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Occupational exposure limits for manufactured nanomaterials, a systematic review

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Abstract

Background

The toxicological properties of manufactured nanomaterials (MNMs) can be different from their bulk-material and uncertainty remains about the adverse health effects they may have on humans. Proposals for OELs have been put forward which can be useful for risk management and workers' protection. We performed a systematic review of proposals for OELs for MNMs to better understand the extent of such proposals, as well as their derivation methods.

Methods

We searched PubMed and Embase with an extensive search string and also assessed the references in the included studies. Two authors extracted data independently.

Results

We identified 20 studies that proposed in total 56 OEL values. Of these, two proposed a generic level for all MNMs, 14 proposed a generic OEL for a category of MNMs and 40 proposed an OEL for a specific nanomaterial. For specific fibres, four studies proposed a similar value but for carbon nanotubes (CNTs) the values differed with a factor ranging from 30 to 50 and for metals with a factor from 100 to 300. The studies did not provide explanations for this variation. We found that exposure to MNMs measured at selected workplaces may exceed even the highest proposed OEL. This indicates that the application and use of OELs may be useful for exposure reduction.

Conclusion

OELs can provide a valuable reference point for exposure reduction measures in workplaces. There is a need for more and better supported OELs based on a more systematic approach to OEL derivation.

Keywords

Occupational exposure limit (OEL), nanoparticles, risk assessment

BACKGROUND

Nanotechnology is an expanding field, with new manufactured nanomaterials (MNMs) and products containing these materials appearing on the market every year. There is also a growing diversity of industries in which MNMs are used such as construction, health care, energy, automobile and aerospace, chemical products, electronics and communication, cleaning and maintenance, textile, and military. This means that a growing number of workers worldwide is potentially exposed to MNMs (Kaluza S *et al.*, 2009). Systematic reviews of exposure studies confirm that workplace exposure to nanoparticles occurs and that control measures can be improved to reduce exposure (Debia, 2016, Ding *et al.*, 2016).

Nanoparticles can be classified into three categories. There are naturally occurring nanoparticles resulting from the nucleation of low-volatile gas-phase compounds followed by growth into small particles such as via volcanic eruptions and forest fires, via erosion. Then, there are also incidental nanoparticles generated (as by-products) of heating and combustion processes, machining and other high-energy processes, also called process-generated nanoparticles or combustion-derived nanoparticles (Donaldson *et al.*, 2005). Finally there are man-made manufactured nanoparticles intentionally produced by industry, as defined by the European Commission (E C 2011), such as carbon nanotubes. Since different sources of nanoparticles require different approaches, in this article we focus only on the third category, i.e. MNMs in the workplace.

Many MNMs are still given the name of their bigger chemical bulk material, but due to their extremely small size (≤100 nm), their physical and chemical properties can be different from those of the ‘mother’ material of the same structure and composition (Kulinowski K and B., 2011). The International Organization for Standardization (ISO) defined bulk material as “a material of the same chemical composition as nano-objects and their agglomerates and aggregates (NOAAs), at a scale greater than the nanoscale.”

The toxicity of MNMs largely depends on numerous physicochemical properties, including size, shape, composition, surface characteristics, charge and solubility. While workers may be exposed to MNMs via inhalation, ingestion or dermal absorption, the inhalation pathway is the most likely to result in larger systemic doses (Oberdorster *et al.*, 2005). Once inhaled, the mechanisms, pattern and efficiency of particle deposition in the respiratory tract remains a function of its aerodynamic diameter, shape and density. Particles with a diameter from 1 to 100 nm show a much higher fraction of deposition in the pulmonary region of the lung compared to larger particles. Of inhaled particles with various diameters, only those in the nanorange are known to systematically translocate from the lungs into the circulatory system through the air-blood tissue barrier and subsequently accumulate in secondary organs and tissues of the body (Geiser and Kreyling, 2010). Due to inherent ethical concerns, most evidence comes from rodent studies, with the most reliable data using quantitative particle biokinetics assessments, which balance the total nanoparticle fractions as measured in the rodent body and total excretion collected between application and autopsy (Geiser and Kreyling, 2010). In a study by Semmler-Behnke et al with nanosized 192Iridium, it was confirmed that nanoparticles are predominantly retained long-term within interstitial spaces of the alveolar region of the rat lung, with limited translocation toward the circulation (Semmler-Behnke *et al.*, 2007). A series of studies of particle inhalation in rodents has shown that nanoparticle translocation into the circulation and to secondary organs remains highly dependent on the nanoparticle physicochemical properties, including size, material, surface charge and surface modifications (Kreyling *et al.*, 2002, Semmler *et al.*, 2004, Kreyling *et al.*, 2009). There is currently no evidence of the nanoparticle translocation to the circulation and to secondary organs beyond 1% of the mass-based dose (Mills *et al.*, 2006, Wiebert *et al.*, 2006, Kreyling *et al.*, 2014). However, this figure is based on extrapolation from animal studies, resulting in the lack of precise information for inhaled MNM bio kinetics and long-term results in the human model. Nevertheless, while acute effects from MNM translocation to secondary organs are not likely to be considerable, it is possible that chronically exposed populations may face greater risks from cumulative, low-dose translocation processes, for example from biopersistent MNMs.

Occupational Exposure Limits (OEL) for chemical substances have long been in use for controlling workplace exposures. In 1887, Germany was the first country to publish selected limit values that were considered occupational exposure limits, but it was only in 1977 that the term had been fully adopted by the International Labour Organization (ILO) and later, in 1981, that the World Health Organization (WHO) started to use the same term: occupational exposure limits (Schulte *et al.*, 2010).

ISO defines OELs as a "maximum concentration of airborne contaminants deemed to be acceptable, as defined by the authority having jurisdiction" (ISO 16972:2010).

Even though there is no generally accepted uniform definition for an OEL, there is at least agreement that they constitute a level of usually airborne exposure to an agent beyond which unacceptable health risks might occur. In this general sense, we will also use the term OEL in this article. OELs are commonly established based on the actual state of the scientific knowledge and intended for protecting against adverse health effects for workers Health-based OELs are usually based on the estimation of a no effect level and therefore they represent an exposure level below which no adverse health effects are expected(Stouten *et al.*, 2008). However, for genotoxic and carcinogenic substances, that have no threshold below which there is no detectable effect, some countries, for example the Netherlands and Germany, have developed what they call risk-based OELs (S E R 2007, B A u A 2013, Ding *et al.*, 2014). These risk concepts define a *tolerable risk* level and an *acceptable risk* level. Germany defines a tolerable risk level with a calculated additional cancer risk of 4:1 000, meaning that statistically 4 out of 1 000 persons exposed to the substance during their working life may develop cancer, and they define an acceptable risk level with a calculated cancer risk level of 4:10 000 (until 2013) and 4:100 000 (at the latest in 2018). In the Netherlands, the levels are respectively 4:1 000 and 1:1 000 000 (new cancers per year). This means that these countries acknowledge that no safe level can be defined, that even the lowest exposures may induce an adverse effect and accept that a certain number of workers may develop cancer each year as a result of the exposure. On the other hand, countries also derive OELs that include technical and economic feasibility considerations for regulatory purposes and these are thus not entirely health or risk based and these are sometimes called administrative OELs. The naming of OELs is quite inconsistent between different national and international bodies.

Within the REACH framework the EU defines derived no-effect levels (DNEL) for substances with a detectable threshold for health-based effects (European Chemical Agency, 2012). For genotoxic carcinogenic substances, without a threshold effect, the EU defines derived minimal effect levels (DMEL), which is a semi-quantitative value. In the US, the American Conferences of Governmental Industrial Hygienists (ACGIH) defines threshold limit values (TLV) for health-based OELs. In their local context, these values may have a distinct and complementary meaning. The values may have been established based on what was considered to be technically feasible, or may have been calculated with the goal of preventing adverse health effects, or for limiting the potential number of health effects.

These factors make it complex to compare the values, although efforts have been made to harmonize procedures for deriving OELs (Deveau *et al.*, 2015).

Regardless of the difficulty of unambiguously defining OELs, they form an important tool for occupational risk management within a health context. They provide a rationale for risk assessment and control measures. Based on long-term analysis of exposures at the workplace, Creely et al. argued that regulation, including the establishment of OELs, has led to a decrease in workplace exposure to a number of hazardous chemicals (Creely *et al.*, 2007).

Moreover, according to common principles in behavioural theory, formulating a goal that has to be achieved is a strong driver for desirable behaviour (Locke and Latham, 2002).

Practice shows that OELs for chemical substances in general must be regarded as being provisional, requiring regular updating to comply with growing knowledge of the hazards. Therefore, insufficient scientific evidence should not be a barrier to accept provisional OELs but in contrary asks for the operationalization of the existing knowledge and if necessary for the application of precautionary measures. In fact, international experts advocate the development of provisional OELs for MNMs (van Broekhuizen and Dorbeck-Jung, 2013, Gordon *et al.*, 2014).

Currently, specific regulatory OELs for MNMs have not been established by the EU or by any national authority and it is expected that it may take a long time before OELs have been derived for all highly diverse frequently used MNMs. This is mainly due to the still existing large gaps in knowledge on particle toxicology, the high diversity of the newly developed, and used, MNMs, the uncertainties about their hazardous nature and the on-going discussions on the metrics to be used for the nano-OELs, be it mass-based or particle number based. Alternatively, generic precautionary particle number based nano reference values (NVR) for groups of nanomaterials have been proposed in some countries (I F A 2009, S E R 2012).

Here the adjective ‘reference’ is used to emphasize that these values are not health-based and indicates that these values should be for risk management: as an incentive to take control measures if the NVR is exceeded (S E R 2012, van Broekhuizen and Dorbeck-Jung, 2013).

For a few specific nanomaterials the industry and research have advised an OEL or a DNEL. NIOSH (2011) proposed an OEL for nano-TiO_2 based on toxicological data and used the US threshold limit value (TLV) for coarse TiO_2 (of 1.5mg/m^3) as a reference. Bayer (Pauluhn, 2010), Nanocyl (Luizi, 2009) and NIOSH (National Institute for Occupational Safety and Health, 2013) proposed OELs for multiwall carbon nanotubes (MWCNTs). DNELs were calculated in an experimental study by Stone et al applying the DNEL methodology with the prescribed assessment factors to MWCNTs, fullerenes, silver (Ag) and titanium dioxide (TiO_2) (Stone, 2009).

Currently, the World Health Organization is preparing a guideline for protecting workers from potential risks of MNMs. One of the questions is: which OEL/reference value should specific nanomaterials or groups of materials be assigned to? So far, there has been limited information on the development and use of OELs for MNMs (Schulte *et al.*, 2010, Gordon *et al.*, 2014). To address this problem, we conducted a systematic review of existing OELs for MNMs and analysed how these values were derived.

OBJECTIVE

To develop an exhaustive list of OELs that have been proposed for MNMs, and to describe differences and similarities in the approaches by which they were derived.

METHODS

Inclusion criteria

We based our inclusion criteria on the PICO approach, which is an acronym that specifies that eligible studies must comply with criteria for one or more of the following elements: participants (P), intervention/exposure (I/E), control (C), outcome (O), and study design (S) (Guyatt *et al.*, 2011, Morgan *et al.*, 2016). These criteria were defined as follows.

Study design: We included all proposals using an exposure limit approach or that proposed a quantitative exposure limit value for an MNM or a group of MNMs for protecting workers exposed to manufactured nanomaterials from adverse health effects. To be included, the studies also had to indicate the process by which the authors derived the OELs.

Participants: the OEL is a tool intended to protect workers potentially exposed to MNMs.

Intervention/Exposure: the OEL should be formulated as a concrete exposure value for a MNM or group of MNMs and should address the MNMs' potential for adverse health effects and it should indicate how the exposure should be measured and expressed.

We considered that the control (C) and outcome (O) elements were not applicable in our specific situation where we are not looking for effects of controlled studies but where we want to list a specific set of OEL proposals

Search methods for inclusion of studies

Electronic searches

We conducted a systematic literature search in PubMed and Embase until 15 February 2016, which was not limited to the English language. The search string contained specific search words for MNMs, such as nanomaterial and synonyms, occupational exposure limit and synonyms, and OELs. We combined both search strings with AND. (See Appendix 1 for the full search strategy)

Searching other sources

We checked the reference lists of all included studies to find additional proposals. We also asked experts involved in the development of the WHO Guidelines on protecting workers from potential risks of manufactured nanomaterials (draft, WHO 2016) or one of the systematic reviews of the WHO guideline to report any proposed OELs for MNMs that they knew of.

Analysis

We grouped the OELs per MNM or group of MNMs and analysed per OEL which process was used to derive the OEL value. Next, we categorised the derivation processes according to Gordon 2014 (Gordon *et al.*, 2014), which we slightly adapted as:

- Traditional quantitative risk assessment (QRA) defined as a stepped approach that starts with assessing toxicological data for substance and selecting a dose – usually a no-observed-adverse-effect-level or benchmark dose to use as a point of departure to calculate a human equivalent concentration and by applying various uncertainty and modifying factors finally arriving at an OEL.
- Bridging or read across defined as applying hazard information of one material (nano- or bulk material) to predict the hazards of another material (Patlewicz *et al.*, 2013); Oomen, 2015 #10}. Even though the methods has been advocated for bulk materials to save time, money and animals, there is no consensus on how to do this (Patlewicz *et al.*, 2013).
- Using environmental exposure limits for particulate matter (World Health Organisation, 2005)
- Grouping defined as an approach that groups MNMs based on a common aspect of the material (Oomen *et al.*, 2015). Even though grouping should be based on similar

principles as read-across, we believe that it is important to distinguish grouping from read-across for one material because of its practical consequences.

Data collection

Two authors (RM, JV) independently extracted the following data per proposal into an Excel sheet: MNM, value(s), measurement metric(s), approach (how were the OELs derived), year of development, country, category of development, key study.

Risk of bias assessment

We did not try to assess the risk of bias in the development process since there are no generally accepted methods to derive OELs.

RESULTS

Results of the searches

Our systematic searches resulted in 498 references. The search in MEDLINE/PubMed resulted in 259 references and the search in Embase in 239, altogether 498 references. In addition, we located 23 potential references from other sources. After removing the duplicates this resulted in 397 references that we screened for inclusion based on title and abstract. This resulted in 73 references that we checked for inclusion based on full text assessment. After the exclusion of those (n = 49) that did not meet our inclusion criteria, we included 24 articles. To prevent double counting of studies, we aggregated articles that described the same values into one study. For example, we aggregated van Broekhuizen 2011, 2012, 2013 and the German Institute of Occupational Safety and Health (IFA) 2016 into one study van Broekhuizen 2012 because IFA 2016 explicitly referred to van Broekhuizen as the source of their values (van Broekhuizen and Reijnders, 2011, van Broekhuizen *et al.*, 2012, van Broekhuizen and Dorbeck-Jung, 2013, Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung, 2016). This finally resulted in the inclusion of 20 studies. Some groups updated their proposals for OELs over time. In this case, we only included the most recent reported value. Many studies included more than one proposal and this resulted in 56 proposals for OELs. See the flow diagram (Figure 1). We have attached also a comprehensive list with all the full text articles that have been screened and included (Appendix 2).

Description of included studies

See Table 1 for a description of included studies.

Nanomaterials addressed

Studies with a general approach

We found two studies that took a generic approach and proposed an OEL for all MNMs. In one study, the OEL was based on environmental exposure limits for particulate matter (PM_x) (Guidotti, 2010). In the other study, the OEL was based on the number of times the potential MNM exposure concentration exceeded the local background level (McGarry *et al.*, 2013).

Studies with a categorical approach

We found six studies that used a categorical approach when they derived an OEL for a group of nanomaterials (British Standards Institution, 2007, Pauluhn, 2011, Kuempel *et al.*, 2012, van Broekhuizen *et al.*, 2012, German Hazardous Substances Committee, 2013, Stockmann-Juvala *et al.*, 2014). Groups were: fibres, granular biopersistent particles (GBP), MNMs with bulk material classified as CMAR-chemicals (carcinogenic, mutagenic, asthmagenic, reproductive risk), MNMs that are soluble, and MNMs that are non-biopersistent.

Studies with a MNM specific approach

Most studies evaluated specific MNMs. There were seven that evaluated TiO_2 (Kuempel *et al.*, 2006, Aschberger *et al.*, 2011, National Institute for Occupational Safety and Health, 2011, Ogura *et al.*, 2011, Warheit, 2013, Stockmann-Juvala *et al.*, 2014, Świdwińska-Gajewska and Czerczak, 2014), six that evaluated carbon nanotubes (Luizi, 2009, Stone, 2009, Pauluhn, 2010, Aschberger *et al.*, 2011, National Institute for Occupational Safety and

Health, 2013, Nakanishi *et al.*, 2015), three evaluated fullerene (Stone, 2009, Aschberger *et al.*, 2010, Shinohara *et al.*, 2011), three evaluated nanosilver (Stone, 2009, Aschberger *et al.*, 2011, Swidwinska-Gajewska and Czerczak, 2015), and one study evaluated amorphous SiO2, low-toxicity dust, nanocellulose and nanoclays (Stockmann-Juvala *et al.*, 2014).

Routes of exposure

All proposals addressed chronic inhalation exposure of the workers. One study also evaluated dermal and oral exposure to carbon nanotubes and fullerene (Stone, 2009). Stone 2009 and Aschberger 2010 also derived OEL values for short-term (15 minutes) inhalation exposure of the workers (Stone, 2009, Aschberger *et al.*, 2010).

There were 15 studies which used traditional quantitative risk assessment (QRA) (Kuempel *et al.*, 2006, Luizi, 2009, Stone, 2009, Aschberger *et al.*, 2010, Pauluhn, 2010, Aschberger *et al.*, 2011, National Institute for Occupational Safety and Health, 2011, Ogura *et al.*, 2011, Shinohara *et al.*, 2011, National Institute for Occupational Safety and Health, 2013, Warheit, 2013, Stockmann-Juvala *et al.*, 2014, Świdwińska-Gajewska and Czerczak, 2014, Nakanishi *et al.*, 2015, Swidwinska-Gajewska and Czerczak, 2015). There were all together six studies that used bridging or read across from short-term in vivo studies as follows. Three studies adjusted OELs that exist for the larger counterpart bulk material (British Standards Institution, 2007, van Broekhuizen *et al.*, 2012, Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung, 2016); four studies used a bridging and a grouping approach (British Standards Institution, 2007, van Broekhuizen *et al.*, 2012, German Hazardous Substances Committee, 2013, Stockmann-Juvala *et al.*, 2014); three studies used only a bridging approach (British Standards Institution, 2007, van Broekhuizen *et al.*, 2012, Stockmann-Juvala *et al.*, 2014); two used only a grouping approach (van Broekhuizen *et al.*, 2012, German Hazardous Substances Committee, 2013). Then there were two studies that used environmental exposure limits for particulate matter (Guidotti, 2010, McGarry *et al.*, 2013), and one study that used both a categorical QRA and a grouping approach based on common aspects of MNMs (Pauluhn, 2011).

None of the studies was based on read across from in-vitro studies.

Geographical location and research groups

The included proposals were performed by a limited number of research groups. There were three studies funded by the EU: the ENHRES programme (Engineered Nanoparticles: Review of Health and Environmental Safety) (Stone, 2009, Aschberger *et al.*, 2011) and the Scaffold programme (Stockmann-Juvala *et al.*, 2014). There were ten studies conducted by national occupational health or technological research institutes. One study from the United Kingdom by the British Standards Institution (British Standards Institution, 2007), three studies from NIOSH in the United States (Kuempel *et al.*, 2006, National Institute for Occupational Safety and Health, 2011, National Institute for Occupational Safety and Health, 2013), one from BAuA in Germany (German Hazardous Substances Committee, 2013), three from NEDO in Japan (Ogura *et al.*, 2011, Shinohara *et al.*, 2011, Nakanishi *et al.*, 2015), and two from Poland (Świdwińska-Gajewska and Czerczak, 2014, Swidwinska-Gajewska and Czerczak, 2015). There were two studies from universities, one from the Netherlands (van Broekhuizen *et al.*, 2012) and the second one from Australia (McGarry *et al.*, 2013). There were four studies by the chemical companies: Bayer (Pauluhn, 2010, Pauluhn, 2011), BASF/Nanocyl (Luizi, 2009), and DuPont (Warheit, 2013). There was also one proposal by an individual editor of a journal in Canada (Guidotti, 2010).

Terminology used

Five research groups used the term occupational exposure limit (OEL) (Pauluhn, 2010, German Hazardous Substances Committee, 2013, Warheit, 2013, Stockmann-Juvala *et al.*, 2014, Nakanishi *et al.*, 2015). For one group this term had a regulatory meaning (German

Hazardous Substances Committee, 2013) but not for the rest (Pauluhn, 2010, Warheit, 2013, Stockmann-Juvala *et al.*, 2014, Nakanishi *et al.*, 2015).

The four proposals by the Japanese research groups also used the term OEL but with a suffix indicating subchronic exposure spanning over 15 years called OEL period-limited or OEL PL (Ogura *et al.*, 2011, Shinohara *et al.*, 2011, Nakanishi *et al.*, 2015).

There were two related groups which used the same data from the ENRHES 2009 project, but used different terms for the OELs. Both Stone et al. and Aschberger et al. applied the methodology as described in the appendix of the European Chemical Agency, REACH project, for deriving DNELs (European Chemical Agency, 2012, Tynkkynen *et al.*, 2015), Aschberger and colleagues used an indicative no effect level (INEL), while Stone et al. used a derived no effect level (DNEL) (Stone, 2009, Aschberger *et al.*, 2010, Aschberger *et al.*, 2011). The reason for this was that the authors want to highlight that the derived INEL values should not be considered as having the same regulatory status as the DNEL values.

Van Broekhuizen proposed a nano reference value (NRV) with a provisional status, not a regulatory one (van Broekhuizen *et al.*, 2012).

Two studies by NIOSH used a recommended exposure limit (REL) which is a term used by NIOSH to describe an OEL, as the Occupational Health and Safety Administration (OSHA) uses permissible exposure limits (PELs) which are mandatory according to regulation (National Institute for Occupational Safety and Health, 2011, National Institute for Occupational Safety and Health, 2013).

The British Standards Institution (BSI) used the term benchmark exposure level (BEL), which indicates fairly well that this is not a health-based recommendation but a tool to help in assessing the need for control measures (British Standards Institution, 2007).

One study used a no effect concentration in air, which is an unusual term that was directly based on the findings of an animal exposure study carried out by the same research group (Luizi, 2009).

One study used particle control values (PCVs), which they defined as a concentration that exceeds three times the local back ground particle concentration in the air. For this concentration value, emission or exposure controls may need to be implemented or modified, or further assessment of the controls be undertaken (McGarry *et al.*, 2013).

Two Polish studies used a maximum admissible concentration-time weighted average (MAC-TWA) (Świdwińska-Gajewska and Czerczak, 2014, Swidwinska-Gajewska and Czerczak, 2015), which is defined as the time-weighted average concentration for a conventional 8-hour workday and a work week, to which workers may be exposed during their whole working life, without any adverse effects on their health.

One study used benchmark occupational exposure level (Guidotti, 2010). This proposal was derived using an environmental approach, and the author suggested this term so that it should not be confused with an OEL.

Kuempel at al. used a benchmark dose approach and determined and extrapolated the values belonging to the lower limit of the 95% confidence interval of the dose that caused a 0.1 % excess risk of lung cancer in rats (BMDL) (Kuempel *et al.*, 2006). They did not use the term OEL and discussed the derived OEL only as a human equivalent exposure estimate.

Exposure metrics used

The majority of OELs are only expressed as mass concentration (μg/m^3). There are, however, some exceptions. There is one proposal expressed in particle concentration (either fibers/cm^3 or particle/ml) for each of the following: MNM (McGarry *et al.*, 2013), fibers (British Standards Institution, 2007, van Broekhuizen *et al.*, 2012, Stockmann-Juvala *et al.*, 2014), GBP for metals and metal oxides (van Broekhuizen *et al.*, 2012), and nanocellulose (Stockmann-Juvala *et al.*, 2014). And there are two proposals expressed in particle- and mass concentrations for GBP insoluble nanomaterials (British Standards Institution, 2007).

Four out of 56 OEL-proposals contain a value both for mass and particle number concentration (British Standards Institution, 2007, German Hazardous Substances Committee, 2013). Only one study had proposals for mass-, particle- and surface concentration (nm^2/cm^3) for nanosilver (Stone, 2009).

For readability and clarity, we transformed all inhalation mass concentration values that were expressed as mg/m^3 into $\mu g/m^3$.

Proposed OELs reported in studies

See Table 2 for OEL values reported in the included studies.

OELs with a general approach

McGarry proposes a particle concentration of three times the local back-ground particle concentration (LBPC) level that indicates particle emission from the process at hand. This would also take into account 'natural' variation of the background level. The authors propose that control measures may need to be implemented if this level is exceeded for more than a total of 30 minutes during a workday, and/or if a single short-term measurement exceeds five times the LBPC. Guidotti proposes as the benchmark occupational exposure level value to simply use the value of 30 $\mu g/m^3$ that is set for particulate matter (PM_x) in ambient air and as agreed upon for the general population in Canada (Guidotti, 2010). He argued that there are many similarities between PM_x and MNMs and that if these values are deemed fit to protect the general population, this probably also protects workers.

OELs for fibres

For fibres, all four included proposals used the same value, a level ten times lower than the asbestos OEL of 0.1 fibres/ml, because of the use of a safety margin of a factor 10. This particular value was chosen because of the assumed physico-chemical similarities with asbestos (British Standards Institution, 2007, van Broekhuizen *et al.*, 2012, German Hazardous Substances Committee, 2013, Stockmann-Juvala *et al.*, 2014). Moreover, Stockmann-Juvala mentioned that this limit is "based on the precautionary principle"(Stockmann-Juvala *et al.*, 2014). Similarly based on what is tolerated for asbestos exposure, the German authority considers a level that is ten times lower an acceptable level (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, 2008, German Hazardous Substances Committee, 2013).

OELs for Granular Biopersistent Nanoparticles (GBP)

For GBPs, van Broekhuizen proposes two groups based on the classification recommended by the German Institute of Occupational Safety and Health (IFA): one category with a density higher than 6000 kg/m^3 and the second one having a lower density than this value (van Broekhuizen *et al.*, 2012). The starting point for the number-based reference values is the calculation of the number of nanoparticles with a diameter of 100 nm that constitute a mass of 0.1 mg/m^3. Values are defined as corrected for the background concentrations.

OELs for non-biopersistent nanoparticles

Van Broekhuizen proposes the same OEL as for the bulk material in the case that the chemical is soluble or not biopersistent (van Broekhuizen *et al.*, 2012).

OELs for specific MNMs

Carbonaceous material

For carbon nanotubes and nanofibers, the proposed OELs differ considerably. The lowest proposed value is 0.67 µg/m^3 (Stone, 2009), which is smaller than 1 µg/m^3 recommended by NIOSH 2013 (National Institute for Occupational Safety and Health, 2013). Nakanishi proposes a value that is at least 30 times larger but that would protect only for 15 years (Nakanishi *et al.*, 2015), while the NIOSH value is calculated based on 45-year working lifetime.

Also for fullerenes, the values differ by a factor of 50 with the same difference that the highest value protects only for15 years (Shinohara *et al.*, 2011). The value proposed by Aschberger at al. 2011 is significantly lower (Aschberger *et al.*, 2011).

With 120 and 240 µg/m^3, the OEL values for carbon black (Kuempel *et al.*, 2006) are much higher than for carbon nanotubes for which the highest value is 50 µg/m^3 (Pauluhn, 2010).

Metals and metaloxides

As for nanosilver, the differences are considerable with 0.098 µg/m^3 based on a large extrapolation factor and effects on the lungs, and 0.67 µg/m^3 based on more systemic effects (Stone, 2009, Aschberger *et al.*, 2010, Aschberger *et al.*, 2011). However, the Polish group proposed 100 to 15 times higher value of 10 µg/m^3 which was already considerably lower than the current value of 50 µg/m^3 (Swidwinska-Gajewska and Czerczak, 2015). The authors provide no clear justification for such high values.

Also for titanium dioxide there is considerable variation. Aschberger 2010 proposed 17 µg/m^3, which is the lowest compared to the other groups. The highest limit was proposed by Warheit 2013 with 5000 µg/m^3 which is almost 300-fold higher (Warheit, 2013). Three studies proposed the same value of 300 µg/m^3 (National Institute for Occupational Safety and Health, 2011, Stockmann-Juvala *et al.*, 2014, Świdwińska-Gajewska and Czerczak, 2014) where we assumed that two of those values were simply taken over from NIOSH, but this was not clearly stated in the papers.

For acute exposure to nanocarbon, only Aschberger and Stone derived values. For inhalation of fullerenes C_{60} the limits were identical, 44.4 µg/m^3 (Stone, 2009, Aschberger *et al.*, 2011). For acute dermal exposure Stone set two limits: 0.414 mg/person bodyweight and 1.241 mg/person bodyweight based on different assumptions in the derivation (Stone, 2009).

Other materials

For other MNMs there are only single values available that are not proposed by other groups such as for low-toxicity dust, nanoclays, nanocellulose (Stockmann-Juvala *et al.*, 2014), CMAR and soluble nanomaterials (British Standards Institution, 2007), and non-biopersistent nanomaterials (van Broekhuizen *et al.*, 2012).

DISCUSSION

In total, we found 56 proposals for OELs for MNMs in 20 papers. Of these two proposed a level for all MNMs, 14 proposed OELs for a category of MNMs and 40 proposed OELs for a specific material. For fibres, four studies proposed a similar value but for CNTs the values differed with a factor of 30 to 50 and for metals with a factor of 100 to 300. We could not explain these differences.

When we compare the exposure levels that have been reported in workplace exposure studies to the OEL values that we have reported here, it seems that there is ample room for a reduction of exposure in workplaces to comply with the proposed OELs. Debia et al. reported occupational exposure to carbon nanofibers (CNFs) in potential exposure situations with values ranging from not detected to 193 fibres/cm^3 for studies that measured particle number concentrations and from not detected to 1 000 µg/m^3 for studies that measured mass concentration (Debia, 2016). Most of these values exceed the proposed OELs discussed in this paper. For CNTs, there were only two exposure situations that exceeded the highest proposed OEL of 50 µg/m^3 but the lowest OEL of 0.67 µg/m^3 was exceeded in almost all situations that reported mass concentrations. For TiO_2 on the other hand, all but one exposure situation was below the NIOSH recommended value of 300 µg/m^3. For nanosilver, only two out of ten exposure situations were below the proposed OEL of 0.33 µg/m^3 based on inhalation exposure. Because these were workplaces that admitted researchers to take measurements, it is conceivable that in many other workplaces exposures will be higher. Applying and using the OELs presented here will be a helpful indication that control measures should be taken.

The strength of our study is that we performed a systematic search to identify developed OELs, assessed them, and listed them in a systematic way. We did not exclude studies based on language or on publication status. We believe that we have compiled a comprehensive list of all available values. The proposed values can be used as reference or benchmark values for comparison with workplace measurement and for risk management.

One of the limitations of our review is that we could not compare in detail the different methodologies used to derive the OELs. However, for those that used quantitative risk assessment, differences in the proposed levels can be explained by the animal studies used, how no-observed-adverse-effect level (NOAEL) were identified in the studies and which adjustment factors were used to extrapolate the results to a human exposure during an entire working life. Another limitation is that the studies did not always report sufficient information on the type of MNM studied. For example, TiO_2 may have different crystal structures with different toxicological properties. From the studies it was not always clear which form of TiO_2 was considered.

Some studies indicated that the values were meant as a time-weighted average (TWA) over an eight-hour working day and a 40-hour workweek. Some advised as well how to calculate a value for a TWA-15 minute for short-term exposure, also referred to as STEL (Short Term Exposure Limit). By definition all OELs are 8 hour-TWA, unless otherwise stated. There is a similar situation with the interpretation of the OELs where some authors mentioned that the proposed values should prevent adverse effects over the time span of a 45-year working life but others only proposed this for a period of 15 years. Another limitation is that OELs assume that the MNMs are measured as primary nanoparticles. However, workplace exposure studies indicate that most MNMs are present in microsized agglomerates, which may also be the case for the rodent studies (Debia, 2016). It is unclear how this would be taken into account.

Progress in the nanotechnology field is continuously growing. In his 2006 article, Maynard presented five challenges regarding nanotechnology research that would span over the following two decades. Among the challenges the author proposed for the next decade the development of "instruments to assess exposure to manufactured nanomaterials" including at the workplace (Maynard *et al.*, 2006). Our review is timely in this fashion, but still more research is needed regarding OELs.

Implications for practice

The OELs listed here can be used as reference or benchmark values for comparison with workplace exposure towards a better understanding of the need for control measures. For some MNM categories such as fibres, one concrete OEL was proposed by four different studies (British Standards Institution, 2007, van Broekhuizen *et al.*, 2012, German Hazardous Substances Committee, 2013, Stockmann-Juvala *et al.*, 2014). For other categories or specific MNMs there is a range of values proposed making it difficult to recommend one value over another. However, given current workplace exposure reports and when using the highest OEL values, this should be an incentive to lower exposures in the workplace.

Implications for research

There is a need to develop a coordinated approach among researchers and relevant stakeholders towards the harmonization of OEL derivation for nanomaterials. This will improve transparency and communication towards stakeholders. Communication will also be improved with a common terminology used by all the parties involved from academia to professionals and workers. Moreover, the recent and emerging need for nanomaterial exposure limits provides a unique opportunity for organizations worldwide to finally find consensus about the naming of OELs.

Currently, there is variation in the selection and analysis of animal studies used to underpin quantitative risk assessment. Using systematic reviews of animal studies, including systematic risk of bias assessment (Hooijmans and Ritskes-Hoitinga, 2013, Hooijmans *et al.*, 2014), would lead to more uniform conclusions. Finally, agreement about interspecies and intraspecies adjustment factors would be needed to come to more similar conclusions and exposure values.

Regular updating of this list will be necessary to keep up with scientific progress in both the field of (nano) particle toxicological research and in the field of OEL derivation.

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Study reference	Professional Group/Institution	Funded by	Country	Nanomaterial(s)
AGS 2013	German Hazardous Substances Committee, German Federal Institute for Occupational Safety and Health (BAuA)	National Institute	Germany	Granular biopersistent particles and non-entangled fibrous nanomaterials
Aschberger 2011	ENRHES project 2009	European project	EU	Carbon nanotubes (multi-walled), fullerenes, nanosilver and nano titanium dioxide
BSI 2007	British Standards Institution	National Institute	UK	Fibrous nanomaterials, CMAR, insoluble and soluble nanomaterials
Guidotti 2010	Archives of Environmental and Occupational Health, journal	Independent	Canada	Environmental fine particulate matter ≤ 2500nm
Kuempel 2006	National Institute for Occupational Safety and Health (NIOSH)	National Institute	USA	Titanium dioxide (ultrafine) and carbon black
Luizi 2009	Nanocyl	Company	Belgium	Carbon nanotubes
McGarry 2013	International Laboratory for Air Quality and Health, Queensland University of Technology	University	Australia	Nanomaterials
Nakanishi 2015	New Energy and Industrial Technology Development Organization (NEDO)	National Institute	Japan	Carbon nanotube group: single-, double- and multi-walled nanotubes
NIOSH 2011	National Institute for Occupational Safety and Health (NIOSH)	National Institute	USA	Titanium dioxide (ultrafine)
NIOSH 2013	National Institute for Occupational Safety and Health (NIOSH)	National Institute	USA	Carbon nanotubes and carbon nanofibers
Ogura 2011	New Energy and Industrial Technology Development	National Institute	Japan	Titanium dioxide

	Organization (NEDO)			
Pauluhn 2010	Institute of Toxicology, Bayer Schering Pharmaceuticals	Company	Germany	Carbon nanotubes (multi-walled)
Pauluhn 2011	Institute of Toxicology, Bayer Schering Pharmaceutical	Company	Germany	Inhaled poorly soluble particles
Shinohara 2011	New Energy and Industrial Technology Development Organization (NEDO)	National Institute	Japan	Carbon fullerenes (C_{60})
Stockmann-Juvala 2014	Scaffold SPD-7	European project	EU	Silicon dioxide (amorphous silica), titanium dioxide, carbon nanofibers, nanocellulose, nanoclays and low-toxicity dusts
Stone 2009	ENRHES project 2009	European project	EU	Carbon nanotubes, fullerenes, metals and metal oxides
Swidwinska 2014	Nofer Institute of Occupational Medicine, Lodz	National Institute	Poland	Titanium dioxide
Swidwinska 2015	Nofer Institute of Occupational Medicine, Lodz	National Institute	Poland	Nanosilver
van Broekhuizen 2012	IVAM, University of Amsterdam	University	The Netherlands	Metals and metal oxides, biopersistent granular nanomaterial
Warheit 2013	DuPont	Company	USA	Titanium dioxide (nanoscale)

Table 1: Description of studies proposing OELs included in the review (N=20)

Category	Study Reference	Nanomaterials and specifications	OEL Name	Mass concentration µg/m³	Particle concentration (particle/ml, fibers/cm³)	Surface concentration (nm²/cm³)	Approach
Inhalation: General Approach							
MNM	Guidotti 2010	Fine particulate matter ≤ 2500nm	BOEL	30			Environmental
MNM	McGarry 2013	Airborne particles from nanotechnology processes	PCVs		3 times LBPC for over 30 minutes		Environmental
Inhalation: Categorical Approach							
CMAR	BSI 2007	CMAR nanomaterials	BEL	0.1 x bulk WEL			Bridging
Fibers	AGS 2013	Non-entangled fibrous NM	Acceptance level (default), respirable fraction		0.01		Bridging/Grouping
Fibers	BSI 2007	Fibrous nanomaterials	BEL		0.01		Bridging/Grouping
Fibers	Stockmann-Juvala 2014	Carbon nanofibers, CNFs	OEL		0.01		Bridging/Grouping
Fibers	van Broekhuizen 2012	Carbon nanotubes, CNTs, insoluble NM with high aspect ratio >3:1	NRV		0.01		Bridging/Grouping
GBP	AGS 2013	in operations with NM: nanosized GBP with no specific toxicity	OEL respirable fraction, default	500			Grouping
GBP	AGS 2013	no specific operations with NM: granular biopersistent particles	OEL respirable fraction	1250			Grouping
GBP	BSI 2007	Insoluble nanomaterials	BEL	0.066 x bulk WEL	20000		Bridging
GBP	Pauluhn 2011	Inhaled poorly soluble particles	DNEL	0.5 µl PMrespirable /m³ x agglomerate density			Categorical QRA/Grouping
GBP	van Broekhuizen 2012	Metals and metal oxides, biopersistent granular NM >6000 kg/m³	NRV		20000		Grouping
GBP	van Broekhuizen 2012	Metals and metal oxides, biopersistent granular NM <6000	NRV		40000		Grouping

		kg/m^3					
Low-toxicity dust	Stockmann-Juvala 2014		OEL	300 (respirable fraction), 4000 (inhalable fraction)			Bridging/Grouping
Non bio-persistent	van Broekhuizen 2012	Non-biopersistent granular NM 1-100 nm	NRV	applicable OEL, WEL			Bridging
Soluble	BSI 2007	Soluble nanomaterials	BEL	0.5 x bulk WEL			Bridging
Inhalation: Specific Approach							
Carbon	Aschberger 2011	Multi-walled carbon nanotubes, MWCNT 10 nm	INEL	1			QRA
Carbon	Aschberger 2011	Multi-walled carbon nanotubes, MWCNT 140 nm	INEL	2			QRA
Carbon	Luizi 2009	Carbon nanotubes, CNTs	No effect concentration in air	2.5			QRA
Carbon	Nakanishi 2015	Carbon nanotube group, SWCNT, DWCNT, MWCNT	OEL 15 years	30			QRA
Carbon	NIOSH 2013	All carbon nanotubes and nanofibers	REL respirable elemental carbon	< 1			QRA
Carbon	Pauluhn 2010	Multi-walled carbon nanotubes, MWCNT Baytubes ®	OEL, inhalable fraction	50			QRA
Carbon	Stone 2009	MWCNT	DNEL chronic inhalation, systemic immune effect	0.67			QRA
Carbon	Kuempel 2006	Carbon black, CB ultrafine	BMDL 45 years (lung dosimetry, model 1)	120			QRA
Carbon	Kuempel 2006	Carbon black, CB ultrafine	BMDL 45 years (lung dosimetry, model 2)	240			QRA
Carbon	Aschberger 2011	Fullerenes, C_{60}	INEL	7.4			QRA
Carbon	Shinohara 2011	Fullerenes, C_{60}	OEL (PL) 15 years	390			QRA
Nanocellulose	Stockmann-Juvala 2014	Nanocellulose	OEL		0.01		Bridging
Nanoclays	Stockmann-	Nanoclays	OEL	300 (respirable fraction), 4000 (inhalable fraction)			Bridging/Grou

	Juvala 2014						ping
Nano silver	Aschberger 2011	Nano Ag	INEL lung function	0.33			QRA
Nano silver	Aschberger 2011	Nano Ag	INEL lung other effects	0.67			QRA
Nano silver	Stone 2009	Nano Ag	DNEL lung exposure, extrapolating factor 10	0.098	1200	2.2×10^{6}	QRA
Nano silver	Stone 2009	Nano Ag	DNEL lung exposure, extrapolating factor 3	0.33	4000	7.2×10^{6}	QRA
Nano silver	Stone 2009	Nano Ag	DNEL liver effect	0.67	7000	1.2×10^{7}	QRA
Nano silver	Swidwinska 2015	Nano Ag	MAC-TWA inhalable fraction	10			QRA
Silicon dioxide	Stockmann-Juvala 2014	Amorphous silica, SiO_2	OEL respirable fraction	300			QRA
Titanium dioxide	Aschberger 2011	TiO_2	INEL	17			QRA
Titanium dioxide	Kuempel 2006	TiO_2 ultrafine	BMDL 45 years (lung dosimetry, model 1)	73			QRA
Titanium dioxide	Kuempel 2006	TiO_2 ultrafine	BMDL 45 years (lung dosimetry, model 2)	140			QRA
Titanium dioxide	NIOSH 2011	TiO_2 ultrafine	REL (up to 10 h/day, 40 h/week)	300			QRA
Titanium dioxide	Ogura 2011	TiO_2	OEL (PL) 15 years	610			QRA
Titanium dioxide	Stockmann-Juvala 2014	TiO_2	OEL respirable fraction	100			QRA
Titanium dioxide	Swidwinska 2014	TiO_2	MAC	300			QRA
Titanium dioxi	Warheit 2013	High surface reactivity anastase-rutile nanoscale	OEL	1000			QRA

de		$TiO2_2$					
Titanium dioxide	Warheit 2013	Low surface reactivity nanoscale TiO_2	OEL	2000			QRA
Dermal							
Carbon	Stone 2009	MWCNT	DNEL dermal chronic exposure, assessment factor 3	0.414 mg/person bodyweight			QRA
Carbon	Stone 2009	MWCNT	DNEL dermal chronic exposure	1.241 mg/person bodyweight			QRA
Oral							
Carbon	Stone 2009	Fullerite, mixture of C_{60} + C_{70}	DNEL oral acute exposure	40 mg/kg body weight			QRA
Carbon	Stone 2009	Water soluble C_{60}, polyalkylsulfonated	DNEL oral chronic exposure	0.17 mg/kg body weight			QRA
Acute							
MNM	McGarry 2013	Airborne particles from nanotechnology processes	PCVs, single short-term measurement		5 times the local particle reference value		Environmental
Carbon	Stone 2009	MWCNT	DNEL acute inhalation, systemic immune effect	4.02			QRA
Carbon	Aschberger 2010	Fullerenes, C_{60}	INEL short term, inhalable fraction	44.4			QRA
Carbon	Stone 2009	MWCNT	DNEL acute inhalation, pulmonary effect	201			QRA
Carbon	Stone 2009	MWCNT	DNEL dermal acute exposure	7448 µg/person bodyweight			QRA
Carbon	Stone 2009	MWCNT	DNEL dermal acute exposure, assessment factor 3	2483 µg/person bodyweight			QRA

Table 2: Proposed Occupational Exposure Limits for Manufactured Nanomaterials

AGS = German Hazardous Substances Committee

BEL = benchmark exposure level

BMDL = benchmark dose lower (95% confidence limit of the benchmark dose, BMD)

BOEL = benchmark occupational exposure level

BSI = British Standards Institution

CMAR = carcinogenic, mutagenic, asthmagenic or a reproductive toxin

CNT = carbon nanotube

DNEL = derived no-effect level

DWCNT = double-walled carbon nanotube

GBP = granular biopersistent particles

INEL = indicative no effect level

LBPC = local background particle concentration

MAC = maximum admissible concentration

MAC-TWA = maximum admissible concentration time weighted average

MNM = manufactured nanomaterial

MWCNT = multi-walled carbon nanotube

NIOSH = National Institute for Occupational Safety and Health (United States)

NM = nanomaterial

NRV = nano reference value

OEL = occupational exposure limit

OEL (PL) = occupational exposure limit period-limited

PCVs = particle control values

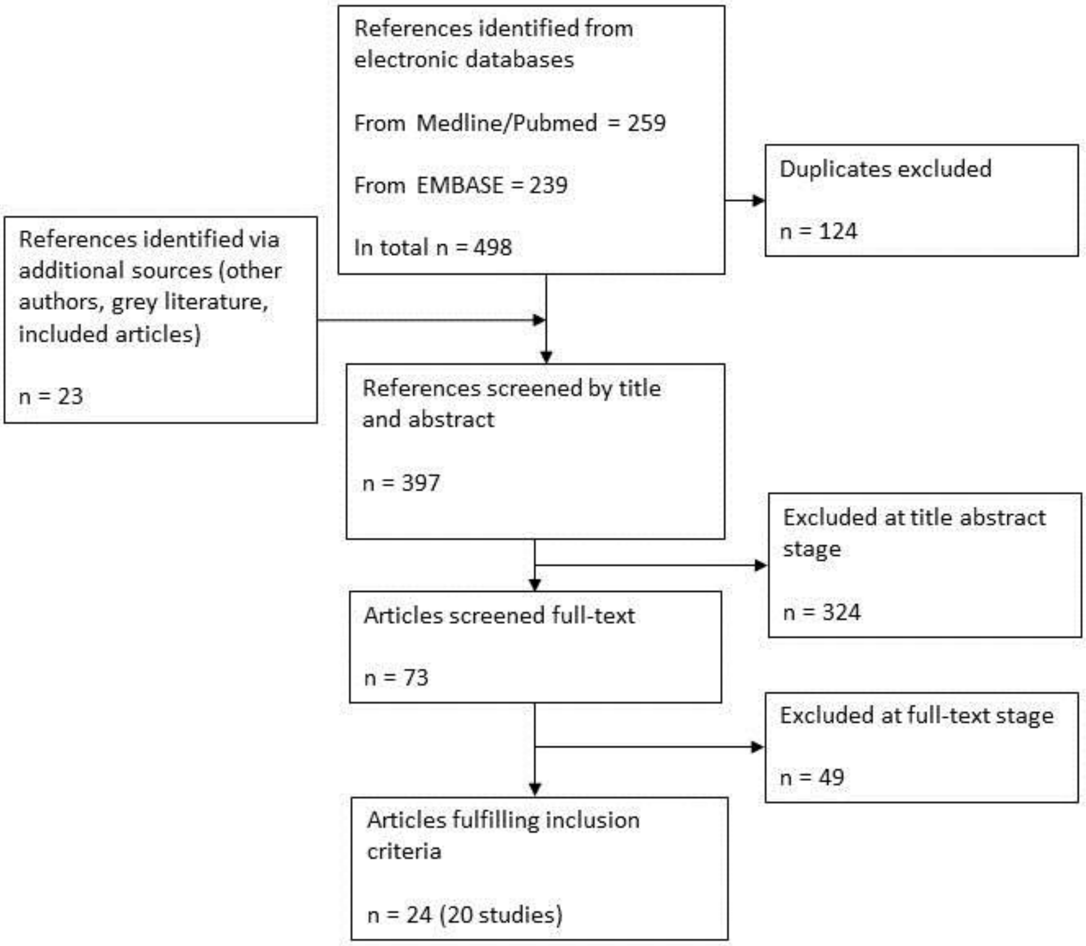
REL = recommended exposure limit

QRA = traditional quantitative risk assessment

SWCNT = single-walled carbon nanotube

TWA = time weighted average exposure over the 8-hour working day

WEL = workplace exposure limit


References identified from electronic databases
From Medline/Pubmed = 259
From EMBASE = 239
In total n = 498
Duplicates excluded
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References identified via additional sources (other authors, grey literature, included articles)
n = 23
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Articles fulfilling inclusion criteria
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