［Review］

The Effectiveness of Specific Risk Mitigation Techniques Used in the Production and Handling of Manufactured Nanomaterials: A Systematic Review

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Abstract **:** Many kinds of manufactured nanomaterials (MNMs) have been developed and used as basic materials of industrial products, and they may pose health risks for workers in not only developed countries but also in developing countries. Few studies have looked at the evidence for effects of controls that mitigate the risk of exposure to MNMs. Therefore, we systematically searched the literature from the year 2000 to 2015. We included studies that compared the use of an exposure control to the situation without such a technique and those that measured the exposure to MNMs as the outcome. In order to evaluate the effectiveness of these controls, we used their "protection factor", defined as the ratio between concentrations without and with the control. We located 1,131 references in PubMed and other lists, and out of these references, 41 studies fulfilled our inclusion criteria. We categorized them as engineering controls such as enclosure, local exhaust ventilation or process automation, and as personal protective equipment (PPE). For enclosure systems we found a protection factor beyond 100. For other engineering controls, the better controls scored 10 to 20, but many cases of local exhaust ventilation had a protection factor of less than 10 and some cases even increased exposure. PPE such as N95 or equivalent filtering respirators had a protection factor of approximately 10 tested with nano-sized aerosols. We conclude that there is low quality evidence that specific engineering controls can reduce exposure to MNMs but that enclosure is considerably more effective. For respiratory protection the evidence is of very low quality due to the lack of field studies. This information can be used to decide about controls when exposure to MNMs exceeds proposed occupational exposure limits or when no toxicological information is available for a MNM.

Keywords **:** manufactured nanomaterials, systematic review, engineering control, respirator, process automation.

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Introduction

"Nanomaterials" are materials of which a single unit is between 1 and 100 nm in size; in other words, nanoscale. According to ISO/TS (International Organization for Standardization/Technical Specification) 80004-2: 2015, a single unit is called a *nano-object*, and is defined as a material with one, two or three external dimensions in the size range of nanoscale. Subcategories of the *nano-object* are *nanoplate, nanofiber*

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and *nanoparticle*, based on the nanoscale dimensions [1]. This definition applies to intentionally produced nanomaterials as manufactured nanomaterials (MNMs). Among the various nanomaterials, carbon black, fumed silica, and titanium dioxide are currently mass-produced and used commonly, while the newer carbon nanomaterial fullerene and the fibrous nanomaterials single- and multi-walled carbon nanotubes (SWCNTs and MWCNTs, respectively) are becoming common, with applications and production expanding from the laboratory to industrial levels. Nanomaterials often have unique optical, electronic, or mechanical properties, but in addition to offering the intended benefits, they may also pose unforeseen adverse environmental, health, and social risks.

Information about the health effects of MNMs has been accumulated over the last decade and some MNMs pose similar health risks as the bulk material. For other MNMs it is clear that the MNM-form and size pose new health risks compared to the bulk material, such as with CNTs. For again other MNMs there is not enough information to be able to assess the health risks. Given that exposure beyond the proposed occupational exposure limits has been reported to occur frequently, there is a need for measures to control exposure [2, 3].

The hierarchy of control measures stipulates that control measures are taken in the following order of priority: 1) Eliminate the hazard, 2) Substitute the hazardous material with a less harmful agent, 3) Change the process, 4) Apply engineering controls, 5) Consider administrative controls, and 6) Use personal protective equipment (PPE). In the case of MNMs, it would be difficult to apply 1) and 2) because MNMs are used because of the specific properties of the material. Therefore the first control measure – 3) to change the process – should always be considered first. However, any combination of the above control measures will potentially minimize the risk.

The World Health Organization (WHO) started to develop guidelines for protecting workers from potential risks of MNMs in 2010. In the process of developing the guidelines, 10 questions were listed that should lead to recommendations, and the WHO Global Network of Collaborating Centers in Occupational Health offered to systematically review the evidence from published research. Some of these reviews have been published already [2, 3]. In our review, we tried to find information to answer the question "What risk mitigation techniques should be used for specific nanomaterials or groups of nanomaterials and specific exposure situations, and what are the criteria for evaluating the effectiveness of the controls?"

Methods

PICO approach

We framed an answerable question according to the PICO acronym (P for Participants, I for Intervention, C for Comparators, and O for Outcomes) [4, 5] and reviewed controlled field and experimental studies on exposure mitigation for workers. We included any controlled study that was either a before-after comparison in which the level of exposure was compared before and after installing controls, or a controlled before-after comparison in which the change in exposure in the intervention group was compared to the change in exposure in the control group.

Participants (P) were workers exposed to or workplaces with exposure to MNMs or products containing MNMs across all the stages of the life cycle (synthesis, manufacture, downstream use, and disposal and recycling). Exposure should include a description of the size or size-distribution of the MNMs and a description of the measurement instruments for the aerosolized MNMs. Exposure to an MNM should fall within the ISO definition: "nanomaterials within the nanotechnology industry as a material with any external dimension in the nanoscale or having internal or surface structure in the nanoscale, with nanoscale defined as the size range from approximately 1 nm to 100 nm" [1].

Studies were included if they evaluated one of the three following intervention categories (I): 1. Any type of ventilation or enclosure system in workplaces that affects air flow velocity or aerosol concentration; 2. Any type of personal protective equipment, including respirators, for workers that has filtration performance against nano-size particles or prevents leakage through structural gaps in the PPE; 3. Any type of management of the work environment using rules for work practices or application and maintenance, such as automation or dustiness controls.

Comparators (C) were no mitigation techniques.

Outcomes (O) were the level of exposure to the nanomaterials as aerosolized MNMs or general nano-size aerosols.

Several scales of effectiveness of mitigation against nanomaterial exposure are potentially available. In this review, we used the protection factor as the measure of effectiveness of a control which was defined as exposure concentrations without and with control for ventilation or other engineering control techniques ($PF_{eng} = C_{without} / C_{with}$), and PF_{res} means the PF ($= C_{out}/C_{in}$; concentrations outside of and inside a respirator) for respirators. PF > 1 means that the exposure is reduced, PF = 1 means no effect on exposure, and PF < 1 means an increase of exposure with the control. The value of PF will be compared to the ratio of real exposure level and occupational exposure limit of specific MNMs, which have been reviewed in previous reports [2, 3].

Sources of information and research strategy

To develop a comprehensive list of potentially relevant studies, PubMed was searched for literature from the year 2000 to the end of 2015. The search strategy and the terms are listed in Table 1.

Study selection

Two reviewers independently checked if any titles and abstracts that came up in the search did not fulfill one or more of the inclusion criteria and thus could be excluded. The remaining articles resulting from this selection process were assessed again by two reviewers based on the full text of the articles to see which articles fulfilled all the inclusion criteria. If there was a disagreement about whether a paper should be included or not, consensus was reached by discussion. Articles that described the same study were included only once, referencing that one study. This resulted in the list of included studies. Studies that did not refer to occupational settings or exposure situations and studies on MNMs that did not fall under the ISO definition were excluded in the selection process.

Data collection process

Each risk mitigation technique in the extracted papers was categorized into a specific control category and a given nanomaterial. A single study could describe several exposure situations and provide a series of outcomes. For example, an investigation conducted on one nanomaterial with three different control measures, or three brands of respirator, or three production systems performed in the same field, was counted as three cases. Globally, the following data were extracted: references, characteristics of the participants and interventions, outcomes, and authors' conclusions.

Table 1. List of terms for search

("nanostructures" [MeSH Terms] OR "nanostructures" [All Fields] OR "nanomaterials" [All Fields] OR "nanoparticles" [MeSH Terms] OR "nanoparticles" [All Fields] OR "nanoparticle" [All Fields] OR "nanofibers" [MeSH Terms] OR "nanofibers" [All Fields] OR "nanofiber" [All Fields])
AND
(exhaust [All Fields] OR "ventilation*" [MeSH Terms] OR "ventilation*" [All Fields] OR "respiration*" [MeSH Terms] OR "respiration*" [All Fields]
OR
"mask*" [All Fields] OR ("ventilator*" [All Fields] AND "mechanical" [All Fields]) OR "mechanical ventilator*" [All Fields] OR "respirator*" [All Fields] OR "personal protective equipment*" [All Fields] OR "PPE*" [All Fields]
OR
"risk reduction*" [All Fields] OR countermeasure [All Fields] OR countermeasures [All Fields] OR countermeasured [All Fields] OR countermeasurements [All Fields]
OR
(automation [All Fields] OR automationof [All Fields] OR automations [All Fields] OR automatization [All Fields] OR automatizational [All Fields]) AND exposure [All Fields]
OR
(wetting [All Fields] OR wettings [All Fields] OR dewetting [All Fields] OR wettingen [All Fields] OR wettinger [All Fields] OR wettingfeld [All Fields] OR wettinglike [All Fields] OR dustiness [All Fields]) AND exposure [All Fields])

Assessment of risk of bias and other methodological quality items in included studies

We assessed the risk of bias in the included studies by using the following three items: 1. Intervention and control condition were comparable with regards to the type of work and working conditions based on the pairs of descriptions with and without intervention; 2. Measurement of the MNM was done with state of the art instruments or methods; 3. The intervention was fully implemented and technically according to the state of the art.

Each item (RB1, RB2, RB3) was scored with yes/no/can't judge and coded as 1/−1/0. Primary data which were presented originally in the paper by the authors was 'yes (1)', and secondary data which were cited from previous papers by the authors was 'no (−1)'. Thus, a score of plus 3 indicates a low risk of bias and a score of −3 a high risk of bias. In addition, we used the following ten items to indicate the methodological quality of each study: precise specification of application area task and workplace; validation in field study; quality assessment; quality management; standard operating procedure; hazard data; exposure data; data on efficacy of controls; data on bias and confounding; and evidence of physico-chemical characterization of MNMs. The score of each item is from −2 to 2, and the total of the scores is from −20 to 20.

Synthesis of study outcomes

Estimation of the protection factors in the situations was based on the values in the papers, such as concentration of airborne MNMs. We narratively described the protection factors for each intervention for each category and did not try to synthesize the findings in a meta-analysis because the exposure data did not lend itself to such an analysis.

Overall assessment of the quality of the evidence

We used a modified GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach to assess the overall quality of the evidence per category of controls [3]. We started with low quality if the evidence was from observational studies and with high quality if the evidence was from randomized studies. We downgraded the evidence by one level if one of the following criteria were met: Most studies with high risk of bias, No direct answer to our PICO question; for example no field studies, Inconsistent outcomes in studies, Imprecision of the study results, Publication bias present.

Results

Results of the search

A total of 1,131 references were identified through the search in the PubMed database. 1,066 records were excluded based on the title. Abstracts of 65 records were checked full-text and of these 27 were excluded. This led to 38 papers that fulfilled our inclusion criteria. We excluded eight studies on risk management and one description of a safety data sheet because the authors did not include any primary study data. Members of the guideline development group also provided lists of related papers for this review using a library for efficacy of control measures named ECEL (Exposure Control Efficacy Library, associated with the Advanced REACH tool) [6]. Most of the references were duplicates, but 12 papers, which covered engineering controls (6) and PPE (6), were added. This resulted in a final list of 41 studies. A flow diagram of the study selection process is shown in Fig. 1.

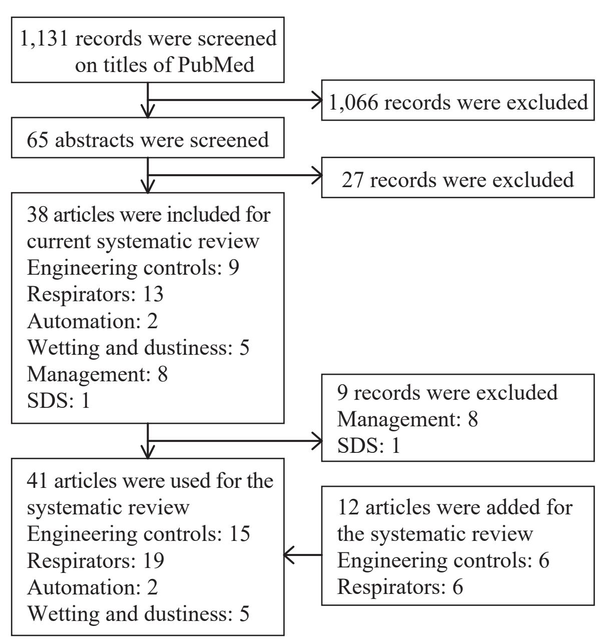

Fig. 1. Flow chart depicting the procedure for selection of relevant papers. SDS: Safety data sheets.

Table 2. List of extracted and reviewed papers and the quality of evidence and risk of bias

Ref. no.	category	authors	year	quality	RB 1	RB 2	RB 3	RB total
7	Engineering control	Dunn KH *et al*	2014	8	1	1	1	3
8	Engineering control	Heitbrink WA *et al*	2015	14	1	1	1	3
9	Engineering control	Lee JH *et al*	2013	6	−1	1	0	0
10	Engineering control	Cena LG & Peters TM	2011	10	1	1	1	3
11	Engineering control	Methner MM	2010	12	1	1	1	3
12	Engineering control	Hämeri K *et al*	2009	6	1	1	1	3
13	Engineering control	Conti JA *et al*	2008	11	−1	0	−1	−2
14	Engineering control	Methner MM	2008	2	1	1	1	3
15	Engineering control	Tsai SJ *et al*	2010	15	0	1	0	1
16	Engineering control	Tsai SJ *et al*	2009	18	1	1	1	3
17	Engineering control	Lo LM, *et al*	2015	14	1	1	1	3
18	Engineering control	Sahu M & Biswas P	2010	15	1	1	1	3
19	Engineering control	Lee MH *et al*	2007	15	0	1	1	2
20	Engineering control	Heitbrink WA & Lo LM	2015	15	−1	1	0	0
21	Engineering control	Han JH *et al*	2008	12	1	1	0	2
22	Respirator	He X *et al*	2014	10	1	1	1	3
23	Respirator	Brochot C *et al*	2012	10	1	1	1	3
24	Respirator	Rengasamy S *et al*	2012	6	1	1	−1	1
25	Respirator	Rengasamy S & Eimer BC	2012	6	1	1	1	3
26	Respirator	Rengasamy S & Eimer BC	2012	6	1	1	−1	1
27	Respirator	Reponen T *et al*	2011	5	1	1	1	3
28	Respirator	Rengasamy S *et al*	2010	6	1	1	1	3
29	Respirator	Golanski L *et al*	2009	8	1	1	1	3
30	Respirator	Rengasamy S *et al*	2009	8	1	1	1	3
31	Respirator	Rengasamy S *et al*	2008	8	1	1	1	3
32	Respirator	Balazy A *et al*	2006	10	1	1	1	3
33	Respirator	Li Y *et al*	2006	−7	−1	−1	−1	−3
34	Respirator	Koivisto AJ *et al*	2015	14	1	1	1	3
35	Respirator	Tsai SJ	2015	7	−1	1	−1	−1
36	Respirator	Rengasamy S & Eimer BC	2011	9	0	1	0	1
37	Respirator	Vo E & Zhuang Z	2013	14	1	1	1	3
38	Respirator	Vo E *et al*	2014	14	1	0	0	1
39	Respirator	Vo E *et al*	2015	13	1	1	1	3
40	Respirator	He X *et al*	2015	13	1	1	1	3
41	Automation	Koivisto AJ *et al*	2012	18	0	1	1	2
42	Automation	Takaya M *et al*	2010	17	1	1	1	3
43	Dustiness	Evans DE *et al*	2013	13	−1	1	0	0
44	Dustiness	O'Shaughnessy PT *et al*	2012	14	−1	1	0	0
45	Dustiness	Lee JH *et al*	2013	6	−1	0	−1	−2
46	Dustiness	Ma-Hock L *et al*	2009	7	−1	1	−1	−1
47	Dustiness	Schneider T & Jensen KA	2008	13	−1	1	0	0

Quality of evidence; very low (−20 to −10), low (−9 to 0), medium (1 to 9), high (10 to 20), RB1, RB2 and RB3 are scores of following items. RB1: intervention and control condition were comparable with regards to the type of work and working conditions based on the pairs of descriptions with and without intervention. RB2: measurement of the MNM was done with state of the art instruments or methods. RB3: the intervention was fully implemented and technically according to the state of the art. RB total is summation of the scores of RB1 to RB3.

Categorization of risk mitigation techniques

We found 15 studies on engineering controls including fume cupboards or local exhaust ventilation (LEV) for MNMs. Nineteen papers on PPE, mainly respirators, were extracted. We found two papers on process automation. One paper reported on the replacement of manual handling by packing processes and on an automated system for MWCNTs. We contacted the authors for additional information because the workplace situation was described ambiguously in the paper. Five papers on dustiness were extracted, but there was no paper on research about how to control the dustiness of MNMs actively. There were no papers on dust control by means of wetting MNMs.

The above 41 papers are listed in Table 2 with total scores of GRADE approach and showing risk of bias (RB1, RB2, RB3 and total scores). The reference numbers in this paper are based on this table.

Effects of enclosure and ventilation

We found 15 studies on engineering controls. One paper on an international survey regarding occupational health and safety programs, engineering controls and PPE, did not contain data on the concentrations of airborne MNMs particles [13] and could not be used for the calculation of PFs. The remaining 14 papers reported on: enclosure systems (down flow clean rooms with ventilated enclosure hood); ventilation (LEV, enclosure type LEV with proper face velocity, process ventilation, biosafety cabinets); specialized ventilation systems (thermal displacement ventilation); and segregation sources (reactor cabinets) [7−12, 14−21].

Based on the scores of the risk of bias in Table 2, we excluded 3 papers because of low scores of the risk of bias, in particular the score of RB1 [9, 15, 20]. The 11 papers reported 27 cases for which we could obtain the PF_{eng} [7, 8, 10−12, 14, 16−19, 21]. The PF_{eng} were calculated by both mass-based concentrations and number-based concentrations, as shown in Fig. 2.

The PF_{eng} of ventilation was less than 10 in the poor cases, and 10 to 20 in the good cases (see Fig. 2). The PF_{eng} > 100 in Fig. 2 means there was no leak, as described in the papers. The recommended face velocity of the enclosure type LEVs ranged from 0.4 to 0.6 m/s [7, 16−18].

One paper concluded that a canopy hood for nano-composite cutting led to an increase in exposure (PF = 0.8) [17]. LEVs with low face velocity provided the lowest PF (= 0.125) and worsened the situation [10]. The authors concluded that poor performance of the custom hood used in the current study may have been exacerbated by its lack of a front sash, its lack of rear baffles to distribute the airflow, and its low face velocity (0.2 m/s).

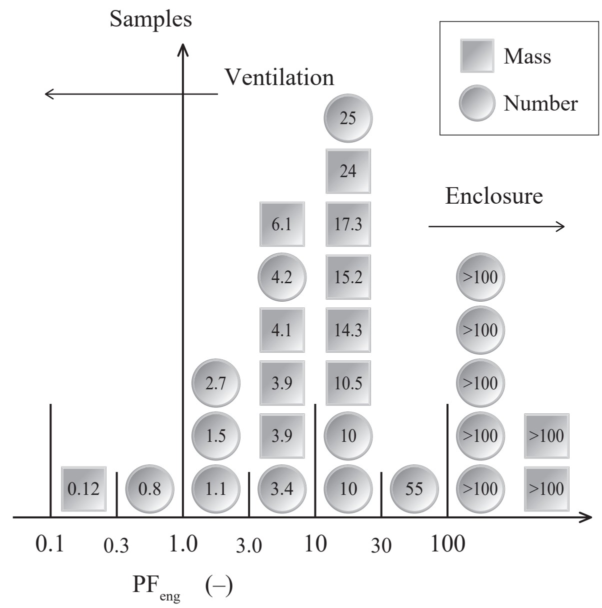

Fig. 2. Protection Factor PF_{eng} at ventilation or other engineering control techniques (27 cases in 11 papers). $PF_{eng} = C_{without}/C_{with}$, where $C_{without}$ is concentration without mitigation techniques and C_{with} is concentration with mitigation techniques. PF > 100 in the Figure means no leak as described in the papers and in most of the cases, enclosure systems were used. Mass means PF_{eng} calculated by mass-based concentrations and Number means PF_{eng} calculated number-based concentrations.

All studies were observational, the majority had low risk of bias, all results were direct answers to our PICO question, and the results were consistent across studies, but no study included measures of precision and we could not establish publication bias. Because imprecision is difficult to establish for exposure measures, we decided not to downgrade them and rated the evidence as low quality.

Effects of suppression and separation of workers

This section corresponded to the categories of '6 Suppression technique' and '7 Separation worker' by Fransman *et al*; that is, process automation and dustiness tests or wetting [6].

We extracted 2 papers covering 5 cases of process automation to obtain the PF_{eng}. One paper reported on a TiO_2 packing machine operation [41] and the other reported on a comparison between a manual MWCNT packing process and an automated packing machine [42]. Even in the use of an automated packing machine, workers can be exposed to nanomaterials when the packing closure is opened and nanomaterials are poured into a silo. At a nanoTiO_2 handling facility, a momentary PF_{eng} = 0.073 was reported [41].

The PF_{eng} of process automation depended on the sampling method, stationary sampling or workers breathing zone sampling (WBZ), at a MWCNT production facility [42]. Besides mass concentrations, elemental carbon mass (EC) concentrations were also measured as an index of airborne MWCNT. In the breathing zone based on total mass, the PF_{eng} was 8.2; in the breathing zone based on respirable mass, the PF_{eng} was only 4.9; and in the breathing zone based on EC mass, the PF_{eng} was 7. With stationary sampling and based on total mass there was no effect of automation, but based on the EC mass the PF_{eng} was 2.5. The automated packing machine was not covered completely, but the workers did not have to fully attend to the operation of the machine.

We found five papers that measured dustiness [43–47]. However, there was no paper that compared changes in the dustiness of nanomaterials, wetting or surface coating of the nanomaterials. However, three papers suggested that nanomaterials had much higher dustiness than pigment grade (submicron size) materials of the same chemical composition and thus could be subject to suppression controls [43, 44, 47].

All studies were observational. For automation, the risk of bias was low and the PICO was directly answered, but there were only two studies with inconsistent results. Therefore we downgraded the evidence by one level to very low quality.

Performance of respirators for nanoparticle aerosols

Respirators are the final resort in risk mitigation for workers handling MNMs. In the extracted papers, filtering facepiece respirators (FFR) or elastomeric half masks with particulate filters (EHR) were studied, and there was one paper on a loose-fitting powered air purifying respirator in the field use handling of MNMs [34]. The classes of the particulate respirators of the FFRs and EHRs in the papers were N95, N99, N100 and P100 certified by US NIOSH (National Institute of Occupational Safety and Health, USA) (84 CFR (Code of Federal Regulations) 11 [48]), or P2, P3, FFP2 and FFP3 according to the European standard EN143 [49] and EN149 [50].

The actual performance of respirators in the workplace is controlled by both filter performance and face-seal leakage, which depends on the with/without fit test, the selection of the size of the respirators, and education in the use of the respirator. It is not easy to define the face-seal leakage, but the total inward leakage (TIL) test of respirators, which includes leakage through the face seal between the respirator and a human subject or a mannequin, is a way to evaluate the performance.

The performance of the respirators depended on the size of aerosol particles. The worst performance was observed in the nanosize most penetrating particle size (MPPS). Eleven papers contained 13 cases that enabled MPPS calculation, which reported on the filtration efficiency of respirators, which did not include face seal leak (Black in Fig. 3) or total inward leakage (TIL) of the respirators (Gray in Fig. 3) [22–32]. The FFR using an electrostatic filter showed 30 to 70 nm of MPPS. This information should be noted as a caution on the mitigation of nanoparticle aerosols. The current official certification programs of particulate filters (84 CFR 11, EN 143, and EN 149) do not focus on nanoparticle aerosols [30].

In 14 papers we found 24 cases to obtain the PF_{res} of FFR and EHR respirators [22, 23, 25, 27-32, 34, 37–40]. Based on the scores of the risk of bias in Table 2, we excluded 5 papers because of low scores [24, 26, 33, 35, 36]. The PF_{res} were obtained from the data on the filtration efficiency of the respirators, which did not include face seal leak (Black in Fig. 4), and on the TIL of the respirators, which included leakage through the face seal (Gray in Fig. 4). Figure 4 shows the range of PFs obtained from the papers.

The values of PF_{res} of the N95 or equivalent grade FFRs were around 10. Higher grade masks, such as P100, had a much higher PF_{res}, which may be acceptable from a hygienic point of view. The PF_{res} of cloth masks

Table 3. List of engineering control techniques and estimated PF_{eng}

Ref no.	nanomaterials	instruments	research target	PF_{eng}
7	NaCl, SF_6, nanoalumina	FMPS CPC	Commercial nano fume hood	No leak
8	Nanographene	DustTrak, FMPS	Process ventilation and process changes	3.9
	Nanographene	DustTrak, FMPS	Downflow clean room with ventilated enclosure hood	No leak
	Nanographene	DustTrak, FMPS	Reactor cabinet	No leak
10	MWCNT	CPC, OPC	Custom made LEV	0.125
	MWCNT	CPC, OPC	BSC	14.3
11	Metal and metal oxides, (Ag, Cu, Co, Ni, Fe, Mn)	Filter sampling, OPC, CPC	A portable HEPA filtered flanged LEV system	15.2 (Cu), 6.1(Ni), 10.5 (Fe), 4.1(Mn)
12	Room aerosols	SMPS, ELPI, OPC	Displacement ventilation by contaminated warm air and cool supplied air	10 or more
14	Nanoscale metal catalytic materials, Mn, Ag and Co	Filter sampling	A portable HEPA filtered flanged LEV system	24 (Mn), 3.9 (Ag), 17.3 (Co)
	Nanoscale metal catalytic materials, Mn, Ag and Co	CPC , OPC	A portable HEPA filtered flanged LEV system	25 (mean of 3 cases)
16	Nanoalumina, Nanosilver	FMPS	Conventional hood: Transferring 100g	4.2 (Transfer), 4.2 (Pour)
	Nanoalumina, Nanosilver	FMPS	By-pass hood: Transferring 100g	1.06 (Transfer), 1.53 (Pour)
17	CNT	FMPS, APS	Enclosure for furnace	10
	CNT	FMPS, APS	BSC w/wo recirculated air through HEPA filter	No leak (fan on), 3.2 (fan off)
	CNT	FMPS, APS	Canopy hood at cutting of nanocomposite sample	0.83 by FMPS, 0.81 by APS
18	TiO_2 synthesis	CPC, SMPS	Laboratory fume hoods, door open	55
	TiO_2 synthesis	CPC, SMPS	Laboratory fume hoods, door close	No leak
19	Welding fume	SMPS	Conventional booth	2.7
	Welding fume	SMPS	Modified booth ventilation system	2200
21	MWCNT	STEM	Ventialtion fan and segregation of source	No leak

($PF_{eng} = C_{w/o} / C_w$; concentrations without and with mitigation techniques), APS: Aerosol particle sizer, LEV: local exhaust ventilation, DustTrak: Aerosol photometer, BSC: Biosafety cabinet, FMPS: Fast Mobility Particle Sizer, SMPS: Scanning Mobility Particle Sizer, MWCNT: Multi-walled carbon nanotubes, CPC: Condensation particle counter, CNT: Carbon nanotube, ELPI: Electrical Low Pressure Impactor, OPC: Optical particle counter, STEM: Scanning transmission electron microscope

was very low. Cloth masks are useless in protecting workers handling nanomaterials. There was one paper on a loose-fitting powered air purifying respirator in which the PFs were measured in 3 human subjects [34], where the values of PFs were over 1.1 million, but those were not included in Fig. 4 because it was an outlier. We anticipate further studies on powered air purifying respirators for the handling of MNMs.

All the studies were observational and all were carried out in the laboratory and not under field conditions. The results across studies were inconsistent. Therefore we downgraded the evidence by one level to very low quality evidence for the effectiveness of respiratory protection.

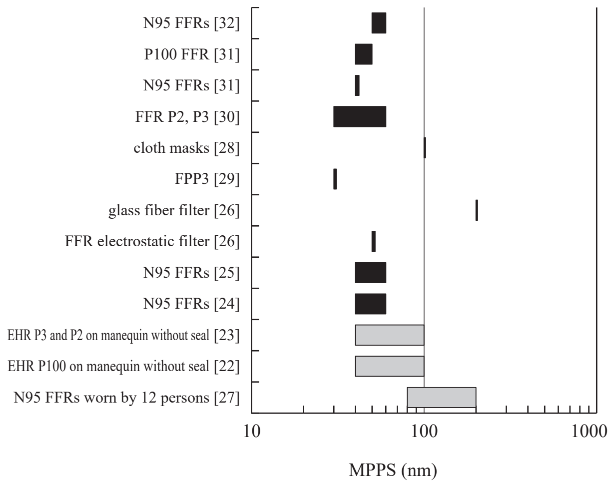

Fig. 3. Most penetrating particle size (MPPS) of studied respirators. Box shows the range of MPPS. Black boxes do not include face seal leak, and Gray boxes are total inward leakage (TIL) of respirator, which included leakage through face seal. Numbers in the brackets are reference number. FFR: filtering facepiece respirator or disposable type respirator. EHR: elastomeric half mask. N95, P100, P2 and P3 mean grades of respirator filters.

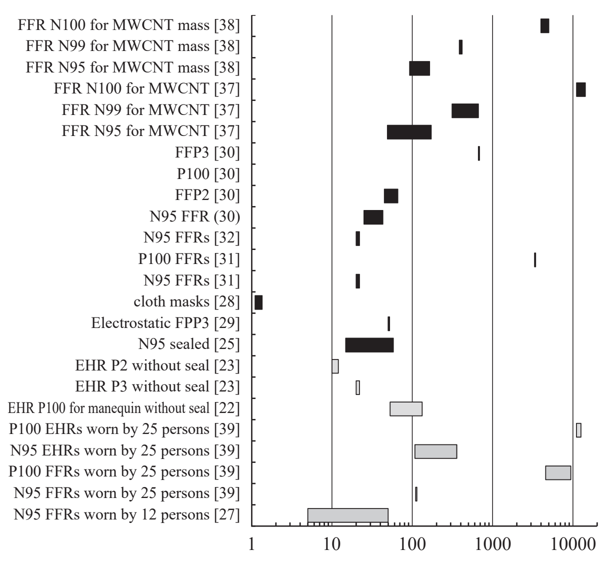

Fig. 4. Protection Factor of Respirators (PF_{res}). Black boxes do not include face seal leak, and gray boxes are total inward leakage (TIL) of respirators, which included leakage through face seal. Numbers in the brackets are reference number. FFR: filtering facepiece respirator or disposable type respirator. EHR: elastomeric half mask. MWCNT: Multi-walled carbon nanotubes. N95, N99, P100, P2, P3, FFP2 and FFP3 mean filtration performances of the respirator filters [48−50].

Discussion

We found 41 papers that indicated the effectiveness of engineering controls and respirators. For ventilation we found that local ventilation can achieve a protection factor of 10 to 20 but also that a canopy hood can even increase exposure. This is due to the face velocity and therefore a velocity of 0.4 to 0.6 m/s is recommended. Only enclosure or segregation yield very good protection factors above 100 and should be used when exposure levels are high. For MNMs in powder form, good practices for ordinary powder handling processes are probably also effective in risk mitigation.

Automated packaging yielded only modest protection factors in a study of exposure to carbon nanotubes (PF_{eng} = 4.9 to 8.2), and in another study of nanoTiO_2 exposure there was still a potential exposure risk when workers opened the packing closure and poured the material into a silo. MNMs have much more dustiness than submicron-size materials of the same chemical composition and therefore preventive measures should be much stricter for MNMs.

The PFs of N95 or equivalent grade FFRs were around 10. Higher grade respirators such as P100 had a much higher PF against nanoparticle aerosols. Cloth masks should not be used for workers handling MNMs. One study evaluated a powered air purifying respirator and found an extremely high protection factor. We anticipate more studies on powered air purifying respirators to MNMs in future.

A strength of this review is that we found that state of the art measurement instruments were used in the papers we reviewed. The aerosol concentrations were measured for both mass-based and count-based concentrations. For example, the scanning mobility particle sizer (SMPS) and the condensation particle counter (CPC) provide count-based concentration, while the gravimetric method using filter sampling provides mass-based concentration. The PF_{eng} was based on both number concentrations and mass concentrations. We did not find a clear difference between the PFs in the two concentrations.

The rating of the evidence of the reviewed papers started as low quality because all the studies were non-randomized and non-controlled. Publication bias can be expected but could not be assessed due to lack of data.

Limitations

Because the papers reviewed did not cover all the categories by Fransman *et al* [6], further studies are needed. More studies are needed on the effectiveness of risk mitigation by LEVs or fume cupboards and how face velocity and the workers' movements influence the outcomes.

Reports on the effectiveness of risk mitigation in automated processes were rare but would be important for workers' health, so further studies are needed in this area, too. Also, there was no paper on the control techniques for dustiness of MNMs, such as any additives.

In this review, the PFs of the respirators were based on concentrations of size-specific nanoparticle aerosols, but most of the test aerosols were sodium chloride aerosols or smoke and not real MNMs. Most reports on the respirators were limited to dust respirators, with the majority of the studies focusing on the filter performance without face seal leakage. In the same way as in ordinary respirator use, the face-seal leakage of respirators should be tested for workers handling any MNMs.

Conclusion

This review shows that there is great variation in the effectiveness of engineering controls and respiratory protection in reducing exposure to MNMs. We suggest that controls should be chosen that have a protection factor that will bring workers' exposure to MNMs below the proposed occupational exposure limits. In case of absence of such exposure limits and in absence of reliable toxicological information, the most protective controls should be used.

Conflict of Interest

The authors have no conflicts of interest.

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工業用ナノマテリアルの製造と取扱いで用いられる個別のリスク低減対策の効果：システマティックレビュー

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要　　旨：多くの工業用ナノマテリアルが産業製品の基本材料として開発され使用されており, それらは開発国だけでなく開発途上国の労働者への健康リスクを持つ可能性がある．工業用ナノマテリアルの曝露低減対策の効果を証明する研究はほとんどないので, 我々は2000年から2015年までに公表され特定された工業用ナノマテリアルのリスク低減対策の研究をシステマティックに調査した．ここでは, 状況に曝露低減対策を入れた場合と入れない場合を比較し, 工業用ナノマテリアルの曝露を測定した研究を採用した．これらの対策の効果を判定するために, 我々は工業用ナノマテリアルの低減対策の効果の尺度として防護係数, 対策の有無による有害物濃度の比として定義される文献を使用した．ここではPubMedの1,131レコードや他の文献リストから, 41の文献を条件に合致したものとして抽出した．そして局所排気装置, 密閉化, プロセス自動化などの工学的対策や, 個人用保護具に分類した．密閉化の対策では, 防護係数が100を超える場合があった．他の工学的対策では, よい結果では防護係数は10から20であったが, 多くの局所排気装置では10以下, 時に状況を悪くする場合もあった．N95や同等のグレードの使い捨て式防じんマスクはナノサイズの試験エアロゾルに対して10程度の防護係数を持っていた．工学的対策は工業用ナノマテリアルへの曝露を低減するが, 密閉化のシステムの方がより効果的であることに弱い証拠があると結論付けた．呼吸用保護具は現場での研究が少ないため弱い証拠があると判定した．工業用ナノマテリアルが職業曝露限界を超える場合, または, その毒性情報がない場合に対策を決定するため上記の情報を使うことができる．

キーワード：工業用ナノマテリアル, システマティックレビュー, 工学的対策, 呼吸用保護具, プロセス自動化.

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