Original Article

Application of Bayesian Network in Occupational Safety and Health: Prediction of Health Hazards from Nanosilver Exposure

Mardhati Zainal Abidin,[a,*] Risza Rusli,[a] Stephen Lim Ming Sern,[a] Norsuzieanah Halil,[a] Shahrulnizam Jamen,[b]

[a] *Chemical Engineering Department & Centre of Advanced Process Safety, Universiti Teknologi PETRONAS, 32610 Seri Iskandar, Perak, Malaysia.*
[b] *NIOSH Wilayah Pantai Timur (Kerteh), Bangunan NIOSH, LOT 12853, Jalan Lapangan Terbang, 24300 Kerteh, Terengganu, Malaysia.*

*Corresponding Author: risza@utp.edu.my

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ABSTRACT : *Nanosilver has been widely used in industries due to its antibacterial, antifungal, and antioxidant properties. However, prolonged exposure to nanosilver imposes negatively upon human health and may cause conditions such as argyria, argyrosis, and DNA damage. In recent times, the rapid diversification of industrial nanosilver without accompanying risk assessment exercises has contributed to a lack of understanding of such hazards, thus leading to negligence in safe work practices and exposing workers to danger. This work demonstrates the Bayesian network (BN) model application to predict the hazards of nanosilver. The model characterises the relationship between the physicochemical properties of nanoparticles and their biological effects on the human body based on expert elicitation and data from independent publications. For hazard prediction purposes, three nanosilver variants of different particle sizes, shapes, surface coatings, administration routes, and applications were chosen. Predictions obtained using the BN model are in line with published experimental studies. The potential health hazard of a nanosilver variant was shown to depend heavily on its physicochemical properties. Resultantly, the BN model developed in this work can make such predictions accurately, even with limited information. The outcome of this work will be useful in supporting the improvement of occupational safety and health practices in the industry.*

Keywords *- Occupational Safety and Health, Health Hazard, Nanomaterials Exposure, Prediction of Health Hazard, Workplace*

1.0 INTRODUCTION

The International Organisation for Standardisation (ISO) defines "nanomaterial" as a "material with any external dimension in the nanoscale or having an internal structure or surface structure in the nanoscale". "Nanoscale" is a length ranging "approximately from 1 nm to 100 nm" (The International Organization for Standardization (ISO), 2015). The European Commission in 2011 defined "nanomaterial" as a "material containing particles in an unbound state or as aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimension is in size range 1–100 nm" [Commission recommendation of 18 October 2011 on the definition of nanomaterial (Text with EEA Relevance) (2011/696/EU), 2011]. Due to their scale, nanoparticles behave and function differently in their bulk form, influenced by quantum and surface effects. Quantum effects refer to changes in optical, electrical, thermal, mechanical, and magnetic properties, whereas surface effects refer to increased reactivity due to increased exterior surface area (Azoulay et al., 2013). As a result, nanomaterials are often regarded as a new form of material with a wide range of applications in the healthcare, textile, cosmetics, agriculture, and construction industries.

Of several metallic nanomaterials, silver nanoparticles (AgNPs) are one of the most vital. They are known for their antibacterial, antifungal, and antioxidant properties. Previous studies indicated that AgNPs limit the progression and growth of many bacteria, including *Bacillus cereus* and *Citrobacter koseri*, and the fungus *Candida albicans*. In particular, their antibacterial capacity is achieved as Ag/Ag+ from AgNPs binds the biomolecules present in microbial cells, thus preventing the replication of bacteria by inducing oxidative stress and cell death (Siddiqi et al., 2018). Consequently, AgNPs have been utilized mainly in the production of housecleaning products and medication.

Although such studies extolled the benefits of AgNPs, they often also emphasise that overt exposure to these particles could deteriorate human health. Numerous *in vivo* studies determined that AgNPs are toxic to the mammalian skin, vascular system, liver, brain, lung, and reproductive organs. They not only accumulate but persist in these tissues, increasing the chances of severe toxicity (Ferdous & Nemmar, 2020; Gosens et al., 2015; Seiffert et al., 2016). Additionally, *in vitro* studies reported that the destructive effect of AgNPs on DNA could potentiate cancer by inducing the expression of genes associated with cell cycle progression (Ferdous & Nemmar, 2020; Kaiser et al., 2013). Several conditions linked to exposure to AgNPs in the workplace have been reported, such as the irreversible pigmentation of the skin (argyria) or of the eyes (argyrosis) (Drake & Hazelwood, 2005; Van de Voorde et al., 2005). Drake & Hazelwood (2005) also reported other indications of toxicity such as upper (nose and throat) and lower (chest) respiratory tract irritation and reduced glutathione levels. The most common impact of prolonged silver exposure at the workplace is argyria. It is caused by the accumulation of Ag compounds in the human body, marked by a turning of the skin colour to blue or blue-grey. In 1935, sixteen workers of a silver-nitrate factory reportedly experienced generalized or local argyria (Harker & Hunter, 1935). A later study further proved that workplace exposure led to argyria, argyrosis and the intravenous accumulation of silver (Rosenman et al., 1979). Silver-related fatalities were reported by Barrie & Harding (1947), where autopsies on three individuals showed that each suffered from argyro-siderosis of the lungs due to years of workplace exposure to inhaled iron-oxide and silver dust. However, a study conducted by Pifer et al. (1989) had also demonstrated that the increased presence of silver in blood, feces, and hair of reclamation workers did not come with significant health effects.

Regardless, the potential of occupational health hazards posed by nanomaterials on humans and the environment calls for enhanced risk-mitigating physicochemical measures to pre-empt their short and long-term toxic effects (Azoulay et al., 2013; Karim et al., 2017; Kim & Yu, 2016; Yokel & MacPhail, 2011). The National Institute for Occupational Safety and Health (NIOSH US) recommended an Immediately Dangerous to Life or Health (IDHL) exposure dosage of 10 mg/m^3 and the Recommended Exposure Limit (REL) was set to 0.01 mg/m^3 for metal dust such as silver on an 8-hour time-weighted average (TWA) concentration basis (National Institute for Occupational Safety and Health, 2016). Various risk assessment and control banding tools have been developed, including GoodNanoGuide (GNG), Stoffenmanager Nano, CB Nanotool 2.0, NanoSafer, ANSES Control Banding, and Queensland control banding worksheet (Winski, 2017). Unfortunately, as both their

particulate and molecular identities are responsible for their biological effects, the consequence of exposure to nanomaterials cannot be accurately predicted from the current understanding of their bulk properties.

Furthermore, the conventional approach to data collection is not robust enough to keep up with the high speed of nanomaterial diversification in the industries. As a result, incomplete nanomaterials data hinders proper occupational health assessment of the workplace. To resolve this issue, the BN model previously published in Marvin et al. (2017) was redeveloped. Subsequently, the newly-derived model was applied towards the prediction of the potential health hazards caused by excessive and prolonged AgNP exposure in the workplace. The integration of risk assessment with BN was proposed through this work due to the displayed ability of our BN model as a machine learning tool towards the prediction of potential health hazards despite incomplete nanomaterial data. Outcomes from simulations additionally suggest that the model would capably capture the interaction and impact of physicochemical property changes within the nanomaterial network itself. In conclusion, the BN model produced in this work could strengthen the case for improving occupational health practices in the nanosilver industry.

2.0 METHOD

The new BN model was developed through a process depicted by the flow chart in Fig. 1.

2.1 Data Collection

The major nanomaterials used in the industries were identified based on published statistics involving ten paint and coating products available in the market and three prominent nanomaterials (i.e., titanium dioxide (TiO_2), silicon dioxide (SiO_2), and silver (Ag)) (*StatNano : Nano Science, Technology and Industry Information*, n.d.). Data for learning and validation were collected from independent results of published studies by Marvin et al. (2017), who had compiled reliable information on the characteristics of nanomaterials from several resources, including physical-chemical property databases and safety data sheets. Crucial parameters were determined that would allow the model to characterise the relationship between the physicochemical properties of nanoparticles and their biological effects on the human body. The data and state were then classified with reference to scientific publications verified by expert elicitation in Marvin et al. (2017), as shown in Tables 1 and 2. Overall, 237 and 48 sets of data were incorporated for learning and validation, respectively.

Table 2 lists the tested endpoints related to the biological effects of a nanomaterial, classified into None, Low, Medium, and High. Tested endpoints must demonstrate significant differences from the control (as reported by the article) to be classified as having a biological effect (Table 3). Notably, this scale reported only the probability of the nanomaterials exerting an effect (strength of the evidence) but not its level of severity. An overall effect node was included to depict the potential that a nanomaterial may exert a biological effect, as calculated from Equation 1.

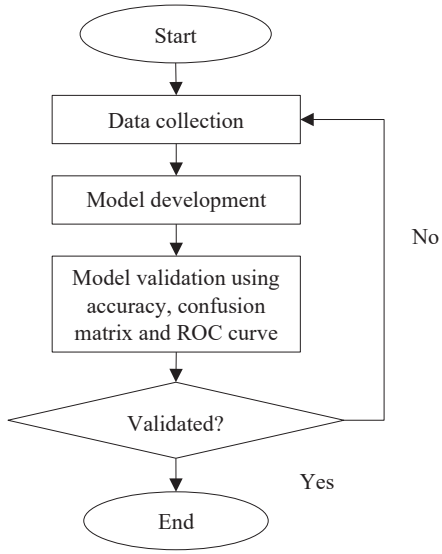


Figure 1 BN Model Development

Table 1 Classification of Data for Model Development

Administration Route	Study Type	Physicochemical Properties	Potential Biological Effect
Inhalation	*In vivo*	Shape	Cytotoxicity
Oral	*In vitro*	Nanoparticle	Neurological effects
Dermal		Surface area	Pulmonary effects
Intravenous		Surface charge	Fibrosis
		Surface coatings	RCNS effects
		Aggregation	Genotoxicity
		Particle size	Inflammation

Table 2 Classification of States for Model Development

Shape	Amorph, Irregular, Sphere
Nanoparticle	Ag, SiO_2, TiO_2
Surface Area	0–15, 15–51, 51–101.25, 101.25–189, 189–2025
Surface Charge	-50–-25, -25–0, 0–-25
Surface Coatings	AHPP, Carbon, Carboxyl, Citrate, Hydroxyl, None, PVP, Silane-Aluminium
Aggregation	High, Low, Medium
Particle Size	0–10, 10–50, 50–100, > 100
Cytotoxicity	High, Low, Medium, None
Neurological Effects	High, Low, Medium, None
Pulmonary Effects	High, Low, Medium, None
Fibrosis	High, Low, Medium, None
RCNS Effects	High, Low, Medium, None

Genotoxicity	High, Low, Medium, None
Inflammation	High, Low, Medium, None

$$HR_i = \sum_{k=1}^{7} BE_{ik} \quad (1)$$

where HR_i is the nanomaterial hazard score of case i and BE_{ik} is the biological effect level score of case i and biological effect k.

Table 3 Criteria for the Classification of Biological Effects (Marvin et al., 2017)

Classification	**Criteria**				***BE*$_{ik}$**
None	Endpoint(s) falling under the defined effects were tested	No significant difference in the tested endpoint compared to control			0
Low	Endpoint(s) falling under the defined effects were tested	A significant difference in the tested endpoint compared to control			1
Medium	Endpoint(s) falling under the defined effects were tested	A significant difference in the tested endpoint compared to control	Dose-response relationship	• Positive indication of an effect in a few tests or in a few animals • < 75% decrease in cell viability	2
High	Endpoint(s) falling under the defined effects were tested	A significant difference in the tested endpoint compared to control	Dose-response relationship	• Positive indication of an effect in several tests or in several animals • > 75% decrease in cell viability	3

2.2 Model Development

Marvin et al. (2017) predictive nanomaterial risk model was redeveloped using GeNie from BayesFusion LLC. Its network of nodes was manually constructed according to the classifications given in Tables 1 and 2. The directions of its arc were drawn based on the input from expert-verified published data. Parameter learning was then executed using the data collected. Once completed, the model was ready for the validation process. Different analyses can be performed to understand the model, such as the strength of influence and sensitivity analysis.

2.3 Model Validation

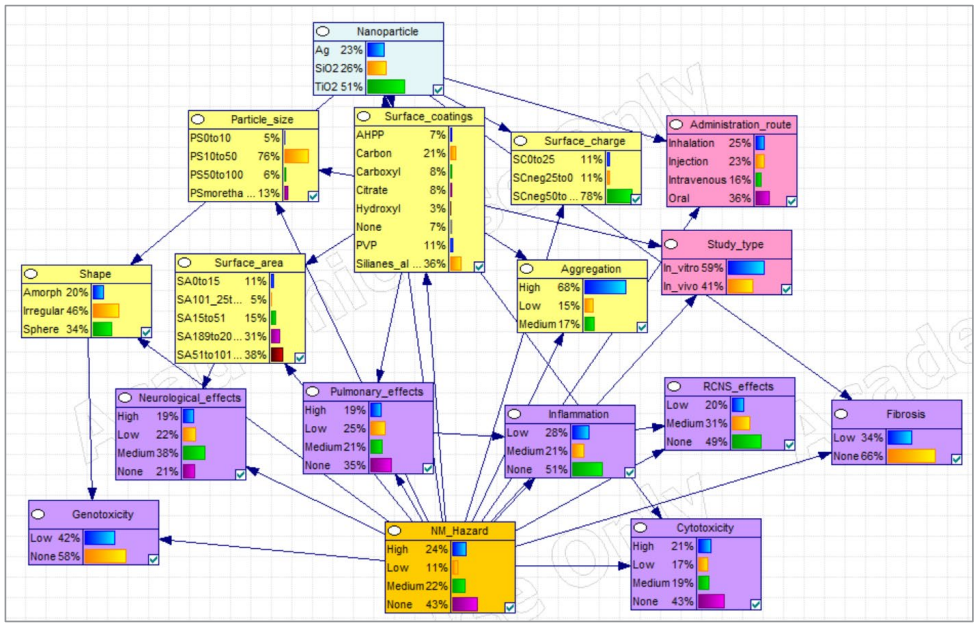
For validation purposes, 48 sets of data were selected randomly from the total data collected on Ag, SiO2, TiO2. These were matched with the developed model before the type of evaluation was selected. The three types of evaluation conducted by GeNIE are test only, leave-one-out cross-validation, and K-fold cross-validation. In this work, a K-fold cross-validation strategy was applied, with K = 10 and class nodes = NM_Hazard. The evaluation process first required the data set to be divided into K parts of equal size. The network was then trained in K-1 parts before a final test was conducted at the end of the last K. The process was repeated K times by selecting different parts of the data for testing. With GeNIe, model usability is evaluated by keeping its core structure fixed, even as parameters are relearned during each fold (BayesFusion LLC, 2020). Three outcomes, namely accuracy, confusion matrix, and receiver operating characteristic (ROC) curve from the validation exercise, would indicate the validity of the model.

3.0 RESULTS

The BN model developed in this work is shown in Fig. 2.

3.1 Accuracy

The ‘Accuracy’ tab showed that the model achieved a 75% accuracy rate by predicting the correct NM_Hazard in 36 out of 48 data sets (Fig. 3). GeNIe had assigned the most probable class node state for each data set in this process. The tab also denoted the model sensitivity and specificity (BayesFusion LLC, 2020). Its sensitivity towards None and Low was similar, with a prediction accuracy of 85.71% (n = 18/21) and 83.33% (n =5/6) for each. The model was less sensitive in predicting the NM_Hazard of High (66.67%, n = 6/9) and Medium (58.33%, n = 7/12) nodes.



Indicator	Definition
	Type of nanoparticles
	Physicochemical properties
	Exposure routes & study types
	Potential biological effects
	NM hazards

Figure 2 BN Model for Nanomaterial Hazard of Titanium, Silicon Dioxide, and Silver

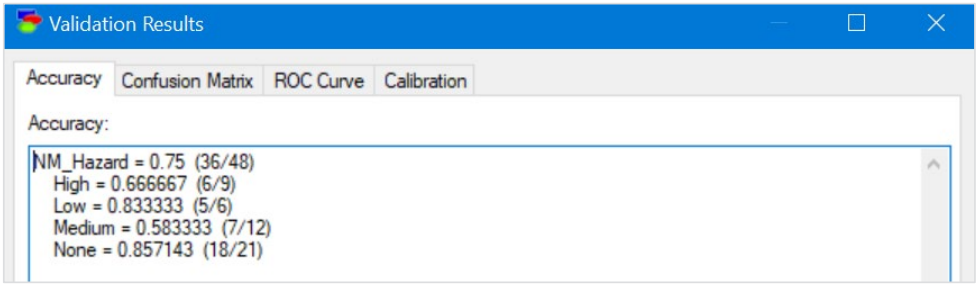


Figure 3 Accuracy of the BN Model for Titanium, Silicon Dioxide, and Silver

3.2 Confusion Matrix

The 'Confusion Matrix' table in Fig. 4 compared prediction directly against the true state of affairs. The columns represent the guesses produced by the model, while rows show how the data sets were actually classified. Here, it is clearly shown that the new BN model was largely successful in correctly assigning the data sets into their appropriate NM_Hazard classes. Bolded numbers were correctly identified instances for each class. However, all off-diagonal cells showed incorrectly identified classes (BayesFusion LLC, 2020).

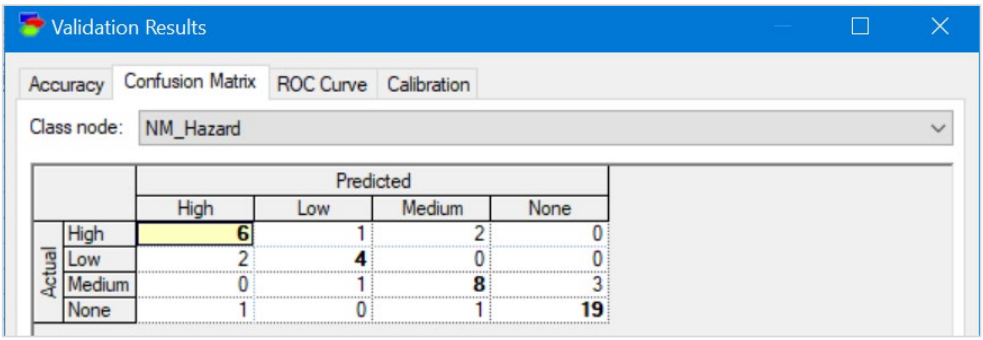
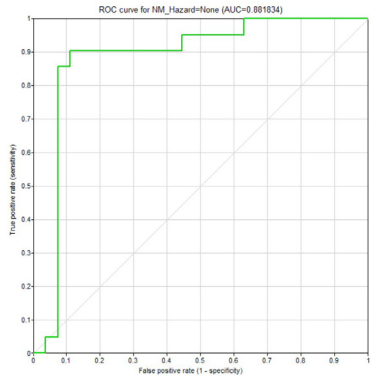


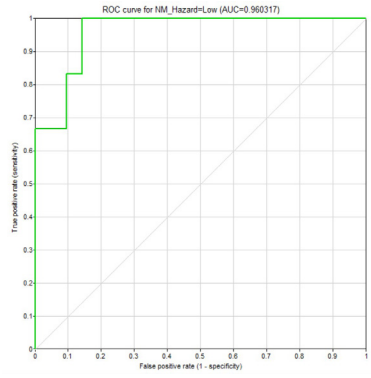
Figure 4 Confusion Matrix of the BN Model for Titanium, Silicon Dioxide, and Silver

3.3 ROC Curve

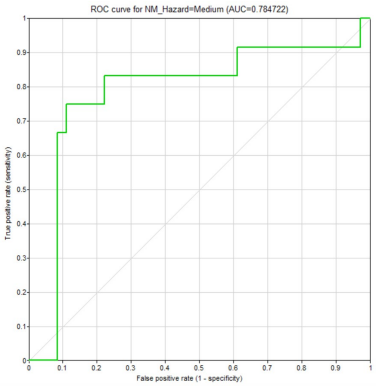
The 'ROC Curve' tab contained the ROC curves for individual data sets of each class variable, expressing the quality of a model-independent classification decision. A curve shows the possible accuracy ranges of the model, limited to a singular point on the curve as per the decision criterion applied by GeNIe. Choosing a different point will affect sensitivity and specificity and thus overall accuracy. The indistinct diagonal line represents a baseline ROC curve of a hypothetical classifier that is insignificant. A functional classifier would produce a curve above this diagonal line. The area under the ROC curve (AUC) is displayed above it. AUC is a simple but imperfect way of expressing the quality of the model using one number (BayesFusion LLC, 2020). Nonetheless, as each classifier (High, Medium, Low, and None) obtained a ROC curve above the diagonal line, it can be concluded that their use for NM_Hazard classification is suitable (Fig. 5).



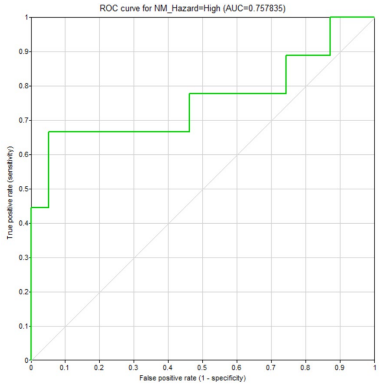
a) ROC curve for NM Hazard = None



b) ROC curve for NM Hazard = Low



c) ROC curve for NM Hazard = Medium



d) ROC curve for NM Hazard = High

Figure 5 ROC Curve of the BN Model for Titanium, Silicon Dioxide, and Silver

4.0 DISCUSSION

In this section, three AgNPs with different physicochemical properties were incorporated as evidence into the BN model for testing and validation purposes. The data are presented in Table 4. These AgNPs are referred to as A, B, and C. Observations of their biological effects were based on pulmonary effects, inflammation, and genotoxicity. These are summarised in Table 5.

In the experimental work conducted by Gosens et al. (2015), three animals per group were exposed to A via intratracheal instillation with doses ranging from 0 to 128 µg/mouse. Their results indicated that although AgNP agglomeration could be observed inside lavaged macrophages, there were neither signs of acute cell damage nor inflammation in the mice. Additionally, no pulmonary effects were reported due to exposure to nanosilver via injection. In a validation exercise, the physicochemical properties of A (particle size, study type, and administration route) were introduced as evidence into the redeveloped BN model produced in this work. Convincingly, the outcomes predicted by the model were "None" for pulmonary effects and inflammation, in line with the published experimental report.

In work conducted by Seiffert et al. (2016), four biological effects (assayed silver levels, distribution of silver particles in the lungs, surfactant composition, and lung function changes) were examined after the exposure of Brown-Norway and Sprague-Dawley rats to B-type AgNP aerosols. The physicochemical properties of B are shown in Table 4. The researchers concluded that exposure to B would cause acute pulmonary neutrophilic inflammation due to the production of proinflammatory and pro-neutrophilic cytokines. Brown-Norway rats were more adversely affected as additional eosinophilic inflammation and deterioration of lung function could be observed. The redeveloped BN model was retested, albeit with the properties of B as newly-introduced evidence. Its functionality was proven once more as the model successfully showed that, in comparison to A, B would impose a greater risk of pulmonary effects and inflammation ("Low" and "Medium"). These predicted changes could have been discerned from the type of evidence provided. The nanoparticles shape and curvature and their administration route are thought to influence cell-binding efficacy and dissolution (Buchman et al., 2019). Findings presented by Helmlinger et al. (2016) suggested that the shape of an AgNP particle greatly dictates dissolution rates and, therefore, its cytotoxicity and antibacterial effects.

Dissolution indicates biodurability and is directly correlated to an entity's potential to influence the long-term toxicity and pathogenicity of the particles deposited in the body. In a biological system, known dissolution rates of the following entities from the highest to the lowest are platelets > spheres glucose synthesis > spheres microwave synthesis ≈ rods > cubes (Helmlinger et al., 2016). This correlation explains why AgNPs persist for at least seven days after inhalation, as published data by Seiffert et al. (2016) indicated that a longer time is required to observe the impact of exposure via inhalation compared to direct instillation.

In the *in vitro* experiments conducted by Kaiser et al. (2013), a different set of parameters were monitored, including apoptosis/necrosis, reactive oxygen species, and genotoxicity. The study showed that the dose and duration of exposure highly influenced genotoxicity. For example, exposure to 5 µg/mL of AgNPs for 48h resulted in DNA strand breaks without significant consequences to health, although adverse effects were observed once the concentration was doubled to 10 µg/mL. Similarly, the percentage of cell death could only be observed at higher concentrations of AgNP exposure. Due to the limitation of the present BN model, a comparison to Kaiser et al.'s study was conducted only for genotoxicity. With its physicochemical properties introduced as evidence, the model classified the effect of C as "None", in agreement with experimental data from the *in vitro* studies. This could be perceived as yet another testament to the model's usability. Furthermore, as C is a mixture of spheres and rods, its biodurability is low compared to other shapes, explaining its non-genotoxic nature. Importantly, the accuracy of its prediction displayed the capability of the BN model to infer a suitable conclusion based on a simple attribute of the nanomaterial of concern.

In conclusion, the comparison shown in Table 5 proved that the BN model is robust enough to produce results already verified through real-world experiments. With a 75% accuracy rate, the model was able to produce accurate predictions with the aid of good quality of data obtained and supported by expert elicitation, as reported by Marvin et al. (2017). Nonetheless, although experts had validated the previous BN model's nodes, states, and linkages, there were certainly ways to improve its reliability. In this current work, a redeveloped BN model was constructed to accept and accrue evidence in the form of physicochemical properties from any published study. This could ensure greater prediction accuracy and thus better assist the assessment of occupational health hazards in the nanosilver industry. In the future, the model algorithm could also be further modified to factor in more evidentiary parameters, such as dose and duration of exposure.

5.0 CONCLUSION

A BN model was developed and used to predict the health hazards imposed by AgNP exposure in this paper. Three case studies were demonstrated with resulting predictions compared to published experimental data. These were consistently in line with published data, indicating that the BN model was able to predict potential health hazards in a nanosilver-centric workplace. The strength of the BN model is derived from its data learning feature and its ability to infer and calculate probabilities according to the newly presented evidence. However, as the BN methodology relies heavily on the initial input, the accuracy of its predictions would only be as good as the quality of the initiating data.

Furthermore, predictions are limited to the properties and effects decided at an early stage of model development. Any other factors that may affect the final results would be disregarded unless included during the development stages. This current study had thence redeveloped the previous BN model to consider nanomaterials' physicochemical properties, as it is likely critical for proper occupational health assessment. The outcomes of this work are vital in supporting the development of a precautionary approach in managing nanomaterial risk and improving occupational health practices in the industry.

Table 4 Nanosilver Physicochemical Properties

Type	References	Particle Size (nm)	Shape	Surface Coating	Surface Charge	Administration Route	Study Type
A	Gosens et al. (2015)	< 20	-	Polyoxy-laurate Tween 20	-	Injection	In vivo
B	Seiffert et al. (2016)	13–16	Nanosphere	Uncoated AgNPs	-	Inhalation	In vivo
C	Kaiser et al. (2013)	25 80–90	Spherical Rods	-	-25	-	In vitro

Table 5 Comparison between Published Experimental Data and Prediction using the BN Model

Type	References	Pulmonary Effect		Inflammation		Genotoxicity Effect		
		Published Experimental Data	Predicted using BN Model	Published Experimental Data	Predicted using BN Model	Published Experimental Data		Predicted using BN Model
A	Gosens et al. (2015)	No noticeable effects	None	No noticeable effects	None	-		-
B	Seiffert et al. (2016)	Acute pulmonary neutrophilic inflammation	Low	Acute pulmonary neutrophilic inflammation	Medium	-		-
C	Kaiser et al. (2013)	-	-	-	-	• 5 µg/mL for 48 h: more DNA strand breaks, an insignificant effect • 10 µg/mL for 48 h genotoxicity: a significant effect		None

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