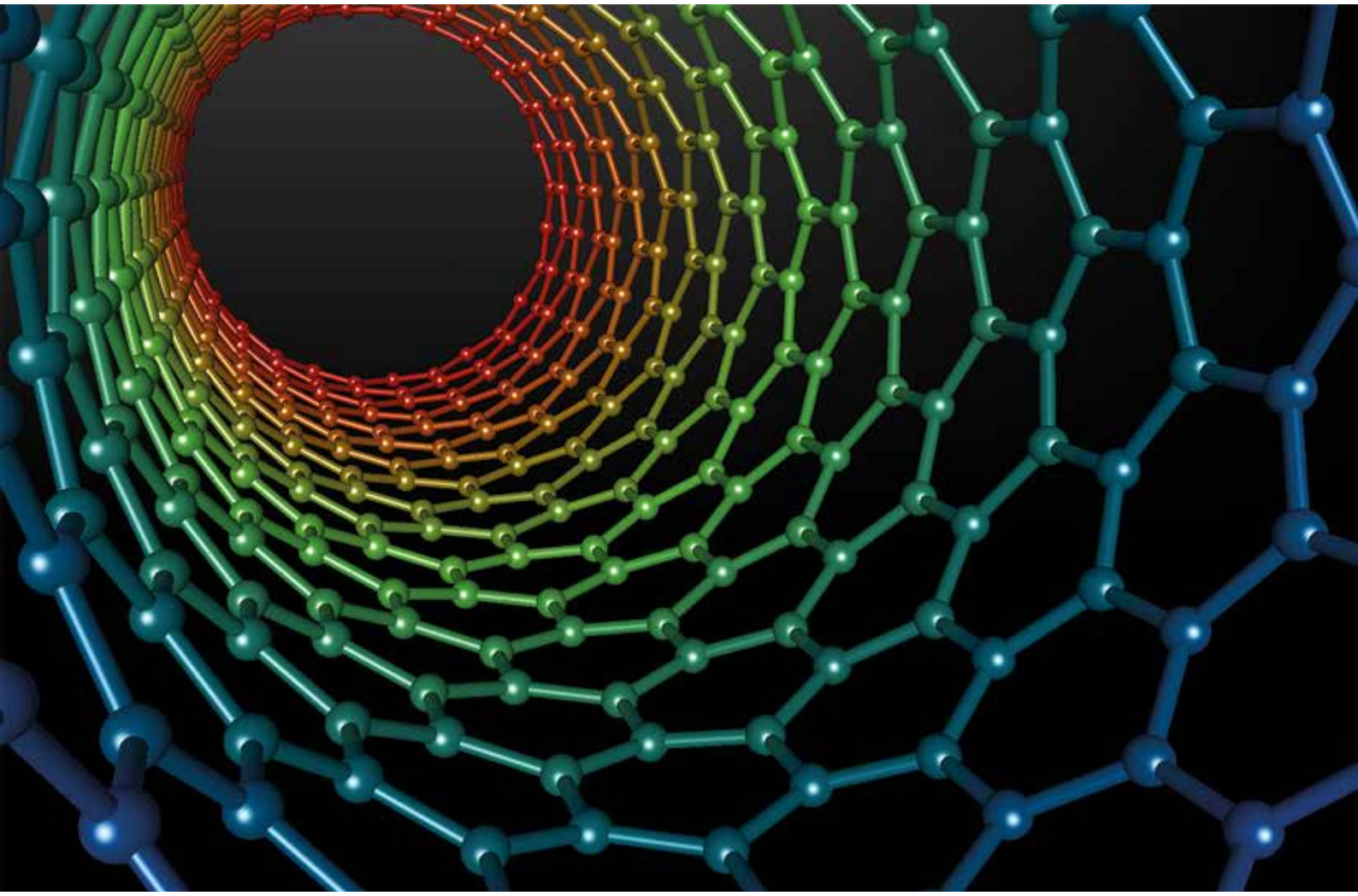
WHO GUIDELINES ON PROTECTING WORKERS FROM POTENTIAL RISKS OF MANUFACTURED NANOMATERIALS



World Health Organization

WHO GUIDELINES ON PROTECTING WORKERS FROM POTENTIAL RISKS OF MANUFACTURED NANOMATERIALS

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WHO guidelines on protecting workers from potential risks of manufactured nanomaterials
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GLOSSARY

Acute exposure
Exposure occurring over a short time, generally less than one day.

Acute effect
A health or physiological effect that occurs suddenly over hours or days, for example lung inflammation resulting from inhalation exposure.

Aerosol
Mixture of small particles (solid, liquid or a mixed variety) and a carrier gas (usually air).

Breathing zone
The area immediately surrounding a worker's nose and mouth from where the majority of air is drawn into their lungs.

Bulk material
The larger counterpart of a nanomaterial not confined to the nanoscale in any dimension, e.g. gold as the bulk material and nano-gold as the nano-form material.

Carbon nanofibres
Cylindrical nanostructures with graphene layers arranged as stacked cones, cups or plates.

Carbon nanotubes
Hollow nano-objects with two similar external dimensions in the nanoscale and the third dimension significantly larger, composed of carbon (ISO/TS 80004-3:2010).

Chronic effect
An effect that occurs or builds up over a long period; for humans over years, for example cardiovascular disease.

Chronic exposure
Exposure over a long period, for humans over years.

Confounder
A factor in an exposure study that is both related to the exposure and to the outcome. The uneven distribution of the confounder will lead to distorted or spurious results.

Control banding
A risk management approach to identify and recommend exposure control measures for potentially hazardous substances for which toxicological information is limited.

Engineering controls
Use of mechanical or technical measures such as enclosure, ventilation and workplace design to minimize exposure.

Fibre diameter
Fibre dimension.

Fibre length
Fibre dimension.

Grading of Recommendations, Assessment, Development and Evaluations (GRADE)
A systematic and explicit approach to making judgements about quality of evidence and strength of recommendations. GRADE also stands for GRADE working group, the group that formulates the guidelines for the approach.

Globally Harmonized System of Classification and Labelling of Chemicals
A classification and labelling system developed by the United Nations, addressing classification of chemicals by types of hazard and proposing harmonized hazard communication elements, including labels and safety data sheets.

Granular biopersistent particles
Particles that are characterized as respirable granular and biopersistent but not fibrous. Also known as "poorly soluble particles" or as "poorly soluble, low-toxicity particles".

Hazard
The inherent potential to cause physical or psychological harm to the health of people.

Manufactured nanomaterials
Solid, particulate substances intentionally manufactured at the nanoscale, consisting of nano-objects with at least one dimension between 1 and 100 nm, and their aggregates and agglomerates.

Multi-walled carbon nanotubes
Tubes of multiple concentric cylindrical one-atom-thick layers of graphene as opposed to single-walled nanotubes (SWCNTs).

Nano-object
A material with one, two or three external dimensions in the nanoscale.

Nano-objects and their aggregates and agglomerates
Nano-objects (< 100 nm) and their aggregates and agglomerates (> 100 nm).

Nanoparticle
Nano-object with all three external dimensions in the nanoscale (< 100 nm diameter).

Nanoscale
Size range from approximately 1 nm to 100 nm.

Occupational exposure limit
Maximum concentration of airborne contaminants deemed to be acceptable, as defined by the authority having jurisdiction (ISO 16972:2010).

Particulate matter
A mixture of solid particles and liquid droplets suspended in the air.

Personal protective equipment
Equipment (clothing, gloves, hard hat, respirator and so on) worn by an individual to minimize risk to the individual's health and safety.

PICO
Systematic framework to answer the scoping questions, used as an acronym: P for Population, I for Intervention, C for Comparator, O for Outcome(s).

Protection factor (PF)
The ratio of exposure level without the controls divided by the exposure level with the controls. If the PF is > 1, controls reduce exposure. A PF of 10 indicates that controls reduce exposure by 90%.

Read across
Transfer of hazard information from one material to another based on similarities between the materials.

Risk of bias
The risk that the results of a study can be distorted due to methodological limitations such as the presence of confounders.

Safety data sheet
Document that provides information on the properties of hazardous chemicals, how they affect health and safety in the workplace and how to manage hazardous chemicals in the workplace (ISO/TR13329:2012).

Short-term exposure limit
Fifteen-minute time-weighted average (TWA) exposure which should not be exceeded at any time during a workday, even if the 8-hour TWA is within the threshold limit value TWA.

Single-walled carbon nanotubes
A cylindrical one-atom-thick layer of graphite called graphene as opposed to multi-walled nanotubes.

Solubility
The ability of a material to release ions in water or in another liquid. Solubility may be expressed by the dissolution rate of the material and may also be described using words such as insoluble, very soluble or poorly soluble.

Threshold limit value
Health-based occupational exposure limit value published by the American Conference of Governmental Industrial Hygienists.

Tiered approach
A stepwise approach in which each step has an increased level of complexity; here it refers to a risk-based approach for conducting an exposure or release assessment to determine whether exposure to manufactured nanomaterials (MNMs) may occur and to determine if there is a need for further risk management steps to be taken.[1]

Time-weighted average
An average concentration of an airborne contaminant that workers may be exposed to, over a period of time such as an 8-hour day or 40-hour week (an average work shift).

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[1] Harmonized tiered approach to measure and assess the potential exposure to airborne emissions of engineered nano-objects and their agglomerates and aggregates at workplaces. Series on the Safety of Manufactured Nanomaterials No. 55. Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. ENV/JM/MONO(2015)19. Paris: Organisation for Economic Co-operation and Development; 2015 (http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2015)19&doclanguage=en, accessed 31 August 2017).

ABBREVIATIONS AND ACRONYMS

CEN	Comité Européen de Normalisation (European Committee for Standardization)
CNFs	carbon nanofibres
CNTs	carbon nanotubes
CUPE	Canadian Union of Public Employees
EC	elemental carbon
ETUC	European Trade Union Confederation
FD	fibre diameter
FL	fibre length
GBP	granular biopersistent particles
GDG	Guideline Development Group
GHS	Globally Harmonized System (of Classification and Labelling of Chemicals)
GLP	good laboratory practice
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GRC	Guidelines Review Committee
IARC	International Agency for Research on Cancer
ILO	International Labour Organization
IOMC	Inter-Organization Programme for the Sound Management of Chemicals
ISO	International Organization for Standardization
ITUC	International Trade Union Confederation
IUF	International Union of Food, Agricultural, Hotel, Restaurant, Catering, Tobacco and Allied Workers' Associations
LMI	low- and middle-income (countries)
MNMs	manufactured nanomaterials
MWCNTs	multi-walled carbon nanotubes
NIOSH	National Institute for Occupational Safety and Health, United States of America (USA)
NOAAs	nano-objects and their aggregates and agglomerates
NP	nanoparticle
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration, USA
PF	protection factor
PICO	Population, Intervention, Comparator, Outcome(s)
PM	particulate matter
PPE	personal protective equipment
SDS	safety data sheet
SME	small and medium-sized enterprises
SWCNTs	single-walled carbon nanotubes
TWA	time-weighted average
USA	United States of America
WHO	World Health Organization
WPMN	(OECD) Working Party on Manufactured Nanomaterials

EXECUTIVE SUMMARY

The term nanomaterials refers to materials that have at least one dimension (height, width or length) that is smaller than 100 nanometres (10^{-7} metre), which is about the size of a virus particle. This particular size dimension represents a major characteristic of manufactured nanomaterials (MNMs). The unique properties of MNMs may result in highly desirable behaviour leading to such varying applications as better paints, better drugs and faster electronics. However, for the same reason, MNMs may also present health hazards that differ from those of the substance in bulk form, and may require different test methods for hazard, exposure and risk assessment from their bulk material counterparts.

The toxicity of MNMs may largely depend on numerous physicochemical properties, including size, shape (i.e. size in a particular dimension), composition, surface characteristics, charge and rate of dissolution. There is currently a paucity of precise information about human exposure pathways for MNMs, their fate in the human body and their ability to induce unwanted biological effects such as generation of oxidative stress. Data from in vitro, animal and human MNM inhalation studies are available for only a few MNMs. So far, no long-term adverse health effects in humans have been observed. This could be due to the recent introduction of MNMs, the precautionary approach to avoid exposure and ethical concerns about conducting studies on humans. This means that, except for a few materials where human studies are available, health recommendations must be based on extrapolation of the evidence from in vitro, animal or other studies from fields that involve exposure to nanoscale particles, such as air pollution, to the possible effects in humans.

The increased production of MNMs and their use in consumer and industrial products means that workers in all countries will be at the front line of exposure to these materials, placing them at increased risk for potential adverse health effects.

Therefore, the World Health Organization (WHO) has developed these guidelines with recommendations on how best to protect workers from the potential risks of MNMs. The recommendations are intended to help policy-makers and professionals in the field of occupational health and safety in making decisions about the best protection against potential risks specific to MNMs in workplaces. These guidelines are also intended to support workers and employers. However, they are not intended as a handbook or manual for safe handling of MNMs in the workplace because this requires addressing more general occupational hygiene issues beyond the scope of these guidelines.

GUIDING PRINCIPLES

The Guideline Development Group (GDG) used a precautionary approach as one of its guiding principles. This means that exposure has to be reduced, despite uncertainty about the adverse health effects, when there are reasonable indications to do so.

In addition, the hierarchy of controls was an important guiding principle. This means that when there is a choice between control measures, those measures that are closer to the root of the problem should always be preferred over measures that put a greater burden on workers, such as the use of personal protective equipment (PPE).

BEST PRACTICE

The GDG considers the following to be best practice in preventing the adverse health effects of MNMs:

- Group nanomaterials into MNMs with specific toxicity, MNMs that are fibres and MNMs that are granular biopersistent particles.
- Educate and train workers in the specific health and safety issues of MNMs.
- Involve workers in all phases of risk assessment and control.

METHODS

For all important issues, systematic reviews of the current state of the science were commissioned to inform the recommendations according to the process set out in the *WHO Handbook for guideline development*. The recommendations were rated as "strong" or "conditional" depending on the quality of the scientific evidence, values and preferences, and costs related to the recommendation. All recommendations were made based on consensus within the GDG.

RECOMMENDATIONS

A. Assess health hazards of MNMs

1. The GDG recommends assigning hazard classes to all MNMs according to the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals for use in safety data sheets. For a limited number of MNMs this information is made available in these guidelines (*strong recommendation, moderate-quality evidence*).
2. The GDG recommends updating safety data sheets with MNM-specific hazard information or indicating which toxicological end-points did not have adequate testing available (*strong recommendation, moderate-quality evidence*).
3. For the respirable fibres and granular biopersistent particles' groups, the GDG suggests using the available classification of MNMs for provisional classification of nanomaterials of the same group (*conditional recommendation, low-quality evidence*).

B. Assess exposure to MNMs

4. The GDG suggests assessing workers' exposure in workplaces with methods similar to those used for the proposed specific occupational exposure limit (OEL) value of the MNM (*conditional recommendation, low-quality evidence*).
5. Because there are no specific regulatory OEL values for MNMs in workplaces, the GDG suggests assessing whether workplace exposure exceeds a proposed OEL value for the MNM. A list of proposed OEL values is provided in Annex 1 of these guidelines. The chosen OEL should be at least as protective as a legally mandated OEL for the bulk form of the material (*conditional recommendation, low-quality evidence*).
6. If specific OELs for MNMs are not available in workplaces, the GDG suggests a stepwise approach for inhalation exposure with, first an assessment of the potential for exposure; second, conducting basic exposure assessment and third, conducting a comprehensive exposure assessment such as those proposed by the Organisation for Economic Co-operation and Development (OECD) or Comité Européen de Normalisation (the European Committee for Standardization, CEN) (*conditional recommendation, moderate-quality evidence*). For dermal exposure assessment, there was insufficient evidence to recommend one method of dermal exposure assessment over another.

C. Control exposure to MNMs

7. Based on a precautionary approach, the GDG recommends focusing control of exposure on preventing inhalation exposure with the aim of reducing it as much as possible (*strong recommendation, moderate-quality evidence*).
8. The GDG recommends reduction of exposures to a range of MNMs that have been consistently measured in workplaces especially during cleaning and maintenance, collecting material from reaction vessels and feeding MNMs into the production process. In the absence of toxicological information, the GDG recommends implementing the highest level of controls to prevent workers from any exposure. When more information is available, the GDG recommends taking a more tailored approach (*strong recommendation, moderate-quality evidence*).
9. The GDG recommends taking control measures based on the principle of hierarchy of controls, meaning that the first control measure should be to eliminate the source of exposure before implementing control measures that are more dependent on worker involvement, with PPE being used only as a last resort. According to this principle, engineering controls should be used when there is a high level of inhalation exposure or when there is no, or very little, toxicological information available. In the absence of appropriate engineering controls PPE should be used, especially respiratory protection, as part of a respiratory protection programme that includes fit-testing (*strong recommendation, moderate-quality evidence*).
10. The GDG suggests preventing dermal exposure by occupational hygiene measures such as surface cleaning, and the use of appropriate gloves (*conditional recommendation, low-quality evidence*).

11. When assessment and measurement by a workplace safety expert is not available, the GDG suggests using control banding for nanomaterials to select exposure control measures in the workplace. Owing to a lack of studies, the GDG cannot recommend one method of control banding over another (*conditional recommendation, very low-quality evidence*).

D. Health surveillance

The GDG cannot make a recommendation for targeted MNM-specific health surveillance programmes over existing health surveillance programmes that are already in use owing to the lack of evidence.

E. Training and involvement of workers

The GDG considers training of workers and worker involvement in health and safety issues to be best practice but cannot recommend one form of training of workers over another, or one form of worker involvement over another, owing to the lack of studies available.

It is expected that there will be considerable progress in validated measurement methods and risk assessment. Therefore, the GDG proposes to update these guidelines in five years' time, in 2022.

RÉSUMÉ D'ORIENTATION

Le terme nanomatériaux fait référence à des matériaux dont au moins une dimension (hauteur, largeur ou longueur) est inférieure à 100 nanomètres (10^{-7} mètre), ce qui correspond approximativement à la taille d'une particule virale. Cette dimension particulière constitue une caractéristique majeure des nanomatériaux manufacturés (NMM). Les propriétés uniques des NMM peuvent aboutir à un comportement très intéressant qui trouve de nombreuses applications comme de meilleures peintures, de meilleurs médicaments et des produits électroniques plus rapides. Néanmoins, pour cette même raison, les NMM peuvent aussi présenter des dangers pour la santé différents de ceux des substances de forme micro/macroscopique et peuvent nécessiter des méthodes de test différentes pour estimer le danger, l'exposition et le risque.

La toxicité des NMM est essentiellement due aux nombreuses propriétés physicochimiques, notamment la taille, la forme (taille dans une dimension particulière), la composition, les caractéristiques de surface, la charge et la vitesse de dissolution. On manque actuellement de données précises sur les voies de l'exposition humaine pour les NMM, leur devenir dans l'organisme et leur capacité à induire des effets biologiques indésirables, comme la génération d'un stress oxydatif. Des données issues d'études d'inhalation de NMM *in vitro*, chez l'animal et chez l'homme ne sont disponibles que pour quelques NMM. Jusqu'à présent, aucun effet indésirable sur la santé n'a été observé chez l'homme à long terme. Cela peut s'expliquer par la récente introduction des NMM, le principe de précaution appliqué pour éviter l'exposition et des considérations éthiques associées aux études conduites chez l'homme. Ainsi, à l'exception de quelques matériaux pour lesquels on dispose d'études chez l'homme, les recommandations sanitaires doivent se fonder sur l'extrapolation des données issues des études *in vitro*, chez l'animal et autres études menées sur le terrain qui impliquent une exposition à des particules nanométriques, comme la pollution atmosphérique, pour évaluer les effets possibles chez l'homme.

La production croissante de NMM et leur utilisation dans des produits de consommation et industriels signifient que les personnes qui travaillent avec ces produits, dans tous les pays, seront en première ligne en termes d'exposition à ces matériaux avec un risque accru d'effets indésirables potentiels sur la santé.

L'Organisation mondiale de la Santé (OMS) a donc élaboré ces lignes directrices qui contiennent des recommandations pour protéger au mieux les travailleurs contre les risques potentiels des NMM. Ces recommandations ont pour vocation d'aider les responsables de l'élaboration des politiques et les professionnels de la santé et de la sécurité au travail à prendre des décisions en matière de protection optimale contre les risques potentiels spécifiquement liés aux NMM sur le lieu de travail. Ces lignes directrices visent également à servir aux travailleurs et aux employeurs. Néanmoins, elles ne constituent pas un manuel pour la manipulation sans danger des NMM sur le lieu de travail ; cette question nécessite d'aborder des problèmes plus généraux de l'hygiène au travail qui sortent du champ d'application de ces lignes directrices.

PRINCIPES DIRECTEURS

L'un des principes directeurs du Groupe d'élaboration des lignes directrices (GDG) est le principe de précaution. Cela signifie que l'exposition doit être réduite, même si l'on n'a aucune certitude concernant les effets indésirables sur la santé, dans les situations où il est raisonnablement indiqué de le faire.

La hiérarchie des contrôles a également constitué un important principe directeur. En l'espèce, quand on a le choix entre différentes mesures de contrôle, les mesures les plus proches de la racine du problème doivent toujours être privilégiées par rapport aux mesures qui pèsent davantage sur les travailleurs, comme le port d'un équipement de protection individuelle (EPI).

MEILLEURES PRATIQUES

Le GDG considère que les meilleures pratiques pour prévenir les effets indésirables des NMM sur la santé sont les suivantes :

- regrouper les nanomatériaux en NMM à toxicité spécifique, NMM sous forme de fibres et NMM sous forme de particules granulaires biopersistantes ;
- éduquer et former les travailleurs aux problèmes de santé et de sécurité spécifiques aux NMM ;
- impliquer les travailleurs dans toutes les phases de l'évaluation et du contrôle des risques.

MÉTHODES

Pour toutes les questions importantes, des revues systématiques de l'état actuel de la science ont été prévues pour éclairer les recommandations conformément au processus décrit dans le *WHO Handbook for guideline development*. Ces recommandations ont été considérées comme « fortes » ou « conditionnelles » selon la qualité des données scientifiques, les valeurs et les préférences, et les coûts associés aux recommandations. Toutes les recommandations ont fait l'objet d'un consensus au sein du GDG.

RECOMMANDATIONS

A. Évaluer les risques sanitaires des NMM

1. Le GDG recommande d'affecter à chaque NMM une classe de danger conformément au Système général harmonisé (SGH) de classification et d'étiquetage des produits chimiques à faire figurer dans les fiches de données de sécurité. Cette information est fournie dans les présentes lignes directrices pour un petit nombre de NMM (*recommandation forte, données de qualité moyenne*).
2. Le GDG recommande de mettre à jour les informations des fiches de données de sécurité relatives au danger spécifique aux NMM ou d'indiquer les critères toxicologiques qui n'ont pas été testés de manière adéquate (*recommandation forte, données de qualité moyenne*).
3. Pour le groupe des fibres respirables et celui des particules granulaires biopersistantes, le GDG suggère d'utiliser la classification existante des NMM aux fins du classement provisoire des nanomatériaux du même groupe (*recommandation conditionnelle, données de faible qualité*).

B. Évaluer l'exposition aux NMM

4. Le GDG suggère d'évaluer l'exposition des travailleurs sur le lieu de travail en employant des méthodes similaires à celles utilisées pour déterminer la valeur limite d'exposition professionnelle (VLEP) spécifique proposée pour un NMM donné (*recommandation conditionnelle, données de faible qualité*).
5. Du fait qu'il n'existe pas de VLEP réglementaires pour les NMM sur le lieu de travail, le GDG suggère d'évaluer si l'exposition sur le lieu de travail excède la VLEP proposée pour un NMM donné. Une liste de VLEP proposées est fournie en **annexe 1** de ces lignes directrices. La VLEP choisie doit être au moins aussi protectrice que celle imposée par la loi pour la forme micro/macroscopique du matériau considéré (*recommandation conditionnelle, données de faible qualité*).
6. Si les VLEP spécifiques pour des NMM donnés ne sont pas disponibles sur le lieu de travail, le GDG suggère d'adopter une approche par étape pour évaluer l'exposition par inhalation : d'abord une évaluation du potentiel d'exposition, puis une évaluation basique de l'exposition, et enfin une évaluation complète de l'exposition, comme celles que propose l'Organisation de coopération et de développement économiques (OCDE) ou le Comité européen de normalisation (CEN) (*recommandation conditionnelle, données de qualité moyenne*). Pour l'évaluation de l'exposition dermique, on ne dispose pas de preuves suffisantes pour recommander une méthode plutôt qu'une autre.

C. Contrôler l'exposition aux NMM

7. Selon le principe de précaution, le GDG recommande d'axer le contrôle de l'exposition sur la prévention de l'exposition par inhalation afin de réduire celle-ci autant que possible (recommandation forte, données de qualité moyenne).
8. Le GDG recommande de réduire les expositions aux NMM systématiquement mesurées sur le lieu de travail, en particulier lors des tâches de nettoyage et de maintenance, de recueil de matériaux issus de réacteurs et d'alimentation des lignes de production en NMM. En l'absence d'informations toxicologiques, le GDG recommande de mettre en œuvre des contrôles rigoureux afin de prévenir l'exposition des travailleurs. Quand ces informations sont disponibles, le GDG recommande d'adopter une approche plus spécifique au contexte (*recommandation forte, données de qualité moyenne*).
9. Le GDG recommande de prendre des mesures de contrôle en respectant le principe de hiérarchie des contrôles : la première mesure de contrôle doit être d'éliminer la source d'exposition avant d'appliquer des mesures de contrôle davantage liées à l'implication des travailleurs, l'EPI ne devant être utilisé qu'en dernier recours. Selon ce principe, les contrôles d'ingénierie doivent être effectués en cas de forte exposition par inhalation ou quand il existe peu ou pas d'informations toxicologiques. En l'absence de contrôles d'ingénierie adéquats, il faut utiliser un EPI, en particulier une protection pour les voies respiratoires, dans le cadre d'un programme de protection qui inclut un test d'aptitude (*recommandation forte, données de qualité moyenne*).
10. Le GDG suggère de prévenir l'exposition dermique en appliquant des mesures d'hygiène au travail, comme le nettoyage des surfaces et le port de gants appropriés (*recommandation conditionnelle, données de faible qualité*).

11. En l'absence d'expert de la sécurité au travail pour effectuer les évaluations et les mesures, le GDG suggère d'employer la méthode dite de gestion graduée des risques liés aux nanomatériaux pour choisir les mesures de contrôle de l'exposition sur le lieu de travail. Le manque d'études sur le sujet ne permet pas au GDG de recommander une méthode plutôt qu'une autre (*recommandation conditionnelle, données de très faible qualité*).

D. Veille sanitaire

En raison du manque de données disponibles, le GDG ne peut pas formuler de recommandations pour des programmes de veille sanitaire ciblée propres aux NMM par rapport aux programmes de veille sanitaire existants.

E. Formation et implication des travailleurs

Le GDG considère la formation des travailleurs et leur implication dans les questions de santé et de sécurité comme les meilleures pratiques, mais il ne peut pas recommander une modalité de formation/implication des travailleurs plutôt qu'une autre, du fait de l'absence d'études disponibles sur le sujet.

Des progrès considérables sont attendus dans le domaine des méthodes validées de mesure et d'évaluation des risques. Le GDG propose donc de mettre à jour ces lignes directrices dans cinq ans, soit en 2022.

SINOPSIS

El término nanomateriales hace referencia a aquellos materiales que tienen al menos una dimensión (altura, anchura o longitud) inferior a 100 nanómetros (10^{-7} metros), que corresponde aproximadamente al tamaño de una partícula vírica. Este tamaño peculiar es una de las principales características de los nanomateriales fabricados (NMF). Las propiedades singulares de los NMF pueden dar lugar a comportamientos muy deseables que los hacen aptos para aplicaciones tan variables como mejores pinturas, mejores fármacos o componentes electrónicos más rápidos. Sin embargo, por este mismo motivo, los NMF también suponer peligros para la salud diferentes de los que conllevan los materiales micro/macroscópicos, y pueden necesitar métodos de evaluación del peligro, la exposición y el riesgo diferentes de los utilizados con estos últimos.

La toxicidad de los NMF puede depender en gran medida de numerosas propiedades fisicoquímicas, como el tamaño, la forma (es decir, su tamaño en una de las tres dimensiones), la composición, las características de su superficie, la carga o la velocidad de disolución. Hay escasa información precisa sobre las vías de exposición humana a los NMF, su destino en el organismo y su capacidad para producir efectos biológicos no deseados, como la generación de estrés oxidativo. Sólo hay datos de estudios in vitro, en animales y en humanos, sobre la inhalación de muy pocos NMF. Hasta la fecha no se han observado efectos adversos a largo plazo en la salud humana. Esto podría deberse a la introducción reciente de los NMF, al principio de precaución aplicado para evitar la exposición y a los problemas éticos relacionados con la realización de estudios en el ser humano. Esto significa que, excepto en relación con los escasos materiales acerca de los cuales hay estudios en humanos, las recomendaciones sanitarias tienen que basarse en la extrapolación a los posibles efectos en humanos de los datos procedentes de estudios in vitro, estudios en animales o estudios de otros ámbitos que implican una exposición a nanopartículas, como los estudios sobre la contaminación atmosférica.

El aumento de la producción de NMF y su uso en productos de consumo e industriales significa que los trabajadores de todos los países estarán en la primera línea de exposición a estos materiales, lo que les supone un mayor riesgo de posibles efectos adversos en la salud.

Por consiguiente, la Organización Mundial de la Salud (OMS) ha elaborado las presentes directrices que contienen recomendaciones sobre la mejor forma de proteger a los trabajadores de los posibles riesgos de los NMF. Dichas recomendaciones se destinan a ayudar a los planificadores de políticas y a los profesionales de la salud y la seguridad laborales a tomar decisiones sobre la mejor protección frente a posibles riesgos específicos de los NMF en los lugares de trabajo. Asimismo, tienen por objetivo servir a los trabajadores y a los empleadores. Sin embargo, no están concebidas como un manual sobre la manipulación segura de los NMF en el lugar de trabajo, dado que ello requeriría abordar cuestiones más generales de higiene laboral que están fuera del alcance de las presentes directrices.

PRINCIPIOS RECTORES

Uno de los principios rectores empleados por el Grupo de Elaboración de Directrices (GED) fue el principio de precaución. Ello significa que, pese a las incertidumbres sobre los efectos adversos en la salud, hay que reducir la exposición siempre que haya indicaciones razonables para ello.

Otro principio rector importante fue la jerarquización de los controles. Esto significa que cuando haya que elegir entre diferentes medidas de control se dará preferencia a las que estén más cerca de la raíz del problema sobre aquellas que supongan una mayor carga para los trabajadores, como el uso de equipos de protección personal.

PRÁCTICAS ÓPTIMAS

El GED considera que las prácticas óptimas para prevenir los efectos adversos de los NMF en la salud consisten en:

- Agrupar los nanomateriales en NMF con toxicidad específica, NMF que son fibras y NMF que son partículas granulares biopersistentes.
- Educar y capacitar a los trabajadores con respecto a los problemas de salud y seguridad específicos de los NMF.
- Implicar a los trabajadores en todas las fases de la evaluación y del control de los riesgos.

MÉTODOS

Para que sirvieran de base a la formulación de recomendaciones de conformidad con el proceso descrito en el *Manual de la OMS para la Elaboración de Directrices*, se encargaron revisiones sistemáticas del estado actual de la ciencia sobre todas las cuestiones importantes. Las recomendaciones se consideraron "firmes" o "condicionales", dependiendo de la calidad de las evidencias científicas, los valores y preferencias, y los costos relacionados con cada recomendación. Todas las recomendaciones se adoptaron por consenso del GED.

RECOMENDACIONES

A. Evaluación de los peligros de los NMF para la salud

1. El GED recomienda que a cada NMF se le asigne una clase de peligrosidad de acuerdo con el Sistema Mundialmente Armonizado de Clasificación y Etiquetado de Productos Químicos para uso en las fichas de datos de seguridad. En las presentes directrices se proporciona esta información con respecto a un reducido número de NMF (*recomendación firme, evidencias de calidad moderada*).
2. El GED recomienda que se actualicen las fichas de datos de seguridad con información acerca de los peligros específicos de los NMF o que se indiquen los criterios de valoración toxicológica que no se han examinado adecuadamente (*recomendación firme, evidencias de calidad moderada*).
3. Con respecto al grupo de las fibras respirables y al grupo de las partículas granulares biopersistentes, el GED propone que se utilice la clasificación existente de los NMF para clasificar provisionalmente los nanomateriales del mismo grupo (*recomendación condicional, evidencias de baja calidad*).

B. Evaluación de la exposición a los NMF

4. El GDG propone que la exposición de los trabajadores en el lugar de trabajo se evalúe con métodos similares a los utilizados para determinar el valor límite de exposición ocupacional (LEO) específico del NMF en cuestión (*recomendación condicional, evidencias de baja calidad*).
5. Como no hay valores reglamentarios específicos del LEO para los NMF en el lugar de trabajo, el GED propone evaluar si la exposición en el lugar de trabajo supera el valor LEO propuesto para el NMF en cuestión. En el anexo 1 de las presentes directrices figura una lista de valores LEO propuestos. El valor LEO elegido debe ser al menos tan protector como el impuesto por la ley para la forma micro/macroscópica del material en cuestión (*recomendación condicional, evidencias de baja calidad*).
6. Si no hay valores LEO específicos para los NMF en el lugar de trabajo, el GED propone un enfoque escalonado para evaluar la exposición por inhalación: primero una evaluación del potencial de exposición, a continuación una evaluación básica de la exposición y, por último, una evaluación integral de la exposición, como las que proponen la Organización de Cooperación y Desarrollo Económicos (OCDE) o el Comité Europeo de Normalización (CEN) (*recomendación condicional, evidencias de calidad moderada*). En lo que se refiere a la exposición dérmica, las evidencias son insuficientes para recomendar un método de evaluación con preferencia a otro.

C. Control de la exposición a los NMF

7. Siguiendo el principio de precaución, el GED recomienda que el control de la exposición se base en la prevención de la exposición por inhalación con el fin de reducirla lo máximo posible (*recomendación firme, evidencias de calidad moderada*).
8. El GED recomienda reducir las exposiciones a una serie de NMF medidos sistemáticamente en el lugar de trabajo, especialmente durante la limpieza y mantenimiento, la recogida de materiales de los reactores y la alimentación de las líneas de producción de NMF. En ausencia de información toxicológica, el GED recomienda que se pongan en práctica los controles más rigurosos para evitar toda exposición de los trabajadores. Cuando haya información al respecto, el GED recomienda un enfoque más específico (*recomendación firme, evidencias de calidad moderada*).
9. El GED recomienda que las medidas de control se basen en el principio de jerarquización de los controles; es decir, la primera medida de control debe ser la eliminación de la fuente de exposición, antes que la aplicación de medidas de control que dependen más de la participación de los trabajadores; los equipos de protección personal deben emplearse solo como último recurso. De acuerdo con este principio, cuando haya un alto nivel de exposición por inhalación o la información toxicológica sea escasa o nula deben utilizarse los controles de ingeniería. En ausencia de controles de ingeniería apropiados deberán utilizarse equipos de protección personal, especialmente de protección respiratoria, en el marco de un programa de protección respiratoria que incluya comprobaciones del ajuste del equipo (*recomendación firme, evidencias de calidad moderada*).
10. El GED propone que se evite la exposición dérmica con medidas de higiene ocupacional, como la limpieza de las superficies y el uso de guantes apropiados (*recomendación condicional, evidencias de baja calidad*).

11. Cuando no haya un experto en seguridad laboral para realizar las evaluaciones y mediciones, el GED propone que se utilice el método de gestión gradual de los riesgos relacionados con los nanomateriales para elegir las medidas de control de la exposición en el lugar de trabajo. Debido a la inexistencia de estudios, el GED no puede recomendar un método de gestión gradual de los riesgos con preferencia a otros (*recomendación condicional, evidencias de muy baja calidad*).

D. Vigilancia sanitaria

Debido a la falta de evidencias, el GED no puede recomendar programas de vigilancia sanitaria específicos para los NMF con preferencia a los programas de vigilancia sanitaria ya existentes.

E. Capacitación y participación de los trabajadores

El GED considera que la capacitación de los trabajadores y su participación en las cuestiones relacionadas con la salud y la seguridad es una práctica óptima, pero, debido a la falta de estudios sobre el tema, no puede recomendar una forma de capacitación ni de participación de los trabajadores con preferencia a otras.

Como son de prever avances considerables con respecto a los métodos de medición validados y a la evaluación de los riesgos, el GED se propone actualizar las presentes directrices dentro de 5 años, es decir, en 2022.

ИСПОЛНИТЕЛЬНОЕ РЕЗЮМЕ

Термин «наноматериалы» означает материалы, у которых хотя бы один размер (высота, ширина или длина) не превышает 100 нанометров (10–7 метров), что примерно соответствует размеру вирусной частицы. Именно этот размерный параметр является главной отличительной особенностью производимых наноматериалов (ПНМ). В силу своих уникальных свойств, ПНМ могут обладать весьма привлекательными характеристиками, благодаря которым их можно широко применять в самых различных областях, в частности, для создания более совершенных красок, более эффективных лекарств и более быстродействующих электронных устройств. Однако по этой же причине ПНМ могут также создавать угрозы для здоровья, не характерные для веществ в объемной форме, и для оценки их опасности, воздействия и связанного с этим риска могут потребоваться иные по сравнению с макроматериалами методы испытаний.

Токсичность ПНМ может быть в значительной степени обусловлена большим числом физико-химических характеристик, таких как размер, форма (т.е. размер в определенной плоскости), состав, характеристики поверхности, заряд и скорость растворения. В настоящее время имеется крайне скудная информация о путях воздействия ПНМ на человека, их «судьбе» в человеческом организме и их способности вызывать нежелательные биологические последствия, в частности, провоцировать окислительный стресс. Ингаляционные исследования in vitro либо с участием животных и людей проводились только по небольшому числу ПНМ. Наблюдениями до сих пор не было зарегистрировано долгосрочных негативных последствий для здоровья человека. Это может объясняться недавним появлением ПНМ, использованием мер предосторожности во избежание их воздействия, а также существованием этических возражений против проведения исследований на людях. Соответственно, если речь не идет о нескольких материалах, по которым имеются результаты исследований на людях, то рекомендации по охране здоровья должны вырабатываться на основе фактических данных исследований, проведенных in vitro и на животных, а также в других областях, связанных с воздействием наночастиц, включая загрязнение воздуха, путем их экстраполяции на возможные последствия для человека.

В результате роста производства ПНМ и их применения в составе потребительской и промышленной продукции производственный персонал во всех странах будет первым контактировать с этими материалами, подвергаясь повышенному риску возможных негативных последствий для здоровья.

В связи с этим Всемирная организация здравоохранения (ВОЗ) разработала настоящие руководящие принципы, включив в них рекомендации о наилучших способах защиты персонала от потенциальных рисков ПНМ. Рекомендации призваны помочь директивным органам и специалистам в сфере охраны и гигиены труда принимать решения о выборе наиболее эффективных средств защиты от возможных специфических рисков, исходящих от ПНМ на рабочих местах. Также предполагается, что этими руководящими принципами смогут воспользоваться персонал и работодатели. Они, однако, не предназначены служить руководством или пособием по безопасному обращению с ПНМ на рабочем месте, поскольку для этого потребовалось бы осветить более широкие вопросы гигиены труда, выходящие за рамки настоящих руководящих принципов.

РУКОВОДЯЩИЕ ПРИНЦИПЫ

Предосторожность была одним из ведущих принципов, на которые ориентировалась Группа по разработке руководящих принципов (ГРП). Он предполагает, что воздействие необходимо ограничивать даже при отсутствии определенности относительно его неблагоприятных последствий для здоровья, если для этого имеются разумные основания.

Другим важным руководящим принципом была иерархия средств контроля. Этот принцип означает, что при возможности выбора мер контроля приоритет должен отдаваться мерам, более тесно связанным с коренной причиной проблемы, а не мерам, которые создают повышенную нагрузку на персонал, таким как использование средств индивидуальной защиты (СИЗ).

ПЕРЕДОВАЯ ПРАКТИКА

ГРП рассматривает перечисленные ниже методы в качестве передовой практики в области профилактики воздействия ПНМ на здоровье:

- распределение наноматериалов по группам: ПНМ со специфической токсичностью, ПНМ, являющиеся волокнами, и ПНМ – гранулярные биоустойчивые частицы;
- информирование и подготовка персонала по специфическим вопросам охраны здоровья и обеспечения безопасности при работе с ПНМ;
- обеспечение участия персонала на всех этапах процесса оценки и контроля рисков.

МЕТОДЫ

По каждому из важных аспектов проблемы было организовано проведение систематического обзора современного состояния научных знаний в целях разработки на их основе рекомендаций, как того требует порядок, изложенный в «Пособии ВОЗ по разработке руководящих принципов». Рекомендациям присваивался статус «настоятельных» либо «условных» в зависимости от качества научных данных, ценностей и предпочтений, а также расходов, связанных с их выполнением. Все рекомендации выносились на основе консенсуса между членами ГРП.

РЕКОМЕНДАЦИИ

A. Оценка опасных для здоровья факторов ПНМ

1. ГРП рекомендует распределить все ПНМ по классам опасности в соответствии с Согласованной на глобальном уровне системой (СГС) классификации и маркировки химических веществ для их указания в паспортах безопасности. По ограниченному числу ПНМ такая информация приведена в данных руководящих принципах (настоятельная рекомендация, научные данные среднего качества).
2. ГРП рекомендует обновить паспорта безопасности, дополнив их информацией о факторах опасности, связанных непосредственно с ПНМ, либо указав, в отношении каких конечных точек токсикологического воздействия не имеется данных надлежащего тестирования (*настоятельная рекомендация, научные данные среднего качества*).
3. В отношении групп респирабельных волокон и гранулярных биоустойчивых частиц ГРП предлагает использовать существующую классификацию ПНМ для предварительного классифицирования наноматериалов той же группы (*условная рекомендация, научные данные низкого качества*).

B. Оценка воздействия ПНМ

4. ГРП предлагает оценивать воздействие на персонал на рабочих местах методами, которые аналогичны использованным для определения предлагаемого значения предельной производственной экспозиции (ППЭ) конкретно для ПНМ (*условная рекомендация, научные данные низкого качества*).
5. Поскольку конкретных нормативных значений ППЭ для ППН на рабочих местах не установлено, ГРП предлагает при оценке исходить из того, превышает ли воздействие на рабочем месте предлагаемое значение ППЭ для ПНМ. Перечень предлагаемых значений ППЭ приводится в Приложении 1 к данным руководящим принципам. Выбранная ППЭ должна обеспечивать как минимум такую же защиту, что и предусмотренная законом ППЭ для объемной формы этого материала (*условная рекомендация, научные данные низкого качества*).
6. В тех случаях когда конкретная ППЭ для ПНМ на рабочих местах отсутствует, ГРП предлагает поэтапный порядок оценки ингаляционного воздействия, предполагающий, во-первых, оценку вероятности воздействия; во-вторых, проведение базовой оценки воздействия; и, в-третьих, проведение комплексной оценки воздействия, аналогичной той, которая предлагается Организацией экономического сотрудничества и развития (ОЭСР) или Европейским комитетом по стандартизации (ЕКС) (*условная рекомендация, научные данные среднего качества*). В отношении оценки кожного воздействия имеющихся фактических данных было недостаточно, чтобы рекомендовать более предпочтительный по сравнению с другими метод оценки воздействия на кожные покровы.

C. Контроль воздействия ПНМ

7. В соответствии с принципом предосторожности, ГРП рекомендует уделять основное внимание в рамках контроля за воздействием предотвращению ингаляционного воздействия в целях его максимально возможного ограничения (*настоятельная рекомендация, научные данные среднего качества*).
8. ГРП рекомендует уменьшить воздействие целого ряда ПНМ, содержание которых последовательно измерялось на рабочих местах, особенно во время уборки и технического обслуживания, забора материала из реакционных емкостей и подачи ПНМ в производственный процесс. При отсутствии токсикологической информации ГРП рекомендует применять наивысший уровень контроля во избежание какого-либо воздействия на персонал. При наличии большего объема информации ГРП рекомендует применять более индивидуальный подход (*настоятельная рекомендация, научные данные среднего качества*).
9. ГРП рекомендует принимать меры контроля, руководствуясь принципом иерархии средств контроля, согласно которому первая мера контроля должна заключаться в ликвидации причины воздействия и лишь после нее внедряются меры контроля, которые в большей степени зависят от участия персонала, а СИЗ используются лишь в качестве крайней меры. В соответствии с этим принципом, в ситуациях высокого уровня ингаляционного воздействия и отсутствия или крайней скудости токсикологической информации следует применять инженерно-технические средства контроля. При отсутствии надлежащих инженерно-технических средств должны использоваться СИЗ, особенно для защиты органов дыхания, в рамках программы по защите органов дыхания, предусматривающей индивидуальную подгонку защитных средств (*настоятельная рекомендация, научные данные среднего качества*).

10. ГРП предлагает предотвращать кожное воздействие при помощи таких мер производственной гигиены, как очистка поверхностей и использование подходящих перчаток (*условная рекомендация, научные данные низкого качества*).
11. При невозможности проведения оценки и измерений инженером по охране труда ГРП рекомендует применять по отношению к наноматериалам метод ранжирования мер контроля (control banding), позволяющий подбирать меры по контролю воздействия на рабочем месте. В связи с недостаточностью исследований на этот счет ГРП не может рекомендовать какой-либо предпочтительный по сравнению с остальными метод ранжирования (*условная рекомендация, научные данные крайне низкого качества*).

D. Наблюдение за состоянием здоровья

Ввиду нехватки фактических данных, ГРП не может сформулировать рекомендацию, которая предусматривала бы разработку адресных, относящихся конкретно к ПНМ программ наблюдения за состоянием здоровья, в отличие от уже существующих и реализуемых программ наблюдения за здоровьем.

E. Подготовка и обеспечение участия персонала

ГРП рассматривает подготовку персонала и его участие в решении вопросов охраны здоровья и обеспечения безопасности в качестве передовой практики, однако по причине недостаточности имеющихся исследований не может рекомендовать какую-либо одну форму подготовки персонала либо какую-либо одну форму обеспечения их участия по сравнению со всеми другими.

В области валидации методов измерений и оценки риска ожидается значительное продвижение вперед. В связи с этим ГРП предлагает обновить настоящие руководящие принципы через пять лет, в 2022 году.

执行概要

纳米材料这一术语指三维空间（高度、宽度或长度）中至少有一维小于100纳米（10^{-7}米）的材料，即大约一个病毒颗粒的尺寸。这一特定尺寸的维度是人工纳米材料的主要特征。人工纳米材料的独特性质可能实现非常理想的性能，从而导致各种不同的应用，如更好的涂料，更好的药物和更快的电子产品等。然而，出于同样的原因，人工纳米材料也可能会造成不同于块体物质的健康危害，并且可能需要不同于其较大块体对应物的检测方法来进行危害、接触量和风险评估。

人工纳米材料的毒性在很大程度上可能取决于许多物理化学性质，包括尺寸、形状（即某一特定维度中的尺寸）、组成、表面特性、电荷和溶解速率等。目前，缺乏精确信息说明人类接触人工纳米材料的途径及其在人体中的结局以及其诱发意外生物效应（例如产生氧化应激）的能力。目前仅具备关于少数人工纳米材料的体外，动物和人类吸入研究数据。迄今为止，尚未观察到对人类的长期不良健康影响。这可能是因为人工纳米材料的应用刚开始不久，而且采取了避免接触的防范措施，另外对人类进行研究存在一系列伦理问题。这意味着，除了少数材料具有可用的人类研究之外，健康建议必须依赖推断，即从涉及与纳米尺度颗粒（例如空气污染）接触的体外研究、动物研究或其它领域研究产生的证据来推断可能对人类的影响。

人工纳米材料的产量增加及其在消费产品和工业产品中的使用意味着所有国家的工人将处于接触这些材料的第一线，使其面临潜在不良健康影响的更大风险。

因此，世界卫生组织（世卫组织）制定了该指南，并就如何最有效地保护工人免受人工纳米材料的潜在风险提出了建议。这些建议旨在帮助职业健康与安全领域的决策者和专业人员决定在工作场所防止人工纳米材料所特有的潜在风险的最佳保护措施。该指南还旨在支持工人和雇主。但不准备作为在工作场所安全处理人工纳米材料的手册，因为这需要处理超出本指南范围的更一般性职业卫生问题。

指导原则

指南制定小组将防范方针作为其指导原则之一。这意味着，只要有合理的迹象表明应减少接触，即使对不良健康影响并不确定，也必须减少接触。

另外，控制措施的等级结构是一项重要指导原则。这意味着如果可在控制措施之间进行选择，那些更接近问题根源的措施应该始终优先于可能对工人造成更大负担的措施，例如使用个人防护装备等。

最佳做法

指南制定小组认为以下是防止人工纳米材料不良健康影响的最佳做法：

- 将纳米材料归为具有特定毒性的人工纳米材料，纤维状人工纳米材料和生物持久性颗粒状人工纳米材料三个组别。
- 就人工纳米材料的具体健康和安全问题对工人进行教育和培训。
- 让工人参与风险评估和控制的各个阶段。

方法

关于所有重要问题，已委托对科学现状进行了系统审查，以便根据《世卫组织指南制定手册》中载明的程序指导提出建议。根据科学证据的质量、价值观和偏好以及与建议有关的费用，将所提建议评定为“强烈”或“有条件”。所有建议都由指南制定小组协商一致提出。

建议

A. 评估人工纳米材料的健康危害

1. 指南制定小组建议根据《全球化学品统一分类和标签制度》（GHS）为所有人工纳米材料确定危险等级以便用于安全数据表。本指南对数量有限的人工纳米材料提供了这方面信息（*强烈建议，证据质量中等*）。

2. 指南制定小组建议更新载有特定人工纳米材料危害信息的安全数据表，或指明哪些毒理学终点没有可用的充分测试（*强烈建议，证据质量中等*）。

3. 对于可吸入的纤维状和生物持久性颗粒状材料，指南制定小组建议使用已有的人工纳米材料危险等级对同组别的纳米材料进行临时分级（*有条件的建议，证据质量低*）。

B. 评估人工纳米材料的接触情况

4. 指南制定小组建议使用类似于拟定人工纳米材料的具体职业接触限值（OEL）时所用的方法来评估工人在工作场所的接触情况（*有条件的建议，证据质量低*）。

5. 由于工作场所没有具体监管人工纳米材料的职业接触限值，因此，指南制定小组建议评估工作场所的接触量是否超过拟议的人工纳米材料职业接触限值。本指南附件1中提供了拟议的职业接触限值表。选定的职业接触限值应至少与法律授权用于块体材料的职业接触限值具有同样的保护作用（*有条件的建议，证据质量低*）。

6. 如果工作场所不具备针对人工纳米材料的具体职业接触限值，指南制定小组建议对吸入接触采用阶梯式方法，第一步评估接触的可能性；第二步评估基本接触情况，第三步按照经济合作与发展组织（经合组织）或欧洲标准化委员会的建议，进行全面接触评估（*有条件的建议，证据质量中等*）。关于皮肤接触评估，证据不足以建议一种最好的皮肤接触评估方法。

C. 控制人工纳米材料的接触量

7. 根据防范方针，指南制定小组建议在控制接触时着重关注防止吸入接触，目的是尽可能减少接触量（*强烈建议，证据质量中等*）。

8. 指南制定小组建议减少与在工作场所持续测量的一系列人工纳米材料的接触，特别是在清洁和维护，从反应容器中收集材料以及将人工纳米材料输入生产流程的过程中。在没有毒理学信息的情况下，指南制定小组建议实施最高级别的控制措施，以防止工人发生任何接触。如果能获得更多信息，指南制定小

组建议采取更加切合具体情况的方法（*强烈建议，证据质量中等*）。

9. 指南制定小组建议根据控制措施的等级结构原则采取相应措施，这意味着第一级控制措施应该是在实施更有赖工人参与的控制措施之前消除接触源，而个人防护装备仅被用作最后手段。根据这一原则，在有高量吸入接触或者在毒理学信息没有或很少的情况下，应采取工程控制措施。如果没有适当的工程控制措施，应使用个人防护装备，特别是呼吸防护装置，作为呼吸防护规划的一部分，包括进行密合度检测（*强烈建议，证据质量中等*）。
10. 指南制定小组建议通过职业卫生措施，如清洁表面和使用适当的手套来预防皮肤接触（有条件的建议，证据质量低）。
11. 如果工作场所没有安全专家进行评估和测量，指南制定小组建议使用纳米材料分级管理方法来选择工作场所的接触控制措施。由于缺乏研究，指南制定小组无法推荐一种最佳的分级管理方法（*有条件的建议，证据质量极低*）。

D. 健康监测

由于缺乏证据，指南制定小组无法建议一项胜过目前使用中的健康监测规划的明确针对人工纳米材料的健康监测规划。

E. 工人的培训和参与

指南制定小组认为，培训工人并让其参与健康和安全问题是最佳做法，但由于缺乏可用的研究，无法建议一种最佳的工人培训方式或最佳的工人参与形式。

预计将在验证测量方法和风险评估方面取得重大进展。因此，指南制定小组建议五年后，即2022年更新本指南。

المبادئ المُسترشد بها

اتبع الفريق المعني بوضع المبادئ التوجيهية نهجاً تحوطياً بوصفه واحداً من المبادئ المُسترشد بها، ما يعني أنه يتعيّن تقليل مستوى التعرض للمواد المصنّعة المتناهية الصغر رغم انعدام اليقين بشأن آثارها الصحية الضارة في الحالات التي توجد فيها مؤشرات معقولة تدلّ على ذلك.

وإضافة إلى ذلك، فإن التسلسل الهرمي لضوابط مكافحة التعرض لهذه المواد هو من المبادئ الهامة المُسترشد بها، ما يعني أنه ينبغي دوماً في الحالات التي يتسنى فيها الاختيار بين تدابير مكافحة التعرض لها أن تُرجّح التدابير التي هي أقرب إلى أساس المشكلة على تلك التي تثقل كاهل العمال بعبء أثقل، مثل استخدام معدات الوقاية الشخصية.

أفضل الممارسات المُتّبعة

فيما يلي الممارسات التي يرى الفريق المعني بوضع المبادئ التوجيهية أنها من أفضل الممارسات المُتّبعة في مجال الوقاية من الآثار الصحية الضارة للمواد المصنّعة المتناهية الصغر:

- تصنيف المواد المتناهية الصغر إلى الفئات التالية: فئة المواد المصنّعة المتناهية الصغر المُحدّدة السمّية وفئة أخرى منها مكونّة من ألياف وفئة ثالثة من المواد المصنّعة المتناهية الصغر المكوّنة من جسيمات حبيبية ثابتة بيولوجياً.
- تثقيف العاملين وتدريبهم على التعامل مع المشاكل التي تطرحها المواد المصنّعة المتناهية الصغر في مجالي الصحة والسلامة.
- إشراك العمال في جميع مراحل تقييم مخاطر تلك المواد ومكافحتها.

الأساليب المُنتهجة

صدر تكليف، في إطار تناول المسائل الهامة، بإجراء استعراضات منهجية لحالة العلوم في الوقت الحاضر للاسترشاد بها في وضع التوصيات وفقاً للعملية المنصوص عليها في دليل المنظمة لوضع المبادئ التوجيهية. وصُنِّفت التوصيات على أنها "قوية" أو "مشروطة" رهناً بنوعية البيّنات العلمية المتوفرة عنها والقيم والتفضيلات المتعلقة بها والتكاليف المُتكبدة عنها، وهي توصيات وُضِعت جميعها بناءً على توافق الآراء داخل الفريق المعني بوضع المبادئ التوجيهية.

التوصيات الموضوعة

ألف: تقدير المخاطر الصحية المترتبة على المواد المصنّعة المتناهية الصغر

١. يوصي الفريق المعني بوضع المبادئ التوجيهية بتحديد فئات المخاطر المترتبة على جميع المواد المصنّعة المتناهية الصغر وفقاً للنظام الموحد عالمياً لتصنيف المواد الكيميائية وتوسيمها من أجل استخدامها في صحائف بيانات السلامة. وتُتاح في هذا المبدأ التوجيهي معلومات عن عدد محدود من المواد المصنّعة المتناهية الصغر (توصية قوية مشفوعة ببيّنات معتدلة الجودة).

ملخص تنفيذي

يشير تعبير "المواد المتناهية الصغر" إلى مواد يقلّ أحد أبعادها، على أدنى تقدير، (سواء ارتفاعها أم عرضها أم طولها) عن ١٠٠ نانومتر (١٠-٧ متر)، أي أنها بحجم جسيم الفيروس تقريباً. ويمثل هذا البُعد من أبعاد حجمها تحديداً سمة رئيسية من سمات المواد المصنّعة المتناهية الصغر، التي قد تؤدي خصائصها الفريدة من نوعها إلى اتباع سلوكيات مرغوب فيها للغاية تفضي إلى استحداث تطبيقات مختلفة، من قبيل تحسين أنواع الدهان والأدوية واستحداث أجهزة إلكترونية أسرع. ولكن هذه المواد المصنّعة المتناهية الصغر قد تشكّل أيضاً، للسبب نفسه، مخاطر صحية تختلف عن المخاطر الناجمة عن المواد السائبة، وقد تتطلب اتباع أساليب اختبار لتقدير أخطارها ومستويات التعرض لها ومخاطرها تختلف عن نظيراتها من المواد السائبة.

وقد تتوقف إلى حد كبير سمّية هذه المواد المصنّعة المتناهية الصغر على العديد من خصائصها الفيزيائية والكيميائية، ومنها حجمها وشكلها (أي حجمها المقيس على أساس بُعد معيّن) وتكوينها وخصائص سطحها وشحنتها ومعدل ذوبانها. ولا يتوفر حالياً إلا القليل من المعلومات الدقيقة عن طرائق تعرض الإنسان لتلك المواد وعن مصيرها داخل جسمه وقدرتها على أن تُحدِث فيه آثاراً بيولوجية غير مرغوب فيها، مثل التعرّض للإجهاد الناجم عن تأكسد المواد. ولا تُتاح البيانات المستقاة من المختبرات والدراسات المتعلقة باستنشاق الإنسان والحيوان للمواد المذكورة إلا بشأن عدد قليل منها حصراً، ولم تُلاحظ حتى الآن أية آثار مضرة تخلّفها هذه المواد على صحة الإنسان في الأجل الطويل، وهو أمر قد يُعزى إلى اعتمادها في الآونة الأخيرة واتباع نهج تحوطي في تجنب التعرض لها وإلى الشواغل الأخلاقية المُثارة بشأن إجراء دراسات عنها على الإنسان. ويعني ذلك أن التوصيات الصحية، باستثناء عدد قليل من المواد التي تُتاح عنها دراسات أُجريت على الإنسان، هي توصيات يجب أن تستند إلى استقراء البيّنات المُستقاة من الدراسات المختبرية أو تلك التي تُجرى على الحيوان أو غيرها من الدراسات المُستمدة من مجالات تتراوح بين تناول التعرض للجسيمات التي يُقاس حجمها بمقياس نانوي مثل تلوث الهواء، والآثار التي يمكن أن تخلّفها على صحة الإنسان.

وتُفسّر زيادة إنتاج المواد المصنّعة المتناهية الصغر واستخدامها في المنتجات الاستهلاكية والصناعية على أنها ستضع العمال في جميع البلدان على خط المواجهة في مجال التعرض لتلك المواد، الأمر الذي سيزيد من خطورة تعرضهم لآثار يُحتمل أن تلحق الضرر بصحتهم.

لذلك وضعت منظمة الصحة العالمية (المنظمة) هذه المبادئ التوجيهية المقترنة بتوصيات بشأن أفضل السبل الكفيلة بحماية العمال من المخاطر المحتملة للمواد المصنّعة المتناهية الصغر، وهي توصيات معدّة لغرض مساعدة راسمي السياسات والمهنيين العاملين في مجال الصحة والسلامة المهنيتين على اتخاذ قرارات بشأن تأمين أفضل مستوى من الحماية ضد المخاطر التي يُحتمل أن تشكّلها هذه المواد في أماكن العمل. وهذه المبادئ التوجيهية معدّة أيضاً لغرض دعم العمال وأرباب العمل، لا لغرض أن تقوم مقام كتيّب أو دليل بشأن المناولة الآمنة للمواد المصنّعة المتناهية الصغر في مكان العمل، لأن ذلك يستدعي تناول مسائل أكثر عمومية بشأن الصحة المهنية لا تندرج ضمن نطاق هذه المبادئ التوجيهية.

سمّية هذه المواد، بفرض ضوابط مكافحة من أعلى المستويات عليها لوقاية العمال من أي تعرض لها. وفي حال توفر المزيد من المعلومات عنها، فإن الفريق المذكور يوصي باتباع نهج معدّ على نحو أكثر تخصيصاً لتحقيق هذا الغرض (توصية قوية مشفوعة ببيّنات معتدلة الجودة).

٩. ويوصي الفريق المعني بوضع المبادئ التوجيهية باتخاذ تدابير مكافحة التعرض للمواد المذكورة بناءً على مبدأ مراعاة التسلسل الهرمي لضوابط مكافحتها، ما يعني أنه ينبغي اتخاذ أولى ضوابط مكافحتها للقضاء على مصدر التعرض لها قبل اتخاذ أخرى لمكافحتها تعتمد بشكل أكثر على إشراك العمال، ولكن شريطة ألا يُلجأ إلى استخدام معدات الوقاية الشخصية إلا كملاذ أخير. ووفقاً لهذا المبدأ، فإنه ينبغي تطبيق ضوابط المكافحة الهندسية بالحالات التي ترتفع فيها معدلات التعرض لاستنشاق المواد، أو بالحالات التي لا تتوفر فيها معلومات عن مدى سميّة تلك المواد أو يتوفر فيها قدر ضئيل جدّاً من المعلومات عنها. وينبغي في حالة انعدام وجود ضوابط هندسية مناسبة استخدام معدات الوقاية الشخصية، وخاصةً معدات وقاية الجهاز التنفسي، وذلك في إطار تنفيذ برنامج معني بوقاية الجهاز التنفسي ينطوي على إجراء اختبارات مدى الملاءمة (توصية قوية مشفوعة ببيّنات معتدلة الجودة).

١٠. ١ويقترح الفريق المعني بوضع المبادئ التوجيهية وقاية الجلد من التعرض لهذه المواد بواسطة اتخاذ تدابير بشأن النظافة المهنية، من قبيل تنظيف السطوح وارتداء القفازات المناسبة (توصية مشروطة مشفوعة ببيّنات متدنية الجودة).

١١. أما في الحالات التي لا تُتاح فيها إمكانية إجراء أحد خبراء شؤون السلامة لتقديرات بشأن المواد المصنّعة المتناهية الصغر أو قياس معدلات التعرض لها في مكان العمل، فإن الفريق المعني بوضع المبادئ التوجيهية يقترح تطبيق عملية تصنيف مخاطر التعرض لتلك المواد إلى نطاقات لتحديد تدابير مكافحة التعرض لها في مكان العمل. وبسبب الافتقار إلى الدراسات في هذا الميدان، فإن من المتعذّر على الفريق أن يوصي بتفضيل اتباع إحدى طرائق تصنيف مخاطر التعرض لها على سواها من الطرائق (توصية مشروطة مشفوعة ببيّنات متدنية الجودة).

دال: ترصّد الآثار الصحية

نظراً إلى انعدام البيّنات، فإن من المتعذّر على الفريق المعني بوضع المبادئ التوجيهية أن يقدم توصية بشأن تفضيل البرامج المُحدّدة الأهداف لترصّد الآثار الصحية للمواد المصنّعة المتناهية الصغر تحديداً على البرامج القائمة لترصّد آثارها الصحية التي يجري فعلاً تطبيقها.

هاء: تدريب العمال وإشراكهم

بالنظر إلى انعدام الدراسات المُتاحة في هذا المجال، فإن الفريق المعني بوضع المبادئ التوجيهية يرى أن تدريب العمال وإشراكهم في قضايا الصحة والسلامة هما من أفضل الممارسات المُتبعة في هذا المضمار، على أنه لا يستطيع أن يوصي بتفضيل تطبيق شكل ما من أشكال تدريب العمال على سواه، ولا بتفضيل شكل معيّن لإشراكهم على غيره.

ومن المُتوقّع إحراز تقدم كبير في تطبيق الأساليب المُصدّقة للقياس وتقدير المخاطر، لذا يقترح الفريق المعني بوضع المبادئ التوجيهية تحديث هذه المبادئ التوجيهية في غضون خمس سنوات من الآن، أي في عام ٢٠٢٢.

٢. ويوصي الفريق المعني بوضع المبادئ التوجيهية بتحديث صحائف بيانات السلامة عن طريق تضمينها معلومات عن المخاطر المترتبة تحديداً على المواد المصنّعة المتناهية الصغر، أو بيان نقاط انتهاء سمّية هذه المواد التي لا تُتاح عنها اختبارات كافية (توصية قوية مشفوعة ببيّنات معتدلة الجودة).

٣. ويقترح الفريق المعني بوضع المبادئ التوجيهية فيما يخص فئة المواد المصنّعة المتناهية الصغر المكونّة من ألياف والتي يمكن استنشاقها وفئة المواد المصنّعة المتناهية الصغر المكوّنة من جسيمات حبيبية ثابتة بيولوجياً أن يُستعان بالتصنيف المُتاح لأغراض تصنيف المواد المتناهية الصغر المُندرجة ضمن نطاق الفئة نفسها تصنيفاً مؤقتاً (توصية مشروطة مشفوعة ببيّنات متدنية الجودة).

باء: تقدير مدى التعرض للمواد المصنّعة المتناهية الصغر

٤. يقترح الفريق المعني بوضع المبادئ التوجيهية تقدير مدى تعرض العمال في أماكن العمل للمواد المصنّعة المتناهية الصغر بواسطة اتباع طرق مماثلة لتلك المُتّبعة في تعيين القيم المُقترحة تحديداً لحدود التعرض المهني لتلك المواد (توصية مشروطة مشفوعة ببيّنات متدنية الجودة).

٥. ونظراً إلى عدم وجود قيم تنظيمية مُحدّدة بشأن حدود التعرض المهني في أماكن العمل للمواد المصنّعة المتناهية الصغر، فإن الفريق المعني بوضع المبادئ التوجيهية يقترح تقدير مديات تعرض يمكن أن تتجاوز ما يُقترح من قيم تُعيّن حدود التعرض المهني لتلك المواد في أماكن العمل. وترد في الملحق ١ من هذه المبادئ التوجيهية قائمة القيم المقترحة لحدود التعرض المهني للمواد المصنّعة المتناهية الصغر. وينبغي أن تؤمن قيمة حد التعرض المهني المختارة حماية تُكافئ على الأقل الحماية المُقرّرة قانوناً بشأن قيم حدود التعرض المهني المُعيّنة للمواد السائبة (توصية مشروطة مشفوعة ببيّنات متدنية الجودة).

٦. ويقترح الفريق المعني بوضع المبادئ التوجيهية في الحالات التي لا تُتاح فيها قيم مُعيّنة لحدود التعرض المهني في أماكن العمل للمواد المصنّعة المتناهية الصغر، اتباع نهج تدريجي بشأن التعرض لاستنشاق تلك المواد، بحيث يقترن أولاً، بإجراء تقدير لاحتمالات التعرض؛ وثانياً، بإجراء آخر أساسي لمديات التعرض؛ وثالثاً، بإجراء تقدير شامل لمديات التعرض، من قبيل التقديرات التي تقترحها منظمة التعاون والتنمية في الميدان الاقتصادي أو اللجنة الأوروبية لتوحيد المقاييس (توصية مشروطة مشفوعة ببيّنات متدنية الجودة). وفيما يتعلق بتعرض الجلد لتلك المواد، لم تتوفر بيّنات كافية لتقديم توصية بشأن تفضيل اتباع طريقة معيّنة في تقدير هذا التعرض على سواها من الطرق.

جيم: ضوابط مكافحة التعرض للمواد المصنّعة المتناهية الصغر

٧. يوصي الفريق المعني بوضع المبادئ التوجيهية بناءً على النهج التحوطي الذي يتّبعه، بأن تركّز ضوابط مكافحة التعرض للمواد على الوقاية من التعرض لاستنشاقها بقصد تقليل مستويات التعرض لها إلى أدنى حد ممكن (توصية قوية مشفوعة ببيّنات معتدلة الجودة).

٨. ويوصي الفريق المعني بوضع المبادئ التوجيهية بتقليل مستويات التعرض لطائفة من المواد المصنّعة المتناهية الصغر التي يُواظب على قياس مستويات التعرض لها في أماكن العمل، وخصوصاً أثناء عمليات التنظيف والصيانة وجمع المواد من الصهاريج الخاصة بالتفاعلات وتلقيم عملية الإنتاج بهذه المواد. كما يوصي الفريق المعني بوضع المبادئ التوجيهية في ظل انعدام المعلومات المتعلقة بمدى

1. INTRODUCTION

The increased production of manufactured nanomaterials (MNMs) and their use in consumer and industrial products means that workers in all countries will be at the front line of any exposure, placing them at risk of potential adverse health effects.

The term "nanomaterials" refers to materials that have at least one dimension (height, width or length) that is smaller than 100 nanometres (10^{-7} metre), which is about the size of a virus particle. This particular size dimension, which falls between single atoms and their bulk material counterparts, represents a major characteristic of MNMs.

The unique properties of MNMs may result in highly desirable behaviour, including but not limited to increased reactivity, or higher conductivity. As such, the past decade has witnessed the exploitation of these unique properties for industrial and consumer applications, and various types of MNMs have found their way into a plethora of sectors, including aerospace, cosmetics, foods, electronics, construction and medicine, among others.

Significant academic and industrial resources have been dedicated to the field of nanotechnology, increasing the scope and number of MNMs that will be available for future use. However, MNMs may also present health hazards that differ from those of the substance in bulk form, and require different test methods for hazard, exposure and risk assessment from their bulk material counterparts.

The World Health Assembly identified the assessment of health impacts of new technologies, work processes and products as one of the activities under the Global Plan of Action on Workers' Health adopted in 2007, and the WHO Global Network of Collaborating Centres in Occupational Health has selected MNMs as a key focus of its activity.

WHO developed these guidelines with the aim of protecting workers from the potential risks of MNMs. The recommendations are intended to help policy-makers and professionals in the field of occupational health and safety in making decisions about protection against the potential risks of MNMs. These guidelines are also intended to support workers and employers. However, the guidelines are not intended as a handbook or manual for safe handling of MNMs in the workplace, because this requires addressing more general occupational hygiene issues beyond the scope of these guidelines.

1.1. THE HEALTH BURDEN FROM MANUFACTURED NANOMATERIALS

At the nanoscale, MNMs may exhibit unique characteristics that distinguish their behaviour from bulk materials and may facilitate interaction with their environment. Of particular importance is their small size, which may allow for increased penetration of environmental and biological barriers. In addition, MNMs have far larger surface areas than similar masses of larger-scale materials. A larger surface area provides a larger interface for molecular and chemical interactions within the external environment, potentially promoting their reactivity.

The multiplicity of novel material designs for the same chemical composition with different physicochemical properties presents significant challenges for risk characterization, because toxicological properties may adapt to changes in their physicochemical properties such as size and shape. Nanomaterials are being used in a rapidly growing number of products and industries.

The number of workers exposed to MNMs is not known but is increasing with the industrial production and use of MNMs.

In the workplace, health hazards can result from inhalation, ingestion or skin absorption of MNMs. The human lungs represent an excellent entry portal for MNMs due to their high surface area, thin epithelial barriers and extensive vasculature; and while dermal and oral exposure may occur, inhalation is more likely to result in a larger systemic dose of MNMs. Currently, inhalation of biopersistent particles and fibres with an asbestos-like morphology is the greatest known health hazard possibly resulting in local inflammation and cancer.

Translocation of inhaled MNMs to the circulation and to secondary organs is estimated to be limited to not more than 1% of the mass-based dose. However, this figure is based on extrapolations from animal studies, resulting in a lack of precise information on biokinetics of inhaled MNMs and their long-term fate in humans. Nevertheless, while acute effects from MNMs' translocation to secondary organs are likely to be minimal, it is possible that chronically exposed populations may face greater risks from cumulative, low-dose translocation processes.

While humans have long been exposed to unintentionally produced nanoparticles, such as those from combustion processes, the recent increase in MNM production demands greater investigation into the potential toxicity and adverse health effects of these materials following exposure. Since newly developed MNMs are not tested sufficiently for possible health hazards, it is generally recommended to take a precautionary approach until testing results are available. This means that MNMs should be considered as hazardous unless there is clear proof that they are not.

The toxicity of MNMs may largely depend on numerous physicochemical properties, including size, shape (i.e. size in a particular dimension), composition, surface characteristics, charge and extent of their dissolution. There is currently a paucity of precise information about human exposure pathways for MNMs, their fate in the human body and their ability to induce unwanted biological effects such as generation of oxidative stress. Data from in vitro and animal in vivo MNM inhalation studies are available for only a few MNMs. So far, only a small number of controlled human exposure studies have assessed the fate and health effects of MNM exposure; this is due mainly to ethical concerns.

Even though there are estimates available of the tonnes (t) of nanomaterials produced annually and used worldwide, the GDG did not find convincing evidence of how these estimates can be correlated with worker exposure. The current estimates of the number of workers potentially exposed to nanomaterials in specific countries indicate that they are still a relatively small proportion of all workers (*1*).

According to one source the volume of MNMs on the market can be ranked as follows (*2*):

1. carbon black (9.6 million t)
2. synthetic amorphous silica (1.5 million t)
3. aluminium oxide (200 000 t)
4. barium titanate (15 000 t)
5. titanium dioxide (10 000 t)
6. cerium dioxide (10 000 t)
7. zinc oxide (8000 t)
8. carbon nanotubes (CNTs) and carbon nanofibres (CNFs), (100–3000 t)
9. silver nanoparticles (20 t).

The focus of these guidelines is on low- and middle-income (LMI) countries where nanotechnology is an important means of economic progress. For example, middle-income countries such as Brazil and South Africa produce MNMs and have research laboratories that produce CNTs. LMI countries produce nanosilver that is incorporated in milk packs, fabrics and clothes and MNMs are also produced for use by the pharmaceutical industry.

However, the implementation of health and safety at work regulations is usually less effective in LMI countries, which means that workers in these countries are at greater risk of the potential negative health effects than their counterparts in high-income countries. This is partly because the use of MNMs is often not known about or well understood. Despite the publication of a large number of scientific articles about nanotechnology by authors from LMI countries, only a few are about the potential toxicity of MNMs and very few report on safety or risk assessment (*3*).

1.2. SCOPE OF THE GUIDELINES AND KEY QUESTIONS

The GDG has identified the following key issues and questions where evidence should be reviewed leading to recommendations that can improve workers' health and safety.

1. **Risks of MNMs**
   Which specific MNMs and groups of MNMs are most relevant with respect to reducing risks to workers and which should these guidelines now focus on, taking into account toxicological considerations and quantities produced and used.
2. **Specific hazard classes**
   Which hazard class should be assigned to specific MNMs or groups of MNMs and how?
3. **Forms and routes of exposure**
   For the specific MNMs and groups of MNMs identified, what are the forms and routes of exposure that are of concern for worker protection?
4. **Typical exposure situations**
   What are the typical exposure situations and industrial processes of concern for relevant specific MNMs or groups of MNMs?
5. **Exposure measurement and assessment**
   How will exposure be assessed and are there alternatives to current exposure assessment techniques for MNMs that should be recommended in LMI countries?
6. **Occupational exposure limit (OEL) values**
   Which OEL or reference value should be used for specific MNMs or groups of MNMs?
7. **Control banding**
   Can control banding be useful to ensure adequate controls for safe handling of MNMs?
8. **Specific risk mitigation techniques**
   What risk mitigation techniques should be used for specific MNMs, or groups of MNMs in specific exposure situations, and what are the criteria for evaluating the effectiveness of controls?
9. **Training for workers to prevent risks from exposure**
   What training should be provided to workers who are at risk from exposure to the specific MNMs or groups of MNMs?

10. **Health surveillance to detect and prevent risks from exposure**
    What health surveillance approaches, if any, should be implemented for workers at risk from exposure to specific MNMs or groups of MNMs?
11. **Involvement of workers and their representatives**
    How will workers and their representatives participate in the workplace risk assessment and management of handling MNMs?

Initially, the GDG had decided that there would be a question about worker involvement in controlling risks of MNM exposure (see question 11). However, preliminary searches found no studies on this topic and the GDG decided it was better formulated as a best practice statement rather than pursuing a systematic review.

For all other questions, the GDG commissioned systematic reviews from teams of authors found through the WHO Global Network of Collaborating Centres.

The systematic reviews to answer question 1 on risks of MNMs and question 9 on worker training were used to inform section 5 on best practices. In occupational health and safety these describe methods or techniques accepted as being the best in protecting workers and are based on consensus among experts. They should be used when implementing the current recommendations.

The review of the literature on hazards of MNMs revealed that there is a general consensus about grouping them, but this did not lend itself very well to making an evidence-based recommendation. The review on worker training did not find specific studies that showed this would lead to a decrease in exposure or to better availability of controls. Nevertheless, the GDG was of the opinion that there are sufficient arguments that worker training is important. Given the complicated nature of the potential health effects of MNMs, worker training was considered to be necessary and regarded as best practice.

1.3. WHO GUIDELINES RELATING TO THIS TOPIC

Despite the increase in MNM production, particles at the nanoscale are not a new phenomenon to nature and biology. In the field of air pollution the presence of nanoscale particles has long been recognized, and there are air quality guidelines that also address nanoparticles even though no specific exposure limits are given for ultrafine particles (*4*,*5*). Air quality is influenced by small particles that are usually divided into particulate matter smaller than 10 micrometres (PM_{10}), smaller than 2.5 micrometres ($PM_{2.5}$) and ultrafine nanoparticles that are smaller than 100 nanometres. The ultrafine particles are naturally occurring in air and a result of combustion processes. However, these guidelines only address MNMs that are intentionally produced.

1.4. OTHER INTERNATIONAL PROGRAMMES ON MNM SAFETY

A number of international organizations are active in the area of nanomaterial safety. The most active and influential are the Organisation for Economic Co-operation and Development (OECD) and the International Organization for Standardization (ISO).

The OECD Working Party on Manufactured Nanomaterials (WPMN) has four steering groups. The first steering group on testing and assessment is in the process of publishing dossiers with data on toxicity testing and physicochemical characterization for 11 nanomaterials. It is also responsible for

updating safety testing guidelines to make them suitable for nanomaterials. The second steering group on risk assessment and regulatory programmes reviews approaches for risk assessment of nanomaterials. The third steering group on exposure measurement and mitigation focuses on developing guidance for exposure assessment and mitigation of exposure to nanomaterials in the workplace, during consumer use of nano-enabled products and for the environment. Finally, the fourth steering group is looking at environmentally sustainable use of nanomaterials. As of 31 May 2016 the OECD working party had published 58 reports in total.[2]

The ISO Technical Committee 229 (TC229) Nanotechnologies has five working groups. Of these, Working Group 3 (WG3) is tasked with developing standards related to the safety of nanomaterials and nanotechnology. As of 22 March 2017 this technical committee had published a total of 55 standards of which 18 were prepared by WG3; they deal directly with the health and safety issues of nanomaterials including specific standards on safe handling of nanomaterials in the workplace aimed at industrial hygienists.[3]

The involvement of experts from the WHO GDG in both the OECD and the ISO programme ensures that information is effectively exchanged between the various international organizations. There are also more formal mechanisms for coordination of work among these three organizations. OECD WPMN is a formal participant in ISO TC229, which allows it to review and comment on all ISO TC229 documents under development, while experts from ISO TC229 can reciprocally participate in the development of OECD WPMN documents. A similar status for the WHO GDG with ISO TC229 would further facilitate expert participation in both groups.

WHO and OECD are also members of the Inter-Organization Programme for the Sound Management of Chemicals (IOMC), which coordinates activities among international public organizations with national body memberships on chemicals in general and on nanomaterials specifically.

These links ensure that the knowledge base and expertise developed by these organizations are effectively shared, resulting in the highest quality guidelines, although goals, approaches and stakeholders may differ. For example, ISO aims to develop standards to facilitate commerce, while OECD addresses the needs of government organizations among its 35 member countries; and WHO addresses the needs of government organizations among its 194 member countries including many that are LMI. Despite these differences, recommendations produced by ISO, OECD and WHO are in general very consistent and aim to proactively minimize workers' exposure even though full information about nanomaterial risks is not yet available.

1.5. TARGET AUDIENCE

These guidelines are targeted at:

- occupational health professionals and policy-makers at the local, national or international level, who are responsible for the health and safety of workers exposed to MNMs;
- workers and their employers with premises with a potential risk of exposure to MNMs.

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[2] http://www.oecd.org/science/nanosafety/publications-series-safety-manufactured-nanomaterials.htm.

[3] http://www.iso.org/iso/home/store/catalogue_tc/catalogue_tc_browse.htm?commid=381983&published=on&includesc=true, accessed 15 May 2017.

2. PROCESS FOR GUIDELINE DEVELOPMENT

2.1. GETTING STARTED

According to established WHO procedures, the Interventions for Healthy Environments Unit in the Department of Public Health, Environmental and Social Determinants of Health, obtained planning approval in 2010 to develop guidelines and established a WHO Guideline Steering Group and a Guideline Development Group (GDG). The GDG was composed of leading experts and end-users responsible for the process of developing the evidence-based recommendations.

Members of the WHO Guideline Steering Group and the GDG are listed in **Tables A.2.1** and **A.2.2** of **Annex 2**. Funding for meetings and the costs of the methodologist were provided by the WHO Department of Public Health, Environmental and Social Determinants of Health. Experts participated in the GDG on an in-kind basis and systematic reviews were conducted by volunteer teams.

The project started with the development of a background paper on the development of guidelines for protecting workers from potential risks of exposure to MNMs by the WHO Guideline Steering Group. In 2010–2011 there were several public calls for experts to join the GDG and External Review Group and to identify volunteers to carry out systematic reviews. Once the GDG was formed it worked to identify key questions through several rounds of the Delphi process (*6*).

A first face-to-face meeting of the GDG was held in Johannesburg, South Africa, on 30 September and 1 October 2013 where GDG experts finalized the key questions to be addressed, found authors for systematic reviews of the evidence and agreed on a plan and timeline for completing the work.

Based on decisions made by the GDG, the systematic reviews were commissioned and drafts discussed at evidence review meetings held in:

- Paris, France, on 9 and 10 February 2015
- Brussels, Belgium on 4 and 5 September 2015
- Dortmund, Germany on 18 and 19 April 2016.

2.2. EVIDENCE REQUIRED TO ADDRESS SCOPING QUESTIONS

To incorporate significant research undertaken in the area of MNM health and safety, teams of researchers were identified who could carry out systematic reviews of the pertinent literature according to the process outlined in the *WHO Handbook for guideline development* (*7*). The systematic review teams are listed in **Table A.2.3** of **Annex 2**.

The first step in the evidence search and retrieval procedure was to identify and define the type of evidence required to address the scoping questions. First, the systematic review teams

reformulated the key questions posed in section 1.2 so that they could be answered by a systematic review. Then they defined the best available evidence to provide the answers. Owing to the complex nature of the issues being addressed, and the scarcity of experimental studies directly assessing the impact of interventions on occupational health and safety, several distinct areas of evidence were required for each scoping question.

2.3. SUMMARY OF EVIDENCE REVIEW PROCESS

Very few existing systematic reviews were found. This is probably because methods for this type of assessment are not very well established in the field of toxicology, occupational health or exposure assessment. Therefore, systematic reviews were commissioned for all questions with the aim of locating studies that could answer the pertinent questions.

2.3.1. The systematic review process

The systematic review process used for each question varied slightly but followed the principles set out in the *WHO Handbook for guideline development*. First, for a study to be included it must comprise the four PICO elements: population, intervention, comparator and outcome(s), which are used to assess the exposure or the intervention (*7*). The PICO approach guarantees that the systematic review process collects the evidence that is needed to answer the question at hand. The searches conducted for the systematic reviews included any observational or experimental study of persons or workplaces exposed to MNMs. For each study, the risk of bias was systematically assessed.

Systematic review conclusions were based on the findings of the included studies. The findings were summarized and provided as support for the recommendations in these guidelines. The summary of findings paragraphs included in the specific recommendations (**section 6**) contain similar information to the summary of findings tables advocated by the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach, even though we could not provide the summary in the same numerical format.

2.3.2. Assessment of overall quality of evidence

The systematic review teams determined the quality of evidence for each conclusion (*7*). The handbook recommends using the GRADE approach for making these assessments (*8*). GRADE allows the reviewer to systematically and transparently grade the quality of the body of evidence for the effectiveness of medical interventions. At the start of the rating it is assumed that the evidence is of high quality and based on randomized clinical trials. The quality of the body of evidence is then downgraded based on five specific qualifiers including risk of bias and inconsistency of results. This results in one of four quality ratings: high, moderate, low or very low quality of evidence.

However, some of the questions that were used to formulate recommendations in these guidelines were very far from clinical intervention questions, so the GRADE approach for interventions could not be applied. Therefore, a modified GRADE approach was used to assess the overall quality of evidence for the systematic reviews that were conducted to answer the non-intervention questions. The adaptation was based on the existing GRADE guidance for qualitative and prognostic studies (*9*,*10*). The guidance on prognostic studies is most applicable also to exposure studies.

The rating process ranked a study design as high quality if it was considered the best for the question at hand. The quality was downgraded if, in one or more domains, criteria for high quality were not met (**Table 1**). Numerical summaries of findings were not provided in all reviews and in those cases the systematic reviewers used GRADE guidance for qualitative studies as summarized in **Table 1**. The reviewers did not use any qualifiers for upgrading the evidence, as is possible in the GRADE approach for non-randomized intervention studies.

TABLE 1. GRADE ADAPTATION: DOMAINS AND CRITERIA TO ASSESS THE QUALITY OF THE EVIDENCE[a]

Domain	Risk of bias/ limitations	Consistency/ coherence	Directness/ relevance	Precision/ adequacy of data	Publication bias
Criteria for high quality	Majority/most important contributing studies do not have methodological limitations.	Majority of the studies have similar findings in size and direction. No contradictory findings that cannot be explained.	Studies address PICO precisely; are performed in the field and representative of the population/ material concerned.	Numerical data provide estimates of precision. If no numerical data, at least two, adequately sized studies available to support a conclusion.	Arguments for or against publication bias provided.

GRADE: Grading of Recommendations, Assessment, Development and Evaluations; PICO: population, intervention, comparator, outcome(s).

[a] Based on the GRADE approach for qualitative and prognostic studies; domains and criteria.

Based on these criteria, each systematic review's conclusion was rated for the quality of the evidence. We interpreted the quality levels as proposed by the GRADE working group as follows:

- High quality – further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality – further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality – further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality – any estimate of effect is uncertain.

2.4. FROM EVIDENCE TO RECOMMENDATIONS

2.4.1. General process

After the systematic reviews had been conducted, the GDG developed recommendations based on the conclusions. To formulate recommendations and to determine the strength of the recommendations, the GDG used the balance between harms and benefits, values and preferences, monetary costs and the quality of evidence. For most of the recommendations, no

numerical values for benefits and harms were available. Therefore, the GDG balanced benefits and harms in a global, qualitative way. Similarly, the costs of an intervention, or the implementation costs of a recommendation, were considered and based on the expert opinion of the GDG members. No formal cost-benefit or cost-effectiveness analyses have been performed.

With each recommendation in these guidelines there is an explanation of how the GDG reached the recommendation based on the evidence. All recommendations were proposed, discussed and based on consensus within the GDG, which was reached through face-to-face meetings. Disagreements were reconciled through adjustments in the recommendations and all GDG members agreed with the final versions.

The strength of the recommendation ranked as either:

- Strong: the GDG agrees that the quality of the evidence combined with certainty about the values, preferences, benefits and feasibility of this recommendation means it should be carried out in most circumstances; or
- Conditional: there was less certainty about the combined quality of the evidence and values, preferences, benefits and feasibility of this recommendation meaning there may be circumstances or settings in which it will not apply.

2.4.2. Workers' values and preferences

Even though the economic benefits of nanotechnology are fully appreciated by all stakeholders, concerns about health and safety risks are especially articulated by workers and their organizations across the globe. The GDG considered the values and preferences of this sector based on the opinion of the groups' members and also conducted a general search for the opinions of key organizations with the following findings.

A few years ago the IUF (International Union of Food, Agricultural, Hotel, Restaurant, Catering, Tobacco and Allied Workers' Associations) called on companies to: adopt a detailed public policy explaining their use of nanomaterials, if any; publish a safety analysis for any nanomaterials being used; issue supplier standards; label all products that contain nanoparticles smaller than 500 nm; and adopt a hierarchy of hazard controls approach to prevent employees' exposure to nanomaterials (*11*). Similar concerns were also expressed by the ITUC (International Trade Union Confederation), an organization that unites hundreds of trade unions worldwide.

In Europe, the European Trade Union Confederation (ETUC) has expressed its concern about health and safety issues surrounding MNMs. The ETUC emphasizes that to achieve sustainable growth, the innovation resulting from nanotechnologies should include social equity, environmental protection and economic efficiency, while ensuring full health and safety protection and protection of the environment. The ETUC has criticized the failure to fund research on health and safety, ethical, social and environmental issues at the same levels as research and development work on nanotechnologies (*12*).

In Canada, the Canadian Union of Public Employees recommends following a precautionary approach that prevents workers' exposure until sufficient data can show there are no harmful effects on human health or the environment (*13*). The Australian Council of Trade Unions has expressed similar concerns (*14*).

3. INDIVIDUALS AND PARTNERS INVOLVED IN GUIDELINE DEVELOPMENT

3.1. WHO GUIDELINE STEERING GROUP

Members of the WHO Guideline Steering Group are listed in **Table A.2.1**, **Annex 2**. They include WHO staff members who are involved in work relevant to the topic of MNM and associated health outcomes. The Guideline Steering Group was involved at all stages of planning, selecting members of the GDG and external review group, review of the evidence and developing potential recommendations at the main expert meetings as well as ongoing consultation on revisions following peer review.

3.2. GUIDELINE DEVELOPMENT GROUP (GDG)

The GDG consists of content experts gathered to investigate all aspects of evidence contributing to the recommendations. This group defined the key questions and priorities of the research, chose outcomes and provided advice on any modifications of the scope as established by the WHO Steering Group. The GDG interpreted the evidence, with explicit consideration of the overall balance of benefits and harms, and ultimately formulated the final recommendations, taking into account diverse values and preferences. The group also determined the strength of the recommendations and responded to external reviews. The complete list of GDG members, their affiliations and geographical locations, can be found in **Table A.2.2** of **Annex 2**.

3.3. SYSTEMATIC REVIEW TEAMS

Systematic reviews were commissioned by WHO staff using external contractors. WHO issued public calls for volunteers to carry out reviews including via the WHO Global Network of Collaborating Centres for occupational health. In addition, the GDG recommended several authors to conduct the systematic reviews based on their knowledge of the field. **Table A.2.3** in **Annex 2** lists the systematic review team authors.

3.4. EXTERNAL REVIEW GROUP

The external review group is composed of technical experts, end-users and stakeholders with a geographical and gender balance. Technical content experts and end-users were selected for their expertise in the subject at hand. The group also includes representatives from professional groups and industry that will be implementing the guidelines. Members were asked to review the material at the end of the development process and they provided extensive comments that

were used to further improve the recommendations and the wording of the text. The list of group members and their affiliations is provided in **Table A.2.4**, **Annex 2**.

3.5. MANAGEMENT OF CONFLICTS OF INTEREST

All members of the GDG and systematic review authors completed WHO declaration of interest forms that were accompanied by **Annex B** (code of conduct for WHO experts) and Annex C (confidentiality undertaking). These were reviewed by the WHO Focal Point and the Ethics, Risk and Compliance office for potential conflicts of interest. Based on their statements there were two requests for further information until finally all of the GDG members and the authors of the systematic review teams were accepted by WHO in their respective roles.

In addition, at the start of each meeting, all members received a briefing about the nature of all types of conflict of interest (i.e. financial, academic/intellectual and non-academic) and were asked to declare to the meeting any conflicts they may have. No member of the GDG or the systematic review team was excluded from his or her respective role.

For transparency purposes only, also the External Review Group members provided declaration of interest forms, as well as confidentiality statements.

4. FORMULATING THE RECOMMENDATIONS

4.1. FOCUS OF THE RECOMMENDATIONS

The specific recommendations 1 to 3 aim to define specific nanomaterials and their health hazards and recommendations 4, 5 and 6 focus on assessing exposures that impact on workers' health and safety. In addition, recommendations 7 to 11 focus on interventions that are generally used to protect workers' health. Finally, the GDG reached conclusions regarding health surveillance for workers and worker training and involvement. These recommendations are listed in sections 6.4 and 6.5.

4.2. GUIDING PRINCIPLES

4.2.1. Precautionary approach

The GDG decided early on that in cases where a health concern is identified but scientific data do not permit an evaluation of the magnitude of the risk based on data from studies in humans, recourse to precaution should be used to reduce or prevent exposure as far as possible. This was seen as an important underlying approach in the interest of protecting workers' health, especially given previous experience with asbestos. Several definitions of a precautionary approach exist. All include a component that urges acting despite uncertainty when there are reasonable indications to do so (*15*).

For MNMs, potentially adverse effects have been identified for a number of materials. New MNMs are constantly being developed but the ability to predict their hazardous properties is still limited (*16*). Therefore, as a precautionary approach, the GDG considered that in the absence of toxicological information, workers should not be exposed. This means that in these cases the strictest control measures to prevent workers' exposure should be in place. Only when toxicological information is available can there be a more tailored control strategy. Along similar lines, the control-banding strategy elaborated in these guidelines is based on the same principles.

4.2.2. Hierarchy of controls

The hierarchy of controls is a concept of risk management that is generally accepted in occupational health and safety. It stipulates that the implementation of controls to reduce workers' exposure should be considered the goal of a successful industrial hygiene programme. The hierarchy of controls is an approach to risk reduction or elimination of hazard or exposure (*17*). The first step should be to try and eliminate the hazard. If that is not possible, the hazardous material should be substituted by a less harmful agent. Then, engineering controls should be applied such as isolation, local exhaust ventilation or dust suppression techniques. If all these are not feasible, then administrative controls should be considered such as worker education, and

training or scheduling. As a last resort, personal protective equipment (PPE) can be used, but reducing the exposure at source provides better protection for workers and better cost-benefit for employers.

Often, there will be a combination of control measures to minimize the risk. For instance, it might be possible to eliminate or reduce the hazardous properties of nanomaterials without altering their beneficial properties. However, in the case of MNMs, substitution is a control measure that will be difficult to realize, because it is all about the very use of the MNMs. Some have argued that substitution is too limited and should be replaced by process change to reduce worker exposure (*18*). Changing the process in such a way that no MNMs will be released into the air should therefore always be one of the first control measures to consider.

5. BEST PRACTICE

The GDG considers it best practice to class MNMs into the following three groups: those with specific toxicity, those that are respirable fibres and those that are granular biopersistent particles.

5.1. CLASSIFICATION OF MNMS

The specific toxicity group consists of (i) MNMs with high dissolution rates through the release of ions or amenable to biodegradation and, (ii) MNMs with low dissolution rates but with high specific toxicity. The latter are MNMs with specific toxicity, which is mediated by the specific chemical properties of their components (*19*).

The respirable fibres group consists of MNMs that are rigid, biopersistent or biodurable and respirable, which have dimensions agreed upon by a WHO working group for man-made mineral fibres in the past. These dimensions are a fibre length (FL)>5 µm, fibre diameter (FD)<3 µm and an aspect ratio (FL/FD)>3 (*20*). Although this group of fibres is characterized as being rigid, it should be kept in mind that there is no consensus on specific criteria for rigidity even though some have proposed crystallinity as a measure of rigidity for MNMs (*21*).

The granular biopersistent particles (GBP) group consists of respirable granular biodurable particles that are characterized by both low dissolution rates and lack of high specific toxicity. GBP are respirable granular and biopersistent but not fibrous (as defined above) and these particles are also known as poorly soluble particles or poorly soluble, low-toxicity particles (*19*).

Forming groups of MNMs with similar properties is important in the absence of information on the hazards of many new materials. This enables the transfer of hazard information, also called bridging or read across, from one material to another. Because there is no general accepted approach on how to do this, the GDG commissioned a systematic review of possibilities to group MNMs based on toxicological considerations. The systematic review was undertaken by Zienolddiny & Skaug (2017) (*22*). The systematic review team located 22 reviews of grouping MNMs, or approaches to transfer hazard information from one MNM to another. To be included in the overview the authors of the reviews had to have considered which mechanisms of action could lead to toxicity of nanomaterials. The systematic review team authors concluded that there is evidence that there are three main mechanisms of toxicity of nanomaterials: specific toxicity of the material, inhalation and biopersistence in the lungs, and one mediated specifically by the fibre structure. For other potentially hazardous properties, such as genotoxicity, there was no consistency in the included reviews that this is inherent to the nanoscale size of the MNMs.

Given that the grouping of MNMs is based on expert opinion, the GDG considered that changes are likely when more research becomes available.

5.2. WORKER INVOLVEMENT

The GDG considers it best practice that workers should be involved in health and safety issues and that this will lead to more optimal control of health and safety risks.

In most countries, worker involvement in health and safety issues is mandatory. Article 19 of the International Labour Organization (ILO)'s C155 Occupational Safety and Health Convention, 1981, stipulates that representatives of workers in the undertaking cooperate with the employer in the field of occupational safety and health. In many other ILO conventions and European Union (EU) directives, the term "worker participation" is frequently used.

5.3. ADDITIONAL TRAINING AND EDUCATION OF WORKERS

The GDG considers it best practice that workers potentially exposed to MNMs should be educated on the risks of MNMs and trained in how they can best protect themselves.

MNMs have risk aspects that are specific to being a nanomaterial and that are not self-evident. For proper control measures to be well implemented, workers need information about these risks. Safety data sheets (SDS) do not always provide reliable information on MNMs and users should be aware of this. In addition, MNMs require specific control measures that can be different from those for the bulk material. This is also recognized by the EU, which has provided specific guidance for workers (*23*).

There are good training materials available, for instance from the National Institute of Environmental Health Sciences in the United States of America (USA) and from the Health and Safety Executive in the United Kingdom of Great Britain and Northern Ireland, which can easily be adapted to local circumstances (*24*,*25*).

Education and training should focus on those aspects of MNMs that are dealt with in these guidelines and that are additional to, or different from, education and training in the safe handling of bulk material chemicals. Topics should include which hazards are specific to MNMs and different from the bulk material; which hazard classes are assigned to MNMs; which routes of exposure are important; which workplace exposures have been measured and which tasks put workers most at risk; how proposed OELs can be interpreted; when and how control banding, specific controls and PPE for MNMs can be used.

ILO Convention 155 concerning Occupational Safety and Health and the Working Environment also states that there should be a national policy to provide information and education and implement training for workers, including necessary further training, qualification and motivation of persons involved, in one capacity or another, in the achievement of adequate levels of safety and health. This also holds for workers exposed to MNMs.

6. SPECIFIC RECOMMENDATIONS

6.1. ASSESS HEALTH HAZARDS OF MNMS

Recommendation 1: The GDG recommends assigning hazard classes to all MNMs according to the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals for use in safety data sheets. For a limited number of MNMs this information is made available in these guidelines (**Table 2**) (**STRONG, moderate quality evidence**).

Recommendation 2: The GDG recommends updating safety data sheets with MNM-specific hazard information, or indicating which toxicological end-points did not have adequate testing available (**STRONG, moderate-quality evidence**).

Recommendation 3: For the respirable fibres and granular biopersistent particles' groups, the GDG suggests using the available classification of MNMs given in **Table 2** for provisional classification of nanomaterials of the same group (**CONDITIONAL, low-quality evidence**).

A list of selected nanomaterials and their up-to-date hazard classes, according to the GHS and as assigned by the systematic review team, is available in Table 2. The most common hazard classes assigned to MNMs are:

- specific target organ toxicity after repeated exposure
- carcinogenicity
- germ cell mutagenicity
- serious eye damage
- respiratory or skin sensitization.

From evidence to recommendation

Evidence

The animal and genotoxicity studies, as collected and reviewed by the OECD and reported in the specific nanomaterial dossiers, formed the evidence for the assignment of hazard classes to the various MNMs. In addition to the OECD data, the evidence for carcinogenic properties was based on assessment of a limited number of MNMs by the International Agency for Research on Cancer (IARC). Based on an assessment of study limitations, the quality of the evidence was rated as moderate to high for the various MNMs.

Recommendation 3 to bridge the hazard classes from specific materials within a group to other materials within that same group, is based on low-quality evidence that the respirable fibres or GBP materials have similar toxicological properties (see Best practice, Classification of MNMs, section 5.1).

Benefits and harms

The benefits of having MNMs properly classified and labelled according to their hazards, in terms of focus on risk and control measures, clearly outweigh the possible harm that the classification might be overly cautious given the lack of information about the hazards of MNMs in general. In some cases, the classification system could also result in underestimation of the hazard.

Values and preferences

The hazard classification forms the basis for labelling products according to their hazards. In many countries, this is legally binding. This information is also included in the SDS informing workers and employers about the safety and hazards of the products they use. Even though the GHS might not be optimal for MNMs, and is being continually developed, it is a systematic approach that is generally recognized globally.

Grouping MNMs with similar properties is important, especially in the absence of information on the hazards of many new materials.

Net benefits worth the costs

Assigning hazard classes to MNMs is not a very costly procedure if data from studies are available.

Strength of the recommendation

Based on the above considerations, the GDG makes a strong recommendation for the assignment of hazard classes to MNMs. For bridging from specific materials within the same group, the recommendation is conditional.

Summary of findings: MNMs and hazard class assignment

Systematic review question: Which hazard classes can be assigned to specific MNMs according to the UN GHS and making use of MNM-specific dossiers as developed by the OECD? The MNM dossiers compiled by the OECD give an overview of the available toxicological data for a number of specific MNMs.

Evidence summary

The systematic review was undertaken by Lee et al. (2017) (26) and was published by WHO.

Number of studies and participants

There were 11 OECD dossiers containing toxicity testing information. These were used by the systematic review team to assign one or more hazard classes, according to the GHS, to the following nanomaterials: fullerene, single-walled carbon nanotubes (SWCNT) and multi-walled carbon nanotubes (MWCNT), silver, gold, silicon dioxide, titanium dioxide, cerium dioxide, dendrimer, nanoclay and zinc oxide in nanoparticle form. For the assessment of carcinogenicity, the review team also used the evidence summaries compiled by IARC on SWCNTs, MWCNTs and titanium dioxide.

Data in the dossiers

Dossiers mostly contained results of in vivo animal studies and in vitro genotoxicity studies supplied by member countries and nongovernmental organizations such as the Business and Industry Advisory Committee to the OECD.

Risk of bias in the included dossiers

The main limitations to the studies included in the dossiers were that they did not fulfil the OECD criteria for good methodological quality, such as being published in a peer-reviewed journal and complying with good laboratory practice (GLP). For some studies, the GLP test data were not fully disclosed because of the company's intellectual property rights. Studies were classified at low risk of bias if they were in the OECD category 1 or 2, complied with GLP, were based on test guidelines and resulted in a peer-reviewed publication; at medium risk of bias if the above applied but there was no compliance with GLP; and at high risk of bias if none of the above applied.

Classification of MNMs

The MNMs were classified as having a specific hazard according to the GHS, having no hazard according to the available studies, or as having no data when these were not available for classification. "No hazard" does not necessarily imply that there is no hazard but only that this was not found in the studies used in the OECD dossiers.

For fullerene, there was evidence that there is no hazard for acute toxicity, skin-, eye- or respiratory damage, germ cell mutagenicity or specific target organ toxicity after repeated exposure but, for the other hazard classes, data were missing.

For SWCNT, there was evidence of a hazard for germ cell mutagenicity (Cat 2) and specific organ toxicity after repeated exposure (Cat 1). For reproductive toxicity no clear hazard could be established based on the available data. There was also evidence of no hazard in acute toxicity, skin damage, respiratory/skin sensitization, or reproductive toxicity. For specific target toxicity after single exposure, there were no data. For carcinogenicity there were no data but there is an IARC classification 3, meaning not classifiable.

For MWCNT, there was evidence of a hazard for eye damage (Cat 2), germ cell mutagenicity (Cat 2), carcinogenicity (Cat 2, IARC 2B/3) and specific organ toxicity after repeated exposure (Cat 1). There was also evidence of no hazard in acute toxicity, skin damage, respiratory/skin sensitization, or reproductive toxicity. For specific target toxicity after single exposure, there were no data.

For silver nanoparticles, there was evidence of a hazard for respiratory/skin sensitization (Cat 1B) and specific target organ toxicity after repeated exposure (Cat 1 2). For acute toxicity, skin corrosion, eye damage, germ cell mutagenicity and reproductive toxicity there was evidence of no hazard. For carcinogenicity and specific target organ toxicity after single exposure, there were no data.

For gold nanoparticles, there was evidence for specific target organ toxicity after repeated exposure (Cat 1). There were no data for the other classes.

For silicon dioxide, there was evidence for specific target organ toxicity after repeated exposure (Cat 2), but no hazard for acute toxicity, skin or eye damage, respiratory or skin sensitization, germ cell mutagenicity and reproductive toxicity. For carcinogenicity and specific organ toxicity after single exposure, there were no data.

For titanium dioxide, there was evidence for possible carcinogenicity ((IARC Cat 2B), reproductive toxicity (Cat 1), and specific organ toxicity after repeated exposure (Cat 1), but also evidence of no hazard for acute toxicity, skin or eye damage, respiratory or skin sensitization or germ cell mutagenicity. There were no data for specific organ toxicity after single exposure.

For cerium dioxide, there was evidence of specific target organ toxicity after repeated exposure (Cat 1), but also evidence of no hazard for acute toxicity. There were no data for the other hazard classes.

For dendrimer and nanoclay, there were no animal toxicity or genotoxicity data to use for classification.

For zinc oxide, there was evidence for specific organ toxicity after repeated exposure (Cat 1) but also evidence of no hazard for acute toxicity, skin or eye damage, germ cell mutagenicity and reproductive toxicity. There were no data for respiratory/skin sensitization, carcinogenicity and specific organ toxicity after single exposure.

For physical hazards, there was evidence that silicon dioxide and titanium dioxide were not flammable or explosive. There was no evidence for the other MNMs.

Quality of the evidence

The evidence was rated as high quality if there was at least one study at low risk of bias; as moderate quality if there was at least one moderate-quality study; and as low quality if there were only studies at high risk of bias. The quality of the evidence for all but one of the classifications of hazards was in the moderate or high category (**Table 2**).

Implementation guidance, research recommendation

Implications for research

There is high to moderate-quality evidence for 11 specific MNMs to be classified according to the GHS. This exercise should also be undertaken for other MNMs not mentioned here. Where data are available, they should be used for the development of SDS.

TABLE 2. CLASSIFICATION OF HAZARDOUS PROPERTIES OF NANOMATERIALS (MNMS) THAT HAVE AN EXISTING OECD DOSSIER

MNM	Acute toxicity	Skin corrosion/ irritation	Serious eye damage/eye irritation	Respiratory or skin sensitization	Germ cell mutagenicity	Carcinogenicity	Reproductive toxicity	Specific target organ toxicity (single exposure)	Specific target organ toxicity (repeated exposure)
Fullerene (C_{60})	No[a]	No	No	No	No	No data[b]	No data	No data	No
SWCNT	No	No	No	No	**Cat 2B[c] (L)[d]**	No data **IARC[e] 3**	No data	No data	**Cat 1 (L)**
MWCNT	No	No	**Cat 2A (H)[g]**	No	**Cat 2 (H)**	**MWCNT–7: Cat 2 (M)[f], IARC 2B Other MWCNTs: IARC 3**	No	No data	**Cat 1 (M)**
AgNP	No	No	No	**Cat 1B (M)**	No	No data	No	No data	**Cat 1 inhalation (H) Cat 2 oral (H)**
AuNP	No data	No data	No data	No data	No data	No data	No data	No data	**Cat 1 inhalation (H)**
SiO_2	No	No	No	No	No	No data	No	No data	**Cat 2 inhalation (H)**
TiO_2	No	No	No	No	No	No data; **IARC 2B**	**Cat 2 (L)**	No data	**Cat 1 inhalation (H)**
CeO_2	No	No data	No data	No data	No data	No data	No data	No data	**Cat 1 inhalation (M)**
Dendrimer	No data	No data	No data	No data	No data	No data	No data	No data	No data
Nanoclay	No data	No data	No data	No data	No data	No data	No data	No data	No data
ZnO	No	No	No	No data	No	No data	No	No data	**Cat 1 inhalation (M)**

AgNP: silver nanoparticles; AuNP: gold nanoparticles; CeO_2: cerium dioxide; MWCNT: multi-walled carbon nanotubes; SiO_2: silicon dioxide; SWCNT: single-walled carbon nanotubes; TiO_2: titanium dioxide; ZnO: zinc oxide.

[a] No: no hazard class assigned based on data.

[b] No data: no studies available in OECD dossier.

[c] GHS categories: Cat 1 usually implies serious and/or irreversible damage; Cat 2 milder or reversible damage. Within a category A implies more serious and B milder damage.

[d] L: low level of evidence.

[e] IARC refers to the International Agency for Research on Cancer categories of confidence in carcinogenicity: IARC Cat 2B = possibly carcinogenic; IARC Cat 3 = not enough evidence to draw conclusion.

[f] M: moderate level of evidence.

[g] H: high level of evidence.

6.2. ASSESS EXPOSURE TO MNMS

Recommendation 4: The GDG suggests assessing workers' exposure in workplaces with methods similar to those used for the proposed specific OEL value of the MNM (**CONDITIONAL, low-quality evidence**).

Recommendation 5: Because there are no specific regulatory OEL values for MNMs in workplaces, the GDG suggests assessing if workplace exposure exceeds a proposed OEL value for the MNM. A list of proposed OEL values is provided in Annex 1 of these guidelines. The chosen OEL should be at least as protective as a legally mandated OEL for the bulk form of the material (**CONDITIONAL, low-quality evidence**).

Recommendation 6: If specific OELs for MNMs are not available in workplaces, the GDG suggests a stepwise approach for inhalation exposure with, first an assessment of the potential for exposure; second, conducting a basic exposure assessment and third, conducting a comprehensive exposure assessment such as proposed by OECD or CEN (**CONDITIONAL, moderate-quality evidence**). For dermal exposure assessment, there was insufficient evidence to recommend one method of dermal exposure assessment over another.

Knowledge about exposure and subsequent risk assessment forms the basis for measures to control exposure. However, without an exposure level that can serve as a benchmark or guideline level that indicates a risk for adverse health effects, it will be difficult to make decisions about control measures.

There are several alternative ways to measure MNM exposure such as the number concentration or the mass concentration of an MNM, where it is unclear which method is best for assessing health risks. Therefore, the GDG recommends using the same method as has been used for proposed OEL values. This determines the measurement method and at the same time enables a comparison with a benchmark level that probably indicates a safe exposure level.

Only when no proposed OEL is available for an MNM does the GDG recommend using a more generic exposure assessment that consists of a tiered approach. In the first tier, a qualitative assessment is made of possible absence or presence of exposure. In the second tier, called a basic measurement, a quantitative assessment is made of the exposure concentration. In the third tier, called a comprehensive measurement, the size distribution, morphology and chemical composition of particles is characterized.

The recommendations are based on the evidence compiled in two systematic reviews on the quality of exposure assessments in studies and on OELs proposed for various MNMs.

A comprehensive and up-to-date list of proposed OEL values for MNMs is available in **Annex 1**, **Table A.1.1**. The values proposed come from a wide range of institutions and countries. Some authors propose one value for all MNMs (general approach), others propose one value for a

group of MNMs (categorical approach), but most propose a value for one specific MNM (specific approach).

The user should be aware that these OELs do not imply a safe level below which adverse health effects do not occur, because they are all based on extrapolation from animal research, or other fields such as air pollution, since there are only very limited data available on long-term human-health effects. Users should make their own choice of the best applicable OEL value. This is similar to the selection of OELs for bulk materials, where a range of values may be available and the user has to make a choice.

Deveau et al. provide a practical framework for how to find the best applicable OEL for a particular problem from a list of varying OELs for one chemical. This approach can also be used for the list of OELs for MNMs (*27*).

The exposure assessment and measurement strategy as proposed by OECD and the Comité Européen de Normalisation (European Committee for Standardization: CEN) distinguishes the following three levels of assessment that can be used as stand-alone modules or embedded in a harmonized tiered approach (*28*).

- The initial assessment provides information on the likelihood of MNMs being released during an activity or process, and usually does not comprise any measurements.
- The basic assessment, using hand-held or personal devices or samplers, measures exposure as particle number concentration(s) or as respirable mass, or both, in the breathing zone or the workstation air and in the background air. These measurements are supported by laboratory analysis of the samples to characterize the MNM(s) either by chemical composition or morphology.
- In addition to the basic assessment, the comprehensive assessment provides a characterization of the aerosols in the breathing zone that enables, for example, estimation of the dose of MNMs that is deposited in the gas-exchange region of the lung.

From evidence to recommendation

Evidence

The evidence for these recommendations is based first on a systematic review of all available proposed OELs (*29*). Since there is no consensus on a valid way of deriving OELs for MNMs, the GDG could not take the quality of the evidence into account and therefore has only formulated conditional recommendations.

Second, the recommendation is informed by a systematic review of exposure measurement methods that shows there is moderate-quality evidence that basic and comprehensive inhalation exposure assessment methods are feasible in practice (*30*). There was only very low-quality evidence about feasibility of measurements for dermal exposure assessment.

Benefits and harms

The benefits of OELs are that they can constitute a benchmark against which local measurements can be compared. The drawback is that many associate the OEL with a safe level below which no adverse health effects will occur. Since both measurements and adverse health effects are uncertain, the OELs can give a false sense of security. However, balancing the two, the GDG decided that the benefits outweigh the harms.

Comprehensive assessment can be time consuming and requires expert knowledge and instrumentation. Many countries would struggle to carry out comprehensive exposure assessments and few companies would be able to pay for such assessments, especially small and medium-sized enterprises (SMEs). Therefore, the GDG recommended the tiered approach.

Values and preferences

The OEL is a familiar concept to stakeholders and widely used for assessing bulk materials. The same holds for the exposure assessment approach, which is used in general for chemicals.

Net benefits and costs

The costs of derivation of an OEL depend on the method, but it is not necessarily expensive. The GDG considers the measurement of MNMs and comparison with OELs to be an important strategy and its costs to be a useful investment in prevention.

The costs for the measurement instruments are considerable – at least several thousand dollars for hand-held particle measurement devices. However, in many countries it is possible to rent the equipment for short periods. The benefit of measuring is that it enables comparison with an OEL and evaluation by means of a before–after comparison to determine whether measures to control exposure are successful.

Strength of the recommendation

Given the difficulty of establishing the quality of the OELs, the recommendation for using them is conditional. Given the complexities and the costs of measurements, the GDG makes a conditional recommendation for the assessment of exposure.

Summary of findings: systematic review of proposed OELs

Systematic review question: Which specific OEL values that should protect workers are proposed for workers or workplaces with potential exposure to an MNM or a group of MNMs based on studies that proposed a value underpinned with empirical research or arguments.

Evidence summary

The systematic review by Mihalache et al. (2017) was published as a journal article (*29*).

Number of studies and participants

Twenty studies from a wide range of countries and institutes that proposed 56 OEL values were included in the systematic review. Of these, two proposed one value for all MNMs, 14 proposed one value for a group of MNMs and 40 proposed a value for a specific MNM.

OELs in studies

All studies that considered inhalation exposure proposed OELs for chronic exposure. One study proposed OELs for dermal and oral exposure for CNTs and fullerenes and two studies derived OELs for acute/peak exposure.

In 15 of the studies the exposure values were derived by extrapolation from animal studies. Two studies derived the OEL from the background level or from an environmental exposure limit. Six studies used a bridging approach to derive an OEL for a group of MNMs, arguing that the risks

will similarly apply to members of the whole group (fibres, GBPs, MNMs with specific toxic bulk material with an OEL, soluble MNMs and non-biopersistent MNMs).

Two studies proposed limits for all MNMs. Six studies proposed OELs for a group of MNMs. The rest proposed OELs for specific MNMs: seven for titanium dioxide (TiO2) nanoparticles, six for CNTs, three for fullerenes, three for silver nanoparticles and one study each for silicon dioxide nanoparticles, low-toxicity dust consisting of GBP, nanocellulose fibres and nanoclays.

Risk of bias in the included studies

One of the study limitations was that the authors did not always give sufficient information about the specific MNM or group of MNMs and the way the OELs were derived. Also, it was unclear if the proposed OELs, especially the number-based OELs for primary nanoscale particles, can be matched with measurements at the workplace where mostly micro-sized agglomerates of MNMs are assessed.

Proposed OELs that are publicly available

Four studies proposed the asbestos OEL of 0.01 fibres/cm^3 for nanofibres.

Four studies proposed values for GBP, of which two studies each had two proposals. One study proposed 500 µg/m3 and 1250 µg/m^3 for the respirable fractions dependent on whether particles exhibited specific toxicity or not. In the other study, the proposals for metal and metal oxide nanoparticles are 20 000 particles/cm^3 and 40 000 particles/cm^3 dependent on particle density.

One study proposed the same OEL for non-biopersistent material as for their bulk material.

For carbonaceous material, proposed OELs ranged from 0.67 µg/m^3 for MWCNT to 390 µg/m^3 for fullerenes.

For nanosilver there are six proposals varying from 0.098 µg/m^3 up to 50 µg/m^3.

There are 10 proposals for TiO_2 nanoparticles from the lowest, 17 µg/m^3, to the highest, 2000 µg/m^3.

Some variations in reported OELs for nanomaterials that are chemically the same are due to different models used to derive OELs and some are due to different physicochemical properties including specific toxicity of nanomaterials.

Quality of the evidence

The GDG did not consider the limitations in the studies because there is no generally accepted way of deriving OELs. There were multiple studies with consistent proposals for fibres only. For all other MNMs there was considerable variation. Therefore, the GDG considered the quality of the evidence as low.

Implementation guidance, research recommendation

Implications for practice

Workplace exposure studies indicate that in most situations, exposure exceeds the majority of the proposed OELs. This should be a strong incentive for exposure control measures.

Implications for research

More studies are needed to derive OELs for specific MNMs. Harmonization of OELs requires agreement about interspecies and intraspecies' adjustment factors and exposure values.

Summary of findings: systematic review on exposure assessment and measurement

Systematic review question: In workers potentially exposed to MNMs or workplaces with exposure to MNMs, which exposure measurement techniques to assess MNMs are feasible based on studies that assessed and measured exposure?

Evidence summary

The systematic review was published by Boccuni et al. (2017) as a journal article (30).

Number of studies and participants

The systematic review included papers on exposure through inhalation and dermal absorption. There were no papers identified on exposure through ingestion. The systematic review identified 59 articles that described 53 measurement techniques. Among these, four papers analysed both inhalation and dermal exposure. Three studies of dermal exposure were conducted in the workplace and one in the laboratory setting. These papers reported very poor data on specific techniques for dermal exposure measurements. Therefore, systematic review conclusions were focused on measurements of exposures through inhalation.

Measurements in studies

There were 53 descriptions of a basic measurement technique and of these there were 13 additional descriptions of a comprehensive technique to assess the presence or absence of MNMs in workplace air. All 53 techniques measured exposure by inhalation; of these, four studies also considered exposure by dermal absorption.

Outcomes in studies

The studies used either a basic assessment technique or a comprehensive technique.

Risk of bias in the included studies

The basic exposure assessment was rated as moderate quality in 40 studies and as high quality in two studies.

The comprehensive exposure measurement was rated as moderate quality in 11 studies and as high quality in two studies.

Exposure measurements carried out

A basic exposure measurement that assesses the presence or absence of MNMs in the workplace air was demonstrated in 53 studies.

A comprehensive exposure measurement was demonstrated in 13 studies.

Comprehensive measurement techniques are more expensive than basic measurement techniques.

Quality of the evidence

The quality of the evidence is moderate for both basic and comprehensive assessments because the majority of the studies demonstrate at least a moderate-quality exposure assessment. There was very low quality and inconsistent evidence on specific techniques of dermal exposure measurement.

Implementation guidance, research recommendation

Implications for practice

The GDG concludes that there is moderate-quality evidence that both basic and comprehensive measurement techniques are feasible in the workplace.

Implications for research

Studies to validate basic and comprehensive measurement techniques including techniques to assess dermal exposure are needed.

6.3. CONTROL EXPOSURE TO MNMS

6.3.1. Focus on prevention of inhalation of MNMs

Recommendation 7: Based on a precautionary approach, the GDG recommends focusing control of exposure on preventing inhalation exposure with the aim of reducing it as much as possible (**STRONG, moderate-quality evidence**).

Recommendation 8: The GDG recommends reduction of exposures to a range of MNMs that have been consistently measured in workplaces especially during cleaning and maintenance, collecting material from reaction vessels and feeding MNMs into the production process. In the absence of toxicological information, the GDG recommends implementing the highest level of controls to prevent any exposure of workers. When more information is available, the GDG recommends taking a more tailored approach (**STRONG, moderate-quality evidence**).

Sometimes, specific types of MNMs are processed in a specific way, such as in an open or closed system during synthesis, and thus this determines the likelihood of exposure. The GDG recommends that under these circumstances, the distinctive processes related to the type of MNM are taken into account in the evaluation of workers' likelihood of exposure and the routes of exposure.

The GDG further notes that there is a need to perform high-quality evaluations of worker exposures to nanomaterials in LMI countries.

From evidence to recommendation

Evidence

The evidence for these recommendations is based on two systematic reviews of studies that measured exposure to specific MNMs in the work environment. One review assessed what the most likely routes of exposure were and during which tasks these exposures occurred. This review was published by Basinas et al. (2017) (*31*). The other review assessed the levels of exposure to MNMs, how well the exposures were measured and during which tasks the exposures occurred. This review by Debia et al. (2016) was published as a journal article (*32*). The studies on inhalation

were considered of high quality, but those on dermal and ingestion exposure contained assumptions that reduced the quality of the evidence. The studies on workplace exposure measurements mostly used well elaborated exposure assessment strategies and were rated as high-quality studies.

Benefits and harms

To be able to implement an effective control strategy, it is important to know if there is exposure to MNMs and what the most important route of uptake is. The recommendation aims at preventing potential harmful effects of MNMs through a focused control strategy.

Values and preferences

The routes of uptake form an important part of the occupational hygiene strategy to reduce exposure to chemicals. There are no specific values or preferences connected to this issue.

Net benefits and costs

It is important to know the routes of exposure. For inhalation exposure, the methods of measurement are well-defined, but for dermal and ingestion exposure this is more complicated and not yet standardized. Certainty about the dermal route of exposure would imply more specific exposure assessment and involve considerably more work and cost.

Strength of the recommendation

For inhalation exposure, based on the above considerations, the recommendation is strong. For dermal exposure, the quality of evidence is low and thus the recommendation is conditional.

Summary of findings: routes of exposure to MNMs

Systematic review question: In workers with potential exposure to MNMs, what are the most likely routes of exposure for specific MNMs and during specific tasks based on workplace measurements of MNMs?

Evidence summary

The systematic review was published by Basinas et al. (2017) (*31*).

Number of studies and participants

There were 107 studies reporting a total of 424 exposure assessment situations, i.e. combinations of activity and type of MNM with workers' potential exposure to MNMs and sufficient data to allow assessment of the likelihood of exposure by route.

Exposures in studies

The exposure assessment situations related to potential workers' exposure to CNTs and CNFs ($N = 63$), Si-based ($N = 42$), TiO_2 ($N = 43$), other metal oxides ($N = 77$), metals ($N = 38$), and other nanomaterials ($N = 61$).

Outcomes in studies

For every exposure assessment situation, the likelihood of a route of exposure was assessed by applying specific criteria. For inhalation exposure, an adapted set of criteria was used based on the CEN Standard (PREN 17058) *Workplace exposure – Assessment of inhalation exposure to nano-objects*

and their agglomerates and aggregates (*33*). Dermal exposure was based on an established source-to-reception model. For each combination of activity and type of MNM, the likelihood of exposure by a particular route was derived by aggregating across the relevant individual assessments.

Risk of bias in the included studies

The main limitations of the studies are listed below:

- The data that were available from studies included in the review comprised measurement in small and research scale-productions and therefore may not adequately represent the exposure conditions in industrial workplaces.
- For the inhalation route, there was a lack of harmonized methods to measure personal exposure at the workers' breathing zone. Most of the evaluated exposure assessments were based on stationary sampling, not necessarily representative of workers' exposure via inhalation.
- For the dermal route only, there were limited indirect measurement data available that resulted from the analysis of collected surface samples.
- No measurement data are available on ingestion exposure.
- Protection provided by PPE was not considered in the review because it is not relevant to determine the route and form of exposure.

Results

There is high-quality evidence that, in general, the form and route of exposure depends mainly on the activity (i.e. process and operational conditions), rather than just on the type of MNM handled (**Annex 3**).

There is also high-quality evidence that the likelihood of exposure is affected by the presence of risk management measures and the scale of production. In principle, both inhalation and dermal exposure are less likely when the process is enclosed. For example, CNTs, Si-based and various metal oxides are processed within enclosed reaction vessels, which makes exposure unlikely during production. Other materials such as TiO2 and metals can be synthesized with flame pyrolysis and mechanical reduction in a not fully enclosed process, which makes exposure more likely to occur.

When a worker can possibly inhale MNMs, potential for dermal exposure also exists. However, for some forms (e.g. when an MNM is in suspension/liquid form), dermal exposure or ingestion exposure can be possible even when inhalation exposure is unlikely.

For the following situations and MNMs, exposure was unlikely:

For CNTs and CNFs, there is high-quality evidence that inhalation exposure usually does not occur in the reaction phase of synthesis and handling and transfer of liquids. There is high-quality evidence that dermal exposure does not occur in the reaction phase of synthesis.

For Si-based nanomaterials, there is high-quality evidence that inhalation and dermal exposure do not occur in the reaction phase of synthesis.

For other metal oxides and mixtures, there is high-quality evidence that inhalation and dermal exposure do not occur in the reaction phase of synthesis.

For other MNMs, there is high-quality evidence that inhalation and dermal exposure do not occur in the reaction phase of synthesis.

Quality of the evidence

Quality of the studies was dependent on the methods used to quantify release and the applicability or not of the adapted set of criteria described in the CEN Standard (PREN 17058) *Workplace exposure – Assessment of inhalation exposure to nano-objects and their agglomerates and aggregates* (*33*).

Conclusions reached using the adapted CEN criteria and both off-line and online data, were considered to be based on high-quality data. For some MNMs there is an established exposure assessment method based on chemical analysis, e.g. for CNT and TiO2. When this chemical analysis was used to quantify the release, the quality was considered high even if no online measurements were available or if the available online measurements for the activity involving MNMs were not considerably higher than background.

For dermal exposure, evidence was considered as high quality if surface contamination was clearly established and/or if release was confirmed through both online and off-line measurements and a transparent description of the process and operational conditions was provided.

Implementation guidance, research recommendation

Implications for practice

The GDG concludes that there is high-quality evidence for workers' inhalation exposure and low-quality evidence for dermal exposure to MNMs in general.

There is also high-quality evidence that in some situations inhalation exposure is unlikely, such as for CNTs and CNFs during handling and transfer of liquid intermediaries and ready-to-use products, and high-quality evidence that dermal exposure does not occur during the reaction phase of synthesis for most MNMs.

There were no studies of ingestion exposure. However, established conceptual models imply that where dermal exposure occurs, ingestion exposure is likely.

Implications for research

There is a need to conduct more representative studies to better estimate workers' inhalation exposure by assessing MNMs at the personal breathing zone, rather than in the near-field. Studies that directly measure dermal and ingestion exposure of workers to MNMs are needed. For all routes of exposure more measurements are needed under real industrial production conditions. More research should be conducted to characterize exposures to nanomaterials in a broad range of industries where nanomaterials are used.

Summary of findings: workplace exposures to MNMs

Systematic review question: In workplaces where MNMs are in use according to the OECD list, does comprehensive measurement of exposure lead to confirmation of exposure to MNMs and if so during which tasks? Any study type in which exposure to MNMs was comprehensively measured was included.

Evidence summary

The systematic review was published by Debia et al. (2016) as a journal article (*32*).

Number of studies and participants

Over the reviewed period (January 2000–January 2015), 50 studies in 72 workplaces with 306 exposure situations were eligible and included in the review. Studies were mainly located in the Republic of Korea and the United States, but none in LMI countries. Most studies (62.5%) were in research laboratories or pilot plants.

Exposures in the studies

Exposures to carbonaceous and metallic nanomaterials and nanoclays were evaluated in the studies.

Outcomes in studies

Authors reported weight-based concentrations (mass concentration), count-based concentrations (number concentration) and off-line qualitative analysis.

Risk of bias in the included studies

The main limitations in the studies were that the exposure measurements were not real breathing zone sampling and not as comprehensive as would be advisable.

Confirmed exposure

Of the 306 exposure situations, there was confirmed exposure in 233 (76%) ranging from 100% for nanoclays, 83% for carbonaceous MNMs and 73% for metallic MNMs.

In 233 of the exposure situations, confirmed workers' exposure was mainly confined to micro-sized agglomerated MNMs with only a few studies reporting the sampling of nanoscale airborne MNMs.

Exposures to carbonaceous MNMs ranged from not detected to 910 $\mu g/m^3$ of elemental carbon (EC) with local engineering controls and from not detected to 1000 $\mu g/m^3$ EC without controls.

Carbon nanofibre exposure ranged from not detected to 1.6 CNF structures/cm^3 with local engineering controls and from 0.09 CNF structures/cm^3 to 193 CNF structures/cm^3 without controls.

Titanium dioxide nanoparticle exposure ranged from 0.24 to 0.43 $\mu g/m^3$ with local engineering controls and from 0.09 to 33 $\mu g/m^3$ without controls.

Aluminium oxide nanoparticle exposure was not detected with local engineering controls and ranged from not detected to 0.157 $\mu g/m^3$ without controls.

Silver nanoparticle exposure ranged from 0.09 to 4.99 $\mu g/m^3$ during dry synthesis with no controls (only general ventilation) and from 0.38 to 0.43 $\mu g/m^3$ during wet synthesis (with fume hood). Reactor cleaning activities yielded the highest exposure, up to 33 $\mu g/m^3$ (with local exhaust ventilation).

Iron nanoparticle exposure ranged from 32 $\mu g/m^3$ with local engineering controls to 335 $\mu g/m^3$ without controls.

In 231 of the exposure situations, workers were exposed to micro-sized agglomerated MNMs and in two of the exposure situations to nanoscale MNMs.

Quality of the evidence

GRADE had to be considerably adapted to fit the type of studies reviewed. Consistent results in several studies with comprehensive measurements were considered high-quality evidence. The GDG judged that given the comprehensiveness of the measurements and the consistency of the results, there was overall high-quality evidence that workers are exposed to micro-sized agglomerated MNMs in workplaces during production and use of products. For the same reasons, the evidence for handling tasks was rated as high quality.

Implementation guidance, research recommendation

Implications for practice

The GDG concludes that there is high-quality evidence that workers are exposed to micro-sized agglomerated nanoparticles and that exposure occurs mostly during handling tasks, cleaning operations and machining of products. There was low-quality evidence of exposure to nanoscale primary airborne nanoparticles in workplaces. There were no studies, and therefore there was no evidence of exposures in LMI countries.

Implications for research

Longitudinal studies evaluating workers' exposure over time are needed. Studies of workers' exposure in LMI countries are also needed.

6.3.2. Use controls to reduce the level of exposure

Recommendation 9: The GDG recommends taking control measures based on the principle of hierarchy of controls, meaning that the first control measure should be to eliminate the source of exposure before implementing control measures that are more dependent on worker involvement, with PPE being used only as a last resort. According to this principle, engineering controls should be used when there is a high level of inhalation exposure or when there is no, or very little, toxicological information available. In the absence of appropriate engineering controls PPE should be used, especially respiratory protection, as part of a respiratory protection programme that includes fit-testing (**STRONG, moderate-quality evidence**).

Recommendation 10: The GDG suggests preventing dermal exposure by occupational hygiene measures such as surface cleaning and the use of appropriate gloves (**CONDITIONAL, low-quality evidence**).

Recommendation 11: When assessment and measurement by a workplace safety expert is not available, the GDG suggests using control banding for nanomaterials to select exposure control measures in the workplace. Owing to a lack of studies, the GDG cannot recommend one method of control banding over another (**CONDITIONAL, very low-quality evidence**).

The GDG considered that in the absence of toxicological information on MNMs, the most stringent control measures should be applied to prevent workers from being exposed. This is also called a no-exposure policy.

Control banding is an approach to risk management for SMEs that can be applied to prevent worker exposures in cases of incomplete information about a nanomaterial. Control-banding strategies are often found in toolkits with categories, or bands, of health hazards, that are combined with exposure scenarios to determine the desired controls. This approach allows users to make meaningful inferences about likely exposures and to make decisions about necessary controls, reducing the exposures within four or five hazard bands (*34*).

When there is only limited toxicological information available for MNMs, or when analogies can be made with hazard properties of similar materials in broad groups, this should lead to control banding. When full toxicological information is available, this should lead to full risk assessment. The GDG therefore notes that control banding does not replace risk assessment, but it can still be beneficial for communication and better risk management.

From evidence to recommendation

Evidence

The evidence for these recommendations is based on two systematic reviews, both of which were published as journal articles. The first, by Myojo, Nagata & Verbeek (2017), reviewed the effects of control measures (*35*). The other, by Eastlake, Zumwalde & Geraci (2016), assessed the effects of the control-banding approach (*36*). For the control measures varying levels of evidence were found and therefore parts of the recommendation are conditional. Overall the risk of bias across studies was low but precision was unclear. For PPE the quality of the evidence was further downgraded because of indirectness, meaning that there were only laboratory studies and no field studies. For control banding there were only two studies, with a high risk of bias.

Control-banding tools such as those listed in the systematic review (*36*) can be used proactively as a low-cost intervention to reduce exposures to nanomaterials in the workplace.

Benefits and harms

There are clear benefits of preventing and decreasing exposure by engineering controls.

Values and preferences

The hierarchy of controls is a generally accepted concept in occupational hygiene, in which increased value is given to what are known as "more preventive" solutions (see Hierarchy of controls). Control banding is an approach that is well understood by employers and employees and seems feasible with bulk materials (*37*).

Net benefits and costs

The costs for full enclosure or process change can be considerable but decrease with the hierarchy of controls. The GDG attaches much weight to more preventive solutions. Control banding requires training but no considerable investments (*38*).

Strength of the recommendation

Based on the above considerations, the GDG makes a strong recommendation for control measures for inhalation exposure but a conditional recommendation for full body protection to prevent dermal exposure and a conditional recommendation for control banding.

Evidence summary of controls to reduce exposure to MNMs

Systematic review question: In workers or workplaces with exposure to MNMs, what is the effect of workplace ventilation, PPE or organization of work aimed at reducing exposure, on the level of exposure to MNMs compared to no controls or protective equipment based on studies that compared a situation with the intervention to a situation without the intervention?

The effect of the controls was expressed as the protection factor (PF), which is defined as the ratio of exposure level (either mass-based or particle-based) without the controls divided by the exposure level with the controls. If the PF is >1 controls reduce exposure. A PF of 10 indicates that controls reduce exposure by 90%.

Evidence summary

The systematic review by Myojo and Nagata (2017) was published as a journal article (*35*).

Number of studies and participants

There were 50 studies with 55 workplaces/participants. Of these studies, 27 were before–after comparisons.

Controls evaluated in studies

There were 14 studies with 27 workplaces that evaluated ventilation, 19 studies with 23 participants evaluated PPE, 16 studies evaluated other control strategies: five on suppression with fluids, two on automation of a process with five workplaces, eight on other organizational strategies, and one on the use of SDS. All studies were about MNM exposure and 15 of these were on exposure to carbon nanotubes.

Outcomes in studies

All outcomes were expressed as a PF.

Risk of bias in the included studies

The main limitations were no control group for the studies on engineering controls and no fieldwork for the respiratory protection studies. Risk of bias in the studies was 2 to 3 on a scale that ranged from –3 to 3, in which –3 meant a very high risk of bias and +3 a very low risk of bias.

Effects of exposure

For engineering controls, enclosure achieved the highest PFs of > 100 (seven cases).

For ventilation, PFs varied from 0.12 to 55 (20 cases) with 15 cases providing PFs >3. For ventilation of fume cupboards, the PF was influenced by the face velocity of the air and the movements of workers. Face velocity is the inward airflow velocity measured in several specific locations across the plane of the fume cupboard sash opening.

For process automation, the PFs varied between 2.5 and 8.2 (five cases) but, owing to interruption of the process by handling material, one case yielded a PF of 0.073. The studies on dustiness and fluid-dust suppression did not provide before–after measurements and did not allow for a PF calculation.

For respiratory protection, masks rated at the protection level of N95 respirators provided a PF of more than 10 in 11 cases. Higher rated P100 respirators provided higher PFs of around 100. One study evaluated a cloth mask which yielded a PF of 1.1 to 1.35. One study reported on a loose-fitting powered air-purifying respirator with PFs over 1.1 million. Most studies were performed in the laboratory under ideal conditions with exposure to sodium chloride as a proxy for MNM because of its size. However, it is unclear whether these results can be extrapolated to mask performance in real workplaces.

Quality of the evidence

Risk of bias in the studies was low. Except for the respiratory protection studies the evidence was direct. The results were consistent across studies. Precision of the effects was unclear because the authors did not provide estimates of statistical precision. Publication bias can be expected, but could not be assessed owing to a lack of data.

The rating of the evidence was defined as low quality at the outset because all studies were non-randomized and non-controlled. The evidence was not upgraded or downgraded.

Implementation guidance, research recommendation

Implications for practice

The GDG concludes that there is only low-quality evidence that exposure to MNMs can be decreased with engineering controls such as enclosure and ventilation, when the specific exposure situations are taken into consideration. There is also only low-quality evidence that respiratory protection can considerably decrease exposure, if the proper type is used and fit-testing is performed for each wearer.

Implications for research

Field studies that evaluate dust control techniques, such as modification and suppression are needed. In addition, studies on the effectiveness of respiratory protection under real workplace conditions are needed.

Evidence summary: control banding for safe handling of manufactured nanomaterials

Systematic review question: In workers or workplaces with potential exposure to MNM, what is the effect of the use of a control-banding tool on controls in place or level of exposure compared to no risk assessment tool or an alternative risk assessment tool based on any type of controlled study?

Evidence summary

The full review was published by Eastlake, Zumwalde & Geraci (2016) as a journal article (*36*).

Number of studies and participants

There were two studies that evaluated 32 different exposure situations. One study was conducted in two MNM research laboratories with exposure to metal and ceramic nanoparticles and CNTs in the United States. The other study reported an additional 27 cases of potential exposure to a variety of MNMs, but did not provide details of the geographical location or the worksite.

Interventions in studies

Both studies were about evaluating potential exposure to a variety of MNMs using the control-banding nanotool developed by Paik, Zalk & Swuste (*38*).

The use of the control-banding nanotool was compared to assessments performed by an experienced occupational hygienist.

Outcomes in studies

The outcome in both studies was the recommendation of an engineering control.

Risk of bias in the included studies

The main limitations were that there was only a qualitative analysis and no exposure measurements. One of the studies did not provide details of the work situations.

Effects of exposure

In the two studies, the recommendations provided using the control-banding nanotool concurred with those of the occupational hygienist in 59% (19/32) of cases. The control-banding nanotool recommended a lower level of control than the occupational hygienist in 28% (9/32) of cases. The control-banding nanotool recommended a higher level of control than the occupational hygienist in 13% (4/32) of cases.

No exposure assessment data were provided to verify that engineering controls recommended by the occupational hygienist reduced exposure potential.

Quality of the evidence

According to GRADE, observational studies start as low-quality evidence, unless they can be upgraded. Based on the limitations of the studies (qualitative analysis, no exposure assessment data, no details about workplaces), the evidence found in this systematic review was downgraded to very low quality.

Implementation guidance, research recommendation

Implications for practice

The GDG concludes that there is only very low-quality evidence that use of the control-banding nanotool leads to similar control measures to those an experienced occupational hygienist would recommend. Professionals, employers and workers would all need training to be able to use the tool.

Implications for research

The low quality of evidence on the effectiveness of control-banding approaches to reduce worker exposure to nanomaterials to safe levels, suggests that more research needs to be conducted

in this area. Specifically, effectiveness of control banding to reduce exposures to MNMs should be evaluated by carrying out measurements selected through the use of control-banding tools (against more comprehensive risk assessment and risk management approaches). Control-banding tools should be further evaluated for use with MNMs. Control-banding tools should be calibrated against exposure measurements and guidance for selection of the appropriate tool for specific situations should be developed.

6.4. HEALTH SURVEILLANCE

The GDG cannot make a recommendation for targeted MNM-specific health surveillance programmes over existing health surveillance programmes that are already in use, due to the lack of evidence.

The GDG further notes that existing occupational health surveillance systems could be implemented to monitor health outcomes possibly associated with MNM exposure where there are health concerns. Given that knowledge of MNMs and their adverse health effects is increasing rapidly, this recommendation should be updated in five years to take into account new findings.

From evidence to recommendation

Evidence

The evidence for this recommendation is based on a small number of non-randomized studies at high risk of bias that did not show the benefits of health examinations.

Benefits and harms

The benefits of health examinations could not be assessed. Setting up a health surveillance system for workers exposed to MNMs would be costly. In addition, it would be difficult, with the current lack of knowledge, to ascribe adverse health effects to MNM exposure.

Values and preferences

It is well known that general health examinations are highly valued by consumers and this is probably also the case for workers (*39*).

Net benefits and costs

Since the GDG could not assess any benefits of health examinations that are specific for MNMs, only considerable costs remain.

Strength of the recommendation

Based on the above considerations, there is no recommendation for specific health examinations.

Summary of findings: health examinations of workers exposed to MNMs

Systematic review question: In workers exposed to MNMs, what is the effect of health surveillance on any adverse health outcome compared to no health surveillance or an alternative form of health surveillance based on any study that described or evaluated health surveillance?

The systematic review was published by Gulumian et al. (2016) as a journal article (*40*).

Number of studies and participants

There were seven studies of which six compared health indicators between exposed and unexposed workers, with 1278 participants. One study described a programme, but did not report any health outcomes. Studies showed that workers were exposed to a mixture of MNMs (3), CNTs (2), nanosilver (1) and TiO_2 (1).

Health examinations in studies

Studies reported on biomarkers from exhaled breath condensate, blood and urine such as markers of oxidative stress and antioxidant enzymes; early health effects such as pulmonary and neurobehavioural test results; and self-reported health outcomes.

Risk of bias in the included studies

The main limitations were that there were no controlled studies with a longitudinal design; all of them were cross-sectional.

Effects of exposure

Two studies found biomarker levels (exhaled breath condensate concentrations of malondialdehyde, 4-hydroxy hexenal (4-HHE) and n-hexanal/aldehyde) elevated in exposed groups compared to unexposed groups.

Early health indicators (lung function parameters) did not deviate from physiologically normal parameters or did not differ between groups.

The prevalence of allergic dermatitis and sneezing was higher among workers exposed to MNMs in one study.

Quality of the evidence

According to GRADE, observational studies start as low-quality evidence unless they can be upgraded. The evidence found in this systematic review was further downgraded because of limitations in study design. There were no reasons to upgrade the evidence.

Implementation guidance, research recommendation

Implications for practice

The GDG concludes that there is only very low-quality evidence on whether targeted nanomaterial health surveillance might reveal early signs of adverse health effects. There was no evidence on specific items that should be included in a surveillance programme.

Implications for research

More research needs to be conducted to (i) identify biomarkers specific to nanomaterial exposures; (ii) identify potential early signs predicting potential long-term adverse health effects, and (iii) validate current medical tests for use in asymptomatic nanomaterial-exposed workers. It is important to emphasize to workers participating in health surveillance that these programmes at this point are research efforts with unproven benefit and health significance to participants.

Exposure registry studies, based on which workers can be followed over time to validate candidate biomarkers, are needed.

6.5. TRAINING AND INVOLVEMENT OF WORKERS

The GDG considers training of workers and worker involvement in health and safety issues to be best practice, but cannot recommend one form of training of workers over another, or one form of worker involvement over another, owing to the lack of studies available.

The GDG commissioned a systematic review to answer the question "what training should be provided to workers?". The question was reformulated to look at the effects of additional training and education on workers potentially exposed to MNMs. The systematic review by von Mering & Schumacher (2017) was published by WHO (*41*). The GDG also conducted preliminary searches to answer the question about worker participation in the workplace risk assessment and management of MNMs. However, no studies were found on this topic.

Summary of findings: training and involvement of workers

Systematic review question: In workers exposed to MNMs, does specific training or education on safe handling of MNMs have an effect on the level of exposure to MNMs or on the level of controls (including PPE) implemented compared to no training, or an alternative form of training?

Evidence summary

The systematic review did not locate any studies on the effects of worker training. There were no studies that established specific workers' training needs related to MNMs.

Research recommendation

Implications for research

The GDG recommends evaluating the effect of worker and employer training on the level of MNM exposure and the installation of controls compared to alternative forms of training, preferably with a controlled before–after design. Similarly, the GDG recommends evaluating the effect of different forms of worker involvement on level of exposure and implementation of controls.

7. IMPLEMENTATION OF THE GUIDELINES

Given the current high exposures to MNMs documented in the exposure review, considerable efforts are needed by all stakeholders to ensure country implementation of these guidelines with a particular focus on LMI countries.

WHO will officially launch these guidelines with its partners from the Collaborating Centres for Occupational Health and nongovernmental organizations in official relations with WHO, in addition to presenting the guidelines for further distribution at diverse forums.

With regard to a corporate launch, discussions will be held internally with the Director Public Health, Environmental and Social Determinants of Health, Department of Communication and the WHO regions to devise a communications plan. This can be achieved through stakeholder networks including those of GDG members and the WHO Global Network of Collaborating Centres.

In addition to this document, simplified summaries will be prepared for employers and workers to ease implementation and monitoring.

8. UPDATING THE GUIDELINES

The field of MNM safety is evolving rapidly. A research agenda set by Stone et al. in collaboration with stakeholders in 2014, foresaw considerable progress in validated measurement methods and the assessment of routes of exposure and monitoring strategies in the short term (*42*). Therefore the GDG proposes to update these guidelines in 2022.

REFERENCES

1. Honnert B, Grzebyk M. Manufactured nano-objects: an occupational survey in five industries in France. Ann Occup Hyg. 2014;58:121–35. doi: 10.1093/annhyg/met058.
2. Types and uses of nanomaterials, including safety aspects. Commission Staff Working Paper. Brussels: European Commission; 2012.
3. Arduin R. Brazilian scenario – sustainable nanotechnology. Venice: Sustainable Nanotechnology Organization; 2015.
4. Air quality guidelines for Europe, 2nd edition. Bonn: World Health Organization; 2000.
5. Air quality guidelines: global update 2005. Copenhagen: WHO Regional Office for Europe; 2006.
6. Brown BB. Delphi process: a methodology used for the elicitation of opinions of experts. Santa Monica (CA): Rand Corp; 1968.
7. WHO handbook for guideline development, 2nd edition. Geneva: World Health Organization; 2014.
8. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6. doi: 10.1136/bmj.39489.470347.AD.
9. Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. BMJ. 2015;350:h870. doi: 10.1136/bmj.h870.
10. Lewin S, Glenton C, Munthe-Kaas H, Carlsen B, Colvin CJ, Gülmezoglu M et al. Using qualitative evidence in decision making for health and social interventions: an approach to assess confidence in findings from qualitative evidence syntheses (GRADE-CERQual). PLoS Med. 2015;12:e1001895. doi: 0.1371/journal.pmed.1001895.
11. IUF (International Union of Food, Agricultural, Hotel, Restaurant, Catering, Tobacco and Allied Workers' Associations). Small particles, big risks: IUF, international NGOs release recommendation on the use of nanotech in foods. 12 March 2015 (http://www.iuf.org/w/?q=node/4073, accessed 15 May 2017).
12. European Trade Union Confederation (ETUC). 2nd resolution on nanotechnologies and nanomaterials; 2010 (https://www.etuc.org/documents/etuc-2nd-resolution-nanotechnologies-and-nanomaterials#.WZrnez4jG70, accessed 30 May 2016).
13. Canadian Union of Public Employees. Fact sheet: Nanomaterials; 2016 (https://cupe.ca/fact-sheet-nanomaterials, accessed 15 May 2017).
14. Australian Council of Trade Unions. Fact sheet; 2009 (http://www.actu.org.au/media/149927/actu_factsheet_ohs_-nanotech_090409.pdf, accessed 15 May 2017).
15. Hau M, Cole D, Vanderlinden L, MacFarlane R, Mee C, Archbold J et al. Development of a guide to applying precaution in local public health. Int J Occup Environ Health. 2014;20:174–84. doi: 10.1179/2049396713Y.0000000051.
16. Nel AE, Nasser E, Godwin H, Avery D, Bahadori T, Bergeson L et al. A multi-stakeholder perspective on the use of alternative test strategies for nanomaterial safety assessment. ACS Nano 2013;7:6422–33. doi: 10.1021/nn4037927.
17. The National Institute for Occupational Safety and Health (NIOSH). Hierarchy of controls (http://www.cdc.gov/niosh/topics/hierarchy/default.html, accessed 15 May 2017).

18. Ellenbecker MJ. Engineering controls as an intervention to reduce worker exposure. Am J Ind Med. 1996;29:303–7. doi: 10.1002/(SICI)1097-0274(199604)29:4<303::AID-AJIM5>3.0.CO;2-P.
19. Gebel T, Foth H, Damm G, Freyberger A, Kramer PJ, Lilienblum W et al. Manufactured nanomaterials: categorization and approaches to hazard assessment. Arch Toxicol. 2014;88:2191–211. doi: 10.1007/s00204-014-1383-7.
20. The WHO/EURO man-made mineral fiber reference scheme. By the WHO/EURO Technical Committee for Monitoring and Evaluating MMMF. Scand J Work Environ Health. 1985;11:123–9.
21. Nagai H, Okazaki Y, Chew SH, Misawa N, Yamashita Y, Akatsuka S et al. Diameter and rigidity of multiwalled carbon nanotubes are critical factors in mesothelial injury and carcinogenesis. Proc Natl Acad Sci U S A. 2011;108:E1330–8. doi: 10.1073/pnas.1110013108.
22. Landvik N, Mohr B, Verbeek J, Skaug V, Zienolddiny S. Criteria for grouping of manufactured nanomaterials to facilitate hazard and risk assessment, a systematic review of expert opinions. Regulatory Toxicology and Pharmacology; 2017. Submitted.
23. Working safely with manufactured nanomaterials, guidance for workers. Luxembourg: European Commission; 2014.
24. Kulinowski K, Lippy B. Training workers on risks of nanotechnology. Washington (DC): US Department of Health and Human Services/National Institutes of Health, National Institute of Environmental Health Sciences; 2011.
25. Health and safety training: a brief guide (INDG345). London: Health and Safety Executive (HSE); 2012 (http://www.hse.gov.uk/pubns/indg345.htm, accessed 12 September 2017).
26. Lee N, Lim CH, Kim T, Son EK, Chung GS, Rho CJ et al. Which hazard category should specific nanomaterials or groups of nanomaterials be assigned to and how? Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.
27. Deveau M, Chen CP, Johanson G, Krewski D, Maier A, Niven KJ et al. The global landscape of occupational exposure limits – implementation of harmonization principles to guide limit selection. J Occup Environ Hyg. 2015;12 Suppl 1:S127–44. doi: 10.1080/15459624.2015.1060327.
28. Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. Harmonized tiered approach to measure and assess the potential exposure to airborne emissions of engineered nano-objects and their agglomerates and aggregates at workplaces. Series on the Safety of Manufactured Nanomaterials, No. 55 (http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2015)19&doclanguage=en, accessed 15 May 2017).
29. Mihalache R, Verbeek J, Graczyk H, Murashov V, van Broekhuizen P. Occupational exposure limits for manufactured nanomaterials, a systematic review. Nanotoxicology. 2017;11:7–19. doi: 10.1080/17435390.2016.1262920.
30. Boccuni F, Gagliardi D, Ferrante R, Rondinone BM, Iavicoli S. Measurement techniques of exposure to nanomaterials in the workplace for low- and medium-income countries: A systematic review. Int J Hyg Environ Health. 2017;220:1089–97. doi: 10.1016/j.ijheh.2017.06.003.
31. Basinas I, Sánchez Jiménez A, Galea K, van Tongeren M, Hurley F. A systematic review of the routes and forms of exposure to engineered nanomaterials. Ann Work Exposure Health; 2017. Submitted.
32. Debia M, Bakhiyi B, Ostiguy C, Verbeek JH, Brouwer DH, Murashov V. A systematic review of reported exposure to engineered nanomaterials. Ann Occup Hyg. 2016;60:916–35. doi: 10.1093/annhyg/mew041.
33. Workplace exposure – assessment of inhalation exposure to nano-objects and their agglomerates and aggregates (BS EN 17058). London: British Standards Institution; 2016.

34. Zalk DM, Heussen GH. Banding the world together; the global growth of control banding and qualitative occupational risk management. Saf Health Work. 2011;2:375–9. doi: 10.5491/SHAW.2011.2.4.375.

35. Myojo T, Nagata T, Verbeek J. The effectiveness of specific risk mitigation techniques used in the production and handling of manufactured nanomaterials: a systematic review. J UOEH. 2017;39:187–99. (https://www.jstage.jst.go.jp/article/juoeh/39/3/39_187/_pdf, accessed 16 September 2017).

36. Eastlake A, Zumwalde R, Geraci C. Can control banding be useful for the safe handling of nanomaterials? A systematic review. J Nanoparticle Res. 2016;18:169. doi: 10.1007/s11051-016-3476-0.

37. Bracker AL, Morse TF, Simcox NJ. Training health and safety committees to use control banding: lessons learned and opportunities for the United States. J Occup Environ Hyg. 2009;6:307–14. doi: 10.1080/15459620902810083.

38. Paik SY, Zalk DM, Swuste P. Application of a pilot control banding tool for risk level assessment and control of nanoparticle exposures. Ann Occup Hyg. 2008;52:419–28. doi: 10.1093/annhyg/men041.

39. Oboler SK, Prochazka AV, Gonzales R, Xu S, Anderson RJ. Public expectations and attitudes for annual physical examinations and testing. Ann Intern Med. 2002;136:652–9.

40. Gulumian M, Verbeek J, Andraos C, Sanabria N, de Jager P. Systematic review of screening and surveillance programs to protect workers from nanomaterials. PLoS One. 2016;11:e0166071. doi: 10.1371/journal.pone.0166071.

41. von Mering Y, Schumacher C. What training should be provided to workers who are at risk from exposure to the specific nanomaterials or groups of nanomaterials? Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

42. Stone V, Pozzi-Mucelli S, Tran L, Aschberger K, Sabella S, Vogel U et al. ITS-NANO – prioritising nanosafety research to develop a stakeholder driven intelligent testing strategy. Part Fibre Toxicol. 2014;11:9. doi: 10.1186/1743-8977-11-9.

ANNEX 1: LIST OF PROPOSED OCCUPATIONAL EXPOSURE LIMIT (OEL) VALUES FOR MNMS

TABLE A.1.1 OCCUPATIONAL EXPOSURE LIMIT VALUES AS PROPOSED FOR MNMS

Category	Study reference	Nanomaterials and specifications	OEL name	Mass concentration µg/m³	Particle concentration (particle/ml, fibres/cm³)	Surface concentration (nm²/cm³)	Derivation approach
Inhalation exposure: general MNM approach							
MNM	Guidotti 2010	Fine particulate matter ≤2500 nm	BOEL	30	ND	ND	Environmental
MNM	McGarry 2013	Airborne particles from nanotechnology processes	PCVs	ND	3 times LBPC for more than 30 minutes	ND	Environmental
Inhalation exposure: categorical MNM approach							
CMAR	BSI 2007	CMAR nanomaterials, NM	BEL	0.1 × bulk WEL	ND	ND	Bridging
Fibres	AGS 2013	Non-entangled fibrous NM	Acceptance level (default), respirable fraction	ND	0.01	ND	Bridging/ grouping
Fibres	BSI 2007	Fibrous NM	BEL	ND	0.01	ND	Bridging/ grouping
Fibres	Stockmann-Juvala 2014	Carbon nanofibres, CNFs	OEL	ND	0.01	ND	Bridging/ grouping
Fibres	van Broekhuizen 2012	Carbon nanotubes, CNTs, insoluble NM with high aspect ratio >3:1	NRV	ND	0.01	ND	Bridging/ grouping

Category	Study reference	Nanomaterials and specifications	OEL name	Mass concentration µg/m³	Particle concentration (particle/ml, fibres/cm³)	Surface concentration (nm²/cm³)	Derivation approach
Inhalation exposure: categorical MNM approach							
GBP	AGS 2013	In operations with NM: nanosized GBP with no specific toxicity	OEL respirable fraction, default	500	ND	ND	Grouping
GBP	AGS 2013	No specific operations with NM: G	OEL respirable fraction	1250	ND	ND	Grouping
GBP	BSI 2007	Insoluble nanomaterials	BEL	0.066 × bulk WEL	20 000	ND	Bridging
GBP	Pauluhn 2011	Inhaled poorly soluble particles	DNEL	0.5 µl PM respirable/m³ × agglomerate density	ND	ND	Categorical QRA/grouping
GBP	van Broekhuizen 2012	Metals and metal oxides, biopersistent granular NM >6000 kg/m³	NRV	ND	20 000	ND	Grouping
GBP	van Broekhuizen 2012	Metals and metal oxides, biopersistent granular NM <6000 kg/m³	NRV	ND	40 000	ND	Grouping
Low-toxicity dust	Stockmann-Juvala 2014		OEL	300 (respirable fraction), 4000 (inhalable fraction)	ND	ND	Bridging/ grouping
Non-biopersistent	van Broekhuizen 2012	Non-biopersistent granular NM 1–100 nm	NRV	Applicable OEL, WEL	ND	ND	Bridging
Soluble	BSI 2007	Soluble nanomaterials	BEL	0.5 × bulk WEL	ND	ND	Bridging
Inhalation exposure: specific MNM approach							
Carbon	Aschberger 2011	Multi-walled carbon nanotubes, MWCNT 10 nm	INEL	1	ND	ND	QRA
Carbon	Aschberger 2011	MWCNT 140 nm	INEL	2	ND	ND	QRA
Carbon	Luizi 2009	Carbon nanotubes, CNTs	No effect concentra-tion in air	2.5	ND	ND	QRA

Category	Study reference	Nanomaterials and specifications	OEL name	Mass concentration µg/m³	Particle concentration (particle/ml, fibres/cm³)	Surface concentration (nm²/cm³)	Derivation approach
Inhalation exposure: specific MNM approach							
Carbon	Nakanishi 2015	Carbon nanotube group, SWCNT, DWCNT, MWCNT	OEL 15 years	30	ND	ND	QRA
Carbon	NIOSH 2013	All CNTs and nanofibres	REL respirable elemental carbon	<1	ND	ND	QRA
Carbon	Pauluhn 2010	MWCNT Baytubes®	OEL, inhalable fraction	50	ND	ND	QRA
Carbon	Stone 2009	MWCNT	DNEL chronic inhalation, systemic immune effect	0.67	ND	ND	QRA
Carbon	Kuempel 2006	Carbon black, CB ultrafine	BMDL 45 years (lung dosimetry, model 1)	120	ND	ND	QRA
Carbon	Kuempel 2006	Carbon black, CB ultrafine	BMDL 45 years (lung dosimetry, model 2)	240	ND	ND	QRA
Carbon	Aschberger 2011	Fullerenes, C60	INEL	7.4	ND	ND	QRA
Carbon	Shinohara 2011	Fullerenes, C60	OEL (PL) 15 years	390	ND	ND	QRA
Nanocellulose	Stockmann-Juvala 2014	Nanocellulose	OEL	ND	0.01	ND	Bridging
Nanoclays	Stockmann-Juvala 2014	Nanoclays	OEL	300 (respirable fraction), 4000 (inhalable fraction)	ND	ND	Bridging/ grouping
Nanosilver	Aschberger 2011	Nano Ag	INEL lung function	0.33	ND	ND	QRA
Nanosilver	Aschberger 2011	Nano Ag	INEL lung other effects	0.67	ND	ND	QRA

Category	Study reference	Nanomaterials and specifications	OEL name	Mass concentration µg/m³	Particle concentration (particle/ml, fibres/cm³)	Surface concentration (nm²/cm³)	Derivation approach
Inhalation exposure: specific MNM approach							
Nanosilver	Stone 2009	Nano Ag	DNEL lung exposure, extrapolating factor 10	0.098	1200	2.2 × 106	QRA
Nanosilver	Stone 2009	Nano Ag	DNEL lung exposure, extrapolating factor 3	0.33	4000	7.2 × 106	QRA
Nanosilver	Stone 2009	Nano Ag	DNEL liver effect	0.67	7000	1.2 × 107	QRA
Nanosilver	Swidwinska 2015	Nano Ag	MAC-TWA inhalable fraction	10	ND	ND	QRA
Silicon dioxide	Stockmann-Juvala 2014	Amorphous silica, SiO_2	OEL respirable fraction	300	ND	ND	QRA
Titanium dioxide	Aschberger 2011	TiO_2	INEL	17	ND	ND	QRA
Titanium dioxide	Kuempel 2006	TiO_2 ultrafine	BMDL 45 years (lung dosimetry, model 1)	73	ND	ND	QRA
Titanium dioxide	Kuempel 2006	TiO_2 ultrafine	BMDL 45 years (lung dosimetry, model 2)	140	ND	ND	QRA
Titanium dioxide	NIOSH 2011	TiO_2 ultrafine	REL (up to 10 h/day, 40 h/week)	300	ND	ND	QRA
Titanium dioxide	Ogura 2011	TiO_2	OEL (PL) 15 years	610	ND	ND	QRA
Titanium dioxide	Stockmann-Juvala 2014	TiO_2	OEL respirable fraction	100	ND	ND	QRA
Titanium dioxide	Swidwinska 2014	TiO_2	MAC	300	ND	ND	QRA
Titanium dioxide	Warheit 2013	High surface reactivity anatase-rutile nanoscale TiO_2	OEL	1000	ND	ND	QRA

Category	Study reference	Nanomaterials and specifications	OEL name	Mass concentration µg/m³	Particle concentration (particle/ml, fibres/cm³)	Surface concentration (nm²/cm³)	Derivation approach
Inhalation exposure: specific MNM approach							
Titanium dioxide	Warheit 2013	Low surface reactivity nanoscale TiO_2	OEL	2000	ND	ND	QRA
Titanium dioxide	Warheit 2013	Pigment-grade TiO_2, particle types	OEL	5000	ND	ND	QRA
Dermal exposure							
Carbon	Stone 2009	MWCNT	DNEL dermal chronic exposure, assessment factor 3	5.9 µg/kg body weight	ND	ND	QRA
Carbon	Stone 2009	MWCNT	DNEL dermal chronic exposure	17.7 µg/kg body weight	ND	ND	QRA
Oral exposure							
Carbon	Stone 2009	Fullerite, mixture of C_{60} + C_{70}	DNEL oral acute exposure	40 mg/kg body weight	ND	ND	QRA
Carbon	Stone 2009	Water-soluble C_{60}, polyalkyl-sulfonated	DNEL oral chronic exposure	0.17 mg/kg body weight	ND	ND	QRA
Acute short-term exposure							
MNM	McGarry 2013	Airborne particles from nanotechnology processes	PCVs, single short-term measure-ment		5 times the local particle reference value	ND	Environmental
Carbon	Stone 2009	MWCNT	DNEL acute inhalation, systemic immune effect	4.02	ND	ND	QRA
Carbon	Aschberger 2010	Fullerenes, C_{60}	INEL short-term, inhalable fraction	44.4	ND	ND	QRA
Carbon	Stone 2009	MWCNT	DNEL acute inhalation, pulmonary effect	201	ND	ND	QRA

Category	Study reference	Nanomaterials and specifications	OEL name	Mass concentration µg/m³	Particle concentration (particle/ml, fibres/cm³)	Surface concentration (nm²/cm³)	Derivation approach
Acute short-term exposure							
Carbon	Stone 2009	MWCNT	DNEL dermal acute exposure	106 µg/kg body weight	ND	ND	QRA
Carbon	Stone 2009	MWCNT	DNEL dermal acute exposure, assessment factor 3	35.5 µg/kg body weight	ND	ND	QRA

AGS: German Hazardous Substances Committee; BEL: benchmark exposure level; BMDL: benchmark dose lower (95% confidence limit of the benchmark dose; BOEL: benchmark occupational exposure level; BSI: British Standards Institute; CMAR: carcinogenic, mutagenic, asthmagenic or a reproductive toxin; CNF: carbon nanofibre; 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; ND: no data; NIOSH: National Institute for Occupational Safety and Health (United States); NM: nanomaterial; NRV: nano reference value; OEL (PL): occupational exposure limit period-limited; OEL: occupational exposure limit; PCVs: particle control values; QRA: traditional quantitative risk assessment; REL: recommended exposure limit; SWCNT: single-walled carbon nanotube; WEL: workplace exposure limit.

ANNEX 2: STEERING GROUP, GUIDELINE DEVELOPMENT GROUP, SYSTEMATIC REVIEW TEAMS AND EXTERNAL REVIEW GROUP

TABLE A.2.1 WHO GUIDELINE STEERING GROUP

Name	Role	Organization
Vladimir MURASHOV	Technical Adviser (Chair)	National Institute for Occupational Safety and Health, Washington, DC, UNITED STATES OF AMERICA (USA)
Evelyn KORTUM	Steering Group Member and WHO Focal Point	WHO, Department of Public Health, Environmental and Social Determinants of Health, Geneva, SWITZERLAND
Aida PONCE DEL CASTILLO	Technical Adviser (Vice-Chair)	European Trade Union Institute, Brussels, BELGIUM
Richard BROWN	Steering Group Member	WHO, Department of Public Health, Environmental and Social Determinants of Health, Geneva, SWITZERLAND
Angelika TRITSCHER	Steering Group Member	WHO, Department of Food Safety and Zoonoses, Geneva, SWITZERLAND
Marco MARTUZZI	Steering Group Member	Environment and Health Intelligence and Forecasting, WHO Bonn Office, GERMANY
Jos VERBEEK	Technical Advisor (Methodologist)	Finnish Institute of Occupational Health, Kuopio, FINLAND

TABLE A.2.2 GUIDELINE DEVELOPMENT GROUP

Name	Affiliation
Delphine BARD	Health and Safety Executive, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND
Derk BROUWER	University of Witwatersrand, SOUTH AFRICA
Mahmoud GHAZI-KHANSARI	Tehran University of Medical Sciences (TUMS), ISLAMIC REPUBLIC OF IRAN
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Evelyn KORTUM	WHO, Department of Public Health, Environmental and Social Determinants of Health, Geneva, SWITZERLAND
Naroo LEE	Korea Occupational Safety and Health Agency (KOSHA), Ulsan, REPUBLIC OF KOREA
Yair Ray LIFSHITZ	Research Center for Ergonomics, Industrial Engineering and Management, Technion – Israel Institute of Technology, Haifa, ISRAEL
Jaroslav MRAZ	National Institute of Public Health, Center of Occupational Health, Prague, CZECH REPUBLIC
Vladimir MURASHOV	National Institute for Occupational Safety and Health, Washington, DC, USA
Toshihiko MYOJO	Institute of Industrial Ecological Sciences, University of Occupational & Environmental Health (UOEH), Iseigaoka, JAPAN
Rolf PACKROFF	Federal Institute for Occupational Safety and Health (BAuA), Dortmund, GERMANY
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Nathalie THIERIET[a]	French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Paris, FRANCE
Jeong-Sun YANG[a]	Korea Occupational Safety and Health Agency (KOSHA), Ulsan, REPUBLIC OF KOREA

[a] GDG members who resigned before the completion of these guidelines.

TABLE A.2.3 SYSTEMATIC REVIEW TEAMS

Question	Experts Involved[a]	Affiliation
Risks of MNMs	Skaug V, Zienolddiny S, Mohr B.	Norwegian Institute of Occupational Health, Oslo, NORWAY
Specific hazard classes	Lee N, Lim CH, Kim T, Sohn EK, Chung GS, Rho CJ, Lee SR, Yu IJ.	Korean Occupational Health and Safety Agency, Ulsan, REPUBLIC OF KOREA
Forms and routes of exposure	Sánchez Jiménez A, Basinas I, Galea K, van Tongeren M, Hurley F.	Institute of Occupational Medicine, Edinburgh, SCOTLAND
Typical exposure situations	Debia M, Bakhiyi B, Ostiguy C, Verbeek J, Brouwer D, Murashov V.	Université de Montréal, Département de Santé Environnementale et Santé au Travail, Montréal, CANADA
Exposure measurement and assessment	Boccuni F, Ferrante R, Gagliardi D, Iavicoli S, Rondinone BM.	INAIL, Italian National Institute for Insurance against Accidents at Work, Rome, ITALY
Occupational exposure limit values	Mihalache R, Verbeek J, Graczyk H, Murashov V, van Broekhuizen P.	Finnish Institute of Occupational Health, Kuopio, FINLAND
Control banding	Eastlake A, Zumwalde R, Geraci C.	National Institute for Occupational Safety and Health, Cincinatti, OH, USA
Specific risk mitigation techniques	Myojo T, Nagata T.	University of Occupational and Environmental Health, Kitakyushu, JAPAN
Health surveillance to detect and prevent risks from exposure	Gulumian M, Verbeek J, Andraos C, Sanabria N, de Jager P.	National Institute of Occupational Health, Johannesburg, SOUTH AFRICA
Training of workers to prevent risks from exposure	von Mering Y, Schumacher C.	Institut für Arbeitsschutz, Deutsche Gesetzlichen Unfallversicherung, Sankt-Augustin, GERMANY
Involvement of workers and their representatives	Andrade, LRB.	FUNDACENTRO, Impactos da nanotecnologia na saúde dos trabalhadores e meio ambiente, Ministerio do Trabalho, São Paulo, BRAZIL

[a] The first person mentioned was the leader of the systematic review team.

TABLE A.2.4 EXTERNAL REVIEW GROUP

Name	Affiliation
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Emmanuel ODJAM-AKUMATEY	Ecological Restorations, Accra, GHANA

Name	Affiliation
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Helene STOCKMANN	Finnish Institute of Occupational Health, Helsinki, FINLAND
Stephen THOMAS	Innovative OHS Risk Solutions, Adelaide, AUSTRALIA
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ANNEX 3: SUMMARY OF EVIDENCE, ROUTES OF EXPOSURE TO MNMS

TABLE A.3.1 ASSESSING INHALATION AND DERMAL EXPOSURE BY ACTIVITY SCENARIO AND TYPE OF MNM

Activity scenario		Quality assigned	Number of					
			CNTs and CNFs		Si-based		TiO_2	
			Inhalation exposure	Dermal exposure[a]	Inhalation exposure	Dermal exposure[a]	Inhalation exposure	Dermal exposure[a]
Machining and abrasion		High	32 (12)	14	3 (2)	1	3 (3)	0
		Medium	821	8	3 (2)	1	4 (3)	0
		Low	4	3	0	0	0	1
Cleaning and maintenance		High	7	8	4	1	0	0
		Medium	4	1	2	3	0	1
		Low	0	2	0	2	1	0
Synthesis	Reaction phase	High	18	17	1	1	7	4
		Medium	6	6	3	2	2	2
		Low	3	4	0	1	2	5
	Collection, sorting and processing	High	11	6	1	0	3	2
		Medium	1	3	0	1	0	2
		Low	0	3	0	0	1	0
Handling and transfer of liquids		High	4	2	2	0	0	1
		Medium	1	3	0	1	0	1
		Low	3	3	1	2	2	0
Weighing and mixing		High	14	13	4	2	1	1
		Medium	2	3	1	2	1	3
		Low	3	3	0	1	2	0
Handling and transfer of powders		High	9 (2)	9	1	1	4	4
		Medium	4	4	0	0	0	0
		Low	2	0	0	0	1	1
Recycling		High	2	0	0	0	0	0
		Medium	0	0	0	0	0	0
		Low	3	5	0	0	0	0

exposure assessment situations							
Other metal oxides and mixtures		Metals		Other MNMs		Total	
Inhalation exposure	Dermal exposure[a]	Inhalation exposure	Dermal exposure[a]	Inhalation exposure	Dermal exposure[a]	Inhalation exposure	Dermal exposure[a]
3 (3)	0	0	0	3 (3)	0	44 (33)	15
1 (1)	0	0	0	3 (3)	0	12 (9)	9
0	0	0	0	0	0	4	4
27	18	13	4	2	0	53	31
0	8	3	9	0	4	9	26
0	1	0	3	2	0	3	8
2	0	4	4	3	2	35	28
2	2	1	3	0	0	14	15
1	3	2	0	1	2	9	15
0	0	1	0	1	0	17	8
6	0	1	2	5	3	13	11
0	6	1	1	2	5	4	15
3	0	0	0	0	0	9	3
0	1	0	0	0	0	1	6
0	2	0	0	0	0	6	7
3	0	0	0	5	2	27	18
3	4	0	0	0	3	7	15
0	2	1	1	2	2	8	9
3 (1)	1	2 (1)	1	4	1	23 (4)	17
0	1	0	0	0	3	4	8
0	0	0	0	0	0	3	1
0	1	0	0	1 (1)	0	3 (1)	1
0	0	0	0	0	0	0	0
1	0	0	0	0	0	4	5

Activity scenario	Quality assigned	Number of					
		CNTs and CNFs		Si-based		TiO_2	
		Inhalation exposure	Dermal exposure[a]	Inhalation exposure	Dermal exposure[a]	Inhalation exposure	Dermal exposure[a]
Spraying and finishing related processes	High	10 (1)	4	4	1	0	1
	Medium	0	4	1	2	2	0
	Low	0	1	0	2	1	2
Feeding into a process	High	6	2	6	0	0	0
	Medium	0	1	0	4	0	0
	Low	0	3	0	2	0	0
Testing and characterization	High	3 (1)	3	1	0	0	0
	Medium	2	2	0	0	0	0
	Low	2	1	0	1	0	0
Extrusion/injection moulding	High	2	1	0	0	0	0
	Medium	1	2	0	0	1	0
	Low	0	0	0	0	1	2
Packing	High	1	1	4	3	3	3
	Medium	2	1	0	0	1	0
	Low	0	1	0	1	0	1
Total		**163 (16)**	**147**	**42 (4)**	**38**	**43 (6)**	**37**

CNF: carbon nanofibres; CNT: carbon nanotubes; MNM: manufactured nanomaterials; Si-based: silicon-based; TiO_2: titanium dioxide.

[a] Indicates that the likelihood for dermal and/or ingestion exposure is considered to be equal. The number of simulation studies is given in parentheses.

exposure assessment situations							
Other metal oxides and mixtures		Metals		Other MNMs		Total	
Inhalation exposure	Dermal exposure[a]	Inhalation exposure	Dermal exposure[a]	Inhalation exposure	Dermal exposure[a]	Inhalation exposure	Dermal exposure[a]
2	1	3	2	5 (2)	1	24 (3)	10
2	0	1	2	2	3	8	11
2	5	1	1	2	3	6	14
8 (3)	1	0	0	3 (3)	0	23 (6)	3
2	5	0	0	0	0	2	10
0	1	0	0	0	0	0	6
0	0	1	1	2	1	7 (1)	5
0	0	1	0	0	1	3	3
0	0	0	1	0	0	2	3
4 (3)	0	0	0	5 (3)	0	11 (6)	1
0	1	0	0	0	2	2	5
0	0	0	0	1	1	2	3
2	1	1	1	5	0	16	9
0	1	1	1	2	3	6	6
0	0	0	0	0	4	0	7
77 (11)	**66**	**38 (1)**	**37**	**61 (15)**	**46**	**424 (53)**	**371**

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