REVIEW PAPER

Applicable risk assessment methods in occupational and environmental exposure to nanoparticles - a narrative review

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ABSTRACT

Nanoparticles (NPs) are a heterogeneous group of materials that have various applications, and their risk assessment is an essential condition. This study aimed to review the applicable risk assessment methods in occupational and environmental exposures to NPs. A literature search for articles published since 2005 in Web of Knowledge, Scopus, PubMed, Science Direct, and Google Scholar, using appropriate keywords such as "Risk Assessment," "Nanoparticle," and "Nanomaterial," revealed 56 articles, which were screened by two researchers. A total of 15 articles were reviewed in full text. In total, 11 applied techniques for NP risk assessment were analyzed. Seven methods were quantitative, and four were qualitative. The quantitative methods were Integrated Probabilistic Risk Assessment (IPRA), Integrated Probabilistic Environmental Risk Assessment (IPERA), Quantitative Structure-Activity QSTR-Perturbation Model, Lung Dosimetry Modeling for Quantitative Risk Assessment (LDMQRA), Physiologically Based Pharmacokinetic Modeling (PBPK), Risk assessment based on toxicokinetic modeling, and Risk assessment of NPs with Spray Application. The qualitative methods were Application of Toxicogenomics for Risk Assessment, Luminous Microbial Array for Toxicity Risk Assessment (Lumi MARA), Control Banding Nano Tool (CBNT), and Stoffenmanager Nano Tool. It can be concluded that each of the studied methods evaluates an NP and is specifically used for that NP. A general risk assessment approach cannot be applied to all NPs but should be separately investigated by different processes.

Keywords: Risk Assessment, Nanoparticles Exposure, Exposure Methods, Review

Introduction

In recent years, the advancement of nanotechnology and its widespread use has increased considerably in various industries, and significant investments have been made around the world in this field.[1] Nanotechnology has created high economic growth and, as a result, new jobs. But despite the development of nanotechnology and their extraordinary advantages, the effects of natural or engineered nanoparticles in the environment and, in particular, the workplace has created a serious concern among biologists and health professionals.[2] It is predicted that about 2 million workers will be exposed to nanoparticles (NPs) in their work environments in the next 15 years.[1,3] Also, with the increase in the production and widespread use of NPs, the exposure potential of workers to these materials will increase.[1] The toxicity of NPs is due to their distinct physicochemical properties, including shape, small size, electrical charge, insolubility, mechanical strength, conductivity, and, especially, the specific surface area. These unique properties allow nanomaterials to interact with biological systems.[4] However, there are few studies on the toxic effects of NPs on different organisms. Also, there is not enough information about how they affect human health because many studies have only

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investigated short-term exposure to NPs. Despite the growing applications and widespread exposure to NPs in different fields, there is still no clear basis for determining occupational exposure limits. Also, different physicochemical properties of NPs than the other harmful substances and compounds, the lack of reliable methods of sampling and analysis by relevant organizations, lack of a proper exposure index agreed by the relevant international organizations, scanty toxicology data of NPs in order to determine the permitted occupational exposure limit, and the lack of enough data in relation to the toxicity of NPs are the problems faced regarding the risk assessment and determination of control levels of NPs.[5] So, given the unique properties of NPs, researchers and related organizations have developed strategies and standardized toxicity testing methods for risk assessment of NPs and investigating NP-induced effects.[6] Consequently, significant efforts have been made to develop novel methods for the risk assessment of NP toxicity. However, the main problem in risk assessment is the lack of sufficient information due to the existence of a bias that can lead to uncertainties in the characteristics of nanomaterials, effect and exposure assessment, and testing considerations.[7] As a result, the risk assessment capability in the accurate estimation of the risk level is decreased. These uncertainties can include lack of adequate knowledge of the physical structure of NPs and their toxicity, different mechanisms of the clearing organs (especially lung) for NPs compared with larger particles, lack of consensus views on exposure indices, lack of exposure information and the population at risk.[8] Therefore, one of the strategies to reduce uncertainties is the use of combined risk assessment methods.[9] Also, in the risk assessment of NPs, in addition to the physicochemical properties, attention to the amount and duration of exposure, toxicokinetic and toxicodynamic properties, and the ability of NPs to become aerosolized or airborne particles is essential.[8]

The risk assessment of NPs can integrate different data from different fields, with relative coverage of challenges in the field of uncertainty. Consequently, risk assessment can help to decide on prevention of disease and environmental risks of NPs.[10] Thus, the use of nanotechnology and insight into the risks of NPs is an essential condition for the safe use of nanotechnology. So, given the increasing use of nanomaterials and the lack of toxicological data relating to nanomaterials, attempt to quantify and identifying simple, quick, easy, and reliable risk assessment techniques are essential in the applications of and exposures to NPs, especially in people exposed to nanomaterials in the occupational environments. Also, because there are various methods described in various studies for various NPs, reviewing the applicable methods is a necessity. Hence, this study aimed to review the scientific literature about the applicable risk assessment methods in occupational and environmental exposures to NPs.

Materials and Methods

By reviewing the scientific literature, a narrative and critical analysis of the retrieved papers about the applicable risk assessment methods in exposure to NPs was performed. In this review, we have mainly focused on occupational and environmental studies, but a number of experimental studies are also mentioned.

Literature search

All the laboratory and experimental data since 2005 related to the risk assessment methods in exposure to NPs were examined. All the data from the scientific literature were obtained via the internet through the available databases which included ISI Web of Science (Institute for Scientific Information), Scopus, Medline (via PubMed), Science Direct, and Google Scholar. Also, the search was conducted using the following keywords in the text format in the title and abstract: “Risk Assessment,” “Nanoparticles,” “Toxicity Assessment,” and “Nanostructures.”

Inclusion Criteria for Study Selection

The inclusion criteria were studies of occupational and environmental exposure to

NPs. Also, the criteria for study selection included risk assessment in occupational and environmental exposure, risk assessment in in vivo and in vitro experimental studies, and original articles published in English and Persian journals. The articles focused on the exposure to and risk assessment of NPs. The studies that had presented applied techniques for risk assessment were also included.

Finally, only those studies that described a suitable technique for assessing the risk of occupational and environmental exposure to NPs were extracted and evaluated. Since 2005, a total of 56 papers have been published; 15 publications were selected for this review. These were environmental studies (N = 4), occupational studies (N = 3), in vivo and in vitro experimental studies (N = 7), and others (N = 1). Figure 1 is a PRISMA flow diagram of the study.

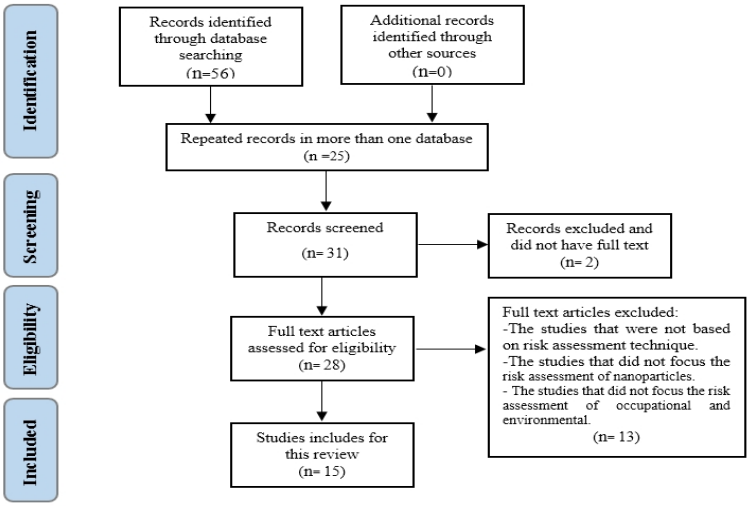


Fig. 1. Flow chart of the study identification and selection process

Results and Discussion

One of the main aspects of NP risk assessment is the knowledge about the properties of the NP being evaluated.[7] Depending on the source information used, the evaluation results may be different. In vivo experimental studies have shown that there is a relationship between the properties of NPs with the exposure probability and the biological effects of them.[11] For example, when the polarizability of the NP increases, their toxic effects decrease. Hence, depending on the type of NPs, different risk assessment approaches are required. The main concepts in risk assessment of NPs include the three main dimensions of the properties of NPs (solubility, isoelectric point, surface area, zeta potential, vanderwaals forces, and shape), exposure assessment (dose-response, kinetics, dynamics, half-time, route of entry, etc.), and risk identification (sarcoma, fibrosis, cancer, inflammation, and immunological response).[11,12] Risk assessment is done to predict the relationship between material characteristics and risk data.

Many different approaches have been developed to evaluate the risk of NPs. Despite this, there is no validated framework for risk assessment of NPs, and therefore, risk assessment for NPs should be done on a case-by-case basis. The risk assessment for NPs is done on the basis of both qualitative and quantitative methods. In the present study, 11 risk assessment methods of NPs that can be applied to occupational and environmental exposure were reviewed.[13]

According to the literature review, the papers outline, in each of the 10 studies reviewed depending on the type of NPs, a risk assessment technique. The results of the 10 methods reviewed have been explained.

Integrated Probabilistic Risk Assessment (IPRA)

The IPRA is a deterministic risk assessment

that is used to assess the risk of nanosilica particles. The risk assessment paradigm in the IPRA method consists of exposure assessment, hazard assessment, and risk characterization. Hazard assessment includes hazard characterization and hazard identification. Margin of exposure is the ratio of tolerable exposure to exposure. In this method, first, the quantification of variability and sources of uncertainty for the nanosilica should be described. Statistical distributions and bootstrap methods are used to quantify uncertainty and variability in the risk assessment (Fig. 2). The nanosilica intake by an individual in one day of exposure is expressed as the individual-day exposure (IDEXP), to quantify variability. Also, IEXP is individual long-term exposure, and BMD is benchmark dose. The IDEXP (μg/kg BW) is calculated using equations 1 and 2:

$$IDEXP=\sum_{k=1}^{P} CONS\times CONC_k \quad (1)$$

$$CONC_k=F\times C_k \quad (2)$$

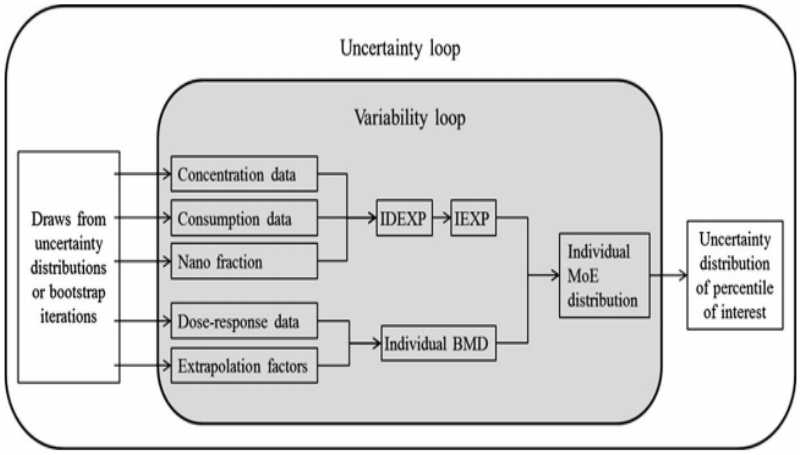


Fig. 2. A schematic diagram of uncertainty and variability loops in IPRA

The consumption of product k (in g/kg body weight) is CONSk; C_k is the concentration of nanosilica in product k (in mg/kg); F is an optional factor that is used to convert silica concentration to nanosilica concentration, and its value is 0.5. By calculating the IDEXP for each of the person-days, the IDEXP distribution is obtained that represents variability in individual human intake. Since the main purpose is to consider chronic toxicity, long-term exposure will be needed. As a result, the IDEXP must be converted into a distribution of individual long-term exposures (IEXP). Another factor is the individual benchmark dose (IBMD) that is expressed as Hazard. The IBMD is the dose at which an individual experiences a predefined response to a substance. Hazard is low if IBMD is high. Equation 3 is used for the IBMD calculation:

$$IBMD=\frac{BMD_{animal}}{EF_{chronic}\times EF_{inter}\times IEF_{intra}} \quad (3)$$

The dose-response modeling of data in an animal study is used to obtain IBMD animal. $EF_{chronic}$, EF_{inter}, and IEF_{intra} are the extrapolation factors for the subchronic-to-chronic extrapolation, interspecies conversion from the animal to human, and intraspecies variation and variability within the human population (deviation from the average human), respectively. The EF_{inter} is based on the test species used, the ratio of animal body weight to human body weight raised to the power 0.75 (Equation 4):

$$EF_{inter}=\frac{dose\ rate_{rat}}{dose\ rate_{human}}=\frac{dose_{rat}/bw_{rat}}{dose_{human}/bw_{human}}=\frac{dose_{rat}}{dose_{human}}\times\frac{bw_{human}}{bw_{rat}}$$
$$=\left(\frac{bw_{rat}}{bw_{human}}\right)^{0.75}\frac{bw_{human}}{bw_{rat}}=\left(\frac{bw_{human}}{bw_{rat}}\right)^{0.25}=\left(\frac{70}{0.25}\right)^{0.25}\approx 4 \quad (4)$$

Finally, for the risk characterization, the distribution of the individual margin of exposure (IMoE) is obtained by dividing IBMD into IEXP (Equation 5):

$$IMoE=\frac{IBMD}{IEXP} \quad (5)$$

If individual exposure is greater than the critical effect dose, a person is at risk. Hence,

when IMoE <1, the individual is at risk. In quantifying uncertainty in IPRA. Exposure and hazard are separately considered. According to Fig. 2, the outer loop is to account for the uncertainty. Generally, seven sources of uncertainty need to be considered: consumption data, concentration data, nanofraction, BMD, subchronic-chronic factor, interspecific factor, and intra-specific factor. The consumption data, concentration data, and nanofraction are needed for the exposure. Uncertainty samples in consumption and concentration data are measured using the bootstrap method in each base product. The uncertainty of the nanofraction (F) is measured by a statistical distribution. The nanofraction (F) can range from zero to one (100%). A logistic-normal distribution by 50th percentile (p50) is equal to 0.5 and by 95th percentile (p95) is equal to 0.8 and is used for modeling the uncertainty of the nanofraction (F). The values of F are fractions bounded by $0 < F < 1$. In the logistic-normal distribution, probability density function is according to Equation 6:

$$f(x)=\frac{1}{\sigma\sqrt{2\pi}}exp\left(-\frac{ln(\frac{x}{1-x})-\mu)^2}{2\sigma^2}\right)\times\frac{1}{x(1-x)} \quad (6)$$

Where,$0 < x < 1$, μ is mean, and σ is standard deviation.

The four factors of uncertainty including BMD_{animal}, $BMD_{chronic}$, EF_{inter}, and IEF_{intra} are considered for hazard. There are two main sources of uncertainty for the BMD_{animal}, model uncertainty and dose-response data. The log-normal distribution is used for quantifying the uncertainty in the EFchronic. The nominal EF_{inter} is calculated from the "quantifying variability in IPRA" section. The IEF_{intra} is both variability and uncertainty. Hence, the IEF_{intra} value is calculated using the X2-distribution statistical method. Finally, by plotting the value of uncertainty for each of these four factors, the IBMD is calculated. In the risk characterization, the IMoE is calculated using the uncertainty distributions of the IEXP and IBMD. Eventually, a simple representation of both the variability and uncertainty of IMoE can be presented in the form of a bar graph.[5]

Integrated Probabilistic Environmental Risk Assessment (IPERA)

The IPERA is a probabilistic modeling approach of combining exposure and effect that is used for risk assessment of nano-TiO_2. Due to the lack of knowledge and data on the environmental fate and toxicity of the engineered TiO_2 NPs, the IPERA approach is used to determine the combined exposure and modeling of their effects. The IPERA approach is like the IPRA method and uses Monte Carlo's two-dimensional design to determine the distribution of the uncertainty and variability, separately, in risk assessment. In this method, the variability and uncertainty modeling of environmental NPs is developed based on the concentration ratio (CR), the concentration of exposure to the concentration of critical effect. As shown in Fig. 3, determination of the quantity of variability and uncertainty in environmental exposure assessment (aquatic environments) is conducted using the multi-media fate model, SimpleBox4Nano (SB4N). This model predicts the concentration of NP exposure. By expanding the model and determining the quantity of variability, the predicted exposure concentration (ExpCs) is determined by a cumulative distribution function. This approach is a probabilistic modeling approach that has many input variables. The output of the algorithm of this model is a 200 × 100 matrix (depending on the aquatic environment) with exposure concentration in which each row represents the distribution of the exposure variability. Consequently, the matrix expresses a special drawing of the distribution of uncertainty. The probabilistic species sensitivity distribution (pSSD) model of Gottschalk and Nowack is used to quantify the variability and uncertainty in hazard assessment. For the SSD, chronic critical effect concentrations (CECs) should be determined.

$$CEC_{chronic}=\frac{CONC}{AF_{time}\times AF_{no\text{-}effect}} \quad (7)$$

The $CEC_{chronic}$ is the natural variation in CEC. CONC, AF_{time}, and $AF_{no\text{-}effect}$ are the limit concentration (derived from toxicological studies), the assessment factor to extrapolate from acute to chronic studies, and the assessment factor to extrapolate from the limit concentration to the critical effect concentration, respectively. Eventually, to determine the risk characteristics, the exposure and hazard assessment are integrated, and the CR is determined:

$$CR = \frac{ExpC}{CEC_{chronic}} \quad (8)$$

A CR value less than 1 indicates a safe situation, and the concentration of exposure is less than the chronic critical effects concentration of the species. A CR value greater than 1 indicates an unsafe situation. The unit at risk as a species in a region is obtained by combining the exposure unit and the effect model. Therefore, the variability distribution describes the diversity between random species in random regions. Finally, a simple representation of both the variability and uncertainty of CR can be presented in the form of a bar graph.[4]

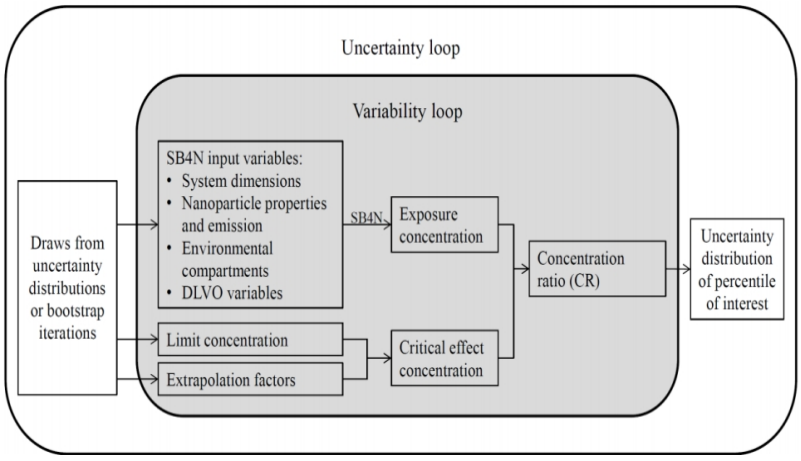


Fig. 3. A schematic diagram of uncertainty and variability loops in the two-dimensional Monte Carlo design used in IPERA

Luminous Microbial Array for Toxicity Risk Assessment (LumiMARA)

In LumiMARA approach, a multi-species microbial bioassay is used to evaluate the effects of engineered NPs of silver (AgNPs) in environmental pollutants. This method is used in the aquatic environment. Therefore, the overall trend for toxicity risk assessment of AgNPs is a potential of a luminous microbial array in a surface-coated test of NPs. First, four spherical AgNPs with an average particle size of 20 nm are produced from nanocomposix. The surface of the AgNPs should be coated with polyethylene (BPEI), citrates (CIT), polyethylene glycol (PEG), and tannic acid (tan). Based on the properties of zeta potential and salt stability, these materials are selected. The UV absorbance at 400 nm wavelength (UV-Vis spectroscopy) is used to measure the salt stability in the four nanoparticles. Also, a scanning electron microscopy is used to observe the combination of surface-charged AgNPs with bacteria. For bioluminescent bacteria exposed to silver NPs, the 50% effective concentration (EC50) was measured. The bioluminescent bacteria applicable for the toxicity risk assessment of NPs are shown in Table 1. In short, in this method, 20 mg/l of silver NPs are prepared and filtered through a 0.20-micron sterile syringe into a clean, sterile container. Also, 2% NaCl solution is added and dissolved with 20 mg/l silver NPs and tested with luminescent bacteria. The bioluminescent bacteria are kept for 1 hour at room temperature before regeneration with a reagent to create a balance. Then, 100 µl of osmotic solution is added to the bacteria (reagent) followed by incubation for 15 minutes at 28 ºC. Individual

bacteria are exposed to the target, i.e., silver NPs at concentrations of 0, 1.25, 2.5, 5, 10, and 20 mg/l for 15 minutes at 28 ºC, to evaluate the toxicity of silver NPs and prevent bacterial growth. After 15 minutes of maintenance in the incubator, they are read by a luminometer. The toxic effects of AgNPs on its bacteria are studied by reducing the light from the luminescent bacteria and observation of the changes in the bacterial growth. The changes include sticking AgNPs on the surface of the bacteria, penetrating AgNPs into the bacteria through the cell membrane, and releasing silver ions from AgNPs. It should be noted that the determination of toxicity screening can also be done by Microtox as a suitable tool for toxicity screening of contamination with only VIBRIO FISCHERI luminescent bacterium.[6]

Table 1. Eleven bioluminescent bacteria strains for LumiMARA

Number	LumiMARA
#1	Photobacterium leiognathi Marine bacteria
#2	Photobacterium phosphoreum
#3	Vibrio fischeri
#4	Photobacterium leiognathi
#5	Photobacterium phosphoreum
#6	Photobacterium phosphoreum
#7	Vibrio harveyi
#8	Vibrio harveyi
#9	Vibrio fischeri
#10	Photorhabdus luminescens (Freshwater bacteria)
#11	Photorhabdus asymbiotica

Quantitative Structure-Activity/Toxicity Relationships Modeling (QSAR/QSTR)

The Novel QSTR-Perturbation Model is a computational tool for NP risk assessment that is used to predict the ecotoxicity and cytotoxicity of NPs coated and uncoated simultaneously under multiple laboratory conditions. The main objective of this modeling is to predict the toxicity of NPs against only one biological target regarding only one type of toxicity test. The model can be designed for 36488 NPs (NP-NPs) with an accuracy greater than 98% in both training and testing. In this method, the evaluation of NP toxicity is conducted by considering six characteristics: toxic effects (m_e), biological targets (b_t), possible shape labels (n_s), size of NPs (d_m), different coating agents (s_c), and assay times (t_a). The t_a is the duration of exposure of biological targets with NPs. The b_t are algae, bacteria, cell lines, crustaceans, plants, fish, and others. The s_c is the different organic molecules. They are considered as an external factor. The combination of the five factors m_e, b_t, n_s, d_m, and t_a represents an experimental condition TEi (cj). For each nanoparticle examined, four different characteristics, including molar volume (V), electronegativity (E), polarity (P), and NP size (L), are considered. The first three properties are the physical properties of the periodic table. Each of the NPs studied is assigned two "positive" and "negative" groups, which indicate the type of toxic effect of the NP in the defined experimental conditions. The toxic effects of the NPs are determined by the experimental conditions. Therefore, if the experimental conditions show high values of toxicity, then it is non-toxic [TEi (C_j) = 1]; otherwise, the composition is toxic [TEi (C_j) = −1]. The equation of QSAR-perturbation model is expressed as follows:

$$TE_i(c_i)_{nw} = a_0 \times TE_i(c_i)_{rf} + \sum b_j \times \Delta\Delta D(c_j) + \sum d_j \times \Delta G\mu_k(PP) + e_0 \quad (9)$$

$$\Delta G\mu_k(PP) = G\mu_k(PP)_{nw} - G\mu_k(PP)_{rf}$$

$$\Delta\Delta D(c_j) = \Delta D_i(c_j)_{nw} - \Delta D_i(c_j)_{rf}$$

$TE_i\ (c_j)_{nw}$ is the new experimental condition that illustrates the toxic effect of an NP in the new state. $TE_i\ (c_j)_{rf}$ is the toxic effect of the NP in the reference state. a_0, b_j, and d_j are the coefficients that can be determined by classification or regression techniques such as linear discriminant analysis or multiple linear regression. $\Delta\Delta D(c_j)$ are the perturbation conditions which indicate differences in the physicochemical properties between the two particles. The $\Delta G\mu_k(PP)$ indicates the differences between the chemical structures of the coating agents in the new and reference state. The chemical structure of each coating agent used for NPs is determined by the following equation:

$\mu_k(PP)$ is the time spectrum of the order k of the matrix bands. The software MODELSLAB is used for calculating μ_k (PP). The NMU is the number of monomer units. For example, the NMU of an organic molecule is equal to 1. The main steps in developing the QSAR-perturbation model are shown in Fig. 4.[14]

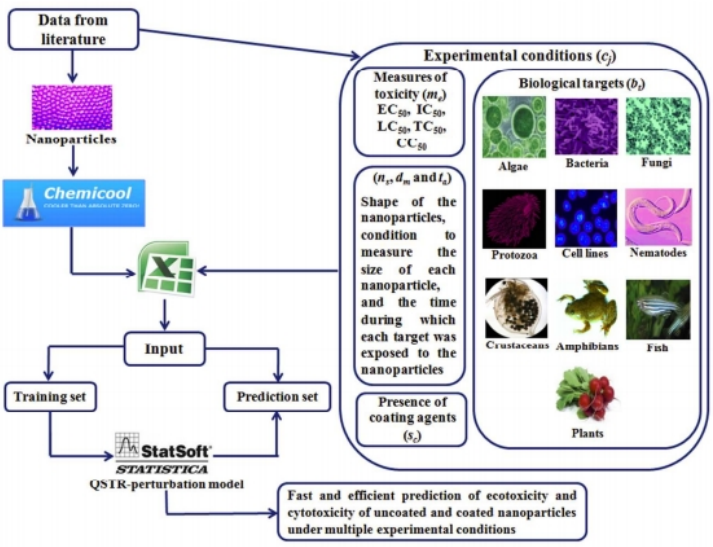


Fig. 4. The main steps in developing the QSAR-perturbation model

Lung Dosimetry Modeling for Quantitative Risk Assessment (LDMQRA)

The LDMQRA is a mechanistic risk assessment method. It has a biological basis for extrapolating of dose data from animal to human and is an approach using the rat-based estimates. This approach is a reasonable approach for quantitative risk assessment in airborne exposure to nanomaterials of TiO_2, carbon black (CB), or diesel exhaust particulate (DEP). Thus, in this method, the surface area of the lung, the animal dose-response data, data related to chronic inhalation, and the average concentration of particles in the air is needed. Consequently, the risk of lung cancer on exposure to nanoparticles of TiO_2, CB, and DEP is estimated. The steps of the LDMQRA method are as follows: A) Select the animal model, and determine the dose metric and disease response. The animal is often a rat. The dose metric is determined by the surface area dose of residual particles in the rat lung, the retained mass lung dose, and the average concentration of airborne exposure. The response is also the evaluation of lung cancer. B) Analyze the dose-response relationships to estimate a critical dose. A critical lung dose (benchmark dose) is defined as the estimated retained dose associated with an increased risk of infection. A multi-stage statistical dose-response model is used to estimate the critical doses or the BMD. C) BMD extrapolation from animals to humans by modifying the species differences in surface area or mass area of the lung. (D) Determine the external exposure of humans (e.g., the concentration of the working lifetime average exposure), which is equivalent to the animal's benchmark dose. The inhalation rate, species differences, lung mass, airborne exposure concentrations, and exposure conditions are used to account for the BMD. The BMD based on the remaining lung dose is used in the human lung dosimetry model to estimate the working lifetime exposure concentration. The rat mean airborne mass concentration is used for the extrapolation of rat airborne exposure BMD to humans. The extraction is done using allometric relationships as follows:

$$\text{BMD human}=[\text{BMD (rat)}(\text{mg/m}^3)\times \text{air inhaled (rat)}(\text{m}^3/\text{d})\times \text{hours exposed (rat)}(6/24)\times \text{days exposed (rat:human)}(260/240)\times \text{(allometric factor)}]/(\text{air inhaled in 8-h workday (human)}\left(\frac{\text{m}^3}{\text{day}}\right) \quad (10)$$

The total lung mass or lung alveolar epithelial surface area (SA) is the "allometric factor."

Lung mass = lung mass (human)/lung mass (rat)

Lung SA = lung SA (human)/lung SA (rat)

Air inhaled (rat) is 0.36 m^3/day; air inhaled in an 8-h workday (human), 9.6 m^3; lung mass (human), 1000 g; lung mass (rat), 2 g; alveolar epithelial SA (human), 143 m^2; and alveolar epithelial SA (rat), 0.48 m^2. Finally, for

extrapolation of the rat lung BMD to humans, it is necessary to estimate the mass concentration of airborne NPs for humans; the SA of the NP dose is converted into a mass dose. The Multiple-Path Particle Deposition Model and survival model are used to estimate the human equivalent airborne mass concentration as the retained lung mass.[12]

Application of Toxicogenomics for Risk Assessment

In this method, toxicogenomic data is used to quantitative risk assessment of lung fibrosis caused by multi-wall carbon nanotubes (MWCNT). In other words, this approach predicts the fibrogenic potency and hazard ranking of different MWCNTs. The potential hazards of MWCNTs can be identified through transcriptomics data of gene in the exposed organs. Therefore, the gene changes and gene expression profiles from the lungs of animals exposed to three individual MWCNTs is used to identify the key biological events in the relationship between MWCNT exposure and lung fibrosis. The lung fibrosis is caused through the framework of an Adverse Outcome Pathway (AOP). In the AOP, there is a significantly perturbed pathway that is categorized along the key events. The BMD should be calculated for each perturbed pathway. A $BMD_{express}$ version 1.4.1 is used for the BMD modeling. The calculated BMD is used to derive transcriptional BMDs for each MWCNT. Gene expression profiles allow simultaneous analysis of changes in the expression of all genes in the tissue or cell type following exposure to the MWCNT NPs. The dose-response and time-series data are required for AOP and human health risk assessment. In the next step, all lung transcription responses to different doses of MWCNT should be considered at post-exposure time points. Toxicogenomics approach emphasizes on the functional pathway analysis and calculation of transcriptional BMDs. Ingenuity Pathway Analysis is used for classifying genes that are significantly affected by exposure to MWCNT. Conventional paths consisting of at least five distinct and significant expressions and displaying the exact Fisher value of $P \leq 0.05$ are considered for further calculations of the paths of BMD values for dependent AOP approaches. Rigorous statistical methods and computational algorithms (ANOVA $P \leq 0.05$ for at least one dose) are used to calculate the transcriptional BMDs. Hill, Power, Linear, and Polynomial are the dose-response models that are used to assess the best fit. Finally, deriving pathway-based points of departure (PODs) is selected based on the AOP relevant pathway or most sensitive or median pathway.[15]

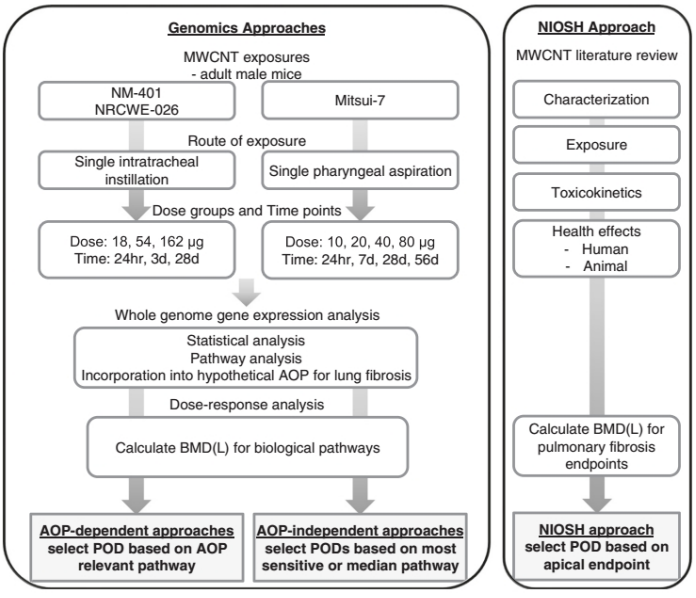


Fig. 5. Genomics approach compared with NIOSH approach for risk assessment of MWCNT

According to extensive review of NIOSH, the health effects of occupational exposures to MWCNT is endpoints reflective of lung fibrosis. The apical endpoint data of lung fibrosis are alveolar connective tissue thickening, alveolar septal thickening, and granulomatous inflammation data fibrosis related apical endpoint. So, NIOSH derive BMDs of MWCNTs using fibrosis related apical endpoint data for pulmonary fibrosis endpoints. The apical endpoint data is used to select the deriving pathway-based PODs. The NIOSH method is a traditional approach. Genomics approach compared with the NIOSH approach for risk assessment of MWCNT is shown in Fig. 5.

Physiologically Based Pharmacokinetic Modeling (PBPK)

This model is used to assess the risk and determine the biodistribution of TiO_2 NPs in the dietary constituents (e.g., foods, beverages, dietary supplements, and drugs). This model is used for NPs with a size of 15 to 150 nm. This model aims to study the absorption, distribution, metabolism, and excretion describing (ADME) of chemicals in a living organism using a differential equation system. The PBPK model is a multi-compartment model. The order of each compartment is parts of the organism, such as a single organ and tissue (e.g., liver) or a group of them. However, the compartment includes the intracellular space of the perfused tissues and organs. Hence, The PBPK determines the ADME of chemical substances and the relationship between the external and internal exposure of different organs/tissues. To this end, the PBPK models the biodistribution of NPs in organs/tissues in the in vivo studies. The kinetic processes are used simultaneously for describing the biodistribution of NPs. The processes considered in this modeling include the ability of NPs to cross the capillary wall and their phagocytosis in the mononuclear phagocyte system (MPS). Exposure assessment is also based on the dietary intake of NPs in a population with different age categories. The Monte Carlo method is used to estimate the nano-TiO_2 intake in any age group, using the normal distribution of Bernoulli. The schematic diagram of the PBPK model for TiO_2 NPs is shown in Fig. 6. The dotted lines represent the symbol of the translocation of NPs through the various biological barriers. Clearance compartments and direct excretion show NPs that deposit in the organs and those that are not absorbed in the intestines after oral uptake.

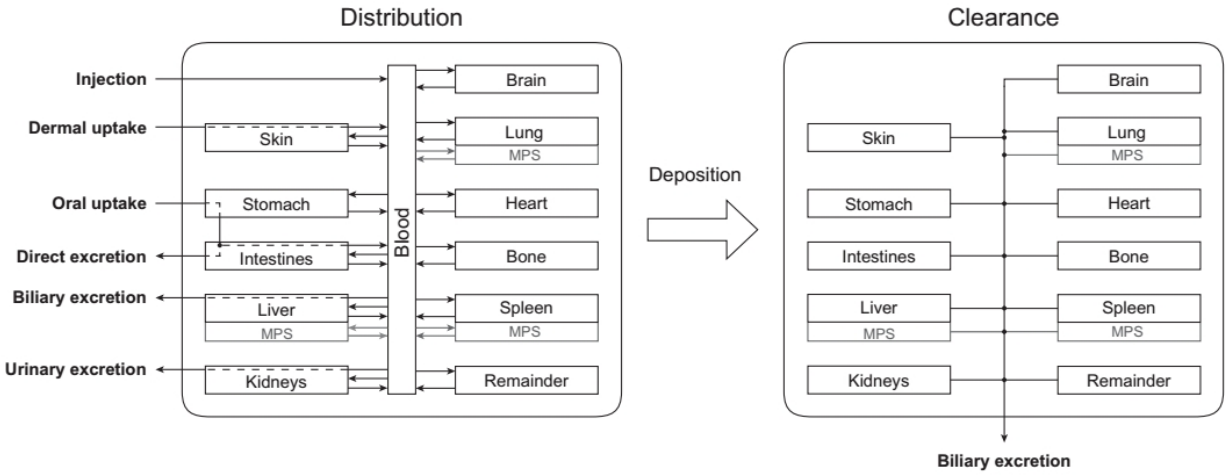


Fig. 6. Schematic diagram of the PBPK model for TiO_2 nanoparticles includes distribution, clearance, and excretion

A membrane-limited model is used for the transportation rate ($K_{trans\_blood\_organ}(min^{-1})$) of NPs from blood to different tissue and their urinary and biliary excretion. The following equation for the calculation of the transportation rate is used:

$$K_{trans\_blood\_organ}=b_{trans\_constant\_organ}\times\frac{Q_{organ\_blood}}{V_{blood}} \quad (12)$$

$b_{trans\_constant\_organ}$ is the permeability of the capillary wall. $b_{trans\_constant\_organ}$ is the NPs transportation constants of the organs. Q_{organ_blood} represents the blood flow through the organ (l/min). V_{blood} is the body blood volume (l).

In the MPS, the particle size is significant for the uptake of NPs, but it is not in the transcapillary pathway. Hence, in the MPS transportation constants of NP, its dose and size are important. In total, determination of the intestinal absorption of NPs of different sizes and concentrations in vitro, determination of the interspecies and intraspecies differences in permeability of NPs; determination of toxicokinetics of NPs, and examination of the NP disposition can help to increase the reliability of the PBPK model further. The predictability of the PBPK model is examined by developing an exposure scenario in in vivo experiments and comparing the simulated results with the evaluated organ levels experimentally.[16]

Risk Assessment based on Control Banding (RACB)

The RACB is a qualitative risk assessment method for nano-TiO_2. In this method, the risk assessment is based on the hazard severity determination with regard to the properties of NPs and the exposure probability determination according to the nature of the work (tasks, operations). The general principles of this approach are provided by the NIOSH based the occupational exposure to NPs. Flowchart of the RACB risk assessment methodology and the hazard severity and exposure probability factors are presented in Fig. 7 and Table 2. The data on hazard severity include hazard of parent material (30 points) and nanomaterial hazard (70 points). The scales of hazard severity are determined in four levels: low (0–25), medium (26–50), high (51–75), and very high (76–100). Also, the scales of exposure probability factors are determined in four levels: extremely unlikely (0–25), less likely (26–50), likely (51–75), and probable (76–100); these are presented in Table 3. The points of all factors should be summed to obtain the score of hazard severity and exposure probability band separately. Risk assessment is done using 4 × 4 scales combination of the hazard severity and exposure probability and called a risk matrix (see Fig. 8-a).

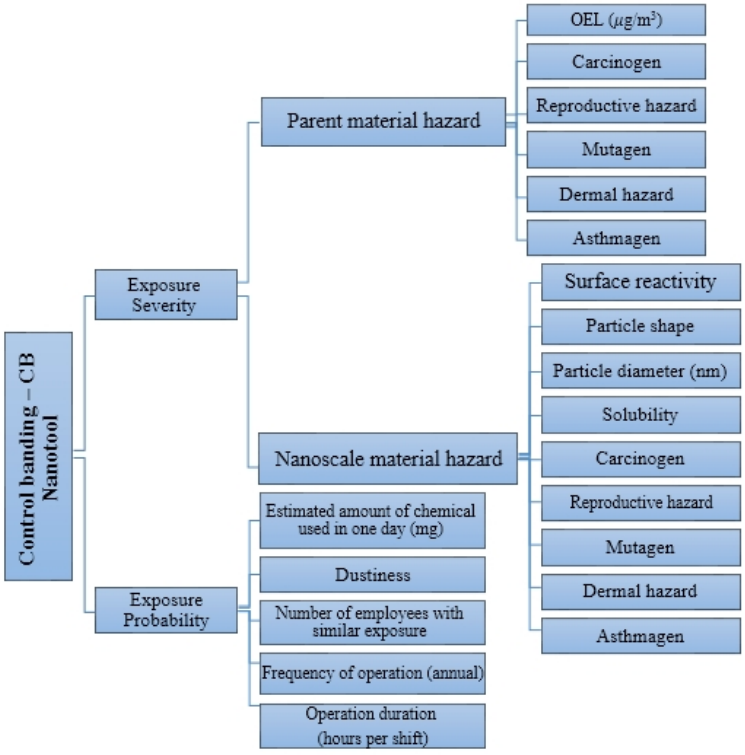


Fig. 7. Flowchart of the Control Banding risk assessment methodology and the hazard severity and exposure probability factors

Table 2. Hazard severity factors of Control Banding Nanotool

Material form	Factor	Characteristics Points assigned			
Parent material hazard	OEL ($\mu g/m^3$)	< 10	10-100	101-1000	> 1000
		10	5	2.5	0
	Carcinogen?	Yes	No	Unknown	
		4	0	3	
	Reproductive hazard?	Yes	No	Unknown	
		4	0	3	
	Mutagen?	Yes	No	Unknown	
		4	0	3	
	Dermal hazard?	Yes	No	Unknown	
		4	0	3	
	Asthmagen?	Yes	No	Unknown	
		4	0	3	
Nanoscale material hazard	Surface reactivity	High	Medium	Low	Unknown
		10	5	0	7.5
	Particle shape	Tubular or fibrous	Anisotropic	Compact or spherical	Unknown
		10	5	0	7.5
	Particle diameter (nm)	1–10 nm	11–40 nm	>40 nm	Unknown
		10	5	0	7.5
	Solubility	Insoluble	Soluble	Unknown	
		10	5	7.5	
	Carcinogen?	Yes	No	Unknown	
		6	0	4.5	
	Reproductive hazard?	Yes	No	Unknown	
		6	0	4.5	
	Mutagen?	Yes	No	Unknown	
		6	0	4.5	
	Dermal hazard?	Yes	No	Unknown	
		6	0	4.5	
	Asthmagen?	Yes	No	Unknown	

Table 3. Exposure probability factors of Control Banding Nanotool

Exposure Factor	Characteristics Points assigned				
Estimated amount of chemical used in one day (mg)	>100	11-100	0-10	Unknown	
	25	12.5	6.25	18.75	
Dustiness	High	Medium	Low	Unknown	
	30	15	7.5	22.5	
Number of employees with similar exposure	>15	11-15	6-10	1-5	Unknown
	15	10	5	0	11.15
Frequency of operation (annual)	Daily	Weekly	Monthly	>Monthly	Unknown
	15	10	5	0	11.15
Operation duration (hours per shift)	>4	1-4	30-60min	<30 min	Unknown
	15	10	5	0	11.15

Finally, the risk is controlled in four levels which include general ventilation (RL1), fume hoods or local exhaust ventilation (RL2), containment (RL3), and seek specialist advice (RL4). The Control Banding tool is accessible at http://controlbanding.net/Services.html. to carry out online risk assessment.[1,7,13]

Risk Assessment based on Stoffenmanager Nanotool

Another qualitative risk assessment nanotool is Stoffenmanager that is a web-based tool. The Stoffenmanager Nano is applicable for operations with manufactured nano-objects and was developed for risk assessment of dangerous substances. In this method, risk assessment consists of the combination of a hazard and exposure band. The hazard band (five levels from A to E) is determined according to the following characteristics: particle size, water solubility, persistent fibers or other structure, toxicological classification, and other information. The hazard band has five levels, from the lowest A to the highest E. The exposure band is based on a conceptual model consisting of the following criteria: time and frequency of

task, emission potential from the source (e.g., substance emission potential), transmission compartment (localized control, segregation, dilution/dispersion, separation, surface contamination), receiver (e.g.,., individual protection equipment). The exposure band is at four levels from 1 (lowest) to 4 (highest). The risk is assigned using a 5 × 4 matrix by combining the hazard and exposure bands. Finally, a three-level risk or priority classification is obtained (see Fig. 8-b). In general, the Stoffenmanager Nano seems to indicate a higher risk level compared with Control Banding Nanotool. The online tool, Stoffenmanager Nano 1.0, is available at http://nano.stoffenmanager.nl/.[7]

Probability \ Severity	Extremely Unlikely (0-25)	Less likely (26-50)	Likely (51-75)	Probable (76-100)
Very high (76-100)	RL3	RL3	RL4	RL4
High (51-75)	RL2	RL2	RL3	RL4
Medium (26-50)	RL1	RL1	RL2	RL3
Low (0-25)	RL1	RL1	RL1	RL2

a

Exposure \ Hazard	A	B	C	D	E
1	3	3	3	2	1
2	3	3	2	2	1
3	3	2	2	1	1
4	2	1	1	1	1

b

Fig. 8. Control Banding Nanotool matrix (a) and Stoffenmanager Nano matrix (b)

Risk assessment using toxicokinetic modeling (internal exposure to target organs such as the liver)

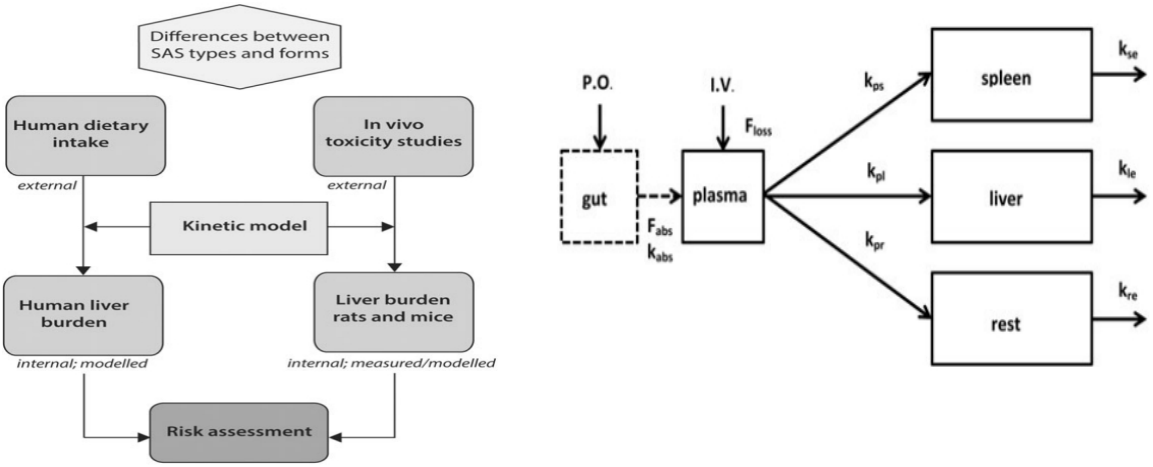
The kinetic modeling is based on the data from Cubadda et al. This approach assesses human health risk on oral ingestion of NPs such as silicon and TiO_2. Thus, the daily consumption of NPs should be considered. The main elements of risk assessment in this methodology are hazard assessment, exposure assessment, and kinetic modeling. Risk assessment is conducted using two different approaches. First, dietary intake, exposure assessment, external doses, and in vivo toxicity data of NPs is estimated. To that end, food or drugs products should be selected, and the total concentration of silica or titanium is determined in products with inductively coupled plasma atomic emission spectroscopy (ICP-AES). Then, dietary intake is estimated in the general population. The hazard assessment of NPs is based on key in vivo toxicity studies. Also, the toxicity data of NPs are determined by physicochemical properties, toxicology, ecotoxicology, environmental, and research publications. In the next step, the external dose levels are used to estimate the internal concentration levels for both human intake and toxicity studies. Subsequently, the risk is evaluated on internal exposure and concentrations of NPs in internal organs (e.g., liver). Hence, the toxicokinetic modeling is used for risk assessment of internal concentration and accumulation of NPs over time. Two routes, oral and IV, are used for kinetic modeling. After oral exposure, the organs studied are liver, spleen, gastrointestinal tract, and mesenteric lymph nodes. After IV exposure, the organs studied are liver, spleen, lungs, heart, brain, kidneys, and testis/ovaries. Therefore, differences in the physicochemical properties of NPs influence the gastrointestinal absorption, kinetic behavior, and toxicity. The absorption and NP concentration in blood, tissues, and organs after oral and IV exposure is collected at different time points for the kinetic modeling. Finally, a kinetic model is developed to estimate the NP concentration in the organs after chronic exposure to NPs. The NP concentrations in organs are calculated using the kinetic constants of the particle type. The NP concentration in human organs is analyzed, and adverse effects will be found. The risk assessment process of kinetic modeling is represented in figure 9-a. The toxicokinetic assessment and kinetic model is illustrated in part 2. Then, the relative distribution of NPs in target organs, such as liver, spleen, and gonads, is determined considering the organs as separate compartments. The scheme of the relative contribution of uptake in liver, spleen, and rest of the compartment of the kinetic model for NPs is represented in Fig. 9-b.

The organ concentrations in the animal studies versus the organ concentrations in humans, estimated from their consumption, is compared and internal doses are estimated (part 4). The internal doses are compared and evaluated for risk assessment.[17-19]

Finally, the following allometric equation is used for the extrapolation of the kinetic model of rat or mouse to humans.

$$K_{\text{other species}} = \left(\frac{W_{rat}}{W_{\text{other species}}}\right)^{1/4} K_{rat} \quad (13)$$

Where W_{rat} is the weight (kg) of rat, and $W_{\text{other species}}$ is the weight (kg) of human or mouse.



a b

Fig. 9. Scheme of the risk assessment process for kinetic modeling and its elements (a), the kinetic model scheme (b)

Risk Assessment of NPs with Spray Application

This method is used to assess the risk of NPs whose application forms are spray. During production and use, NPs of synthetic amorphous silicon dioxide (SAS) in a glass cleaner are used with a spray application. Thus, a central element of this methodology is the physicochemical characterization of the substance. Data sources of substance including comprehensive literature review are used for the assessment of the toxicological and ecological characteristics. Risk assessment in this method includes exposure and hazard assessment. Exposure assessment includes the human and environmental process. Human exposure assessment is during the production process and the application by consumers during the cleaning event, and environmental assessment is during the general consumption. Exposure information to NPs in the production and consumption process depends on the physicochemical properties of the NPs and the rate of the production process. Therefore, the particle size distribution of the NPs should be determined. In the consumption process also, the conditions, frequency, duration, and route of exposure to NPs via the inhalational, dermal, or oral route are very important. In human exposure, the main route of exposure is inhalation. Consumer exposure and environmental exposure can be modeled. The software ConsExpo 4.1 is used for modeling of consumer exposure, and the software EUSES 2.1 is used for modeling of environmental exposure. The software output will estimate the amount of inhaled NPs. Hazard assessment includes human and environmental hazard assessment, and the hazards of the NPs are identified during the production and consumer use phases. The available sources for hazard identification of NPs include the toxicological data from comprehensive literature review and kinetic data (including adsorption, deposition, and elimination processes) by in vivo experiments; investigations of acute and chronic toxicity of the substance; cytotoxicity, skin sensitization, genotoxicity, and carcinogenicity of NPs; and investigations of the specific properties of NPs. Ultimately, on the basis of the exposure conditions and taking

into account the toxicity of NPs (identified hazard), the risk is determined at low, medium, and high level.[20] An overview of the methodological approach and the structure blocks of this risk assessment method is shown in Fig. 10.

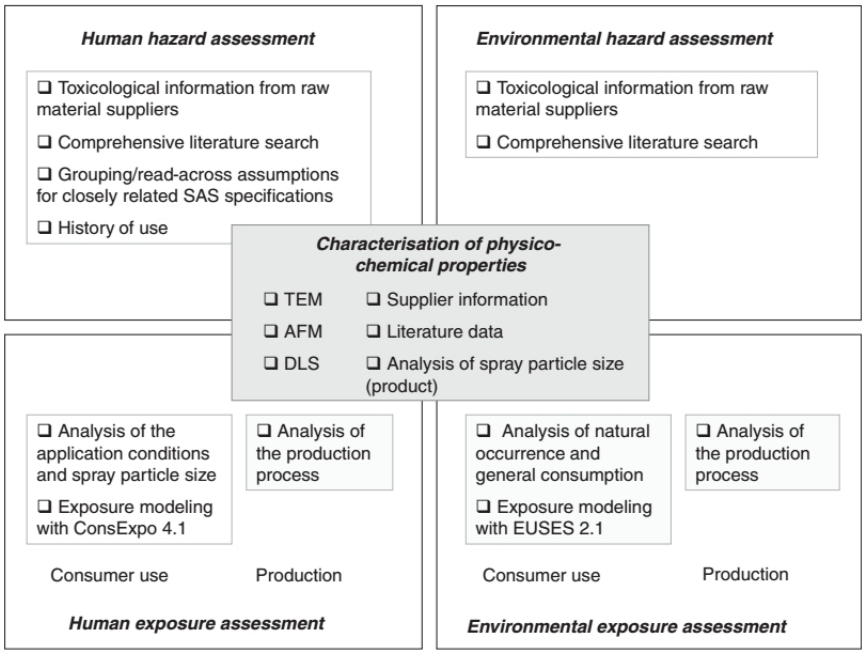


Fig. 10. A conceptual model of methodology and structural blocks in evaluating the risk of sprayed silicon nanoparticles

The risk assessment techniques described in accordance with their application characteristics and the type of NPs are summarized in Table 4.

According to the present study, four methods of CBNT, Stoffenmanager Nano, PBPK, IPERA, and lung dosimetry modeling, were used to evaluate the risk of nano-TiO_2. There are three methods to assess the risk of SAS that include IPRA, kinetic modeling, and risk assessment of artificial silicon dioxide nanoparticles in the formulation of glass cleaner. Since the NPs are a heterogeneous group of substances and also their applications are varied, it can be concluded that an approach may not necessarily apply to all NPs. The methodology of IPRA and IPERA can quantify the uncertainty and variability separately. This is important because of the uncertainty in the variation existing due to the lack of information. The CBNT and Stoffenmanager Nano approaches provide a framework for managing occupational risk against "uncertainty" that combine various parameters of NPs (shape, size, and SA) with exposure levels (consumption) and provides an appropriate control approach based on the level of risk obtained.

Kinetic modeling approaches analyze the behavior and toxicity of NPs in the body based on the physiological application. Therefore, the approaches consider oral absorption processes, distribution from blood to various organs, especially the liver, and excretion through bile and urine.[19] The most important ability of the kinetic models is the assessment of the ability of the NPs to pass through a cell membrane. The lung dosimetry model also estimates the risk of lung cancer associated with both the average particle mass concentration in the air and the dose remaining in the lung (as SA or particle mass) using chronic inhalation data on exposure to TiO_2, CB, and diesel exhaust NPs. The QSTR-perturbation model is a powerful predictive tool for assessing the ecotoxicity and cytotoxicity of different NPs. This approach provides an important insight into several key characteristics of NPs to understand their biological behavior.[8] Toxicogenomics-based

methods assess the risk of toxicity using gene expression profile in exposure to NPs and, as a result, predict the incidence of lung fibrosis potentially in in vivo studies. One of the biological evaluation methods is the use of bioluminescent bacteria to assess the acute toxicity of silver NPs, and their benefits include simplicity, speed, low cost, repeatability, and the ability to perform in laboratory environments. The risk assessment of nanosilica in a glass cleaner formulation is a special method for compounds that can be in a spray form and based on hazard and exposure assessment.

Table 4. Summary of risk assessment methods based on the type of NPs and evaluation approach

ID	Athure, year	Risk Assessment Method	Assessment approach	Assessment type	Nanoparticle	Studied properties of nanoparticles	Exposure
1	Jacobs et.al 2015	Integrated Probabilistic Risk Assessment (IPRA)	Monte Carlo model based on variability and uncertainty	Quantitative	Nano silica	Size and concentration	Oral
2	Jacobs et.al 2016	Integrated Probabilistic Environmental Risk Assessment (IPERA)	Monte Carlo model based on variability and uncertainty	Quantitative	Engineering Titanium Dioxide (TiO_2)	Size and concentration	Oral
3	Jung et.al 2015	Luminous Microbial Array for Toxicity Risk Assessment (Lumi MARA)	Based on the bioluminescent bacteria	Qualitative	Silver nanoparticles	Surface Area	Dermal
4	Kleandrova et.al 2014	Quantitative Structure-Activity QSTR-Perturbation Model	Based on the ecotoxicity and cytotoxicity	Quantitative	Various nanoparticles	Shape, molar volume, electronegativity, polarity and size	Inhalation
5	Kuempel et.al 2008	Lung Dosimetry Modeling for Quantitative Risk Assessment (LDMQRA)	Based on Lung Dosimetry	Quantitative	TiO_2, carbon black (CB), diesel exhaust particulate(DEP)	Specific surface area and size	Inhalation
6	Labib et.al 2016	Application of Toxicogenomics for Risk Assessment	Based on Toxicogenomic	Qualitative	single/multi-wall carbon nanotubes (MWCNT)	Different physic-chemical properties	Inhalation
7	Bachler et.al 2014	Physiologically Based Pharmacokinetic Modeling (PBPK)	Pharmaco-kinetic	Quantitative	Nano-TiO_2	Shape, Size and Surface Area	Oral
8	Silva et.al 2015 Shafeii et. al 2017, Zalk et.al 2009	Control banding Nano tool (CBNT)	the risk matrix (severity & probability)	Qualitative	Nano-TiO_2	Shape, Size and Surface Area	General
9	Silva et.al 2015	Stoffenmanager Nano Tool	Nanomatrix (Hazard & Exposure)	Qualitative	Nano-TiO_2	Shape, Size and Surface Area	General
10	Van Kesteren et.al 2014, Heringa et.al 2016, Bakand et.al 2016	Risk assessment based on Toxicokinetic Modeling in target organ	Kinetic	Quantitative	Synthetic Amorphous Silica (SAS), Nano-TiO_2	Form Size and Surface Area, particle fraction, physicochemical properties	Oral
11	Michel et.al 2013	Risk assessment of NPs with Spray Application	Spray	Quantitative / Qualitative	Synthetic Amorphous Silicon (SAS)	Size, surface area and zeta potential	Inhalation

Conclusion

To conclude, each of the studied methods evaluates an NP and is specifically used for that NP. However, it should be noted that a general risk assessment approach cannot be applied to all NPs but should be separately investigated by different processes. In general, all the above mentioned risk assessment approaches can be performed in both occupational and environmental exposure.

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Conflict of interest statement

The authors have no conflict of interest to declare.

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