Update on the Environmental Health and Safety of Cellulose Nanomaterials

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TAPPI

CN Life Cycle Risk Assessment & EHS Roadmap Identified Identified Key Knowledge Gaps

Assessed 59 Scenarios, including:

* Worker
  - Inhalation exposure to dry particles
  - Manipulating composites
* Consumer
  - Cosmetics (dermal)
  - Food contact (oral)
  - Abrasion/wear
* Environmental
  - Water; waste; recycling; re-use

Shatkin, J. A., & Kim, B. (2015). Cellulose nanomaterials: life cycle risk assessment, and environmental health and safety roadmap. *Environmental Science: Nano*, 2(5), 477-499.

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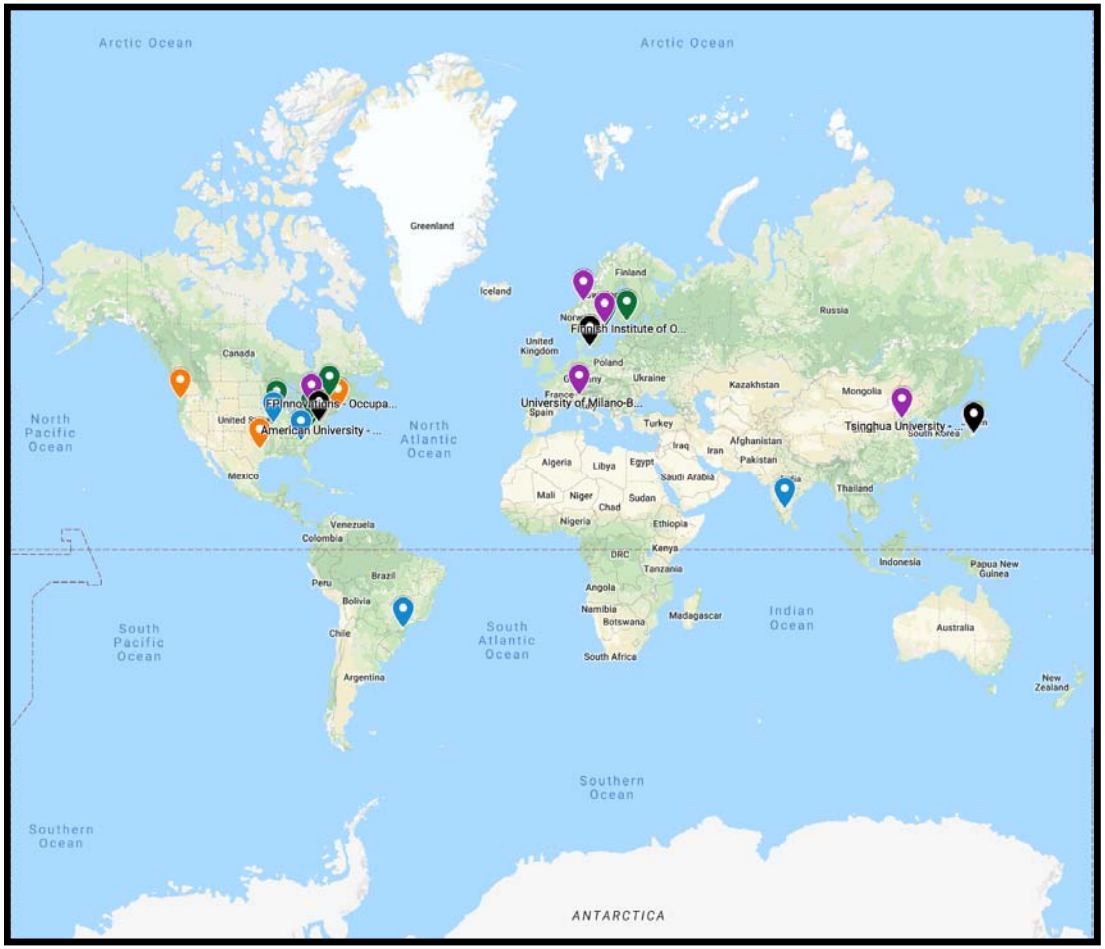
Global Map of Cellulose Nanomaterial Safety Research



Worldwide Efforts include:

- Occupational Safety Research
- Biocompatibility and Tissue Engineering
- Toxicity Testing Methods
- Food Safety
  - P3Nano Food Safety Study Project

Available at: **www.vireoadvisors.com/cellulose-nanomaterial-safety-research-map/**

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What Vireo Advisors Does

P^{3}Nano

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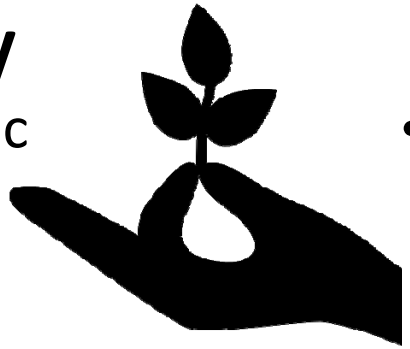
Worker Safety

- Inhalation Study Analysis
- Worker Guidance

Consumer Safety

- Safety for Cosmetic Applications
- Safety of Composites



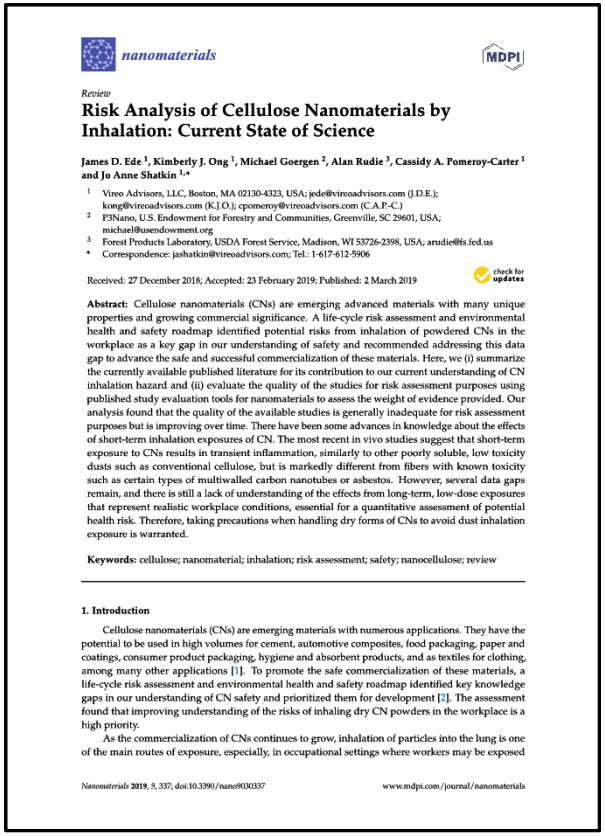
Environmental Safety

- Analysis of Available Data for Safety Demonstration

U.S. Endowment for Forestry and Communities

EHS of Cellulose Nanomaterials

Worker Safety | Consumer Safety | Environmental Safety



nanomaterials MDPI

Review

Risk Analysis of Cellulose Nanomaterials by Inhalation: Current State of Science

James D. Ede [1], Kimberly J. Ong [1], Michael Goergen [2], Alan Rudie [3], Cassidy A. Pomeroy-Carter [1] and Jo Anne Shatkin [1,*]

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check for updates

Abstract: Cellulose nanomaterials (CNs) are emerging advanced materials with many unique properties and growing commercial significance. A life-cycle risk assessment and environmental health and safety roadmap identified potential risks from inhalation of powdered CNs in the workplace as a key gap in our understanding of safety and recommended addressing this data gap to advance the safe and successful commercialization of these materials. Here, we (i) summarize the currently available published literature for its contribution to our current understanding of CN inhalation hazard and (ii) evaluate the quality of the studies for risk assessment purposes using published study evaluation tools for nanomaterials to assess the weight of evidence provided. Our analysis found that the quality of the available studies is generally inadequate for risk assessment purposes but is improving over time. There have been some advances in knowledge about the effects of short-term inhalation exposures of CN. The most recent in vivo studies suggest that short-term exposure to CNs results in transient inflammation, similarly to other poorly soluble, low toxicity dusts such as conventional cellulose, but is markedly different from fibers with known toxicity such as certain types of multiwalled carbon nanotubes or asbestos. However, several data gaps remain, and there is still a lack of understanding of the effects from long-term, low-dose exposures that represent realistic workplace conditions, essential for a quantitative assessment of potential health risk. Therefore, taking precautions when handling dry forms of CNs to avoid dust inhalation exposure is warranted.

Keywords: cellulose; nanomaterial; inhalation; risk assessment; safety; nanocellulose; review

1. Introduction

Cellulose nanomaterials (CNs) are emerging materials with numerous applications. They have the potential to be used in high volumes for cement, automotive composites, food packaging, paper and coatings, consumer product packaging, hygiene and absorbent products, and as textiles for clothing, among many other applications [1]. To promote the safe commercialization of these materials, a life-cycle risk assessment and environmental health and safety roadmap identified key knowledge gaps in our understanding of CN safety and prioritized them for development [2]. The assessment found that improving understanding of the risks of inhaling dry CN powders in the workplace is a high priority.

As the commercialization of CNs continues to grow, inhalation of particles into the lung is one of the main routes of exposure, especially, in occupational settings where workers may be exposed

- Summarize published studies for their contribution to our current understanding of CN inhalation hazard
- Evaluate studies *for risk assessment purposes* using published evaluation tools

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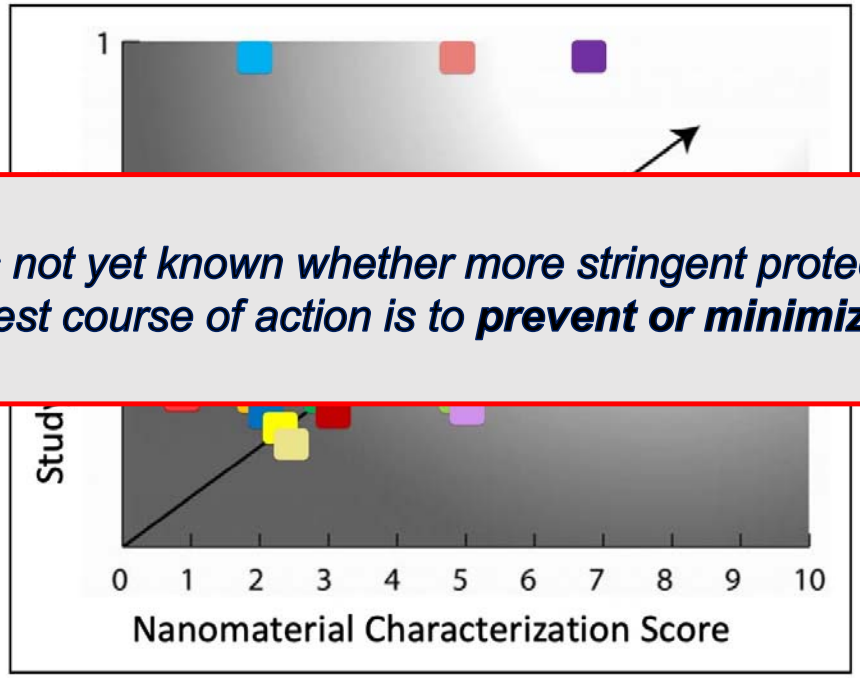
EHS of Cellulose Nanomaterials

Worker Safety | Consumer Safety | Environmental Safety



Legend

In Vivo Studies

- O'Connor 2014
- Yanamala 2014
- Farcas 2016

In Vitro Studies

- Clift 2011
- Endes 2014
- Yanamala 2016
- Menas 2017
- Lopes 2017
- Ilves 2018

CONCLUSIONS

- Quality of the available studies is **generally inadequate for risk assessment** purposes but is improving over time.

It is not yet known whether more stringent protections are needed for CNs than for other dusts, so the safest course of action is to prevent or minimize the potential for exposure to dried forms of CNs.

soluble, low toxicity dusts such as conventional cellulose.

- However, several **data gaps remain**, and there is still a lack of understanding of the effects from long-term, low-dose exposures.

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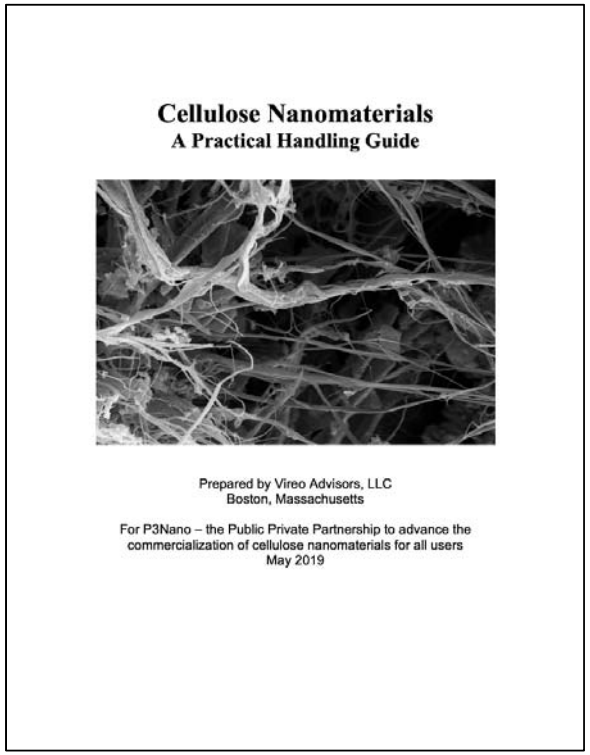
Cellulose Nanomaterials
A Practical Handling Guide

Prepared by Vireo Advisors, LLC
Boston, Massachusetts

For P3Nano – the Public Private Partnership to advance the commercialization of cellulose nanomaterials for all users
May 2019

Cellulose Nanomaterial Worker Handling Guide

- Developed in collaboration with P3Nano
- Guide for people working with CNs
  - Written for non-experts
  - Safety concerns, current knowledge, and best available safety management practices

Available at: http://tappinano.org/whats-up/hse-summary/

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EHS of Cellulose Nanomaterials

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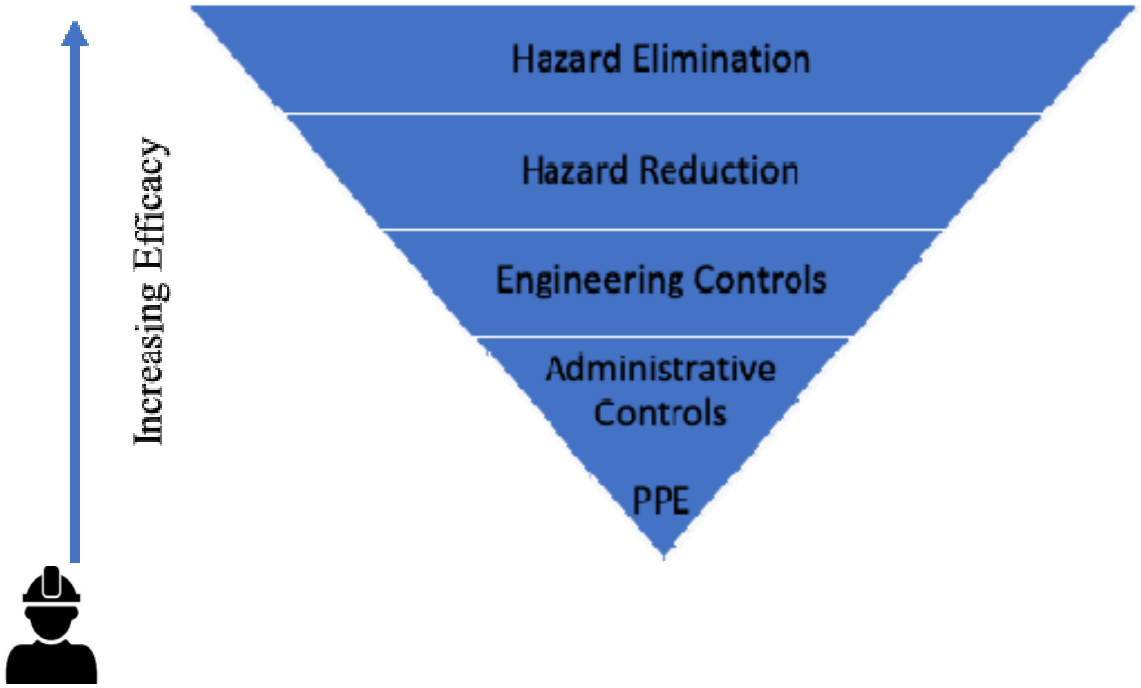
Cellulose Nanomaterial Worker Handling Guide



Exposure Route	Recommended Practices	PPE
Inhalation (Breathing)	• Handle dry materials in controlled environments (e.g., glove boxes, glove bags, or hoods) • If possible, use materials in liquid suspensions, slurries, or gels	• Respirators
Oral (Ingestion)	• Do not eat or drink in working areas • Remove PPE when not handling materials	• Gloves • Masks
Dermal (Skin)	• Handle materials in closed environments • Pay particular attention when handling wet forms of nanomaterials and nanomaterials in matrices (e.g., master batches) • Avoid splashing when handling wet materials	• Gloves • Lab coats
Ocular (Eyes)	• Handle materials in closed environments • Avoid splashing when handling wet materials	• Goggles • Glasses

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EHS OF CELLULOSE NANOMATERIALS

Worker Safety | **Consumer Safety** | Environmental Safety

Food | Cosmetics | Composites

PROJECT OBJECTIVES

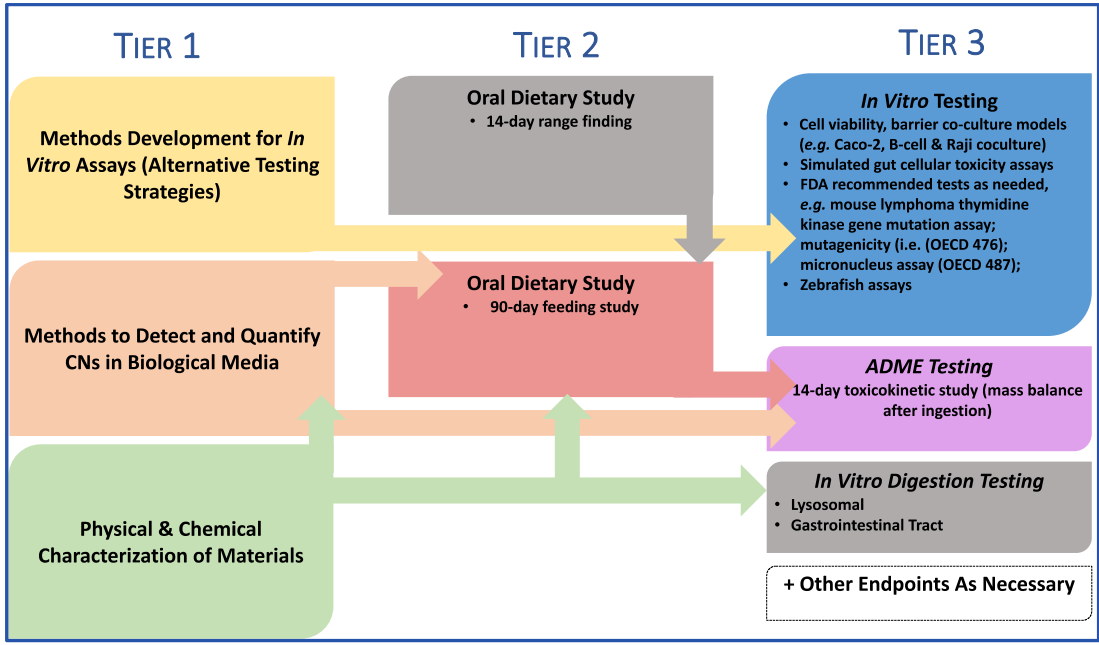
Focused Oral Toxicity Studies to Address Gaps

Build a set of methods and a data set demonstrating safety;
Conduct studies in commercial testing labs to compare oral uptake of new forms of cellulose to Existing GRAS;
Develop a suite of assays to address nano exposure and toxicity;

Tiered Testing Approach – Minimize Initial Effort & Inform Design To achieve demonstration of safety

- **COLLABORATORS**
  - Vireo Advisors – PI / Project Coordinator
  - American University/NIST
  - Baylor University School of Medicine
  - Harvard School of Public Health
  - Oregon State University
  - Commercial testing labs - GLP Studies
  - Independent peer reviewers
  - GRAS Advisor
  - APPTI/ Agenda 2020 Nano Committee

- **FUNDING PARTNERS**
  - Alberta Innovates
  - P3Nano (public private partnership with US DPL)
  - Industry – international producers/end users
  - US Govt. Granting Agencies



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EHS of Cellulose Nanomaterials

Worker Safety | **Consumer Safety** | Environmental Safety

Food | **Cosmetics** | Composites

Data Suggests CNC & CNF Similar Safety to Conventional Cellulose for Use in Cosmetics

SUMMARY:

Test	Cellulose Nanocrystals	Cellulose Nanofibrils
Skin Irritation	**Non-irritating** **Non-corrosive**[1]	No studies publicly available.
Eye Irritation	No studies publicly available.	No studies publicly available.
Skin Sensitization	**Non-sensitizing**[1]	No studies publicly available.
Acute Toxicity	**No mortality or adverse effects observed.**[1]	No studies publicly available.
Repeat Dose Toxicity	**No mortality or adverse effects observed (28 day).**[1]	**Vireo Food Safety Study**

1. O'Connor et al., 2014 Commercialization of Cellulose Nanocrystal Production: A Business Case Focusing on the Importance of Proactive EHS Management.
2. Ong et al., 2017. Establishing the safety of novel bio-based cellulose nanomaterials for commercialization. NanoImpact **6**, 19-29.

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EHS of Cellulose Nanomaterials

Worker Safety | **Consumer Safety** | Environmental Safety

Food | **Cosmetics** | Composites

Data Suggests CNC & CNF Similar Safety to Conventional Cellulose for Use in Cosmetics

SUMMARY:

	Cellulose Nanocrystals	Cellulose Nanofibrils
Sub-chronic (90 day) Toxicity	**Vireo Food Safety Study**	**Vireo Food Safety Study**
Mutagenicity/ Genotoxicity	**No evidence genotoxic.[1]**	**No evidence genotoxic.[2]**
Skin Photoirritation	No studies publicly available.	No studies publicly available.
Phototoxicity Testing (sun-exposed)	No studies publicly available.	No studies publicly available.

1. O'Connor et al., 2014 Commercialization of Cellulose Nanocrystal Production: A Business Case Focusing on the Importance of Proactive EHS Management.
2. Pitkänen et al., 2014. Characteristics and safety of nano-sized cellulose fibrils. Cellulose **21** 3871-86.

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EHS of Cellulose Nanomaterials

Worker Safety | **Consumer Safety** | Environmental Safety

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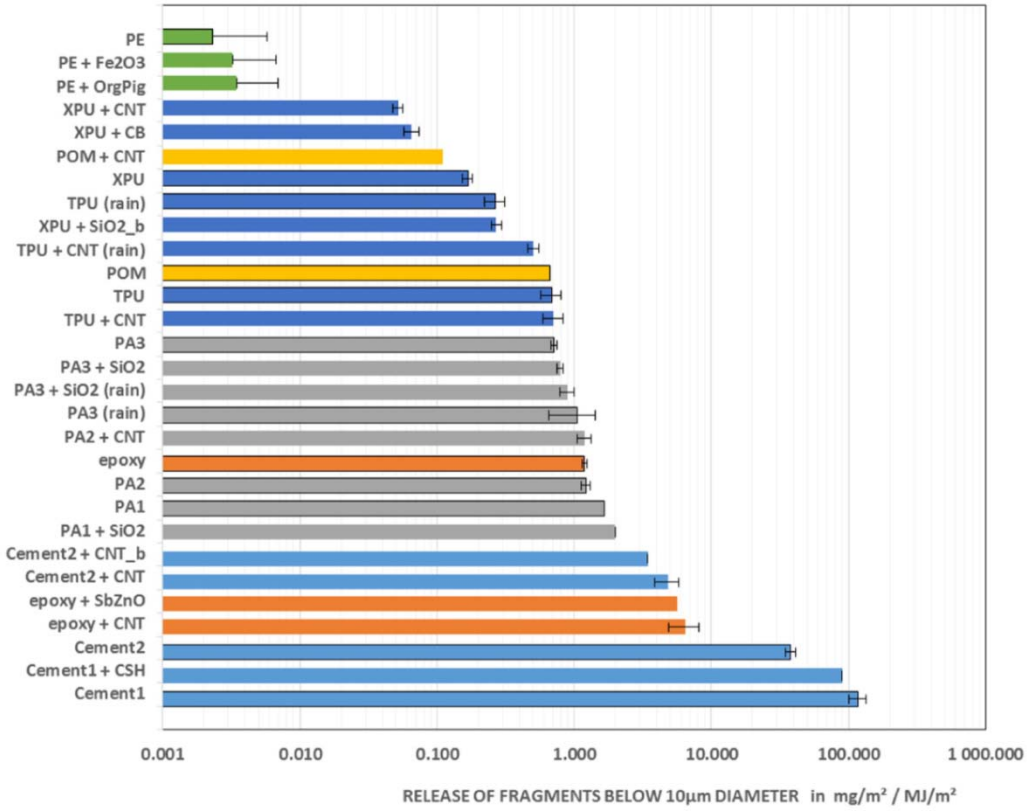

Wohlleben et al., 2016 NanoImpact

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EHS of Cellulose Nanomaterials

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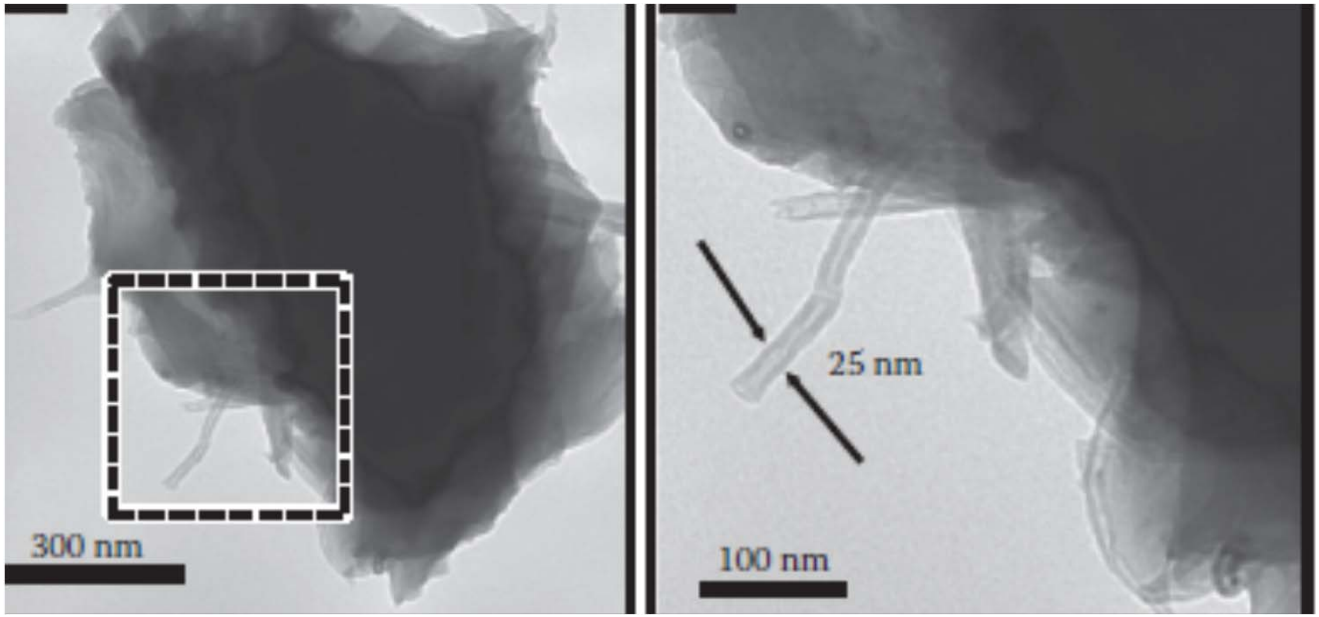
Knowledge from Studies with Carbon Nanotube Composites:



Adapted from: Peters TM, Ch 8. Managing Risks in Occupational Environments, in Shatkin, 2012. *Nanotechnology Health and Environmental Risks, 2nd Edition. CRC Press.*

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EHS of Cellulose Nanomaterials

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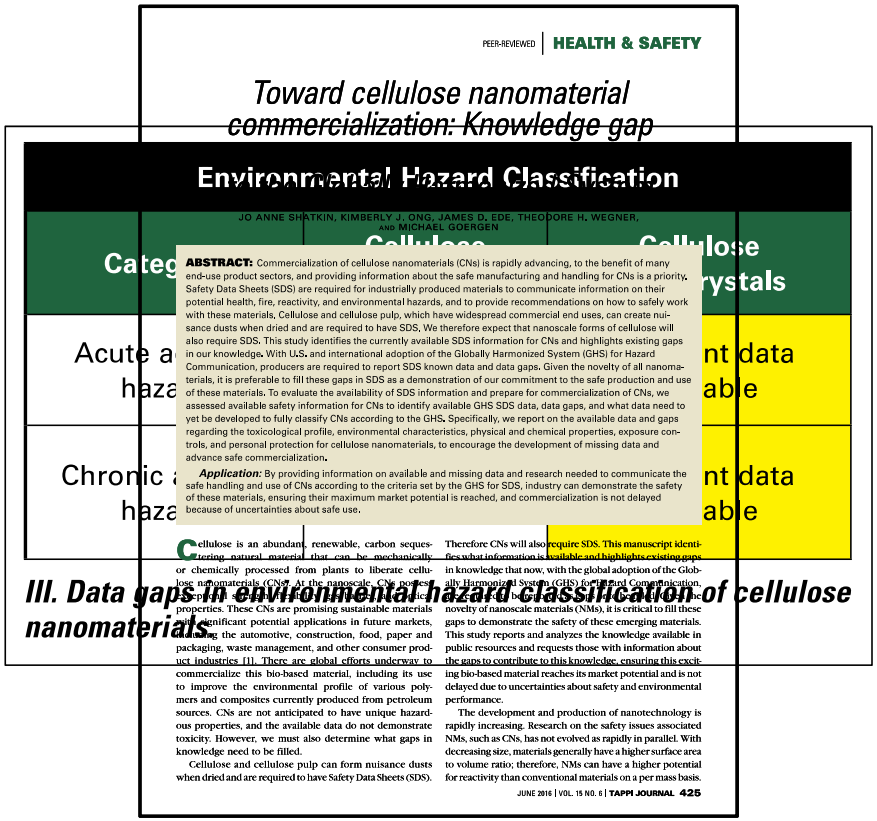

PEER-REVIEWED | HEALTH & SAFETY

Toward cellulose nanomaterial commercialization: Knowledge gap

JO ANNE SHATKIN, KIMBERLY J. ONG, JAMES D. EDE, THEODORE H. WEGNER, AND MICHAEL GOERGEN

ABSTRACT: Commercialization of cellulose nanomaterials (CNs) is rapidly advancing, to the benefit of many end-use product sectors, and providing information about the safe manufacturing and handling for CNs is a priority. Safety Data Sheets (SDS) are required for industrially produced materials to communicate information on their potential health, fire, reactivity, and environmental hazards, and to provide recommendations on how to safely work with these materials. Cellulose and cellulose pulp, which have widespread commercial end uses, can create nuisance dusts when dried and are required to have SDS. We therefore expect that nanoscale forms of cellulose will also require SDS. This study identifies the currently available SDS information for CNs and highlights existing gaps in our knowledge. With U.S. and international adoption of the Globally Harmonized System (GHS) for Hazard Communication, producers are required to report SDS known data and data gaps. Given the novelty of all nanomaterials, it is preferable to fill these gaps in SDS as a demonstration of our commitment to the safe production and use of these materials. To evaluate the availability of SDS information and prepare for commercialization of CNs, we assessed available safety information for CNs to identify available GHS SDS data, data gaps, and what data need to yet be developed to fully classify CNs according to the GHS. Specifically, we report on the available data and gaps regarding the toxicological profile, environmental characteristics, physical and chemical properties, exposure controls, and personal protection for cellulose nanomaterials, to encourage the development of missing data and advance safe commercialization.

Application: By providing information on available and missing data and research needed to communicate the safe handling and use of CNs according to the criteria set by the GHS for SDS, industry can demonstrate the safety of these materials, ensuring their maximum market potential is reached, and commercialization is not delayed because of uncertainties about safe use.

Cellulose is an abundant, renewable, carbon sequestering natural material that can be mechanically or chemically processed from plants to liberate cellulose nanomaterials (CNs). At the nanoscale, CNs possess [illegible] properties. These CNs are promising sustainable materials with significant potential applications in future markets, including the automotive, construction, food, paper and packaging, waste management, and other consumer product industries [1]. There are global efforts underway to commercialize this bio-based material, including its use to improve the environmental profile of various polymers and composites currently produced from petroleum sources. CNs are not anticipated to have unique hazardous properties, and the available data do not demonstrate toxicity. However, we must also determine what gaps in knowledge need to be filled.

Cellulose and cellulose pulp can form nuisance dusts when dried and are required to have Safety Data Sheets (SDS). Therefore CNs will also require SDS. This manuscript identifies what information is available and highlights existing gaps in knowledge that now, with the global adoption of the Globally Harmonized System (GHS) for Hazard Communication, [illegible] novelty of nanoscale materials (NMs), it is critical to fill these gaps to demonstrate the safety of these emerging materials. This study reports and analyzes the knowledge available in public resources and requests those with information about the gaps to contribute to this knowledge, ensuring this exciting bio-based material reaches its market potential and is not delayed due to uncertainties about safety and environmental performance.

The development and production of nanotechnology is rapidly increasing. Research on the safety issues associated NMs, such as CNs, has not evolved as rapidly in parallel. With decreasing size, materials generally have a higher surface area to volume ratio; therefore, NMs can have a higher potential for reactivity than conventional materials on a per mass basis.

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Environmental Hazard Classification

Categ	Cellulose	Cellulose rystals
Acute a haza		nt data able
Chronic haza		nt data able

III. Data gaps in environmental hazard classification of cellulose nanomaterials.

Endpoint	CNC	CNF
Biodegradation		
• Aerobic biodegradation		
• Anaerobic biodegradation		
Environmental Toxicity		
Aquatic Plants		
Bacteria		
Aquatic Invertebrates		
• Acute Toxicity		
• Chronic Toxicity		
Fish		
• Acute Toxicity		
• Chronic Toxicity		

Kovacs et al., 2010; Vartiainen et al., 2011; Celndaniel et al., 2014; Pereira et al., 2014; Harper et al., 2016; Due et al., 2016; Ong et al., 2017

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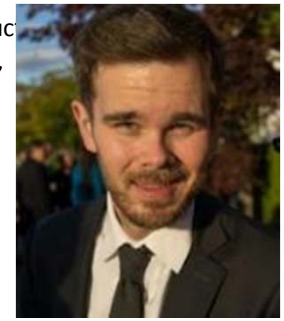
THE VIREO ADVISORS TEAM

Dr. Jo Anne Shatkin is an expert in novel product safety and environmental and health policy issues, with over 20 years experience leading projects in risk analysis, safety and regulatory policy work including numerous publications.

She is founder and president of Vireo Advisors in Boston, Massachusetts.



Dr. James D. Ede is a toxicologist experienced in testing strategies for novel materials, including molecular, biochemical and cellular techniques, and is experienced in life cycle risk assessment

Dr. Kimberly J. Ong is a biologist and environmental scientist. Dr. Ong is an expert in developing protocols specific for novel material testing to improve reliability for risk and exposure assessment, and is experienced in regulatory analysis for novel products.

Cassidy Pomeroy Carter holds a Bachelor's degree in biology. She has science and technology policy experience and has worked on emerging technologies, innovation, and risk assessment.

Dr. Shaun Clancy is a chemist with over 30 years experience in the chemicals industry, directing programs in health, safety, and regulatory affairs in major corporations.

Leslie Hockman has industry experience working for a commercial manufacturer of cellulose nanomaterials, and is Vireo's administrator.

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Thank you

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