Demonstrating the Safety of Cellulose Nanomaterials – High Performance Bio-based Materials

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ABSTRACT

Commercialization of cellulose nanomaterials (CN) is rapidly advancing to the benefit of many end use product sectors and disseminating knowledge regarding the safe manufacturing and handling for CN is a priority. There is significant interest in a breadth of application categories from packaging and construction materials to transportation, food, electronics and consumer products. Each application can trigger different regulatory requirements, from safety data sheet development to premarket regulatory reviews. This presentation will discuss the current efforts to establish safety determinations for CN in the U.S. and beyond. Specifically, we report on the data available and an analysis of current gaps for cellulose nanomaterials with regard to the toxicological profile, environmental characteristics, physical and chemical properties, and exposure data, to inform the development of key information to advance safe commercialization.

1. BACKGROUND

Cellulose is the most abundant organic material on earth; it is a renewable, biodegradable and natural material that can be mechanically and/or chemically processed from plants to liberate cellulose nanomaterials. At the nanoscale, cellulose nanomaterials (CN) possesses exceptional strength, flexibility, gas barrier and optical properties. These CN are promising sustainable materials with significant potential applications in markets including the automotive, food, construction, paper and packaging, waste management, and other consumer product industries, including its use to improve the environmental profile of a diversity of polymers composites currently produced from petroleum sources [1]. There are global efforts underway to commercialize various forms of CN, typically these are cellulose nanocrystals (CNC) and cellulose nanofibrils (CNF). While the safety of cellulose has been established in its long commercial history, these novel forms must also be demonstrated to meet current regulatory and workplace safety standards for diverse applications. While CN are not anticipated to have unique or hazardous properties and the available data also do not demonstrate any novel toxicity, we have identified gaps in knowledge, important to address to claim the safety and sustainability of this important bio-based material.

The development and production of nanomaterials and nano-enabled technologies is rapidly increasing, while research on the safety issues associated with nanomaterials, such as CN, have not evolved as rapidly in parallel. With decreasing size, materials generally have a higher surface area to volume ratio; therefore, nanomaterials can have a higher potential for reactivity than conventional materials on a per mass basis. Furthermore, since it is not fully understood how changing the physical-chemical (pchem) properties (*e.g.* charge, surface coating, shape, *etc.*) of any given nanomaterials contributes to differences in behavior and toxicity [2]; studying specific nanomaterials and benchmarking them against conventional materials is still necessary. Here we report on findings from two related efforts to assess the state of knowledge about environmental, health and safety aspects of CN, and identify considerations and data needs important to address now, as producers prepare for commercialization

2. APPROACH

We conducted two related efforts to characterize the state of knowledge, identify data gaps, and establish priorities for filling these gaps for CN safety in the form of an environmental health and safety (EHS) roadmap. First, we conducted a life cycle risk assessment (NANO LCRA) [2] to identify and prioritize relevant occupational, consumer and environmental scenarios on the basis of relative importance for safety assessment and research to address safety data gaps. Next, we performed a cross walk of data availability and gaps to classify hazards according to the Globally Harmonized System for Classification and Labeling (GHS), and identify information needs for Safety Data Sheet (SDS) development.

Conventional risk analysis and life cycle analysis approaches for nanomaterials are currently fraught with methodological issues due to the need for novel metrics and the requirement for significant data development. Such analyses can be burdensome and are sometimes infeasible for early-stage and pre-commercial technology developers, depending on their proximity to market. The research value of NANO LCRA is that the analysis identifies the most significant health and environmental data issues and gaps from a toxicity (hazard) and exposure (risk) perspective, resulting in a targeted, prioritized and focused research plan (a "roadmap") designed to fill them. Two dimensions of NANO LCRA distinguish it from traditional risk analysis: broad consideration of potential exposures to substances as they occur in products across the life cycle, linking the product life cycle to occupational, public and environmental effects; and a progressively more intensive analysis as products progress from research and development stages to commercialization. NANO LCRA develops and analyzes scenarios: events that could occur and that might result in nanomaterial exposure, and from the analysis prioritizes research to address uncertainties. The event might be an

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expected event, such as a machine cleanout, which could emit nanomaterials, or it might be an unexpected event, such as an accidental release of nanomaterials. NANO LCRA informs product design and safety data development incrementally, in a “stage-gate-like” process, fostering sustainable product design in real time.

Our second effort, the SDS Gap Analysis, considered data on conventional forms of cellulose as starting points, with the potential for them to become analog materials for bridging safety data to nano-forms. These were complimented by publically reported studies with different forms of CN, and organized by GHS category and endpoint. For several categories, it was not clear whether values would be different for nanoscale versions. Then, in each category, data were used to evaluate hazard classifications (*e.g.* based on flammability or toxicity) and gaps in data availability, or adequacy for classification, were identified for CNC and CNF.

3. RESULTS AND DISCUSSION

The available data from over 50 references reviewed indicate that a variety of CN forms and biological endpoints have been investigated, including the contribution of variables such as physico-chemical properties, length of exposure, cell types and organisms, and dose metrics. These influencing variables and their effects were not uniform across studies making it difficult to compare results and assert a unifying weight-of-evidence conclusion based on the data for any particular exposure route or material. That is, while the published and reported data indicate low toxicity, the differences in materials and study design limit the ability to compare results. As with most substances in commerce today, few studies were available on longer-term exposures (chronic and subchronic). Further, specific quantitative exposure data for likely occupational, consumer and environmental routes of exposure were not found.

In the GHS analysis, 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. Data gaps can affect several SDS sections, shown in Figure 1; some sections are missing several data types. We note, though that this situation exists for many chemicals that have long been in commerce.

The NANO LCRA revealed that occupational inhalation exposure associated with handling CN as a dry powder was the highest priority data gap to fill. Addressing this data gap includes the challenge of quantitative measurement for exposure assessment. A second priority data gap concerned the toxicity of CN in consumer use products, such as packaging, particularly for food contact uses. Details of the analysis and roadmap were previously reported and are summarized briefly here [2].

3.1 Exposure assessment

Does exposure to free CN particles in dust occur in the workplace? Currently there are few studies reporting measurements of CN in occupational environments [3-5] so it remains a data gap whether exposure controls are required. If so, data are needed on whether the nanoscale attributes of CN create any exposures that are different from conventional cellulose dust. Importantly, methods are needed to assess potential workplace exposure. Most CN producers generate materials in aqueous solution and then incorporate them into composite matrices, limiting dust exposure. A key need is to conduct exposure measurements in occupational environments, a challenge due to 1) the high aspect ratio of the CN, 2) the anticipated low concentration, and 3) the high background concentration of cellulose, especially for paper and board applications. Determining the release of CN from cellulose based materials requires distinguishing conventional cellulose from CN in environmental media. Thus, confirmatory and quantitative measurement and detection methods for CN in occupational environments is an important current data gap and roadmap priority.

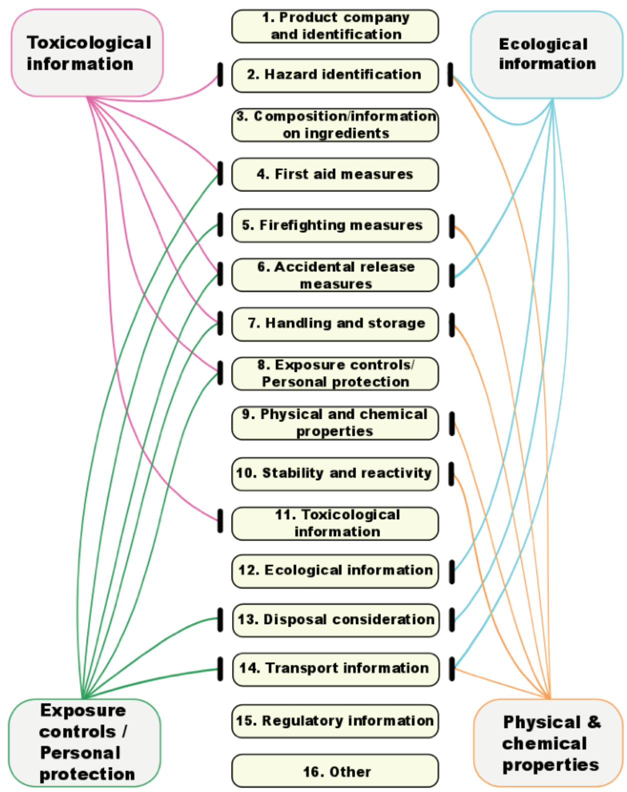

Figure 1. The 4 types of data gaps (toxicological information, ecological information, exposure controls/ personal protection, and physical and chemical properties) and their relationship to the SDS sections, according to the GHS.

In terms of potential consumer and environmental exposures from products containing CN, lack of measurements is an important gap to fill for assessing safety in different application categories. Biodegradation data have been reported, and not surprisingly, CN is readily biodegradable, limiting its persistence or bioaccumulation in the environment. While this is a logical finding, as cellulose is an abundant material already present in vast quantities in the environment [and is used as an energy source and exploited for biofuel], it is reassuring to have data that demonstrate biodegradability for nanoforms.

3.1 Health and environmental data gaps

Gaps in the available health and environmental data of CN represent the most significant information need in the compilation of data for SDS according to the GHS. Although most studies to date indicate these materials are not hazardous to health or the environment, toxicity and ecotoxicity data are inadequate for several GHS health and environmental hazard classifications. These classifications are essential to determine signal words, hazard statements, precautionary statements and hazard pictograms that form the foundation of SDS Section 2, Hazard Identification. Table 1 shows the availability of data in the public domain for GHS health hazard classification.

Table 1. Data Gaps in GHS Health Hazard Classifications of Cellulose Nanomaterials

Health Hazard Classification Category	CNF	CNC
Acute Toxicity		
Oral[1]	No[1]	Sufficient
Dermal	No	Insufficient
Inhalation	Insufficient[2]	Insufficient
Skin Corrosion	No	Sufficient
Skin Irritation	No	Sufficient
Eye Damage/Eye Irritation	No	Insufficient
Respiratory/Skin Sensitization	No	Insufficient
Germ Cell Mutagenicity	Sufficient[3]	Sufficient
Carcinogenicity	No	No
Reproductive Toxicity	Insufficient	No
STOT Single Exposure	Insufficient	Insufficient
STOT Multiple Exp.	No	No
Aspiration Hazard	Insufficient	Insufficient

[1] No data publicly available.
[2] Data are insufficient for hazard classification.
[3] Sufficient data for hazard classification.

3.2 Toxicity data gaps and affected SDS sections

The NANO LCRA and gap analysis revealed that most of the studies found CN to have a low or non-toxic impact to human health and the environment, especially at realistic exposure levels. A few reports suggest, as with most poorly soluble low toxicity dusts, that high doses may cause adverse effects in the lung if inhaled. The existing knowledge gaps, particularly for inhalation and oral exposures, as well as longer term studies, preclude a complete dossier of safety demonstration. The preliminary low toxicity profile of CN can be improved by further studies that would evaluate the release and fate of CN during production and from consumer products; estimate actual and longer-term exposures, while assessing a more comprehensive breadth of toxicity pathways and endpoints, particularly those relevant for human health.

As with most nanomaterials, the majority of available studies reflect the assessment of inhalation effects of potential relevance for workplace exposure, should conditions exist that create airborne release of particles. The studies suggest potential adverse effects from inhalation of unbound airborne CN particles, as might be anticipated from inhaling any poorly soluble dust. However, these studies leave uncertain whether the observed effects are transient or persistent, as well as the whether these exposures might realistically occur during manufacturing. The knowledge that most CN materials are produced in a liquid slurry reduces concerns about inhalation exposures during production, but data gaps persist due to the lack of available testing methods to quantitatively assess exposure.

Our reviews indicate a deficiency of published data, *in vitro* and *in vivo*, on health endpoints associated with longer term exposures, such as carcinogenicity, neurotoxicity, and reproductive effects. Not surprisingly, there is a similar dearth of information on these endpoints for conventional celluloses, where only one study assessed carcinogenicity in cellulose and microcrystalline cellulose, finding no significant effects in rats from the 72-week oral study published in 1963 [6]. For example, there is but a single report on neurotoxicity of CNs. Researchers in Finland employed an *in vivo* nematode model with a primitive nervous system, *C. elegans*, to study neurotoxic and behavioral endpoints [7]. They report that CNF did not cause adverse neurologic effects [8]. The majority of currently reported data support the notion that CN are similar to conventional celluloses and demonstrate little to no toxicity. However, additional studies for the categories in Table 1 where the available data are either *not available* or *insufficient* will allow us to complete the hazard classification.

4. RECOMMENDATIONS

CN are an important emerging class of sustainable materials with potential applications in a variety of future markets. CN are not anticipated to have significant hazardous properties and our analysis supports this view; however, we have identified gaps in knowledge for CN that under the GHS criteria, are required to be identified in hazard communications with the statement '*data not available*'. These data gaps prevent a thorough determination of potential physical, health and environmental hazards of CN and communication of these hazards to workers. Given the novelty of manufactured nanomaterials, it is beneficial toward their commercialization to be proactive in demonstrating CN safety and undertake efforts to fill these knowledge gaps.

It should be emphasized that much of the data highlighted above is representative of only a small number of CNCs and CNFs; here the emphasis has been on a few forms of unmodified wood-derived CN, CNC generated by a sulfate process or CNF from mechanical grinding, with or without

TEMPO oxidation. The diversity of production processes under development, and the investigation into surface functionalization of CN to impart important properties for applications, indicates special consideration should be given when these emerging methods result in CN with unique surface characteristics, physical/chemical properties, and formulations or additives. Such differences may affect the health, environmental, physical-chemical and exposure data for these materials and require specific consideration for hazard classification.

A major hurdle in the development of CN toxicity data is attributed to a lack of standardized and validated testing protocols for nanomaterials. Many of the classic standardized testing protocols used to assess the toxicity and ecotoxicity of chemicals are not applicable or require modification for these materials. However, a number of agencies have provided recommendations and guidance for the collection of toxicological and ecotoxicological data of nanomaterials [9]-[12]. It will be helpful to advance the use of alternative testing strategies (ATS) for assessing the toxicity of nanomaterials to inform on select endpoints, as discussed in detail in the NANO LCRA and Roadmap [2].

Based on our analyses we have created an EHS Roadmap that prioritizes the studies recommended to reduce the uncertainties represented by current data gaps. As already mentioned, the development of methods to detect and quantitatively measure CN in occupational environments, despite high background levels of particles including cellulose, are important to establishing safe working practices, and top the priority list. Measurement and detection of CN in other media, including water, biological tissues, and product matrices (e.g. polymers, paperboard) are also important priorities for assessing exposure and safety in specific application categories. Further priorities include assessment of whether nano-forms of CN differ from conventional celluloses in food packaging and related uses, which is not anticipated, but would be confirmed with additional studies. Finally, the roadmap recommends sustainability measurement and reporting, because of the strong demand for bio-based, and non-toxic materials to demonstrate they are "bio-preferred." Beyond these, others priorities arise depending on the specific application category, which can be assessed through the NANO LCRA framework. Contributing to this knowledge database will reduce uncertainty and increase confidence in safety, critical for CN commercialization.

5. ACKNOWLEDGEMENTS

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