Predicting Toxicity Behaviour of Engineered Nanomaterials Using Adaptive Neuro-Fuzzy Inference Systems

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Abstract-**Nanotechnology is the fabrication and manipulation of novel material at size of 100 nm or less and is increasingly becoming a promising areas in various human endeavor because of their novel and unique characteristics. Nano-materials are commonly applied in medicine, Engineering and agricultural industries. Considering the Environmental and Health implications, nanomaterials could be harmful because of their distribution through environment, aquatic and human systems. Their novel and unique properties have made its transportation and distribution easy into human body system through the skin, lungs, gastrointestinal tract. However, many toxicological studies have shown inherent toxicity of some nano-particles to living organisms, and their potentially harmful effects on environment and aquatic systems (ecotoxicity) for which relatively tedious animal testing procedures have been documented for their characterization. In view of the increasing number of nanoparticles manufactured and the variety of their intrinsic properties especially sizes and coatings, it is therefore necessary to explore alternative approach that avoids conducting test on every nano-particle produced. The objective of the study is to develop screening protocol to assess, evaluate, and manage the inherent risks using neuro-fuzzy inference systems. This paper therefore focuses on the capability of Neuro- fuzzy system to model physicochemical properties and toxic effect of nanomaterials. Hence, the main motivation of this research work is to assist the users of nanomaterials in classifying, assessing and determining the risk of nanomaterials toxicity**.

Index Terms—**Characterization, Machine learning, Fuzzy Logic, Neuro-fuzzy, Nanomaterials, Nanotechnology, Environmental, Health, Safety, Risk assessment, Toxicity**

I. INTRODUCTION

Nanotechnology is the fabrication and manipulation of novel material at size of 100 nm or less and is increasingly becoming a promising areas in various human endeavor because of their novel and unique properties. Nano-particles are commonly applied in medicine, Engineering and agricultural industries. The unique properties of these materials can be manipulated for beneficial purposes and at the same time may also have side effects through toxicological and environmental impacts [1], [2]. The increasing rate of manufacturing nanomaterials and the end-users exposure to a wide variety of nanoproducts has brought about awareness about safety and health consequences of biological systems and environment. Because of the intrinsic properties, these engineered NMs have ability to easily gain access into human body, accumulate in cells, and cause health challenges [3], [4], [5]. In recent years, it has been shown from various studies, that ENMs have hazardous potentials and harmful to human health. According to [6], it was shown that carbon nanotubes (CNTs) have the potential to induce reactive oxygen species (ROS) and pulmonary effects. Further studies have also reported that titanium dioxide (TiO_2) nano-particles have the tendency of inducing cytotoxic [7], genotoxic [8] and inflammatory effects [9]. Similarly, it was also reported that silver nanoparticle has the ability of inducing harmful effects arising from exposure to nanosilver. More detailed information about the inherent negative effects of various ENMs has been documented by several researchers [8], [9], [10]. The apprehensions of the potential harmful effects of nanomaterials constitute serious setback to nanotechnology commercialization. The objective of the study is to develop screening protocol to assess, evaluate, and manage the inherent risks. To achieve this, it is imperative to develop models, tools and an acceptable mechanism for screening, predicting and monitoring the application of nanomaterials. In machine learning modeling, it is the specific type of biological activity, such as cell cytotoxicity that will be modeled and predicted toxicological endpoint which measures the toxic effect of a nanomaterial on human health or the environment will be predicted by machine learning models provided sufficient toxicity data is provided as input Here, Neuro-Fuzzy systems have been explored as an alternative to establish the relationship between physicochemical properties and biological activity. In this modeling, the important descriptors such as size, shape, and surface charge, can be measured by means of various experimental techniques. With the so far established consensus on measurement and modeling descriptors of traditional (Q)SAR analysis, these descriptors are to be applied for nano-Intelligent system[11], [12], [13], [14]. The first step in modeling ENM toxicity is the identification of toxicity-related characteristics that can be used as descriptors of harmful effects of ENMs. The characteristics and properties which are recommended list of almost all

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nanotoxicologists as important determinants of toxicity include: size distribution, agglomeration state, shape, crystal structure, chemical composition, surface area, surface chemistry, surface charge, exposure time, dosage and porosity. This paper will therefore explore the capability of neuro-fuzzy systems to model physicochemical properties and toxic effect of nanomaterials in view of the imprecision and uncertainty surrounding the prediction of nanomaterials toxicity.

II. NEURO-FUZZY SYSTEMS AND MODELLING TECHNIQUES

In this study the neuro-fuzzy systems are applied to relate the biological endpoints of a series of nanomaterials to their physicochemical properties in a quantitative way [15], [16], [17], [18].

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A. Neuro-Fuzzy Systems

Fuzzy systems and neural networks have been applied in various social, economic, scientific and engineering areas such as industrial process control, medical instrumentation information systems and decision analysis. The basic concept of fuzzy logic control (FLC) is to build a model of a human control expert to control a system without applying mathematical model. Fuzzy inference systems (FISs) are often known as fuzzy-rule-based systems are used to model imprecise, vague and uncertain situations. A fuzzy inference system (FIS) consists of the fuzzification, rule base or knowledge base, Inference system and de- fuzzification components [19], [20]. Although it is possible for neural network to learn from the given data and recognize the pattern inherent in such data, the trained neural network is often referred to as a black box. This is because it is neither possible to extract knowledge from such neural network nor have a simplified learning procedure through integration of knowledge into the neural network. On the contrary, a fuzzy logic controller is designed to works with the structured knowledge expressed as rules and as such virtually all the components of the fuzzy system are highly transparent and can easily be interpreted. However, there is no mechanism to choose various design parameters and hence the tuning of these parameters is generally attained by trial and error techniques. This new hybrid system combines the well-established advantages of both methods, compliments one another and avoids the disadvantages of both.

In this paper, the developed Neuro-fuzzy model is based on the hybrid fuzzy system and neural networks [21],[22]. A fuzzy neural network is made up of a set of fuzzy if-then rules which describes the input-output mapping relationship of the network. The antecedents of fuzzy rules provides the partitioning of the input space into a number of linguistic term sets while the consequent part can be chosen as a fuzzy membership function (Mamdani model) [21],[22], a singleton value, or a mathematical expression of a linear combination of input variables as in Takagi Sugeno model. For simplicity, the Mamdani model is adopted in this section. This model can be given in the following form: Rule k :if x_1 is A_1 and x_2 is A_2…and xn is An, then $Y=b$ (1).

where xi represents the input variable, y denotes the output variable, Ai is the linguistic term of the antecedent part, b is the constant consequent part, and n is the number of input variables. The structure of Mamdani neuro-fuzzy is shown in Fig. 1, where n and m are the number of input variables and the number of fuzzy sets respectively. The network structure consists of four layers. It uses, $Ii^{(l)}$,$O_i^{(l)}$ $l=1,2,3,4$ *to* denote the input and output of the ith node in layer L respectively. The operations performed in the nodes of each layer are as described below:

Layer 1: In this layer**,** there are n nodes. These nodes only transmit input values to layer 2:

$$I_i^{(l)}=xi,\ O_i^{(l)}=I_i^{(l)} \quad i=1,2,3,4 \qquad (2)$$

Layer 2: The nodes in this layer show one linguistic label of the input variables in layer 1. This implies that the degree of membership value of input value to a fuzzy set is calculated in this layer.

The input and output in this layer are determined as follows:

$$I_{ij}^{(2)} = O_i^{(1)} = \mu_{ij}(x_i) = e^{-(xi-mij)/\sigma ij)^2} \quad i=1,2,3,.....n \quad j=1,2...m \qquad (3)$$

where $\mu_{ij}(x_i)$ is fuzzy membership function, mij and σij are, respectively, the center and the width of the Gaussian membership function μ_{ij}

Layer 3: Layer 3 has m nodes. The output of each node in this layer is computed by the fuzzy AND operation. In this layer, the application of product operation gives the firing strength of each rule. The input and output in this layer are as shown in "(4)":

$$I_{ij}^{(3)}=\prod O_{ij}^{(2)}=\prod \mu_{ij},\ O_j^{(3)}=I_j^{(3)} \quad i=1,2,3,.....n \quad j=1,2...m \qquad (4)$$

Layer 4: This layer has a single node which computes the overall output as the sum of all incoming signals. The input and output in this layer are as shown in "(5)":

$$I_{ij}^{(3)}=\sum_{j=1}^{n} wjOj^{(3)},\ O^{(4)}=I^{(4)} \qquad (5)$$

where wj is the weight associated the j-th node in layer 3 with the single node in layer 4 (output layer).

In Mamdani model, the antecedent parameters of Gaussian membership function are m_{ij} and σ_{ij} while the consequent parameters are the weights w_{ij}

In the backward pass, the error signal calculated as the difference between the actual output and the calculated output of the model is propagated backward and both the antecedent and consequent parameters are updated by applying the following formulas:

$$\left.\begin{aligned} m_{ij}(t+1)&=m_{ij}(t)-\eta\frac{\partial Ep}{\partial mij}\\ \sigma_{ij}(t+1)&=\sigma_{ij}(t)-\eta\frac{\partial Ep}{\partial \sigma ij}\\ w_j(t+1)&=wj(t)-\eta\frac{\partial Ep}{\partial wj}\end{aligned}\right\} \qquad (6)$$

where $\frac{\partial Ep}{\partial mij}$, $\frac{\partial Ep}{\partial \sigma ij}$ and $\frac{\partial Ep}{\partial wj}$ are computed by the following equations:

$$\left.\begin{aligned} \frac{\partial Ep}{\partial mij}&=\frac{\partial Ep}{\partial \mu ij}.\frac{\partial \mu ij}{\partial mij}=(y_{act}-y_{cal})wj\\ &\prod_{i=1,j\neq i}^{n}\mu ij.e^{-(xi-mij)/\sigma ij)^2}.2(xi-mij)/\sigma ij^2\end{aligned}\right\} \qquad (7)$$

$$\frac{\partial Ep}{\partial \sigma ij}=\frac{\partial Ep}{\partial \mu ij}\frac{\partial \mu ij}{\partial \sigma ij}=(y_{act}-y_{cal})$$

$$\text{wj}\prod_{i=1,j\neq i}^{n}\mu ij.e^{-(xi-mij)/\sigma ij)^2}.2(xi-mij)^2/\sigma ij^3$$

$$\frac{\partial Ep}{\partial \text{wj}}=\frac{\partial Ep}{\partial \text{yact}}\frac{\partial yact}{\partial \text{wj}}=(y_{act}\text{-}y_{cal})\prod_{i=1}^{n}\mu ij$$

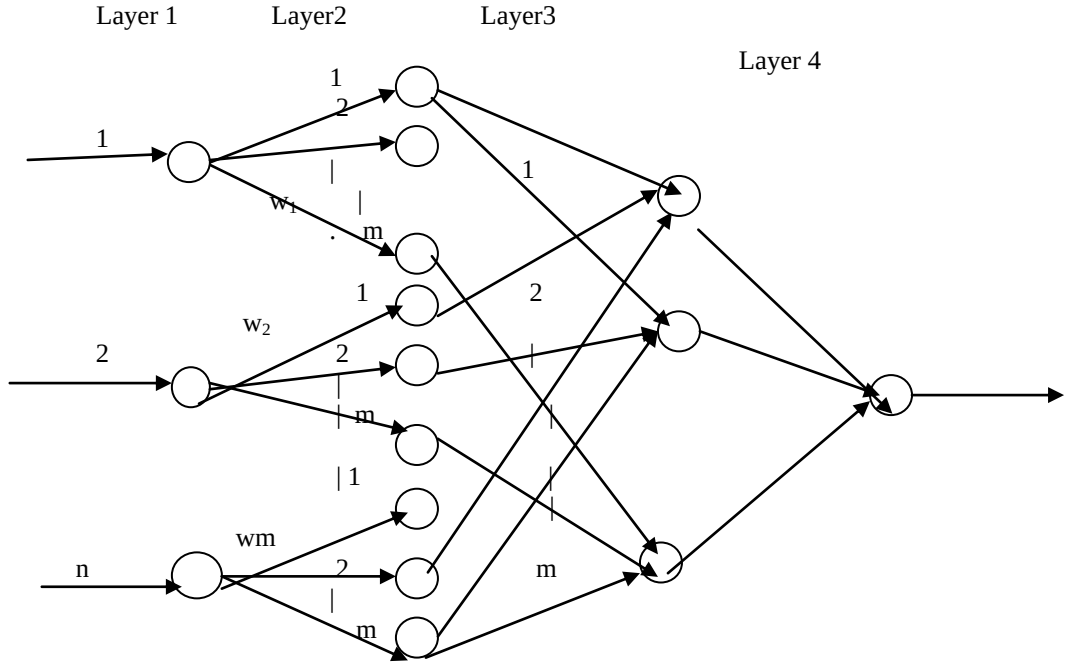

Fig.1. Structure of Mamdani Neuro-Fuzzy Network

III. SELECTION OF CASE STUDY MATERIALS

Data for the implementation of the models were obtained from Arts et al., 2015 and Dossiers of the OECD Working Party on Manufactured NMs. Sponsorship Program on the testing of NMs (OECD, 2015a,b,c,d;
The DF4nanoGrouping process permits NMs to be assigned to any of the four main groups, to sub-group active NMs and to determine and evaluate the required information for hazard and risk assessment [23].

- MG1: This group have soluble and non-biopersistent nanomaterials which depend on chemical structure for hazard assessment.
- MG2: This group has bio-persistent, High Aspect Ratio(HAR) nanomaterials which have shown certain level of rigidity and meets WHO conditions for respirable fibres.
- MG3: These are passive, bio-persistent, non-fibrous which are neither MG1 nor MG2 nanomaterials. They do not (i) show high surface reactivity; (ii) do not exhibit toxic effects (chemical composition do not possess active ingredients; no known cellular effects); and (iii) are immobile (agglomerates in biological fluids). From the In-vivo test, the passive nature of NMs is confirmed due to lack of elicit apical toxic effects.
- MG4: These are active bio-persistent, non-fibrous nanomaterials with harmful potential. Arts et al. (2015) proposed assigning NMs to MG4 by considering chemical composition, dissolution in biological media, surface reactivity, dispersibility, or cellular effects. In vivo, active NMs can exhibit apical toxic effects at a lower concentration.

IV. PREDICTION OF TOXICITY

In this paper, the measured properties are size, surface area, water solubility, solubility in biological media, Surface Reactivity, exposure time, Surface Charge, aspect ratio, concentration(Nanomaterial Class :-1(non-toxic material) ,1(toxic material)). In Computational Intelligent Nanomaterials Toxicity (CINT) software (developed by the author), classification of toxic nanomaterials is performed. The focus of this paper is to predict Cytotoxicity (EC_{50}) and classify species of nanomaterials as either toxic(active) or non toxic(Passive) materials.

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TABLE I
DF4NANO GROUPING CRITERIA

DF4nano grouping Tier	Grouping criterion	Threshold value for grouping	Main group (MG) assignment or indication
Tier1 Intrinsic material properties	Water solubility	>100 mg/L	MG1
	Particle size and shape	Aspect ratio>3:1,length>5 μm,diameter<3 μm	MG2
	Composition; including impurities	≥0.1% of component with GHS classification for systemic effects	MG4
Tier2 System-dependent properties In vitro effects	Dissolution in biological fluids	>100 mg/L	Globular NMs: >100 mg/L: Indication for MG1 Fibres: <100 mg/L: Indication for MG2
	Surface reactivity	≥10% of Mn_2O_3 reactivity, which is equal to: ≥0.19 mUFRAS/m^2*h	MG4
	Dispersibility	AAN <3 or diameter <100 nm	MG2 or MG4, as applicable
	Cellular effects	Effect at _10 mg/cm2	MG4
Tier3 In vivo screening	Toxic potency	STIS NOAEC; four ranges: I: <0.1 mg/m^3 II: <1 mg/m^3 III: <10 mg/m^3 IV: ≥10 mg/m^3	Ranges I-III: Confirmation of MG2 or MG4; subgrouping of MG4; Range IV: Confirmation of MG3
	Biopersistence	t_{50} < 40 days	Confirmation of MG1

Source: Josje H E Arts et al., 2015

TABLE II
TRAINING METAL OXIDES AND METAL SULPHATES NANOMATERIALS'SAMPLES

Listed species of a nanomaterial	Water solubility mg/L	Solubility in Biological media mg/L	Surface Reactivity μUFRAS/m^2.h	Surface Charge mv	Nanomaterial Size (nm)	Specific Surface area (m^2/g)	Exposure Time (day)	Aspect Ratio	Cytotoxicity (EC_{50}) mg/m^3	Class Label
CeO_2 A	9.0	9.0	0.0073	16.0	9.7	66.0	44.0	0.97	8.0	1
CeO_2 B	19.0	8.0	0.0324	42.0	40.0	27.0	44.0	4.0	7.9	1
CeO_2 C	18.0	7.255	0.0434	15.0	15.0	48.0	50.0	1.5	7.5	1
CeO_2 D	18.0	7.25	0.0424	16.0	10.0	61.0	44.0	1.0	7.6	1
CeO_2	19.5	8.018	0.0324	17.0	70.2	33.0	46.0	7.0	7.7	1
TiO_2 1	0.08	0.063	0.0244	-17.0	21.0	51.0	44.0	2.0	9.0	1
TiO_2 2	0.08	0.073	0.0245	-17.0	27.0	40.0	42.0	2.7	9.5	1
TiO_2 3	0.07	0.015	0.0243	-20.0	25.0	45.0	41.0	2.5	8.5	1
$BaSO_4$ NM220	6.0	0.675	0.0503	-39.0	32.0	41.4	30.0	3.2	10.6	-1
ZnO NM-110	0.0	98.0	0.078	20.0	70.0	12.0	35.0	7.0	15.0	-1
ZnO NM-111	0.0	99.0	0.0389	21.0	82.0	15.0	14.0	8.0	16.5	-1
CuO NM	18.0	120.0	2.205	28.0	10.0	47.0	20.0	4.0	17.0	-1

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TABLE III
TESTING METAL OXIDES AND METAL SULPHATES NANOMATERIALS'SAMPLES

Listed species of a nanomaterial	Water solubility mg/L	Solubility in Biological media mg/L	Surface Reactivity μUFRAS/ m^2.h	Surface Charge mv	Nanomaterial Size (nm)	Specific Surface area (m^2/g)	Exposure Time (day)	Aspect Ratio	Cytotoxicity (EC_{50}) mg/m^3	Class Label
CeO_2 A	9.0	9.0	0.0073	16.0	9.7	66.0	44.0	0.97	8.0	1
CeO_2 B	19.0	8.0	0.0324	42.0	40.0	27.0	44.0	4.0	7.9	1
CeO_2 C	18.0	7.255	0.0434	15.0	15.0	48.0	50.0	1.5	7.5	1
CeO_2 D	18.0	7.25	0.0424	16.0	10.0	61.0	44.0	1.0	7.6	1
CeO_2	19.5	8.018	0.0324	17.0	70.2	33.0	46.0	7.0	7.7	1
TiO_2 1	0.08	0.063	0.0244	-17.0	21.0	51.0	44.0	2.0	9.0	1
TiO_2 2	0.08	0.073	0.0245	-17.0	27.0	40.0	42.0	2.7	9.5	1
TiO_2 3	0.07	0.015	0.0243	-20.0	25.0	45.0	41.0	2.5	8.5	1
$BaSO_4$ NM220	6.0	0.675	0.0503	-39.0	32.0	41.4	30.0	3.2	10.6	-1
ZnO NM-110	0.0	98.0	0.078	20.0	70.0	12.0	35.0	7.0	15.0	-1
ZnO NM-111	0.0	99.0	0.0389	21.0	82.0	15.0	14.0	8.0	16.5	-1
CuO NM	18.0	120.0	2.205	28.0	10.0	47.0	20.0	4.0	17.0	-1
Fe2O3 Hematite	0.8	0.5	0.0372	-27.0	15	85.0	38.0	1.5.0	?	?

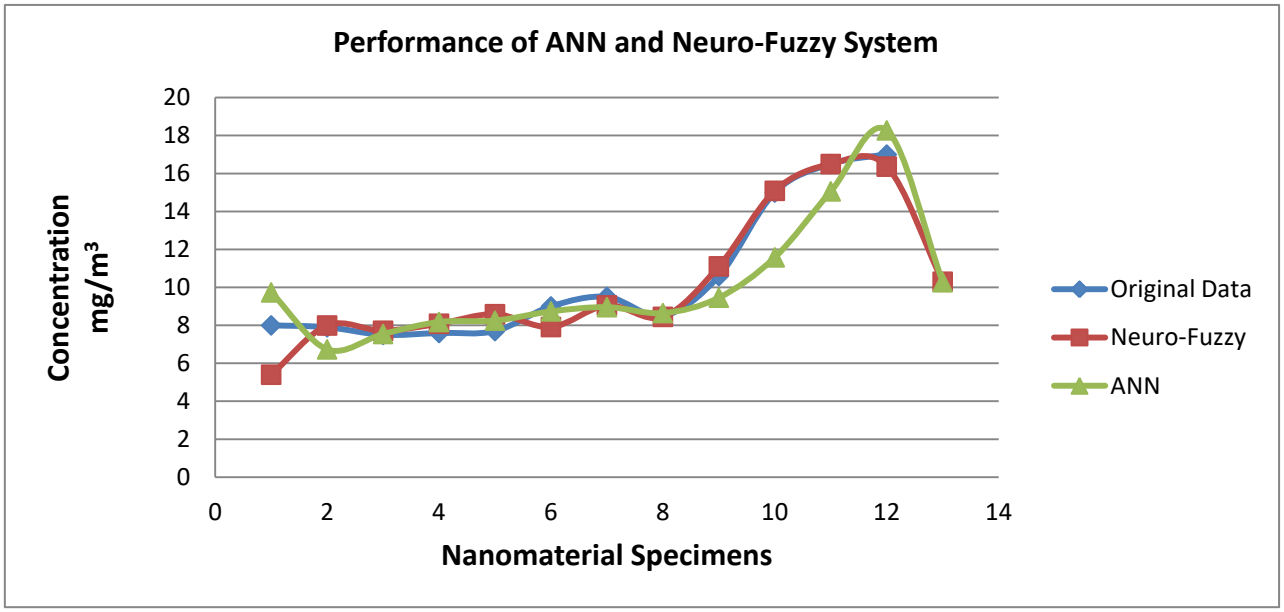

Fig. 2. Prediction of Cytotoxicity (EC_{50})

TABLE IV
PERFORMANCE OF ANN, AND NEURO- FUZZY MODELS

	RMSE	R^2	Predicted Cytotoxicity(EC_{50}) mg/m^3
ANN	1.837	0.9243	10.28
Neuro-Fuzzy System(Mamdani model)	0.824	0.969	10.30

V. RESULTS AND DISCUSSION

Considering the grouping criteria in Table I, for this case study (Metal oxides and metal sulphates), five materials (10nm CuO, ZnONM-110 and NM-111, $BaSO_4$ NM-220, 15nmFe_2O_3) are passive NMs while eight materials(CeO_2 NM-A, NM-B, C,D TiO_2 NM-1-3 are active(Toxic NMs).

The predicted toxicity(Cytotoxicity(EC_{50}) of 15nm Fe_2O_3 ≈10mg/m^3 using the training and testing datasets as shown in Tables II and III respectively

The toxic potency (STI NOAEC) according to tier 3 in Table I is ≥10mg/m^3. The performance of the two models, ANN and Neuro Fuzzy system are very competitive. For the testing phase, Neuro-Fuzzy has the lowest RMSE of 0.824 against standard ANN model as shown in the Table IV and also has R^2 96.9%. In essence, the results of the two models are highly competitive for the prediction of cytotoxicity value. The predicted curves of the two techniques show little deviation from the experimental curves. Fig 2 shows the value of predicted cytotoxicity curve by ANN and Neuro Fuzzy system models. This also confirms the classification of 15nmFe_2O_3 as passive (non-toxic) nanomaterial.

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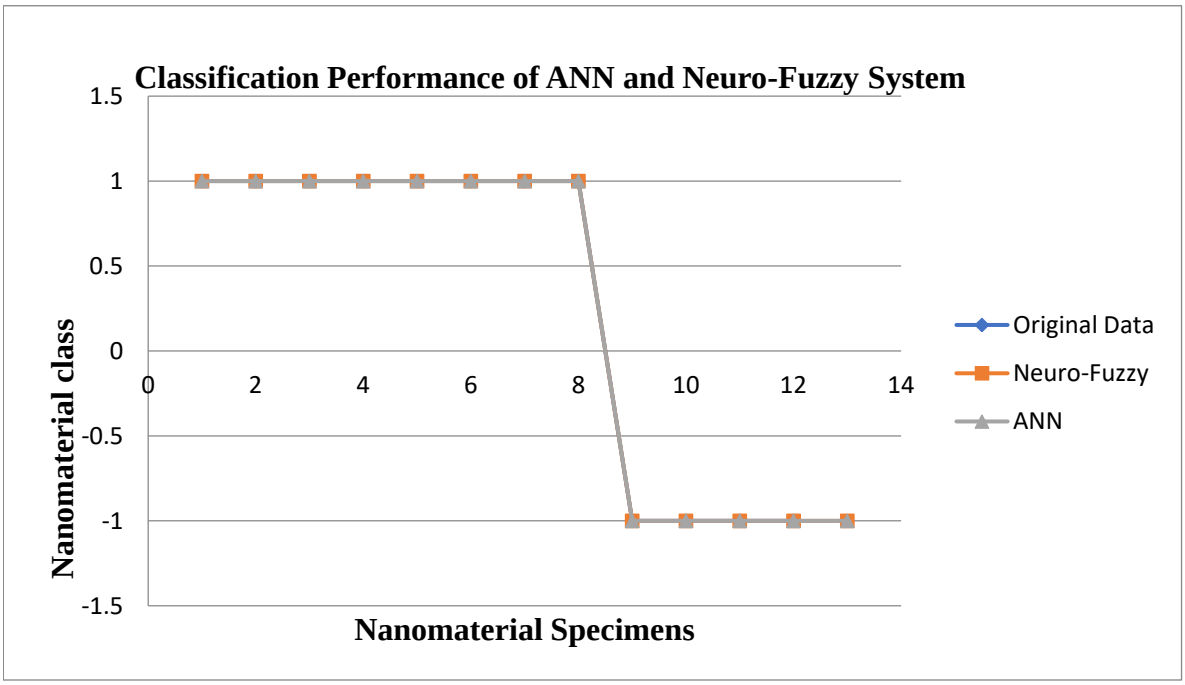

Fig. 3. Classification of Nanomaterial

VI. CONCLUSION

This study developed and compared the performance of ANN and Neuro-Fuzzy models to predict toxicity. The study and understanding of the ANN and Neuro-Fuzzy systems and their roles in regression and classification capabilities were achieved. These techniques were implemented using the Microsoft C# programming language to perform regression and classification task for the nanomaterial toxicity. The hybrid Neuro-Fuzzy systems therefore provided means of predicting the toxicity of nanomaterials. This also confirms the classification of $15nmFe_2O_3$ as passive (non-toxic) nanomaterial with no root mean square error, and the 100% correlation coefficient among other correlations for the data sets. . In view of the uncertainty surrounding the classification of nanomaterials and prediction of toxicity of nanomaterials, standard Fuzzy Logic(FL) and deep learning concept will be considered as part of the future work.

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