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

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1. Introduction

Metalworking fluids (MWF) are widely used in machining operations to reduce mechanical and thermal load of the tool tip and reduce friction which results in longer tool life, better surface quality and lower cutting forces [1], [2]. The global metalworking fluids market size is estimated to be valued at $ 10 billion in 2023 with more than 2 million tons annual usage and it is projected to increase 3% year-over-year [3], which poses important costs and environmental and occupational problems. Depending on the workpiece, production costs and other factors, cost of cutting fluids may rise to 7-17% of a production shop total cost, [4], [5]. In contrast with the 2-4% for tooling expenditures commonly considered in machining [6], the costs related to cutting fluids are very relevant.

Apart from costs, serious environmental and occupational concerns are also linked with the application of cutting fluids [4]. The National Institute for Occupational Safety and Health (NIOSH) reported important evidences of health effects of MWF mist exposures in their referent publication [7], especially diseases for respiratory tracts including hypersensitivity, pneumonitis and asthma, and they defined the recommended exposure limit (REL) to 0.5 mg/m^3 (or 0.4 mg/ m^3 thoracic fraction). This is mainly explained by the mist generation of MWFs whose size ranges from 0.1 to 10 µm aerosols and more than 75% of MWF particulate matter is located in the sphere of respirable fraction (particle sizes less than 5 µm) that poses the highest risk for the human body [1].

In 2010, Mirer [8] 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 reduce the exposure

limits. In his review from MWF hazards publications from 1998 to 2010, 26 works were identified related to cancer; 56 related to respiratory effects; 32 related to skin effects and skin penetration. More recently, Park [9] 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 associated with attributable risks of 2-30 per thousand, which cannot be considered acceptable.

According to a review about occupational exposures to MWFs conducted in 2003 [10], it was stated that industrial practices are far away from a safety limit exposure which should be set to 0.1 mg/m^3 or lower. For instance, according to those reviews, 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 would be 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 operations [11].

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 can be conducted under many situations; however, dry machining is considered acceptable by the manufacturers when it ensures better or at least equal quality of product and material removal rate as obtained in wet machining [4]. The high temperatures at the cutting zone reduces tool life increasing the cutting costs, and only specific combinations of cutting tool materials and workpiece materials can be successfully applied in dry machining such as milling and turning cast iron in open-faced operations where chips can be easily move away [12], [13]. As shown in [13], Caterpillar Inc. has tried dry machining in a number of machining operations during the past 20 years and although the new tool coatings have been helpful, machining performance cannot reach the one obtained using MWFs.

Besides dry machining, near-dry machining has been extensively investigated in past decades. Some of these near-dry cooling strategies are Minimum Quantity Lubrication (MQL), solid lubrication, air cooling, cryogenic cooing and High Pressure Jet Assisted Machining (HPJAM) [4], [12], [14]. However, the effectiveness of near-dry technologies is also limited. For instance, the machining costs of cryogenic cooling are high although it showed enhanced productivity and product quality in terms of tool life, especially for difficult-to cut materials. The use of air, water vapor and other eco-friendly lubrication and cooling media have also their own limitations. Also, high pressure jet assisted cooling has not found wide applications in the industry on account of lack of knowledge

about the basic method [4]. Despite the efforts of developing different near-dry strategies, it seems that there is a consensus that only MQL can have a real potential to partially replace MWFs under some circumstances [4]. In fact, at industrial level, some companies are making efforts to move to MQL systems for a more sustainable process [19]. For instance, Ford Motor Company has a total of over 400 MQL CNC machining centers in numerous global transmission and engine plants running MQL operations [15].

A 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 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 [16]. Furthermore, MQL eliminates investments into sumps, recyclers, containers, pumps, and filtration devices, and there are no costs for cleaning and drying the chips before their disposal or cleaning the work pieces prior to the next process.

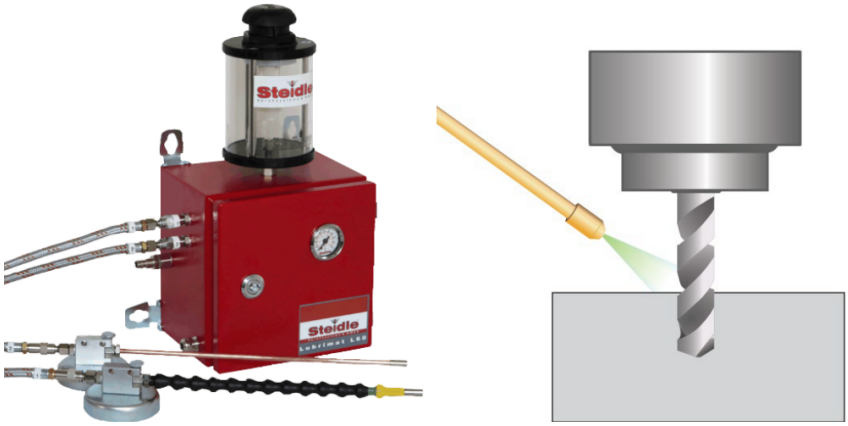

Figure 1. Example of Minimum Quantity Lubrication (MQL) equipment and application.

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 [5]. In open-faced operations of these materials, dry or air cooling machining can be conducted although MQL is an effective alternative. However, when machining difficult-to cut alloys, the excessive heat generated makes MWFs to be still mandatory due to the limited cooling capability of MQL systems. To overcome this limitation, Nanofluid MQL (NMQL) has been 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 a base oil increases the MQL performance due to an increased thermal conductivity which results in an increased heat removal rate and, additionally, the nanoparticles reduce the friction induced by the

rolling effect of nanoparticles at the tool–chip interface lowering forces and cutting temperatures [17]. The outperforming NMQL systems with respect to MQL has been observed by many researchers [18]–[21], improving surface finish, lower cutting forces, lower cutting temperatures and longer 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], [22]–[27].

Due to the minimum use of lubricant, MQL systems usually present lower emissions than flood lubricant systems. As shown in Figure 2, adapted from [32], the emissions under MQL systems are almost 50% less than their equivalent flood systems. However, if flow rate is set too high or viscosity lubricant is low, the mist generated can be important [28], [29]. In fact, some studies have revealed that the emissions in MQL systems can be even higher than flood emissions [30]. It should be noted that if oil mist may entail safety issues, the situation is exacerbated if nanoparticles are added, producing airborne nanoparticles.

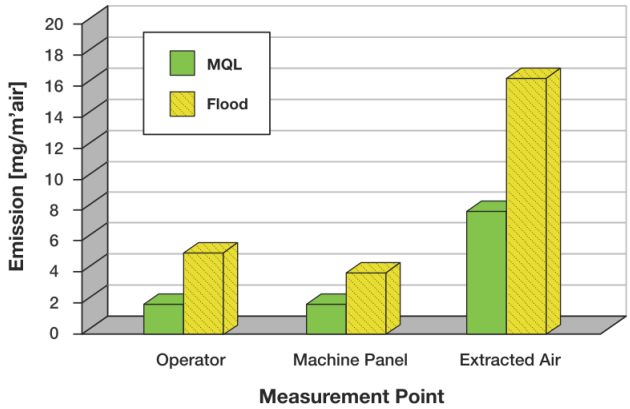

Figure 2. Comparison of emissions between MQL and flood cooling systems. Source: [15], [31]

Interestingly, a complete review about the potential toxicity of the NMQL technique has not been covered yet in any research work, although some researchers pointed out that this issue should be studied in detail [32]–[34]. A recent work [17] 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 the guidelines for nanoparticles selection from the toxicity point are important topics that should be investigated. Furthermore, current legislation information about permissible exposure limits (PEL) and recommended exposure limits (REL) should be provided to help understand practitioners the potential toxicity of NMQL. This review tries to provide updated information in this field and facilitate 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, XXXXXXXXXx.

2. Nanoparticles exposure pathways in MQL

It is well-known that nanoparticles may enter to the human body through 4 possible routes: inhalation, ingestion, injection, and dermal absorption. In occupational settings, inhalation is by far the most significant route of exposure for nanoparticles. Inhalable Particles can be classified as PM_{10} (Particulate Matter 10), $PM_{2.5}$ (Particulate Matter 2.5) and UFP (Ultrafine Particles) [35]. PM_{10} are particles with an aerodynamic diameter of 10 micrometers or smaller that can reach the upper respiratory tract, including the nose and throat. $PM_{2.5}$ are fine particles with an aerodynamic diameter of 2.5 micrometers or smaller that can penetrate deeper into the respiratory system, reaching the bronchi and lungs. Finally, UFP are particles with diameters less than 100 nanometers, i.e., nanoparticles, which makes them able to permeate physiological barriers of living organisms, causing harmful biological reactions [36]. To put in context the size issue, Figure 3 shows a scale of different biological systems, where it can be noted that nanoparticles are in the same order of magnitude than DNA, all one order lower than human cells, which explains the high toxicity of these types of particles. A special characteristic of the nanoparticles toxicity due to their small size is the translocation, the passage of nanoparticles into the blood, which lets the nanoparticles to travel from the respiratory system to other distant organs and tissues, including the central nervous system. The mainly result of the translocation is the generation of many diverse health diseases such as neurological diseases (Alzheimer's and Parkinson's diseases), gastro-intestinal diseases (Crohn's disease, colon cancer), lymphatic system diseases (Podoconiosis Kaposi's sarcoma), etc. [37].

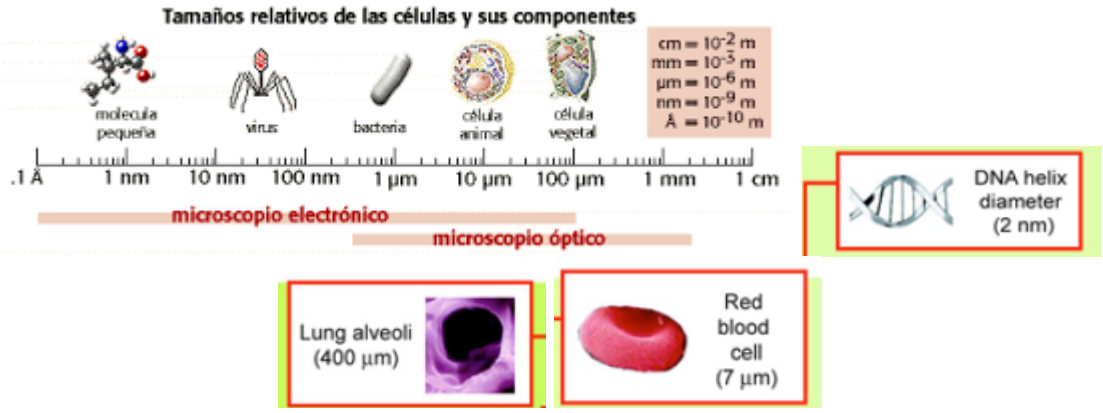

Figure 3. Scale to illustrate the potential interaction between nanoparticles and biological systems. REHACER FIGURA CON GOTAS DE MIST (1-5 MICRAS), macrófagos 25-50 MICRAS,

In NMQL operations, high flow rates and low nanofluid viscosity may generate mist producing airborne nanoparticles [38]. The droplet size and size distribution of that mist is defined by the nozzle distance and the air pressure [39]. Furthermore, the mist evaporation and dispersion produced by the rotation of tools and workpieces can contribute to the production of airborne nanoparticles [1]. Commonly, the droplet size of mist in MQL systems is in the range from 0.1 μm to 10 μm, being smaller when the cutting temperature increases [30]. Nanoparticles usually added in the MQL 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.

3. Nanoparticles toxicity studies: *in vitro* and *in vivo*

Toxicity studies can be 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 nanoparticles 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. For instance, the cell types include human lung cells such as A549 Cells (alveolar basal epithelial cells) and BEAS-2B Cells (immortalized human bronchial epithelial cells); 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) [17], [36]. 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 [40], the response of cells from the pulmonary, cardiovascular, hepatic, renal and developmental systems to a panel of nanoparticles can be comparable and enabled a similar ranking of toxicity. Therefore, although cells may vary in their sensitivity to nanoparticles toxicity, the overall pattern of response measured is often similar.

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*. The body's

metabolism, distribution, and excretion of substances can affect their toxicity, and these processes are often absent or misrepresented *in vitro* studies. An example of such difference is that soluble nanoparticles remain trapped in an *in vitro* system, whereas, soluble material constituents may be removed *in vivo* [40]. Furthermore, the duration of exposure *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. Finally, a comprehensive validation and evaluation of which *in vitro* method is sufficiently sensitive and suitable for evaluating specific long-term effects does not yet exist.

On the other hand, *in vivo* studies are usually conducted on hamsters, rats, mice, Daphnia magna neonates, bacteria (E. coli), algae and zebrafish embryos and larvae to assess nanoparticle toxicity in animals and aquatic environments [41]. *In vivo* studies include acute toxicity studies to assess adverse effects of a single exposure to a substance over a short period, usually within 24 to 48 hours; 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. In contrast to inhalation, where the test substance is administered as an aerosol or vapor via the nose, mouth, or nose and mouth, for intratracheal instillation, a bolus injection is given directly into the lungs. Since the local dose, administration and possible system-dependent alterations resemble actual life situations more accurately, inhalation is the preferred exposure route for the toxicity testing of respirable substances [42]. However, compared to inhalation, intratracheal instillation is cheaper and easier to use and allows for a more controlled application. Due to the high costs, the long duration and for reasons of animal welfare *in vivo* methods have to be supplemented by *in vitro* methods.

An important issue dealing with *in vitro* and some *in vivo* studies (i.e., intratracheal studies), is that nanoparticles must be dispersed to prepare suspensions. This might introduce further non-physiological observations as these nanoparticles have altered surface characteristics, agglomeration and deposition patterns differing from their airborne counterparts [40]. As more and improved exposure assessments for aerosolized nanoparticles in occupational and other settings become available, the measured aerosol concentrations and particle size distributions might be used to estimate deposited and retained mass doses of nanoparticles in pulmonary alveolar region of humans and animals. Some efforts have been conducted to estimate lung deposition after occupational exposure to nanomaterials in order to recommend *in vitro* testing concentrations [43].

4. Toxicity of NMQL nanoparticles

Many different types of nanoparticles have been investigated in MQL applications. Table 1 shows the most commonly used nanoparticles in MQL systems with their main characteristics and properties. As observed, a wide range of compositions, shapes, thermal conductivities, Mohs hardness and densities is available for its use in NMQL. Besides these properties, it is also important to consider the safety datasheets of each nanoparticle. Materials safety data sheets contain essential information about the hazards (H statements) and precautions (P statements) related to the use and storage of each nanoparticle. In Table 1, the classification of the substance based on the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) in accordance with 29 CFR 1910 from the Occupational Safety and Health Administration (OSHA) is included. The H and P common statements for all the nanoparticles in dry powder, according to a particular supplier (US Research Nanomaterials, Inc.), are listed below.

- Hazards statements:

H319 Causes serious eye irritation.

H335 May cause respiratory irritation.

-Precautions statements:

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.

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.

P403 + P233 Store in a well-ventilated place. Keep container tightly closed.

P405 Store locked up.

P501 Dispose of contents/container to an approved waste disposal plant.

Table 1. Main properties of nanoparticles applied in NMQL

NP	Shape	Thermal	Mohs	Density	Hazards

		conductivity (W/mK)[1]	Hardness[2]	(kg/m^3)	identification[3]
Metal oxides					
Al_2O_3	Spherical	36	9	3,975	Eye irritation (Category 2A), H319; Respiratory system, H335
SiO_2	Spherical	1.34	7	2,400	
CuO	Spherical	18	3.5	6,400	
ZrO_2	Spherical	1.85	6.5	5,560	
Fe_2O_3	Spherical	12.55	5.5-6.5	5,240	
TiO_2	Spherical	8.79-13.39	6.5	4,230	Eye irritation (Category 2A), H319; Specific target organ toxicity-single exposure (Category3), Respiratory system, H335
ZnO	Spherical	27.20	4.5	5,630	
Carbon-based structures					
Fullerene (C60)	Spherical	0.4	10	1,650	Eye irritation (Category 2A), H319; Respiratory system, H335
Nanodiamond (ND)	Spherical	2,300	10	3,500	
Single-walled Carbon nanotube (SWCNT)	Tubular	3,000-5,000	10	2,100	
Multi-walled Carbon nanotube (MWCNT)	Tubular	3,000-5,000	10	2,100	
Graphite (GR)	Layered	167.36	1-2	2,260	
Graphene (GNP)	Layered	3,000-5,000	10	2,267	
Graphene oxide (GO)	Layered	600-5,000		1,360	
SiC	Spherical	370	9.5	3,216	
Metal Sulphides and Boron Nitrides					
MoS_2	Spherical-flaky	138	1-1.5	4,800	Eye irritation (Category 2A), H319; Respiratory system, H335
WS_2	Flaky	53	1-1.5	7,500	
hBN (hexagonal Boron nitride)	Spherical	27	1.5	2,300	

[1] From database: https://thermtest.com/thermal-resources/materials-database. For comparison purposes, water: 0.6 W/mk; vegetable oils: 0.18 W/mk.
[2] A hardness of 6.5 on 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 Hall-Petch relationship [44].
3 From supplier US Research Nanomaterials, Inc. https://www.us-nano.com

Important research reviews about toxicity of nanoparticles can be found in [41], [45]–[49], where detailed information about the nanoparticles mechanisms of toxicity are given. Nanoparticles can be cytotoxic, 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 and cause mutations that can lead to cancer. The main toxicity mechanism produced by nanoparticles is due to the production of excess reactive oxygen species (ROS). Moderate levels of ROS play specific roles in the modulation of several cellular events, including signal transduction, proliferative response, gene expression and protein redox regulation. However, the presence of high ROS levels are indicative of oxidative stress and can damage cells by peroxidizing lipids, altering proteins, disrupting DNA, interfering with signaling functions, and modulating gene transcription and finally ending up in cancer or other diseases [47].

The following subsections review relevant toxicity studies about nanoparticles commonly applied to 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. These nanoparticles present a high cytotoxicity and extreme attention to safety utilization is needed [50]. A good comparison of toxicity of oxides nanoparticles can be found in [33], [51].

Zhang et al. [50], found that four types of metal oxide nanoparticles, ZnO, TiO_2, SiO_2, and Al_2O_3, lead to cellular mitochondrial dysfunction, morphological modifications and apoptosis at the concentration range of 0.25-1.50 mg/mL. ZnO was the most toxic nanomaterials followed by TiO_2, SiO_2, and Al_2O_3 nanoparticles in a descending order. Kim et al. [52] studied the cytotoxicity of ZnO, Al_2O_3 and TiO_2 in human lung epithelial cells (A549 carcinoma cells and L-132 normal cells), showing that ZnO presents the highest cytotoxicity in terms of cell proliferation, cell viability, membrane integrity and colony formation. Al_2O_3 and TiO_2 showed little adverse effects on cell proliferation and cell viability although TiO_2 induced oxidative stress in a concentration- and time-dependent manner. Al_2O_3 was presented as less toxic than the other nanoparticles even after long time exposure.

Karlsson et al, [51], analyzed the cytotoxicity of different metal oxide nanoparticles (CuO, TiO_2, ZnO, Fe_3O_4, Fe_2O_3) by exposing them to human lung epithelial cell line A549. CuO nanoparticles were most potent regarding cytotoxicity and DNA damage and caused oxidative lesions and induced significant increase in intracellular ROS. ZnO showed effects on cell viability as well as DNA damage, whereas the TiO_2 particles (a mix of rutile and anatase types) only caused DNA damage. For iron oxide particles very low toxicity was found. 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 it is tested to be biocompatible in its spherical shape, changes notably if it is presented in rod-shape, as shown by Lee et al. [53].

Remzova et al. [54], compared the toxicological effects of pristine TiO_2, ZnO, SiO_2, and coated SiO_2 nanoparticles in human lung cells. While the pristine TiO_2 and coated SiO_2 nanoparticles (coating based on –methyl and –octyl) did not exhibit any cytotoxic effects up to the highest tested concentration, the pristine SiO_2 and ZnO nanoparticles significantly reduced cell viability. Besides, although the ZnO and SiO2 nanoparticles exhibited statistically significant high-toxicity towards the A549 human lung cells, no statistically significant cytotoxic effect was observed for the coated SiO_2 and TiO_2 nanoparticles, even up to their highest tested concentration of 250 µg/L. Wei et al, [55] 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 olfactory route, according to their results in mice.

Brown et al. [56], studied different nanoparticles including metal oxides (Al_2O_3, TiO_2, Fe_2O_3, and ZnO) and metals (Ag) in different types of essays. They studied the toxicity in mammalian cells *in vitro* (macrophages, hepatocytes and alveolar epithelial cells) and aquatic environmental organisms (Raphidocelis subcapitata Daphnia magna, Lumbriculus variegatus). The authors observed that a very similar pattern of nanoparticle toxicity was observed across mammalian, *in vitro* and *in vivo* (rodent), and aquatic ecotoxicological models. Al_2O_3, TiO_2 and Fe_2O_3 nanoparticles did not induce any significant change in cells after 24h exposure. ZnO and Ag were consistently demonstrated to be the most toxic nanoparticles across the cross-species battery of tests employed in the study. The toxicity of the nanoparticle panel was ranked as ZnO > Ag > TiO_2 > Fe_2O_3 > Al_2O_3.

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 exhibits low toxicity profile.

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, SWCNTs and MWCNTs), graphene and graphite nanoplatelets/nanosheets/nanoribbons, graphene oxide, etc., are having more attention in last decade.

A comparative study about the inhalation toxicity of MWCNTs, graphene, graphite nanoplatelets

and low surface carbon black was presented by Ma-Hock et al. [57]. For the study, male Wistar rats were exposed head-nose to atmospheres of the respective materials for 6 hours per day on 5 consecutive days under different concentrations (0.1 – 10 mg/m^3). No adverse effects were observed after inhalation exposure to 10 mg/m^3 graphite nanoplatelets or relatively low specific surface area carbon black. Increases of lavage markers indicative for inflammatory processes started at exposure concentration of 0.5 mg/m^3 for MWCNTs and 10 mg/m^3 for graphene.

The researchers have highlighted the special hazards associated with CNTs in comparison to other carbon-based nanoparticles. In a recent review about toxicity of carbon nanotubes by Kobayashi et al. [58], it was highlighted that the exposure to CNTs induces sustained inflammation, fibrosis, gene damage in the lung and lung cancer following long-term inhalation. Furthermore, CNTs presented high biopersistence in animal studies.

Mollá et al. [59], studied the toxicity of graphene nanoparticles of 10-55 μm size formed by 2–6 graphene sheets on cell lines A549 and Caco-2, and it was estimated a toxicity value of 205 ppm for inhalation route. The toxicity of non-oxidized forms of graphene may depend on size and surface reactivity, as well as agglomeration of materials, and are likely less toxic than various forms of graphene oxide, for which toxicity has been shown to be more persistent [60]. Other long types of nanoparticles such as graphene oxide nanoribbons have been also shown to be more toxic than their variants in nanoplatelets form [61].

Some researchers have compared the toxicological profile of carbon-based nanoparticles with respect to metal-based nanoparticles. In [62], the authors investigated the toxicity effects TiO2, carbon black, ZnO and SiO2 in human corneal epithelial cells (HCECs) and human conjunctival epithelial cells (HCjECs). The toxicity of these nanoparticles were ZnO > Carbon black > SiO_2, while TiO_2 demonstrated no toxicity. In a comparison study between metal oxide nanoparticles and different types of carbon nanoparticles conducted by Karlsson et al. [51], it was observed a low toxicity of spherical carbon nanoparticles of 30 nm diameter, less than metal oxide nanoparticles. However, the CNTs analyzed were shown to be highly cytotoxic producing DNA damage. Yang et al. [63], conducted a comparative study of the toxicity of carbon black, SWCNTs, SiO_2 and ZnO nanoparticles. According to their results, ZnO induced the most remarkable cytotoxicity by promoting intracellular oxidative stress whereas CNTs presented more DNA damage. SiO_2 and carbon black also reported relevant toxicity values but lower than ZnO. Angoth et al. [64], studied the *in vitro* toxicity of carbon nanoparticles on five different cell lines and compared their toxicity with crystalline SiO_2. The authors observed greater cytotoxic effect of carbon nanoparticles than

SiO_2 nanoparticles, with a TC50 values (toxic concentration 50, i. e., concentration of particles inducing 50% cell mortality) in the range 28.29–46.35 μg/mL. A review of carbon nanotubes toxicity published in [65] presented an analysis of previous research on rodent studies in which test dusts were administered intratracheally or intrapharyngeally to assess the pulmonary toxicity of manufactured CNTs. The comparative studies showed that CNTs were more toxic than quartz (SiO_2 crystalline) whereas ultrafine carbon black was shown to produce minimum lung responses. A more recent review by Raja et al. [66] has been published about toxicity of carbon nanoparticles. According to the citations and tables provided in this review, it can be stated that MWCNTs and SWCNTs are 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 MQL. However, other carbon-based nanoparticles with spherical shape or with low aspect to ratio are much less toxic.

4.2.2. Metal Sulphides 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 nanofluids for MQL. Some studies related to nanoparticles toxicity have revealed that these group of nanoparticles present low toxicity in comparison to other nanoparticles. For instance, in Appel et al. [67] the authors studied the toxicity of pristine MoS_2 and WS_2 in a series of biocompatibility tests, including live − dead cell assays and ROS generation assays in human epithelial kidney cells (HEK293f). Genotoxicity and genetic mutagenesis were also evaluated for both nanoparticles. Cell viability was unaffected and the exposure of bacterial cells to these nanoparticles failed to generate genetic mutation, highlighting their biocompatibility. Pardo et al. [68], reported that MoS_2 and WS_2 nanoparticles remained non-toxic to cells representing the respiratory, immune and metabolic systems compared to equivalent concentrations (up to 100 μg/mL in the medium) of SiO_2, and carbon black nanoparticles, which induced cell death. Similar conclusions were reached by Teo et al. [69], 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 [70] studied the cytotoxic effect of unmodified MoS_2 nanoparticles toward human bronchial (BEAS-2B) and alveolar (A549) cells. The cells were exposed with different particle size of MoS_2 in concentrations range 1-200 μg/mL for 24, 48, and 72 h. Weak cytotoxic effects on BEAS-2B and A549 cells was observed, together with a reduction of cell viability to approx. 60-70% at concentrations of 2.5 and 5 μg/mL, which means a

low toxicity in comparison to other common nanoparticles. Hao et al. [71] studied MoS_2, TiS_2 and WS_2 nanosheets and no significant *in vitro* cytotoxicity was found on 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 remarked as a safer nanoparticle due to its low toxicity, capability of biodegradation, and rapid excretion.

Boron nitride has a stable hexagonal structure 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 has been investigated as an alternative to CNTs to overcome cytotoxicity limitations. Chen et al. [72] showed that hBN nanotubes were noncytotoxic on *in vitro* tests over HEK cells. While MWCNTs induce apoptosis, hBN nanotubes with similar dimensions than those of MWCNTs did not appear to inhibit cell growth or induce apoptotic pathways in the cells. However, more recently, research about toxicity on both lung alveoli and HEK cells has been published with opposite results [73]. 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. [74] 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.

The reviewed studies indicate transition metal dichalcogenides (MoS_2 and WS_2) exhibit very low toxicity when compared to other nanoparticles and it seems the safest group of nanoparticles that can be used for NMQL. On the other hand, according to recent research hBN nanotubes seems to be highly toxic, at least similar to CNTs.

4.3. Comparison of nanoparticles toxicity

According to previous studies, a relative comparison of toxicity about nanoparticles applied in NMQL systems can be formulated. Furthermore, specific works such as [17], [40], [51], [56], [75] compared the toxicity of some nanoparticles and they can be served as a guide for elaborating the comparison chart. However, it should be noted that many factors may influence nanoparticles toxicity (exposure times, concentrations, particle shape, etc.), and the nanoparticles toxicity may slightly vary. This is the main reason why some research works may present contradictory results.

In any case, an approximate classification of nanoparticles toxicity can be of interest for practical purposes, especially for those practitioners interested in formulating nanofluids for MQL applications. Table 2 shows the proposed classification of nanoparticles toxicity that 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.

Table 2. Relative classification of nanoparticles toxicity applied in MQL related to inhalation.

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

5. Key factors of nanoparticles foxicity

A well understanding of the mechanisms that produce the toxicity is critical to develop safer nanofluids for MQL operations. Therefore, a comprehensive analysis of research studies found in the literature related to the influence of physicochemical parameters on nanoparticles toxicity is of great importance. Besides the chemical composition of nanoparticles, many researchers have proven that the following physicochemical properties have a direct impact on nanoparticles toxicity [76]: size, shape, surface properties, state of agglomeration/aggregation and solubility (Figure 4). The next subsections analyze the effect of each physicochemical property on toxicity in order to facilitate the definition of some guidelines related to safer nanofluids formulation (Section X).

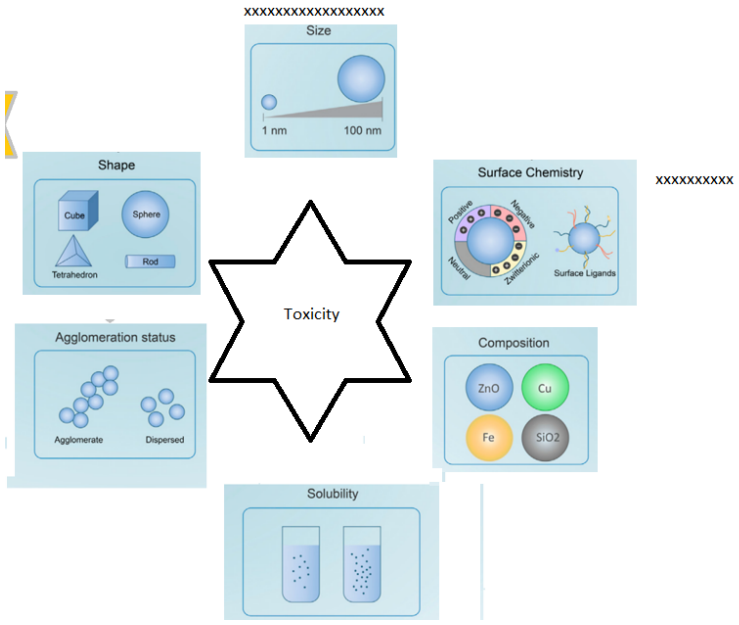

Figure 4. Physicochemical properties affecting nanoparticles toxicity.

5.1. Size

Particle size is the main physicochemical property that contributes to cytotoxicity. The smaller size of nanoparticles enables higher permeability of cell membranes to interact with organelles such as mitochondria, lysosomes, and nucleus, finally causing cell damage [76]. In the literature it is stated that size and surface nanoparticles charge are key factors to particle distribution one entering the body, where smaller nanoparticles present greater bio-distribution and accumulation in comparison to larger materials of the same chemical composition [40].

Kim et al. [77] 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 SiO_2 it was observed a higher toxicity of those with minor size. Similar conclusions were reached by Sahu et al. [78], where after a size-dependent study, ZnO particles exhibited nearly equal toxicity profile in L-132 cells while in THP-1 cells nano ZnO showed more toxicity than its micron size, confirming that besides a size relation, the toxic response varies depending on type of cell exposed due to differential sensitivity. Hsiao and Huang [79] 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 [70] assessed that the cytotoxic effect of MoS_2 nanoparticles (100 nm) and microparticles (2 microns) 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. [80], 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 nanoparticles distribution along organs and tissues [81], [82]. Semmler-Behnke et al. [83] observed that 1.4 nm gold nanoparticles were able to cross the air/blood barrier of the lungs much more efficiently than 18 nm gold, showing that nanoparticles may interact dynamically with proteins and cells, which determines their accumulation in different organs. Furthermore, it seems that there is a correlation between the nanoparticles size and their retention in the human body. Oberdorster et al. [84], reported that nanoparticles of 20 nm TiO_2 presented two times more retention in the lungs (500 days versus 170 days) than 250 nm TiO_2 particles.

5.2. Shape

Nanoparticles shapes are usually spheres, cylinders, fibers, wires, rods, sheets and flakes. It has been proved that similar nanoparticles with different shapes may end with different toxicity levels [76]. Hadji and Bouchemal [85] highlighted that cell uptake and intracellular distribution is dependent of particle shape, where non-spherical particles present better escaping capability to macrophages, higher margination and adhesion to the endothelial wall, longer circulation time and slower elimination rate.

A common property related to shape of nanoparticles is the aspect ratio (i.e., the ratio length/width). Nanoparticles with an aspect ratio higher than 3:1 are defined as a high aspect ratio nanoparticle (HARN). HARNs include nanotubes, nanowires and nanorods. Best known of all HARNs are carbon nanotubes (CNTs), which are long, thin cylindrical structures comprising single or multiple layers of concentric graphene sheets. Park et al. [86] compared the toxicity of two different aluminum oxide nanorods (AlNRs) commercially available *in vivo* and *in vitro*. Considering aspect ratio, one was 6.2 ± 0.6 (long-AlNRs) and the other was 2.1 ± 0.4 (short-AlNRs). In mice, long-AlNRs induced longer and stronger inflammatory responses than short-AlNRs. In *in vitro* tests on six cell lines, long-AlNRs generally produced stronger toxicity than short-AlNRs.

Lee et al. [53] investigated cytotoxicity to mouse macrophage cells (RAW 264.7) using different iron oxide nanoparticles: micro-sized Fe_2O_3, nano-sized 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 greatest extent of necrosis possibly associated with the resulting high surface area. Authors stated that nanoparticles

toxicity has to be evaluated based on shape as well as size, because changes in shape and size are accompanied by alterations in surface area, which relate closely to cytotoxicity. Similar conclusions were reached by Hsiao and Huang [79], where nanorod ZnO particles were more toxic than the corresponding spherical ones.

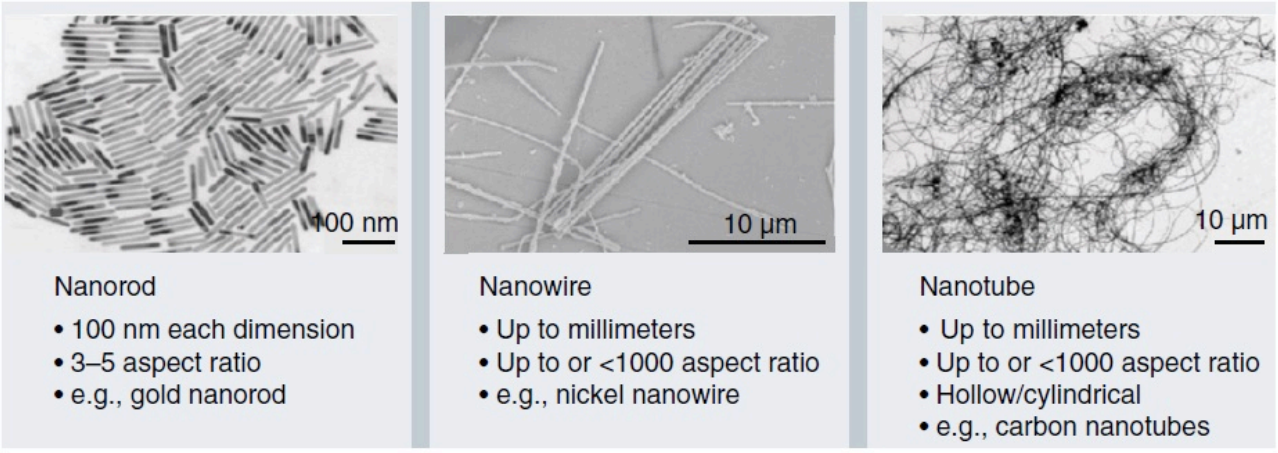

Figure 1. Images and characteristics of the different types of high aspect ratio nanoparticles.
Gold nanorod image used with permission from [11].

Figure 5. Poner algo así? Con NP de diferentes geometrías y tamaños…. Indicando + tóxico cuanto más pequeño y más HARN. Source: Lee 2014 y Donaldson 11

The best known and studied of the HARNs are carbon nanotubes. CNTs are considered a potential toxicology profile due to their resemblance to asbestos fibers [87] and might pose a special cancer hazard to the lungs, pleural and peritoneal mesothelium [88]. 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 [87]. Width or diameter is the main factor that determines aerodynamic diameter, which is the property that controls whether, or where, in the respiratory tract any particle deposits. Once deposited, length is the factor that determines whether a fiber can be effectively cleared from beyond the ciliated airways by macrophages and whether the attempt of macrophages to phagocytose the fibers leads to inflammation.

Cohignac et al. [89] 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. According to their results, the shape (tubular for CNT versus spherical for the other carbon- or titanium-based nanomaterials) seems to be the most important characteristic to overall induce or block autophagy, a degradative process through which cells can recycle intracellular waste products to maintain cellular homeostasis.

Jiang et al. [90], found genotoxicity to be the main toxicity category for unmodified and functionalized SWCNTs. Different lengths were studies, i.e., shorter SWCNTs (average length of 1 μm) and longer SWCNTs (average length of 15 μm). The SWCNTs with a shorter length showed a higher toxicity, which might be due to the short tubes being more mobile and less prone to aggregation, making the penetration easier compared to long tubes. Donaldson et al. [87] analyzed the toxicity of HARNs and described the physicochemical parameters than can be modified to a safer HARNs design. In this work, it was stated that the toxicity of fiber HARNs is different from other HARNs that are not long enough, and indicated that lengths lower than 5 μm can be subjected to macrophage clearance, but lengths longer than 15 μm and with biopersistence capability can lead to cancer and fibrosis. Cui et al. [91] studied the uptake and exocytosis of 3 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 on length.

Graphene oxide nanosheets toxicity was analyzed by Rodriguez et al. [92] and the effects of lateral dimensions of GO sheets in acute and chronic pulmonary responses after single intranasal instillation in mice were investigated. In their work, micrometer-sized GO induces stronger pulmonary inflammation than nanometer-sized GO, despite reduced translocation to the lungs. Similarly, the cytotoxicity of graphene nanoplates (20 μm lateral (Gr20), 5 μm lateral (Gr5), and <2 μm lateral (Gr1)) ranging from 8–25 nm in thickness were analyzed by Roberts et al. [93]. *In vivo* studies were conducted by exposing mice to different doses through pharyngeal aspiration. They demonstrated that graphene nanoplates with large lateral dimensions (5–20 μm) have a more detrimental impact on the lungs than their smaller counterparts (<2 μm).

5.3. Surface properties

Surface properties of nanomaterials, especially charge and surface modifiers, are important factors that influence on nanoparticles toxicity [94]. The surface charge of a particle can influence the adsorption of ions, contaminants, the interaction of the particle with biomolecules, uptake into cells and the way the cells react when exposed to the particle. In fact, zeta potential has already been adopted to characterize the surface charge of nanoparticles and to predict nanoparticles toxicity [95]. Nanoparticles with positive zeta potential are more prone to impart toxicity than those with negative zeta potential, partially because those nanoparticles have higher electrostatic interactions to negatively charged cellular membranes, thus increasing cellular uptake of nanoparticles, leading to more cell damages [96]. In addition, surface charge may influence the agglomeration state of nanoparticles, which impacts their aerodynamic behavior when aerosolized [94] which in turns

influences on the toxicity itself. For instance, Gilbertson et al. [97] studied the influence of surface charge on the embryonic zebrafish mortality for a safer MWCNTs design, and they observed that surface charge was the best predictor of zebrafish mortality at 24 hpf (hours post-fertilization). Similar negative effect was observed by Baek et al. [98], where ZnO particles with positive charge showed greater ROS production than those with negative charge.

Control of surface properties and functionalization is essential to ensure colloidal stability of nanoparticles suspended in a base fluid [99]. At the scale of nanofluids, the particle-surface-to-particle-volume ratio is so high that all the interactions are controlled by short-range forces like 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 repulsion is achieved by means of the adsorption to the particle surface of polymeric chains of surface modifiers (surfactants) that extend into the surrounding medium resulting in steric repulsion. In this case, stabilization of nanofluids is performed by adding non-ionic surfactants such as polyethylene glycols (PEG) and polyvinylpyrrolidone (PVP). However, the preferred and most effective stabilization mechanism involves electrosteric repulsion. In this case, both electrostatic and steric repulsion are combined, with the help of the addition of charged polymeric chains. Stabilization of nanofluids is performed by means of the addition of ionic surfactants (cationic or anionic) that generate a charged medium surrounding the polymeric chains adsorbed to the particle surface. Functionalization of the nanoparticles is then achieved without undergoing chemical reactions by the addition of surfactants such as sodium dodecyl sulphate (SDS), sodium dodecylbenzene sulphonate (SDBS), cetyl trimethylammonium bromide (CTAB) and benzalkonium chloride (BAC). **Figure 6** summarizes common methods for dispersion and stabilization of nanoparticles including a classification of the surface modification mechanisms and surfactants.

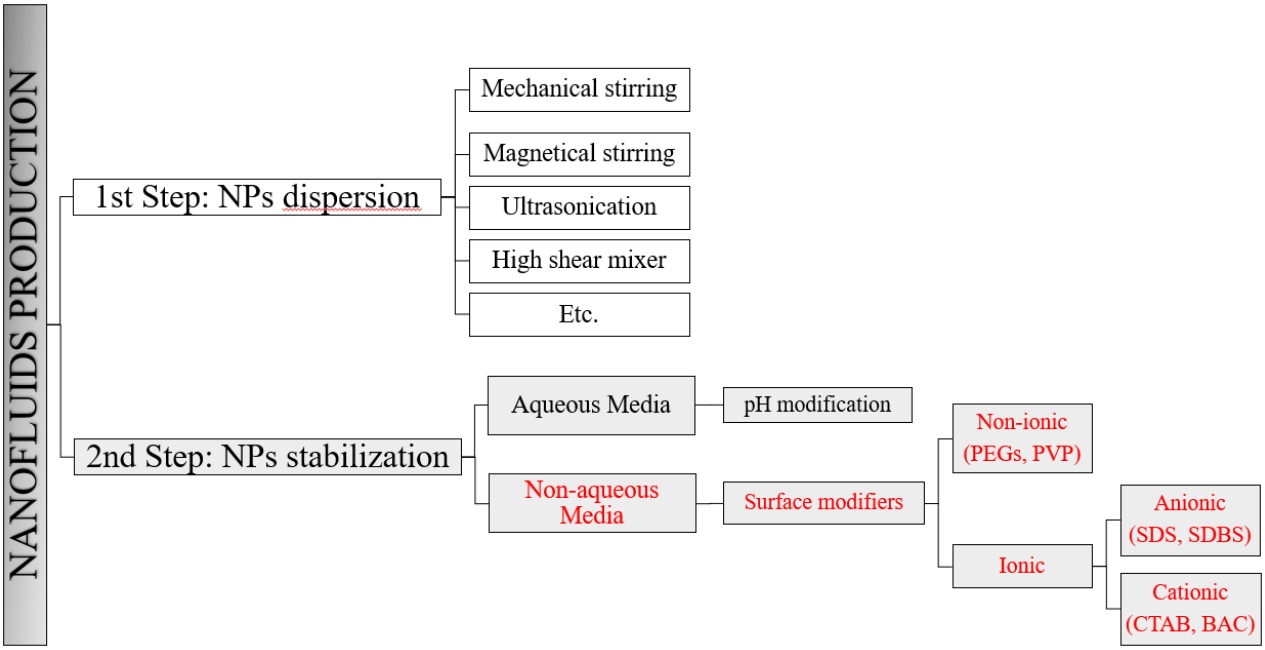

Figure 6. Classification of dispersion and stabilization mechanisms of nanoparticles.

As stated above, surface modifiers are usually needed in nanofluids for MQL applications (oil media), and the influence of these surface modifiers on nanoparticles toxicity should be also considered. Oleszczuk et al. [100] studied the effect of the surfactants CATB, SDS and Triton X-100 (PEG) on the toxicity of ZnO, TiO_2 and Ni nanoparticles towards Daphnia magna. The presence of surfactants considerably reduced the toxicity of all tested nanoparticles, and the authors suggested that the presence of the surfactants was related with the formation of nanoparticles aggregates that inhibited the availability of nanoparticles for D. magna. Zhang et al. [101] explored the cytotoxicity of eleven commonly used surface modifiers in two cell lines, human epidermal keratinocyte (HaCaT) and lung fibroblast (CRL-1490) cells. Six of the eleven surface modifiers were cytotoxic, especially those surfactants with long aliphatic chains, both cationic (CTAB, oleylamine, tetraoctylammonium bromide, and hexadecylamine) and anionic (SDS), the latter in 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 affect the cytotoxicity results. Wang et al. [102] analyzed cytotoxicity of gold nanoparticles in sphere and nanorod shape, being the nanorod proved to be highly toxic but not due to the shape, but 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. [103]. In this work, CTAB-gold nanorods with various aspect ratios had similar abilities to induce cell apoptosis and autophagy by damaging mitochondria and activating intracellular ROS. 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.

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 nanoparticles chemistry, charge, and hydrophobicity through the formation of a coating with different physical-chemical properties, which results in altering their toxicity [94]. Vranic et al. [104] investigated the effects of amino or 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. Zhang et al. [105] analyzed the cytotoxicity of Al_2O_3 nanoparticles to Caco-2 cells and Caenorhabditis elegans 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 than the pristine ones. Remzova et al. [54] compared the toxicological effects of pristine TiO_2, ZnO, SiO_2, and SiO_2 nanoparticles coated with –methyl and –octyl functional groups. While the pristine TiO_2 and coated SiO_2 nanoparticles did not exhibit any cytotoxic effects up to the highest tested concentration, the pristine SiO_2 and ZnO nanoparticles significantly reduced cell viability. Besides, although the ZnO and SiO_2 nanoparticles exhibited statistically significant high-toxicity towards the A549 human lung cells, no statistically significant cytotoxic effect was observed for the coated SiO_2 (both –methyl and –octyl) and TiO_2 nanoparticles, even up to their highest tested concentration of 250 μg/L. The toxicity of non-coated SiO_2 was explained by the formation of ROS inside the cells, due to Si–OH surface groups or by membrane damage mediated by hydrogen bonding. In case of insoluble coated SiO_2 (–octyl and –methyl) nanoparticles, no cytotoxicity towards the A549 cells was observed in both assays. This could be explained by the suppression of ROS formation, due to the presence of surface functionalities that inhibit the reactivity of the Si–OH groups. Goodman et al. [106] 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 the cationic one.

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 [94]. Li et al. [106] analyzed different CNTs functionalized with common anionic, nonionic, and cationic surface groups and assessed their cytotoxicity in THP-1 and BEAS-2B cells. The anionic group (carboxylate and polyethylene glycol) led to lowest toxicity, the neutral and weakly cationic functional groups (amines) presented intermediary toxicity whereas the strongly cationic group (polyetherimide) exhibit the largest toxicity. However, different results about toxicity of functionalization were reported by Jiang et al. [90]. In their research work, the authors analyzed genotoxicity and oxidative stress for raw and functionalized SWCNTs in yeast cells. The results indicated that DNA damage and oxidative stress were the dominant mechanisms of action for all the SWCNTs, but functionalization of SWCNTs led to elevated overall toxicity, where the carboxylated SWCNTs induced a greater toxicity than the hydroxylated SWCNTs. In another research [107], the toxicity of pristine MWCNTs carboxylic acid functionalized MWCNTs was analyzed on RAW264.7 cells by looking at the cell viability, phagocytic activity, production of cytokines and intracellular ROS. According to their results, both MWCNTs decreased viability of murine macrophage RAW 264.7 cells but the modification with carboxyl group did not exert obvious impact on the interaction of MWCNTs with macrophages.

5.4. Agglomeration/Aggregation and solubility

Apart from those factors mentioned above, the agglomeration/aggregation and solubility of nanoparticles also affect their toxicity [76]. Both aggregation and agglomeration are assemblies of nanoparticles. Aggregation refers to strong and dense particle collectives whereas agglomeration is when particles are combined loosely via weak forces, like van der Waals forces or electrostatic forces, which can be simply broken by mechanical forces. The size of these agglomerates can affect their deposition in all regions of the respiratory tract and their biodistribution resulting in different toxicity profiles. According to Bruinink et al. [108], agglomeration of nanoparticles after uptake reduces translocation across primary barriers such as lungs, skin or the gastrointestinal tract, preventing exposure of other organs. It should be noted that the agglomeration depends not only on intrinsic physicochemical properties like size, shape, surface chemistry, but also on extrinsic factors of surrounding media such as pH, ionic strength, etc. [76].

For example, Murugadoss et al [109] studied two TiO_2 nanoparticles with different primary sizes (17 and 117 nm) and prepared ad-hoc suspensions composed of small or large agglomerates with similar dispersion medium composition. The authors found that large agglomerates of 17 nm TiO_2 caused stronger toxicity responses and DNA damage in monocytic cell lines, compared to small agglomerates. However, it was observed that large agglomerates of 117 nm TiO_2 caused higher

pulmonary cytotoxicity in the mice inhalation study and more blood DNA damage in gavaged mice than small agglomerates, and they concluded that large agglomerates do not appear less active than small agglomerates. However, Lim et al. [110] prepared three different types of agglomerates of nano-sized carbon black and aerosolized for a nose-only exposure of male Sprague-Dawley. Only mild to moderate respiratory effects were found at 9 mg/m^3 for 13 weeks and the agglomeration did not affect the toxicity of nano-sized carbon particles.

As mentioned above (**Figure 6**), control of nanoparticles dispersion is first made by different techniques being the ultrasonic treatment 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 is needed. Cheng and Cheng [111] observed that the agglomeration state of nanoparticles is dependent on the sonication time leading to different toxicity values. The MWCNTs prepared with the longer sonication time resulted in severe developmental toxicity; however, the shorter sonication time did not induce any obvious toxicity in the tested developing zebrafish embryos. The explanation was the difference in the nanoparticles length after sonication. For 24 h sonication, the average length was about 0.8 ± 0.5 μm whereas the average length for 48h was about 0.2 ± 0.1 μm.

Furthermore, dissolution of nanoparticles can also induce toxicity based on the release of metal ions [112]. For instance, metal ions such as Zn^{2+} and Cu^{2+} released from ZnO and CuO can cause damage to proteins, which can inactivate certain metalloproteins by dislodging metal ions within them [113]. Wang et al. [114] evaluated the dissolution of different metal oxides at different pH values. Lower pH values were shown to promote the release of metal ions which was shown to be responsible of higher toxicity for ZnO and CuO.

The dissolution capability of airborne nanoparticles after inhalation and deposition in the respiratory tract naturally affects the nanoparticles persistence and subsequent fate in the organ and entire organism. The dissolution of the deposited nanoparticles therefore contributes to clearance from the respiratory tract [42]. Depending on the solubility, the International Commission on Radiological Protection (ICRP) proposed three different classes to categorize particulate matter which differ by their pulmonary clearance in humans: soluble material exhibits a retention half-time of less than 10 days, partly soluble matter has a retention half-time between 10 to 100 days and poorly soluble material has retention times over 100 days [42]. Dissolution is dependent on the chemical and physical properties (size, surface area, etc.) of particles and fibers and also of the suspension medium including its ionic strength, pH, and temperature [115]. Generally, as the nanoparticle size decreases

to provide colloidal stability, their dissolution increases due to the higher specific surface available [116]. The dissolution is not only affected by the nanoparticle size, but by their shape and surface morphology [116]. Misra et al. [117] investigated different shapes of CuO nanoparticles for its application in ecotoxicological studies. Spherical nanoparticles of 7 nm diameter and rod-shaped nanoparticles of 7 x 40 nm size were studied, and the spherical ones were shown to dissolve faster than rod-shaped particles. It should be noted that the dissolution is also influenced by the nanoparticles agglomeration. Agglomeration will decrease available external specific surface area and hence influence the ion release kinetics of nanoparticles thus reducing the extent of dissolution [115].

6. Legislation

Currently, there is a lack of specific regulations to engineered nanoparticles in EU, USA or any other countries. The Occupational Safety and Health Administration (OSHA) in the United States has only published exposure limits for titanium dioxide (TiO_2) nanoparticles and carbon nanotubes and nanofibers [118]. According to this organism, the permissible exposure limit (PEL) for TiO_2 is 15 m g/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 National Institute for Occupational Safety and Health (NIOSH) is a research and education institution that provides recommendations for occupational safety which are usually more conservative than OSHA legal terms. According to NIOSH, the recommended exposure limits (REL) are of 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 hours per day during a 40-hour work week [119]. For carbon nanotubes, in the 2010 draft Current Intelligence Bulletin (CIB) Occupational Exposure to Carbon Nanotubes and Nanofibers [120], NIOSH indicated that the risks could occur with exposures less than 1 µg/m3 but that the analytic limit of quantification was 7 µg/m^3 elemental carbon (EC) 8-h TWA. Based on subsequent improvements in sampling and analytic methods, NIOSH is now recommending an exposure limit at the current analytical limit of quantification of 1 µg/m^3 [121]. 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 [122], and for silver nanoparticles the REL value is set to 0.9 µg/m^3 as an airborne respirable 8-h TWA concentration [123].

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 the exposure in a higher degree than their corresponding micro particles due to the higher toxicity of nanoscale particles. In fact, as reported in [124], even when relatively innocuous in bulk or as a microscale particulate, may be markedly toxic in the form of nanoparticles. In a report of workplace exposure to nanoparticles [125], 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 propose to limit the exposure to nanoparticles at least around 8 times more than the corresponding limits for microparticles. For instance, the British Standards Institution (BSI) suggested benchmark exposure levels for four nanoparticle hazard types [126]. For insoluble nanomaterials a general benchmark level of 0.066 × WEL (WEL refers to Workplace Exposure Limit, i.e., the Exposure Standard) of the corresponding microsized bulk material (expressed as mass concentration) was proposed; for fibrous nanomaterials the proposed benchmark level is 0.01 fibres/ml; for highly soluble nanomaterials a benchmark of 0.5 × WEL of the corresponding microsized bulk material was proposed; for substances classified as carcinogenetic, mutagenic, asthmagenic or reproductive (CMAR) in their coarse form, the same hazards will be considered for the nano form and the suggested benchmark level was 0.1 × WEL (mass concentration) of the corresponding microsized material. **Table 3** summarizes current regulations showing PEL and REL values for different nanoparticles and potential PEL values according to NIOSH statement and the suggested benchmark exposure levels from BSI.

Table 3. Permissible Exposure Limits (PEL) and Recommended Exposure Limits (REL) for an 8-h TWA. Possible PELs values according to NIOSH statement and benchmark exposure levels from BSI are also shown. POR COMPLETAR

Particles	**PEL for microscale particles (OSHA)**	**REL for microscale particles (NIOSH)**	**PEL for nanoparticles (OSHA)**	**REL for nanoparticles (NIOSH)**	**Potential PEL according to Note 1**	**Potential PEL according to Note 2**
TiO_2	15 (PEL)	2.4 REL	0.3	0.3	-	-
MoS_2	15	5	-	-		
ZnO	15 (total) 5 (resp)	15 (total) 5 (resp)	-	-		
Al_2O_3	15 (total) 5 (resp)	-	-	-		
Graphite	15 (total) 5 (resp)	-	-	-		
Fe_2O_3	10	5	-	-		
Carbon black	3.5	3.5	-	-		
CuO	0.1	0.1	-	-		
SiO_2*	15 (total)? 5 (resp)	15 (total)? 5 (resp)	-	-		
Ag	0.01	0.01	??	$0.9 \cdot 10^{-3}$	-	-
Carbon nanotubes	-	-	0.007 0 o.oo1?	0.007 0 o.oo1?	-	-

-: Non-established
*: Values for amorphous silica, commonly used as nanoparticle. For crystalline (quartz), the maximum OEL in some European countries is 150 µg/m^3 whereas mostly it is equal or below 100 µg/m^3 for the inhalable dust fraction

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, and it states "similarly for other particulate materials, if the toxicity varies by particle size (at the same mass dose), distinct exposure limits for distinct particle size fractions might be a reasonable approach for protecting exposed workers".

Note 2: Suggested benchmark exposure levels from British Standards Institution (BSI) [126].

In addition to the legislation in terms on nanoparticles exposures, it is well-known the negative health effect of MWF exposures at the workplace [7]. 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-hour expressed as a total proportion of particles [127]. The NIOSH organism defines the REL value to 0.5 mg/m^3 (or 0.4 mg/m^3 thoracic fraction), measured as an inhalable fraction based on a reference time of 10 hours [7].

7. Guidelines for safety use of nanofluids in NMQL systems

Guidelines and recommendations for a safer design of engineered nanoparticles have been provided in the literature [128]–[130]. For the application of nanoparticles in NMQL (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:

- **Proper oil base selection**

The main lubricating component of MQL systems is the base oil and thus, its selection will define the main performance of the lubricating system. According to vendor's recommendations [29], synthetic esters are preferable for machining processes where the lubricating effect is of prime importance. These lubricants are designed for low viscosity while maintaining a high boiling and flash point. This gives better results under load and generates 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 [29]. Much of the risk involved in working with cutting oils derives from the use of mineral oils as they have poorly defined chemical compositions, impurities from refining processes, and contaminants produced by the heat of the cutting tool, etc. Using highly refined mineral oils is preferred to reduce potential carcinogens from base oils [131].

As an alternative to mineral oils, vegetable oils (natural esters) can be also applied due to their good lubrication ability and biodegradability, and most of the research works that can be found in the literature mainly apply vegetable oils such as soybean, peanut, maize, rapeseed, palm, castor, and sunflower oil in MQL systems. Compared to mineral oil, vegetable oil has the advantages of

renewability, low toxicity, and easy biodegradation. Mineral oil may cause more serious damage to human body than vegetable oil. Elimination of oil from the lungs can occur by expectoration (coughing up phlegm or mucus) or, if the oil is a vegetable or animal product, it may be metabolized (digested by the macrophages) and removed. On the contrary, true mineral oil (a petroleum product) is inert and indigestible by macrophages; it acts as a foreign body in the lungs and accumulates there resulting in pulmonary paraffinoma, an advanced lipoid pneumonia [131].

However, raw vegetable oils are not recommended as they are prone to oxidation and gum 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 [132], where oxidations and insufficient extreme-pressure performance are stated as the main limitations for their application in MQL. Common commercial lubricants applied in MQL are vegetable oils with additives to prevent oxidation.

The importance of proper oil base selection can be observed in [133], 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 emissions of aerosol mist that can harm operators. Small droplets tend to stay suspended in the air longer, are more easily inhaled to the human body, and more difficult to remove with mist collectors. MQL vendor's recommended 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 [29]. Tai et al. [15] studied the application of MQL in automotive powertrain machining lines, and highlighted the issue of mist emissions in MQL. In [134], it was measured that thin, low-viscosity lubricants (< 20 mm^2/s) generate high emission values. The emission level is also proportional to the amount of fluid entering the system; thus, optimizing the flow rate for a certain machining process can further improve the air quality. Note that the PEL value to total airborne particulate concentrations is currently set to 5 mg/m^3 from OSHA.

- **Proper nanoparticle selection**

Nanoparticles are selected according to the requirements of the nanofluid. In MQL applications, the nanofluid should provide anti-friction, anti-wear and good cooling capability to improve the machining performance. However, nanoparticles characteristics differ between them, and some of them may be more adequate for cooling (small sizes and higher aspect to 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). Once the main properties of nanoparticles are set, the selection should include the potential toxicity that can be assumed in the MQL system. For instance, machine-tools with an emission extraction closer to the work with very limited emissions, may include moderate and high nanoparticles in the nanofluid formulation. In cases where the MQL equipment is applied without safety equipment, although the emissions were minimum, only very low or low nanoparticles toxicity would be recommended.

- **Selection/Modification of physicochemical properties**

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

- Select larger nanoparticles. In general, larger nanoparticles within nanoscale lead to lower toxicity profiles and reduces translocation capability. However, in case of too long nanoparticles (fiber like nanoparticles), e.g., CNTs or graphene nanoplates, length should be lower than 5 μm, which seems a critical value for an effectively clearance by macrophages. In some cases, smaller nanoparticles may be preferred since they facilitate the dissolution and its clearance.
- Reduce the aspect to 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 the nanoparticles similar to asbestos (fiber like nanoparticles), with show the worst toxicity.
- Avoid nanoparticles that may release toxic ions after dissolution (e.g., ZnO and CuO).

- **Application of surfactants and surface modifiers**

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

- Avoid the use of specific coatings that are lipophilic.

- In case of surface modifiers, covalent functionalization with anionic and hydrophilic surface groups could potentially decrease their toxicity (e.g., carboxylate 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.

Besides safer-design considerations of nanofluids for MQL, extraction systems may be required, especially if using moderate to high toxic nanoparticles and low viscosity nanofluids, where mist is easily generated. Unlike conventional extraction systems in wet machining where air is extracted through the upper part of the machine, MQL emission extraction is often more effective closer to the work [29]. Some machine manufacturers offer extraction openings that are incorporated into the spindle head allowing extraction to take place very near to the cutting zone. Additionally, respirators with high-filtration efficiency can be used to avoid the operator's exposure to the airborne present near the machining area [135], although this alternative may hinder MQL implementation in industry.

A natural improvement of nanofluids in MQL can be the used of nanofluids in electrostatic minimum quantity lubrication (EMQL). EMQL is a new green technology using the synergetic effects between electrostatic spraying and minimum quantity lubrication. The equipment is basically a modification of MQL systems adding a high-voltage electrostatic power supply. Lubricants are directly charged using an electrode, which is embedded in the oil hose. The charged lubricants are then broken into charged air-lubricant mists by the compressed air [136]. This system enhances the adsorbability of oil mists on the machining zone, followed by an improved machining performance and reduced oil mist concentration. In a recent review about this MQL evolution [137], it was stated that the problem of high oil mist concentration in conventional MQL can be reduced by approximately 6.2%–68.3% compared with conventional air-assisted MQL, and the consumption of lubricants may be reduced by 60% compared with the conventional MQL.

8. Conclusions

9. References

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