Possible Health Risk of Cellulose-Based Materials

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Abstract Cellulose-based products are currently receiving tremendous attention from researchers all over the world. It can be used in wide variety of applications including water treatment industry. However, there are scarce publications that touch on the possible risk that evolved from the usage of cellulose-based materials. This mini review aims to cover the respiratory risk possibility of nanocellulose by summarizing the findings by various researchers of their in vivo test. It was concluded that cautions need to be taken when handling the materials to prevent the exposure to higher risk.

Keywords Cellulose · Green technology · Risk evaluation · Adsorbent

1 Introduction

Over the last decades, development of green products for replacement of current conventional adsorbent has garnered tremendous attention from global researchers. Biosorbent is an eco-friendly type of adsorbent, usually made up from waste using safe chemicals and manufactured for sorption application. Bio-based materials were reported to dominate the market for sustainable materials due to its comparable performance at a lower manufacturing cost. Natural polymer that can be found abundantly in the world, cellulose, is currently in the list of sustainable materials of high interest by the academician and people from the industries. The term 'nanotechnology' was first employed by Eric Dexler Kim, which defines as the study of materials having dimensions between 1 and 100 nm [1, 2]. Unique properties of nano-sized cellulose (NC) have made them the emerging potential candidate for biosorbent and

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in other wide range of applications. To name a few, NC are largely studied for applications in water treatment application to remove various types of pollutants, whilst it is also employed in medical sector as drug delivery carrier and for wound dressings. However, the utilization of NC as adsorbent has raised few concerns on its possible risk [3]. Owing to its nanoscale size, it might be able to permeate through the skin and cell membranes [4]. Thus, it is very important to critically evaluate the toxicity of NC as well as the health hazards that may occur.

Two types of cellulose-based biosorbent that being evaluated in this chapter are nanocrystal cellulose (NCC) and nanofibre cellulose (NCF). Generally, toxicology studies for NC are very challenging due to the complexity of the mechanism. There are many toxicological inducers that could affect the toxicity of the NC such as the material size, shapes, surface reactivity and many more. Differences in techniques applied for synthesising the NC could also alter its psychochemical properties and produce adverse effect to the health. Concerns about the health implications of the synthesised NC for biosorption application has been raised as the long-term effects of the exposure are still unknown. There is also a raised concern on the possibility of substance inhalation during material handling. To date, the literature discussing on NC toxicity is still scarce. Nevertheless, the number of in vitro and in vivo study of NC materials keep increasing over the years due to increasing interest among researchers and the government [5]. In order to assess the risk possesses by the nanomaterial, which in this case is NC, variety of risk analysis tools and assessment technique has been proposed [6–9]. Nonetheless, according to Grieger et al. [10], the advantages and drawbacks of the framework and assessment method cannot be outline as there are only a few that utilized the approaches while the rest reported only the initial screening.

2 Risk Assessment

Risk can be defined as possible harm that may pose to the users. In other word, it can be defined as product of hazard and exposure as explained by Shatkin and Kim [11]. All chemicals and utilization of any substance should have a thorough safety assessment to be done first in order to classify whether it is safe for usage or the other way round. Generally, the parent of NC, bulk cellulose is deemed as not toxic and safe to use but safety of NC as biosorbents is still a challenge due to complex system and uncertainties. Even though it has the same chemical structure as the parent derivatives, NC possess different physicochemical properties. Varying size, shape, surface reactivity and charge are some of the factors that contributes to the different toxicity of NC. It was resulted from different treatments done to the bulk cellulose.

NCC has higher crystallinity compared to NCF due to removal of amorphous region in one of the many steps in producing NCC. Dimension of NCC usually in the range of 50–500 nm in length and 3–5 nm width while NCF was reported to have length of 500–2000 nm with width of 4–20 nm [12]. Other than that, other

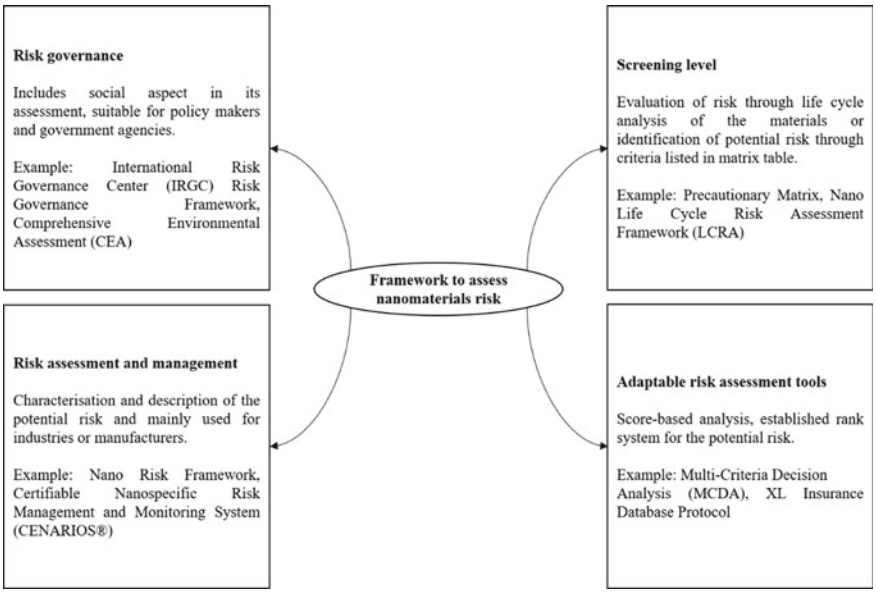

Fig. 1 Frameworks to assess nanomaterials risk

factors that could influence the toxicity are from biochemical mechanism such as necrosis, necroptosis, oxidative stress, DNA damage and many more [13]. Despite of material size affecting its toxicity, it is also dependant on the type of NC-based biosorbent studied. Large specific surface of NC provides higher affinity in absorbing biomolecules and thus producing toxicity via biochemical reaction. Other than that, NC biosorbent are usually tailored for its application for environmental remediation. If the target pollutant is negatively charged, the biosorbent used would be cationic for them to bind with each other. A researcher stated that the charges of NC significantly affect the cellular uptake, meaning that NC could possibly attached on living cell membranes and accumulates [10]. Figure 1 shows the summary of the nanomaterials risk assessment framework.

3 Toxicity of Nanocellulose

Increasing study in utilization of NC in various applications makes the evaluation of toxicology effect became vital for public health regulators. Cellulose is grouped in Generally Regarded As Safe (GRAS) substance by the Food and Drug Administration (FDA), but it is extremely important to declare whether NC based materials are regarded as safe too. Limited literature published on the toxicological effect of NC does not help to close the knowledge gaps and instead, raises public concern due

to some contradicted findings between researchers. Some classified the NC as non-toxic while some found out that NCC possess more health risk compared to NCF [14, 15]. Exposures to NC can occur in many ways, primarily from inhalation. Thus, more studies were directed towards pulmonary toxicity, which is the medical term for foreign materials that entered the respiratory system and have adverse health impact. The word 'in vivo' refers to a study that is conducted in a living organism, whether animal model or by human clinical trials. Rats and rabbit are two of common animals that were tested for in vivo studies in the laboratory. To conduct these studies, certain regulations must be followed and permission need to be obtained before commencing the animal testing. The effect of NC varies according to parameters tested and time of exposure. It can be as early as 1 h or even progressing for months to thoroughly assess the risk when continuously exposed to the substance. Toxicity assessment was divided according to human organ systems.

There are three division in the respiratory system which are nasal-pharyngeal-laryngeal, tracheobronchial and alveolar division where the exchange of gas occurs. Yanamala et al. [16] did pharyngeal aspiration test on a female mice C57BL/6 exposed to NCC. Two types of NCC were used which were freeze-dried product and 10 wt% suspension of NCC. The NCC was manufactured in Forest Products Laboratory via typical 64 wt% sulfuric acid hydrolysis method. Pharyngeal test is done by placing the NC under the animal's tongue at its base and extending the tongue so that the aspiration of substance would happen due to the rat reflexes.

Outcome from the tests indicates that the respiratory system damaged the tissue and gave inflammatory effect, with oxidative stress depends on the dosage of NCC. It should be noted that different effect was demonstrated when different types of NC and different mean of delivery was employed. For instance, a group of researchers explored the same parameter that was conducted to several rats but using NCF instead of NCC [17]. Also, the method of delivery was by exposure to aerosol. Inflammatory response was detected after 1 day of exposure, proving the effect of NC exposure to the respiratory system. Table 1 addressed some of respiratory system studies done by past researchers. Generally, all foreign particles that goes into the lung are considered as potential hazard, unless it is proven otherwise.

4 Conclusion

It is hard to conclude on one conclusion since there are many variables that need to be taken into account. Even with only single dosage, the animal needs longer time for recovery and these could worsen if it were exposed continuously in a long time. For studies that were conducted less than one month, it is hard to observe the histopathological changes that occur in the lungs. However, from the tests done by researchers, it was proved that NC does affect the respiratory system and therefore, precaution are needed when handling the materials.

Table 1 In-vivo test done by various researchers

NC type	Animal strain	Maximum Dose (mg/kg)	Dose frequency	Experimental details	References
NCF	Mouse (C57BL/6)	0.9	Single	• Spotted lung recovery in 4 weeks • Increasing neutrophil amount in bronchoalveolar lavage fluid (BALF) • Carboxymethylated NCF gave lower inflammation reaction compared to NCF	[18]
NCF	Mouse (BALB/c)	4	Single	• Lung recovery in 2 weeks • Increasing cytokines	[19]
NCF	Mouse (C57BL/6)	2	Single	• Lung recovery was observed within 4 weeks • NCF were administered in 4 different forms • Agglomeration was observed	[20]
TEMPO-NCF			Single	• Dosage of either 10, 40, 80 or 200 μg per mouse • Higher dose produce higher cellulosic accumulation in bronchi and alveoli	[21]
NCC	Mouse (C57BL/6)	10	Single	• Rcovery in 1 day • NCC were administered in 2 forms • Inflammatory cells and damaged tissue were observed • NCC suspension gave higher oxidative stress compared to powdery NCC	[16]

(continued)

Table 1 (continued)

NC type	Animal strain	Maximum Dose (mg/kg)	Dose frequency	Experimental details	References
NCC	Mouse (C57BL/6)	2	Twice per week	• Test was done for 3 consecutive weeks • Recovery took 3 months • Chronic inflammation was observed	[22]

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