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Review

Nanofluid Minimum Quantity Lubrication (NMQL): Overview of Nanoparticle Toxicity and Safer-Design Guidelines

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Abstract: Minimum Quantity Lubrication (MQL) has received much attention from the research community as a potential lubricating system to reduce environmental hazards and health issues that can be commonly found in flood cooling/lubricating systems based on metalworking fluids. The addition of nanoparticles in MQL systems (NMQL) has led to improved machining performance, increasing the cooling capability and reducing friction and tool wear, and some researchers have proved the applicability of this type of system for difficult-to-cut materials. However, the mist generated by MQL systems due to both the MQL system itself and the machining operation may pose an additional hazard to operators which is being overlooked by the research community. These hazards become more severe when using nanoparticles, but unfortunately very few works have paid attention to nanoparticle toxicity as applied in MQL systems, and this issue should be clearly understood before encouraging its implementation in industry. Furthermore, current legislation does not help since regulation of permissible exposure limits when dealing with nanoparticles is still ongoing in most cases. In this work, the toxicity of nanoparticles applied in MQL systems is analyzed, and recent research on studies of nanoparticle toxicity both in vitro and in vivo is presented. A relative comparison of toxicity is provided for those nanoparticles that have been reported in the literature as potential additives for MQL. The review is focused on analyzing the main factors of toxicity of nanoparticles which are identified as size, shape, surface properties, agglomeration and solubility. This review presents guidelines for safer nanolubricant formulations, guiding practitioners towards proper NMQL implementations in industry. Furthermore, current occupational exposure limits and recommendations are provided for all the nanoparticles potentially used in MQL systems, which is of interest in terms of work safety.

Keywords: nanoparticles; Minimum Quantity Lubrication; NMQL; toxicity; nanolubricants; safer design; work safety

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1. Introduction

Metalworking fluids (MWFs) are widely used in machining operations to reduce mechanical and thermal load on the cutting tool tip and reduce friction, resulting in longer tool life, better surface quality and lower cutting forces [1–4]. The global MWFs market size is estimated to be valued at USD 10 billion in 2023 with more than 2 million tons annual usage, and it is projected to increase 3% year-on-year [5], which poses important cost, environmental, and occupational problems. Depending on the workpiece, production costs, and other factors, cost of cutting fluids may rise to 7–17% of the production shop

total cost [6,7]. In contrast with the 2–4% for tooling expenditures commonly considered in machining [8], the costs related to cutting fluids are very significant.

Apart from economic considerations, the application of MWFs poses serious environmental and occupational hazards that have been continuously reported in the literature [6]. The National Institute for Occupational Safety and Health (NIOSH) reported important evidence of health effects of MWF mist exposure in their reference publication [9], reporting most common respiratory tract diseases such as hypersensitivity, pneumonitis and asthma. Since particle size in MWF mist ranges from 0.1 to 10 microns and particle sizes less than 5 microns are in the range of the respirable fraction, MWF mist entails an important health risk to workers [1]. For this reason, NIOSH recommended an exposure limit (REL) of 0.5 mg/m^3 (or 0.4 mg/m^3 thoracic fraction) in the workplace.

In 2010, Mirer [10] conducted a literature review from 1998 to 2010 in order to highlight the risk to health of MWF aerosols at levels of 0.5 mg/m^3 and below, in an attempt to pressure national regulators to reduce this exposure limit. In his review of about 227 publications related to MWF hazards from 1998 to 2010, 26 works were identified related to cancer, 56 related to respiratory effects, and 32 related to skin effects and skin penetration, indicating the need of considering lower exposure limits. More recently, Park [11] presented a risk assessment of MWF-exposed workers between 2000 and 2019, and it showed that exposure at 0.1 mg/m^3, four times lower value than that recommended by NIOSH, is still associated with attributable lifetime risks of respiratory diseases in the range of 2–30 per thousand, which cannot be considered acceptable.

Unfortunately, industrial practices are far away from a safety limit exposure of MWF aerosols, which should be set to 0.1 mg/m^3 or lower. According to a review of occupational exposure to MWFs conducted in 2003 [12], the average exposure to mineral oil mist and water-mix MWFs may be around 0.67 mg/m^3 and 0.13 mg/m^3, respectively, but if the average exposure at shop-floor facilities is set to cover 90 percent of the reviewed cases, the corresponding values scaled up to 3 mg/m^3 and 2 mg/m^3, respectively. The exposure is more relevant in grinding processes, where it has been shown that the mist generation rate is often an order of magnitude higher than that in turning/milling operations [13].

To avoid or limit the use of MWFs in machining processes, dry and near-dry machining strategies have been extensively investigated in the past decades. Dry machining is by far the most desirable technique; however, its application is limited to specific cases, where dry machining results in equal or higher performance in terms of quality and material removal rates that those obtained in wet machining [6]. The high temperatures in the cutting zone reduce tool life, thus increasing the cutting costs, and only specific combinations of cutting tool materials and workpiece materials can be successfully applied in dry machining (e.g., milling and turning cast iron in open-faced operations where chips can be easily moved away [14,15]). For instance, a report on dry machining limitations stated that some companies, such as Caterpillar Inc. (Irving, TX, USA), have tried dry machining in a number of machining operations in recent years but, despite the advances in tool coatings, machining performance still cannot compare with that obtained using MWFs [15].

Besides dry machining, near-dry machining has been extensively investigated in recent decades. Some of these near-dry cooling strategies are Minimum Quantity Lubrication (MQL), solid lubrication, air cooling, cryogenic cooling and High Pressure Jet Assisted Machining (HPJAM) [6,14,16]. However, the effectiveness of near-dry technologies is also limited. For instance, the machining costs of cryogenic cooling are too high, despite the improvement of tool life and product quality, and other technologies such as HPJAM are still not mature enough to be adopted in industry [6]. Despite the efforts of developing different near-dry strategies, it seems that there is a consensus that only MQL may have the potential to partially replace MWFs under some circumstances [6]. In fact, at the industrial level, some companies are making efforts to move to MQL systems for a more sustainable process. For instance, the Ford Motor Company has a total of over 400 MQL CNC machining centers in numerous transmission and engine plants worldwide [17].

An MQL system is a lubrication method that delivers a small amount of lubricant precisely to the machining tool/workpiece interface (Figure 1). The lubricant is delivered as an aerosol or fine droplets through a nozzle or a series of nozzles in order to minimize the amount of lubricant used while still providing effective lubrication. In fact, MQL systems apply on tools 5 to 80 mL/h of lubricant, which is a much lower flow rate than the 30,000–60,000 mL/h typically used with flood coolants [18]. Furthermore, this technology removes the need for pumps, filtration devices, etc., and reduces the total cost of cooling/lubrication and clearing and disposal of chips.

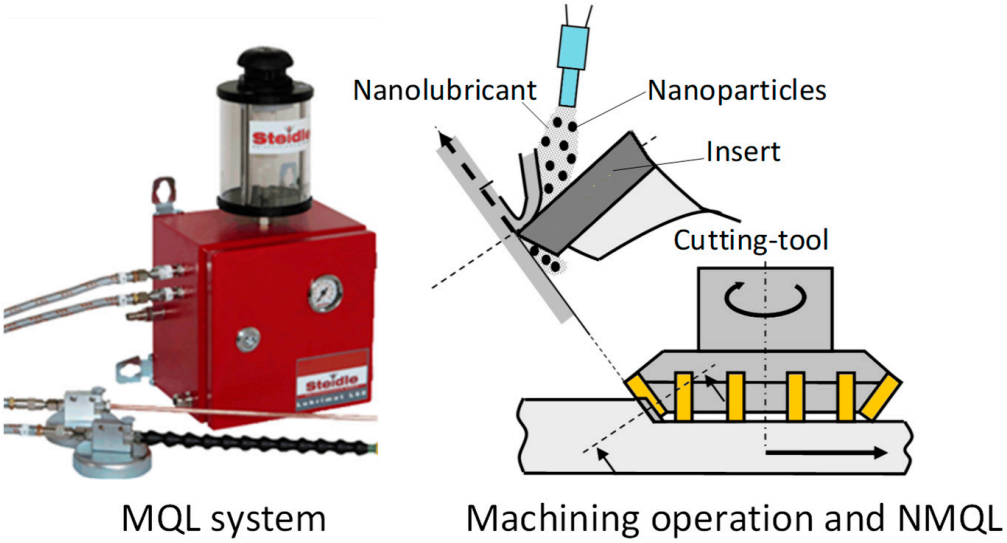

Figure 1. Example of Minimum Quantity Lubrication (MQL) equipment and application adding nanoparticles.

MQL can be successfully applied to drilling, tapping, reaming, sawing and broaching of aluminum alloys, steels and cast iron where dry machining may not be possible [7]. In open-faced operations with these materials, dry or air cooling machining is more appropriate, although MQL is also an effective alternative. However, when machining difficult-to cut alloys, the excessive heat generated makes MWFs still mandatory due to the limited cooling capability of MQL systems. To overcome this limitation, Nanofluid MQL (NMQL) has emerged in the last decade as a potential solution for these situations. The addition of nanoparticles such as SiO_2, MoS_2, TiO_2, MWCNTs, etc., to an oil base increases the MQL performance in two ways: (i) it increases the thermal conductivity which results in an increased heat removal rate and (ii) reduces the friction induced by their rolling effect at the tool–chip interface, thus lowering forces and cutting temperatures [19]. The superior performance of NMQL systems with respect to MQL has been observed by many researchers [20–24], improving surface finish, lowering cutting forces and cutting temperatures, and increasing tool life. The research on NMQL has been intensified in recent years, and several reviews have been published to clarify the state of the art in this field [2,25–32].

Due to the minimum use of lubricant, MQL systems usually present lower emissions than flood lubricant systems. As shown in Figure 2, adapted from [18], the emissions under MQL systems are almost 50% less than their equivalent flood systems. However, if flow rate is set too high or viscosity of lubricant is low, the mist generated can be important [18,33]. In fact, some studies have revealed that the emissions in MQL systems can be even higher than flood emissions under some circumstances [34]. It should be noted that if oil mist may entail safety issues, the situation is exacerbated if nanoparticles are added, producing airborne nanoparticles.

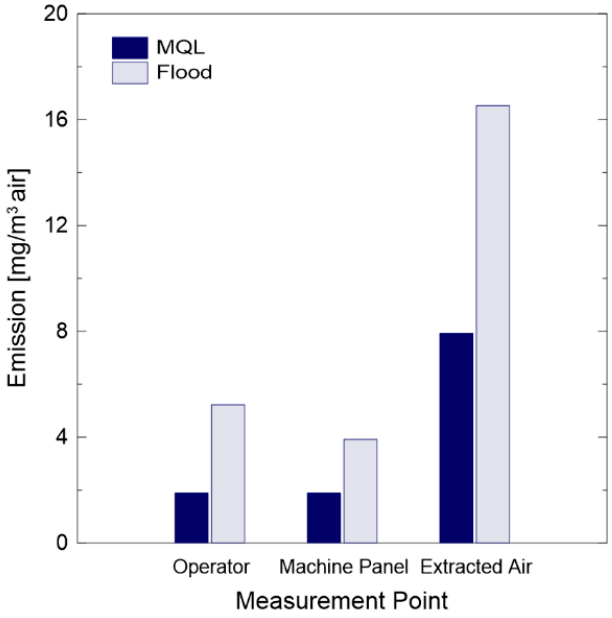

Figure 2. Comparison of emissions between MQL and flood cooling systems. Measurements taken on the operator, the machine itself and inside the machine. Source: [18].

Interestingly, a complete review of the potential toxicity of the NMQL technique has not been performed yet in any research work, although some researchers have pointed out that this issue should be studied in detail [35–37]. A recent work [19] tried to shed some light on this topic, presenting a review of toxicity studies related to nanoparticles that are commonly applied in NMQL, giving some practical information about their potential hazard. However, a more detailed study of toxicity needs to be provided. The physicochemical parameters that should be considered when formulating nanofluids to minimize toxicity, and guidelines for nanoparticle selection from the toxicity point of view, are important topics that should be investigated. Furthermore, current legislation information about occupational exposure limits should be provided to help practitioners understand the potential toxicity of NMQL. This review tries to provide updated information in this field and facilitates the implementation of NMQL in industry, considering the potential toxicity of the mist and airborne nanoparticles and the safety measurements required.

This work is organized as follows. First, the method of nanoparticle exposure and types of toxicity studies are briefly explained. Then, a review of toxicity studies of nanoparticles that have potential use in MQL systems is presented, grouping the nanoparticles in three groups: metal-based, carbon-based, and metal sulfides/boron nitrides. According to the review of toxicity studies, a comparison of toxicity between nanoparticles is provided. Next, the specific physiochemical properties that may reduce or increase nanoparticle toxicity are reviewed, and current regulations in terms of nanoparticle exposure limits are reported. As a result of the review work, guidelines and recommendations for safer nanolubricant design in MQL systems are given, and a conclusion section ends the manuscript.

2. Nanoparticle Exposure Pathways in NMQL

It is well-known that nanoparticles may enter the human body through four possible routes: inhalation, ingestion, injection, and dermal absorption. In NMQL applications, the most significant route of exposure found is inhalation. Inhalable particles can be classified as PM10 (Particulate Matter 10), PM2.5 (Particulate Matter 2.5) and UFP (Ultrafine Particles) depending on the particle size, which in turn determines the capacity of the particles to penetrate the respiratory system of the human body [38]. According to this classification, PM10 (particles with aerodynamic diameter of 10 μm or smaller) can reach the upper respiratory tract, including the nose and throat; PM2.5 (aerodynamic diameter of 2.5 μm or smaller) can penetrate deeper into the respiratory system, reaching the bronchi and lungs;

and UFP (diameters less than 100 nanometers, i.e., nanoparticles), are able to permeate physiological barriers of living organisms, causing harmful biological reactions [39]. Therefore, UFP stand as the most hazardous category of air particulate matter. Their small size allows them to be taken up by cells and transported through biological systems, crossing biological barriers and entering the bloodstream. This phenomenon is called translocation, which lets the nanoparticles travel from the respiratory system to other distant organs and tissues, including the central nervous system. The main result of such translocation is the generation of many diverse health impacts such as neurological diseases, gastro-intestinal diseases, lymphatic system diseases, etc. [40].

To put the size issue in context, Figure 3 shows a scale of different biological systems, where it can be seen that nanoparticles are in the same order of magnitude as DNA and one order of magnitude smaller than human cells, which explains the high toxicity of these types of particles. The droplet size of mist in MQL and NMQL systems is in the range from 0.1 µm to 10 µm, being smaller when the cutting temperature increases [34]. Nanoparticles usually added in NMQL systems are in the range of 30–70 nm, although particles larger than 100 nm due to the agglomeration phenomenon can be easily found in mist droplets.

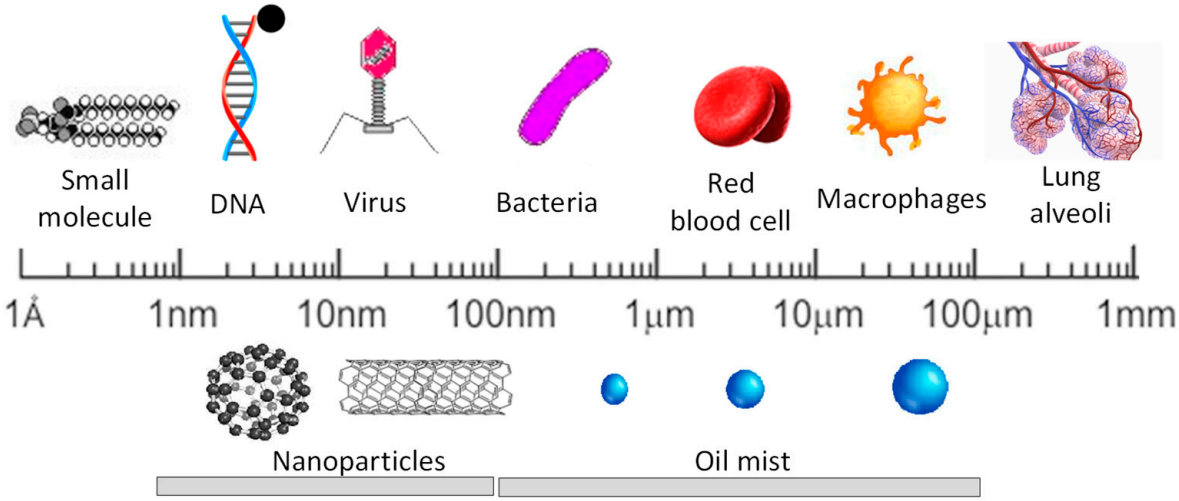

Figure 3. Scale to illustrate the potential interaction between nanoparticles and biological systems.

3. Nanoparticle Toxicity Studies: In Vitro, In Vivo and In Silico

Toxicity studies are commonly conducted using both in vitro and in vivo methods. In vitro studies offer a controlled environment and cost-effectiveness but may not fully replicate the complexity of a living organism. In vivo studies provide a more holistic view of toxicity but are often more expensive and ethically challenging. For nanoparticle toxicity studies, in vitro cell culture studies are the most common type of studies conducted by researchers.

For in vitro studies, different human cell types are used to analyze the specific toxicity of nanoparticles considering their translocation capability. Commonly employed cell types include human lung cells such as A549 cells (alveolar basal epithelial cells) and BEAS-2B cells (immortalized human bronchial epithelial cells); epidermal cells such as HaCaT cells (immortalized keratinocyte cell line from adult human skin); liver cells for liver toxicity studies such as HepG2 cells (hepatocellular carcinoma cell line); kidney cells for renal toxicity such as RPTECs (human renal proximal tubular epithelial cells); or central nervous system cells for neurotoxicity studies such as SH-SY5Y cells (human neuroblastoma cell line) [19,39]. Common types of cell culture studies are cytotoxicity studies (e.g., cell viability assays), genotoxicity studies (e.g., comet assays to detect DNA damage), inflammation studies (e.g., cytokine release assays), oxidative stress studies (e.g., reactive oxygen species (ROS) assays) and apoptosis studies (e.g., apoptosis assays for necrosis determination). It is interesting to note that, according to some investigations [41], the response of different

types of cells (e.g., hepatic, pulmonary, renal, etc.) to nanoparticle exposure can present a similar pattern but with different sensitivities.

It should be noted that in vitro studies present some limitations. For instance, the concentrations of substances tested in vitro might not accurately reflect real exposure levels in vivo. Furthermore, four key processes determine the fate of a substance in the body resulting in different levels of toxicity: absorption, distribution, metabolism and excretion (ADME). The ADME processes are often absent or misrepresented in in vitro studies. An example to illustrate this problem is found when soluble nanoparticles are studied. These nanoparticles may remain trapped in an in vitro system, whereas they may be removed in vivo [41]. Furthermore, the duration of exposure in in vitro studies is typically shorter compared to the potential long-term exposure in real-life scenarios. Chronic effects might not be adequately assessed in short-term in vitro experiments. Despite these limitations, in vitro studies are still fundamental for hazard screening studies and toxicity ranking.

On the other hand, in vivo studies are usually conducted to evaluate the risk to humans and animals (hamsters, rats, mice, fish such as zebrafish) or for the environment (microcrustaceans—*Daphnia magna* neonates, bacteria—*E. coli*, algae—*R. subcapitata*) [42]. In vivo studies include acute toxicity studies to assess the adverse effects of a single exposure to a substance over a short period, usually within 24 to 48 h; chronic toxicity studies that are focused on long-term effects; genotoxicity studies to examine whether a substance can damage the genetic material (DNA) of cells; and immunotoxicity and neurotoxicity studies. To analyze inhalation toxicities, both inhalation and intratracheal instillation studies may be conducted. Inhalation is preferred for testing respirable substances since it resembles actual life situations. However, intratracheal instillation, where a solution is directly administered into the bloodstream by injection, has become a cheap and easy solution commonly applied by researchers [43]. It should be noted that due to time and cost limitations and, especially, due to animal welfare, in vivo methods must be supplemented by in vitro methods. Furthermore, according to the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, the replacement, reduction and refinement (3Rs) of the use of animals in these procedures is clearly promoted.

An important issue when dealing with in vitro and some in vivo studies (i.e., intratracheal studies), is that nanoparticles must be dispersed to prepare suspensions which may result in significantly different results from the actual inhalation exposures due to agglomeration and deposition issues [41]. Some efforts have been made in this regard, with some recommendations about in vitro testing concentrations for specific occupational exposures to nanomaterials given particle size distribution, aerosol concentration, nanoparticle aspect ratio and exposure duration [44].

Due to the limitations of current in vivo and in vitro approaches, computational approaches named in silico studies are being considered as cost-effective alternatives. In silico models use computational methods to simulate how nanoparticles interact with cells, tissues, and organisms without the need for physical experimentation. Quantitative Structure-Activity Relationship (QSAR) modeling applied to nanoparticles (also named nano-QSAR) are used as computational methods to predict nanotoxicity by relating their physicochemical properties to observed toxicological outcomes. These models are mathematical functions that describe statistical dependencies between the variance in the molecular structures and the variance in a modeled biological activity for a group of sufficiently similar chemicals.

However, the main drawback of in silico models is the scarcity of experimental data related to nanotoxicity, and they currently have limited applicability. Recent advances in in silico models can be found in [45,46], and [47] also provides an in silico model for toxicity of metal oxides using physicochemical properties which is available as open source code.

Table 1 summarizes the main advantages and limitations of in vitro, in vivo and in silico toxicity studies.

Table 1. Summary of advantages and limitations of in vitro, in vivo and in silico toxicity studies.

Type of Study	Advantages	Limitations
In vitro	Cost-effective approach. Allows a controlled environment for deriving effective conclusions. Some efforts have been made in this regard with some recommendations about in vitro testing concentrations for specific occupational exposures to nanomaterials given particle size distribution, aerosol concentration, nanoparticle aspect ratio and exposure duration.	Concentrations of substances tested in vitro might not accurately reflect real exposure levels in vivo. In vitro studies may not fully replicate the complexity of a living organism. Biological processes such as absorption, distribution, metabolism and excretion (ADME) are often absent or misrepresented. Chronic effects might not be adequately assessed.
In vivo	Provides a more holistic view of toxicity. The real effect on the biological system can be derived. For testing respirable substances, inhalation exposures are preferred to intratracheal instillation since it resembles real-life situations.	Expensive and ethically challenging, currently limited by the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.
In silico	Cost-effective alternative to in vitro and in vivo approaches.	Limited applicability due to the current scarcity of experimental data related to nanotoxicity.

4. Toxicity of NMQL Nanoparticles

Many different types of nanoparticles have been investigated in NMQL applications. Table 2 shows the most commonly used nanoparticles in NMQL systems with their main characteristics and properties. As observed, a wide range of compositions, shapes, thermal conductivities, Mohs hardnesses and densities is available for use in NMQL systems. Besides these properties, Table 2 also includes information from the safety datasheets of each nanoparticle. This safety information is based on the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) in accordance with the collection of regulations given in 29 CFR 1910 from the Occupational Safety and Health Administration (OSHA). The hazards (H statements) and precautions (P statements) commonly found in dry powder nanoparticles are listed below.

- Hazard statements: H319 Causes serious eye irritation; H335 May cause respiratory irritation.
- Precaution statements:
    a. Prevention: P261 Avoid breathing dust/fume/gas/mist/vapors/spray; P264 Wash skin thoroughly after handling; P271 Use only outdoors or in a well-ventilated area; P280 Wear protective gloves/eye protection/face protection.
    b. Response: P304 + P340 If inhaled: Remove victim to fresh air and keep at rest in a position comfortable for breathing; P305 + P351 + P338 If in eyes: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
    c. Storage: P403 + P233 Store in a well-ventilated place. Keep container tightly closed; P405 Store locked up.
    d. Disposal: P501 Dispose of contents/container at an approved waste disposal plant.

Important research reviews on the toxicity of nanoparticles can be found in [39,42,49–52], where detailed information about nanoparticles' mechanisms of toxicity is given. Nanoparticles can be cytotoxic, i.e., toxic to cells which may undergo necrosis or apoptosis (a form of programmed cell death), and genotoxic, with the ability to damage the DNA of a cell. Genotoxicity may cause mutations that can lead to cancer, which is referred to as mutagenicity. The main toxicity mechanism produced by nanoparticles is due to the production of excess reactive oxygen species (ROS) caused by oxidative processes. Several physiological functions of living organisms are controlled thanks to the presence of moderate levels of ROS. However, an oxidative stress occurring owing to the presence of high ROS levels can be considered harmful, and is the cause of nanoparticles damaging cells by altering proteins,

damaging cellular membrane, disrupting DNA and even inducing cancer or other diseases (Figure 4) [51].

Table 2. Main properties of nanoparticles applied in NMQL.

NP	Typical Shape	Thermal Conductivity (W/mK) [1]	Mohs Hardness [2]	Density (kg/m^3)	Hazards & Precautions [3]
		Metal oxides			
Al_2O_3	Spherical	36	9	3975	H319, H335
SiO_2	Spherical	1.34	7	2400	P261, P264, P271, P280,
CuO	Spherical, rod, platelet	18	3.5	6400	P304 + P340
ZrO_2	Spherical, rod	1.85	6.5	5560	P305 + P351 + P338
Fe_2O_3	Spherical, rod	12.55	5.5–6.5	5240	P403 + P233
TiO_2	Spherical, rod, tubular	8.79–13.39	6.5	4230	P405
ZnO	Spherical, rod	27.20	4.5	5630	P501
		Carbon-based structures			
Fullerene (C60)	Spherical	0.4	3–4	1650	
Nanodiamond (ND)	Spherical	2300	10	3500	
Single-walled carbon nanotube (SWCNT)	Tubular	3000–5000	1–3	2100	H319, H335 P261, P264, P271, P280, P304 + P340 P305 + P351 + P338 P403 + P233 P405 P501
Multi-walled carbon nanotube (MWCNT)	Tubular	3000–5000	1–3	2100	
Graphite (GR)	Platelet, rod	167.36	1–2	2260	
Graphene (GNP)	Sheets, platelet	3000–5000	2–3	2267	
Graphene oxide (GO)	Sheets, platelet	600–5000	2	1360	
SiC	Spherical, rod	370	9	3216	
		Metal Sulfides and Boron Nitrides			
MoS_2	Sheets, rods, spherical	138	1–1.5	4800	H319, H335 P261, P264, P271, P280, P304 + P340 P305 + P351 + P338 P403 + P233 P405 P501
WS_2		53	1–1.5	7500	
hBN		27	2–4	2300	

[1] From database: https://thermtest.com/thermal-resources/materials-database (accessed on 9 October 2024). For comparison purposes, water: 0.6 W/mK; vegetable oils: 0.18 W/mK. [2] A hardness of 6.5 on the Mohs scale is equivalent to 69 hardness Rockwell C (HRC). The hardness value shown is the bulk hardness, the hardness of nanoparticles may be higher due to the Hall-Petch relationship [48]. [3] From supplier datasheets US Research Nanomaterials, Inc. (Houston, TX, USA) https://www.us-nano.com (accessed on 9 October 2024). All nanoparticles present the same H and P statements.

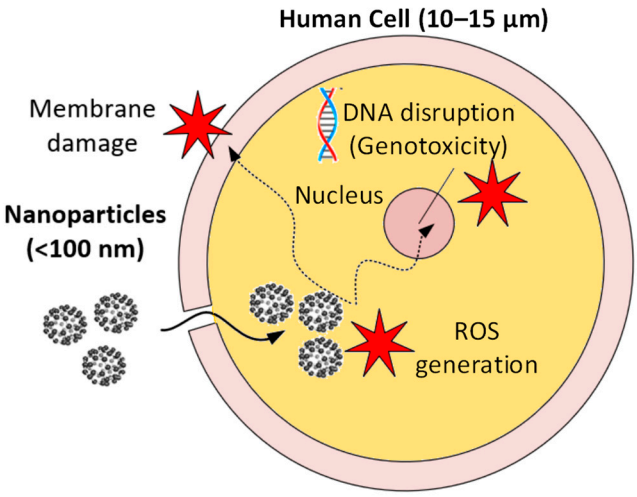

Figure 4. Potential toxicity of nanoparticles. ROS generation, membrane damage and DNA disruption.

The following subsections review relevant toxicity studies about nanoparticles commonly applied in NMQL systems based on both in vitro and in vivo studies.

4.1. Metal-Based Nanoparticles

Among metal-based nanoparticles, metal oxides such as CuO, ZnO, SiO_2, Al_2O_3 and Fe_2O_3 have been investigated in NMQL applications. Most of these nanoparticles exhibit high cytotoxicity, and extreme attention to safety measures is needed [53]. A good comparison of toxicity of oxide nanoparticles can be found in [36,54].

Zhang et al. [53] studied the effect of different metal oxide nanoparticles with a similar particle size of around 20 nm, at a concentration range of 0.25–1.50 mg/mL. The study included ZnO, TiO_2, SiO_2, and Al_2O_3 nanoparticles and all of them were found to lead to cellular dysfunction and apoptosis of in vitro human fetal lung fibroblasts (HFL1 cells). Of these, ZnO was the most toxic nanomaterial followed by TiO_2, SiO_2, and Al_2O_3 nanoparticles in descending order. Kim et al. [55] studied the cytotoxicity of ZnO, Al_2O_3 and TiO_2 in human lung epithelial cells (A549 carcinoma cells and L-132 normal cells). From the results obtained, it was concluded that ZnO presented the highest cytotoxicity in terms of cell viability while Al_2O_3 was less toxic than the other nanoparticles even after long-term exposure. Regarding TiO_2 nanoparticles, they showed little adverse effects on cell viability although oxidative stress was produced depending on the concentration tested and exposure time.

Karlsson et al. [54] analyzed the cytotoxicity of different metal oxide nanoparticles (CuO, TiO_2, ZnO, Fe_3O_4, Fe_2O_3) by exposing human lung epithelial cell line A549 to them. CuO nanoparticles were most potent in terms of cytotoxicity and DNA damage, caused oxidative lesions and induced a significant increase in intracellular ROS. ZnO produced DNA damage effects and low cell viability whereas the TiO_2 particles only caused DNA damage. For iron oxide particles, very low toxicity was found at the concentration range of 40–80 μg/mL. It should be noted that the same composition of nanoparticles may present different toxicities depending on different physicochemical properties. For instance, the iron oxide that tested as biocompatible in a spherical shape changes notably if it is presented in a rod shape, as shown by Lee et al. [56].

Remzova et al. [57] compared the toxicological effects of pristine TiO_2, ZnO, SiO_2, and coated SiO_2 nanoparticles on A549 human lung cells. According to these authors' results, pristine TiO_2 and coated SiO_2 nanoparticles (powders with a methylated surface and an octylated surface) did not exhibit any cytotoxic effects even when the tested dose was high (250 μg/mL), whereas the pristine SiO_2 and ZnO nanoparticles significantly reduced cell viability at concentration values one order lower (25 μg/mL). Wei et al. [58] showed that SiO_2 nanoparticles may cause unexpected cardiovascular toxic effects after respiratory exposure, suggesting their translocation from the lung into the systemic circulation. Additionally, SiO_2 nanoparticles may target the brain through the olfactory route, according to their results in mice.

Brown et al. [59] studied different nanoparticles including metal oxides (Al_2O_3, TiO_2, Fe_2O_3, and ZnO) and metals (Ag) in different biological systems. They studied the toxicity in mammalian cells in vitro (macrophages, hepatocytes and alveolar epithelial cells), aquatic organisms (*Raphidocelis subcapitata* and *Daphnia magna*), sediment-dwelling blackworms (*Lumbriculus variegatus*), and rats exposed via intratracheal instillation. The authors observed a similar pattern of nanoparticle toxicity in this cross-species comparison. Al_2O_3, TiO_2 and Fe_2O_3 nanoparticles did not induce any significant change in mammalian cells after 24h exposure at a concentration range of 1–150 μm. The results of the study demonstrated that ZnO and Ag were the most toxic nanoparticles across all the biological systems employed in the study. The toxicity of ZnO and Ag was followed by TiO_2, Fe_2O_3, and Al_2O_3 in descending order. The study provided different sensitivities for each model under research, and the authors recommended the use of macrophage and daphnia models to assess the toxicity and ecotoxicity of nanoparticles when dealing with mammalian cells.

According to these research works, CuO, ZnO and crystalline SiO_2 are highly toxic, amorphous SiO_2 is moderately toxic, and Al_2O_3, TiO_2 and Fe_2O_3 exhibit low toxicity profiles.

4.2. Non-Metal-Based Nanoparticles

4.2.1. Carbon-Based Nanoparticles

Carbon black has been the most common nanoparticle in the past, and nowadays more advanced carbon-based nanoparticles such as carbon nanotubes (CNTs) in their single-walled and multi-walled shape (SWCNTs and MWCNTs), graphene, graphene oxide, graphite, etc., are receiving more attention.

A comparative study about the inhalation toxicity of MWCNTs, graphene, graphite nanoplatelets and carbon black (a low surface area type with 32 m^2/g) was presented by Ma-Hock et al. [60]. These nanoparticles were analyzed under different concentrations (concentrations from 0.1–10 mg/m^3) on male Wistar rats that were exposed head-nose for 6 h per day on five consecutive days. For exposure rates of 10 mg/m^3, both graphite nanoplatelets and carbon black presented no adverse effects. However, markers related to inflammatory processes started to appear at exposure concentrations of 0.5 mg/m^3 and 10 mg/m^3 for MWCNTs and graphene, respectively.

The researchers have highlighted the special hazards associated with CNTs in comparison to other carbon-based nanoparticles. In a recent review of toxicity of carbon nanotubes by Kobayashi et al. [61], it was highlighted that exposure to CNTs produces sustained inflammation, fibrosis, gene damage in the lung, and may occasionally lead to lung cancer after long-term inhalation. The research also indicated the high biopersistence of CNTs in animal studies.

Mollá et al. [62] studied the toxicity of graphene nanoparticles of 10–55 μm size formed by two to six graphene sheets on cell lines A549 (human fibroblast) and Caco-2 (human colon carcinoma), and they estimated a toxicity value of 205 ppm for the inhalation route. The toxicity of non-oxidized forms of graphene may depend on size, surface reactivity and agglomeration, and they are likely less toxic than various forms of graphene oxide, which tend to be more persistent [63]. Other long types of nanoparticles such as graphene oxide nanoribbons have also been shown to be more toxic than their variants in nanoplatelet form [64].

Some researchers have compared the toxicological profile of carbon-based nanoparticles with respect to metal-based nanoparticles. In [65], the authors investigated the toxicity effects of TiO_2, carbon black, ZnO and SiO_2 in human corneal epithelial cells (HCECs) and human conjunctival epithelial cells (HCjECs) in in vitro studies. The toxicity of these nanoparticles were ZnO > Carbon black > SiO_2, while TiO_2 demonstrated no toxicity even at the highest concentration tested, 400 μg/mL. In a comparison study of in vitro toxicity between metal oxide nanoparticles and different types of carbon nanoparticles in A549 cell lines, a low toxicity of spherical carbon nanoparticles of 30 nm diameter was observed, less than metal oxide nanoparticles [54]. However, the CNTs analyzed were shown to be cytotoxic and genotoxic even at the lowest concentration tested (2 μg/mL). Yang et al. [66] conducted a comparative study of the toxicity of carbon black, SWCNTs, SiO_2 and ZnO nanoparticles. Among the group of nanoparticles tested, ZnO transition metal oxide was the material inducing the most remarkable cytotoxicity due to the intracellular oxidative stress caused. SiO_2 and carbon black reported relevant but lower toxicity values, whereas CNTs resulted in the particle with the highest DNA damage. Angoth et al. [67] studied the in vitro toxicity of carbon nanoparticles on five different cell lines and compared their toxicity with crystalline SiO_2 (quartz). Carbon nanoparticles led to greater cytotoxic effects than SiO_2 nanoparticles, with TC50 values (concentration of particles inducing 50% cell mortality) ranging from 28.29–46.35 μg/mL. A review of carbon nanotube toxicity published in [68] presented research to assess their pulmonary toxicity. In order to do this, test dusts were administered intratracheally or intrapharyngeally. The comparative studies showed that CNTs were more toxic than crystalline SiO_2 whereas ultrafine carbon black produced minimum lung responses. Finally, Raja et al. [69] reviewed the toxicity of

different carbon-based structures and concluded that MWCNTs and SWCNTs were more cytotoxic than carbon quantum dots, graphene, fullerene and nanodiamonds.

According to these research works, it seems that CNTs and similar long carbon-based particles can be classified as high cytotoxic nanoparticles, and special care should be applied when using them in any process where mist may be generated such as NMQL. However, other carbon-based nanoparticles with spherical shape or with low aspect ratio are much less toxic.

4.2.2. Metal Sulfides and Boron Nitrides

Transition metal dichalcogenides (MoS_2 and WS_2) have been widely used as solid lubricants and they are currently used as nanoparticles to reduce friction coefficient in NMQL nanofluids. Some studies related to nanoparticle toxicity have revealed that these group of nanoparticles present low toxicity in comparison to other nanoparticles. For instance, in Appel et al. [70], the authors studied the toxicity of pristine MoS_2 and WS_2 in a series of biocompatibility tests in human epithelial kidney cells (HEK293f) and their genotoxicity in bacterial strains (*S. typhimurium* TA100). Cell viability was unaffected and no genetic mutation was found, highlighting their biocompatibility. Pardo et al. [71] tested MoS_2 and WS_2 nanoparticles in bronchial cells and observed their non-toxicity at concentrations up to 100 μg/mL in comparison to SiO_2 and carbon black nanoparticles which induced cell death. Similar conclusions were reached by Teo et al. [72], where they compared the toxicity of MoS_2 and WS_2 with respect to graphene oxide and halogenated graphene, and they concluded that MoS_2 and WS_2 were much less hazardous. Zapór [73] studied the cytotoxic effect of unmodified nano and micro MoS_2 particles at concentrations ranging 1–200 μg/mL and different exposure times of 24, 48, and 72 h. Human bronchial (BEAS-2B) and alveolar (A549) cells were exposed resulting in weak cytotoxic effects, together with a 60–70% reduction of cell viability at the highest dose tested (200 μg/mL) and the longest exposure time (72 h), which means a low toxicity in comparison to other common nanoparticles. Hao et al. [74] studied MoS_2, TiS_2 and WS_2 nanosheets and no significant in vitro cytotoxicity was found in mouse macrophage (RAW 264.7), human epithelial kidney cells (HEK293T) and mouse breast cancer (4T1) cell lines. To study the biodistribution and clearance behavior of nanoparticles, in vivo studies on mice were conducted through intravenous injection of polyethylene glycol (PEG) functionalized MoS_2, TiS_2 and WS_2. The clearance of MoS_2 nanoparticles was much higher than the other nanoparticles, and MoS_2 was highlighted as a safer nanoparticle due to its low toxicity, capability of biodegradation, and rapid excretion.

Boron nitride has a stable hexagonal structure (denoted as hBN) analogous to that of graphite and has excellent lubricating properties. It has good chemical inertness and it is a good thermal conductor that leads to better heat dissipation. For this reason, hBN nanotubes have been investigated as an alternative to CNTs to overcome cytotoxicity limitations. Chen et al. [75] showed that hBN nanotubes were non-cytotoxic in in vitro tests over HEK cells. While MWCNTs induce apoptosis, hBN nanotubes with similar dimensions to those of MWCNTs did not appear to inhibit cell growth or induce apoptosis. However, more recently, research about toxicity on both lung alveoli and HEK cells has been published with opposite results [76]. In their results, the authors indicated that hBN nanotubes were cytotoxic for all cell types studied and, in most cases, were more cytotoxic than CNTs. Mao et al. [77] studied the toxicity of hBN nanodots on human umbilical vein endothelial cells, and their results showed cytotoxicity in terms of disturbances in cell proliferation, DNA replication-related genes and induced oxidative stress. They also stated a higher toxicity in comparison with graphene nanodots.

According to previous research, the best candidate materials to be safely used in NMQL applications seem to be the transition metal dichalcogenides (MoS_2 and WS_2) as they were demonstrated to exhibit very low toxicity compared to other nanoparticles. On the contrary, hBN nanotubes were recently reported to be highly toxic, at least similar to CNTs.

4.3. Comparison of Nanoparticles' Toxicity

According to previous studies, a relative comparison of the toxicity of nanoparticles applied in NMQL systems can be formulated. Furthermore, specific works such as [19,41,54,59,78] compare the toxicity of some nanoparticles and they have been used to elaborate the toxicity classification table of nanoparticles shown in Table 3. From this classification, it can be concluded that oxides of transition metals (Cu and Zn) present the highest toxicity. Toxicity of carbon-based nanoparticles is moderate to high depending on the morphology of the particles. Aluminum, titanium, iron and silicon oxides present low toxicities with the exception of crystalline silicon oxide. Finally, metal sulfides are classified as nanoparticles with the lowest toxicity.

Table 3. Relative classification of nanoparticles' toxicity applied in NMQL related to inhalation. Note that toxicity may vary depending on different physicochemical properties, exposure times and concentrations.

Very High	High	Moderate	Low	Very Low
CuO ZnO	MWCNTs SWCNTs Graphene oxide hBN SiO_2 (crystalline)	Graphene SiO_2 (amorphous) ZrO_2 Fullerene (C60) Nanodiamond (ND) Carbon Quantum Dot (QD) Carbon Black	SiC Al_2O_3 Graphite TiO_2	WS_2 MoS_2 Fe_2O_3 Fe_3O_4

However, it should be noted that many factors may influence nanoparticle toxicity (exposure times, concentrations and physicochemical properties) which is the main reason why some research works may present contradictory results. In any case, an approximate classification of nanoparticle toxicity can be of interest for practical purposes, especially for those practitioners interested in formulating nanofluids for NMQL applications. The proposed classification of nanoparticle toxicity may serve as a first step for NMQL nanoparticle selection prior to more specific studies. The value of safety inhalation exposures of each nanoparticle is provided in Section 6, according to current legal regulations.

5. Key Factors of Nanoparticle Toxicity

The potential toxicity and health effects of nanoparticles are determined by various factors beyond their chemical composition, the dose and exposure duration, including their size, shape, surface area, surface chemistry, agglomeration, solubility, charge, size distribution, etc. [79]. Therefore, a comprehensive review of the influence of physicochemical parameters on nanoparticle toxicity is critical to develop safer nanofluids for NMQL operations. Besides the chemical composition of nanoparticles, many researchers have proven that the following physicochemical properties have a relevant impact on nanoparticles toxicity [80]: size, shape, surface properties, state of agglomeration/aggregation and solubility (Figure 5). The next subsections analyze the effect of these physicochemical properties on toxicity in order to facilitate the definition of some guidelines related to safer formulation of nanofluids (Section 7).

5.1. Size

Particle size is the main physicochemical property that contributes to cytotoxicity. The smaller the nanoparticle size, the higher the permeability of cell membranes to interact with organelles (e.g., mitochondria, lysosomes, etc.). This higher permeability can be considered a potential cause of cell damage [80]. It can be concluded from the literature review that nanoparticle size and surface charge are key factors to particle distribution once entering the body. In this regard, it is stated that bio-distribution and accumulation of

smaller nanoparticles is higher than those for larger nanoparticles of the same chemical composition [41].

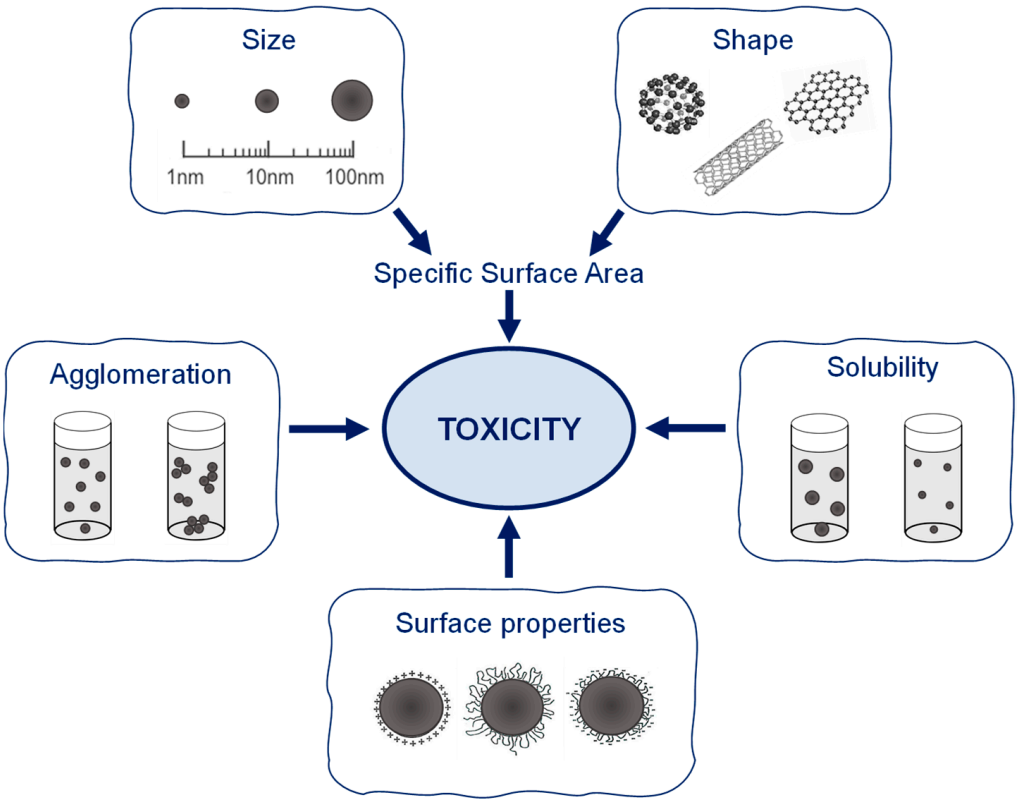

Figure 5. Physicochemical properties affecting nanoparticle toxicity.

Kim et al. [81] analyzed different sizes (20 nm and 100 nm) of SiO_2 and ZnO nanoparticles to study their cytotoxicity on U373MG human glioblastoma cell lines. The results showed no influence of size in the ZnO case, but in the case of SiO_2 a higher toxicity of those with smaller size was observed. It should be noted that, besides a size relationship, the toxic response depends on the sensitivity of the type of cell exposed, as shown in [82], where micro and nano ZnO particles exhibited nearly equal toxicity profile in L-132 cells but nano ZnO reported higher toxicity than its micron-size form in THP-1 cells. Hsiao and Huang [83] studied the toxicity of different nanoparticles such as TiO_2 and ZnO on human lung epithelium cells (A549), and the authors found that smaller nanoparticles had greater toxicity than larger ones. Zapór [73] assessed that the cytotoxic effect of MoS_2 nanoparticles (100 nm) and microparticles (2 µm) scale toward human bronchial (BEAS-2B) and alveolar (A549) cells, and the nanoparticles were observed to be slightly more cytotoxic. Similar conclusions were found by Gurr at el. [84], where TiO_2 particles of size 10–20 nm induced oxidative DNA damage and lipid peroxidation in BEAS-2B cells (human bronchial epithelial cell line), whereas particles with 200 nm or higher did not induce oxidative stress.

Additionally, particle size has been proved to be a critical factor that influences nanoparticle distribution among organs and tissues [85,86]. Semmler-Behnke et al. [87] compared the ability of gold nanoparticles to cross the air/blood barrier of the lungs. It was observed that 1.4 nm nanoparticles were able to do so in a much more efficient way than 18 nm gold. As a result, the accumulation of 1.4 nm nanoparticles in different organs is higher due to the smaller particle size. Furthermore, it seems that there is a correlation between the nanoparticles size and their retention in the human body. Oberdorster et al. [88] reported that nanoparticles of 20 nm TiO_2 presented two times greater retention in the lungs (500 days versus 170 days) than 250 nm TiO_2 particles.

5.2. Shape

Nanoparticle shapes are usually spheres, rods, tubes, platelets, sheets, flakes, fibers or wires. It has been proved that similar nanoparticles with different shapes may have different toxicity levels [80] (Figure 6). Hadji and Bouchemal [89] highlighted that cell uptake and intracellular distribution is dependent on particle shape, where non-spherical particles present better escape capability to macrophages, higher margination and adhesion to the endothelial wall, longer circulation time and slower elimination rate. Special attention must be paid to the definition of High Aspect Ratio Nanoparticles (HARN) and their biological behavior as asbestos. According to the World Health Organization [90], those nanoparticles with an aspect ratio above 3 (the ratio of its longest dimension to its shortest one) where the short dimension is less than 3 μm and the longest one is higher than 5 μm belong to a nanofiber class and have a similar potential toxicity to asbestos. The reason behind the high toxicity of nanofibers is that they are too long to be cleared by macrophages and may pose a cancer hazard to the lungs [91,92]. Note that below 5 μm, these type of HARNs are considered as nanoparticles rather than nanofibers. Some examples of HARNs are nanotubes, nanoplatelets, nanowires and nanorods.

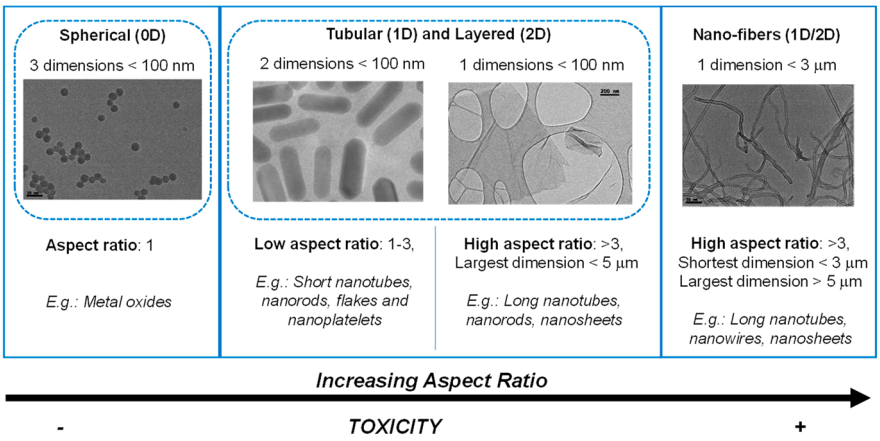

Figure 6. Influence of aspect ratio on toxicity. Geometries with high aspect ratio such as nanowires and long nanotubes commonly present the highest toxicity profile.

Park et al. [93] compared the toxicity of two different commercial aluminum oxide nanorods with differences in their aspect ratio, 6.2 ± 0.6 versus 2.1 ± 0.4. In mice, longer nanorods induced stronger inflammatory responses than the shorter ones. Similar conclusions were found after conducting in vitro tests on six cell lines: the long aluminum oxide nanorods generally produced stronger toxicity than the shorter nanorods. Lee et al. [56] investigated cytotoxicity to mouse macrophage cells (RAW 264.7) using different iron oxide nanoparticles: microsized and nanosized spherical Fe_2O_3, and rod-shaped Fe_2O_3 with an aspect ratio of 20 to 30. In their results, the authors revealed that higher cytotoxicity was found in rod-shaped nanoparticles presenting a high degree of membrane damage and greater extent of necrosis, possibly associated with the resulting high specific surface area. The authors stated that nanoparticle toxicity has to be evaluated considering both shape and size, since they define the surface area as closely related to cytotoxicity. For the same mass, nanoparticles with larger specific surface area present a larger surface area to interact with cellular components, increasing their cytotoxicity [94]. Similar conclusions were reached by Hsiao and Huang [83], where nanorod ZnO particles were more toxic than the corresponding spherical ones.

From HARNs, long CNTs are assumed to present a high toxicology profile due to their resemblance to asbestos fibers. Besides the biopersistence property (the retention of the fibers in lung tissue) that depends on the composition of the fibers, the width and length of the fibers seem to be related to their pathogenicity [92]. While the width or diameter affects the aerodynamic behavior of the particle and influences the mechanism of entry into

the respiratory tract, the length determines how the particle can be effectively cleared by macrophages [92].

Cohignac et al. [95] conducted a comparison study about the toxicity of different nanoparticles including MWCNTS, carbon black and TiO_2, with different shapes (tubular or spherical), length (short or long CNTs), size (nano or micro TiO_2), and other physicochemical characteristics on RAW 264.7 murine macrophages. According to their results, the shape seems to be the most important characteristic to induce or block nanoparticle clearance.

Jiang et al. [96] found genotoxicity to be the main toxicity category for unmodified and functionalized SWCNTs. Different lengths were studied, i.e., shorter SWCNTs (average length of 1 μm) and longer SWCNTs (average length of 15 μm) and ROS production was analyzed in yeast cells for different concentrations (2, 8, and 32 μg/mL). In this case, since the yeast cells' size was 3–4 μm, the uptake of nanoparticles via phagocytosis cannot occur, and the main mechanism of cell interaction is penetration. Shorter CNTs less prone to aggregation more easily penetrate, which in turns results in higher toxicity. Donaldson et al. [92] analyzed the toxicity of HARNs and described the physicochemical parameters than can be applied to safer HARNs design. In this work, the authors remarked that the toxicity of fiber HARNs is different from other HARNs that are not as long, and it was indicated that lengths lower than 5 μm can be subjected to macrophage clearance, but nanoparticles of length greater than 15 μm with biopersistence capability can lead to cancer and fibrosis. Cui et al. [97] studied the uptake of three different lengths of SWCNTs, 0.6 μm, 0.3 μm and 0.19 μm, in macrophages. For these lengths, the authors showed that the cellular accumulation of SWCNTs was independent of length.

Graphene oxide (GO) nanosheet toxicity was analyzed by Rodriguez et al. [98] in mice after single intranasal instillation for a period of 90 days after single instillation (50 μg per mouse). In their work, micrometer-sized GO (ranging between 1 and 30 μm) induces stronger pulmonary inflammation than nanometer-sized GO (size smaller than 300 nm) despite presenting lower lung deposition. In their work, MWCNTs with similar lateral dimensions to the micrometer sized GO were used as a benchmark due to their high cytotoxicity. Only MWCNTs produced granulomatous inflammation after exposure. Similarly, the cytotoxicity of graphene nanoplatelets ranging from 8–25 nm in thickness was analyzed by Roberts et al. [63]. In vivo studies were conducted by exposing mice to different doses through pharyngeal aspiration at doses of 4–40 μg/mouse for different exposure times. They demonstrated that graphene nanoplates with large lateral dimensions (5–20 μm) caused greater lung inflammation and injuries than their smaller counterparts (<2 μm).

5.3. Surface Properties

Surface properties, especially charge and surface modifiers, are important factors that influence nanoparticle toxicity since they have an impact on cellular uptake [99]. One of the physical properties which gives information about nanoparticles' surface charge is the zeta potential. This parameter indicates the electrical charge (positive or negative) at the slipping plane formed between the solid particle and the surrounding media and can be used to predict nanoparticle toxicity [100]. Positively charged nanoparticles have a higher impact on toxicity than negatively charged, partially because negatively charged cellular membranes are more prone to interact with the former, leading to higher cellular uptake [101]. Note that if particles are toxic, higher particle uptake (i.e., higher bioavailability) correlates with higher toxicity [94]. Therefore, the charge of the nanoparticle may induce cytotoxicity. In addition, surface charge may influence the agglomeration state of nanoparticles, which impacts their aerodynamic behavior when aerosolized, which in turns influences toxicity [99]. For instance, Gilbertson et al. [102] studied the influence of surface charge on the mortality of embryonic zebrafish for a safer MWCNTs design, and they observed that surface charge was the best predictor of zebrafish mortality at 24 hpf (hours post-fertilization). A similar negative effect was observed by Baek et al. [103], where ZnO particles with positive charge showed greater ROS production than those with negative charge.

One of the key features of nanofluids is the colloidal stability of the nanoparticles in suspension. To ensure this stability over time, control of surface properties and further functionalization can be necessary (e.g., attach different elements—ions, molecules, polymers—on the nanoparticles' surface) [104]. Nanoparticle interactions are controlled by short-range Van der Waals attraction and surface forces. In aqueous media, attractive forces are overcome by electrostatic repulsion achieved thanks to pH modification resulting in positive or negative nanoparticle surface charge. However, in non-aqueous media (e.g., nanolubricants), steric or electrosteric repulsion is required. Steric repulsion is achieved by adding non-ionic surfactants composed of non-charged polymeric chains that adsorb on the nanoparticle surface and extend into the surrounding medium. Common non-ionic surfactants include polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP). In the case of electrosteric repulsion, ionic surfactants (cationic or anionic) are used to generate a charged medium surrounding the polymeric chains adsorbed to the particle surface. This last mechanism is the most effective stabilization mechanism and can be achieved without undergoing chemical reactions by the addition of surfactants such as sodium dodecyl sulphate (SDS), sodium dodecylbenzene sulfonate (SDBS), cetyl trimethylammonium bromide (CTAB), and benzalkonium chloride (BAC). Figure 7 summarizes common methods for dispersion and stabilization of nanoparticles including a classification of the surface modification mechanisms and surfactants.

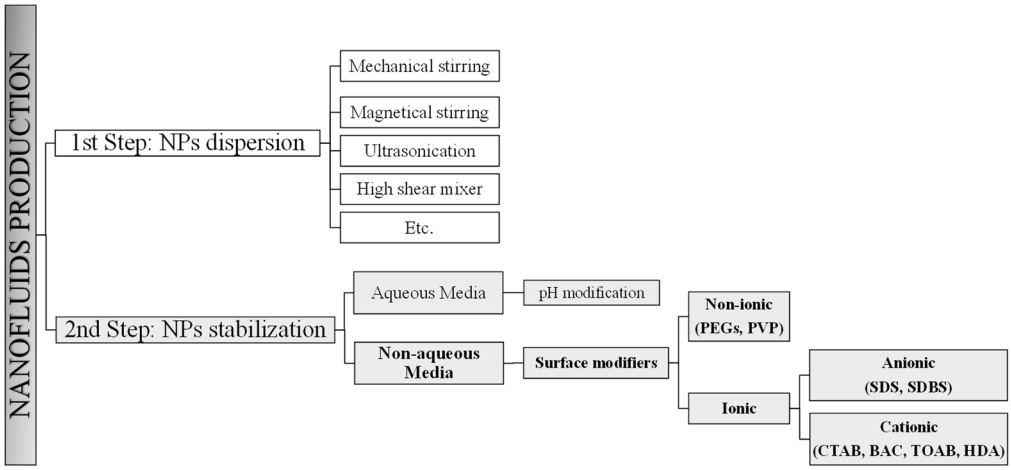

Figure 7. Classification of dispersion and stabilization mechanisms of nanoparticles.

As stated above, surface modifiers are usually needed in nanofluids for NMQL applications (oil media), and the influence of these surface modifiers on nanoparticle toxicity should also be considered. Oleszczuk et al. [105] studied the effect of the surfactants CTAB, SDS and PEG on the toxicity of ZnO, TiO_2 and Ni nanoparticles on Daphnia magna organisms. Although surfactants are intended to improve colloidal stability, the interparticle interactions can lead to changes in the possible formation of aggregates. Therefore, not only the nanoparticle surface charge but also the aggregate size influences toxicity due to the addition of surfactants. The authors concluded that the toxicity of the nanoparticles was reduced with the addition of the tested surfactants, probably due to the formation of aggregates that inhibited the availability of nanoparticles to the crustaceans. Zhang et al. [106] explored the cytotoxicity of eleven commonly used surface modifiers in two cell lines, human epidermal keratinocyte (HaCaT) and lung fibroblast (CRL-1490) cells. The eleven surface modifiers analyzed were the following: four cationic (CTAB, oleylamine, tetraoctylammonium bromide-TOAB, and hexadecylamine-HDA), four neutral (triphenylphosphine-PPh3, tributylphosphine-PBu3, dodecanethiol, p-Aminothiophenol) and three anionic (tetradecylphosphonic acid, myristic acid, SDS). From all the tested surface modifiers, all cationic modifiers and the amino compounds were found to be cytotoxic to both cell lines. The SDS modifier was also found to be toxic but to a lower extent. Other

neutral/anionic agents (sulfur, phosphorous, and carboxylic compounds) showed low or no toxicity under the testing conditions. In addition, exposure time and the use of different cell lines also affected the cytotoxicity results. Wang et al. [107] analyzed cytotoxicity of gold nanoparticles in sphere and nanorod shape; the nanorod proved to be highly toxic but not due to its shape, rather because of the presence of CTAB surfactant. Similarly, in the case of gold nanoparticles, it was shown that the aspect ratio was not the key aspect that led to toxicity, but the surface chemistry as reported by Wan et al. [108]. In this work, the authors analyzed the cytotoxicity of CTAB-gold nanorods with different aspect ratios (1, 2, 3 and 4) with no significant difference, showing that CTAB surface modifiers clearly had an impact on cell viability. However, gold nanorods functionalized with a mixture of surface modifiers (CTAB/polystyrene sulfonate, CTAB/allylamine hydrochloride, CTAB/polystyrene sulfonate/allylamine hydrochloride) displayed low toxicity and did not induce cell death. As reported in [109,110], there is a consensus about the order of surfactant toxicity as follows: cationic > anionic > non-ionic.

Another mechanism for surface modification is chemical functionalization of nanoparticles. In this route, nanoparticles are first functionalized and the obtained solid material is then dispersed in the base fluid. This functionalization is known to change nanoparticle chemistry, charge, and hydrophobicity through the formation of a coating with different physical-chemical properties, which results in alteration of their toxicity [99]. Vranic et al. [111] investigated the effects of amino and carboxyl functionalization of rhodamine-labeled SiO_2 nanoparticles on cellular uptake and cytotoxicity. In their investigation, they concluded that carboxyl-functionalized SiO_2 nanoparticles were internalized by macrophages more efficiently with lower cytotoxicity than plain SiO_2 nanoparticles. The amino-functionalized nanoparticles also reported lower cytotoxicity than the plain ones, but higher than the carboxyl-functionalized. Zhang et al. [112] analyzed the cytotoxicity of Al_2O_3 nanoparticles to CACO-2 cells and Caenorhabditis elegans bioassay using different surface coatings. Hydrophilic and lipophilic coatings were studied, and they showed that lipophilic coatings were more toxic than the pristine state of the nanoparticles, and the hydrophilic coating presented similar results to the pristine ones. Remzova et al. [57] carried out a comparative study on the toxicological effects of non-modified pristine SiO_2, and SiO_2 nanoparticles under non-ionic functionalization with –methyl and –octyl functional groups. Toxicity towards the A549 human lung cell line was tested at different doses and the results showed a high toxicity for pristine SiO_2 at low doses (above 25 μg/mL). On the other hand, no statistically significant cytotoxic effect was observed for the functionalized SiO_2 (both –methyl and –octyl), even at the highest testing dose (250 μg/mL). The reduction in toxicity after functionalization (both –methyl and –octyl) can be explained by the inhibition of Si-OH groups, present in pristine SiO_2, generating insoluble particles with reduced formation of ROS inside the cells. Goodman et al. [113] studied the toxicity of gold nanoparticles functionalized with cationic and anionic side chains, ammonium-functionalized versus carboxylate-functionalized. The results showed that anionic functionalization (carboxylation) presented lower toxicity than cationic functionalization.

In CNTs, carboxylation makes the nanotubes more hydrophilic and less agglomerated and makes them more vulnerable to oxidative destruction by peroxidases, which reduces their biopersistence significantly [99]. Li et al. [101] analyzed different CNTs functionalized with common anionic, nonionic/neutral, and cationic surface groups and assessed their cytotoxicity in THP-1 and BEAS-2B cells. The anionic and neutral group (carboxylate and PEG) led to lowest toxicity, the weakly cationic functional groups (amines) presented intermediary toxicity (slightly higher than pristine nanoparticles), whereas the strongly cationic group (a cationic polymer for functionalization, polyetherimide -PEI) exhibit the highest toxicity.

Hydroxylation has also been reported as a functionalization of nanoparticles than can reduce cytotoxicity. Hydroxylation, as carboxylation, is a way to enhance hydrophilicity which seems to reduce cytotoxicity by altering the cell uptake efficiency [114]. In [115], the cytotoxicity of pristine MWCNTs together with carboxylated and hydroxylated MWCNTs

were studied on the human lung A549 epithelial cell line. The results showed that the pristine MWCNTs presented higher cytotoxicity versus the functionalized ones. The authors also suggested that the agglomeration of the functionalized MWCNTs could explained these cytotoxic differences. In [114], cytotoxicity of hydroxylated MWCNTs was analyzed on human normal liver L02 cell lines. The results demonstrated that hydroxylation significantly reduces the oxidative stress in comparison to the pristine MWCNTs. However, different results regarding toxicity of functionalization were reported by Jiang et al. [96]. In their research work, the authors analyzed genotoxicity and oxidative stress for raw and functionalized (carboxylated and hydroxylated) SWCNTs in yeast cells. It was reported that the mechanisms of action for all the SWCNTs tested (raw and functionalized) were DNA damage and oxidative stress. However, functionalized SWCNTs showed a higher overall toxicity, being more significant for the carboxylated SWCNTs than the hydroxylated ones. In another study [116], the toxicity of pristine and carboxylic functionalized MWCNTs was analyzed on RAW 264.7 cells. According to their results, both MWCNTs decreased viability of murine macrophage RAW 264.7 cells but the modification with a carboxyl group did not result in any significant impact on toxicity results.

5.4. Aggregation/Agglomeration

In addition to the physicochemical properties explained above, the ability of nanoparticles to form clusters or assemblies of nanoparticles via aggregation and agglomeration also affects their toxicity [80]. Aggregation refers to a non-reversible assembly due to strong interactions and the formation of dense particle collectives, whereas agglomeration is a reversible assembly due to weak interaction surface forces, like Van der Waals forces or electrostatic forces, which can be simply broken by applying mechanical external forces. Nanoparticle agglomeration outside the body reduces toxicity since bigger clusters of nanoparticles can be caught in the upper respiratory tract. According to Bruinink et al. [117], after cell uptake, agglomeration reduces translocation, thus limiting toxicity, but agglomeration after translocation across the primary barriers may produce their accumulation and increase their adverse effects. It should be noted that agglomeration depends not only on intrinsic physicochemical properties like size, shape, and surface chemistry, but also on extrinsic factors related to medium properties such as pH, ionic strength, etc. [80]. As can be expected, nanoparticles may aggregate/agglomerate differently in biological systems than in a controlled laboratory environment, which makes the study of the resulting impact on toxicity challenging.

As mentioned above (Figure 7), control of nanoparticle dispersion is performed by different techniques, ultrasonic treatment being the most effective to reduce the agglomerate size. After dispersion, it is well known that raw nanoparticles tend to reagglomerate very easily, and different surface modifiers and/or functionalization are needed. Cheng and Cheng [118] observed that the agglomeration state of functionalized MWCNTs is dependent on the sonication time, leading to different toxicity values in zebrafish embryos. While the functionalized MWCNTs prepared with a longer sonication time (48 h) resulted in smaller agglomerates (0.2 ± 0.1 μm) leading to a severe toxicity profile, those prepared with a shorter sonication time (24 h) presented larger agglomerates (about 0.8 ± 0.5 μm) and did not induce any obvious toxicity. On the other hand, some authors have studied the effect of the primary size of the nanoparticles at the agglomeration state on cytotoxicity. For example, Murugadoss et al. [119] studied two TiO_2 nanoparticles with different primary sizes (17 and 117 nm) and different suspensions composed of small or large agglomerates with suspensions prepared at different pH values. The authors found that the toxicity of agglomerates (up to 300 nm size) from small and large nanoparticles was, in most cases, indistinguishable and, in some cases, agglomerates from larger nanoparticles even reported slightly higher toxicity.

It is important to remark that some contradictory results are found in the literature about the effect of agglomeration on toxicity, and current research is limited [117]. Mutlu et al. [120] analyzed the aggregation effect of SWCNT on lung toxicity through intra-

tracheal studies on mice. After thirty days of administration, granuloma-like structures were observed in those treated with the aggregate formulation while they were absent in those treated with the dispersed SWCNTs. The authors concluded that the toxicity of SWCNTs in in vivo studies could be more attributable to the aggregation phenomenon than to the aspect ratio itself. On the other hand, Lim et al. [121] prepared three different types of agglomerates (average diameter in suspensions of 219, 1875 and 7140 nm) of nano-sized carbon black (14 nm particle size) and aerosolized for a nose-only exposure of male Sprague-Dawley. It was observed that the agglomeration of the carbon black nanoparticles did not affect the toxicity and only mild to moderate respiratory effects were found at 9 mg/m^3 for 13 weeks.

5.5. Solubility

The dissolution capability of airborne nanoparticles after inhalation and deposition in the respiratory tract naturally affects the nanoparticles' clearance, persistence and translocation. In this regard, particulate matter is classified into three different categories according to the pulmonary clearance capability in humans. The categories defined by the International Commission on Radiological Protection (ICRP) are as follows: (i) soluble material, which exhibits a retention half-life of less than 10 days; (ii) partly soluble matter, which presents a retention half-life between 10 to 100 days; and (iii) poorly soluble material, for particulate matter where retention times are higher than 100 days [43]. Therefore, non-dissolvable nanoparticles might have prolonged persistence in biological systems, potentially leading to accumulation in organs or tissues, which can cause long-term toxicity. In contrast, they may not cause immediate toxicity if they are chemically inert or if the body is able to excrete them effectively. On the other hand, soluble nanoparticles present lower toxicity compared to non-dissolvable particles if they break down into non-toxic components. However, dissolvable nanoparticles can be more toxic because they release ions or other reactive species as they break down. These ions may cause oxidative stress, inflammation, or interfere with cellular processes, leading to toxicity [43]. This is the case with ZnO and CuO nanoparticles, where metal ions such as Zn^{2+} and Cu^{2+} are released causing important cytotoxicity [122].

Soluble or partially soluble nanoparticles are commonly metal and metal oxide nanoparticles. Some of them are defined as quick-soluble, such as ZnO or CuO, while others are slow-soluble nanoparticles such as TiO_2 or Fe_2O_3 [123,124]. Both Fe_2O_3 and TiO_2 are considered low-soluble nanoparticles with a low toxicity profile [124].

Generally, as the nanoparticle size decreases to provide colloidal stability, their dissolution increases due to the higher specific surface available [125]. Misra et al. [126] investigated different shapes of CuO nanoparticles for their application in ecotoxicological studies. Spherical nanoparticles of 7 nm diameter and rod-shaped nanoparticles of 7×40 nm size were studied, and the spherical ones were shown to dissolve faster than rod-shaped particles. In addition to nanoparticle size, dissolution is dependent on chemical and physical properties of particles and fibers together with the suspension medium's properties such as ionic strength, pH, and temperature [127]. For instance, Wang et al. [128] evaluated the dissolution of different metal oxides at different pH values. According to their results, lower pH values increased the release of metal ions which was shown to be responsible for higher toxicity for ZnO and CuO. It should be noted that the dissolution is also influenced by the nanoparticles' agglomeration, since it decreases the specific surface area which influences the ion release process [127].

Other nanoparticles such as CNTs, graphene, graphite, SiC and metal sulfides and boron nitrides are generally insoluble or low-soluble in water and organic solvents. In fact, the insolubility of CNTs (SWCNTs and MWCNTs) is considered similar to asbestos and this is the reason why the length of the nanotubes is important to the resulting biopersistence [61].

To summarize the main influence of physicochemical properties on nanoparticle toxicity reviewed above, Table 4 is presented. As it shows, many physicochemical properties may be modified to reduce the toxicity profile of nanofluids in industrial scenarios.

Table 4. Concluding remarks from Section 5 to highlight the main relationships between physicochemical properties and nanoparticle toxicity.

Physicochemical Properties	Concluding Remarks
Size	Low nanoparticle size increases biodistribution and accumulation/retention leading to higher cytotoxicity.
Shape	Nanoparticles with higher aspect ratios for a given mass present higher specific surface area which is associated with higher cell reactivity and cytotoxicity. Special care is given when dealing with nanofibers which present a toxicity similar to asbestos, proven highly cytotoxic and genotoxic particles.
Surface properties	Positive surface charge (zeta potential) increases nanotoxicity while surfactants modify nanoparticle interactions with the following toxicity order: strong cationic (CATB, BAC, PEI functionalization) > weakly cationic (amine functionalization) > anionic (PEG, PVP, carboxyl functionalization) > non-ionic (hydroxyl functionalization). Anionic/non-ionic surfactants and anionic/non-ionic functionalized groups seems to reduce the potential nanoparticle toxicity. Anionic surfactants and hydroxyl functionalization typically increase hydrophilicity reducing nanoparticles' toxicity profile.
Aggregation/Agglomeration	Agglomerated nanoparticles are larger and may not penetrate cells as easily as individual, smaller nanoparticles. Agglomerates might be less reactive than dispersed nanoparticles, although their accumulation after crossing primary barriers can cause more severe toxicity.
Solubility	Nanoparticle solubility affects potential toxicity. Soluble nanoparticles that do not release ions are less cytotoxic than insoluble or partly soluble nanoparticles.

6. Regulation

Concerning occupational health and safety, there is a lack of specific regulations around engineered nanoparticles in the EU, the USA, or any other countries. In addition, there is no generally accepted way of deriving the occupational exposure limits (OELs) related to nanoparticles, which results in differences between OEL values. These variations are also reflected in the names of the OELs such as Threshold Limit Values (TLV) in use by occupational hygienists, Permissible Exposure Levels (PEL) in use by the OSHA in the US, Recommended Exposure Limits (REL) in use by the NIOSH and Derived No-Effect Levels (DNEL) in use by the EU REACH agency. Other commonly used names are Recommended Benchmark Levels (RBL), Benchmark Exposure Levels (BEL) and Nano Reference Values (NRV). Basically, these are all concentrations of chemicals that should be considered for workplace safety [129].

Considering as reference the OSHA levels from the US, only exposure limits for titanium dioxide (TiO_2) nanoparticles and carbon nanotubes and nanofibers have been published [130]. According to this organization, the PEL for TiO_2 is 15 mg/m^3, based on the airborne mass fraction of total TiO_2 dust, and 0.3 mg/m^3 for TiO_2 nanoparticles. While OSHA oversees legal regulations, the NIOSH institution provides recommendations for occupational safety which are usually more conservative than OSHA legal terms. According to NIOSH, the REL are 2.4 mg/m^3 for TiO_2 dust, and 0.3 mg/m^3 for TiO_2 nanoparticles as time-weighted average (TWA) concentrations for up to 10 h per day during a 40-h work week [131]. For carbon nanotubes, in the 2010 draft Current Intelligence Bulletin (CIB) Occupational Exposure to Carbon Nanotubes and Nanofibers [132], NIOSH indicated that risks could occur with exposures less than 1 μg/m^3; however, they set the analytic limit of quantification to 7 μg/m^3 elemental carbon (EC) 8-h TWA. Based on subsequent improvements in sampling and analytic methods, NIOSH is currently recommending an exposure limit of 1 μg/m^3 [133]. For silver particles, NIOSH recommend a REL of 10 μg/m^3 as an 8-h TWA for total silver (metal dust) according to the PEL value reported by

OSHA [134], and for silver nanoparticles the REL value is set to 0.9 μg/m^3 as an airborne respirable 8-h TWA concentration [135].

Apart from TiO_2, nanotubes and silver nanoparticles, there is no regulation of other nanoparticles and OSHA suggests that employers should minimize worker exposure by using the hazard control measures and best practices identified in the materials' safety data sheets. However, there is a consensus in limiting exposure to a greater degree than their corresponding microparticles due to the higher toxicity of nanoscale particles. In fact, as reported in [136], even when particles are innocuous in bulk or in microscale form, nanoparticles may be markedly toxic. In a report on workplace exposure to nanoparticles [137], it was highlighted that some research works reported a 5 to 10-fold higher potency of the nanomaterials (calculated on a volume basis) with respect to the toxicity of similar particles at microscale. For this reason, some researchers and organizations have proposed to limit the exposure to nanoparticles by at least 8 times more than the corresponding limits for microparticles [131]. In the same vein, the British Standards Institution (BSI) suggested benchmark exposure levels for four nanoparticle hazard types [138]. The four types defined by the standard are insoluble, fibrous, soluble and CMAR (carcinogenetic, mutagenic, asthmagenic or reproductive) nanoparticles, and the corresponding benchmark exposure levels are as follows:

- Soluble nanoparticles: 0.066 × WEL (WEL refers to Workplace Exposure Limit, i.e., the exposure standard) of the corresponding microsized bulk material expressed as mass concentration.
- Fibrous nanoparticles: 0.01 fibers/mL.
- Highly soluble nanomaterials: 0.5 × WEL.
- CMAR nanoparticles: 0.1 × WEL of the corresponding microsized material.

Table 5 summarizes current regulations, showing PEL and REL values for different particles at the microscale (dust) and nanoscale according to OSHA and NIOSH. As can be seen, at the nanoscale, exposure limits are only indicated for TiO_2 and carbon nanotubes. To provide some guidance on possible exposure limits for other nanoparticles, Table 5 also shows potential OEL values based on the idea of limiting exposure to nanoparticles by at least 8 times more than the corresponding limits for microparticles. Similarly, the last column in Table 5 presents potential OEL values for nanoparticles considering the suggested benchmark exposure levels from British Standards Institution (BSI) [138]. Both sets of potential OEL values may be of interest to future policymakers and regulators.

Table 5. Exposure limits from OSHA and NIOSH (source: https://www.osha.gov/chemicaldata/ (accessed on 9 October 2024)) and recommended OEL values according to NIOSH statement and benchmark exposure levels from BSI (notes 1 and 2) for some common particles used as nanoparticles.

Particles	Regulatory Entity					
	OSHA	NIOSH	OSHA	NIOSH	According to Note 1	According to Note 2
Particle Size	Microscale (dust)		nanoscale			
Exposure Limit	PEL [+]	REL [^]	PEL [+]	REL [^]	OEL	OEL
Carbon black	3.5 mg/m^3	3.5 mg/m^3	-	-	0.44 mg/m^3	0.23 mg/m^3
Carbon nanotubes	-	-	1 μg/m^3	1 μg/m^3	-	-
TiO_2	15 mg/m^3 (total dust)	2.4 mg/m^3	0.3 mg/m^3	0.3 mg/m^3	0.3 mg/m^3	1 mg/m^3
SiO_2 *	80 mg/m^3/%SiO_2	6 mg/m^3	-	-	0.75 mg/m^3	0.4 mg/m^3
CuO	1 mg/m^3 (dust) 0.1 mg/m^3 (fume)	1 mg/m^3 (dust) 0.1 mg/m^3 (fume)	-	-	13 μg/m^3	7 μg/m^3
ZnO	15 mg/m^3 (total dust) 5 mg/m^3 (fume)	15 mg/m^3 (dust) 10 mg/m^3 (fume)	-	-	1.25 mg/m^3	0.66 mg/m^3
Al_2O_3	15 mg/m^3 (total dust) 5 mg/m^3 (resp. fraction)	10 mg/m^3 (total dust) 5 mg/m^3 (resp. fraction)	-	-	0.63 mg/m^3	0.33 mg/m^3
Fe_2O_3	10 mg/m^3	5 mg/m^3	-	-	0.63 mg/m^3	0.33 mg/m^3
Graphite	15 mg/m^3 (total dust) 5 mg/m^3 (resp. fraction)	2.5 mg/m^3	-	-	0.31 mg/m^3	0.16 mg/m^3
MoS_2	15 mg/m^3 (total dust) 5 mg/m^3 (resp. dust)	5 mg/m^3	-	-	0.63 mg/m^3	0.33 mg/m^3

Table 5. *Cont.*

Particles	Regulatory Entity					
	OSHA	NIOSH	OSHA	NIOSH	According to Note 1	According to Note 2
SiC	15 mg/m^3 (total dust) 5 mg/m^3 (resp. fraction)	10 mg/m^3 (total dust) 5 mg/m^3 (resp. fraction)	-	-	0.63 mg/m^3	0.33 mg/m^3
WS_2	5 mg/m^3	10 mg/m^3 (total dust) 5 mg/m^3 (resp. fraction)	-	-	0.63 mg/m^3	0.33 mg/m^3
Graphene/Graphene oxide	-	-	-	-	-	-
hBN	-	-	-	-	-	-

-: Non-established; *: Values for amorphous silica. For crystalline (quartz), 50 µg/m^3 for both PEL and REL; ^ 10-h time-weighted average; + 8-h time-weighted average. Note 1: NIOSH defines a REL value of TiO_2 as 8 times lower than REL 2.4 mg/m^3 for the fine TiO_2 [131]. In this case, 8-fold reduction in exposure limits is applied for nanoparticles with respect to their microscale limits. This factor is considered here as a rough guide for other nanoparticles. Note 2: Suggested benchmark exposure levels from British Standards Institution (BSI) [138]. It suggests 0.066 × PEL for insoluble nanoparticles. In order to consider a most restrictive result, both CuO and ZnO are also considered insoluble as most nanoparticles.

In addition to the legislation in terms of nanoparticle exposure, the negative health effect of MWF exposures in the workplace is well-known [9]. According to OSHA regulations, the PEL value for mineral oil mist is defined as 5 mg/m^3 as a time-weighted average for 8-h expressed as a total proportion of particles, whereas the value is set to 15 mg/m^3 for vegetable oil mist [139,140]. The NIOSH organism defines the REL value as 0.5 mg/m^3 (or 0.4 mg/m^3 thoracic fraction) for oil mist in metalworking operations, measured as an inhalable fraction based on a reference time of 10 h [9].

7. Guidelines

Guidelines and recommendations for a safer design of engineered nanoparticles have been provided in the literature [141–143]. For the application of nanoparticles in NMQL systems (i.e., nanofluids for improving anti-wear, anti-friction and cooling with respect to conventional MQL systems), and according to the review conducted above, the following guidelines are proposed.

7.1. Proper Oil Base Selection

The main lubricating component of MQL systems is the base oil, thus its selection will define the main performance of the lubricating system. According to vendor's recommendations [18], synthetic esters are preferable for machining processes where lubrication is critical. These lubricants present low viscosity and high boiling and flash points which result in a better lubrication performance and fewer vapors than conventional mineral oils. In addition, ester oils and fatty alcohols have very good biodegradability and very low toxicity.

To minimize harmful byproducts (fumes, etc.), lubricants with additives containing organic chlorine or zinc and mineral oil-based products with high aromatic compound content should be avoided [18]. When applying mineral oils, highly refined mineral oils are recommended to reduce potential carcinogens [144]. As an alternative to mineral oils, vegetable oils (natural esters) can be also applied due to their good lubrication ability and biodegradability. Most of the research works in MQL that can be found in the literature mainly apply vegetable oils such as soybean, peanut, maize, rapeseed, palm, castor, and sunflower oils. Compared to mineral oil, vegetable oil has the advantages of renewability, low toxicity, and easy biodegradation. Mineral oil may cause more serious damage to the human body than vegetable oil. Elimination of oil from the lungs can occur by expectoration or it can be metabolized and removed in the case of vegetable or animal oils. On the contrary, mineral oils are inert and indigestible by macrophages, which results in accumulation in the lungs and may induce pulmonary diseases (e.g., pneumonia due to exogenous oil in the alveoli) [144].

However, raw vegetable oils are not recommended as they are prone to oxidation and gumming up of the machine and any component they come in contact with in a relatively

short time. A review of vegetable oil-based nanolubricants in machining can be found in [145], where oxidation and insufficient extreme-pressure performance are stated as the main limitations for their application in MQL systems. Common commercial lubricants applied in MQL systems are vegetable oils with chemical modifications (hydrogenation, esterification, etc.) with additives such as antioxidants, viscosity modifiers, corrosion inhibitors, antiwear agents, etc.

The importance of proper oil base selection can be observed in [146], where two oils with similar lubricating performance provided different results in MQL systems due to the influence on viscosity and the generation of mist. Oils with lower viscosities will present higher volume flow rates under the same MQL settings, and thus, a more efficient lubrication performance. However, it should be noted that lower viscosities increase the emission of aerosol mist which can harm operators. Small droplets tend to stay suspended in the air longer, are more easily inhaled into the human body, and more difficult to remove with mist collectors. MQL vendors recommend lubricants with a kinematic viscosity range of 10 to 50 mm^2/s and, in some cases, up to 100 mm^2/s at 40 °C [18]. Tai et al. [17] studied the application of MQL in automotive powertrain machining lines and highlighted the issue of mist emissions in MQL systems. In [147], it was observed that thin, low-viscosity lubricants (<20 mm^2/s) generate high emission values. The emission level is also proportional to the air quantity and speed applied in the system; thus, a correct setting of the flow rate is needed to improve the air quality. Note that the PEL value for mineral and vegetable oil mist is currently set to 5 and 15 mg/m^3, respectively, from OSHA, and the REL value from NIOSH in metalworking fluids mist is 0.5 mg/m^3.

7.2. Proper Nanoparticle Selection

Nanoparticles are selected according to the requirements of the nanofluid. In NMQL applications, the nanofluid should provide anti-friction, anti-wear and good cooling capability to improve the machining performance. However, nanoparticle characteristics vary, and some of them may be more adequate for cooling (small sizes and higher aspect ratio nanoparticles, e.g., CNTs) while others may be more adequate to reduce the wear of frictional surfaces (i.e., cutting-tool surface) due to the creation of tribofilms (e.g., WS_2 and MoS_2 are typical examples of tribofilm formation). Recent research has reported the main characteristics of nanoparticles for their use in NMQL systems, which can be used for proper nanoparticle selection [148]. Table 6 shows a summary of potential benefits of adding nanoparticles to lubricants for NMQL applications.

Once the main properties of nanoparticles are set, the selection should include the potential toxicity that is admissible in the NMQL application under study. For instance, machine tools with emission extraction closer to the work with very limited emissions, may include moderate nanoparticles in the nanofluid formulation. In cases where the NMQL equipment is applied without specific safety equipment (safety glasses for eye protection, highly efficient face masks for respiratory protection and other body and skin personal protection equipment specified in the corresponding materials' safety data sheets), although the emissions were minimal, only nanoparticles with a very low toxicity would be recommended. Unlike conventional extraction systems typically placed at the upper part of the machine tool, NMQL emission extraction is often more effective closer to the work [18]. In general, it is recommended that extraction systems be incorporated into the spindle head to remove the emissions very near to the cutting zone. Additionally, respirators with high filtration efficiency can be used to avoid operator exposure to airborne particles present near the machining area [149], although this alternative may hinder NMQL implementation in industry.

Table 6. Main characteristics of nanoparticles for their use in NMQL systems. Source [148].

Nanoparticles	Anti-Friction	Anti-Wear	Cooling	Mending	Polishing	Toxicity
WS_2	+	+++	+	++	+	+
MoS_2	++	+++	++	++	+	+
Fe_2O_3	+++	++	+	+++	++	+
Al_2O_3	+++	+	+	+++	+++	+
SiC	+++	+	++	+++	+++	+
Graphite	+	++	++	++	+	+
TiO_2	+++	++	+	+++	++	+
SiO_2	+++	+	+	+++	++	++
Graphene	+	+	+	+	+	++
ZrO_2	+++	+	+	+++	++	++
Fullerene (C60)	+++	+	+	+++	+	++
Nanodiamond	+++	+	+++	+++	+++	++
Graphene Oxide	+	++	+++	++	+	+++
SWCNT	++	+	+++	+	+	+++
MWCNT	++	+	+++	+	+	+++
hBN	+++	++	+	+++	+	+++
ZnO	+++	++	+	+++	++	+++
CuO	+++	++	+	+++	+	+++

Anti-friction: shape-dependent; from sliding to rolling. Anti-wear: material-dependent; capability of tribofilm formation. Cooling: material-related; property related to nanoparticle itself. Mending: size-dependent and surface-dependent; spherical better than tubular or sheets/plates; larger nanoparticles as CNTs, low mending capability. Polishing: hardness-dependent and workpiece-material-dependent; higher hardness gives better polishing behavior, although scratches may be produced. (+) Low impact; (++) Medium impact; (+++) High impact.

7.3. Selection/Modification of Physicochemical Properties

Apart from selecting the nanoparticles to be applied in the nanolubricant for NMQL application, different physicochemical properties may be adjusted to minimize nanoparticle toxicity. As stated in this review, many physicochemical properties such as size, shape, surface modifiers, etc., are related to nanoparticle toxicity. Some general guidelines to minimize the toxicity impact of the selected nanoparticle are listed below:

- Select larger nanoparticles. In general, larger nanoparticles within nanoscale lead to lower toxicity profiles and have reduced translocation capability. However, in case of overlong nanoparticles (fiber-like nanoparticles), e.g., CNTs or graphene nanoplates, length should be lower than 5 μm, which seems a critical value for effective clearance of nanoparticles by macrophages. In some cases, smaller nanoparticles may be preferred since they facilitate dissolution and clearance.
- Reduce the aspect ratio. In general, the lowest toxicity profile is related to spherical shapes. Any increase in the aspect ratio seems to increase the toxicity profile. The worst case scenario is nanoparticles similar to asbestos (fiber-like nanoparticles), which show the worst toxicity.
- Partially soluble nanoparticles are easier to clear and they are preferred if there is no release of toxic ions. Ions release, as occurs with ZnO and CuO nanoparticles, must be avoided.

7.4. Application of Surfactants and Surface Modifiers

Surfactants and nanoparticle surface modifiers are commonly used to ensure colloidal stability of nanoparticles suspended in a base fluid, and to prevent nanoparticles reagglomerating. In those cases, special attention should be taken to avoid increasing the toxicity profile of the nanofluid. The following guidelines are provided to limit toxicity due to these additives.

- In the case of surface modifiers, covalent functionalization with anionic/neutral and hydrophilic surface groups could potentially decrease their toxicity (e.g., carboxylate, hydroxylate and polyethylene glycol). Avoid cationic functional groups (e.g., CTAB, BAC).

- Avoid positive zeta potential when formulating nanofluids. Nanoparticles with negative zeta potential are less prone to impart toxicity.

Figure 8 summarizes previous guidelines for safer nanofluids in NMQL applications. Besides these guidelines, special attention should be paid to the expected evolution of the NMQL technology. Recent research [150,151] has shown the benefits of using the synergetic effects between electrostatic spraying and minimum quantity lubrication which results in the so-called Electrostatic Minimum Quantity Lubrication (EMQL) technology. This new green technology is basically a modification of MQL systems by adding a high-voltage electrostatic power supply. Lubricants are directly charged using an electrode, which is embedded in the oil hose, and when the lubricant is atomized with compressed air, the resulting mist is charged. This system facilitates the adsorption of the oil mists on the machining zone which results in a better lubrication applying less lubricant quantity [150]. In a recent review of this MQL evolution [151], it was stated that the problem of high oil mist concentration in conventional MQL can be reduced by approximately 6.2–68.3% and the consumption of lubricants may be reduced by 60% which may reduce the health issue concerns if nanoparticles are added into the system.

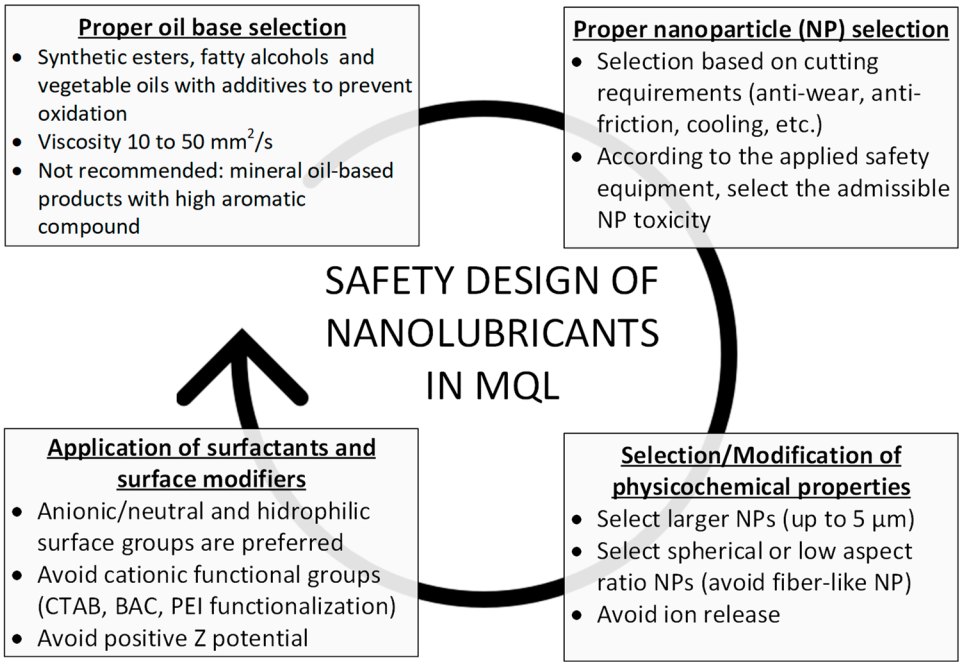

Figure 8. Guidelines for safety design of nanolubricants in NMQL systems.

8. Conclusions

NMQL has been shown to be a promising lubricating system that can reduce environmental and health hazards in machining processes. However, the potential hazard that nanoparticles pose when mist is generated by these systems has not been studied in detail. This review has considered recent toxicological studies about nanoparticle toxicities, in order to highlight which nanoparticles should be avoided and which may be used under certain safety measurements. Permissible and recommended exposure limits according to current EU and USA regulations have been provided, and recommended limits according to the British Standards Institution are also given in those cases where exposure limits are still under evaluation.

For practitioners, this work has presented guidelines for safer design of nanolubricants applied to NMQL systems which are summarized as follows:

- It is recommended to use vegetable oils as lubricant due to their renewability, low toxicity, and easy biodegradation. Moreover, vegetable oil may cause less serious damage to the human body than mineral oil.

- Regarding nanoparticle selection based on chemical composition, metal sulfides are the best choice with the lowest toxicity. Carbon-based materials present medium to high toxicity while oxides of transition metals are not recommended due to their very high toxicity.
- It is important to pay attention to some physicochemical properties that can reduce toxicity, for example particle size and shape. Smaller particles with lower aspect ratio such as spherical particles are preferred over nanotubes and nanosheets.
- Selection of soluble nanoparticles that do not release ions, which are less cytotoxic than insoluble or partly soluble nanoparticles.
- For nanolubricant production, some surfactant additives may be required to ensure stability. It is recommended to avoid the use of cationic surfactants and cationic functionalization groups and also to avoid positive zeta potential.

As a general recommendation, nanoparticle selection for NMQL must meet an agreement between health issues and machining performance. The formulation of hybrid nanofluids may be an option to balance both characteristics and derive better nanolubricants for NMQL applications.

The main limitation of this work is that most of the studies reported are related to in vitro studies, with a lack of in vivo studies covering long-term or chronic exposure in humans or animals, which would be more relevant for NMQL applicability. Therefore, future work should focus on analyzing mist emission levels in current MQL/NMQL industrial environments under different extraction systems, and on gathering relevant in vivo or industrial studies related to health issues due to nanoparticle mist exposure to support the conclusions derived in this work. These actions may help future regulators establish appropriate exposure levels to ensure workers' safety when implementing NMQL systems. Additionally, the impact of nanolubricants on the environment should also be analyzed. However, considering the quantity applied in NMQL systems that may reach the soil and water sewers, the impact is expected to be limited.

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References

1. Schwarz, M.; Dado, M.; Hnilica, R.; Veverková, D. Environmental and Health Aspects of Metalworking Fluid Use. *Pol. J. Environ. Stud.* **2015**, *24*, 37–45.
2. Chinchanikar, S.; Kore, S.S.; Hujare, P. A Review on Nanofluids in Minimum Quantity Lubrication Machining. *J. Manuf. Process.* **2021**, *68*, 56–70. [CrossRef]
3. Tiwari, A.; Singh, D.K.; Mishra, S. A Review on Minimum Quantity Lubrication in Machining of Different Alloys and Superalloys Using Nanofluids. *J. Braz. Soc. Mech. Sci. Eng.* **2024**, *46*, 112. [CrossRef]
4. Ali, S.H.; Yao, Y.; Wu, B.; Zhao, B.; Ding, W.; Jamil, M.; Khan, A.; Baig, A.; Liu, Q.; Xu, D. Recent Developments in MQL Machining of Aeronautical Materials: A Comparative Review. *Chin. J. Aeronaut.* 2024; *in press*. [CrossRef]
5. Kaitwade, N. Metalworking Fluids Market Outlook (2023 to 2033). 2023. Available online: https://www.futuremarketinsights.com/reports/metal-working-fluids-market (accessed on 9 October 2024).
6. Najiha, M.S.; Rahman, M.M.; Yusoff, A.R. Environmental Impacts and Hazards Associated with Metal Working Fluids and Recent Advances in the Sustainable Systems: A Review. *Renew. Sustain. Energy Rev.* **2016**, *60*, 1008–1031. [CrossRef]
7. Weinert, K.; Inasaki, I.; Sutherland, J.W.; Wakabayashi, T. Dry Machining and Minimum Quantity Lubrication. *CIRP Ann.* **2004**, *53*, 511–537. [CrossRef]
8. Klocke, F.; Eisenblaetter, G. Dry Cutting. *CIRP Ann. Manuf. Technol.* **1997**, *46*, 519–526. [CrossRef]

9. NIOSH. *Occupational Exposure to Metalworking Fluids. Criteria for a Recommended Standard*; Education and Information Division of the National Institute for Occupational Safety and Health (NIOSH): Cincinnati, OH, USA, 1998.
10. Mirer, F.E. New Evidence on the Health Hazards and Control of Metalworking Fluids since Completion of the OSHA Advisory Committee Report. *Am. J. Ind. Med.* **2010**, *53*, 792–801. [CrossRef]
11. Park, R.M. Risk Assessment for Metalworking Fluids and Respiratory Outcomes. *Saf. Health Work* **2019**, *10*, 428–436. [CrossRef]
12. Simpson, A.T.; Stear, M.; Groves, J.A.; Piney, M.; Bradley, S.D.; Stagg, S.; Crook, B. Occupational Exposure to Metalworking Fluid Mist and Sump Fluid Contaminants. *Ann. Occup. Hyg.* **2003**, *47*, 17–30. [CrossRef]
13. Shen, B. Minimum Quantity Lubrication Grinding Using Nanofluids. Doctoral Dissertation, University of Michigan, Ann Arbor, MI, USA, 2008.
14. Goindi, G.S.; Sarkar, P. Dry Machining: A Step towards Sustainable Machining—Challenges and Future Directions. *J. Clean. Prod.* **2017**, *165*, 1557–1571. [CrossRef]
15. Carter, N. *Tribology and Lubrication Technology*; STLE: Park Ridge, IL, USA, 2009.
16. Singh, T.; Singh, P.; Dureja, J.S.; Dogra, M.; Singh, H.; Bhatti, M.S. A Review of near Dry Machining/Minimum Quantity Lubrication Machining of Difficult to Machine Alloys. *Int. J. Mach. Mach. Mater.* **2016**, *18*, 213–251. [CrossRef]
17. Tai, B.L.; Stephenson, D.A.; Furness, R.J.; Shih, A.J. Minimum Quantity Lubrication (MQL) in Automotive Powertrain Machining. *Procedia CIRP* **2014**, *14*, 523–528. [CrossRef]
18. Walker, T. *MQL Handbook*; Unist Company: Grand Rapids, MI, USA, 2013.
19. Nouzil, I.; Eltaggaz, A.; Pervaiz, S.; Deiab, I. Toxicity Analysis of Nano-Minimum Quantity Lubrication Machining—A Review. *Lubricants* **2022**, *10*, 176. [CrossRef]
20. Bai, X.; Li, C.; Dong, L.; Yin, Q. Experimental Evaluation of the Lubrication Performances of Different Nanofluids for Minimum Quantity Lubrication (MQL) in Milling Ti-6Al-4V. *Int. J. Adv. Manuf. Technol.* **2019**, *101*, 2621–2632. [CrossRef]
21. Baldin, V.; da Silva, L.R.R.; Gelamo, R.V.; Iglesias, A.B.; da Silva, R.B.; Khanna, N.; Rocha Machado, A. Influence of Graphene Nanosheets on Thermo-Physical and Tribological Properties of Sustainable Cutting Fluids for MQL Application in Machining Processes. *Lubricants* **2022**, *10*, 193. [CrossRef]
22. Duan, Z.; Yin, Q.; Li, C.; Dong, L.; Bai, X.; Zhang, Y.; Yang, M.; Jia, D.; Li, R.; Liu, Z. Milling Force and Surface Morphology of 45 Steel under Different Al_2O_3 Nanofluid Concentrations. *Int. J. Adv. Manuf. Technol.* **2020**, *107*, 1277–1296. [CrossRef]
23. Marques, A.; Paipa Suarez, M.; Falco Sales, W.; Rocha Machado, Á. Turning of Inconel 718 with Whisker-Reinforced Ceramic Tools Applying Vegetable-Based Cutting Fluid Mixed with Solid Lubricants by MQL. *J. Mater. Process. Technol.* **2019**, *266*, 530–543. [CrossRef]
24. Namlu, R.H.; Lotfi, B.; Kılıç, S.E. Enhancing Machining Efficiency of Ti-6Al-4V through Multi-Axial Ultrasonic Vibration-Assisted Machining and Hybrid Nanofluid Minimum Quantity Lubrication. *J. Manuf. Process.* **2024**, *119*, 348–371. [CrossRef]
25. Kumar, A.; Sharma, A.K.; Katiyar, J.K. State-of-the-Art in Sustainable Machining of Different Materials Using Nano Minimum Quality Lubrication (NMQL). *Lubricants* **2023**, *11*, 64. [CrossRef]
26. Dubey, V.; Sharma, A.K. A Short Review on Hybrid Nanofluids in Machining Processes. *Adv. Mater. Process. Technol.* **2023**, *9*, 138–151. [CrossRef]
27. Sharma, A.K.; Tiwari, A.K.; Dixit, A.R. Effects of Minimum Quantity Lubrication (MQL) in Machining Processes Using Conventional and Nanofluid Based Cutting Fluids: A Comprehensive Review. *J. Clean. Prod.* **2016**, *127*, 1–18. [CrossRef]
28. Cui, X.; Li, C.; Ding, W.; Chen, Y.; Mao, C.; Xu, X.; Liu, B.; Wang, D.; Li, H.N.; Zhang, Y.; et al. Minimum Quantity Lubrication Machining of Aeronautical Materials Using Carbon Group Nanolubricant: From Mechanisms to Application. *Chin. J. Aeronaut.* **2022**, *35*, 85–112. [CrossRef]
29. Patole, P.B.; Kulkarni, V.V.; Bhatwadekar, S.G. MQL Machining with Nano Fluid: A Review. *Manuf. Rev.* **2021**, *8*, 13. [CrossRef]
30. Balasuadhakar, A.; Thirumalai Kumaran, S.; Ahmed, F. A Review on the Role of Nanoparticles in MQL Machining. *Mater. Today Proc.* **2023**, *72*, 2828–2832. [CrossRef]
31. Hamed Adibi, O.H.; Rezaei, S.M. Effects of Minimum Quantity Lubrication (MQL) on Grinding Processes Using Eco-Friendly Nanofluids: A Review. *Adv. Mater. Process. Technol.* **2024**, *10*, 1666–1707. [CrossRef]
32. Chu, A.; Li, C.; Zhou, Z.; Liu, B.; Zhang, Y.; Yang, M.; Gao, T.; Liu, M.; Zhang, N.; Dambatta, Y.S.; et al. Nanofluids Minimal Quantity Lubrication Machining: From Mechanisms to Application. *Lubricants* **2023**, *11*, 422. [CrossRef]
33. Mondragón, R.; Abellán-Nebot, J.V.; Habib, K.; Serrano, J. Tribological Analysis and Operation Issues of SiO2 Nanolubricants for MQL Machining Operations. *Key Eng. Mater.* **2023**, *960*, 11–20. [CrossRef]
34. Wang, Y.; Murga, A.; Long, Z.; Yoo, S.J.; Ito, K. Experimental Study of Oil Mist Characteristics Generated from Minimum Quantity Lubrication and Flood Cooling. *Energy Built Environ.* **2021**, *2*, 45–55. [CrossRef]
35. Ben Said, L.; Kolsi, L.; Ghachem, K.; Almeshaal, M.; Maatki, C. Application of Nanofluids as Cutting Fluids in Machining Operations: A Brief Review. *Appl. Nanosci.* **2022**, *13*, 4247–4278. [CrossRef]
36. Krajnik, P.; Pusavec, F.; Rashid, A. Nanofluids: Properties, Applications and Sustainability Aspects in Materials Processing Technologies. In *Advances in Sustainable Manufacturing*; Springer: Berlin/Heidelberg, Germany, 2011; pp. 107–113.
37. Seyedmahmoudi, S.H.; Harper, S.L.; Weismiller, M.C.; Haapala, K.R. Evaluating the Use of Zinc Oxide and Titanium Dioxide Nanoparticles in a Metalworking Fluid from a Toxicological Perspective. *J. Nanoparticle Res.* **2015**, *17*, 104. [CrossRef]
38. Agency for Toxic Substances and Disease Registry. *Guidance for Inhalation Exposures to Particulate Matter*; U.S. Department of Health and Human Services, Public Health Service: Atlanta, GA, USA, 2020.

39. Kumah, E.A.; Fopa, R.D.; Harati, S.; Boadu, P.; Zohoori, F.V.; Pak, T. Human and Environmental Impacts of Nanoparticles: A Scoping Review of the Current Literature. *BMC Public Health* **2023**, *23*, 1059. [CrossRef] [PubMed]
40. Buzea, C.; Pacheco, I.I.; Robbie, K. Nanomaterials and Nanoparticles: Sources and Toxicity. *Biointerphases* **2007**, *2*, MR17. [CrossRef] [PubMed]
41. Kermanizadeh, A.; Gosens, I.; MacCalman, L.; Johnston, H.; Danielsen, P.H.; Jacobsen, N.R.; Lenz, A.-G.; Fernandes, T.; Schins, R.P.F.; Cassee, F.R.; et al. A Multilaboratory Toxicological Assessment of a Panel of 10 Engineered Nanomaterials to Human Health–ENPRA Project–The Highlights, Limitations, and Current and Future Challenges. *J. Toxicol. Environ. Health B Crit. Rev.* **2016**, *19*, 1126210. [CrossRef]
42. Ramanathan, A. Toxicity of Nanoparticles_Challenges and Opportunities. *Appl. Microsc.* **2019**, *49*, 2. [CrossRef]
43. Bierkandt, F.S.; Leibrock, L.; Wagener, S.; Laux, P.; Luch, A. The Impact of Nanomaterial Characteristics on Inhalation Toxicity. *Toxicol. Res.* **2018**, *7*, 321–346. [CrossRef]
44. Gangwa, S.; Brown, J.S.; Wang, A.; Houck, K.A.; Dix, D.J.; Kavlock, R.J.; Cohen Hubal, E.A. Informing Selection of Nanomaterial Concentrations for ToxCast in Vitro Testing Based on Occupational Exposure Potential. *Environ. Health Perspect.* **2011**, *119*, 1539–1546. [CrossRef]
45. Raies, A.B.; Bajic, V.B. In Silico Toxicology: Computational Methods for the Prediction of Chemical Toxicity. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2016**, *6*, 147–172. [CrossRef]
46. Li, J.; Wang, C.; Yue, L.; Chen, F.; Cao, X.; Wang, Z. Nano-QSAR Modeling for Predicting the Cytotoxicity of Metallic and Metal Oxide Nanoparticles: A Review. *Ecotoxicol. Environ. Saf.* **2022**, *243*, 113955. [CrossRef]
47. Subramanian, N.A.; Palaniappan, A. NanoTox: Development of a Parsimonious in Silico Model for Toxicity Assessment of Metal-Oxide Nanoparticles Using Physicochemical Features. *ACS Omega* **2021**, *6*, 11729–11739. [CrossRef]
48. Hernández Battez, A.; González, R.; Viesca, J.L.; Fernández, J.E.; Díaz Fernández, J.M.; Machado, A.; Chou, R.; Riba, J. CuO, ZrO_2 and ZnO Nanoparticles as Antiwear Additive in Oil Lubricants. *Wear* **2008**, *265*, 422–428. [CrossRef]
49. Sengul, A.B.; Asmatulu, E. Toxicity of Metal and Metal Oxide Nanoparticles: A Review. *Environ. Chem. Lett.* **2020**, *18*, 1659–1683. [CrossRef]
50. Najahi-Missaoui, W.; Arnold, R.D.; Cummings, B.S. Safe Nanoparticles: Are We There Yet? *Int. J. Mol. Sci.* **2021**, *22*, 385. [CrossRef]
51. Sharifi, S.; Behzadi, S.; Laurent, S.; Forrest, M.L.; Stroeve, P.; Mahmoudi, M. Toxicity of Nanomaterials. *Chem. Soc. Rev.* **2012**, *41*, 2323–2343. [CrossRef] [PubMed]
52. Kumar, V.; Sharma, N.; Maitra, S.S. In Vitro and in Vivo Toxicity Assessment of Nanoparticles. *Int. Nano Lett.* **2017**, *7*, 243–256. [CrossRef]
53. Zhang, X.Q.; Yin, L.H.; Tang, M.; Pu, Y.P. ZnO, TiO_2, SiO_2, and Al_2O_3 Nanoparticles-Induced Toxic Effects on Human Fetal Lung Fibroblasts. *Biomed. Environ. Sci.* **2011**, *24*, 661–669. [CrossRef]
54. Karlsson, H.L.; Cronholm, P.; Gustafsson, J.; Möller, L. Copper Oxide Nanoparticles Are Highly Toxic: A Comparison between Metal Oxide Nanoparticles and Carbon Nanotubes. *Chem. Res. Toxicol.* **2008**, *21*, 1726–1732. [CrossRef]
55. Kim, I.-S.; Baek, M.; Choi, S.-J. Comparative Cytotoxicity of Al2O3, CeO2, TiO2 and ZnO Nanoparticles to Human Lung Cells. *J. Nanosci. Nanotechnol.* **2010**, *10*, 3453–3458. [CrossRef]
56. Lee, J.H.; Ju, J.E.; Kim, B.I.; Pak, P.J.; Choi, E.K.; Lee, H.S.; Chung, N. Rod-Shaped Iron Oxide Nanoparticles Are More Toxic than Sphere-Shaped Nanoparticles to Murine Macrophage Cells. *Environ. Toxicol. Chem.* **2014**, *33*, 2759–2766. [CrossRef]
57. Remzova, M.; Zouzelka, R.; Brzicova, T.; Vrbova, K.; Pinkas, D.; Rőssner, P.; Topinka, J.; Rathousky, J. Toxicity of TiO_2, ZnO, and SiO_2 Nanoparticles in Human Lung Cells: Safe-by-Design Development of Construction Materials. *Nanomaterials* **2019**, *9*, 968. [CrossRef]
58. Wei, W.; Yan, Z.; Liu, X.; Qin, Z.; Tao, X.; Zhu, X.; Song, E.; Chen, C.; Ke, P.C.; Leong, D.T.; et al. Brain Accumulation and Toxicity Profiles of Silica Nanoparticles: The Influence of Size and Exposure Route. *Environ. Sci. Technol.* **2022**, *56*, 8319–8325. [CrossRef]
59. Brown, D.M.; Johnston, H.J.; Gaiser, B.; Pinna, N.; Caputo, G.; Culha, M.; Kelestemur, S.; Altunbek, M.; Stone, V.; Roy, J.C.; et al. A Cross-Species and Model Comparison of the Acute Toxicity of Nanoparticles Used in the Pigment and Ink Industries. *NanoImpact* **2018**, *11*, 20–32. [CrossRef]
60. Ma-Hock, L.; Strauss, V.; Treumann, S.; Küttler, K.; Wohlleben, W.; Hofmann, T.; Gröters, S.; Wiench, K.; van Ravenzwaay, B.; Landsiedel, R. Comparative Inhalation Toxicity of Multi-Wall Carbon Nanotubes, Graphene, Graphite Nanoplatelets and Low Surface Carbon Black. *Part. Fibre Toxicol.* **2013**, *10*, 23. [CrossRef] [PubMed]
61. Kobayashi, N.; Izumi, H.; Morimoto, Y. Review of Toxicity Studies of Carbon Nanotubes. *J. Occup. Health* **2017**, *59*, 394–407. [CrossRef] [PubMed]
62. Mollá, F.A.; Alvaro, J.A.H.; Sánchez, O.A.; Fito-López, C.; González, I.C. Nanosafety Analysis of Graphene-Based Polyester Resin Composites on a Life Cycle Perspective. *Nanomaterials* **2022**, *12*, 2036. [CrossRef] [PubMed]
63. Roberts, J.R.; Mercer, R.R.; Stefaniak, A.B.; Seehra, M.S.; Geddam, U.K.; Chaudhuri, I.S.; Kyrlidis, A.; Kodali, V.K.; Sager, T.; Kenyon, A.; et al. Evaluation of Pulmonary and Systemic Toxicity Following Lung Exposure to Graphite Nanoplates: A Member of the Graphene-Based Nanomaterial Family. *Part. Fibre Toxicol.* **2016**, *13*, 34. [CrossRef]
64. Chng, E.L.K.; Chua, C.K.; Pumera, M. Graphene Oxide Nanoribbons Exhibit Significantly Greater Toxicity than Graphene Oxide Nanoplatelets. *Nanoscale* **2014**, *6*, 10792–10797. [CrossRef]

65. Li, X.; Kang, B.; Eom, Y.; Zhong, J.; Lee, H.K.; Kim, H.M.; Song, J.S. Comparison of Cytotoxicity Effects Induced by Four Different Types of Nanoparticles in Human Corneal and Conjunctival Epithelial Cells. *Sci. Rep.* **2022**, *12*, 155. [CrossRef]
66. Yang, H.; Liu, C.; Yang, D.; Zhang, H.; Xi, Z. Comparative Study of Cytotoxicity, Oxidative Stress and Genotoxicity Induced by Four Typical Nanomaterials: The Role of Particle Size, Shape and Composition. *J. Appl. Toxicol.* **2009**, *29*, 69–78. [CrossRef]
67. Angoth, B.; Lingabathula, H.; Gandamalla, D.; Yellu, N.R. Cytotoxicity Evaluation of Carbon Nanomaterials on Human Cell Lines Using MTT Assay. *Int. J. Pharm. Pharm. Sci.* **2014**, *2014*, 379–382.
68. Lam, C.W.; James, J.T.; McCluskey, R.; Arepalli, S.; Hunter, R.L. A Review of Carbon Nanotube Toxicity and Assessment of Potential Occupational and Environmental Health Risks. *Crit. Rev. Toxicol.* **2006**, *36*, 189–217. [CrossRef] [PubMed]
69. Raja, I.S.; Song, S.J.; Kang, M.S.; Bin Lee, Y.; Kim, B.; Hong, S.W.; Jeong, S.J.; Lee, J.C.; Han, D.W. Toxicity of Zero-and One-Dimensional Carbon Nanomaterials. *Nanomaterials* **2019**, *9*, 1214. [CrossRef] [PubMed]
70. Appel, J.H.; Li, D.O.; Podlevsky, J.D.; Debnath, A.; Green, A.A.; Wang, Q.H.; Chae, J. Low Cytotoxicity and Genotoxicity of Two-Dimensional MoS_2 and WS_2. *ACS Biomater. Sci. Eng.* **2016**, *2*, 361–367. [CrossRef] [PubMed]
71. Pardo, M.; Shuster-Meiseles, T.; Levin-Zaidman, S.; Rudich, A.; Rudich, Y. Low Cytotoxicity of Inorganic Nanotubes and Fullerene-like Nanostructures in Human Bronchial Epithelial Cells: Relation to Inflammatory Gene Induction and Antioxidant Response. *Environ. Sci. Technol.* **2014**, *48*, 3457–3466. [CrossRef] [PubMed]
72. Teo, W.Z.; Chng, E.L.K.; Sofer, Z.; Pumera, M. Cytotoxicity of Exfoliated Transition-Metal Dichalcogenides (MoS_2, WS_2, and WSe_2) Is Lower than That of Graphene and Its Analogues. *Chem.—Eur. J.* **2014**, *20*, 9627–9632. [CrossRef]
73. Zapór, L. Rocznik Ochrona Środowiska Cytotoxicity Elicited by Molybdenum Disulphide in Different Size of Particles in Human Airway Cells. *Rocz. Ochr. Sr.* **2019**, *21*, 794–809.
74. Hao, J.; Song, G.; Liu, T.; Yi, X.; Yang, K.; Cheng, L.; Liu, Z. In Vivo Long-Term Biodistribution, Excretion, and Toxicology of PEGylated Transition-Metal Dichalcogenides MS_2 (M = Mo, W, Ti) Nanosheets. *Adv. Sci.* **2017**, *4*, 1600160. [CrossRef]
75. Chen, X.; Wu, P.; Rousseas, M.; Okawa, D.; Gartner, Z.; Zettl, A.; Bertozzi, C.R. Boron Nitride Nanotubes Are Noncytotoxic and Can Be Functionalized for Interaction with Proteins and Cells. *J. Am. Chem. Soc.* **2009**, *131*, 890–891. [CrossRef]
76. Horváth, L.; Magrez, A.; Golberg, D.; Zhi, C.; Bando, Y.; Smajda, R.; Horváth, E.; Forró, L.; Schwaller, B. In Vitro Investigation of the Cellular Toxicity of Boron Nitride Nanotubes. *ACS Nano* **2011**, *5*, 3800–3810. [CrossRef]
77. Mao, Y.; Guo, Q.; Geng, X.; Zeng, H.; Liu, S.; Yin, X.; Yang, Z. Hexagonal Boron Nitride Nanodots Inhibit Cell Proliferation of HUVECs and the Underlying Mechanism. *Colloid Interface Sci. Commun.* **2023**, *56*, 100738. [CrossRef]
78. Lanone, S.; Rogerieux, F.; Geys, J.; Dupont, A.; Maillot-Marechal, E.; Boczkowski, J.; Lacroix, G.; Hoet, P. Comparative Toxicity of 24 Manufactured Nanoparticles in Human Alveolar Epithelial and Macrophage Cell Lines. *Part. Fibre Toxicol.* **2009**, *6*, 14. [CrossRef] [PubMed]
79. Oberdörster, G.; Maynard, A.; Donaldson, K.; Castranova, V.; Fitzpatrick, J.; Ausman, K.; Carter, J.; Karn, B.; Kreyling, W.; Lai, D.; et al. Principles for Characterizing the Potential Human Health Effects from Exposure to Nanomaterials: Elements of a Screening Strategy. *Part. Fibre Toxicol.* **2005**, *2*, 8. [CrossRef] [PubMed]
80. Zhang, N.; Xiong, G.; Liu, Z. Toxicity of Metal-Based Nanoparticles: Challenges in the Nano Era. *Front. Bioeng. Biotechnol.* **2022**, *10*, 1001572. [CrossRef] [PubMed]
81. Kim, J.E.; Kim, H.; An, S.S.A.; Maeng, E.H.; Kim, M.K.; Song, Y.J. In Vitro Cytotoxicity of SiO_2 or ZnO Nanoparticles with Different Sizes and Surface Charges on U373MG Human Glioblastoma Cells. *Int. J. Nanomed.* **2014**, *9*, 235–241. [CrossRef]
82. Sahu, D.; Kannan, G.M.; Tailang, M.; Vijayaraghavan, R. In Vitro Cytotoxicity of Nanoparticles: A Comparison between Particle Size and Cell Type. *J. Nanosci.* **2016**, *2016*, 4023852. [CrossRef]
83. Hsiao, I.L.; Huang, Y.J. Effects of Various Physicochemical Characteristics on the Toxicities of ZnO and TiO2 Nanoparticles toward Human Lung Epithelial Cells. *Sci. Total Environ.* **2011**, *409*, 1219–1228. [CrossRef]
84. Gurr, J.R.; Wang, A.S.S.; Chen, C.H.; Jan, K.Y. Ultrafine Titanium Dioxide Particles in the Absence of Photoactivation Can Induce Oxidative Damage to Human Bronchial Epithelial Cells. *Toxicology* **2005**, *213*, 66–73. [CrossRef]
85. De Jong, W.H.; Hagens, W.I.; Krystek, P.; Burger, M.C.; Sips, A.J.A.M.; Geertsma, R.E. Particle Size-Dependent Organ Distribution of Gold Nanoparticles after Intravenous Administration. *Biomaterials* **2008**, *29*, 1912–1919. [CrossRef]
86. Raftis, J.B.; Miller, M.R. Nanoparticle Translocation and Multi-Organ Toxicity: A Particularly Small Problem. *Nano Today* **2019**, *26*, 8–12. [CrossRef]
87. Semmler-Behnke, M.; Kreyling, W.G.; Lipka, J.; Fertsch, S.; Wenk, A.; Takenaka, S.; Schmid, G.; Brandau, W. Biodistribution of 1.4-and 18-Nm Gold Particles in Rats. *Small* **2008**, *4*, 2108–2111. [CrossRef]
88. Oberdorster, G.; Ferin, J.; Lehnert, B.E. Correlation between Particle Size, In Vivo Particle Persistence, and Lung Injury. *Environ. Health Perspect.* **1994**, *102* (Suppl. S5), 173–179. [PubMed]
89. Hadji, H.; Bouchemal, K. Effect of Micro- and Nanoparticle Shape on Biological Processes. *J. Control Release* **2022**, *342*, 93–110. [CrossRef] [PubMed]
90. WHO. *Determination of Airborne Fibre Number Concentrations: A Recommended Method, by Phase-Contrast Optical Microscopy (Membrane Filter Method)*; World Health Organization: Geneva, Switzerland, 1997.
91. Donaldson, K.; Poland, C.A. Inhaled Nanoparticles and Lung Cancer—What We Can Learn from Conventional Particle Toxicology. *Swiss Med. Wkly.* **2012**, *142*, w13547. [CrossRef] [PubMed]
92. Donaldson, K.; Murphy, F.; Schinwald, A.; Duffin, R.; Poland, C.A. Identifying the Pulmonary Hazard of High Aspect Ratio Nanoparticles to Enable Their Safety-by-Design. *Nanomedicine* **2011**, *6*, 143–153. [CrossRef]

93. Park, E.J.; Lee, G.H.; Shim, J.H.; Cho, M.H.; Lee, B.S.; Kim, Y.B.; Kim, J.H.; Kim, Y.; Kim, D.W. Comparison of the Toxicity of Aluminum Oxide Nanorods with Different Aspect Ratio. *Arch. Toxicol.* **2015**, *89*, 1771–1782. [CrossRef]
94. Huang, Y.-W.; Cambre, M.; Lee, H.-J. The Toxicity of Nanoparticles Depends on Multiple Molecular and Physicochemical Mechanisms. *Int. J. Mol. Sci.* **2017**, *18*, 2702. [CrossRef]
95. Cohignac, V.; Landry, M.J.; Ridoux, A.; Pinault, M.; Annangi, B.; Gerdil, A.; Herlin-Boime, N.; Mayne, M.; Haruta, M.; Codogno, P.; et al. Carbon Nanotubes, but Not Spherical Nanoparticles, Block Autophagy by a Shape-Related Targeting of Lysosomes in Murine Macrophages. *Autophagy* **2018**, *14*, 1323–1334. [CrossRef]
96. Jiang, T.; Amadei, C.A.; Gou, N.; Lin, Y.; Lan, J.; Vecitis, C.D.; Gu, A.Z. Toxicity of Single-Walled Carbon Nanotubes (SWCNTs): Effect of Lengths, Functional Groups and Electronic Structures Revealed by a Quantitative Toxicogenomics Assay. *Environ. Sci. Nano* **2020**, *7*, 1348–1364. [CrossRef]
97. Cui, X.; Wan, B.; Yang, Y.; Ren, X.; Guo, L.H. Length Effects on the Dynamic Process of Cellular Uptake and Exocytosis of Single-Walled Carbon Nanotubes in Murine Macrophage Cells. *Sci. Rep.* **2017**, *7*, 1518. [CrossRef]
98. Rodrigues, A.F.; Newman, L.; Jasim, D.; Mukherjee, S.P.; Wang, J.; Vacchi, I.A.; Ménard-Moyon, C.; Bianco, A.; Fadeel, B.; Kostarelos, K.; et al. Size-Dependent Pulmonary Impact of Thin Graphene Oxide Sheets in Mice: Toward Safe-by-Design. *Adv. Sci.* **2020**, *7*, 1903200. [CrossRef]
99. Oberdörster, G.; Castranova, V.; Asgharian, B.; Sayre, P. Inhalation Exposure to Carbon Nanotubes (CNT) and Carbon Nanofibers (CNF): Methodology and Dosimetry. *J. Toxicol. Environ. Health B Crit. Rev.* **2015**, *18*, 121–212. [CrossRef] [PubMed]
100. Cho, W.S.; Duffin, R.; Thielbeer, F.; Bradley, M.; Megson, I.L.; MacNee, W.; Poland, C.A.; Tran, C.L.; Donaldson, K. Zeta Potential and Solubility to Toxic Ions as Mechanisms of Lung Inflammation Caused by Metal/Metal Oxide Nanoparticles. *Toxicol. Sci.* **2012**, *126*, 469–477. [CrossRef] [PubMed]
101. Li, R.; Wang, X.; Ji, Z.; Sun, B.; Zhang, H.; Chang, C.H.; Lin, S.; Meng, H.; Liao, Y.P.; Wang, M.; et al. Surface Charge and Cellular Processing of Covalently Functionalized Multiwall Carbon Nanotubes Determine Pulmonary Toxicity. *ACS Nano* **2013**, *7*, 2352–2368. [CrossRef] [PubMed]
102. Gilbertson, L.M.; Melnikov, F.; Wehmas, L.C.; Anastas, P.T.; Tanguay, R.L.; Zimmerman, J.B. Toward Safer Multi-Walled Carbon Nanotube Design: Establishing a Statistical Model That Relates Surface Charge and Embryonic Zebrafish Mortality. *Nanotoxicology* **2016**, *10*, 10–19. [CrossRef] [PubMed]
103. Baek, M.; Kim, M.K.; Cho, H.J.; Lee, J.A.; Yu, J.; Chung, H.E.; Choi, S.J. Factors Influencing the Cytotoxicity of Zinc Oxide Nanoparticles: Particle Size and Surface Charge. In *Proceedings of the Journal of Physics: Conference Series*; Institute of Physics Publishing: Bristol, UK, 2011; Volume 304.
104. Nagarajan, R. *Nanoparticles: Building Blocks for Nanotechnology*; UTC: Greenwich, UK, 2023; Volume 16.
105. Oleszczuk, P.; Jośko, I.; Skwarek, E. Surfactants Decrease the Toxicity of ZnO, TiO_2 and Ni Nanoparticles to Daphnia Magna. *Ecotoxicology* **2015**, *24*, 1923–1932. [CrossRef]
106. Zhang, Y.; Newton, B.; Lewis, E.; Fu, P.P.; Kafoury, R.; Ray, P.C.; Yu, H. Cytotoxicity of Organic Surface Coating Agents Used for Nanoparticles Synthesis and Stability. *Toxicology In Vitro* **2015**, *29*, 762–768. [CrossRef]
107. Wang, S.; Lu, W.; Tovmachenko, O.; Rai, U.S.; Yu, H.; Ray, P.C. Challenge in Understanding Size and Shape Dependent Toxicity of Gold Nanomaterials in Human Skin Keratinocytes. *Chem. Phys. Lett.* **2008**, *463*, 145–149. [CrossRef]
108. Wan, J.; Wang, J.H.; Liu, T.; Xie, Z.; Yu, X.F.; Li, W. Surface Chemistry but Not Aspect Ratio Mediates the Biological Toxicity of Gold Nanorods in Vitro and in Vivo. *Sci. Rep.* **2015**, *5*, 11398. [CrossRef]
109. Miyazawa, T.; Itaya, M.; Burdeos, G.C.; Nakagawa, K.; Miyazawa, T. A Critical Review of the Use of Surfactant-Coated Nanoparticles in Nanomedicine and Food Nanotechnology. *Int. J. Nanomed.* **2021**, *16*, 3937–3999. [CrossRef]
110. Fröhlich, E. The Role of Surface Charge in Cellular Uptake and Cytotoxicity of Medical Nanoparticles. *Int. J. Nanomed.* **2012**, *7*, 5577–5591. [CrossRef]
111. Vranic, S.; Watanabe, E.; Miyakawa, K.; Takeuchi, S.; Osada, Y.; Ichihara, S.; Zong, C.; Wu, W.; Sakurai, T.; Sato, A.; et al. Impact of Surface Modication on Cellular Uptake and Cytotoxicity of Silica Nanoparticles. *Res. Sq.* **2020**, *10*, 1–20. [CrossRef]
112. Zhang, S.; Chu, Q.; Zhang, Z.; Xu, Y.; Mao, X.; Zhang, M. Responses of Caenorhabditis Elegans to Various Surface Modifications of Alumina Nanoparticles. *Environ. Pollut.* **2021**, *271*, 116335. [CrossRef] [PubMed]
113. Goodman, C.M.; McCusker, C.D.; Yilmaz, T.; Rotello, V.M. Toxicity of Gold Nanoparticles Functionalized with Cationic and Anionic Side Chains. *Bioconjug Chem.* **2004**, *15*, 897–900. [CrossRef] [PubMed]
114. Zhang, X.; Zhu, Y.; Li, J.; Zhu, Z.; Li, J.; Li, W.; Huang, Q. Tuning the Cellular Uptake and Cytotoxicity of Carbon Nanotubes by Surface Hydroxylation. *J. Nanopart. Res.* **2011**, *13*, 6941–6952. [CrossRef]
115. Zhou, L.; Forman, H.J.; Ge, Y.; Lunec, J. Multi-Walled Carbon Nanotubes: A Cytotoxicity Study in Relation to Functionalization, Dose and Dispersion. *Toxicol. In Vitro* **2017**, *42*, 292–298. [CrossRef]
116. Dong, X.; Liu, L.; Zhu, D.; Zhang, H.; Li, Y.; Leng, X. Effects of Carboxylated Multiwalled Carbon Nanotubes on the Function of Macrophages. *J. Nanomater.* **2015**, *2015*, 638760. [CrossRef]
117. Bruinink, A.; Wang, J.; Wick, P. Effect of Particle Agglomeration in Nanotoxicology. *Arch. Toxicol.* **2015**, *89*, 659–675. [CrossRef]
118. Cheng, J.; Cheng, S.H. Influence of Carbon Nanotube Length on Toxicity to Zebrafish Embryos. *Int. J. Nanomed.* **2012**, *7*, 3731–3739. [CrossRef]

119. Murugadoss, S.; Brassinne, F.; Sebaihi, N.; Petry, J.; Cokic, S.M.; Van Landuyt, K.L.; Godderis, L.; Mast, J.; Lison, D.; Hoet, P.H.; et al. Agglomeration of Titanium Dioxide Nanoparticles Increases Toxicological Responses in Vitro and in Vivo. *Part. Fibre Toxicol.* **2020**, *17*, 10. [CrossRef]
120. Mutlu, G.M.; Budinger, G.R.S.; Green, A.A.; Urich, D.; Soberanes, S.; Chiarella, S.E.; Alheid, G.F.; McCrimmon, D.R.; Szleifer, I.; Hersam, M.C. Biocompatible Nanoscale Dispersion of Single-Walled Carbon Nanotubes Minimizes in Vivo Pulmonary Toxicity. *Nano Lett.* **2010**, *10*, 1664–1670. [CrossRef]
121. Lim, C.-H.; Kang, M.; Han, J.-H.; Yang, J.-S. Effect of Agglomeration on the Toxicity of Nano-Sized Carbon Black in Sprague-Dawley Rats. *Environ. Health Toxicol.* **2012**, *27*, e2012015. [CrossRef] [PubMed]
122. Chang, Y.N.; Zhang, M.; Xia, L.; Zhang, J.; Xing, G. The Toxic Effects and Mechanisms of CuO and ZnO Nanoparticles. *Materials* **2012**, *5*, 2850–2871. [CrossRef]
123. Keller, J.G.; Persson, M.; Müller, P.; Ma-Hock, L.; Werle, K.; Arts, J.; Landsiedel, R.; Wohlleben, W. Variation in Dissolution Behavior among Different Nanoforms and Its Implication for Grouping Approaches in Inhalation Toxicity. *NanoImpact* **2021**, *23*, 100341. [CrossRef] [PubMed]
124. Hadrup, N.; Saber, A.T.; Kyjovska, Z.O.; Jacobsen, N.R.; Vippola, M.; Sarlin, E.; Ding, Y.; Schmid, O.; Wallin, H.; Jensen, K.A.; et al. Pulmonary Toxicity of Fe_2O_3, $ZnFe_2O_4$, $NiFe_2O_4$ and $NiZnFe_4O_8$ Nanomaterials: Inflammation and DNA Strand Breaks. *Environ. Toxicol. Pharmacol.* **2020**, *74*, 103303. [CrossRef] [PubMed]
125. Anastasiadis, S.H.; Chrissopoulou, K.; Stratakis, E.; Kavatzikidou, P.; Kaklamani, G.; Ranella, A. How the Physicochemical Properties of Manufactured Nanomaterials Affect Their Performance in Dispersion and Their Applications in Biomedicine: A Review. *Nanomaterials* **2022**, *12*, 552. [CrossRef] [PubMed]
126. Misra, S.K.; Dybowska, A.; Berhanu, D.; Croteau, M.N.; Luoma, S.N.; Boccaccini, A.R.; Valsami-Jones, E. Isotopically Modified Nanoparticles for Enhanced Detection in Bioaccumulation Studies. *Environ. Sci. Technol.* **2012**, *46*, 1216–1222. [CrossRef]
127. Utembe, W.; Potgieter, K.; Stefaniak, A.B.; Gulumian, M. Dissolution and Biodurability: Important Parameters Needed for Risk Assessment of Nanomaterials. *Part. Fibre Toxicol.* **2015**, *12*, 11. [CrossRef]
128. Wang, D.; Lin, Z.; Wang, T.; Yao, Z.; Qin, M.; Zheng, S.; Lu, W. Where Does the Toxicity of Metal Oxide Nanoparticles Come from: The Nanoparticles, the Ions, or a Combination of Both? *J. Hazard. Mater.* **2016**, *308*, 328–334. [CrossRef]
129. Deveau, M.; Chen, C.P.; Johanson, G.; Krewski, D.; Maier, A.; Niven, K.J.; Ripple, S.; Schulte, P.A.; Silk, J.; Urbanus, J.H.; et al. The Global Landscape of Occupational Exposure Limits—Implementation of Harmonization Principles to Guide Limit Selection. *J. Occup. Environ. Hyg.* **2015**, *12*, S127–S144. [CrossRef]
130. OSHA. *OSHA Fact Sheet. Working Safely with Nanomaterials*; OSHA: Washington, DC, USA, 2013.
131. NIOSH. *Current Intelligence Bulletin: Occupational Exposure to Titanium Dioxide*; NIOSH: Washington, DC, USA, 2011.
132. NIOSH. *Current Intelligence Bulletin: Occupational Exposure to Carbon Nanotubes and Nanofibers, Draft for Public Comment*; NIOSH: Washington, DC, USA, 2010.
133. NIOSH. *Current Intelligence Bulletin 65: Occupational Exposure to Carbon Nanotubes and Nanofibers*; NIOSH: Washington, DC, USA, 2013.
134. Safety, O.; Administration, H. Silver, Metal & Soluble Compounds (as Ag). Available online: https://www.osha.gov/chemicaldata/519 (accessed on 9 October 2024).
135. NIOSH. *Current Intelligence Bulletin: Health Effects of Occupational Exposure to Silver Nanomaterials*; NIOSH: Washington, DC, USA, 2021.
136. Katsnelson, B.A.; Privalova, L.I.; Kuzmin, S.V.; Gurvich, V.B.; Sutunkova, M.P.; Kireyeva, E.P.; Minigalieva, I.A. An Approach to Tentative Reference Levels Setting for Nanoparticles in the Workroom Air Based on Comparing Their Toxicity with That of Their Micrometric Counterparts: A Case Study of Iron Oxide Fe_3O_4. *ISRN Nanotechnol.* **2012**, *2012*, 143613. [CrossRef]
137. OSHA E.U. *Workplace Exposure to Nanoparticles*; EU: Bilbao, Spain, 2008.
138. BSI. *Nanotechnologies–Part 2: Guide to Safe Handling and Disposal of Manufactured Nanomaterials*; BSI: London, UK, 2007.
139. NIOSH. *Oil Mist (Mineral)*; NIOSH: Washington, DC, USA, 2019.
140. NIOSH. *Vegetable Oil Mist*; NIOSH: Washington, DC, USA, 2019.
141. Lin, S.; Yu, T.; Yu, Z.; Hu, X.; Yin, D. Nanomaterials Safer-by-Design: An Environmental Safety Perspective. *Adv. Mater.* **2018**, *30*, e1705691. [CrossRef] [PubMed]
142. Hwang, R.; Mirshafiee, V.; Zhu, Y.; Xia, T. Current Approaches for Safer Design of Engineered Nanomaterials. *Ecotoxicol. Environ. Saf.* **2018**, *166*, 294–300. [CrossRef] [PubMed]
143. Morose, G. The 5 Principles of "Design for Safer Nanotechnology". *J. Clean. Prod.* **2010**, *18*, 285–289. [CrossRef]
144. Brown, N.J. Health Hazard Manual for Cutting Oils, Coolants, and Metalworking Fluids. 1991. Available online: https://ecommons.cornell.edu/items/e567278d-18f7-412b-9661-3a20ac4b0bd1 (accessed on 9 October 2024).
145. Zhang, X.; Li, C.; Zhou, Z.; Liu, B.; Zhang, Y.; Yang, M.; Gao, T.; Liu, M.; Zhang, N.; Said, Z.; et al. Vegetable Oil-Based Nanolubricants in Machining: From Physicochemical Properties to Application. *Chin. J. Mech. Eng. (Engl. Ed.)* **2023**, *36*, 76. [CrossRef]
146. Cabanettes, F.; Faverjon, P.; Sova, A.; Dumont, F.; Rech, J. MQL Machining: From Mist Generation to Tribological Behavior of Different Oils. *Int. J. Adv. Manuf. Technol.* **2017**, *90*, 1119–1130. [CrossRef]
147. *Fachausschuss Information Sheet No. 006 Low-Emission Metalworking with Minimum Quantity Lubrication (MQL)*; Deutsche Gesetzliche Unfallversicherung e.V. (DGUV): Berlin, Germany, 2021; Available online: https://publikationen.dguv.de/widgets/pdf/download/article/4329 (accessed on 9 October 2024).

148. Abellán-Nebot, J.V.; Habib, K.; Mondragón, R.; Khan, A.M. Application of Hybrid Nanofluids in MQL Assisted Machining Operations. Exploring Synergies and Establishing Guidelines. *Int. J. Precis. Eng. Manuf.-Green Technol.* 2024; *to be published*.
149. Makhesana, M.A.; Patel, K.M.; Krolczyk, G.M.; Danish, M.; Singla, A.K.; Khanna, N. Influence of MoS_2 and Graphite-Reinforced Nanofluid-MQL on Surface Roughness, Tool Wear, Cutting Temperature and Microhardness in Machining of Inconel 625. *CIRP J. Manuf. Sci. Technol.* **2023**, *41*, 225–238. [CrossRef]
150. Lv, T.; Huang, S.; Liu, E.; Ma, Y.; Xu, X. Tribological and Machining Characteristics of an Electrostatic Minimum Quantity Lubrication (EMQL) Technology Using Graphene Nano-Lubricants as Cutting Fluids. *J. Manuf. Process.* **2018**, *34*, 225–237. [CrossRef]
151. Xu, X.; Lv, T.; Luan, Z.; Zhao, Y.; Wang, M.; Hu, X. Capillary Penetration Mechanism and Oil Mist Concentration of Al2O3 Nanoparticle Fluids in Electrostatic Minimum Quantity Lubrication (EMQL) Milling. *Int. J. Adv. Manuf. Technol.* **2019**, *104*, 1937–1951. [CrossRef]