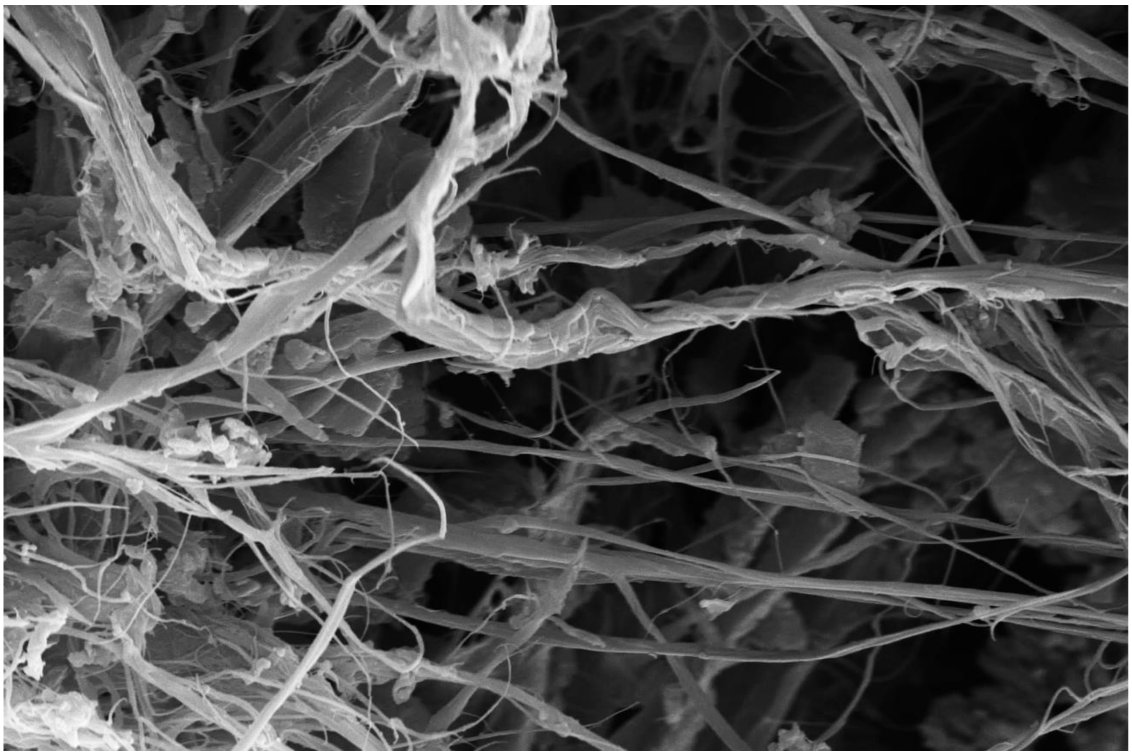
# Cellulose Nanomaterials
## A Practical Handling Guide



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## Introduction

Cellulose nanomaterials, including cellulose nanocrystals (CNC) cellulose nanofibrils (CNF), and TEMPO CNF, are natural materials derived from cellulose, an abundant substance found in many plants. Cellulose nanomaterials are being evaluated for use in pharmaceuticals, cosmetics, food, food packaging, materials strengthening, electronics, displays, and many other applications. Among the important properties of cellulose nanomaterials are their viscosity, light weight, absorbency, and high strength. They hold great potential in a variety of applications and offer important functional and societal benefits. While there is a long history of safe use of cellulose, the novelty of deriving nanoscale forms of cellulose raises questions about safe handling practices.

This document is intended as a guide for people working with cellulose nanomaterials. It explains some of the safety concerns, the current knowledge addressing these concerns, and safety management practices for the workplace. It is based on expert knowledge as well as publicly available resources including government agency guidance and peer reviewed literature. This guidance does not replace current industry practices or standards and is intended to provide supplemental information useful for people working with cellulose nanomaterials.

The document is structured for *three separate audiences*. Clicking on the hyperlink which appears in the below list for each audience will advance the reader directly to the section intended for that audience.

I. The Essentials are intended for people who may not be working directly with cellulose nanomaterials themselves *but who work with or make decisions affecting those who do*. The information presented to this audience has been distilled to essential elements.
II. Safety Practices for Cellulose Nanomaterials in the Workplace are intended for people who *work directly with cellulose nanomaterials and are seeking guidance to use them safely* but may not need to know the details supporting how safe practices and risk assessments are developed. This is for people want to know that the practices they follow are sound but may not be interested in the toxicology and chemistry studies that support the practices.
III. The section on Getting into the Details is intended for *people who want / need to know the details* of toxicology, eco-toxicology, physical chemical properties/ characterization, and other research to better understand the potential hazards of cellulose nanomaterials and how this information is used for risk assessment and mitigation.

## I. The Essentials

**What are cellulose nanomaterials?** Cellulose nanomaterials are materials derived from a common plant component: cellulose. As nanomaterials—a term generally used to describe materials with one or more dimensions under 100 nanometers—they have unique properties that distinguish them from conventional (non-nano) materials. These characteristics, which may include special chemical and physical properties, provide useful benefits in many applications but also warrant additional safety considerations for those handling them.

**Why do nanomaterials raise safety concerns?** From a safety perspective, the key question is whether the changes in the physical properties of nanoscale materials impact safety or health. This question has been, and continues to be, the focus of many studies, and the results have been varied, depending on factors such as the composition of the particles and the surface characteristics of the materials.

**Which nanomaterial characteristics raise potential safety concerns?** One property that is of particular interest from a safety perspective is how nanoscale particles can disperse in air. Because of their light weight, some nanoparticles in dry powder form are easily suspended and don't settle quickly. These particles may be small enough to travel deeply into the lungs. From a health and safety perspective, understanding and mitigating the effect of inhaling airborne nanomaterials is especially important. However, individual nanoparticles often become tightly connected to one another and, in turn, those groups of particles often loosely associate with other particles. The properties of these larger collections of nanoparticles (termed aggregates and agglomerates, respectively) may differ from those of the individual nanoparticles. For example, agglomerates can have sizes of over 1000 nm, making them more susceptible to gravity and settling and less likely to travel deep into the lungs. When discussing nanomaterials, it is important to understand both the form of a nanomaterial, the size of that form, and how these properties impact key safety characteristics. Other relevant considerations include shape (fibers can behave differently from other particle shapes), surface chemistry/surface modifications for functionalization (which can affect toxicity), and the presence of other materials in cellulose nanomaterial mixtures (such as biocides which may be used for preservation).

**How are people exposed to nanomaterials?** Exposures can occur at different parts of the product life cycle, but people who work with materials in their raw form or in mixtures generally experience the most exposure to any material because exposure often occurs daily and includes direct handling. Depending on the form of the material and how it is handled, exposure can occur by breathing, touching, or accidentally eating materials while working. Because of the higher likelihood of exposure among workers, occupational safety is a priority in many nations and in industrial culture. As a result, workers as a group are unique compared to other classes of people potentially exposed to nanomaterials. As an example of this uniqueness, workers are considered to be a Sensitive Population under the US Toxic Substances Control Act, and their welfare is given special consideration.

**Which workplace types present potential nanomaterial exposures?** There are many workplaces where materials are used including:

- **laboratories** where preparation and evaluation may take place
- **manufacturing facilities** where materials may be prepared in significant quantities
- **processing facilities** where materials are incorporated or transformed into products
- **packaging facilities** where materials or products containing them are prepared for distribution
- workplaces associated with the **transportation of materials** or products containing them
- workplaces where **products are used** and/or disposed of
- **destruction/reprocessing/recycling facilities** for materials and products containing them

The type and level of exposure will be unique to each workplace, but some types of workplaces, such as manufacturing and laboratory settings, generally have greater opportunity for worker exposures than others.

**Are cellulose nanomaterials safe to work with?** Studies about the safety of cellulose nanomaterials are increasing, and research on their use and safety continues. Based on the information available to date, cellulose nanomaterials appear to be of low toxicity to people, animals, and the environment. While encouraging, it is important to note that there are still unanswered questions regarding certain types of hazards and exposures that have yet to be evaluated. <u>The main workplace safety concern is inhaling particles when not properly controlled while working with them in dry form.</u>

**How can safety be practiced in the workplace?** As research continues to fill data gaps, safety practices for workplaces that handle cellulose nanomaterials could become more protective than the existing data indicate are needed. Seeking expert help to develop safety practices is recommended. For example, having a team of industrial hygienists conduct a workplace assessment with specialized equipment can be useful to assess exposure and develop safe handling practices. Although research has found that standard workplace safety measures can prevent exposure to nanoscale materials, implementing extra precautionary measures serves to increase the margin of safety while data gaps remain. Box 1 offers an overview of how exposures are managed in the workplace. The next section of this guide provides more detailed information on specific workplace safety practices.

**Box 1.** The [Exposure Control Hierarchy] developed by safety professionals provides a framework for managing occupational exposures:

1. **Engineering controls** include good ventilation and enclosing processes. These practices reduce the need for workers to take their own actions by isolating processes that can lead to exposure.
2. **Administrative controls** include procedures for workers to follow that outline how to reduce/eliminate exposures. Even when engineering controls are in place, the addition of administrative controls is a recommended practice.
3. **Personal protective equipment (PPE)** can be an effective addition to good workplace practices. However, the use of PPE can provide a false sense of improved safety if it is not implemented well. To be effective, it is essential that workers understand and follow the use requirements for each piece of PPE. Because inhalation of dry particles is a particular point of concern, some workplaces may benefit from the establishment of formal respiratory protection programs to provide equipment and training to workers.

## II. Safety Practices for Cellulose Nanomaterials in the Workplace

**Is it safe to work with cellulose nanomaterials?** All materials in the workplace should be handled carefully, but with proper handling practices, working with cellulose nanomaterials can be safely managed. Studies to date do not indicate any unique health hazards, and while additional research is needed, early indications suggest cellulose nanomaterials behave similarly to conventional cellulose dust as well as many known and long-used poorly soluble, low toxicity materials. However, it is never a good idea to inhale foreign particles or fibers into the lung. The main workplace safety concern associated with cellulose nanomaterials is inhaling particles when working with them in dry form.

**If cellulose nanomaterials are safe, why are special health and safety practices needed?** There is a growing body of research indicating that current cellulose nanomaterials are not particularly hazardous (see above), but data gaps and uncertainty remain. Proper handling is therefore a critical component of safe use, and until more research is available, risk assessors and safety professionals recommend implementing layers of safety as a precaution.

**What aspects of cellulose nanomaterial safety have not been adequately explored?** Generally speaking, research has not identified serious acute impacts associated with single or short-term exposures to cellulose nanomaterials, though there are indications of transient lung inflammation when inhaling dry powder forms. In addition, not all forms of cellulose nanomaterials have been tested, nor have all types of exposures been evaluated. One notable gap is research on repeated, chronic exposures, especially by inhalation, such as those that may be experienced in a workplace. Workplace exposures also have not been well characterized.

**How are safety practices for cellulose nanomaterials developed?** Minimizing unintended and uncontrolled exposures in the workplace is a recommended practice for handling any material, and the safety practices that have long been in place for non-nanomaterials also work for nanomaterials, including cellulose nanomaterials (*e.g.*, US NIOSH "Approaches to Safe Nanotechnology" – 2009; UK HSE "Nanoparticles: An Occupational Hygiene Review" – 2004). Safety practices for conventional materials provide a foundation for nanomaterial safety practices, but consideration should be given to the nanoscale nature of these materials.

**What practices are better for safe handling of cellulose nanomaterials?** There is a hierarchy of methods used when designing controls for workplace safety (NIOSH, 2009). If hazard elimination is not possible, methods (listed in order of preference) are:

- Engineering controls such as ventilation and enclosing processes
- Administrative controls such as establishing workplace practices that guide workers to reduce exposures
- Personal protective equipment (PPE) such as respirators, dust masks, and gloves. The use of all PPE must be done in a manner that assures effectiveness. Compliance with legal requirements such as those of the US

Occupational Safety and Health Administration, PPE manufacturer directions and industrial hygiene guidance is essential.

Following this hierarchy, relying primarily on engineering controls and secondarily on administrative controls and PPE will result in the highest levels of protection. If you are working with these materials, make sure you are aware of engineering and administrative controls and practices that help reduce exposures, including all PPE requirements. These practices are in place to help keep you safe.

**How will this guide help me work with cellulose nanomaterials safely?** The goal of this document is to provide guidance on how to handle cellulose nanomaterials in a manner that ensures a high level of safety. Although the available data indicate cellulose nanomaterials are not very toxic, as a precautionary approach, cellulose nanomaterials in dry form should be handled as if they present potential hazards. This guide highlights state-of-the-art practices and safety information from a practical perspective to provide the information needed to handle cellulose nanomaterials safely.

## Workplace Protection – General Practices

Cellulose nanomaterials are similar to many other nanomaterials in that they are derived from conventional (non-nano) materials. Information is often available on the conventional forms, and this knowledge should be considered when developing protective work practices for nanomaterials. However, it should not be assumed that the information for a conventional material is predictive for the nanoforms; knowledge pertaining to conventional materials should be considered informative, not definitive, when applied to nanomaterials. Nevertheless, the general considerations pertinent to nanomaterials are the same as for chemical substances with some additions.

Importantly, when handling any potentially hazardous material, appropriate controls should be considered *before any work actually takes place*. Particular care should be taken when conducting activities where potential exposures may be overlooked (*e.g.*, during cleaning, equipment maintenance, loading and unloading materials from hoods and glove boxes). In addition, people handling cellulose nanomaterials should be aware of the safety practices listed below:

- Review Safety Data Sheets and labels before handling any materials. Understand that cellulose nanomaterials may have surface modifications for functionalization or may be preserved in mixtures using biocides; these considerations can have important safety implications.
- Seek information related to common exposures in your workplace type. Box 2 presents some common exposure scenarios.
- Understand that nanomaterials can be too small to see. They may be found in the air or on surfaces but not be visible. Do not assume that because materials cannot be seen they are not there.
- Be aware of how equipment used might impact safety and ask if any additional precautions might be needed when using specialized machinery.

- Ensure engineering controls that help control exposure (*e.g.*, ventilation) are functioning properly before handling materials.
- Understand and adhere to requirements for PPE (*e.g.*, gloves, aprons, respirators).

**Box 2**. Exposure scenario examples

a. **In the laboratory or a student maker space** – Nanomaterial handling in laboratories may present inhalation (breathing), ingestion (swallowing), dermal (skin), or ocular (eye) exposures. In many labs, nanomaterials are handled under highly controlled settings, such as glove boxes or in fume hoods with rigorous ventilation. However, lab spaces and workspaces may be close together, and hygiene practices in workspaces, such as desk areas, are likely to be less rigorous than in lab spaces.

b. **In the pilot facility** – Pilot facilities blend practices used in the lab with those used in full production. These facilities present opportunities to identify the need for new exposure management practices. In such cases, increased emphasis on the use of PPE and administrative controls may be needed until engineering controls can be developed.

c. **In production** – Ideally, by the time a nanomaterial is produced in commercial quantities, the manufacturing process has been well developed, and potential release and exposure points have been identified. Production process design should include implementing controls to eliminate releases and minimize exposures, especially for obvious release points. Obvious release/exposure points include intentional releases that occur, for example, when materials are added or removed from the process, when products are packed for shipping or when samples are taken for quality control.

d. **During clean-up** – Production processes may result in nanomaterial byproducts that are not used commercially. Examples include waste materials, materials in filters, residue materials in vessels and releases to waste water. Practices for the handling of these materials during cleanout must include ways to mitigate potential exposures.

## Recommended Practices by Exposure Route

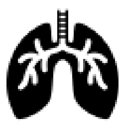
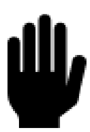
To handle nanomaterials safely, it is essential to understand the material forms and use that information to determine potential exposures and exposure routes. Nanomaterials in dry form are generally very finely divided solids, but nanomaterials may also be available in liquid and solid forms, where solid forms are larger and can include aggregates, agglomerates and other collections in micron and larger sizes that are too large to inhale. **Table 1** provides an overview of exposure considerations by nanomaterial form, while **Box 3** reviews safe handling practices organized by route of exposure. These resources are followed by a list of sound practices for PPE use, and a small section on additional safety considerations associated with nanomaterial handling (shape and physical hazards).

**The main workplace safety concern associated with cellulose nanomaterials is inhaling particles when working with them in dry form.**

**Table 1. Exposure Considerations by Nanomaterial Form**

| Nanomaterial Forms | | Primary Exposure Route | Notes on Exposure |
|---|---|---|---|
| Dry forms | Individual particles | Inhalation (breathing) | • Particles can travel places where they are not detected (*e.g.*, through seams of protective garments)<br>• Precautions should be taken even if need is not obvious |
| Dry forms | Collections of particles (aggregates and agglomerates) | Inhalation (breathing) | • Collections are larger (sometimes 100 to >1000 times) than the individual nanoparticles<br>• Knowledge about how to prevent exposures to large particles is extensive<br>• Commonly practiced protective measures are often effective |
| Liquid and solid forms | | Dermal (skin) | • Inhalation risk is lower<br>• Good industrial hygiene practices should limit ingestion and ocular (eye) exposures (though protective measures should still be taken)<br>• Splashing and atomization increase risk of dermal (skin), inhalation (breathing), and ocular (eye) exposures |

**Box 3**. The following is a list of recommended practices organized by route of exposure. It includes practices that support or implement engineering and administrative controls, as well as PPE recommendations. By the hierarchy of controls, engineering and administrative controls tend to be more effective, but the importance of proper PPE use should not be overlooked.

| **Exposure Route** | **Recommended Practices** | **PPE** |
|---|---|---|
| <br>Inhalation (Breathing) | • Handle dry materials in controlled environments (e.g., glove boxes, glove bags, or hoods)<br>• If possible, use materials in liquid suspensions, slurries, or gels<br>• Adhere to requirements of formal respiratory protection programs in your workplace, if applicable | • Respirators |
| <br>Oral (Ingestion) | • Do not eat or drink in working areas<br>• Remove PPE when not handling materials | • Gloves<br>• Masks |
| <br>Dermal (Skin) | • Handle materials in closed environments<br>• Pay particular attention when handling wet forms of nanomaterials and nanomaterials in matrices (e.g., master batches)<br>• Avoid splashing when handling wet materials | • Gloves<br>• Lab coats<br>• Disposable clothing covers<br>• Face shields (if splashing is a concern) |
| <br>Ocular (Eyes) | • Handle materials in closed environments<br>• Avoid splashing when handling wet materials | • Goggles (if splashing is a concern)<br>• Glasses |

## Recommended Practices for PPE Use

Box 3 highlights recommended PPE by exposure route. Although other methods to prevent workplace exposures (*e.g*., engineering and administrative controls) are preferred to PPE, PPE is one of the main ways you can protect yourself when working with cellulose nanomaterials. With PPE it is important to always adhere to requirements set forth in formal respiratory protection programs at an organization or institution, if applicable. To ensure efficacy, it is important to follow these recommended practices related to PPE use:

- Ensure proper fit. It should not be assumed equipment is effective simply because it is being worn.
- Dispose of and clean PPE properly to avoid secondary exposures.
- Confirm the integrity of PPE before and during use. The efficacy of PPE can be compromised if the equipment is damaged, as in the case of ripped gloves or clothing. Replace damaged equipment with undamaged PPE, and immediately dispose of defective PPE so it cannot be inadvertently used again.

## Additional Considerations (Shape and Physical Hazards)

### *Nanomaterial shape*

Nanomaterials can differ not only in size but also in shape, and shape can have an appreciable safety impact. In particular, nanomaterials with fibrous shapes, such as cellulose nanofibers, raise special concerns. This is because some conventional fibrous materials, such as asbestos, present unique health impacts, especially in the lungs. These hazards are collectively referred to as the fiber paradigm.

The small size of cellulose nanofibers distinguishes them from conventional materials that are described by the fiber paradigm. Although some forms of cellulose nanomaterials may be described as fibers, **cellulose nanomaterials do not appear to meet the fiber paradigm** (Ilves et al., 2018). That said, conventional cellulose fibers may, at a minimum, cause irritation and lung inflammation (Cullen et al., 2000), so exposure to powders should be avoided. Good laboratory and industrial hygiene practices should be in place to minimize all unnecessary chances of exposure.

### *Physical hazards*

In addition to health concerns, there are also potential physical hazards presented by dry nanomaterials. In particular, some nanomaterials, including cellulose nanomaterials, are susceptible to combustion and explosion. In the United States, these hazards are governed by a variety of standards published and enforced by the Occupational Safety and Health Administration (OSHA). Combustible dusts are also covered by the US OSHA General Duty Clause, which requires that all workplaces be free of recognizable hazards. Keeping workplaces clean to avoid dust buildup is crucial. Attention should also be paid to storage conditions. Working with non-dry forms of nanomaterials, such as liquid suspensions or gels, can greatly reduce the risk of combustion or explosion in the workplace.

## III. Getting into the Details

Risk assessment practitioners and others recognize that Risk = Hazard x Exposure. While this is not a mathematical equation, it demonstrates that risk is a combination of the two elements and, moreover, that each of the elements can be considered individually. This section of the guide describes these two aspects in greater detail, focusing on how exposure can be controlled in the workplace to reduce risk and what is known about cellulose nanomaterial toxicity/hazards.

### Identifying and Managing Exposure to Cellulose Nanomaterials

#### *Identifying points of exposure*

Because exposure is a key component of risk, understanding and mitigating risk requires identifying potential points of exposure. A relatively recent addition to the risk assessment toolbox is the use of Life Cycle Risk Assessment (LCRA), which evaluates scenarios within a product life-cycle on the basis of potential exposure to a material, as well as the availability of safety information. This analysis, when combined with the potential hazards of a material, helps professionals characterize the safety landscape and develop risk management practices.

Shatkin and Kim (2015) applied LCRA to cellulose nanomaterials (NANO LCRA) and found that occupational inhalation is a primary safety concern. The study also identified exposures during recycling, especially during subprocesses such as cutting, as priorities for filling data gaps. Information such as this can help researchers and safety professionals better focus limited resources. More information on NANO LCRA findings can be viewed in the Supplemental Information.

#### *Assessing exposure*

Generally, exposure assessment requires the expertise of industrial hygiene professionals, who are trained in conducting sampling in workplaces and have access to specialized equipment for measuring exposure. Seeking expert assistance for workplace exposure assessments is recommended. For example, the US National Institute for Occupational Safety and Health (NIOSH) conducts free, confidential workplace surveys in the United States, with specific sampling equipment, and provides recommendations for managing workplace exposures. There are also some private organizations that perform similar services internationally.

#### *Managing exposure*

Once potential exposures are identified, they can be controlled to reduce risk. Professionals use the Exposure Control Hierarchy to rank methods by which exposures can be managed.
The Exposure Control Hierarchy includes the elements depicted in
**Figure *1***.

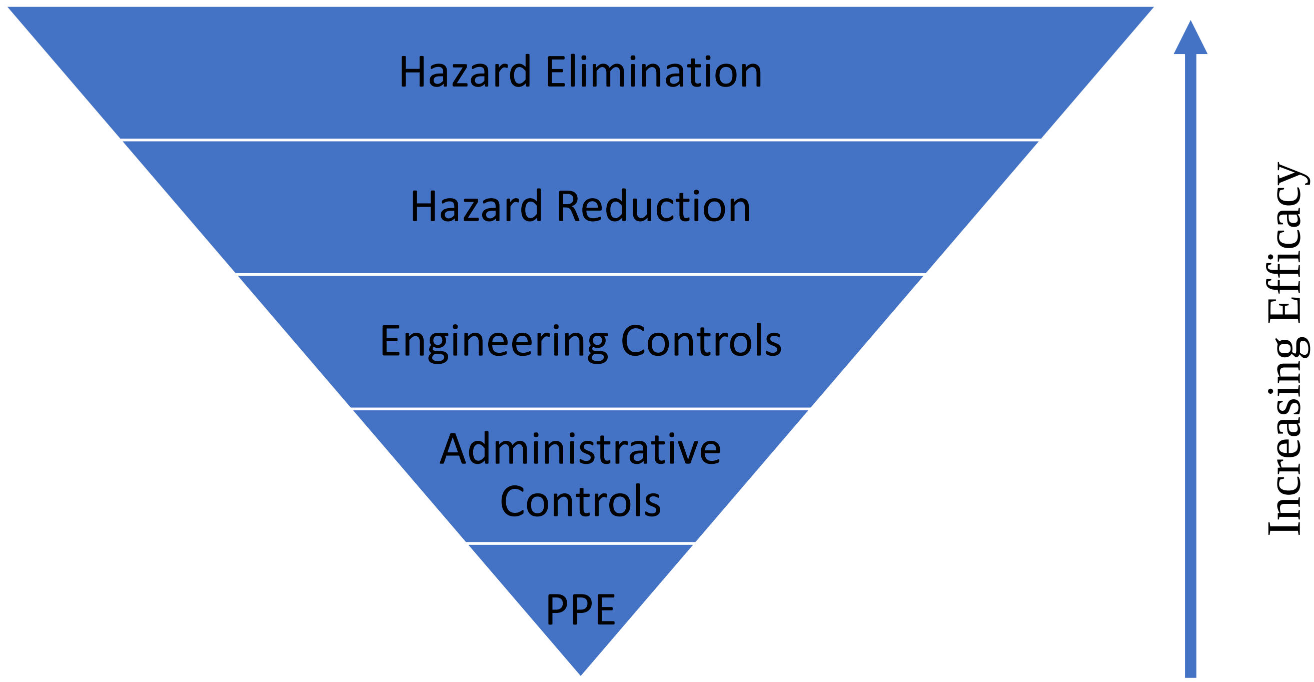



**Figure 1. Exposure Control Hierarchy**

This discussion assumes the use of cellulose nanomaterials provides benefits that cannot be easily achieved with other materials. It is therefore not practical to consider elimination, but the other elements of the hierarchy can help reduce exposure. **Table 2** describes these elements in greater detail.

**Table 2. Exposure Control Hierarchy**

| Hierarchy Element | Description | Notes |
|---|---|---|
| Hazard reduction | Practices used to reduce the overall hazard levels in the workplace (here, measures to reduce the amount of material used in the production process) | Using materials only in amounts needed to obtain the desired effect is a common theme of Good Manufacturing Practice (GMP) across industries and can help reduce exposure. |
| Engineering controls | Controls engineered into work environments, such as ventilation, exhaust equipment, recirculation, filtration of ambient air, and enclosures for work areas | Engineering controls can be automated to help ensure workers are protected even if they disregard safe working practices or fail to wear PPE correctly. |

*(Table continued on next page.)*

**Table 3 (cont.). Exposure Control Hierarchy**

| Hierarchy Element | Description | Notes |
|---|---|---|
| Administrative controls | Well-defined procedures and practices based on a detailed understanding of the potential hazards associated with equipment, processes, and materials employed | During process development, each step should be evaluated for potential hazards and exposures, and mitigating practices should be defined. |
| PPE | Garments and equipment designed to protect workers from exposure | PPE offers some protection in the event that other elements fail, but PPE cannot offer full protection. As work procedures are developed, PPE requirements should be defined and tailored to the process and material employed. |

Specific recommendations for workers are described in the section of this document devoted to Safety Practices for Cellulose Nanomaterials in the Workplace.

## Cellulose Nanomaterial Toxicity/Hazards

Toxicology studies assess the potential for toxicity based on exposure routes including those resulting from ingestion (oral toxicity), skin contact (dermal toxicity), eye contact (ocular toxicity), and breathing (inhalation toxicity).

At a high level, mechanisms of toxicity can be described as either chemical or physical. Materials that have chemical toxicity interact and/or interfere with biological organisms at the cellular level, targeting cellular mechanisms or biological pathways. Materials that have physical toxicity may not interfere with these mechanisms but can result in effects such as inflammation or mucus generation when present in cells. These types of effects are common for particulate materials. Some materials, including nanomaterials, can cause a combination of chemical and physical toxicity; this is the case, for example, for materials with surface modifications (Ilves et al., 2018), such as functionalization (where additional chemical groups are added to a surface) or modifications resulting from treatment (where a treatment, such as oxidation, changes the composition of the particle surface). Both of these types of modifications can alter the health impacts of the material.

In addition to toxicity, materials can also present physical and chemical hazards, such as explosivity and poor biodegradability.

**Table 3** presents an overview of information available on hazards associated with cellulose nanomaterials.

**Table 3. Cellulose Nanomaterial Hazards**

| Hazard | Result | References |
|---|---|---|
| Inhalation toxicity | Currently available results do not indicate that cellulose nanomaterials behave with different potency or toxicity mechanism from conventional forms of cellulose. | Studies summarized in Ede et al., 2019, especially Ilves et al., 2018 (see summary in Supplemental Information) |
| Inhalation toxicity | No forms of cellulose appear to meet the fiber paradigm. | Ilves et al., 2018; Park et al., 2018 (see summary in Supplemental Information) |
| Oral toxicity | In short-term studies, oral exposure did not result in significant toxicity. | See summary table in Supplemental Information |
| Dermal toxicity | Researchers have not observed impacts in dermal toxicity evaluations, including those assessing irritation or sensitization to the skin or eyes. | See summary table in Supplemental Information |
| Genotoxicity | Testing for CNC and CNF does not indicate that cellulose nanomaterials adversely affect DNA or cause genetic toxicity. | See summary table in Supplemental Information |
| Physical and chemical hazards (e.g., explosivity, biodegradability) | Studies examining physical and chemical hazards have reported findings indicating cellulose nanomaterials present minimal hazard potential. | See summary table in Supplemental Information |

*In general, the data available at the time of publication of this document do not indicate any unique health hazards associated with cellulose nanomaterials.*

Despite progress to date, however, many questions about the safe levels of exposure in the workplace remain (*e.g.*, whether existing occupational exposure limits for cellulose dusts are sufficiently protective for cellulose nanomaterials; see Supplemental Information for details). This is not because there are particular concerns with cellulose nanomaterials but rather because much of the available data was not generated for the purpose of supporting risk assessments (Ede *et al*., 2018). Specific limitations associated with toxicity studies are described below:

- Most toxicity studies to date have examined one, or a few, high doses of cellulose nanomaterials that are not representative of realistic workplace exposure levels. Toxicity evaluations have exposed test animals to concentrations of cellulose nanomaterials far exceeding those that should ever be found in a workplace, and even at the extreme concentrations, responses have been similar to those expected due to exposure to large quantities of particulates generally. More information can be viewed in the Supplemental Information.
- Many studies observe effects only 24 hours after exposure, before any short-term effects from the initial exposure can resolve. Additional work on chronic exposure is needed to draw conclusions about long-term effects. More information can be viewed in the Supplemental Information.
- Toxicity studies often evaluate the material being considered as a “single” material. In actual use scenarios, however, there are usually other materials present either intentionally (as in a mixture) or unintentionally (as when there are impurities). Because the presence of other materials can alter toxicity, when designing hazard controls, it is important to consider the presence of other materials and their potential impacts. For example, biological materials such as cellulose can have microbial contaminants. More information can be viewed in the Supplemental Information.

Until more research is available, risk assessors and safety professionals recommend additional safety practices as a precaution; however, current uncertainty makes it challenging to manage risk solely by managing hazards. The practices required, such as modifying a material to alter its hazard, may also change the application properties that confer its benefits. It is often easier and more effective to manage exposure potential, which is why managing exposure is the focus of this guide.

## Summary

- Cellulose nanomaterials are fascinating materials that can provide a variety of benefits to society when used responsibly.
- Cellulose nanomaterials can be handled safely through the use of common industrial hygiene and good manufacturing practices. Notable among these is the Exposure Control Hierarchy.
- The safety information available today does not indicate any area of particular toxicological concern, but because conventional cellulose dust is an irritant, it is expected that cellulose nanomaterial dusts will also be irritants.
- NANO Life Cycle Risk Assessment concludes that **the main workplace concern for nanocellulose nanomaterials is the potential for inhalation when working with dry powder forms**. Using available protective practices according to the exposure control hierarchy can address this type of exposure.
- Because of uncertainty about health effects, precaution is recommended, including exposure elimination even though the data suggest cellulose nanomaterials may be of low toxicity.
- Obtaining expert help is recommended. Experts can use specialized equipment for exposure assessment and recommend safe handling practices.
- Additional research to better understand exposure and chronic impacts will be beneficial.

## Resources

There are a number of resources available for safety professionals and workers to consult when developing and implementing safe workplace practices:

a) US OSHA Webpage on Nanotechnology - https://www.osha.gov/dsg/nanotechnology/index.html
b) US NIOSH Approaches to Safe Nanotechnology - https://www.cdc.gov/niosh/docs/2009-125/pdfs/2009-125.pdf
c) OSHA Fact Sheet Working Safely with Nanomaterials - https://www.osha.gov/Publications/OSHA_FS-3634.pdf
d) US NIOSH Nanomaterial Guidance for SMEs https://www.cdc.gov/niosh/docs/2016-102/default.html
e) OECD Nano Safety - http://www.oecd.org/science/nanosafety/
f) NNI Nano Safety page - https://www.nano.gov/you/environmental-health-safety
g) US NIOSH Information on Control Banding - https://www.cdc.gov/niosh/topics/ctrlbanding/
h) TAPPI Nanotechnology Division EHS page - http://www.tappinano.org/whats-up/hse-summary/
i) UK HSE Nanoparticles: An Occupational Hygiene Review - http://www.hse.gov.uk/research/rrpdf/rr274.pdf.
j) European Agency for Safety and Health at Work Fact Sheet: Tools for the Management of Nanomaterials in the Workplace and Prevention Measures - https://osha.europa.eu/en/tools-and-publications/publications/e-facts/e-fact-72-tools-for-the-management-of-nanomaterials-in-the-workplace-and-prevention-measures/view
k) NIOSH Japan Nanomaterials in Workplaces - https://www.jniosh.johas.go.jp/en/publication/nanomaterial.html.
l) Canadian Centre for Occupational Health and Safety OSH Answers Fact Sheets: Nanotechnology - https://www.ccohs.ca/oshanswers/chemicals/nanotechnology.html
m) European Agency for Safety and Health at Work Tools for the Management of Nanomaterials in the Workplace and Prevention Measures - https://osha.europa.eu/en/tools-and-publications/publications/e-facts/e-fact-72-tools-for-the-management-of-nanomaterials-in-the-workplace-and-prevention-measures/view
n) Institute of Occupational Medicine Exposure to Nanomaterials: Key projects - https://www.iom-world.org/research/our-work/exposure-to-nanomaterials/

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## Featured references with highlights

Shatkin et al.
*Chemical Society Reviews*
2018
"Current characterization methods for cellulose nanomaterials," Section 12
Reviews characterization methods for both *in vivo* and *in vitro* studies. Provides a decision tree that considers the potential product life-cycle.
3 pages of references; one page of pertinent OECD and ISO methods

Cullen et al.
*Journal of Applied Toxicology*
2000
"Pulmonary and intraperitoneal inflammation induced by cellulose fibers"
Cellulose fibers produce an acute inflammatory response to high dose administration; the response decreases with time even if the dose is maintained. The response is less severe than for crocidolite asbestos and resolves much more quickly.
>70 references

Ilves et al.
*Nanotoxicology*
2018
"Nanofibrillated cellulose causes acute pulmonary inflammation that subsides within a month"
Nanofibrillated cellulose (NC) is less inflammogenic than carbon nanotubes (CNT). Unfunctionalized NC is more inflammatory than the anionically-treated NCs tested. Responses range from comparable to an increased response compared to conventional cellulose.
>50 references

Ede et al.
*Nanomaterials*
2019
"Risk analysis of cellulose nanomaterials by inhalation: Current state of science"
The quality of available information is not sufficient for risk analysis, but it is improving. Short term exposures result in transient inflammation that resolves relatively quickly compared to materials like CNT and asbestos. There is a data gap regarding chronic exposures at realistic concentrations.
>50 references

Shatkin & Kim
*Handbook of Nanocellulose and Cellulose Nanocomposites, Volume 1*
2017
Chapter 21: “Environmental health and safety of cellulose nanomaterials and composites”
Cellulose nanomaterials are in early stage development and safety concerns have not been identified. As the volume of nanocellulose used increases, more information will be needed to ensure that areas of concern are identified and addressed. Identifies a variety of specific information needs regarding metrology, toxicology, ecotoxicology, and exposure.
>50 references

Ong et al.
*NanoImpact*
2017
“Establishing the safety of novel bio-based cellulose nanomaterials for commercialization”
Presents a safety testing plan for lignin-coated cellulose nanofibrils (L-CNF) and lignin-coated cellulose nanocrystals (L-CNC) based on nano-life cycle risk assessment and recommendations from various regulatory agencies. Testing plan includes physico-chemical characterization, human health effects testing, and environmental effects testing. Together with published studies examining the effects of related and conventional substances, results demonstrate that L-CNF and L-CNC are relatively non-toxic, especially at environmentally realistic concentrations (much like their conventional cellulosic counterparts).
>50 references

## Supplemental Information

### Evidence that response to inhalation of CNF does not differ from response to inhalation of cellulose

Toxicity results following acute exposure to CNF via inhalation do not present particular concern, but one study using high doses of CNF did result in inflammatory responses in rat lungs (Ilves et al., 2018). The inflammation was similar in response and duration to that seen for conventional cellulose fibers and was greatly improved 28 days after the initial high-dose exposure, indicating the inflammatory response was transient.

### Evidence that cellulose nanomaterials do not adhere to the fiber paradigm

Fibrous materials attract unique safety concerns because of their comparison to asbestos. Park et al. (2018) exposed mice to CNF, CNC, carbon nanotubes (CNT), and crocidolite asbestos via inhalation. The mice responded to the cellulose nanomaterials (and CNT) very differently than they did to asbestos. Although responses were observed for all of the materials, the characteristics of the asbestos response were unique. The authors concluded that the cellulose nanomaterials did not behave "asbestos-like."

### Evidence that CNC is of low toxicity

Some toxicology evaluation results are displayed below. The table lists results from a variety of tests (based on Organisation for Economic Co-operation and Development [OECD] Test Guidelines) for a single type of CNC with a particle size distribution in water ranging between 10-1000 nm, peaking at about 100 nm.

**Supplemental Table 1. Published OECD Toxicity Testing Results for CNC**

| OECD Test Guideline | Results |
|---|---|
| OECD 403 – Acute Inhalation Toxicity | No mortality or signs of gross toxicity, adverse effects, abnormal behaviors or abnormalities. Based on the maximum attainable test concentration. LC50 > 0.26 mg/L |
| OECD 404 – Inhalation/Corrosion | No corrosive effects were observed. NCCTM has a primary irritation index of zero. |
| OECD 406 – Skin Sensitization | Found to be non-sensitizing at 1.1 mg/L (intradermal) and 103 mg/L (topical induction and challenge phase) |
| OECD 407 – 28-day Oral Repeated Dose | No toxicity was observed at any dose. All parameters (neurological, body weight, weight gain, food consumption) were not different from controls. The NOEL was considered to be >2000 mg/kg/day |

*(Table continued on next page.)*

**Supplemental Table 1 (cont). Published OECD Toxicity Testing Results for CNC**

| OECD Test Guideline | Results |
|---|---|
| OECD 425 – Oral Single Dose | No effects observed at highest concentration tested. Not considered to present a significant hazard if swallowed. LD50 > 2000 mg/kg |
| OECD 429 – Skin Sensitization | Not considered to be a contact dermal sensitizer at concentrations <10.7% |
| OECD 471 – Bacterial Reverse Mutation (genotoxicity) | Shown to not be mutagenic up to the maximum concentration tested of 5 mg/plate |
| OECD 473 – *In-vitro* Chromosome Aberration (genotoxicity) | Did not induce chromosome aberration in cultured Chinese hamster ovary cells at a maximum test concentration of 5 mg/mL |
| OECD 474 – *In-vivo* Erythrocyte Micronucleus (genotoxicity) | Did not induce micronuclei in the mouse micronucleus test at a maximum tested dose of 2000 mg/kg |

## Evidence that cellulose nanomaterials present low physical and chemical hazards

Safety data sheets available via the TAPPI Nano EHS website report low physical and chemical hazards.

## More information about occupational exposure limits

Occupational exposure limits (OELs) have been established for many substances. OELs provide confidence that a material can be used safely up to certain threshold limits. Each OEL requires a significant effort to ensure that there is a good foundation for setting an exposure limit. Unfortunately, for some nanomaterials, practitioners have assumed that OELs for conventional forms are applicable for nanoscale forms of the same composition. In the absence of material-specific data to demonstrate that OELs for nano and non-nano forms are the same, this assumption should not be accepted. There are a number of differences between nano and non-nano forms of a material that can impact OELs including the fact that nanoscale forms are often more reactive than non-nano forms. OELs for non-nanomaterials may not be sufficiently protective for nanoscale materials, so limits for nano and non-nano forms of a material must be set separately.

Determining appropriate OELs requires methods with sufficient sensitivity to detect typical workplace concentrations of nanomaterials. For cellulose nanomaterials, these might include:

- Scanning Mobility Particle Sizer (SMPS)
- Optical Particle Sizer (OPS)
- Tapered Element Oscillating Microbalance (TEOM)
- Scanning Electron Microscopy (SEM) of particles collected on filter
- Midget impingers for personal monitoring (Roberts et al., 2018)

Working with experts to obtain data is recommended. For example, in the United States, US NIOSH conducts free confidential surveys as described in Section III.

### More information about unrealistic exposure levels in available toxicology studies

Toxicity evaluations performed to date have exposed test animals to concentrations of cellulose nanomaterials far exceeding those likely to occur in a workplace. The US NIOSH has conducted exposure assessments in a variety of cellulose nanomaterial pilot production facilities and has generally found very low total exposure levels (personal communication with NIOSH Nanotechnology Field Studies team cited in Ede et al., 2019). In these assessments, the maximum estimated concentration of airborne cellulose was more than ten times lower than the OSHA 5 mg/m$^3$ permissible exposure limit for the respirable fraction of cellulose dust. These levels were observed during milling and cutting of a polymer composite containing cellulose nanomaterials. The NIOSH evaluation presents an encouraging perspective that nanocellulose can be used safely, though the evaluation was conducted in pilot facilities rather than fully operational manufacturing sites. Comparable assessments need to be performed in commercial production environments to confirm that these results are predictive.

### More information about short-term effect bias in available toxicology studies

Because many studies observe effects only 24 hours after exposure, it is not possible to determine whether observed effects were transitory or persistent. More recent publications (*e.g*., Ilves et al., 2018 and Park et al., 2018) have evaluated longer-term responses (*i.e*., at 14- and 28- days post-exposure) to cellulose nanomaterials by inhalation routes of exposure. These studies demonstrate that for short-term CNF exposures, initial inflammatory effects may subside by 28 days (similar to other poorly soluble, low toxicity dusts).

### More information about mixtures

The presence of other materials can significantly impact toxicity (*e.g*., when endotoxins are present). In fact, there are many examples where toxicity from one material was initially misattributed to another. In designing hazard controls, it is important to consider the presence of other materials and their potential impacts.

In some formulations, the presence of other materials is intentional, as in mixtures. Many nanomaterials are intended to be added to other materials, such as in composites. Shatkin and Kim (2015) considered 59 exposure scenarios that could result in exposures to cellulose nanomaterials and/or their composites and identified the life cycle stage where exposure could occur. Many of the potential exposures occurred in the workplace where good hygiene practices are common and where the Exposure Control Hierarchy should be effective.

## Supplemental Table 3. Top NANO LCRA scenarios for filling data gaps for cellulose nanomaterials

| Scenario | Life cycle stage | Potential Hazard | Hazard Type | Exposure Pathway |
|---|---|---|---|---|
| Processed material is dried and then accidentally inhaled by a facility employee | Production | Inhalation contact with CN particles | Occupational | Inhalation |
| Application of dry nanocellulose to create film product contacting facility employees via inhalation | Manufacturing | Inhalation contact with CN particles | Occupational | Inhalation |
| Mixing dry CN with other materials to manufacture a product and powder inhaled by employee | Manufacturing | Inhalation contact with CN particles | Occupational | Inhalation |
| Facility employee contacts CN particles; incidental inhalation with airborne CN particles | Manufacturing | Inhalation contact with CN particles | Occupational | Inhalation |
| Release to environment via wastewater | Postconsumer/end of life | Physical impacts on receiving waters | Environmental | Environmental |
| Degradation in landfill | Postconsumer/end of life | Degradation of CN particles | Environmental | Environmental |
| Stored CN becomes unstable and explodes | Manufacturing | CN particles/energetic release | Occupational | Direct contact |
| Paper shredded at a recycling facility (dry); accidental contact with facility employee via inhalation | Postconsumer/end of life | Inhalation of CN particles and matrix | Occupational | Inhalation |
| Material disposed of in landfill to biodegrade; intentional contact with environment | Postconsumer/end of life | Environmental contact with CN particles | Environmental | Environmental |
| Spray application; accidental inhalation | Application/use | Inhalation of wet CN in matrix | Consumer | Inhalation |
| Migration to food; ingestion of CN particles by consumer | Application/use | Ingestion of CN particles in matrix | Consumer | Ingestion |

After Shatkin, J. A.; B. Kim, Cellulose nanomaterials: Life cycle risk assessment, and environmental health and safety roadmap, *Environmental Science: Nano*, 2, 477-299, (2015).