Toward cellulose nanomaterial commercialization: Knowledge gap analysis for Safety Data Sheets according to the Globally Harmonized System

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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 exceptional strength, flexibility, gas barrier, and optical 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, are required to be reported as gaps or to be filled. Given the 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.

Because cellulose dust is considered a respiratory irritant, the small size of CNs might further aggravate this reaction to dust. Occupational safety measures specific to CNs might need to be taken to prevent inhalation exposures. Furthermore, because we do not fully understood how changing the physical-chemical properties (e.g., charge, surface coating, shape, etc.) of any given NM contributes to differences in behavior and toxicity [1], studying specific NMs and benchmarking them against bulk materials is still necessary.

Working with NMs, particularly in powder form, can result in occupational exposure; therefore, it is important to develop safety measures and guidance to foster safe working environments. SDS provide information on the potential health, fire, reactivity, and environmental hazards of a chemical. They also recommend how to safely work with specific hazardous chemicals. Currently, there are no specific requirements for developing SDS for NMs. Changes in the future reporting status of NMs might affect these requirements, and it is in the best interest of suppliers to ensure they are providing the best information possible with their materials.

Large-scale commercialization of CNs is anticipated and pilot-scale production has already begun. Therefore, an analysis of current knowledge and available data on CN safety is necessary to develop GHS-compliant SDS and identify the areas in which there is missing data or information ('data gaps'). While we focus on CNs, the information reported here will also aid the development of SDS for other nanoscale material. This study is an effort to document what is known, and what data are needed, to address key safety gaps.

The Globally Harmonized System of Classification and Labeling of Chemicals

The Globally Harmonized System of Classification and Labeling of Chemicals (GHS) was developed by the United Nations as a non-legally binding system of hazard communication [2]. It aims to harmonize the classification and communication of hazardous properties of chemicals worldwide, thereby enhancing human health and environmental protection, facilitating trade, and reducing the costs and needs for testing. The GHS covers all hazardous chemicals and is intended for workers, consumers, emergency responders, and the public.

The GHS consists of 16 categories (**Table I**) of safety information to report the physical, health, and environmental hazards of a chemical substance, and are required for all substances that meet certain hazard classifications. In the United States, the Occupational Safety and Health Administration (OSHA) does not require sections 12-15, but these sections are mandatory in the European Union and elsewhere. A key difference between the former Material Safety Data Sheet (MSDS) and the now required GHS-compliant SDS is that all sections have specific data elements to be included. If no data are available, the SDS must state "data not available."

METHODS

We reviewed and analyzed publicly available literature and resources, including published non-peer reviewed reports and conference presentations. Other data might exist outside of the public domain, thus one aim in publishing this report is to identify those additional sources of data for future incorporation.

To identify gaps in CN knowledge, we analyzed data on conventional forms of cellulose and two forms of CN — cellulose nanocrystals (CNCs) and cellulose nanofibrils (CNFs) — derived primarily from wood. The goal was to systematically collect data, assess these data against the guidance for the 16 GHS sections, and then determine where data were lacking. The focus was primarily on GHS compliance for meeting U.S. requirements under the OSHA Hazard Communication Standard [3], and the European Classification and Labeling (CLP) [2], assuming manufacturers will want to be compliant in both geographies. An issue is that CNF terminology is not harmonized, so in some cases the long-used cellulose microfibrils, which are not new materials, might have been reported as CNF, hence there might be some data misclassification regarding data availability. Further, in many cases, the only available information is for conventional forms, such as dried cellulose pulp or powder, microcrystalline cellulose, or cellulose dust. Therefore, the SDS gap analysis considered data on these conventional forms of cellulose as starting points, with the potential for them to become analog materials to "read across." For several categories, it is not clear whether values would be different for nanoscale versions, and these cases are highlighted. Because of concerns expressed by governmental agencies and other stakeholders about increased biological activity of NMs, it will be important to obtain these data before commercialization or mass production to determine whether conventional cellulose data can be used as an indicator of hazard potential.

Although we have data for several GHS categories, most require additional investigations to confirm and strengthen these datasets to allow GHS-compliant reporting and/or classification. The GHS has specific criteria for hazard classification, including appropriate models, dosing parameters, and cut-off values; therefore, even when data are available, they might not be sufficient to allow hazard classification. In some instances, hazard classification is based on the total weight of evidence, with all available and relevant information considered together, and the quality and consistency of data are important. Because of that, we grouped information based on whether there were data available, and if data were available, whether it was adequate to classify under GHS guidelines. Designations included 1) no data available, 2) insufficient data, and 3) sufficient data available.

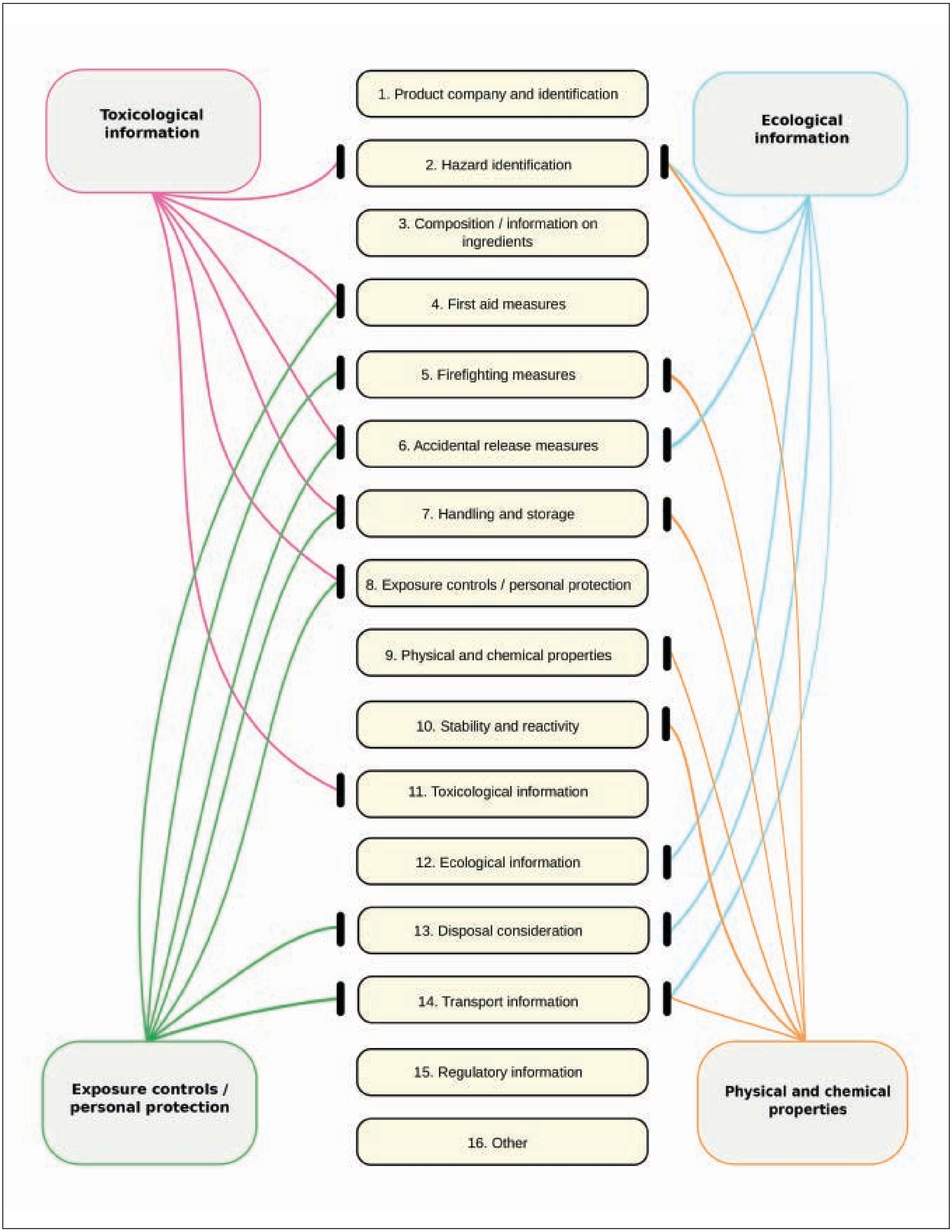
RESULTS AND DISCUSSION

Four overarching CN data gaps were identified: 1) toxicological data, 2) ecological data, 3) physical and chemical property data, and 4) exposure control and personal protection information. These data gaps affect the completion of many SDS sections (**Fig. 1**), and some sections are missing many types of data. A detailed discussion of each data gap follows.

SDS Section	Required Information for Substances[1]
1. Identification of substance or mixture and supplier	(1) GHS product identifier and other common names or synonyms, (2) recommended use of the chemical and any restrictions on use, (3) suppliers details, (4) emergency phone number.
2. Hazard(s) identification	(1) GHS hazard classification, (2) GHS label elements (signal word, hazard statement, pictogram/hazard symbol, precautionary statement), (3) description of any other hazards not otherwise classified.
3. Composition/information on ingredients	(1) Chemical identity, (2) common name and synonyms, (3) chemical abstract service number and other unique identifiers, (4) impurities and stabilizing additives.
4. First-aid measures	(1) First-aid instructions by relevant route of exposure, (2) recommendations for immediate medical care and special treatment, (3) most important acute or delayed symptoms or effects.
5. Fire-fighting measures	(1) Suitable (and unsuitable) extinguishing equipment, (2) hazards from combustion, (3) protective equipment and precautions for firefighters.
6. Accident release measures	(1) Personal precautions, protective equipment and emergency procedures, (2) environmental precautions, (3) cleanup procedures.
7. Handling and storage	(1) Precautions for safe handling, (2) conditions for safe storage and storage requirements, including incompatibilities.
8. Exposure control/personal protection	(1) Control parameters (such as occupational exposure limit values), (2) appropriate engineering controls, (3) personal protective measures and any special requirements for personal protective equipment.
9. Physical properties	Description of physical and chemical properties: appearance, odor, odor threshold, pH, melting point/freezing point, initial boiling point and range, flash point, evaporation rate, flammability (solid, gas), upper/lower flammability or explosive limits, vapor pressure, vapor density, relative density, solubility(ies), partition coefficient (n-octanol/water), auto-ignition temperature, decomposition temperature, and viscosity.
10. Stability and reactivity	(1) Reactivity, (2) chemical stability, (3) possibility of hazardous reactions, (4) conditions to avoid, (5) incompatible materials, (6) hazardous decomposition products.
11. Toxicological information	(1) Information on likely routes of exposure (and indication if information unknown), (2) delayed, immediate and chronic effects from short- and long-term exposure, (3) numerical measures of toxicity, (4) symptoms related to the physical, chemical and toxicological characteristics.
12. Ecological information	(1) Data from toxicity tests performed on aquatic and/or terrestrial organisms, (2) persistence and degradability, (3) potential for bioaccumulation, (4) mobility in soil, (5) other adverse effects.
13. Disposal considerations	(1) Description of waste residues and information on safe handling, (2) methods of disposal, including disposal of contaminated packaging.
14. Transport information	(1) United Nations number, (2) United Nations proper shipping name, (3) transport hazard class(es), (4) packing group number, (5) environmental hazards, (6) guidance on transport in bulk, (7) special precautions.
15. Regulatory information	Safety, health, and environmental regulations specific for the product in question.
16. Other information	Information on the preparation of the SDS, including when it was made and last known revision.

[1] Separate, additional information for mixtures of substances is required.

I. Required sections and content of Globally Harmonized System (GHS) Safety Data Sheets (SDS).



1. The four types of data gaps (toxicological information, ecological information, exposure controls/personal protection, and physical and chemical properties) and their relationship to the SDS sections, according to the GHS.

Health and environmental data gaps

Gaps in the available health and environmental data of CNs represent the most significant information needs in the compilation of GHS-compliant SDS. Although most collected data to date suggest these materials are not hazardous, missing toxicity and ecotoxicity data prevent completion of health and environmental hazard classifications for the GHS. These classifications are essential to determine signal words, hazard statements, precautionary statements, and hazard pictograms that form the foundation of Section 2, Hazard Identification.

A major hurdle in the development of CN toxicity data is attributed to a lack of standardized and validated tests for NMs. Many of the classic standardized testing protocols used to assess the toxicity and ecotoxicity of chemicals are not applicable for these materials. However, a number of agencies have provided recommendations and guidance for the collection of toxicological and ecotoxicological data of NMs [4-7].

Toxicity data gaps and affected SDS sections

Without toxicological data to inform the health hazard classification, many components of the GHS cannot be determined, including signal words, hazard statements, and hazard symbols/pictograms. In addition, precautionary statements related to the prevention, response, storage, and disposal of CNs cannot be determined without first determining a substance hazard classification. These precautionary statements

SECTION 2. HAZARDS IDENTIFICATION

NOTE: *The hazardous properties of this substance have not been evaluated. The classifications are based on available information for materials of similar chemistry.*

2.1 Classification of the substance or mixture

STOT SE 3 (H335: May cause respiratory irritation)

2.2 Label elements

Hazard pictogram: GHS07: Exclamation mark

Signal word*:* WARNING

Hazard statements

H335: May cause respiratory irritation

Precautionary statements

Precautionary statements – prevention
P210: If dry, keep away from all ignition sources including heat, sparks, open flames. Prevent dust accumulations to minimize explosion hazard.
P261: Avoid breathing dust
P262: Do not get in eyes, on skin, or on clothing
P271: Use only outdoors or in a well-ventilated area
P280: Wear protective gloves/protective clothing/eye protection/face protection

Precautionary statements – response
P304+P340: IF INHALED Remove victim to fresh air and keep at rest in a position comfortable for breathing.
P305+P351+P338: IF IN EYES Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P312: Call a POISON CENTER or doctor/physician if you feel unwell.

Precautionary statements – disposal
P501: Dispose of contents/container in accordance with local/regional/national/international regulation.

Supplemental Hazard information (EU): not applicable

2.3 Other hazards
Explosion hazard: Strong explosion hazard if dust is dispersed into air at high enough concentrations

2. A U.S. Occupational Safety and Health Administration and European Union Classification and Labeling compliant example hazard classification for a cellulose nanomaterials SDS Section 2, including hazard pictogram, signal word, hazard statement and precautionary statements based on currently available data. Note that classifications might change, based on the specific cellulose nanomaterial, its properties, and method of manufacture.

Health Hazard Classification		
Category	**Cellulose Nanofibrils**	**Cellulose Nanocrystals**
Acute Toxicity		
Oral[1]	No data available	Sufficient data available
Dermal	No data available	Insufficient data
Inhalation	Insufficient data[2]	Insufficient data
Skin corrosion	No data available	Sufficient data available
Skin irritation	No data available	Sufficient data available
Eye damage/Eye irritation	No data available	Insufficient data
Respiratory/Skin sensitization	No data available	Insufficient data
Germ cell mutagenicity	Sufficient data available[1]	Sufficient data available
Carcinogenicity	No data available	No data available
Reproductive toxicity	Insufficient data	No data available
Specific Target Organ Toxicity		
Single exposure	Insufficient data	Insufficient data
Multiple exposure	No data available	No data available
Aspiration hazard	Insufficient data	Insufficient data

[1] For one type of cellulose nanocrystal (CNC) only; data from outside standard research literature.

[2] Data are insufficient for hazard classification purposes.

II. Data gaps in health hazard classifications of cellulose nanomaterials.

form the foundation for several SDS sections. Thus, gaps in the toxicological data for CN have cascading effects on the quality and completeness of several SDS sections, including Sections 2 (hazard identification), 4 (first aid measures), 6 (accidental release measures), 7 (handling and storage), 8 (exposure controls/personal protection), and 11 (toxicological information), as in Fig. 1. **Figure 2** shows a template for Section 2 of CNs SDS, including the appropriate hazard statements and pictogram, based on available data for CNs.

Although the majority of currently reported data support the notion that CNs are not differently hazardous than conventional forms of cellulose, data for many categories of health hazards are either not available or insufficient to complete classification. Publicly available toxicity data for one form of CNC were determined to be sufficient for classification under GHS criteria for the endpoints of skin corrosion, skin irritation, acute oral toxicity, and germ cell mutagenicity hazard classification. CNC and CNF data are available for several other hazard categories, but are insufficient to inform health hazard classification under the GHS; in addition, several categories currently have no data available (**Table II**). The available CNF toxicological data are sufficient to complete the health hazard classification for germ cell mutagenicity; the remaining categories either have no data available or the available data are insufficient for classification (Table II). An analysis of the data gaps in the toxicological literature follows.

Short-term exposure

Several studies examine the acute toxicity of conventional celluloses via inhalation, ingestion, and eye or skin contact. Oral, dermal, and inhaled administrations of conventional cellulose in rats did not cause death [8]. Researchers found no signs of cellulose inhalation toxicity in rats, with LC50 values exceeding 5800 mg/m^3, and limited acute inflammatory effects that generally resolved after 30 days [9]. Inhalation exposure to high concentrations of cellulose (dust overload conditions) were associated with long term effects such as lung lesions [10]. Ingestion of cellulose did not have any significant toxicological consequence and one study found an LC50 value exceeding 5000 mg/kg [10]. Studies examining the acute exposure of cellulose to the eye and skin have found it to be non-irritating and non-sensitizing [8,11]. Until correlations between conventional cellulose and CN toxicity can be determined, the applicability of these findings for CNs are the best available data, but remain uncertain.

Currently, there are limited toxicological data available on short term exposures (inhalation, ingestion, eye or dermal) to CNFs. Pharyngeal aspiration of CNF was associated with an acute immune response in mice; however biocide was a potential contaminant and therefore these data cannot be used for classification [12]. Another study examining pharyngeal aspiration of CNF found generally negative, but not completely consistent, genotoxic effects [13]. There are currently no data available examining the acute oral, dermal, or eye exposures to CNF. The acute toxicity of CNFs represents a significant knowledge gap, and toxicological data needs to be generated for classification of this material. In comparison, more toxicity data on short term CNC exposures have been generated.

Acute inhalation toxicity of CNCs has been investigated in vitro using three-dimensional cell models of human airway barriers [14,15] and in vivo with an acute inhalation toxicity study in rats [16]. Researchers found limited cytotoxicity and inflammation in vitro and no mortality, gross toxicity, adverse effects, or behavioral changes in vivo [17]. Another study in a conference report suggests that inflammatory effects were observed 24 hours after single dose exposures but these resolved by 28 days post exposure [18]. These single dose studies provide limited information in terms of an acute toxicity estimate (ATE) criteria needed for classification under GHS, and were conducted under dust overload conditions in mice. The studies are not appropriate as a basis for inhalation hazard classification; more studies examining the acute inhalation toxicity of CNCs are required. However they provide supportive evidence for transitory irritant effects from dust exposure in the lungs, similar to that observed for cellulose.

The weight of available evidence suggests that inhalation of cellulose dust causes transitory irritation following exposure in the respiratory tract, and studies in CNC to date support this. Based on cellulose studies, and the available data for CNs, dry, powdered CNs can be classified according to the GHS as category 3 for "specific target organ toxicity single-exposure" (STOT SE 3), a category for transitory effects following a single exposure [19], until more data can be collected specifically examining CN inhalation toxicity.

One study examining the acute oral toxicity of CNCs reported low toxicity. No toxicological effects were observed 14 days after oral ingestion of 2000 mg/kg CNCs [16]. This ATE excludes classification in categories 1 through 4 under GHS, providing a strong indication of low toxicity but also a small weight of evidence. Conventional cellulose has long been used as a common food additive to improve the fiber content and texture of foods and suggests CNs likely have a similarly low oral toxicity.

Studies examining acute dermal exposure to CNC do not provide sufficient ATE required for toxicity classification. O'Connor et al. examined dermal toxicity of CNCs; however, a maximum examined dose of 103 mg/L is insufficient to exclude classification under the GHS (doses up to 2000 mg/kg can be classified) [16]. However, current studies are sufficient to warrant skin corrosion and skin irritation classification. O'Connor et al. determined that CNCs had an irritation index score of 0 and no corrosive effects in rabbits (Organisation for Economic Co-operation and Development 404); were non-sensitizing after intradermal or topical application; and were not a contact dermal sensitizer [16]. Thus, under the GHS for skin corrosion/irritation and skin sensitization, CNCs are 'Not Classified'. However, no data are available on the potential for CNCs to be respiratory sensitizers, representing a knowledge gap in CNC toxicity.

To date, no in vivo studies have been completed examining eye irritation following CN exposure. An in vitro toxicity study utilizing human corneal epithelial cells (HCE-T) found that 1 h exposure to 0.4% CNC significantly reduced cell viability [20]. However, the suitability of this in vitro test for eye irritation remains to be determined. Further information is required on the potential for CNC to cause eye damage or eye irritation.

Long-term exposure

A review of studies examining the long term oral exposure of conventional cellulose revealed no indication of toxicity, even when contributing to a relatively high percentage (up to 30%) of the diet [11]. Few studies have been completed on the consequences of long term inhalation exposure. One occupational study reported reduced lung function upon exposure to cellulose dust associated with paper production, though effects are not directly attributable to cellulose [21]. No studies have examined the long term consequences of cellulose exposure via the eye or skin.

There is also a paucity of data on the long term effects of CNC and CNF, with no data available for long term inhalation, eye or skin exposure, and only a few studies have examined the long term oral toxicity of CNCs. After repeated oral exposure for 28 days, no toxicity was observed in rats and no significant differences in neurological function, body weight, or food consumption were documented (NOEL > 2000 mg/kg) [16]. It should be highlighted that these data are for a single material; it is not clear whether these data are representative of CNCs produced by other processes with different physical-chemical properties.

Other measures of toxicity

There is a significant knowledge gap in the data on the immunotoxicity and neurotoxicity of cellulose and CNs. While there is not a hazard category specific to immunotoxicity or neurotoxicity, these types of data contribute to classification of Specific Target Organ Toxicity (STOT) – Single and Repeat Exposure. To date, few studies have examined the immunotoxicity of CNs and no studies could be located that examined the neurotoxicity of these materials. Further studies are required to characterize these toxicological effects.

There is no evidence to date to suggest that conventional or nano-forms of cellulose are genotoxic. In a series of unpublished reports submitted to the World Health Organization (WHO), several assays were used to investigate the genotoxic potential of types of cellulose, including the bacterial reverse mutation assay, the mouse lymphoma forward mutation assay, and the mammalian cell micronucleus test. All genotoxic assays were negative after cellulose exposure, even at the highest doses examined (e.g., 5000 mg kg^{-1} bw for mammalian cell micronucleus test) [8].

Similar to results obtained with cellulose, a survey of the literature suggests that CNs are not genotoxic. While in vitro tests can be used for GHS classification, in vivo tests are the standard, and these studies suggest CNF and CNCs are not genotoxic. No genotoxic effects were observed in in vivo pharyngeal aspiration of CNF in mice (>200 μg/mouse) [13], nor following CNC exposure (>2000 mg/kg), as assayed with the erythrocyte micronucleus test (Organisation for Economic Co-operation and Development 474) [16]. In vitro studies with CNFs did not result in genotoxicity using a variety of endpoints, including the Ames, comet, and micronucleus assays [13,22-24]. One study examining CNC derived from types of cotton and curacua in vitro found limited DNA damage in human fibroblasts and lymphocytes [25]; however, the majority of in vitro investigations on CNC indicate they are not genotoxic [16,26].

Several chronic ingestion studies also suggest a lack of carcinogenic activity for conventional cellulose materials [27]. For example, high oral exposures (30% of diet for 72 weeks) of cellulose did not change tumor incidence [8]. Following chronic ingestion of cellulose (diets containing 4.5-46%), animals did not exhibit any tumor promoting activities in the colon, mammary gland, and bladder, despite high oral doses [28-31]. High cellulose diets (4.5% or 9%) reduced the incidence of colonic neoplasia and number of colonic tumors in an induced tumor model, compared to a nutritional and calorically equivalent cellulose-free diet [29]. No data are available on the carcinogenicity of CNs; further studies are needed for classification.

The majority of data collected on the reproductive toxicity and teratogenicity of cellulose have found no adverse effects. Some studies show that a moderate level of cellulose in the diet might actually improve fertility. For example, Mohiti-Asli et al. (2012) found that the inclusion of 3% cellulose in the diet improved the rate of egg production and fertility in hens [32]. No evidence of any effects on fetuses was found. One study fed pregnant rats 25 g or 50 g microcrystalline cellulose kg-1 in the diet during gestation and found no adverse or teratogenic effects [8]. To date, few studies have examined the reproductive toxicity and teratogenicity of CNC or CNF. One 5-day study of CNF exposure had no reproductive effect on the in vivo egg laying ability of the invertebrate *Caenorhabditis elegans* [22]. Further studies examining the reproductive toxicity of CNs are needed for classification of this endpoint for CNs by the GHS.

Ecological data gaps and affected SDS sections

Although not required by OSHA, for a SDS compliant with European requirements, some gaps in the ecological toxicity data should be addressed. Gaps in the ecological data prevent environmental hazard classification (**Table III**) and preclude determination of major components of the GHS. Therefore, the precautionary statements derived from these classifications (related to the prevention, response, storage and disposal of CNs) cannot be determined and limit the quality and completeness of several SDS sections, including Sections 2 (hazard identification), 6 (accidental release measures), 12 (ecological information), 13 (disposal consideration), and 14 (transport information) (Fig. 1).

Environmental Hazard Classification		
Category	**Cellulose Nanofibrils**	**Cellulose Nanocrystals**
Acute aquatic hazard	Sufficient data available	Sufficient data available
Chronic aquatic hazard	Insufficient data	Sufficient data available

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

As Suggested by ISO/TR 13329	Other
• Primary particle size (average and range) • Particle size distribution • Agglomeration state/ Aggregation size • Shape and aspect ratio • Specific surface area • Dispersibility • Crystallinity • Dustiness	• Dust deflagration index • Surface chemistry/ Elemental composition • Surface charge (zeta potential) • Mass concentration • Particle number concentration • Composition/Purity • Surface contamination • Solubility/Dispersibility

IV. Physical and chemical measurements recommended for nanomaterials.

Available ecological data for CNs are sufficient to complete several environmental hazard classifications. Adequate data are available to determine the acute aquatic hazard of CNF and CNC. CNCs were shown to be non-toxic in acute and chronic ecological toxicity assays and are not acutely toxic in zebrafish embryos [33,34], rainbow trout [34], water fleas, fairy shrimp, and *Hydra attenuate* [34]. CNF were not acutely toxic in zebrafish embryos [33] or bacteria [35]. CNCs are not toxic to water fleas, microalgae, fathead minnows, and *H. attenuata* [34]. However, a knowledge gap exists in the chronic ecotoxicity data of CNFs, and further studies would address this gap for unmodified CNs.

Other needed ecological data for CN include environmental persistence, degradability, bioaccumulation, and mobility in soil. Currently, there are limited data regarding the bioaccumulative potential and soil mobility of CNC and CNF. Not surprisingly, CNs are readily biodegradable. Using EN 14046, Vikman et al. found more than 60% degradation of CNF-based products after 65 days [36]. Similarly, under controlled composting conditions,

Physical-Chemical Property	CNF-1	CNF-2	CNC-4	CNF-3
Source	Wood	Wood	Wood	Wood
Method	Enzymatic	Mechanical	H_2SO_4	TEMPO
Surface chemistry	Hydroxyl	Hydroxyl	Sulfate	carboxylate
Particle size and distribution			Length:130±67 Width: 5.9±1.8	
Shape	Network	Network	Bundles	Ribbon
Crystalline fraction	0.30	0.55	0.60	0.05
Aspect ratio			23±12	

V. Comparison of physical and chemical properties of wood-derived CNCs and CNFs [43].

unfunctionalized CNF were more than 70% degraded after 28 days and more than 90% degraded after 90 days [12]. Kummerer et al. documented 54% biodegradation of CNC after 28 days [37]. A separate study using the standard Organisation for Economic Co-operation and Development 301 method found 42% biodegradation of CNC after 10 days [16].

Physical chemical property data gaps

The SDS requires a minimum set of physical-chemical property data, many of which are not pertinent to all CNs (e.g., partition coefficients, vapor density). Given that physical-chemical properties specific to NMs might affect their toxicity and behavior [38], a new set of properties might need to be developed for NM SDS (**Table IV**). No set of internationally harmonized minimum characterization requirements for NMs exists, but a number of recommendations have been released [39-42]. Suppliers of SDS should refer to these and ensure accurate measurement and reporting of the most relevant properties for their materials. Most properties will be specific to a manufacturer's nanoscale substance. It is imperative that guidance for standardized measurement of these properties continues to be developed to ensure consistency.

The measurement of a number of nano-specific physical-chemical properties are recommended by the International Standards Organization (ISO) Technical Committee 229 on Nanotechnologies in Standard ISO/TR 13329 [42], as they relate to hazard characteristics and testing. At a minimum, the properties in Table IV should be measured and reported for specific CNs. Additional properties listed are from other NM safety guidance documents and are currently recommended for assessing environmental safety and health impacts of CNs.

Physical chemical data gaps and affected SDS sections

Data on the physical-chemical properties from Sections 9 and 10 are needed to complete physical hazards identification (Section 2) and will need to be completed specifically for each producers' materials. To highlight how CNs can vary with production technique, Sacui et al. characterized the physical-chemical data of several CNCs and CNFs; the results from their study are summarized in **Table V** [43]. Manufacturers will need to ensure thorough characterization of their materials to label products with appropriate signal word and pictogram, and determine the relevant hazard class, hazard statements and precautionary statements for SDS Section 2. A lack of knowledge of specific hazards arising from combustion, potential for self-ignition, and storage or combination with incompatible products hinders, and can endanger, firefighting, clean up, handling and storage, and/or transport efforts (SDS Sections 5, 6, 7, and 14; Figs. 1 and 2).

Cellulose has not been assigned a flammability rating by the National Fire Protection Association, but might be flammable under certain conditions (NIOSH 1995). Studies indicate that CNF, CNC-sulfated, and CNC-neutral forms might demonstrate different thermal stabilities (unpublished data, D. Fox); thus, changing the surface chemistry and other properties of the CNs will likely affect flammability [44]. Conventional cellulose dust is combustible at 240°C [45] and is classified as "Explosion Class St 2 – Strong Explosion" based on a dust deflagration index of (Kst) 229 [46,47]. If in dry powder form, NMs might pose a greater explosion hazard than conventional materials because of their high surface area-to-volume ratio [48]. Therefore, the upper and lower flammability and explosivity limits, dust deflagration index, and auto-ignition temperatures are important gaps to fill for any materials that might be used or stored in dried form.

For many of the characteristics required to complete SDS Sections 9 and 10, suppliers will need to perform experiments on their own materials. Difficulties in gathering physical-chemical data are partially attributed to a lack of standardized or validated measurements for NMs. To be able to fill the data gaps regarding physical-chemical properties of CNs, more specific guidance regarding acceptable and standardized NM measurements are needed in the near future.

Exposure controls and personal protection data gaps

Few studies have reported measurements of CNs in occupational environments [16,35], so it remains a data gap whether exposure controls are required. If so, data are needed on whether the nanoscale attributes of CNs differ from conventional cellulose dust, and whether different types of respiratory protection are warranted. Several organizations provide general recommendations and guidance for the protection of the health and safety of workers from occupational exposure to NMs [49,50]. Information on personal precaution and personal protective equipment measures that can be taken to mitigate potential risks from CN exposure during production or accidental release are mainly based on cellulose dust information. Exposure controls are process-specific and must be considered in the manufacturing context. For example, if the material remains in solution and is never dried, the likelihood of inhalation exposure is significantly reduced.

Occupational safety data gaps and affected SDS sections

Key issues for occupational safety guidance on NMs relate to explosivity, skin and eye contact, and inhalation. Ingestion exposure in the workplace is not likely to occur, unless accidentally, or if large amounts of dust are in the air. Not enough information is available on potential inhalation exposure to CNC and CNF. Consequently, current exposure limits are based on cellulose dust and might not be adequately protective for CN dust inhalation exposure. SDS sections affected by these missing data include first aid, firefighting, accidental release measures, handling and storage, exposure controls and personal protection, disposal considerations, and transport (SDS Sections 4-8, 13, and 14, respectively).

Occupational exposure limits (OELs) are based on risk assessments of human and animal effects data. OELs include considerations for exposure controls and feasibility of measurement by analytical techniques. Not enough occupational data or inhalation toxicity data exists for CNC or CNF to determine material-specific OELs for airborne dusts. However, assessments by the National Institute for Occupational Safety and Health of nanoforms of well-studied substances, such as nanoscale forms of titanium dioxide [51] and carbon nanotubes [52], suggest that levels lower than conventional forms might be appropriate. No regulatory OELs have been published for NMs, but general guidance from the British Standards Institute [53] and others [51,52,54] have been developed. For fibrous NMs (aspect ratio greater than 3:1, and length greater than 5000 nm), a limit of 0.01 fibers/mL has been proposed, because of evidence that fibrous materials might be biopersistent in the lungs if inhaled [53,54]. For insoluble NMs, British Standards Institute SI [53] proposed a factor of 0.066*OEL of the microsized bulk material, based on calculations of nano-titanium dioxide [55]. However, the recommended exposure limits have since been increased in an update for ultrafine and fine titanium dioxide [51]; therefore, this calculation should be considered conservative.

Given that there are few data on the dermal and ocular toxicity of CN, it may be prudent to protect the skin and eyes against these materials. Aerosolized NMs likely do not penetrate gloves [56], but powder and colloidal NMs can penetrate some commonly used materials, such as nitrile gloves used for more than 5 h [57]. NMs can infiltrate and collect on laboratory coats made of nonwoven fabrics, especially cotton polyester weaves [56,57]. To determine whether eye protection is necessary, more data on the ocular toxicity of CNs should be developed.

Occupational exposure can occur during many stages of manufacturing of CNs [58]. Given that there are no OELs specific to CNs and there are limited toxicity data, it is good practice to keep exposure as low as possible and monitor and record exposure levels until more data are available for CNs. No data exist to indicate that cellulose NM will be irritating at low concentrations. However, given that there is a lack of data in areas relevant to human health, it is prudent to apply precautions. Since the responsibility of protecting workers is often placed on employers (e.g., OSHA [59] and the European Union's OSH [60]), it is imperative that data gaps that hamper development of OELs for CNs are quickly filled.

CONCLUSIONS AND RECOMMENDATIONS

CNs are promising sustainable materials with potential applications in a variety of future markets. The compilation of GHS-compliant CN SDS is an essential step toward their commercialization and will help ensure these materials reach their full market potential. CNs are not anticipated to have significant hazardous properties, and data collected to date supports this notion. However, we have identified gaps in knowledge for CNs that under the new GHS criteria are required to be identified with the statement "data not available." These data gaps prevent a thorough determination of potential physical, health, and environmental hazards of CNs and communication of these hazards to workers. Given the novelty of manufactured NMs, it is beneficial toward their commercialization to fill these knowledge gaps and proactively demonstrate CN safety.

Much of the data highlighted here previously is representative of only a small sample of CNCs and CNFs. Here the emphasis has been on unmodified wood-derived CNs. Given the multitude of production processes under development, and the investigation into surface functionalization for specific attributes, special consideration should be given when these methods result in CNs with unique surface characteristics, physical-chemical properties, formulations, or additives. Such differences can have consequences for the health, environmental, physical-chemical, and exposure data for these materials, with cascading effects on their hazard classification.

A focused effort to collect and report key data in the identified knowledge gaps will allow for the compilation of GHS-compliant SDS that establish the safety of CNs. This includes addressing the missing health, environmental, physical-chemical, and exposure data for CNs. Contributing to this knowledge will reduce uncertainty, critical for CN commercialization. **TJ**

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ABOUT THE AUTHORS

We chose this topic to research because we wanted to identify the knowledge base on safety for cellulose nanomaterials as a starting place for safety demonstration and research needs, and to prepare Safety Data Sheets that producers can use.

This work is complementary to other safety reviews that focus either on human or environmental impacts more broadly. It looks through the specific lens of the Globally Harmonized System for Classification and Labeling, so it is practical for producers and users who need this information.

The biggest challenge has been our wanting to gain access to information that is not in the public domain. We are hoping that by publishing this work, others will share their data and we can expand the public knowledge base.

We were surprised by the extent of data gaps and that there are similar gaps for many long-used substances, including cellulose pulp. The standards for data development have changed over time. New chemicals are inherently safer because they generally must be demonstrated to be safe.

Mills can use the information in this paper to develop Safety Data Sheets and safe working practices.

As a next step, we are working to identify partners to address the most important data gaps.

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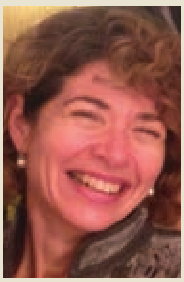
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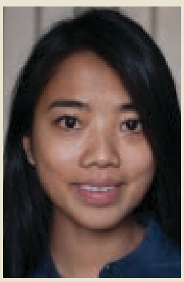
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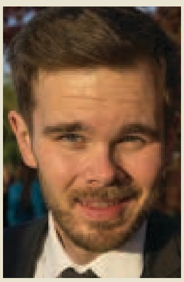
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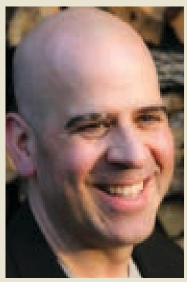
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