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MACHINE LEARNING-BASED PREDICTION OF METAL OXIDE NANOPARTICLE TOXICITY USING PHYSICOCHEMICAL AND EXPOSURE-DEPENDENT PARAMETERS

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Abstract
Metal oxide nanoparticles are widely used in pharmaceutical, biomedical, environmental, and industrial applications; however, their potential toxicity remains an important safety concern. This study evaluated the toxicity of selected metal oxide nanoparticles using physicochemical, chemical, exposure-dependent, and machine learning-based approaches. The analysis included five nanoparticles: Al_2O_3, CuO, Fe_2O_3, TiO_2, and ZnO. Variables considered included nanoparticle type, core size, hydrodynamic size, surface charge, surface area, exposure time, dosage, chemical/electronic descriptors, number of oxygen atoms, and toxicity class. A total of 881 observations were analyzed, of which 476 were toxic and 405 were non-toxic. Nanoparticle-wise analysis showed that CuO and ZnO had stronger toxic tendencies, while TiO_2, Al_2O_3, and Fe_2O_3 were mostly or completely associated with non-toxic outcomes. Toxic observations were generally associated with higher core size, positive surface charge, higher dosage, and longer exposure time. Machine learning models, including Logistic Regression, Random Forest, and Gradient Boosting, were applied for toxicity classification. Gradient Boosting achieved the best performance with 91.6% accuracy, 83.5% F1-score, and 0.976 ROC-AUC, followed closely by Random Forest. Feature importance analysis identified dosage as the most influential predictor of toxicity. Overall, the findings suggest that ensemble-based machine learning models can support preliminary in silico nanotoxicity screening and safer metal oxide nanoparticle design.

Keywords: *Metal oxide nanoparticles; Nanotoxicity; Machine learning; Toxicity prediction; Physicochemical properties*

1. Introduction

Nanotechnology is an emerging area of biological, pharmaceutical, biomedical, and environmental research, due to the unique physicochemical properties of nanoparticles in comparison to bulk materials. The nanoscale size, high ratios of surface area to volume of the particles, their surface reactivity and tunable structural properties make them potentially useful for use in a variety of applications, such as drug delivery, diagnostics, imaging, antimicrobial systems, biosensing, and the development of therapies. Due to their variety of sources, attributes, applications, toxicity, and regulations, the study of nanoparticles and nanostructured materials has surged in recent years (Jeevanandam et al., 2018). They are also widely used and have spurred interest in the biological interactions and safety aspects of nanoparticles.

Because of their potential applications in pharmaceuticals and biomedical applications, especially for drug delivery systems, nanoparticles have proven to be promising. The nanobased drug delivery system has the capability to enhance the solubility, stability, bioavailability, targeted delivery, and controlled release of drugs, which are valuable for the development of modern drugs (Patra et al., 2018). Precision engineered nanoparticles are also being developed for the more effective and target specific delivery of drugs, with particle design being modified to enhance circulation and tissue targeting, and to enhance therapeutic responses (Mitchell et al., 2021). Moreover, therapeutic nanoparticles have been investigated for targeted delivery applications, such as cancer therapy, regenerative medicine, and other biomedical applications (Yetisgin et al., 2020). Metal nanoparticles and nanocarriers have also been the focus of interest as delivery systems, but there are limitations with regard to stability, toxicity, biodistribution and clinical translation (Chandrakala et al., 2022).

Metal oxide nanoparticles have been the focus of significant research due to their stability, reactivity and wide biological and biomedical relevance among various nanomaterials. Metal oxide Nanoparticles finds applications in drug delivery system, antimicrobial system, biosensors, tissue engineering, imaging, and other biomedical materials applications (Nikolova & Chavali, 2020). The use of nanoparticles in industrial, environmental, pharmaceutical and biomedical

applications makes them particularly important, e.g., Al_2O_3, CuO, Fe_2O_3, TiO_2, and ZnO. However, as they are being used more and more, safety and toxicity issues are important, and have been raised.

Physical and chemical properties are important in determining the toxicity of nanoparticles. Cellular interaction, uptake and retention, aggregation, oxidative stress, and biological response are some of the parameters that can depend on particle size, hydrodynamic size, surface charge, surface area, composition, shape, and surface chemistry (Sukhanova et al., 2018). Nanoparticle properties and interactions with cellular components can impact cellular uptake, retention and toxicity effects (Augustine et al., 2020). There has been extensive discussion on the general properties, applications and toxicities of nanomaterials, which can have beneficial or harmful effects when they have specific properties and exposed under specific conditions (Ibrahim Khan et al., 2019).

Nanoparticles are small, enabling them to interact closely with biological membranes, proteins, organelles and genetic material. The interactions that occur may lead to cellular uptake, membrane disruption, generation of reactive oxygen species, mitochondrial dysfunction, inflammation and genotoxicity. Surface charge is particularly relevant as the positive charge of a nanoparticle could bind to the negatively charged cell membrane, which can make it more likely that the cell will take up the particle and damage the cell membrane. Also, dosage and exposure duration are important factors to consider with regard to toxicity; higher doses and longer exposures could result in greater stress and biological damage to cells. It would, therefore, be better to take into account several physicochemical and the exposure-related factors than only one property of a given NP for toxicity evaluation.

Because of their extensive applications in cosmetics, food, biomedical materials and industrial applications, the titanium dioxide (TiO2) nanoparticles are among the most frequently studied metal oxide nanoparticles. But human exposure to TiO_2 nanoparticles has led to safety issues and previous reviews have found possible adverse effects depending on the route of exposure, physico-chemical properties of the particle, and the biological system (Baranowska-Wójcik et al., 2020). This is an indication that caution should be exercised in assessing metal oxide nanoparticles even in commercial or biomedical products that are broadly used.

Traditional experimental toxicity testing is valuable and provides important biological information, but may be time consuming, costly, and limited by cell lines, organisms, assays, and exposure conditions. Nanoparticle toxicity depends on several interacting factors and can thus vary between experiments. This results in the demand for a computational method that can assist in early-stage toxicity testing and aid in the identification of potentially toxic nanoparticles before going into a full scale laboratory development program. In this regard, machine learning approaches offer advantages as they can be used to describe complex relationships between physicochemical, chemical and exposure-related variables.

For the present study, the toxicity of selected metal oxide nanoparticles was assessed with respect to physicochemical, chemical and exposure related parameters. The nanoparticles analyzed were Al_2O_3, CuO, Fe_2O_3, TiO_2, and ZnO; the variables analyzed were the type of nanoparticle, core size, hydrodynamic size, surface charge, surface area, exposure time, dosage, chemical descriptors, number of oxygen atoms, and toxicity class. The observations were divided into two categories: toxic and non-toxic. The aim of the study was to analyse the distribution of toxicity, to identify the toxicity patterns for different types of nanoparticles, to compare the characteristics of the particles with respect to exposure and toxicity, and to build toxicity classification machine learning models. The relevance of this work to pharmaceutical and biological research is based on the need for the safety of nanoparticles in drug delivery systems, diagnostics, biomedical applications, and nanomedicine. Using predictive toxicity modelling to identify the key factors associated with the toxicity of nanomaterials and to minimize the need for repeated experimental testing can help the development of safer nanomaterials. For this, the present study uses descriptive analysis and machine learning classification to assess the toxicity of metal oxide nanoparticles and find key predictors related to toxic effects.

2. Methodology

2.1 Study Design

In the present study, a computational nanotoxicity prediction study has been designed to investigate the toxicity behavior of metal oxide nanoparticles based on their physicochemical, chemical and exposure related parameters. The primary objective of the analysis was to identify which variables were most important in the development of toxicity and to categorize the observations as toxic or non-toxic. The methodological workflow consisted of data preparation, toxicity distribution analysis, toxicity assessment at the level of the nanoparticles, comparison of the physicochemical and exposure-related parameters, development of machine learning models, evaluation of the models, and identification of important predictors.

2.2 Data Source and Variables

The analysis was carried out using observations obtained from the publicly available Nanoparticle Toxicity Dataset on Kaggle (UCI Machine Learning, 2024). The analysis was performed on the observations that were related to five metal oxide nanoparticles namely Al_2O_3, CuO, Fe_2O_3, TiO_2 and ZnO. The variables were: type of nanoparticles, size of core, hydrodynamic size, surface charge, surface area, chemical/electronic descriptors, exposure time, dosage, number of oxygen atoms, and toxicity class. The toxicity class was used as the outcome variable and was categorized into two groups: toxic and non-toxic. The other variables were selected for the predictive analysis because they are structural, surface-related, chemical and exposure dependent factors that could affect nanoparticle toxicity.

2.3 Data Preprocessing

Observations were screened for completeness, consistency and duplication prior to analysis. To have a consistent classification, the toxicity class was standardized as toxic and non-toxic. The type of the nanoparticles was considered as a categorical variable, while the core size, hydrodynamic size, surface charge, surface area, exposure time, dosage and chemical descriptors as numerical. Repeated observations were detected in the preprocessing stage, as these observations may contribute to improving the model's performance. To get a more accurate estimate of predictive accuracy, the repeated observations were removed from the machine learning evaluation, which was then interpreted.

2.4 Descriptive and Nanoparticle-Wise Toxicity Analysis

Descriptive analysis was performed to determine the overall distribution of toxic and non-toxic observations. The number and percentage of observations in each toxicity class were calculated and visualized using a pie chart. Nanoparticle-wise toxicity analysis was then conducted for Al_2O_3, CuO, Fe_2O_3, TiO_2, and ZnO by calculating the number of toxic observations, non-toxic observations, total observations, and toxicity percentage for each nanoparticle type. A stacked percentage bar chart was used to compare the toxic and non-toxic proportions within each nanoparticle group. This analysis helped determine whether toxicity varied according to nanoparticle type.

2.5 Analysis of Physicochemical, Chemical, and Exposure-Related Parameters

Physicochemical, chemical, and exposure related parameters were compared between toxic and non-toxic observations to find any patterns of toxicity. The core size, hydrodynamic size, surface charge and surface area mean values were used to assess the structural and surface differences between both classes of toxicity. The dose- and time-dependent toxicity patterns were evaluated using exposure time and dosage. To see if chemical composition of the molecules played a role in the toxicity classification, chemical descriptors such as electronegativity-related descriptor and number of oxygen atoms were also compared between toxic and non-toxic observations.

2.6 Machine Learning Model Development and Evaluation

Physicochemical, chemical and exposure-related variables were used to create machine learning classification models for prediction of toxicity. The models evaluated were Logistic Regression, Random Forest and Gradient Boosting. A linear model (Logistic Regression) was chosen as a baseline model, and two non-linear models, Random Forest and Gradient Boosting, were selected to capture non-linear relationships between nanoparticle characteristics and toxicity. The type of the nanoparticles (categorical) was coded prior to model training, while numerical were used as predictive features. Various metrics like accuracy, F1 score and ROC-AUC were used to evaluate the model's performance. The accuracy was calculated as the overall percentage of true positive and true negative classifications, the F1-score was used to measure the balance between the precision and recall for the different classification tasks, and the ROC-AUC for each model to measure its capacity to distinguish between the toxic and non-toxic observations.

2.7 Feature Importance and Computational Tools

To determine the key predictors for nanoparticle toxicity classification, feature importance analysis was conducted. Ensemble-based models were used to investigate the relative contribution of such factors as dosage, exposure time, particle type, chemical descriptors, core size, surface charge, surface area and hydrodynamic size of the NP.

3. Results

3.1 Distribution of Toxicity Classes

To assess the toxicity profile of metal oxide nanoparticles, a total of 881 observations were analyzed. The observations were sorted into two outcome categories: toxic and non-toxic. These two numbers are shown in Figure 1 as a percentage of the total number of observations, and toxic observations made up a slightly higher percentage than non-toxic observations.

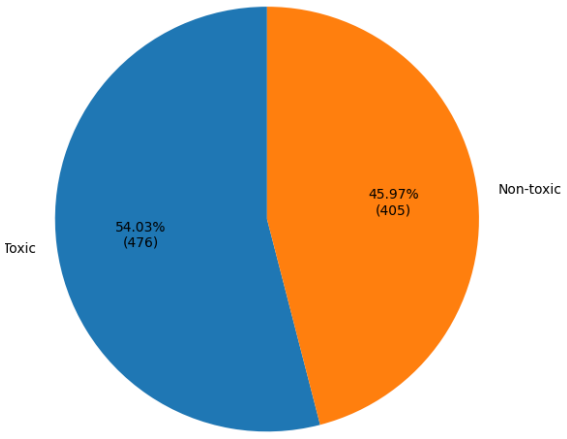

Figure 1. Proportional distribution of toxic and non-toxic observations.

Figure 1 shows that there were roughly equal numbers of toxic and non-toxic observations. The equilibrium is crucial as it minimizes the risk of strong class bias in the process of toxicity classification. Table 1 shows that 405 observations were classified as non-toxic and 476 as toxic. The toxic observations made up 54.03% and the non-toxic observations made up 45.97% of the total observations. Overall, therefore, a slightly higher proportion of toxic observations were recorded.

Table 1. Distribution of toxic and non-toxic observations

Toxicity class	Number of observations	Percentage
Toxic	476	54.03%
Non-toxic	405	45.97%
Total	**881**	**100%**

3.2 Toxicity Profile of Metal Oxide Nanoparticles

However, there was clear distinction in the toxicity profile of the five metal oxide nanoparticles in the study, namely, Al_2O_3, CuO, Fe_2O_3, TiO_2, and ZnO. The details can be seen in Table 2 below wherein the number of observations is highest for ZnO with 594 observations followed by TiO_2 with 200 observations. CuO, Al_2O_3, and Fe_2O_3 have fewer observations.

In terms of toxicity, CuO has the highest toxic proportion with 40 observations from the total 51 observations being marked as toxic which translates to 78.4% toxicity. Next in line is ZnO with a relatively higher toxic proportion at 430 observations from the total 594 being marked as toxic with the percentage of toxicity being 72.4%. The lowest proportion of toxicity occurs in TiO_2 with six observations from a total of 200 being marked as toxic giving a proportion of 3.0%. None of the observations made for Al_2O_3 and Fe_2O_3 are toxic since both are marked as non-toxic.

Table 2. Nanoparticle-wise toxicity profile

Nanoparticle	Toxic observations	Non-toxic observations	Total observations	Toxicity percentage
Al_2O_3	0	18	18	0.0%
CuO	40	11	51	78.4%
Fe_2O_3	0	18	18	0.0%
TiO_2	6	194	200	3.0%
ZnO	430	164	594	72.4%

This can be further elucidated through Figure 2, which provides a stacked percentage bar chart for the nanoparticle-wise toxicity trend. As depicted in the figure below, the percentage of toxic and non-toxic data is displayed for each type of nanoparticle. From the figure below, it is evident that the toxic percentage was higher for CuO and ZnO, whereas Al_2O_3 and Fe_2O_3 recorded 100% non-toxic data.

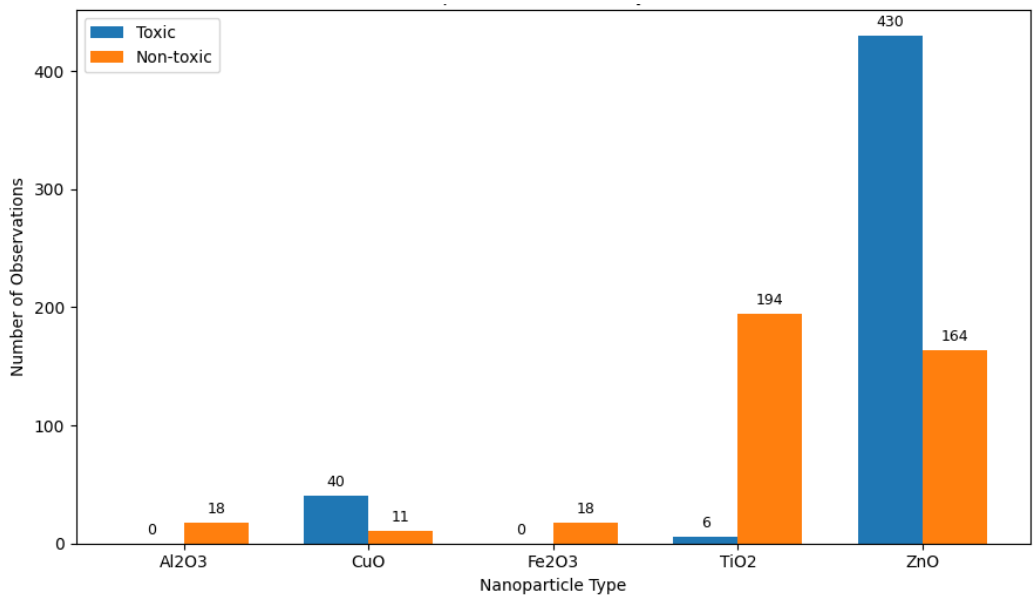

Figure 2. Nanoparticle-wise toxicity percentage distribution of metal oxide nanoparticles.

3.3 Physicochemical Characteristics Associated with Toxicity

Physicochemical properties comparison revealed significant differences between toxic and non-toxic observations. In terms of the core size property, toxic observations had a significantly higher mean value of 63.41 compared to 47.97 in non-toxic observations. This implies that larger core sizes were mostly linked to toxic results. The core size property does

not provide sufficient insight into the phenomenon of nanoparticle toxicity because of its complex nature, which involves interactions between the type of nanoparticle, surface charge, surface area, hydrodynamic size, dose, and time of exposure. Another critical physicochemical characteristic that differed significantly between toxic and non-toxic observations was the surface charge. Toxic observations had a positive mean surface charge of 6.79 compared to a negative mean value of -4.41 for non-toxic observations. This implies that nanoparticles with a positive charge were more likely to result in toxic reactions. The surface charge property influences nanoparticle interactions with cell membranes and cellular uptake processes, among other mechanisms.

Hydrodynamic size did not exhibit significant variation between the two toxicity categories. Hydrodynamic sizes for non-toxic observations ranged at around 522.81, compared to those of toxic observations at about 506.10. From this trend, hydrodynamic size did not significantly impact toxicity of nanoparticles, and therefore needs to be understood in conjunction with nanoparticle type, dosage, duration of exposure, charge on the nanoparticle, and chemical descriptions. On the other hand, surface area exhibited an unexpected trend. Surface areas for non-toxic observations were higher, at approximately 61.11, when compared to those of toxic observations which were relatively lower at around 25.88. While the role of surface area in nanoparticle reactions is widely acknowledged, this finding shows that surface area alone was not the most determinant factor in causing toxicity of nanoparticles. Toxicity seemed to have been brought about by a number of properties.

3.4 Exposure-Dependent Toxicity Pattern

Variables relating to exposure exhibited significant variations between toxic and non-toxic results. In relation to exposure duration, the mean value for toxic results was higher than that for non-toxic results, namely 32.12 and 21.98 respectively. As well, toxic results exhibited significantly higher mean dosage of about 46.33, as opposed to non-toxic results which exhibited a relatively lower mean dosage of around 31.80. This suggests that exposure duration and dosage of nanoparticles could affect the toxicity of the nanoparticles studied. High dosage might result in increased interaction of nanoparticles with living systems, while high exposure duration might cause nanoparticle buildup within cells.

3.5 Role of Chemical Descriptors in Toxicity Classification

The descriptors related to chemical and electronic properties also played a role in differentiating the observations of toxic from those of non-toxic. Electronegativity descriptor indicated a slight mean difference in favor of observations of toxicity, but the number of oxygen atoms had a larger mean in the group of non-toxic observations at 1.66 as opposed to 1.01 for toxic observations.

It can be concluded that chemical composition-related factors were among the determinants of toxicity classification. Nevertheless, their impact seemed to depend on other factors like nanoparticle types, doses, charge, and exposure time. Thus, chemical descriptors might increase the accuracy of predictions of toxicity in combination with other factors.

3.6 Predictive Performance of Machine Learning Models

To classify observations as toxic or non-toxic, machine learning models were used based on physicochemical, chemical, and exposure variables. The models that were considered for analysis include Logistic Regression, Random Forest, and Gradient Boosting. It can be seen from Table 3 below that models based on ensemble algorithms performed better than Logistic Regression. Gradient Boosting turned out to have the highest level of accuracy, reaching 91.6%. The F1-score and ROC-AUC score are 83.5% and 0.976, respectively. Random Forest proved to be effective too; however, its accuracy is slightly lower, at 90.4%. The F1-score and ROC-AUC score are 79.8% and 0.972, correspondingly.

Table 3. Predictive performance of machine learning models

Model	Accuracy	F1-score	ROC-AUC
Logistic Regression	82.7%	71.5%	0.913
Random Forest	90.4%	79.8%	0.972
Gradient Boosting	91.6%	83.5%	0.976

Figure 3 below depicts the comparison of performances of the machine learning algorithms. As shown in the graph below, Gradient Boosting outperformed Random Forest especially in F1-score and ROC-AUC metrics. Moreover, both ensemble learning methods exhibited higher predictive powers compared to logistic regression, implying that there was non-linearity in the relation between nanoparticle properties and their toxic effects. This means that ensemble methods were appropriate for classifying nanoparticles' toxicity.

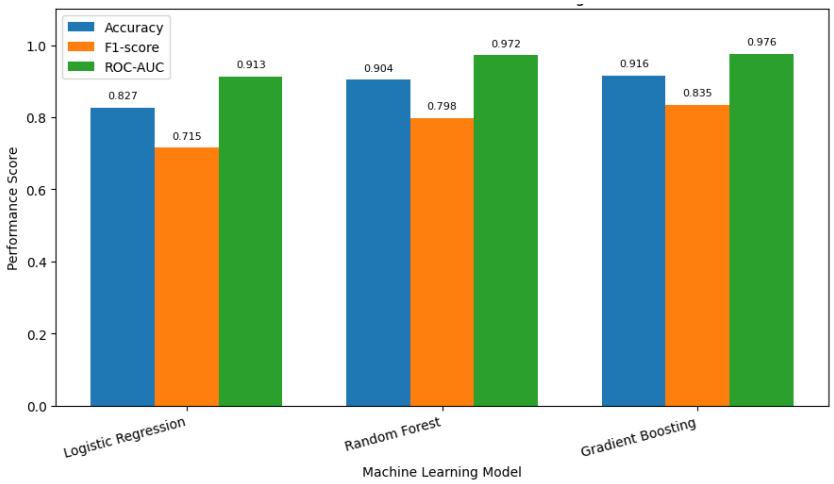

Figure 3. Comparative predictive performance of Logistic Regression, Random Forest, and Gradient Boosting models for nanoparticle toxicity classification.

3.7 Important Predictors of Nanoparticle Toxicity

According to the feature importance analysis, the dose is the most important predictor for toxicity prediction. It means that the concentration of nanoparticles had a significant effect on how observations were labeled as either toxic or non-toxic. Important features contributing to the outcome include the number of oxygen atoms, electronegativity-related descriptor, exposure time, surface area, nanoparticle type, core size, surface charge, and hydrodynamic size. The significance of dose and exposure time reveals how important the exposure time is for the determination of toxicity. Also, it means that the inherent property of nanoparticles was important in the classification of the toxicity of the material. Therefore, toxicity is defined by a combination of factors such as physicochemical properties, chemical descriptors, and exposure conditions.

The results indicate that the toxicity of metal oxide nanoparticles depends on the nanoparticle types, physicochemical properties, chemical descriptors, dosage, and exposure time. Specifically, the toxicity of CuO and ZnO nanoparticles was greater than that of TiO_2, Al_2O_3, and Fe_2O_3 particles, which did not exhibit any or little toxicity at all. Toxic nanoparticles were mainly associated with large core sizes, positive surface charges, and high dose and exposure times.

In terms of their performances, among the tested machine learning algorithms, Gradient Boosting demonstrated better results than others, while being closely followed by the Random Forest model. High ROC-AUC values for the two algorithms reflect good discriminative capability between toxic and non-toxic samples. Thus, in general, the obtained results demonstrate the applicability of the machine learning approach for nanotoxicity in silico analysis.

4. Discussion

To assess the toxicity profile of metal oxide nanoparticles, several methods were employed in the current research including physicochemical parameters, chemistry-related parameters, exposure-related parameters, and machine learning methods. According to the obtained results, 54.03% of the observed cases were considered toxic and 45.97% cases were not toxic. The distribution was fairly balanced, hence, sufficient numbers of toxicity classes are available for comparisons. As per the distribution, toxic nanoparticles were slightly more in number. Therefore, the metal oxide nanoparticles may pose some biological risk depending upon the physicochemical and exposure conditions. Previously, it has been stated that toxic effects of nanoparticles depend upon nanoparticle features, biological endpoints, and exposure conditions rather than mere presence of materials in organisms (Shin et al., 2015; Forest et al., 2019; Forest, 2022).The pattern of toxicity based upon nanoparticles revealed that CuO and ZnO were most likely to cause toxic effects whereas TiO_2, Al_2O_3, and Fe_2O_3 were associated with non-toxic effects. In terms of proportion, CuO and ZnO posed high toxicity, where 78.4% and 72.4% toxic effects were seen. Therefore, it is evident from the above figures that nanoparticle type was responsible for causing toxicity. The higher toxicity due to CuO could be related to mechanisms such as oxidative stress, ions released by nanoparticle, inflammation caused, membrane destruction, and cellular injuries. Likewise, higher toxicity of ZnO could be attributed to its mechanisms of metal dissolution, generation of reactive oxygen species, mitochondrial dysfunction, and cell damages. However, TiO_2 had low toxic proportion, while Al_2O_3 and Fe_2O_3 had no toxic records within the reviewed papers. However, this does not imply absolute safety for these materials in all possible exposure conditions. The degree of toxicity is associated with many variables, such as nanoparticle dosage, exposure time, size, physicochemical properties, biological endpoint, etc. For instance, TiO_2 nanomaterials' biological activity is known to depend on their physicochemical properties and protein corona (Kose et al., 2020). Moreover, some other studies reported toxicological effects of TiO_2 nanoparticles at certain exposure parameters. Therefore, toxicity highly depended on the particular experimental conditions (Shabbir et al., 2021).The comparison of physicochemical properties revealed that toxic observations had larger mean core size than non-toxic ones. Specifically, toxic observations had the mean core size of about 63.41, whereas non-toxic observations had smaller core sizes – about 47.97. Thus, core size was an important contributor to the toxicity classification. Nevertheless, the effect of nanoparticles cannot be attributed to size only because the biological response to a nanoparticle is a result of the interaction of several physicochemical properties (hydrodynamic

size, surface charge, surface area, chemical composition, dosage, exposure time). Earlier research indicated that physicochemical properties such as particle size, charge, surface chemistry, and surface characteristics contributed to the toxicity and classification of oxide nanoparticles (Shin et al., 2015; Ha et al., 2018).The surface charge was also different for toxic and non-toxic observations. Toxic observations had larger mean positive surface charge (about 6.79), while non-toxic observations had lower mean negative surface charge (-4.41). The observation suggested that positively charged particles were more toxic. The positive charge allows nanoparticles to attract negatively charged cell membranes. Consequently, it increases the possibility of interaction with biological cells resulting in increased uptake, aggregation, and intracellular stress. Descriptor-based and classification studies previously highlighted the importance of surface-related descriptors for the development of nanotoxicity models (Jha et al., 2018; Ha et al., 2018).Hydrodynamic size and surface area were less related to the biological effects of nanoparticles. The mean hydrodynamic size of non-toxic observations was slightly larger than that of toxic observations (about 47.29 vs. 43.47). In addition, the surface area of non-toxic observations was larger than that of toxic nanoparticles (about 4915 vs. 4415). It means that surface area could not be considered an essential factor that affected the biological response to nanoparticles. In fact, toxicity was related to the combination of several properties and biological factors, such as nanoparticle composition, surface charge, dosage, exposure time, and chemical properties. Such conclusion is also supported by recent computational studies indicating the importance of comprehensive descriptors in predicting nanoparticle toxicity (Choi et al., 2018; Jha et al., 2018).Exposure-related variables demonstrated their correlation with the biological effect of nanoparticles. The mean dosage of toxic observations was larger than that of non-toxic nanoparticles (about 46.33 vs. 31.80). Moreover, the mean exposure time for toxic observations was significantly larger than that for non-toxic ones (about 32.12 vs. 21.98). The obtained results indicate dose- and time-dependent toxicity of nanoparticles. Larger dosage leads to higher probability of interaction with biological entities, while extended exposure can increase oxidation and biological damage to cells. Previously conducted studies proved the importance of such parameters for nanotoxicity predictions (Choi et al., 2018; Forest et al., 2019). Chemical and electronic descriptors also played a role in the classification of nanoparticles based on their toxicity. Electronegativity-related descriptor was slightly higher for toxic observations, while the number of oxygen atoms was higher for non-toxic observations. These results indicate that chemical composition-dependent parameters might affect the reactivity, dissolution, oxidative capacity, and biological behavior of nanoparticles. Descriptor-based nanotoxicity prediction approaches have attracted attention as one way to integrate various aspects of materials' and experiments' properties into the predictions (Jha et al., 2018; Subramanian & Palaniappan, 2021).Machine learning revealed the superiority of ensemble models over the linear approach. Specifically, Gradient Boosting provided the highest prediction accuracy (91.6%), F1-score (83.5%), and area under the ROC curve (AUC) (0.976) compared to Random Forest, which had an accuracy of 90.4%, F1-score of 79.8%, and AUC of 0.972. Logistic Regression provided worse predictive performance (accuracy = 82.7%, F1-score = 71.5%, and AUC = 0.913). The outperformance of Gradient Boosting and Random Forest indicates the existence of non-linear associations between nanoparticle type, dosage, exposure time, core size, surface charge, surface area, and chemical descriptors. Several similar investigations have suggested that artificial intelligence and machine learning models are helpful in predicting nanoparticle toxicity when several predictors are used (Banaye Yazdipour et al., 2023; Ahmadi et al., 2024).The analysis of feature importance revealed that dose was the most significant predictor, followed by chemical descriptors, exposure time, surface area, type, core size, surface charge, and hydrodynamic size of nanoparticles. It confirms the conclusion that nanotoxicity cannot be explained with one factor, but depends on the interaction between different factors related to exposures and nanomaterials. These results also prove that computational nanotoxicity prediction approaches can be used as supplementary tools in nanotoxicology to facilitate hazard assessment and nanomaterial development (Forest, 2022; Banaye Yazdipour et al., 2023).Despite the insightful conclusions made, there are several limitations of this research that should be acknowledged. First, only five metal oxides were analyzed, which might be problematic regarding generalization to other types of nanomaterials. Furthermore, biological parameters like cell type, species type, toxicity endpoint, test protocol, and omic-level changes were insufficiently represented in the dataset. Indeed, earlier work has emphasized the significance of biological factors in interpreting effects of nanoparticles in cells (Forest et al., 2019; Furxhi et al., 2019). Overall, these results imply that CuO and ZnO need special toxicological attention, and ensemble machine learning algorithms like Gradient Boosting and Random Forest can help with predicting preliminary nanotoxicity profiles

5. Conclusion

It was shown that metal oxide nanoparticle toxicity depends on the interaction between the type of nanoparticle, physicochemical properties, chemical descriptors, dosage, and exposure time. Among all types of nanoparticles studied, CuO and ZnO demonstrated higher tendencies to nanotoxicity, while TiO_2, Al_2O_3, and Fe_2O_3 nanoparticles mostly demonstrated non-toxic results under the conditions used in the current study. Toxic behavior was found to be correlated with increased core size, increased surface charge, increased dosage, and longer exposure time; thus, both material properties and environmental factors appear to be key drivers of nanoparticle toxicity. It could be noted that machine learning was effective in predicting the tendency to nanoparticle toxicity. Among different methods, gradient boosting appeared to produce the highest accuracy, closely followed by the random forest method, and logistic regression showed relatively weak prediction performance. Since the highest accuracy was achieved by ensemble models, it could be inferred that the relationships between features in nanoparticle toxicity are rather complex and non-linear in nature. According to the analysis of feature importance, the dosage of nanoparticles appeared to have the largest impact on toxicity, followed by chemical descriptors, exposure time, surface area, nanoparticle type, core size, surface charge, and hydrodynamic size.

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