boxes), toxicity investigation (yellow), and regulations (orange) since their discovery in 1991. Inlet figure shows the number of primary research articles on CNT toxicity and all other CNT-related primary research identified from a Scopus keyword search. Research into CNTs across all disciplines has reached a plateau at over 8000 publications annually. Toxicological research spiked in the early 2010s up to approximately 150 annual publications but has since fallen to under 100 annual publications in recent years. *NNI: National Nanotechnology Initiative **[G]**, ISO/TC 229: International Organization for Standardization Technical Committee **[G]**, EPA SNUR: US Environmental Protection Agency, Significant new use rules **[G]**, TSCA: Toxic substances control act **[G]**, ECHA: European chemicals agency **[G]**, EU REACH regulations: The Regulation on the registration, evaluation, authorization and restriction of chemicals **[G],** and NIOSH: National Institute for Occupational Safety & Health **[G]**.

In this Perspective, we discuss the chemical identity, diversity, and nomenclature of CNTs, materials characterization and the reporting/standardization of methods thereof, toxicological and environmental considerations throughout the CNT life cycle, economic and sustainability considerations, and policy recommendations. We discuss known risks of CNT exposure to humans and the environment, and the challenges in adequately investigating health and environmental effects given: 1) the diversity of CNT classes, morphology, and chemistry, 2) characterization issues of CNTs, 3) the potential routes of exposure, 4) the lack of health-based occupational exposure limits, 5) the lack of appropriate exposure metrics, and 6) the knowledge gaps between safety assessments and research use of CNTs. Finally, we highlight the need to better understand the fate, exposure, transport, and effects of nanomaterials across the life cycle of CNTs, to build consensus on testing methodologies, to embrace the principles of sustainability and green chemistry when engineering carbon nanomaterials, to inform the implementation of regulatory measures for the design, quality, standardization, and safety of CNT products as well as policies to control unsafe or unwarranted use of nanoscale materials.

[h1] CNT Chemical Diversity and Taxonomy

CNTs exist in diverse forms that exhibit a wide variety of physical and chemical properties (**Figure 2**). The physical characteristics of CNTs, such as the number of walls, diameter, chirality, and length determine their intrinsic physicochemical and electronic properties.[33]

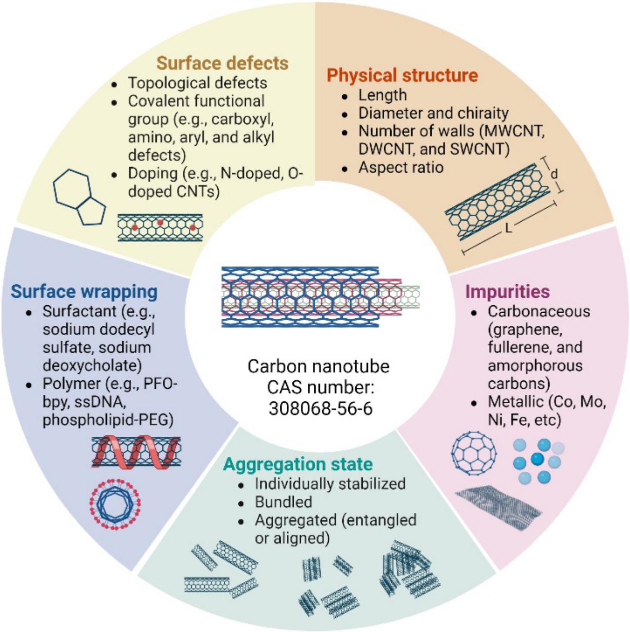


Figure 2 | Physical and chemical diversity of carbon nanotubes. CNTs can exist in many different chemical and physical forms, many of which have different applications as well as toxicological impacts. The diversity of CNT form and function is not reflected by the nomenclature, as exemplified by a single Chemical Abstract Service (CAS) number to refer to all CNT materials.

[h2] Physicochemical identity of CNTs

The number of walls that a CNT is made up of controls many of their properties. Single-walled carbon nanotubes (SWCNTs) consist of one tube, while multi-walled carbon nanotubes (MWCNTs) consist of two or more single tubes nested within each other. The diameter of MWCNTs can be extended to 100 nanometers and the distance between the two walls is 3.5 angstroms, similar to the distance between the two graphene layers in graphite.[34] At increasing diameter and number of walls, MWCNTs tend to exhibit clear metallic properties. Other related CNT materials are sometimes studied intensively enough to be incorporated into the lexicon, such as double-walled carbon nanotubes (DWCNTs) and few-walled CNTs (FWCNTs), for instance.[4] DWCNTs consist of two coaxially aligned SWCNTs. Electronic and physical coupling between the two walls leads to new properties not observed in SWCNTs and other MWCNTs, e.g., superconductivity and wavefunction mixing.[35-38]

Tube length, geometry, and degree of structural perfection strongly influence the properties of CNTs, such as their electrical and thermal conductivity and fluorescence efficiency.[39,40] CNTs range from 10 nanometers to several centimeters in length in an as-synthesized form.[41] There are approximately 126 distinct nanotube chiralities **[G]** (distinct physical structures) within the diameter range of 0.5–1.5 nanometers.[4] The chirality determines the physical and electronic characteristics of nanotubes, including whether they are metallic, semiconducting, or semimetallic.[4] In principle, CNTs should be cylindrical layers of structurally perfect graphene. In practice, these layers have defects, which can lead to geometrical distortions (e.g., kinks) and significantly different properties. Importantly, MWCNTs tend to have more defective structures, whereas SWCNTs, DWCNTs, and FWCNTs usually have high structural order. Correspondingly, industry reports often group DWCNTs and FWCNTs in the SWCNT class[42].

[h2] Synthesis and post-processing

The synthetic process used to produce nanotubes dictates many of their properties and physicochemical diversity. Major synthesis methods include arc discharge[1], laser ablation[43], chemical vapor deposition (including the HiPco[44] and CoMoCAT processes[45]), and enhanced direct injection pyrolytic synthesis (eDIPs)[46]. Different synthetic methods result in diverse chirality and length distributions, structural defect density, yields, and impurities, such as metal catalysts, amorphous carbon, soot, graphite, and non-tubular fullerenes. The purity of commercialized CNTs ranges from ~50% to >99.9%. Post-processing methods are used to remove impurities, defective CNTs, add dopants or chemical modifications, and to produce dispersions, matrices, or structures such as ordered CNT assemblies[47-55] (described in further detail below). Technological advancements in CNT purification enable scalable purification of CNT types, including separation of SWCNTs from MWCNTs[56], separation of lengths[57], separation of metallic vs. semiconducting tubes[58,59], and isolation of single chiralities[47,60,61].

CNTs can be modified by post-processing techniques that control their aggregation state, such as surfactant or polymeric wrapping and surface functionalization. As synthesized, CNTs form aggregates due to strong van der Waals interactions between adjacent CNTs. These aggregated CNT bundles can be individually dispersed depending on the desired physicochemical or electronic properties. Colloidal stability of individualized CNTs in organic or aqueous solutions can be obtained via physical disruption of inter-tubular forces and the inclusion of polymers[47,57], surfactants[8,62], polar organic solvents[48], super acids[49], or biomaterials[63,64]. Ionic[48] or superacid dissolution[49] can spontaneously suspend CNTs in a liquid. Aqueous suspensions of CNTs typically take advantage of hydrophobic or π-π interactions between CNTs and amphipathic excipients[47,60], and/or the formation of micellar structures between the dispersants and CNTs[8]. Organic polymers, such as poly-[(9,9-dioctylfluorenyl-2,7-diyl)-alt-co-(6,6′)-(2,2′-bipyridine)] can yield spontaneous selective dispersion of a single chirality in toluene[47]. Due to the non-destructive nature of the separation and dispersion process, such CNTs exhibit low defect densities and long average lengths. Biocompatible materials such as phospholipid-poly(ethylene glycol)[57], or biopolymers such as single-stranded DNA[65,66], enable suspensions with high colloidal stability in biological media. Biocompatible SWCNT suspensions are under substantial investigation for bioimaging[67], sensing[68], and nanocomposite applications[69] (**Box 1**).

Box 1 | Strategies to confer biocompatibility of carbon nanotubes.

Physical Modification of the CNT surface. Surface functionalization involves covalent modification of the surface of CNTs with hydrophilic functional groups, such as hydroxyl, carboxyl, or amine moieties.[165] These functional groups improves the dispersibility of CNTs in aqueous solutions and can mitigate cellular immune responses to CNTs, enhance their stability, and facilitate interactions with biomolecules. Chemical grafting of biocompatible polymers, e.g., polyethylene glycol (PEG) onto carboxylated or amine-functionalized CNTs can further improve biocompatibility of CNTs, significantly reducing oxidative stress to cells.[166] Additionally, surface functionalization can impart specific properties to CNTs, such as facilitating the incorporation of targeting ligands or drug/gene-loading capabilities, further expanding their biomedical potential.[15,70,71] Another technique to enhance biocompatibility is non-covalent coating of CNTs with a layer of biocompatible materials. These biocompatible polymers coat CNTs, forming a protective layer around them, reducing their cytotoxicity, and preventing aggregation in aqueous media–all of which are key parameters that relate to potential toxicological effects of CNTs. Additionally, the polymer shell can act as a barrier, minimizing the interaction between CNTs and biological systems, thus reducing adverse biological effects. For example, SWCNTs encapsulated in PEG derivatives have demonstrated long blood circulation time (up to 20 hours)[167] and have been extensively used in bioimaging[57,67]. Wrapping with single-stranded DNA can confer colloidal stability and biocompatibility even in the lysosome[160,168] and has resulted in CNT materials that do not trigger inflammatory, cytotoxic, or genotoxic responses in cells and mice for several months.[65]

Processes of CNT Purification. CNT compositional purity is a key parameter determining potential toxicological effects. Therefore, extensive research has been conducted to identify strategies to either synthesize high-purity CNT materials or develop methods of processing to remove synthetic impurities and defective CNTs. In recent years, commercial grade SWCNTs have achieved upwards of 99.9% pure SWCNT materials such as IsoSol-S100® from NanoIntegris Inc. With current bulk production methods, it is possible to selectively synthesize SWCNTs or MWCNTs, and in the case of SWCNTs, it is possible to synthesize single-chirality CNT.[169] Much research is underway to further tune synthetic methods to result in CNT samples with narrow diameter distributions.[170]

During the synthesis process, heavy metal catalysts are often used to seed the synthesis of a CNT. Residual heavy metal and carbonaceous impurities embedded in CNT samples can be toxic[104] and can be removed with various post-processing methods such as oxidative treatment,[171,172] aqueous two-phase extraction,[58] gel chromatography,[90] or density gradient ultracentrifugation.[35,56,57] These purification methods can not only remove impurities but also can be used to efficiently sort CNTs by metallic/semiconducting nature, chirality, length, diameter, or number of walls – all of which can play a role in potential toxicities.[47,56-61]

The toxicological impact of CNT has been shown to be mitigated by dispersing aggregations or bundles into individually dispersed CNTs. This is typically achieved by tip ultrasonication in the presence of CNT dispersing agents, e.g., amphipathic surfactants and biocompatible polymers, which serve to coat the CNT sidewall and prevent re-bundling between CNTs, followed by ultracentrifugation to remove bundled CNTs and carbonaceous impurities.

Surface defect topography plays a significant role in CNT interactions with biological molecules and the biocompatibility of CNTs. Smoother surfaces minimize the risk of cellular damage and reduce the potential for biofouling or immune responses.[34,178,179] Synthetic techniques such as thermal annealing or plasma treatment can be employed to control the surface roughness of CNTs, mitigating CNT toxicity.[180,181]

Continued on next page

Box 1 | Strategies to confer biocompatibility of carbon nanotubes, continued

Incorporation into biocompatible devices. By combining CNTs with biocompatible materials like biopolymers or hydrogels, the resulting composite materials can inherit the favorable properties of both components.[69,182,183] The biocompatible matrix prevents CNT leakage, reduces their toxicity, and facilitates their integration into biological systems. Using CNTs as scaffolds in tissue engineering has been shown to promote cell adhesion, proliferation, and differentiation with no significant cytotoxicity. CNTs can also enhance the mechanical properties of the scaffolds, making them more suitable for load-bearing applications such as in bone nanocomposites.

Incorporating CNTs into implantable or wearable devices could facilitate long-term use of CNTs *in vivo* and translational potential. CNTs can be encapsulated into microfiber textiles to fabricate wearable optical textiles to monitor local oxidative stress[17] or be incorporated into semi-permeable implantable membranes or nanoneedle arrays to monitor disease biomarkers.[68]

Ways to degrade. To address toxicity risk arising from bio-persistence and bioaccumulation of CNTs, methods of CNT degradation have been developed. These methods involve the chemical oxidation of CNT sidewalls with hypochlorite or hypochlorous acid, which then results in wall failure and the generation of small fragments of non-toxic carbonaceous material.[185] Enzymes, neutrophils, and macrophages have been shown to biodegrade CNTs in vitro and in vivo through enzymatic oxidation.[129-131] These methods can be further tuned to ensure that CNT do not biopersist and are appropriately disposed of following end-of-life usage of any CNT composite material.

Moreover, covalent functionalization of CNTs can modulate their physicochemical properties and vastly increases their chemical diversity. Modifications with hydrophilic functional groups, such as carboxyl or amine moieties, can improve solubility in aqueous media, potentially making CNTs useful for gene or drug delivery applications.[70,71] The incorporation of sp^2 defects by DNA functionalization[72], oxygen doping[73], and molecularly tunable covalent sp^3 quantum defects (sometimes called organic color centers)[74] modulates the electronic and fluorescence properties of SWCNTs and introduces new functionality and chemical sensitivities for applications such as biosensors.[14,75,76]

Finally, macroscopic state of aggregation has emerged in the past decade as an important factor affecting the physicochemical properties of CNTs. Whereas early CNTs were used as powders or dispersions, techniques emerged in the late 2000s to form macroscopic materials (fibers, yarns, wires, tapes, sheets, fabrics, etc.) with controlled CNT alignment and packing[50-55]. CNTs assembled into well-defined structures are useful for applications such as electronics, textile coatings, and printing applications.[51] Commercialization of these materials is at an earlier stage, however, with production at the sub-ton level[77].

[h2] Database definition of CNTs

Despite the diversity of CNT types and classification methods, their structural and functional diversity is largely not reflected by regulatory bodies or databases. The Chemical Abstracts Service (CAS) **[G]** database has classified all CNT types with the same CAS number (308068-56-6) regardless of physical structure, synthesis method, or chemical functionalization. All commercial CNT materials are currently listed under this number. Although as-produced CNT materials and purified CNT materials exhibit physical, chemical, and toxicological heterogeneities, these differences are not reflected in this taxonomy. As a result, the properties of CNT materials cannot be differentiated by nomenclature. For comparison, fullerenes, another carbon allotrope nanomaterial, have unique CAS numbers to reflect each chemical formula and size[78], facilitating comparisons between materials. The CAS number of C_{60} (buckminsterfullerene) is 99685-

96-8, whereas that of C_{70} is 115383-22-7, and C_{76} is 142136-39-8. Regarding the taxonomy of a less chemically definable material, potentially more analogous to CNTs, polymers may provide the best example. Polyethylene, for example, has multiple CAS numbers depending on stereochemistry and chemical modification, such as branching versus linear. Branched polyethyleneimine can be comprised of a heterogenous number of branch points and molecular weights and is classified under different CAS numbers depending on the average molecular weight (e.g., 9002-98-6 for average MW: 25000g/mol, or 25987-06-8 for average MW: 800g/mol).

A similarly granular approach as with fullerenes and polymers, in order to differentiate types of CNT materials to best account for their many differences, should be applied to CNT materials. Although chemical differences, which the CAS database was intended to catalog via chemical formula, do not account for almost any of the differences in CNT material properties, it may still be possible to separate some of the CNT forms in this and other databases. The CAS database was recently expanded to include the differences between single and multiple walls, as well as individual manufactured forms. New registry numbers include single-walled/SWCNTs (2923219-92-3) and multi-walled/MWCNTs (2923220-20-4). In addition, specific CAS registry numbers now exist for CNT materials produced by manufacturers (e.g., SG65i CoMoCAT, Mitsui-7, and many others) where substantial information is publicly available (the full list of CAS registry numbers is available at SciFinder.com).

We propose that, to best facilitate comparisons and prevent confusion, CNT product manufacturers and academics use these more specific CAS numbers in product listings and publications, instead of the overarching CNT CAS number, when possible. Designation and listing of current and new CNT-based products could better facilitate assessment and differentiation of the health and safety characteristics of CNT materials produced at scale. Academic researchers should reference more specific registry numbers to provide clarity when making research claims, to prevent incorrect conflation and generalization. As databases, such as that maintained by CAS, are only useful when updated and utilized, we also propose that new/unique CNT materials be included in the registry when commercialized and used/cited for commercial and academic purposes. Additional designations may also be needed for CNTs in non-raw form, as incorporated in products e.g., differentiating highly structured macroscopic CNT materials (yarns, tapes, fabrics, etc.) from CNT powders. More discussion on this topic is provided in a later section.

There are both advantages and limitations in this approach to increase the granularity of CNT classification. The benefits of augmenting and using multiple CAS registry designations to account for the variety of CNT materials could improve research reproducibility by facilitating more precise methodological reporting, help scientists assess the toxicological and environmental effects of the many forms of CNTs, and provide policymakers with better guidelines for CNT use based on their specific toxicological and environmental considerations. The limitation of this approach is the reduction in simplicity of the existence/use of one CAS registry number for all CNTs. However, because it is now apparent that different forms of CNTs can exhibit properties so different from each other that the CNTs barely resemble each other physicochemically, an adjustment is needed in the usage of CNT definitions and nomenclature so as not to confuse researchers, regulatory bodies, and the public.

[h1] CNT Characterization and Reporting Standards

Many fundamental studies and technological applications, as well as meaningful toxicological and environmental studies, require well-defined CNT structures, with known and well-characterized physicochemical properties. Reliable and robust characterization methods have been extensively investigated. In this section, we introduce various metrological methods to characterize CNTs and their biological effects (**Table 1**), and we discuss the lack of standardization on minimal metrology information for CNT toxicity studies.

Material characterization	
Length Aspect ratio Diameter	AFM[68] SEM & TEM[1,79]
Diameter Chirality distribution	Raman spectroscopy[15,140] NIR fluorescence spectroscopy[8] UV-visible-NIR absorption spectroscopy[8] Scanning tunneling microscopy[82] Rayleigh scattering spectroscopy[2]
Number of walls Chirality distribution	X-Ray Diffraction[86,87]
Aggregation state Dispersion quality in solution	AFM[141] Zeta potential[141] UV-Vis-NIR absorption spectroscopy[8,142] Neutron scattering[83-85]
Concentration	UV-Vis-NIR absorption spectroscopy[143,144]
Metallic impurities	TGA[79,88] SEM & TEM[79,80] Glow discharge mass spectrometry[91] Energy-dispersive X-ray spectroscopy[88]
Chemical defects Sample composition	UV-Vis-NIR absorption spectroscopy[74] TGA[79,88,89] Raman spectroscopy[74,145] Fourier-transform infrared spectroscopy[15,79] X-ray photoelectron spectroscopy[74,79]
Biological Toxicity Assessment	
Cytotoxicity	Cell viability e.g., ATP assay[146], trypan blue cell counting[147], LDH assay[147,148] Cell proliferation e.g., WST-1 assay[148] Biomarkers for cell death mechanisms e.g., PARP (apoptosis) [149], RIP (necrosis)[149], GSDMD (pyroptosis)[150], Caspase[150] Autophagy activation[151]
Genotoxicity	γH2AX detection[152,153] Micronucleus assay[154,155]
Immune response	Proinflammatory cytokine measurement, e.g., IL-1β, IL-4, TNF-α[156,157] Activation of pattern recognition receptor pathways, e.g., NLRP3 inflammasome activation[158] Inflammatory markers, e.g., white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils[65] Immune cell activation[157]
Oxidative stress	Acellular oxidative potential assay[159] ROS measurement[146,153]
Cell/organelle morphology	Brightfield microscopy TEM[153,160] Membrane damage by L-leucyl-L-leucin methyl ester[156,161]
Absorption, distribution, metabolism, and excretion	NIR fluorescence imaging[13] Raman mapping[162] Confocal fluorescence microscopy[163,164]
In vivo toxicity	Survival[65] Weight change[65] Tissue- or organ-specific damages e.g., serum biomarker for hepatic injury or renal function[65] Blood oxygenation[65]

Table 1 | Characterization parameters and methodologies for safety assessment of CNTs.

[h2] Characterization methods in research journals

To characterize CNT morphology, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are used to assess geometrical properties and topological defects, such as the collapse of CNTs, pentagon-heptagon pairs, missing carbon atoms, length, and diameter.[1,15,79,80] Atomic force microscopy is used to characterize the length distribution of CNTs, surface wrappings, aggregation states, and chemical functionalization.[68,81] Scanning tunneling microscopy[82] and Rayleigh scattering spectroscopy[2] provide information on the electronic properties of CNTs, in addition to information about the diameter and chirality of the sample. Neutron scattering has been used to assess dispersion quality,[83] concentration-dependent liquid crystal morphology of CNTs,[84] and the stacking pattern of MWCNTs.[85] X-ray diffraction is used to infer the chirality distribution and wall numbers of a sample.[86,87] Dynamic light scattering can measure the relative changes in hydrodynamic size of CNTs in liquid media.[66] Thermogravimetric analysis allows direct measurements of the mass composition of CNTs and metallic impurities.[15,79,88,89] UV-visible-NIR absorption spectroscopy permits the quantification of CNT concentration and identification of the chirality distribution, the presence of carbonaceous impurities, and aggregation state.[8,66,68,90] Raman spectroscopy is used to study the lattice vibration properties of CNTs that relate to structure (diameter and chirality) and defect density.[15,74] NIR fluorescence spectroscopy measures the fluorescence emission of semiconducting SWCNTs, allowing the characterization of certain chiralities and fluorescent quantum defects[8,73,74]. Fourier-transform infrared spectroscopy has been used to identify covalent functionalization of CNTs, such as carboxylation and oxygen doping.[15,79] X-ray photoelectron spectroscopy is used to determine the distribution and bonding of heteroatom dopants.[74,79] Metallic impurities in CNT materials can be characterized by SEM, TEM, energy-dispersive X-ray spectroscopy, and various atomic spectroscopy methods such as glow discharge mass spectrometry.[88,91]

[h2] Gaps in nanometrology techniques

To facilitate meaningful toxicological and environmental assessments, including life cycle management **[G]** and life-cycle assessment **[G]** of CNTs in research and industry, the field must adopt standards of methodological reporting and sample characterization methods. Given the vast diversity of CNT forms and processing methods, and the absence of a standardized classification system and characterization methods,[92] CNT health risks could be either over- or under-estimated, complicating inter-study evaluation. Several reporting guidelines can be adapted to establish standards of minimal information that should be reported in CNT research. To improve transparency and reproducibility in nanomedicine, researchers have suggested a minimum information standard for literature investigating bio-nano interactions (MIRIBEL **[G]**: Minimum Information Reporting in Bio-Nano Experimental Literature), including material characterization, biological characterization, and details of experimental protocols.[93] The guideline also provides a comprehensive description of how to address safety and efficacy concerns with respect to toxicity and long-term biocompatibility in novel nanomaterials. However, the essential characterization methods and reporting parameters guiding the study of CNT materials have not yet been established as a field-wide standard, complicating comparison between studies and preventing clarity on the forms of CNTs that pose toxicological risk.

[h1] Toxicological Considerations of CNTs

The US Occupational Safety and Health Administration sets 1 μg/m^3 as an 8-hour time-weighted average of exposure limits of respirable CNTs and requires employers to protect workers from excessive exposure. The limit is based on the National Institute of Occupational Safety and Health (NIOSH) Recommended Exposure Limit **[G]**.[28] Extrapolation of animal dose-response data[94,95] estimated that 0.2–2 μg/m^3 of respirable CNT exposure raises a 10% excess risk of early-stage adverse lung effects in humans. The NIOSH guideline states that all types of CNTs should be considered as a respiratory hazard and have the same exposure limit until animal research studies can fully explain the mechanisms that potentially impact the CNT toxicity, such as length, number of walls, and surface chemistry. In this section, we discuss the diverse and mixed results in CNT toxicity research and knowledge gaps in the risk assessment of CNT exposure to humans throughout the life cycle of CNTs.

[h2] Text analysis in CNT toxicity research

A textual analysis of over 1,800 toxicological CNT studies indicates diverse and inconsistent toxicological effects of CNTs (**Figure 3**). We analyzed the titles and abstracts of the toxicological CNT literature conducted between 2001 and March 2023 via Scopus **[G]** (Supplementary Table 1). The type of CNT (SWCNT vs. MWCNT), toxicological effect studied (cytotoxicity, oxidative stress, genotoxicity, immune response, bioaccumulation, etc.), model organisms, administration route, and cell/tissue type were classified via keyword search. We found that CNT toxicology research focuses most commonly on MWCNTs (62.7%), but the literature is often ambiguous. For example, the analysis found that over 13% of the published CNT toxicological literature did not specify whether they were single- or multi-walled in the abstract. Reporting inconsistencies arose from the broad range of CNT physical forms, including CNT length, number of walls, aspect ratio, aggregation state, chemical modification, and compositional purity, as well as a lack of standardized taxonomy and methodologies. Key physical parameters that may elicit toxicity concerns were not fully accessible from the text analysis. Cells were the most common biological model (74%), with rodents second (31.5%); virtually no studies have been conducted on humans (such as phenomenological studies) or other higher mammals, potentially hindering translation of toxicological findings. Toxicological effects on lung and liver tissues in mice were the most widely investigated. Pulmonary cytotoxicity, immune response, oxidative stress, and genotoxicity comprised the majority of studied toxicities.

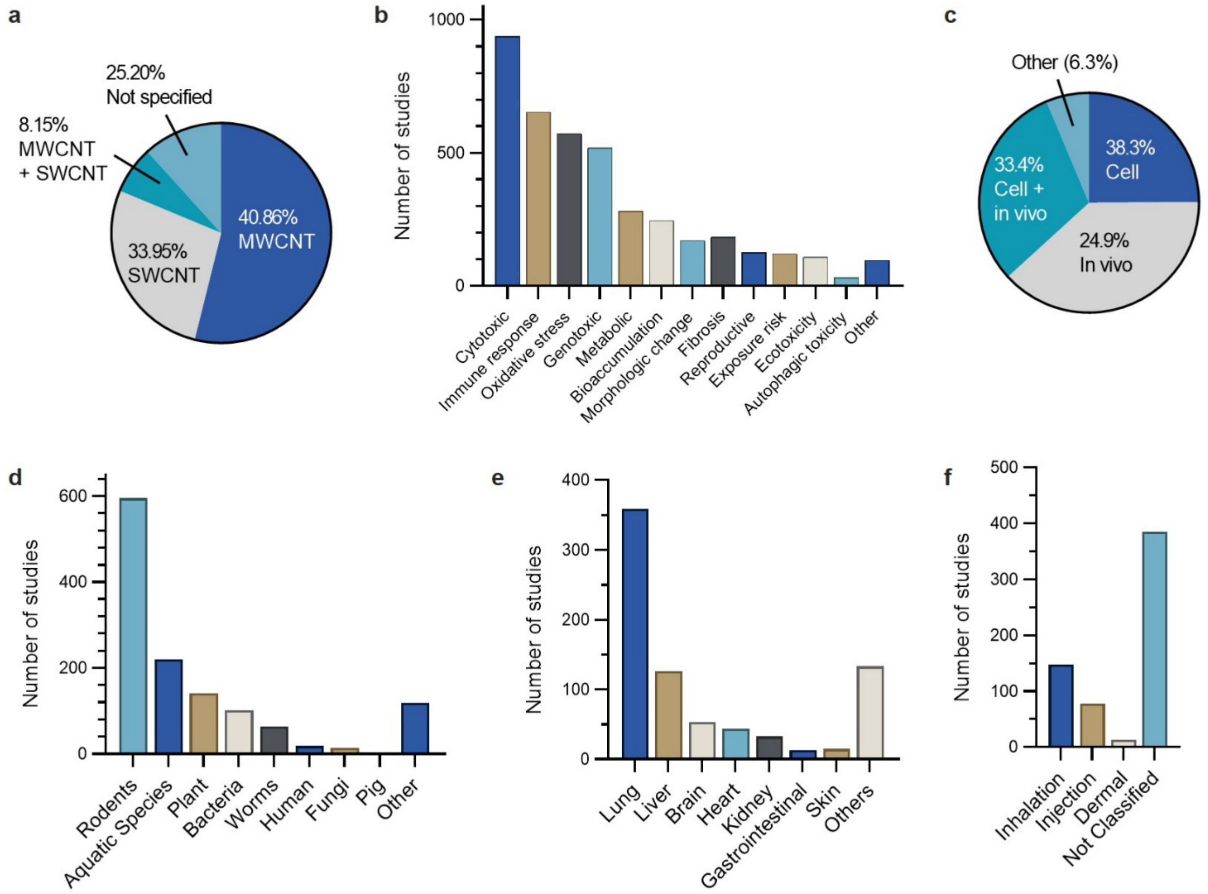


Figure 3 | Textual analysis of CNT toxicity literature. Textual analysis of title and abstract of 1878 toxicological papers indexed on Scopus between January 2001 and March 2023 reveals inconsistent reporting standards and barriers to translation of toxicological findings. **a,** Number of walls (SWCNT vs. MWCNT) studied in the toxicity literature. Over 70% of studies investigate toxicological effects of MWCNTs, while only 40% study toxicological effects of SWCNTs. Over 13% of papers do not identify the specific CNT form used for study in the abstract or title. **b,** Studied toxicity effect. **c,** Fraction of in vivo studies. 38% were conducted only in cells. **d,** Types of studied organisms for *in* vivo studies. The vast majority of in vivo studies were conducted in rodents; virtually no studies are done in humans or higher mammals. **e,** Of toxicity studies done in mammals, the distribution of types of cell, tissue, and organs. **f,** Of toxicity studies done in mammals, the exposure routes studied.

[h2] Mixed results in CNT toxicity assessments

Several studies found that MWCNTs can induce malignant mesotheliomas in rodents upon inhalation,[96] intrascrotal[97] or intraperitoneal injection,[98] or intratracheal instillation[99]. MWCNTs in the lung can cause inflammation and generate reactive oxygen species, leading to tissue and DNA damage.[100] In vivo toxicity studies found that inflammatory and profibrotic responses of MWCNTs in mouse lung were much more pronounced upon exposure to longer MWCNTs.[101] Due to their physical stability and high-aspect ratio, MWCNTs may not be easily cleared from the body, resulting in persistent inflammation, fibrosis, and granuloma formation.[96,102] These studies suggest that the deleterious effects of MWCNTs can be attributed to the high aspect ratios of MWCNTs and sizes (such as 0.5–10 μm in length).[102] These physical dimensions are similar to asbestos fibers that are known to cause severe lung diseases such as asbestosis and mesothelioma. Further comparative studies, to assess the effects of diameter, functionalization, and impurities on these toxicities, are warranted.

Regarding SWCNTs, the W.H.O. concluded that there is insufficient evidence to indicate that they have carcinogenic effects.[103] Studies showed that SWCNTs can induce inflammation in rodents when inhaled in large doses, but heavy metal catalyst impurities present in unpurified CNT samples are highly correlated with cytotoxic effects.[103-105] For CNTs processed for biological applications, no adverse effects associated with long-term exposure and/or bioaccumulation have been reported.[42,59]

[h2] Bridging knowledge gaps

Gaps in our current understanding of the health risks associated with CNTs stem in part from inconsistent methodological standardization and reporting[60]. The variety of CNT forms and functionalities, and the toxicological dependence on their synthesis and preparation, are often not accounted for in the CNT toxicology literature. At minimum, the number of walls, length, aggregation state, chemical functionalization, effective concentration, dose applied, amount of carbonaceous and catalytic impurities, route of administration, and duration of exposure must be reported to facilitate meaningful comparisons between studies and to highlight the key parameters that confer toxicological risk. Minimum reporting standards for physicochemical parameters of nanomaterials have been proposed so that occupational safety and health regulators properly assess any toxicological concerns and overcome regulatory hurdles.[93,106]

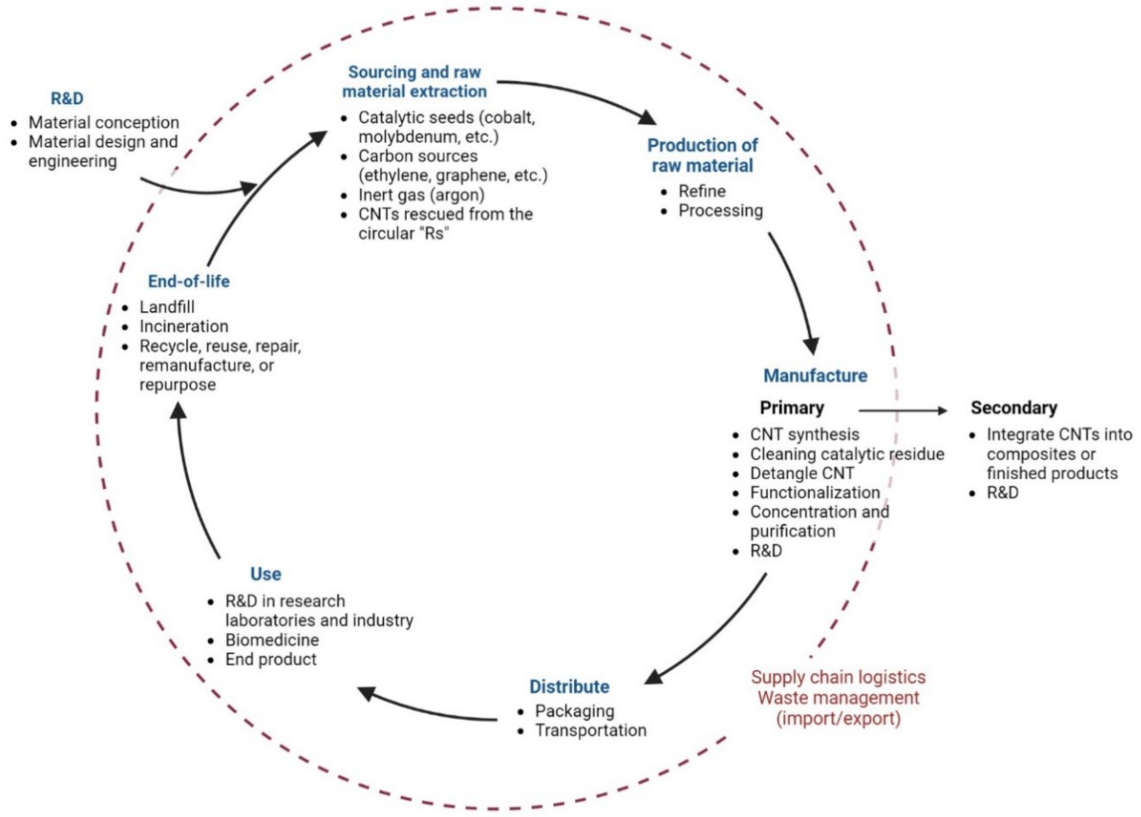
Most risk assessments of CNTs have been focused on certain types and forms of CNTs, such as raw, as-produced MWCNTs or SWCNTs, and only a few phases in the CNT life cycle, such as synthesis. CNT forms that either satisfy prerequisites for a mineral fiber, such as low solubility and high aspect ratio (a length longer than 5 μm and diameter less than 3 μm), or are minimally processed and contain catalytic or carbon impurities, have been extensively investigated for toxicological risk.[96,100,102,104,105] The extent to which these animal data may predict clinically significant, environmentally and physiologically relevant toxicological effects in humans is unclear, hindering the establishment of a quantitative CNT-toxicity relationship. Quantitative structure-activity relationship (QSAR) research on MWCNTs found that it was possible to identify key structural characteristics that predict toxic effects on cells and to design CNTs with desirable bioactivity and safety profiles.[107,108] Increasingly, computational analyses of CNT structure-function relationships may serve to facilitate our understanding of the underlying features contributing to CNT toxicity. For practical uses, risk assessments must be extended primarily to widely-used CNT formulations and products with a proper evaluation of the range of doses and appropriate characterization of CNT types. For example, CNT risk evaluation in pre-clinical and translational studies must be conducted with conditions relevant to the likely exposures to humans and other organisms, such as specific forms of CNTs with relevant doses, cell types, and meaningful endpoints. Further, safety and risk assessments should be undertaken across each phase of the CNT life cycle, as assessments will vary considerably across each stage.

A balanced assessment of the risks for CNTs must consider positive contributions alongside negative impacts across entire value chains. With the wide array of applications in multiple industries, from electronics to healthcare, CNTs could potentially offer substantial technological and economic potential while promoting improved human health, safety, and sustainable ecosystems. Therefore, both benefits and risks must be properly evaluated. Presently, significant knowledge and data gaps, and regulatory and scientific uncertainties, exist in toxicological assessments of CNTs, both in the physical characteristics underlying potential CNT effects on human health, and the routes of potential exposure that may arise along all stages of the CNT life cycle.

[h2] Life-cycle assessment of toxicological potential

Toxicological risk of CNTs should be assessed for relevant CNT material as-manufactured, and throughout their life cycle, from sourcing to consumer product to end-of-life, in order for regulatory bodies to accurately account for both potential positive and negative impacts from their adoption on occupational workers, consumers, and the environment (**Figure 4**). The few existing real-world studies regarding CNT toxicity focus on the occupational exposure of industry workers in the manufacturing phase of the CNT lifespan[109,110]. Dermal contact with spills or dust from the production during the formulation process by secondary manufacturers using CNTs in composites, or embedded into other materials, is another likely pathway for occupational exposure.[110] A 2017 International Agency for Research on Cancer (IARC) Working Group Report **[G]** on the carcinogenic risks of CNTs found that a key route of exposure amongst occupational workers was CNT dust that entered the air while handling raw CNT material.[111] Although this finding merits a careful evaluation of risks when handling and using CNTs for research and industrial applications, steps can be taken to address potential avenues of pulmonary exposure and to minimize risks of occupational and public exposure. A simulated workplace study of scooping and sweeping CNT powders found that dustiness **[G]** was a major determinant of the exposure of workers and accounted for approximately 70% of the variability in exposure.[112,113] The total and respirable dustiness of the CNT powders spanned two orders of magnitude (0.3–37.9%).[113] For several CNT types, significant respirable dustiness was observed, suggesting that workplace procedures may result in inhaled airborne dust. For example, SWCNTs synthesized by the HiPco process exhibited 31.8 ± 3.3% respirable dustiness.[113] Through the appropriate crafting of occupational health regulations (e.g., engineering controls or personal protective equipment), CNT inhalation may be reduced, mitigating potential toxicological risks associated with CNT manufacturing.

a



b

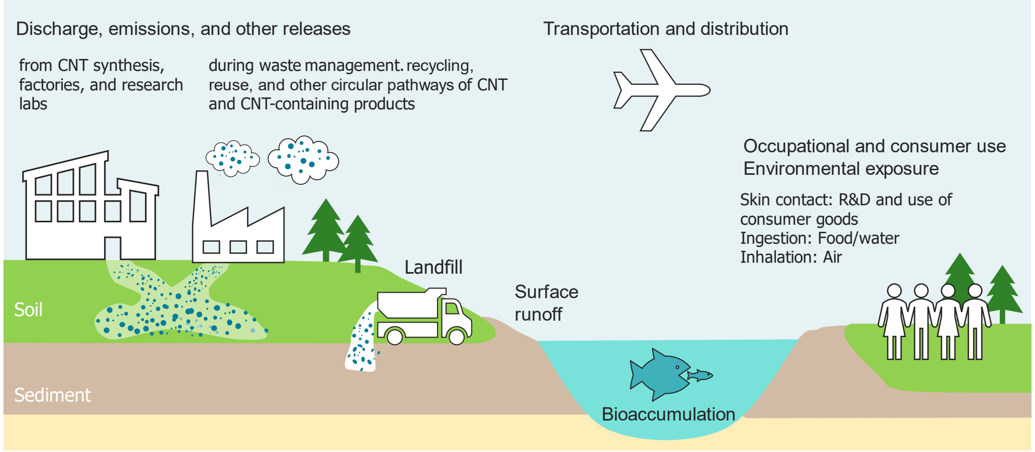


Figure 4 | Environmental pathways and potential exposure routes of CNTs in a life cycle perspective. a. Stages of CNT life cycle. **b.** Potential routes of exposure of CNTs across life cycle

Toxicological impact studies should be expanded beyond the respirable risks for occupational workers, to assess the risk on other exposure routes throughout their entire value chain. Research on consumer exposures or workers in downstream industries (e.g., recycling and waste management) remain incomplete. Studies regarding toxicological effects associated with CNT exposure in their form factor of intended usage (such as nanocomposites) will help policymakers craft effective regulations to protect consumers. Studies on the long-term fate of CNTs in various formulations and the potential for environmental release of CNTs in the various end-of-life pathways will ensure that the risks of CNTs are appropriately assessed, that any potential impacts are mitigated, and that all negative externalities are properly accounted for.

CNT-containing waste is generated at the end of the CNT product life and at each step of the life cycle. Waste containing CNTs is currently managed along with conventional waste or through existing mechanisms that fall within the confines of existing law (e.g. hazardous waste classification via the Resource Conservation and Recovery Act **[G]**) without sufficient knowledge of the associated risks and impacts on human health or the environment.[114] This issue is due to the lack of federal or international standards for CNT disposal. End-of-life toxicological considerations are particularly important for understanding if CNTs and CNT-incorporating materials can be safely reused, repurposed or recycled, or, if life cycle extension pathways are not feasible, that they are safely disposed. The vast majority of CNTs in industrial processes are currently used as components of batteries or as part of nanocomposite materials. At the end-of-life, these materials are typically managed in landfills, incinerated, and some are exported to developing economies where there is a dearth of tracking of responsible end-of-life management.[115,116] Almost no research has been conducted on the toxicological or ecological impact of CNTs that are aerosolized and dispersed via incineration of CNT-containing nanocomposites, or via landfill rainwater-mediated CNT-escape. Extensive research into the toxicological impacts that CNTs can have following their disposal is warranted.

[h1] Environmental Safety Concerns of CNTs

As CNTs move into large-scale production and expand into many industries and applications, it is inevitable that gradual losses or accidental release of CNTs will cause them to enter the environment at each stage of the life cycle.[117,118] In this section, we review the possible routes of environmental exposure that span the entire life cycle of products and applications. We also discuss knowledge and data gaps about CNTs and the environment, including the effects of CNTs on carbon emissions, biopersistence and bioaccumulation, and ecotoxicity, among other aspects.

[h2] Life-cycle assessment of ecological toxicity risk

CNTs can enter the environment via (1) discharge/leakage/loss/emissions during R&D, processing/production of raw material, manufacturing, transport, and storage of intermediate and finished products, (2) release of CNTs during the use phase, (3) release from waste and end-of-life activities, and (4) diffusion, transport and transformation in air, soil, and water (**Figure 4**). Modeling studies of the environmental release and exposure to CNTs found that the estimated CNT concentration in air and water was 1–17 pg/m^3 and 0.6–25 pg/L, respectively.[119] The models predict an increasing amount of CNTs accumulating in soil and sediment (23.9–137 and 40–1558 ng/kg per year, respectively). Some evidence indicates that CNTs that make their way into the soil do not pose a risk of contamination of groundwater due to the high aspect ratio of CNTs and the small pore size of soil.[120,121]

The environmental effects of the CNT production stages has been investigated via life-cycle assessment.[122,123] Healy et al. developed process-based cost models for various CNT synthesis processes[123] for use as a basis for tracking life cycle inventories for materials and energy. These inventories were used to estimate the impact of CNTs using a multifactorial life cycle assessment. The study found that the life cycle impacts are dominated by energy, specifically the electricity used in CNT synthesis and purification. However, as CNT bulk synthesis is still in its nascency, energetic impacts may be offset as factories scale-up production. A 2014 assessment found that up to 94% of the energetic impacts of CNTs may be reduced as CNT production capacities increase, and manufacturers can harness larger production volumes to recycle unused feedstock.[124] The environmental impact varied by the synthesis methods of CNTs and can be minimized by optimization in production stages.

[h2] Bridging knowledge gaps

There has been a predominant focus on the environmental impact of the CNT production stage, specifically energy inputs and emissions, with minimal to no integration of comprehensive environmental impacts from a life cycle perspective, such as water use, water quality, soil quality, biodiversity, ecotoxicity resource depletion, waste management, etc. Life cycle environmental analyses must account for the range of impacts of release throughout all stages of the life cycle of a material, including novel composite materials and the emissions and other impacts involved in transport, disposal, or other end-of-life pathways. Additionally, common life-cycle assessment database categories require geographic, temporal, and technological differentiation for an accurate life cycle assessment and regionally explicit life cycle inventory data for emissions, water consumption, and land use. Although there have been modest methodological developments to assess such impacts at a regional scale (e.g., water scarcity at the watershed level or land use impacts on an ecoregion level), much work is needed to integrate regionalization into life-cycle assessments, to adapt new safety assessment tools and approaches for a true understanding of life cycle impacts.[125,126]

The lack of standardized tools to evaluate exposure or environmental release hampers robust assessment of environmental effects and management of CNTs. Most metrological devices, such as the condensation particle counter and the optical particle counter, do not represent the exact exposure to CNTs; measurements using a differential mobility analyzing system also do not always provide accurate information due to the arc charge caused by the charged CNTs in the differential mechanical mobility system.[127] Despite these limitations in assessing exposure to nanomaterials or CNTs, guidelines and reports have been published to harmonize strategies for exposure measurement.[128]

[h2] Weighing positive and negative environmental impacts of CNTs

Considering the physical stability of CNTs, environmental persistence and long degradation time raise concerns about environmental damage, bioaccumulation, and human health.[122] Scalable and ecologically friendly methods for CNT disposal have been explored to minimize any environmental risks throughout the lifespan of academic or industrially used CNTs (**Box 1**).[129-132] Recent studies have reported the biodegradation mechanisms for CNTs, such as enzymatic oxidation via horseradish peroxidase and myeloperoxidase from human neutrophils.[130] The processes involve CNT oxidation by hypochlorous acid that is generated during enzymatic reaction, and sodium hypochlorite or hypochlorous acid has since been shown to oxidize and degrade CNTs.

To accurately gauge the net environmental impact of CNTs, their potential positive effects must also be weighed by regulators and policymakers. Although there are clear routes for negative environmental and ecological impacts of CNTs, there are also potential beneficial effects of CNTs that may mitigate certain potential negative impacts. Due to their unique material properties, CNTs have been researched for environmental remediation purposes as varied as radionuclide removal from wastewater and as highly efficient chemical adsorbents,[133] for photodiodes in solar panels, and other renewable energy applications,[134] and in developing more efficient batteries.[135] Furthermore, environmental impacts that CNTs mitigate, for example, by obviating the demand for primary extraction of energy and resource intensive materials such as steel or concrete[134,136,137], must be evaluated to better account for the full picture of their effect on the environment.

[h1] Sustainability and Inclusion of CNTs in the Circular Economy

Sustainability is a balance between the economics and the least energy- and resource-intensive pathways that result in the best environmental performance and social outcomes across life cycles. Addressing sustainability will require embracing a systems-level and transparent approach to social, environmental, and economic factors throughout a material's life cycle and being responsible stewards of valuable resources (**Figure 5**). Research priorities should aim to level-set, harmonize, and elevate the disparate knowledge and information gaps and disparities regarding chemical identity, toxicity, and environmental impacts of CNTs so that a more sustainable path can be forged, paving the way to alignment with the UN Sustainable Development Goals (UN SDG) **[G]**.[138] Unless there is standardization in CNT taxonomy, metrology, and methodological reporting, it will be difficult to measure or report on sustainability in a meaningful way.

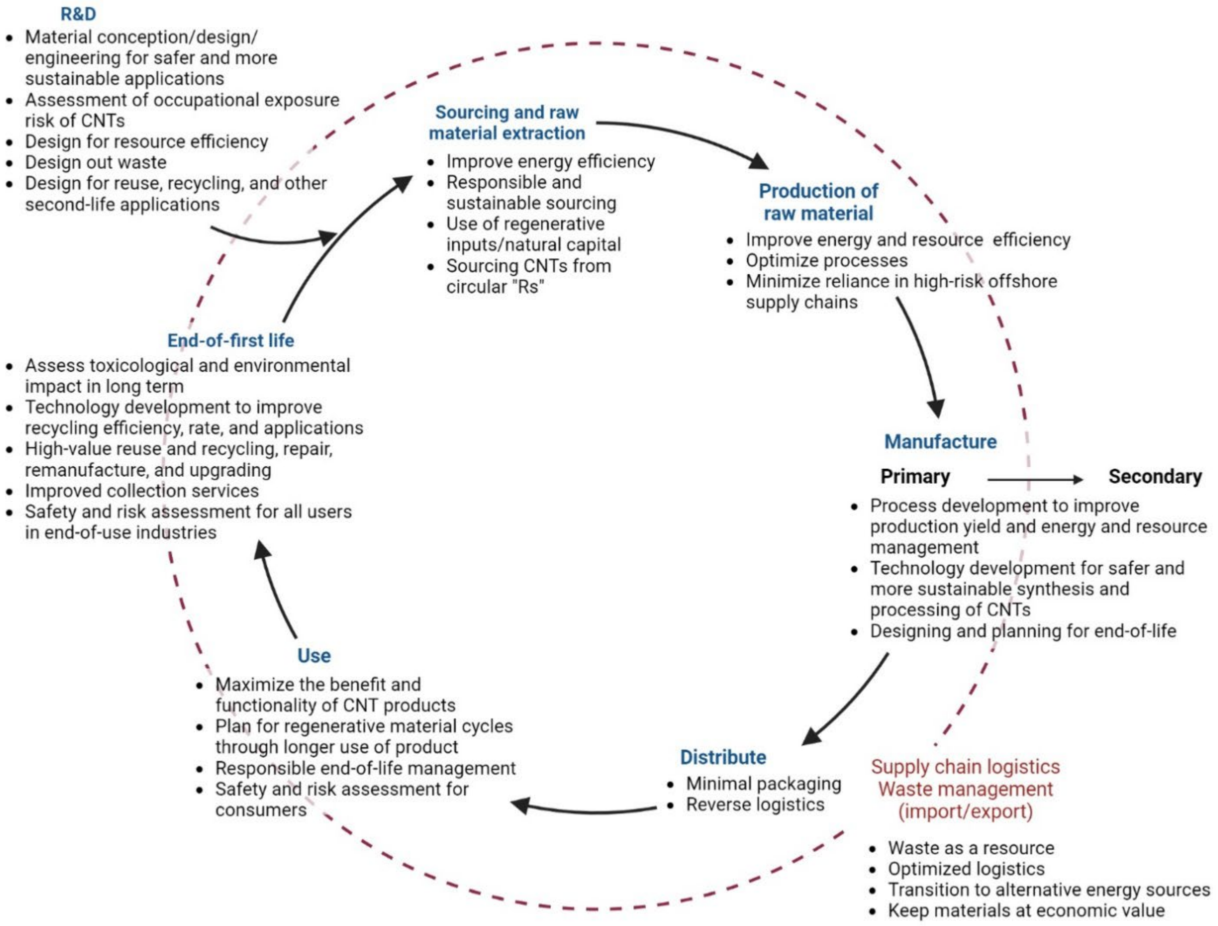


Figure 5 | Components of a holistic approach to promote sustainability of CNT materials from a life cycle perspective. Sustainability considerations include social, economic, and environmental dimensions and include stakeholders such as occupational workers, consumers, non-consumers, and other organisms.

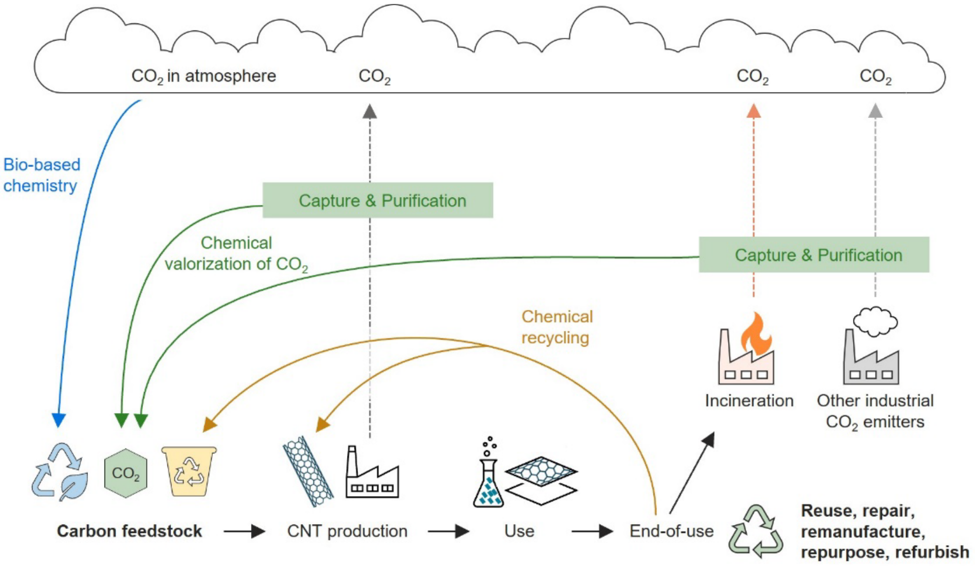
The circular economy is an economic framework that encourages system innovation and focuses on managing resources and increasing resource efficiency. Some of the main principles are: to keep materials in play and at an economic value for as long as possible; designing for circularity and eliminating waste through re-engineering of materials; using waste as a resource; regenerative inputs and systems; and balancing flow and controlling finite stocks. A circular economy leverages several business models such as product life extension via the circular "Rs" (reuse, repair, remanufacture, repurpose, redesign, recycle, etc.); collaborative consumption; and product-as-a-service. However, shifting towards a circular economy does not guarantee improved environmental performance, positive social outcomes, or economic progress across life cycles. Therefore, if a circular economy is implemented based on improper policies, is not measured, or is incongruous with sustainability, it will generate negative rebound effects. For instance, CNTs classified as a toxic or hazardous substance or hazardous waste that, at the end-of-life, are recirculated back into the economy through one of the circular "Rs" could, if not carefully assessed and measured, have deleterious effects on human health and the environment. On the other hand, it is possible that CNTs classified as hazardous but, via appropriate treatment become nonhazardous, would not be captured via the circular "Rs" and instead be disposed of, losing an opportunity to promote sustainability. Designing and planning for end-of-life in the early stages of CNT research and development across value chains reduces future waste volumes and aligns with the principles of a circular economy.

To ensure a successful transition to sustainable, climate-neutral growth, carbon management solutions embedded across the carbon life cycle should be an essential part of any sustainability and circular economy strategy. A circular carbon economy is a framework for managing carbon at every point throughout the life cycle that taps into the carbon cycle (**Box 2**). For instance, the carbon feedstock to produce CNTs could originate from bio-based chemistry **[G]**, chemical valorization of CO_2 **[G]**, and chemical recycling of CNTs or CNT products. As the demand for CNTs has been increasing rapidly in diverse applications, macroscale CNT materials hold enormous promise for meeting the world's materials needs while also developing more sustainable building blocks for the economy and reducing CO_2 emissions.[137,139]

Box 2 | Promoting a sustainable circular carbon economy in energy and material transitions

“Carbon-to-value” technologies that explore advanced carbon chemistries and advanced carbon materials could be transformative in sustainability and climate reduction strategies by reducing emissions without risking stranded assets and a complete re-engineering of the energy sectors. Such techniques enable continued use of the world’s current energy production and delivery infrastructure, leaving a greater number of energy source options available for fueling the economy in a low-carbon and, perhaps, more sustainable manner. Developing ways of capturing the carbon emissions from fossil fuels or other CO_2 sources and upgrading them to advanced solid carbon materials,[186] can help create economies of scale in CNT manufacturing. Carbon feedstock can be obtained through (1) bio-based chemistry that captures atmospheric carbon via photosynthesis using renewable biological resources such as biomass, (2) chemical valorization of emitted and captured CO_2 and other greenhouse gas emissions that are produced from industrial sites before it enters the atmosphere, e.g., methane pyrolysis that directly converts methane in natural gas to hydrogen and solid carbon materials, and (3) chemical recycling of CNT waste that otherwise would be incinerated or sent to landfill (see the schematic below). At the end of first use, the CNT or CNT composite can be repaired, reused, remanufactured, repurposed, or refurbished.

Concurrent with energy transitions is a “materials” transition. Supplementing or displacing high energy and CO_2-intensive materials (steel, aluminum, and other metals, concrete, and plastics) with pyrolyzed carbon from methane emissions promotes a circular carbon economy and could be used in industries ranging from construction to transportation to decrease the demand for resource-intensive primary minerals and materials. Additionally, from a life cycle perspective, it could also reduce the overall social, environmental, and economic impacts across global supply chains. For instance, replacing or supplementing energy and resource-intensive metals with CNTs will reduce the overall demand for primary materials extraction and associated processing and production. The mining, processing, and refining of metals and critical minerals is not only energy and resource intensive, but also engulfed in a very complicated global supply chain in high geographical concentration production areas with unstable and corrupt governments, well-documented human rights violations, and deficient safety and environmental laws.[187-189]



[h1] Policy Challenges & Considerations

Regulatory aspects of CNTs are the subject of much debate.[23-26] Currently, regulatory, safety, and handling guidelines for occupational exposure (academic research, R&D laboratory workers), manufacturers (production and maintenance workers), disposal, recycling, and other end-of-life pathways, and consumer exposure are unclear.[109,110,117,118] The uncertainties involved arise against the backdrop of evolving public perceptions regarding the safety of "free" CNTs and the safety of products or materials containing CNTs.

As CNTs begin to enter into industrial applications, legitimate concerns about their toxicological and environmental impacts remain. In addition, it remains an open question about how to effectively regulate nanomaterials, broadly speaking, to ensure safety to all stakeholders, while not unduly hindering innovation or the safe usage of nanomaterials for low-risk applications. TSCA Section 4 **[G]** gives the U.S. Environmental Protection Agency authority to require manufacturers (including importers) or processors to test chemical substances and mixtures, including nanoscale materials, and to develop data about health or environmental effects when there is insufficient data for EPA risk assessors to be able to determine the effects. EPA has also allowed the manufacture of new nanoscale materials under the terms of certain regulatory exemptions, but only in circumstances where exposures were tightly controlled to protect against unreasonable risks. Manufacturers and researchers thus should continue to demonstrate a safety profile of CNTs that shows that the benefits outweigh the costs for that specific application. In addition, the toxicological tolerance of CNTs is highly dependent on the use-case. For usages such as in batteries, wherein CNTs can replace heavy metals, the toxicological considerations may be substantially different than toxicological considerations of certain CNT nanocomposites.

A clear set of guidelines, best practices, and standard operating procedures, formulated with input from academia, industry, non-governmental organizations, and regulatory bodies will provide regulatory and scientific certainty and greatly improve the public understanding of and public trust in CNTs. Properly scoped and framed life-cycle assessments using regionally-appropriate data sets can demonstrate some of the environmental, health, and safety aspects to a broader public. With globally-linked supply chains, impacts are not confined to one industry or one region of the world. Capturing data across the broad spectrum will provide insights into potential trade-offs, unintended consequences, and how and where risks can shift.

Closing data and knowledge gaps and identifying policies for safe CNT usage are needed across the entire CNT life cycle. Full life cycle implications will encourage systems-level thinking among policymakers. Leveraging science-based assessments enables analysis and insights to overcome systemic biases and achieve better policy outcomes. Standardized life cycle sustainability assessments can offer a more holistic, integrated, and transdisciplinary framework. In addition, policies should encourage working symbiotically across supply chains to create value, for example, using waste as a valuable feedstock in another process or industry. End-of-life considerations should enter the decision-making process at the R&D phase.

[h1] Conclusions and Outlook

The increasing use of CNTs, and concomitant concerns about their potential toxicological and environmental impacts, highlight the unmet need for a standardized, science-based approach to assess their risks and exposures from a life cycle perspective and to provide accurate information on these risks to policymakers. Issues with CNT taxonomy, standardization of measurements, and gaps in information on toxicology and environmental impact present challenges to this effort. These concerns can be addressed, but only with the adoption of broader and more consistent classification, field-wide standards in metrology, and consistent methodology in processing, and toxicological and environmental analysis across the full life cycle of the materials. The construction of a comprehensive, novel framework to classify, characterize, and assess potential health, environmental, and safety impacts of CNTs will have a significant positive impact on research and industry by creating a uniform playbook that establishes a baseline for the CNT community.

To establish robust and consensus policies, several open questions should be addressed. First, metrological methods will need to be standardized and reported for comparison between studies and interpretation of key physical characteristics that confer toxicological risk. Second, a common classification and identification system must be adopted to allow for consistent communication among researchers, industries, and policymakers. Towards achieving this goal, we suggest that as-produced CNT forms each receive a unique CAS number, and that these numbers are used by academia and industry, to facilitate reproducibility and comparison between studies. Third, safety and risk assessments should expand beyond the general occupational health and safety in manufacturing and handling to include all stages of the CNT life cycle. Properly addressed, these actions will provide regulators with the tools to selectively regulate the subsets of the CNTs deemed to be high risk while ensuring that any restrictions on synthesis, production, manufacturing, use, transportation, and disposal are minimally disruptive to the emerging field of carbon nanomaterials. Fourth, transitioning to a circular carbon economy will mean that researchers work to design out waste or use waste as a resource. This will require entities upstream to work throughout the supply chain, including downstream entities, to create value and maintain materials in use. Fifth, for CNTs that do enter the environment as waste, effective methods for CNT removal or remediation in waste systems should be further investigated. Finally, working towards a coordinated system for classifying and testing CNTs and establishing a central repository of open-source scientific information, risks, benefits, and uncertainties related to CNTs will help alleviate regulatory barriers to international trade and commerce.

Finally, we identified that CNTs hold promise for future decarbonization and sustainability strategies. From a life cycle perspective, the use of CNTs may have far fewer energy and material requirements and environmental and social consequences by reducing the demand for primary resource extraction and processing of energy-intensive metals, minerals, and materials and the associated complicated supply chains.[139] Of course, any movement along this pathway must give due consideration to ensuring social equity, human health, and environmental safety throughout the life cycle. Approaching this from a systems perspective presents opportunities to expand innovation of carbon material-enabled applications in industrial, commercial, and medical sectors, support a dynamic and skilled workforce, ensure responsible development, use, and end-of-life management from lab to market and help the world meet global climate targets and sustainability goals. As society progresses towards a clean energy and materials revolution, it will be imperative that the field of advanced materials, including carbon nanomaterials, has a clear and consistent path from development to end-of-life, underpinned by appropriate, science-driven, standardized characterization and classification, shepherded by life cycle-based policies, and guided by informed industry best practices and solid evidence of harm and benefit to people and the environment.

Acknowledgements

We thank Michael Dennis, Jeffery Wilson, Mark A. Schmidt, Chen Chen, Matteo Pasquali, and Jeffery Fagan for their helpful discussions.

This work was supported in part by the NIH (R01-EB033651, D.A.H. and M.K. and Cancer Center Support Grant P30-CA008748, D.A.H.), the National Science Foundation CAREER Award (1752506, D.A.H.), the Department of Defense Congressionally Directed Medical Research Program (W81XWH2210563, D.A.H.), the Ara Parseghian Foundation (D.A.H.), the Honorable Tina Brozman Foundation for Ovarian Cancer Research (D.A.H.), and the Ovarian Cancer Research Alliance and the Edmée Firth Fund for Research in Ovarian Cancer (D.A.H.). M.K. was supported by the NIH (K99-EB033580) and the Marie-Josée Kravis Women in Science Endeavor Postdoctoral Fellowship.

Author contributions

M.K., D.G., P.V.J. E.Z., and R.M. researched data for the article. M.K., D.G., P.V.J., R.M. and D.A.H. contributed substantially to discussion of the content. M.K., D.G., R.M., and D.A.H wrote, reviewed, and/or edited the manuscript before submission.

Competing interests

D.A.H. is a co-founder and officer with equity interest in Lime Therapeutics, Inc., and co-founder with equity interest in Selectin Therapeutics Inc., and Resident Diagnostics, Inc., and a member of the scientific advisory board of Concarlo Therapeutics, Inc., Nanorobotics Inc., and Mediphage Bioceuticals, Inc. P.V.J. is a co-founder and officer with equity interest in Lime Therapeutics, Inc. The remaining authors declare no competing interests.

Data availability

Textual analysis presented in Figures 1 and 3, including the search terms and the classification data are available in the public github repository (github.com/mijinee/HellerLab_MSKCC/).

Glossary [G]

INTERNATIONAL CHEMICAL SECRETARIAT (CHEMSEC)
An independent non-profit organization that advocates for substitution of toxic chemicals to safer alternatives. ChemSec advocates in favor of stricter regulatory controls on potentially hazardous chemicals and works with businesses on reducing the production and use of hazardous substances in their products and supply chains.

CHIRALITY
Conceptualizing a SWCNT as the rolled-up tube of a hexagonal lattice of carbon atoms, there are a number of vectors it can be rolled up along. This vector is denoted by two integers n and m with $n \geq m$, and expressed as (n,m). One extreme is the $(n,0)$ CNTs, called *zigzag*. On the other end is *armchair*, (n,n) CNTs. All other CNTs are termed *chiral*. (n,m) SWCNT is metallic if $2n+m$ is a multiple of 3 and is semiconducting otherwise.

EU OBSERVATORY FOR NANOMATERIALS (EUON)
A web-based platform that provides information on nanomaterials, their properties, and their safe use in various products. It is managed by the European Chemicals Agency (ECHA) and aims to support the safe and sustainable use of nanomaterials in the EU.

CHEMICAL ABSTRACTS SERVICE (CAS)
A source of chemical information. The CAS Registry contains information on more than 130 million organic and inorganic substances and more than 64 million protein and nucleic acid sequences and identifies each compound with a specific CAS registry number, index name, and graphic representation of its chemical structure.

LIFE CYCLE MANAGEMENT (LCM)
The process of managing a product, service, or system throughout its entire life cycle, from conception and development to retirement and disposal. It involves activities such as planning, designing, manufacturing, marketing, and support, with the goal of maximizing value, efficiency, and sustainability at each stage while considering environmental and social impacts.

LIFE CYCLE ASSESSMENT
A technique used to assess the environmental impacts of a product or service throughout its entire life cycle, from raw material extraction to end-of-life disposal. It considers factors such as resource use, energy consumption, emissions, and waste generation.

MINIMUM INFORMATION REPORTING IN BIO-NANO EXPERIMENTAL LITERATURE (MIRIBEL)
A published standard of information reporting to improve reproducibility, increase quantitative comparisons of different bio-nano materials, and facilitate meta-analysis and in-silico modeling of bio-nano interactions. It consists of materials characterization, biological characterization, and details of experimental protocols.

NIOSH RECOMMENDED EXPOSURE LIMIT (REL)
The maximum allowable level of exposure to hazardous substances set by the National Institute for Occupational Safety and Health (NIOSH). These limits serve as guidelines to protect workers from the adverse health effects associated with various chemical, physical, and biological agents encountered in the workplace.

SCOPUS
An abstract and citation database that covers a wide range of scientific, technical, medical, and social science literature.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC)
An intergovernmental agency that is part of the World Health Organization. Its mission is to promote international collaboration in cancer research and to identify causes of cancer and strategies for cancer prevention.

DUSTINESS
Dustiness is the tendency of particles to become airborne in response to a mechanical or aerodynamic stimulus.

RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)
A US federal law that governs the disposal of hazardous waste. It regulates the generation, transportation, treatment, storage, and disposal of hazardous waste, as well as the remediation of contaminated sites.

UN SUSTAINABLE DEVELOPMENT GOALS (UN SDG)
A set of 17 goals adopted by the United Nations in 2015 as a universal call to action to end poverty, protect the planet and ensure that all people enjoy peace and prosperity. The goals cover a range of issues, including poverty, health, education, gender equality, clean water and sanitation, climate action, and sustainable cities and communities.

BIO-BASED CHEMISTRY
The branch of chemistry that utilizes renewable biological resources, such as plants and microorganisms, to develop and produce chemicals, materials, and energy sources.

CHEMICAL VALORIZATION OF CO_2
Conversion of carbon dioxide into valuable chemical compounds or fuels through various chemical processes, aiming to reduce greenhouse gas emissions and promote sustainable resource utilization.

TSCA SECTION 4
A section of the Toxic Substances Control Act (TSCA), a United States federal law, that regulates the manufacturing, importation, use, and disposal of chemical substances to protect human health and the environment from unreasonable risks. This section grants the Environmental Protection Agency (EPA) the authority to require testing and reporting of chemical substances to assess their potential risks to human health and the environment.

NATIONAL NANOTECHNOLOGY INITIATIVE (NNI)
A US federal program that coordinates research and development efforts in nanotechnology across various government agencies to advance understanding and applications of nanoscale science and engineering.

INTERNATIONAL ORGANIZATION FOR STANDARDIZATION TECHNICAL COMMITTEE 229 (ISO/TC 229)
A committee responsible for developing and promoting international standards in the field of nanotechnologies to ensure safe and reliable practices.

US ENVIRONMENTAL PROTECTION AGENCY SIGNIFICANT NEW USE RULES (EPA SNUR)
Regulations that require manufacturers and importers to notify the EPA before introducing a new chemical substance or significant new use of an existing substance that may pose a risk to human health or the environment.

EUROPEAN CHEMICALS AGENCY (ECHA):
An agency of the European Union responsible for implementing regulations related to the registration, evaluation, authorization, and restriction of chemical substances to ensure their safe use within the EU.

THE REGULATION ON THE REGISTRATION, EVALUATION, AUTHORIZATION, AND RESTRICTION OF CHEMICALS (REACH):
A set of regulations enacted by the EU to improve the protection of human health and the environment from risks posed by chemical substances, and to enhance the communication of information on their properties and safe use.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH):
A US federal agency responsible for conducting research, providing recommendations, and developing regulations and guidelines to promote safe and healthy working conditions, primarily focusing on protecting workers from occupational hazards.

References

1. Iijima, S. Helical microtubules of graphitic carbon. *Nature* **354**, 56-58 (1991).
2. Takakura, A. et al. Strength of carbon nanotubes depends on their chemical structures. *Nat Commun* **10**, 3040 (2019).
3. Ruoff, R.S. & Lorents, D.C. Mechanical and thermal properties of carbon nanotubes. *Carbon* **33**, 925-930 (1995).
4. Dresselhaus, M.S., Dresselhaus, G. & Saito, R. Physics of carbon nanotubes. *Carbon* **33**, 883-891 (1995).
5. Kim, P., Shi, L., Majumdar, A. & McEuen, P.L. Thermal transport measurements of individual multiwalled nanotubes. *Phys Rev Lett* **87**, 215502 (2001).
6. Frank, S., Poncharal, P., Wang, Z.L. & Heer, W.A. Carbon nanotube quantum resistors. *Science* **280**, 1744-1746 (1998).
7. Liang, W. et al. Fabry - Perot interference in a nanotube electron waveguide. *Nature* **411**, 665-669 (2001).
8. O'Connell, M.J. et al. Band gap fluorescence from individual single-walled carbon nanotubes. *Science* **297**, 593-596 (2002).
9. Salvetat, J.P. et al. Mechanical properties of carbon nanotubes. *Appl Phys A* **69**, 255-260 (1999).
10. Choi, C. et al. Twistable and stretchable sandwich structured fiber for wearable sensors and supercapacitors. *Nano Lett* **16**, 7677-7684 (2016).
11. Chen, J.S. et al. Room temperature lasing from semiconducting single-walled carbon nanotubes. *ACS Nano* **16**, 16776-16783 (2022).
12. Srivastava, A., Srivastava, O.N., Talapatra, S., Vajtai, R. & Ajayan, P.M. Carbon nanotube filters. *Nat Mater* **3**, 610-614 (2004).
13. Galassi, T.V. et al. An optical nanoreporter of endolysosomal lipid accumulation reveals enduring effects of diet on hepatic macrophages in vivo. *Sci Transl Med* **10**, eaar2680 (2018).
14. Kim, M. et al. Detection of ovarian cancer via the spectral fingerprinting of quantum-defect-modified carbon nanotubes in serum by machine learning. *Nat Biomed Eng* **6**, 267-275 (2022).
15. Tan, J.M., Bullo, S., Fakurazi, S. & Hussein, M.Z. Preparation, characterisation and biological evaluation of biopolymer-coated multi-walled carbon nanotubes for sustained-delivery of silibinin. *Sci Rep* **10**, 16941 (2020).
16. Zhang, X.A. et al. Dynamic gating of infrared radiation in a textile. *Science* **363**, 619-623 (2019).
17. Safaee, M.M., Gravely, M. & Roxbury, D. A wearable optical microfibrous biomaterial with encapsulated nanosensors enables wireless monitoring of oxidative stress. *Adv Func Mater* **31**, 2006254 (2021).
18. Xu, S., Liu, J. & Li, Q. Mechanical properties and microstructure of multi-walled carbon nanotube-reinforced cement paste. *Constr Build Mater* **76**, 16-23 (2015).
19. www.nanocore.com
20. Maheswaran, R. & Shanmugavel, B.P. A Critical Review of the Role of Carbon Nanotubes in the Progress of Next-Generation Electronic Applications. *J. Electron. Mater.* **51**, 2786-2800 (2022).
21. Global carbon nanotubes market size by type (SWCNT, MWCNT), by application (plastics & composites, electrical & electronics, energy), by geographic scope and forecast. *Verified Market Research* (2022).
22. Valsami-Jones, E. & Lynch, I. How safe are nanomaterials? *Science* **350**, 388-389 (2015).
23. Heller, D.A. et al. Banning carbon nanotubes would be scientifically unjustified and damaging to innovation. *Nat Nanotechnol* **15**, 164-166 (2020).
24. Hansen, S.F. & Lennquist, A. SIN List criticism based on misunderstandings. *Nat Nanotechnol* **15**, 418-418 (2020).
25. Hansen, S.F. & Lennquist, A. Carbon nanotubes added to the SIN List as a nanomaterial of Very High Concern. *Nat Nanotechnol* **15**, 3-4 (2020).
26. Fadeel, B. & Kostarelos, K. Grouping all carbon nanotubes into a single substance category is scientifically unjustified. *Nat Nanotechnol* **15**, 164-164 (2020).
27. Castillo, A.P.D. & Krop, H. (ETUI, The European Trade Union Institute; 2020).
28. Occupational exposure to carbon nanotubes and nanofibers. National Institute for Occupational Safety and Health (NIOSH) *Current Intelligence Bulletin 65* (2013).

29. Realizing the promise of carbon nanotubes: Challenges, opportunities, and the pathway to commercialization. National Nanotechnology Initiative (NNI) *Technical Interchange Proceedings* (2014).
30. Multi-walled carbon nanotubes; Significant new use rule. U.S. Environmental Protection Agency (US EPA) *Federal Register* **76**, 26186-26192 (2011).
31. Significant new use rule on certain chemical substances. U.S. Environmental Protection Agency (US EPA) *Federal Register* **82**, 45990-45995 (2017).
32. Toxic substances control act inventory status of carbon nanotubes. U.S. Environmental Protection Agency (US EPA) *Federal Register* **73**, 64946-64947 (2008).
33. Castagnola, V. et al. Towards a classification strategy for complex nanostructures. *Nanoscale Horiz* **2**, 187-198 (2017).
34. Balasubramanian, K. & Burghard, M. Chemically functionalized carbon nanotubes. *Small* **1**, 180-192 (2005).
35. Kalbac, M., Green, A.A., Hersam, M.C. & Kavan, L. Probing charge transfer between shells of double-walled carbon nanotubes sorted by outer-wall electronic type. *Chemistry* **17**, 9806-9815 (2011).
36. Moore, K.E., Tune, D.D. & Flavel, B.S. Double-walled carbon nanotube processing. *Adv. Mater.* **27**, 3105-3137 (2015).
37. Shi, W. et al. Superconductivity in bundles of double-wall carbon nanotubes. *Sci Rep* **2**, 625 (2012).
38. Noffsinger, J. & Cohen, M.L. Electron-phonon coupling and superconductivity in double-walled carbon nanotubes. *Phys Rev B* **83**, 165420 (2011).
39. Hecht, D., Hu, L. & Grüner, G. Conductivity scaling with bundle length and diameter in single walled carbon nanotube networks. *Appl Phys Lett* **89**, 133112 (2006).
40. Harrah, D.M. & Swan, A.K. The role of length and defects on optical quantum efficiency and exciton decay dynamics in single-walled carbon nanotubes. *ACS Nano* **5**, 647-655 (2011).
41. Zhang, R., Zhang, Y. & Wei, F. Controlled synthesis of ultralong carbon nanotubes with perfect structures and extraordinary properties. *Acc Chem Res* **50**, 179-189 (2017).
42. Zeng, L. & Attwood, J. Advanced materials primer: carbon nanotubes. *BloombergNEF* (2021).
43. Scott, C.D., Arepalli, S., Nikolaev, P. & Smalley, R.E. Growth mechanisms for single-wall carbon nanotubes in a laser-ablation process. *Appl Phys A* **72**, 573-580 (2001).
44. Nikolaev, P. et al. Gas-phase catalytic growth of single-walled carbon nanotubes from carbon monoxide. *Chem. Phys. Lett.* **313**, 91-97 (1999).
45. Lolli, G. et al. Tailoring (n,m) Structure of single-walled carbon nanotubes by modifying reaction conditions and the nature of the support of CoMo catalysts. *J Phys Chem B* **110**, 2108-2115 (2006).
46. Saito, T. et al. Selective diameter control of single-walled carbon nanotubes in the gas-phase synthesis. *J Nanosci Nanotechnol* **8**, 6153-6157 (2008).
47. Graf, A. et al. Large scale, selective dispersion of long single-walled carbon nanotubes with high photoluminescence quantum yield by shear force mixing. *Carbon* **105**, 593-599 (2016).
48. Pénicaud, A., Poulin, P., Derré, A., Anglaret, E. & Petit, P. Spontaneous dissolution of a single-wall carbon nanotube salt. *J Am Chem Soc* **127**, 8-9 (2005).
49. Ramesh, S. et al. Dissolution of Pristine Single Walled Carbon Nanotubes in Superacids by Direct Protonation. *J Phys Chem B* **108**, 8794-8798 (2004).
50. Li, Y.-L., Kinloch, I.A. & Windle, A.H. Direct Spinning of Carbon Nanotube Fibers from Chemical Vapor Deposition Synthesis. *Science* **304**, 276-278 (2004).
51. Headrick, R.J. et al. Versatile acid solvents for pristine carbon nanotube assembly. *Sci Adv* **8**, eabm3285 (2022).
52. Ge, L., Sethi, S., Ci, L., Ajayan, P.M. & Dhinojwala, A. Carbon nanotube-based synthetic gecko tapes. *Proc Natl Acad Sci U S A* **104**, 10792-10795 (2007).
53. Zhang, M., Atkinson, K.R. & Baughman, R.H. Multifunctional Carbon Nanotube Yarns by Downsizing an Ancient Technology. *Science* **306**, 1358-1361 (2004).
54. Vigolo, B. et al. Macroscopic fibers and ribbons of oriented carbon nanotubes. *Science* **290**, 1331-1334 (2000).
55. Ericson, L.M. et al. Macroscopic, neat, single-walled carbon nanotube fibers. *Science* **305**, 1447-1450 (2004).
56. Ghosh, S., Bachilo, S.M. & Weisman, R.B. Advanced sorting of single-walled carbon nanotubes by nonlinear density-gradient ultracentrifugation. *Nat Nanotechnol* **5**, 443-450 (2010).

57. Gao, Z. et al. Optical detection of individual ultra-short carbon nanotubes enables their length characterization down to 10 nm. *Sci Rep* **5**, 17093 (2015).
58. Fagan, J.A. et al. Isolation of >1 nm diameter single-wall carbon nanotube species using aqueous two-phase extraction. *ACS Nano* **9**, 5377-5390 (2015).
59. Tanaka, T., Jin, H., Miyata, Y. & Kataura, H. High-yield separation of metallic and semiconducting single-wall carbon nanotubes by agarose gel electrophoresis. *Appl Phys Express* **1**, 114001 (2008).
60. Zheng, M. et al. DNA-assisted dispersion and separation of carbon nanotubes. *Nat Mater* **2**, 338-342 (2003).
61. Liu, H., Nishide, D., Tanaka, T. & Kataura, H. Large-scale single-chirality separation of single-wall carbon nanotubes by simple gel chromatography. *Nat Commun* **2**, 309 (2011).
62. Blanch, A.J., Lenehan, C.E. & Quinton, J.S. Optimizing surfactant concentrations for dispersion of single-walled carbon nanotubes in aqueous solution. *J Phys Chem B* **114**, 9805-9811 (2010).
63. Kato, H., Nakamura, A. & Horie, M. Acceleration of suspending single-walled carbon nanotubes in BSA aqueous solution induced by amino acid molecules. *J. Colloid Interface Sci.* **437**, 156-162 (2015).
64. Yamada, K. et al. Single walled carbon nanotube-based junction biosensor for detection of Escherichia coli. *PLOS ONE* **9**, e105767 (2014).
65. Galassi, T.V. et al. Long-term in vivo biocompatibility of single-walled carbon nanotubes. *PLOS ONE* **15**, e0226791 (2020).
66. Williams, R.M. et al. Noninvasive ovarian cancer biomarker detection via an optical nanosensor implant. *Sci Adv* **4**, eaaq1090 (2018).
67. Godin, A.G. et al. Single-nanotube tracking reveals the nanoscale organization of the extracellular space in the live brain. *Nat Nanotechnol* **12**, 238-243 (2017).
68. Harvey, J.D. et al. A carbon nanotube reporter of microRNA hybridization events in vivo. *Nat Biomed Eng* **1**, 0041 (2017).
69. Lekshmi, G. et al. Recent Progress in Carbon Nanotube Polymer Composites in Tissue Engineering and Regeneration. *Int J Mol Sci* **21** (2020).
70. Demirer, G.S. et al. High aspect ratio nanomaterials enable delivery of functional genetic material without DNA integration in mature plants. *Nat Nanotechnol* **14**, 456-464 (2019).
71. Kam, N.W., O'Connell, M., Wisdom, J.A. & Dai, H. Carbon nanotubes as multifunctional biological transporters and near-infrared agents for selective cancer cell destruction. *Proc Natl Acad Sci U S A* **102**, 11600-11605 (2005).
72. Lin, Z. et al. DNA-guided lattice remodeling of carbon nanotubes. *Science* **377**, 535-539 (2022).
73. Ghosh, S., Bachilo, S.M., Simonette, R.A., Beckingham, K.M. & Weisman, R.B. Oxygen doping modifies near-infrared band gaps in fluorescent single-walled carbon nanotubes. *Science* **330**, 1656-1659 (2010).
74. Piao, Y. et al. Brightening of carbon nanotube photoluminescence through the incorporation of sp^3 defects. *Nat Chem* **5**, 840-845 (2013).
75. Kwon, H. et al. Optical probing of local pH and temperature in complex fluids with covalently functionalized, semiconducting carbon nanotubes. *J Phys Chem C* **119**, 3733-3739 (2015).
76. Mann, F.A., Galonska, P., Herrmann, N. & Kruss, S. Quantum defects as versatile anchors for carbon nanotube functionalization. *Nat Protoc* **17**, 727-747 (2022).
77. Taylor, L.W. et al. Improved properties, increased production, and the path to broad adoption of carbon nanotube fibers. *Carbon* **171**, 689-694 (2021).
78. Armarego, W.L.F. Purification of Laboratory Chemicals (8th Edition). 1065-1106, Butterworth-Heinemann (2017).
79. Wepasnick, K.A., Smith, B.A., Bitter, J.L. & Howard Fairbrother, D. Chemical and structural characterization of carbon nanotube surfaces. *Anal Bioanal Chem* **396**, 1003-1014 (2010).
80. Suenaga, K. et al. Imaging active topological defects in carbon nanotubes. *Nat Nanotechnol* **2**, 358-360 (2007).
81. Harvey, J.D. et al. A carbon nanotube reporter of microRNA hybridization events in vivo. *Nat. Biomed. Eng.* **1**, 0041 (2017).
82. Kim, P., Odom, T.W., Huang, J. & Lieber, C.M. STM study of single-walled carbon nanotubes. *Carbon* **38**, 1741-1744 (2000).
83. Wang, H. et al. Dispersing single-walled carbon nanotubes with surfactants: A small angle neutron scattering study. *Nano Lett* **4**, 1789-1793 (2004).

84. Mirri, F. et al. Quantification of carbon nanotube liquid crystal morphology via neutron scattering. *Macromolecules* **51**, 6892-6900 (2018).
85. Burian, A., Dore, J.C., Fischer, H.E. & Sloan, J. Structural studies of multiwall carbon nanotubes by neutron diffraction. *Phys Rev B* **59**, 1665-1668 (1999).
86. Futaba, D.N., Yamada, T., Kobashi, K., Yumura, M. & Hata, K. Macroscopic wall number analysis of single-walled, double-walled, and few-walled carbon nanotubes by X-ray diffraction. *J Am Chem Soc* **133**, 5716-5719 (2011).
87. Miyata, Y., Yanagi, K., Maniwa, Y., Tanaka, T. & Kataura, H. Diameter analysis of rebundled single-wall carbon nanotubes using X-ray diffraction: Verification of chirality assignment based on optical spectra. *J Phys Chem C* **112**, 15997-16001 (2008).
88. Kolodiazhnyi, T. & Pumera, M. Towards an ultrasensitive method for the determination of metal impurities in carbon nanotubes. *Small* **4**, 1476-1484 (2008).
89. Bom, D. et al. Thermogravimetric analysis of the oxidation of multiwalled carbon nanotubes: evidence for the role of defect sites in carbon nanotube chemistry. *Nano Lett* **2**, 615-619 (2002).
90. Liu, H., Nishide, D., Tanaka, T. & Kataura, H. Large-scale single-chirality separation of single-wall carbon nanotubes by simple gel chromatography. *Nat Commun* **2**, 309 (2011).
91. Grinberg, P., Methven, B.A.J., Swider, K. & Mester, Z. Determination of metallic impurities in carbon nanotubes by glow discharge mass spectrometry. *ACS Omega* **6**, 22717-22725 (2021).
92. Harmonized tiered approach to measure and assess the potential exposure to airborne emissions of engineered nano-objects and their agglomerates and aggregates at workplaces. *Safety of Manufactured Nanomaterials* OECD Environment Directorate (2015).
93. Faria, M. et al. Minimum information reporting in bio–nano experimental literature. *Nat Nanotechnol* **13**, 777-785 (2018).
94. Ma-Hock, L. et al. Inhalation toxicity of multiwall carbon nanotubes in rats exposed for 3 months. *Toxicol Sci* **112**, 468-481 (2009).
95. Pauluhn, J. Subchronic 13-week inhalation exposure of rats to multiwalled carbon nanotubes: toxic effects are determined by density of agglomerate structures, not fibrillar structures. *Toxicol Sci* **113**, 226-242 (2010).
96. Oyabu, T. et al. Biopersistence of inhaled MWCNT in rat lungs in a 4-week well-characterized exposure. *Inhalation Toxicol* **23**, 784-791 (2011).
97. Sakamoto, Y. et al. Induction of mesothelioma by a single intrascrotal administration of multi-wall carbon nanotube in intact male Fischer 344 rats. *J Toxicol Sci* **34**, 65-76 (2009).
98. Takagi, A., Hirose, A., Futakuchi, M., Tsuda, H. & Kanno, J. Dose-dependent mesothelioma induction by intraperitoneal administration of multi-wall carbon nanotubes in p53 heterozygous mice. *Cancer Sci* **103**, 1440-1444 (2012).
99. Numano, T. et al. MWCNT-7 administered to the lung by intratracheal instillation induces development of pleural mesothelioma in F344 rats. *Cancer Sci* **110**, 2485-2492 (2019).
100. Yamashita, K. et al. Carbon Nanotubes Elicit DNA Damage and Inflammatory Response Relative to Their Size and Shape. *Inflammation* **33**, 276-280 (2010).
101. Cole, E. et al. Multiwalled carbon nanotubes of varying size lead to dna methylation changes that correspond to lung inflammation and injury in a mouse model. *Chem Res Toxicol* **32**, 1545-1553 (2019).
102. Sweeney, S. et al. Multi-walled carbon nanotube length as a critical determinant of bioreactivity with primary human pulmonary alveolar cells. *Carbon* **78**, 26-37 (2014).
103. Grosse, Y. et al. Carcinogenicity of fluoro-edenite, silicon carbide fibres and whiskers, and carbon nanotubes. *Lancet Oncology* **15**, 1427-1428 (2014).
104. Ge, C. et al. The contributions of metal impurities and tube structure to the toxicity of carbon nanotube materials. *NPG Asia Materials* **4**, e32-e32 (2012).
105. Rodríguez-Yáñez, Y. et al. Commercial single-walled carbon nanotubes effects in fibrinolysis of human umbilical vein endothelial cells. *Toxicol in Vitro* **29**, 1201-1214 (2015).
106. Pettitt, M.E. & Lead, J.R. Minimum physicochemical characterisation requirements for nanomaterial regulation. *Environ Intl* **52**, 41-50 (2013).
107. Trinh, T.X. et al. Quasi-SMILES-based nano-quantitative structure–activity relationship model to predict the cytotoxicity of multiwalled carbon nanotubes to human lung cells. *Chem Res Toxicol* **31**, 183-190 (2018).

108. Puzyn, T., Leszczynska, D. & Leszczynski, J. Toward the development of "Nano-QSARs": advances and challenges. *Small* **5**, 2494-2509 (2009).
109. Bergamaschi, E. et al. Occupational exposure to carbon nanotubes and carbon nanofibres: More than a cobweb. *Nanomaterials* **11**, (2021).
110. Guseva Canu, I. et al. Human exposure to carbon-based fibrous nanomaterials: A review. *Int J Hyg Environ Health* **219**, 166-175 (2016).
111. IRAC Working Group on the Evaluation of Carcinogenic Risks to Humans. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. *Some Nanomaterials and Some Fibres,* International Agency for Research on Cancer (2017).
112. Brouwer, D.H., Links, I.H.M., De Vreede, S.A.F. & Christopher, Y. Size Selective Dustiness and Exposure; Simulated Workplace Comparisons. *Ann. Occup. Hyg.* **50**, 445-452 (2006).
113. Evans, D.E., Turkevich, L.A., Roettgers, C.T., Deye, G.J. & Baron, P.A. Dustiness of Fine and Nanoscale Powders. *Ann Occup Hyg* **57**, 261-277 (2013).
114. OECD. Nanomaterials in waste streams. (2016).
115. Abalansa, S., El Mahrad, B., Icely, J. & Newton, A. Electronic waste, an environmental problem exported to developing countries: The GOOD, the BAD and the UGLY. *Sustainability* **13** (2021)..
116. UN Environment, Global Environment Outlook 6 (2019).
117. Petersen, E.J. et al. Potential release pathways, environmental fate, and ecological risks of carbon nanotubes. *Environ Sci Tech* **45**, 9837-9856 (2011).
118. Nowack, B. et al. Potential release scenarios for carbon nanotubes used in composites. *Environ Intl* **59**, 1-11 (2013).
119. Gottschalk, F., Kost, E. & Nowack, B. Engineered nanomaterials in water and soils: A risk quantification based on probabilistic exposure and effect modeling. *Environ Toxicol Chem* **32**, 1278-1287 (2013).
120. Jaisi, D.P. & Elimelech, M. Single-walled carbon nanotubes exhibit limited transport in soil columns. *Environ Sci Tech* **43**, 9161-9166 (2009).
121. Kasel, D. et al. Limited transport of functionalized multi-walled carbon nanotubes in two natural soils. *Environ Pollut* **180**, 152-158 (2013).
122. Helland, A., Wick, P., Koehler, A., Schmid, K. & Som, C. Reviewing the environmental and human health knowledge base of carbon nanotubes. *Environ Health Perspect* **115**, 1125-1131 (2007).
123. Healy, M.L., Dahlben, L.J. & Isaacs, J.A. Environmental assessment of single-walled carbon nanotube processes. *J Ind Ecol* **12**, 376-393 (2008).
124. Gavankar, S., Suh, S. & Keller, A.A. The role of scale and technology maturity in life cycle assessment of emerging technologies: A case study on carbon nanotubes. *J Ind Ecol* **19**, 51-60 (2015).
125. Fadeel, B. et al. Advanced tools for the safety assessment of nanomaterials. *Nat Nanotechnol* **13**, 537-543 (2018).
126. Pfister, S., Oberschelp, C. & Sonderegger, T. Regionalized LCA in practice: The need for a universal shapefile to match LCI and LCIA. *Int J LCA* **25**, 1867-1871 (2020).
127. Ku, B.K., Maynard, A.D., Baron, P.A. & Deye, G.J. Observation and measurement of anomalous responses in a differential mobility analyzer caused by ultrafine fibrous carbon aerosols. *J Electrostat* **65**, 542-548 (2007).
128. Brouwer, D. et al. Harmonization of measurement strategies for exposure to manufactured nano-objects; report of a workshop. *Ann Occup Hyg* **56**, 1-9 (2012).
129. Bianco, A., Kostarelos, K. & Prato, M. Making carbon nanotubes biocompatible and biodegradable. *Chem Comm* **47**, 10182-10188 (2011).
130. Kagan, V.E. et al. Carbon nanotubes degraded by neutrophil myeloperoxidase induce less pulmonary inflammation. *Nat Nanotechnol* **5**, 354-359 (2010).
131. Kagan, V.E. et al. Lung macrophages "digest" carbon nanotubes using a superoxide/peroxynitrite oxidative pathway. *ACS Nano* **8**, 5610-5621 (2014).
132. Allen, B.L. et al. Biodegradation of single-walled carbon nanotubes through enzymatic catalysis. *Nano Lett* **8**, 3899-3903 (2008).
133. Ren, X., Chen, C., Nagatsu, M. & Wang, X. Carbon nanotubes as adsorbents in environmental pollution management: A review. *Chem Eng J* **170**, 395-410 (2011).
134. Wong, K.V. & Bachelier, B. Carbon nanotubes used for renewable energy applications and environmental protection/remediation: A review. *J Energy Resour Technol* **136** (2013).

135. Zheng, M. et al. Carbon nanotube-based materials for lithium–sulfur batteries. *J Mater Chem A* **7**, 17204-17241 (2019).
136. Zhang, P., Su, J., Guo, J. & Hu, S. Influence of carbon nanotube on properties of concrete: A review. *Constr Build Mater* **369**, 130388 (2023).
137. Licht, S. et al. Amplified CO2 reduction of greenhouse gas emissions with C2CNT carbon nanotube composites. *Mater Today Sustain* **6**, 100023 (2019).
138. UN General Assembly, Transforming our world: the 2030 Agenda for Sustainable Development. A/RES/70/1 (2015).
139. Pasquali, M. & Mesters, C. We can use carbon to decarbonize—and get hydrogen for free. *Proc Natl Acad Sci U S A* **118**, e2112089118 (2021).
140. Rao, A.M. et al. Diameter-selective raman scattering from vibrational modes in carbon nanotubes. *Science* **275**, 187-191 (1997).
141. Sun, Z. et al. Quantitative evaluation of surfactant-stabilized single-walled carbon nanotubes: dispersion quality and its correlation with zeta potential. *J Phys Chem C* **112**, 10692-10699 (2008).
142. Naumov, A.V., Ghosh, S., Tsyboulski, D.A., Bachilo, S.M. & Weisman, R.B. Analyzing absorption backgrounds in single-walled carbon nanotube spectra. *ACS Nano* **5**, 1639-1648 (2011).
143. Sanchez, S.R., Bachilo, S.M., Kadria-Vili, Y., Lin, C.-W. & Weisman, R.B. (n,m)-specific absorption cross sections of single-walled carbon nanotubes measured by variance spectroscopy. *Nano Lett* **16**, 6903-6909 (2016).
144. Nair, N., Usrey, M.L., Kim, W.-J., Braatz, R.D. & Strano, M.S. Estimation of the (n,m) concentration distribution of single-walled carbon nanotubes from photoabsorption spectra. *Anal Chem* **78**, 7689-7696 (2006).
145. Sebastian, F.L. et al. Absolute quantification of sp^3 defects in semiconducting single-wall carbon nanotubes by Raman spectroscopy. *J Phys Chem Lett* **13**, 3542-3548 (2022).
146. Ghanbari, F. et al. Mitochondrial oxidative stress and dysfunction induced by single- and multiwall carbon nanotubes: A comparative study. *J Biomed Mater Res A* **105**, 2047-2055 (2017).
147. Hillegass, J.M. et al. Assessing nanotoxicity in cells in vitro. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **2**, 219-231 (2010).
148. Wörle-Knirsch, J.M., Pulskamp, K. & Krug, H.F. Oops They Did It Again! Carbon Nanotubes Hoax Scientists in Viability Assays. *Nano Lett* **6**, 1261-1268 (2006).
149. Wajant, H., Pfizenmaier, K. & Scheurich, P. Tumor necrosis factor signaling. *Cell Death Differ.* **10**, 45-65 (2003).
150. Frank, D. & Vince, J.E. Pyroptosis versus necroptosis: Similarities, differences, and crosstalk. *Cell Death Differ* **26**, 99-114 (2019).
151. Wu, L. et al. Tuning cell autophagy by diversifying carbon nanotube surface chemistry. *ACS Nano* **8**, 2087-2099 (2014).
152. Mah, L.J., El-Osta, A. & Karagiannis, T.C. γH2AX: A sensitive molecular marker of DNA damage and repair. *Leukemia* **24**, 679-686 (2010).
153. Guo, Y.-Y., Zhang, J., Zheng, Y.-F., Yang, J. & Zhu, X.-Q. Cytotoxic and genotoxic effects of multi-wall carbon nanotubes on human umbilical vein endothelial cells in vitro. *Mutat Res Genet Toxicol Environ Mutagen* **721**, 184-191 (2011).
154. Sommer, S., Buraczewska, I. & Kruszewski, M. Micronucleus assay: The state of art, and future directions. *Int J Mol Sci* **21** (2020).
155. Horibata, K. et al. In vivo genotoxicity assessment of a multiwalled carbon nanotube in a mouse ex vivo culture. *Genes Environ* **44**, 24 (2022).
156. Yamaguchi, S.-I. et al. Carbon nanotube recognition by human Siglec-14 provokes inflammation. *Nat Nanotechnol* (2023).
157. Koyama, S. et al. In vivo immunological toxicity in mice of carbon nanotubes with impurities. *Carbon* **47**, 1365-1372 (2009).
158. Hornung, V. et al. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. *Nat Immunol* **9**, 847-856 (2008).
159. Pal, A.K., Bello, D., Budhlall, B., Rogers, E. & Milton, D.K. Screening for oxidative stress elicited by engineered nanomaterials: evaluation of acellular DCFH assay. *Dose Response* **10**, 308-330 (2012).
160. Jena, P.V. et al. A carbon nanotube optical reporter maps endolysosomal lipid flux. *ACS Nano* **11**, 10689-10703 (2017).

161. Maejima, I. et al. Autophagy sequesters damaged lysosomes to control lysosomal biogenesis and kidney injury. *Embo j* **32**, 2336-2347 (2013).
162. Gravely, M. & Roxbury, D. Multispectral fingerprinting resolves dynamics of nanomaterial trafficking in primary endothelial cells. *ACS Nano* **15**, 12388-12404 (2021).
163. Arora, S. et al. In vitro cytotoxicity of multiwalled and single-walled carbon nanotubes on human cell lines. *Fuller Nanotub* **23**, 377-382 (2015).
164. Antonucci, A. et al. Carbon nanotube uptake in cyanobacteria for near-infrared imaging and enhanced bioelectricity generation in living photovoltaics. *Nat Nanotechnol* **17**, 1111-1119 (2022).
165. Karousis, N., Tagmatarchis, N. & Tasis, D. Current progress on the chemical modification of carbon nanotubes. *Chem. Rev.* **110**, 5366-5397 (2010).
166. Zhang, Y. et al. Mechanistic toxicity evaluation of uncoated and pegylated single-walled carbon nanotubes in neuronal PC12 cells. *ACS Nano* **5**, 7020-7033 (2011).
167. Liu, X. et al. Optimization of surface chemistry on single-walled carbon nanotubes for in vivo photothermal ablation of tumors. *Biomaterials* **32**, 144-151 (2011).
168. Gravely, M., Safaee, M.M. & Roxbury, D. Biomolecular functionalization of a nanomaterial to control stability and retention within live cells. *Nano Lett* **19**, 6203-6212 (2019).
169. Sanchez-Valencia, J.R. et al. Controlled synthesis of single-chirality carbon nanotubes. *Nature* **512**, 61-64 (2014).
170. Liu, B., Wu, F., Gui, H., Zheng, M. & Zhou, C. Chirality-controlled synthesis and applications of single-wall carbon nanotubes. *ACS Nano* **11**, 31-53 (2017).
171. Feng, Y., Zhou, G., Wang, G., Qu, M. & Yu, Z. Removal of some impurities from carbon nanotubes. *Chem. Phys. Lett.* **375**, 645-648 (2003).
172. Mercier, G. et al. Selective removal of metal impurities from single walled carbon nanotube samples. *New J Chem* **37**, 790-795 (2013).
173. Muller, J. et al. Structural defects play a major role in the acute lung toxicity of multiwall carbon nanotubes: Toxicological aspects. *Chem Res Toxicol* **21**, 1698-1705 (2008).
174. Bai, W., Raghavendra, A., Podila, R. & Brown, J.M. Defect density in multiwalled carbon nanotubes influences ovalbumin adsorption and promotes macrophage activation and CD4(+) T-cell proliferation. *Int J Nanomedicine* **11**, 4357-4371 (2016).
175. Yamamoto, G. et al. Structure–property relationships in thermally-annealed multi-walled carbon nanotubes. *Carbon* **66**, 219-226 (2014).
176. Ren, F. et al. Controlled cutting of single-walled carbon nanotubes and low temperature annealing. *Carbon* **63**, 61-70 (2013).
177. Mombini, S. et al. Chitosan-PVA-CNT nanofibers as electrically conductive scaffolds for cardiovascular tissue engineering. *Int J Biol Macromol* **140**, 278-287 (2019).
178. Qin, Z. et al. Carbon nanotubes/hydrophobically associated hydrogels as ultrastretchable, highly sensitive, stable strain, and pressure sensors. *ACS Appl Mater Interfaces* **12**, 4944-4953 (2020).
179. Zhang, M. et al. A simple method for removal of carbon nanotubes from wastewater using hypochlorite. *Sci Rep* **9**, 1284 (2019).
180. Sun, E. et al. A semi-continuous process for co-production of CO_2-free hydrogen and carbon nanotubes via methane pyrolysis. *Cell Rep Phys Sci* **4**, 101338 (2023).
181. International Energy Agency, The role of critical minerals in clean energy transitions (2021).
182. UN Economic and Social Council. Combating transnational organized crime and its links to illicit trafficking in precious metals and illegal mining, including by enhancing the security of supply chains of precious metals: Resolution/adopted by the Economic and Social Council. E/2019/100 19c Crime prevention and criminal justice. (2019).
183. Responsible Mining Foundation, Responsible Mining Index Report 2020. (2020).