WHO Guidelines on "Protecting Workers from Potential Risks of Manufactured Nanomaterials“

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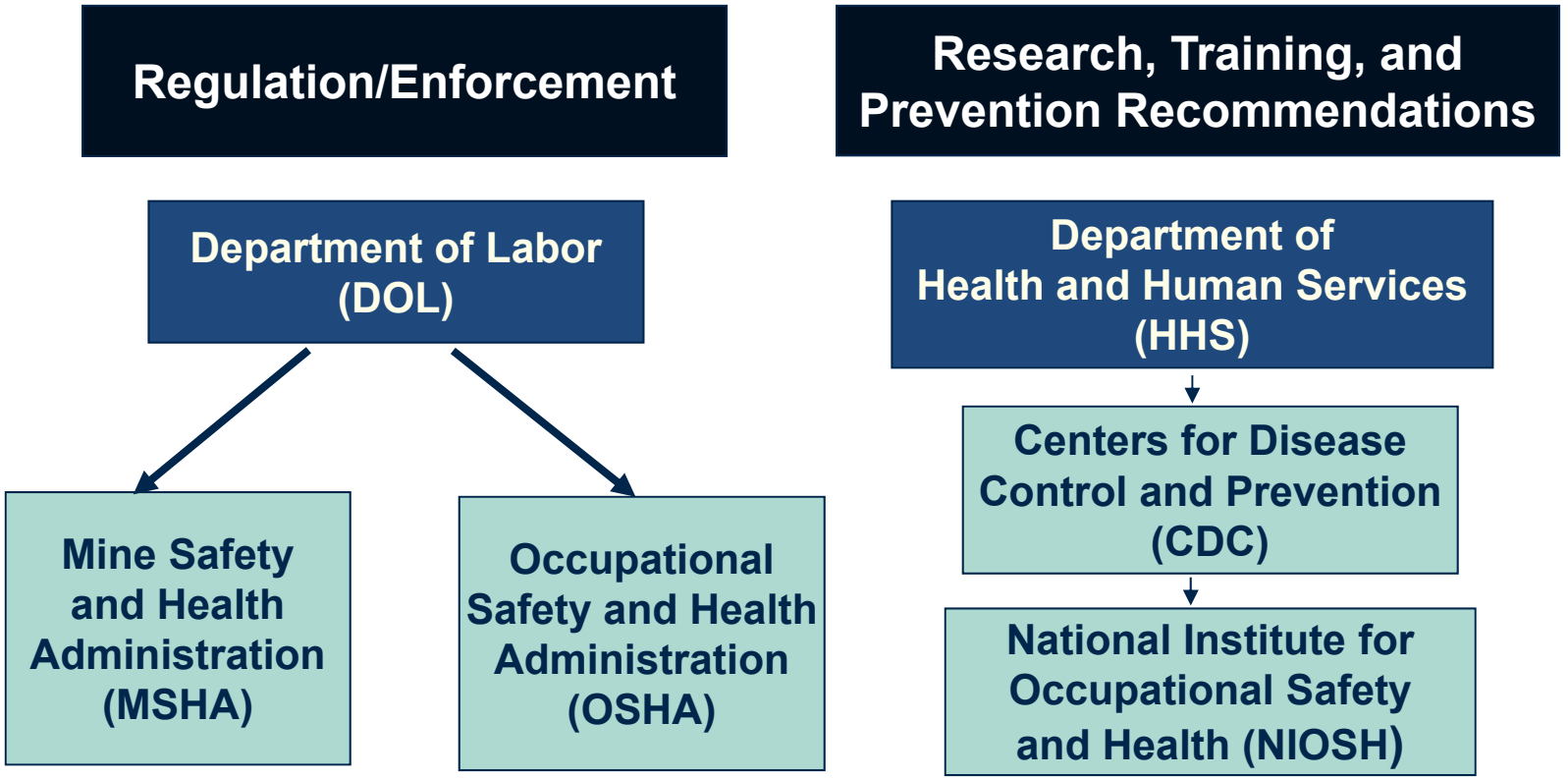
Occupational Safety & Health in the USG



NIOSH Mission

- Generate new knowledge in the field of occupational safety and health

- Transfer that research knowledge into practice.

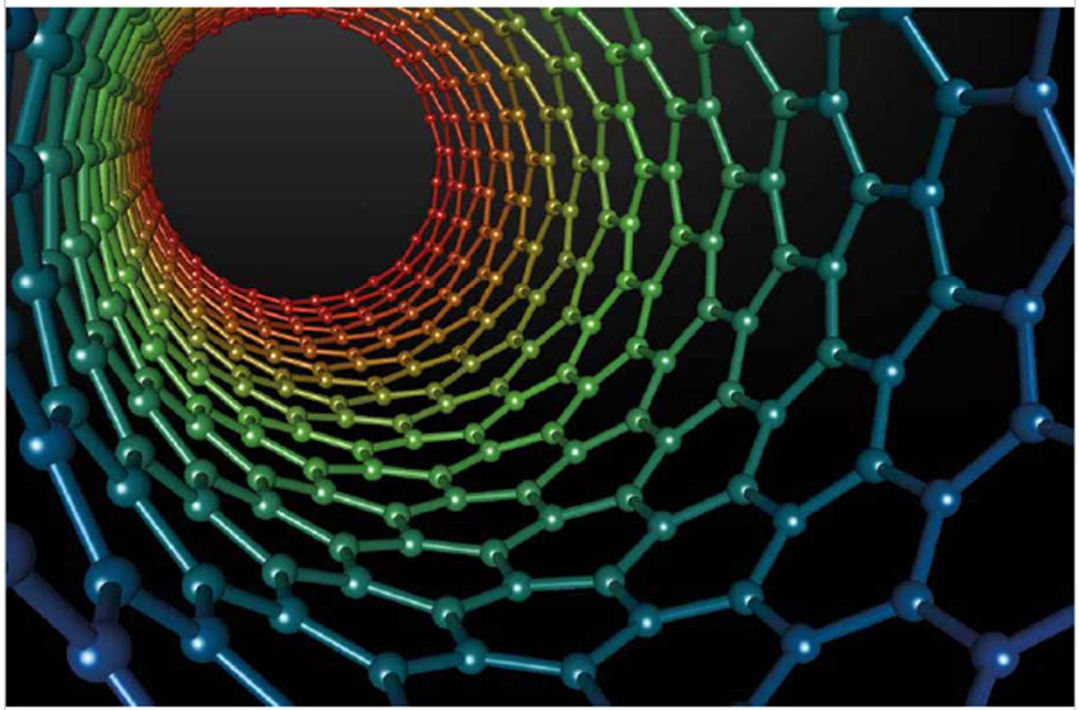
NIOSH Statutory Mandates

- NIOSH is mandated by the Occupational Safety and Health Act of 1970 to:
  - Produce criteria identifying toxic substances
  - Explore new problems … created by new technology
  - Provide criteria so that no employee will suffer material impairment of health

NIOSH Nanotechnology Research Center (NTRC)

- Chartered in 2004
- Over 50 projects; 90 scientists
- Cross-Institute matrix for greatest efficiency
- Published over 1,200 papers in scientific journals (2004—2016)
- Developed public-private partnerships with companies and universities to achieve greatest research impact
- Provides strong guidance to protect the nanotechnology workforce
- Leverages collaborations with other government agencies
- Uses **public health risk model** to achieve responsible development

WHO GUIDELINES ON PROTECTING WORKERS FROM POTENTIAL RISKS OF MANUFACTURED NANOMATERIALS



World Health Organization

94 p

WHO Guideline Process

- Relevant Question

- PI/ECO(S) [**P**opulation/situation-**I**ntervention/**E**xposure-**C**omparison-**O**utcome-(**S**tudy)] Question
  - Answerable with research

- Systematic Review
  - Protocol
  - Evidence summary / profiles
  - Judgement of the quality of the evidence : grading tables (GRADE)

- Recommendations (GRADE – **G**rading of **R**ecommendations, **A**ssessment, **D**evelopment and **E**valuation)

- 11 guideline questions developed (Delphi)
  - **Prioritization** of nanomaterials for reducing risks
  - **Hazard categories** for safe handling
  - **Highest exposure** situations and assessments
  - **Risk management** through training, health surveillance, risk mitigation, effectiveness of control measures
- 1 question on worker involvement in workplace risk assessment and management could not have systematic review due to lack of studies and was formulated as a best practice (*How will workers and their representatives participate in the workplace risk assessment and management of handling MNMs?*)

10 Questions, 10 systematic reviews

1 *Risk priority:* 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 *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?

10 Questions, 10 systematic reviews (cont.)

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 low- and medium-income countries?

6 *Occupational exposure limits (OELs):* 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?

10 Questions, 10 systematic reviews (cont.)

8 *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:* What training should be provided to workers who are at risk from exposure to the specific MNMs or groups of MNMs?

10 *Health surveillance:* What health surveillance approaches, if any, should be implemented for workers at risk from exposure to specific MNMs or groups of MNMs?

Timeline

2010 planning approval by WHO

2010-2013 background paper, experts, systematic review volunteers, key questions

2013-2016 expert meetings, systematic reviews

- 30 September – 1 October 2013 - meeting Johannesburg, NIOH
- 9-10 February 2015 - meeting Paris, ANSES
- 3-4 September 2015 - meeting Brussels, ETUI
- 18-19 April 2016 - meeting Dortmund, BAuA

2017 WHO clearance

- 12 December 2017 – publication of the WHO guidelines on nanomaterial safety
- http://apps.who.int/iris/bitstream/10665/259671/1/9789241550048-eng.pdf

Guiding principles

1 *Precautionary approach:* 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

2 *Hierarchy of controls:* The implementation of controls to reduce workers' exposure should be considered the goal of a successful industrial hygiene programme:

- eliminate the hazard;
- substitute the hazardous material by a less harmful agent;
- apply engineering controls such as isolation, local exhaust ventilation or dust suppression techniques;
- consider administrative controls such as worker education, and training or scheduling;
- use as a last resort, personal protective equipment (PPE).

Best practice

1 *Classification of nanomaterials:* Class MNMs into three groups:

- specific toxicity: (i) MNM 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;
- respirable fibres: rigid, biopersistent or biodurable and respirable MNM, which have dimensions agreed upon by WHO working group for man-made mineral fibres (fibre length > 5 μm, fibre diameter < 3 μm and aspect ratio > 3);
- granular biopersistent particles: respirable granular biodurable particles that are characterized by both low dissolution rates and lack of high specific toxicity.

2 *Worker involvement:* Workers should be involved in health and safety issues. This will lead to more optimal control of health and safety risks.

3 *Training and education of workers:* Workers potentially exposed to MNMs should be educated on the risks of MNMs and trained in how they can best protect themselves.

Recommendations: Grouping

- Assess health hazards (3)
- Assess exposure (3)
- Control exposure (5)
- Recommendations could not be made (2)

Recommendations: Assess Health Hazards

1 Assign hazard classes to all MNMs according to the Globally Harmonized System 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.

2 Update safety data sheets with MNM-specific hazard information or indicate which toxicological end-points did not have adequate testing available.

3 For the respirable fibres and granular biopersistent particles' groups, use the available classification of MNMs for provisional classification of nanomaterials of the same group.

Assess Health Hazards: Table 2

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 (M)[f]	No data	No data	Cat 1 (L)
MWCNT	No	No	Cat 2A (H)[g]	No	Cat 2 (H)	MWCNT–7: Cat 2 (M), IARC 2B Other MWCNTs: IARC 3 (M)	No	No data	Cat 1 (M)
AgNP	No	No	No	Cat 1B (H)	No	No data	No	No data	Cat 1 inhalation (M) Cat 2 oral (M)
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	No data	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 (H)
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)

Recommendations: Assess Exposure

4 Assess workers' exposure in workplaces with methods similar to those used for the proposed specific occupational exposure limit (OEL) value of the MNM.

5 Because there are no specific regulatory OEL values for MNMs in workplaces, assess 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.

6 If specific OELs for MNMs are not available in workplaces, use 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. For dermal exposure assessment, there was insufficient evidence to recommend one method of dermal exposure assessment over another.

Assess Exposure: example from Annex 1

Category	Study reference	MNM and specs	OEL name	Mass concentr. µg/m³	Particle concentr. (particle/ml, fibres/cm³)	Surface concentr. (nm²/cm³)	Derivation approach
Inhalation exposure: general MNM approach							
MNM	Guidotti 2010	Particles ≤ 2500 nm	BOEL	30	ND	ND	Environmental
MNM	McGarry 2013	Airborne particles from NT 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, 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	OEL	ND	0.01	ND	Bridging/ grouping

Recommendations: Control Exposure

7 Focus control of exposure on preventing inhalation exposure with the aim of reducing it as much as possible.

8 Reduce 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, implement the highest level of controls to prevent workers from any exposure. When more information is available, take a more tailored approach.

9 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 personal protective equipment (PPE) being used only as a last resort.

Recommendations: Control Exposure

10 Prevent dermal exposure by occupational hygiene measures such as surface cleaning and the use of appropriate gloves.

11 When assessment and measurement by a workplace safety expert is not available, use control banding for nanomaterials to select exposure control measures in the workplace. Owing to a lack of studies, one method of control banding over another cannot be recommended.

Recommendations could not be made

12 *Health Surveillance:* A recommendation for targeted MNM-specific health surveillance programmes over existing health surveillance programmes that are already in use cannot be made owing to the lack of evidence.

13 *Training and involvement of workers:* One form of training of workers over another, or one form of worker involvement over another, cannot be recommended owing to the lack of studies available.

Next steps

Implementation:

- considerable efforts are needed by all stakeholders to ensure country implementation of these guidelines with a particular focus on low and middle income countries;

- communication plan through stakeholder networks including the WHO Global Network of Collaborating Centres;

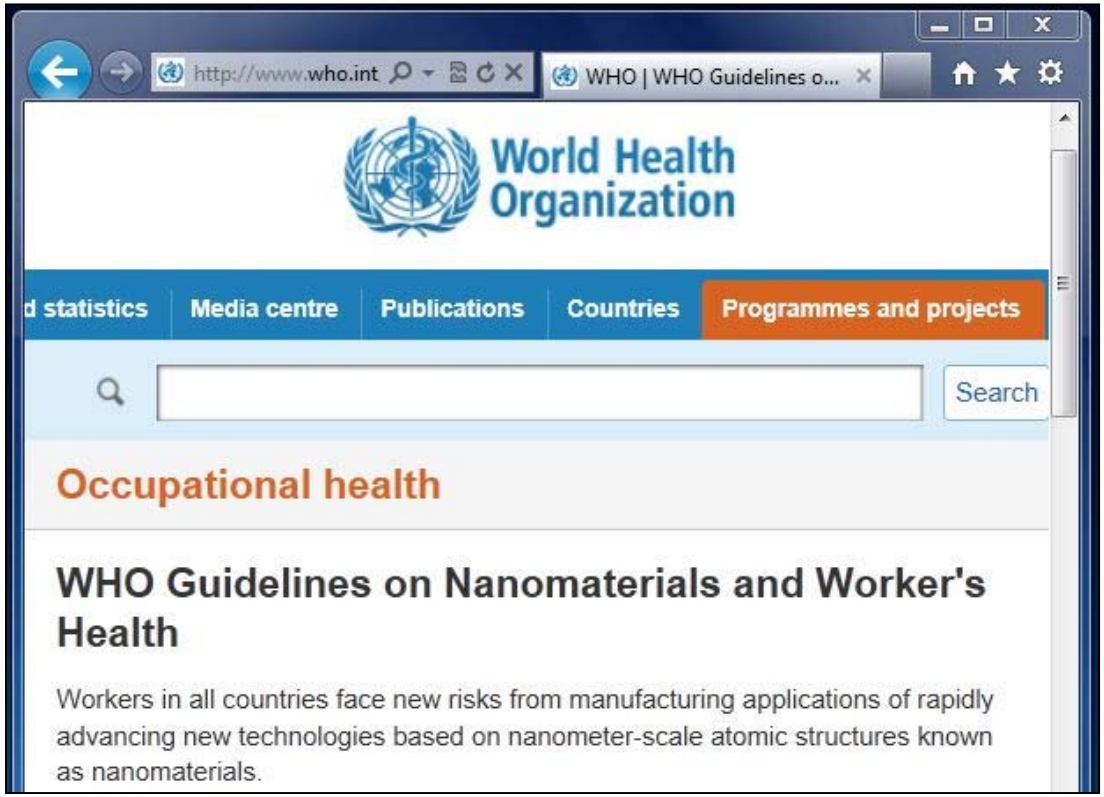
- simplified summaries will be prepared for employers and workers to ease implementation and monitoring.

Updating guidelines:

- proposal to update these guidelines in 2022.

Communication

- Dedicated public nanotechnology page at www.who.int/occupational_health/topics/nanotechnologies/en/



Suggested questions for breakouts

1 *How these guidelines could be utilized in your organization?*

2 *What should the guidelines implementation phase focus on?*

3 *Are there particular recommendations requiring more in-depth guidance?*

4 *Are there any specific areas that these guidelines missed?*

5 *Are there any additional thoughts about these guidelines?*

Thank you!


NIOSH
World Health Organization
OECD
unitar
United Nations Institute for Training and Research

A WHO guideline…..

- **Assists** policy makers or other stakeholders to make **informed decisions**
- **Contains** recommendations about health interventions (clinical, public health or policy)
- WHO has adopted internationally recognized standards and methods for guideline development to ensure that guidelines are **free from bias, meet a public health need**

A recommendation:

- **Provides information** about what policy-makers, health-care providers or patients should do
- **Implies a choice** between different interventions that have an impact on health and that have implications for the use of resources.

Principles of recommendations:

- Based on a comprehensive and objective assessment of the available evidence.
- Protocolled process of how, by whom, and on what basis a recommendation has been developed.

Problem:
Oxman, Lavis & Fretheim, Lancet. 2007;369(9576):1883-9.

WHO guidelines are insufficiently transparent and not evidence based

- Lack of use of systematic reviews
- Lack of transparency about judgements
- Too much dependence on expert opinion
- Lack of emphasis on adapting global guidelines to end users' needs
- Tension between time taken and when advice needed
- Lack of resources

Quality of the evidence: GRADE

- Strongly **evidence-based**
- GRADE **rates** the quality of the evidence:
  - the extent to which we have ***confidence in an estimate of the effect***
- Can be applied to risk or aetiology reviews
- Used to **judge** the strength of a recommendation

Systematic Review

"A review in which bias has been reduced by the systematic identification, appraisal, synthesis, and, if relevant statistical aggregation of all relevant studies on a specific topic according to a predetermined and explicit method."

Quorum 1999

"A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used."

Prisma 2009

A good systematic review

1. Answers a clearly defined question: P(I/E)COS
2. Has clear inclusion / exclusion criteria
3. Explains how studies were located and search strategy
4. Has study selection and data-extraction in duplicate
5. Explains handling of missing data
6. Assesses risk of bias in primary studies
7. Explains how data were combined
8. Includes a sensitivity analysis of risk of bias, assumptions
9. Assesses publication bias
10. Evaluates the quality of evidence with GRADE

All this is in a protocol to prevent data-driven analysis (Prospero)

1. Clearly defined question

- P I/E C O S relates question to research
- Can needle stick injuries be prevented?
  - Blunt (I) versus sharp (C) needles to prevent needle stick injuries (O) in surgeons (P)
  - Randomised Controlled Trials (S)
- Where does exposure to nanomaterials occur?
  - In workplaces where exposure to manufactured nanomaterials has been measured appropriately (P), what is the exposure level (O) categorised according to task (E) in any survey (S)

6. Risk of Bias Primary Studies

- Not all studies provide equally valid results
- Studies that measured exposure according to a widely-accepted protocol
  - Some fulfill this criterion better than others
  - Those that don’t are less valid, at more risk of bias
- Blinded outcome assessment

7. Combination of studies

- How to synthesize the results?
- No two studies alike
- Define in advance when studies considered similar enough to be combined
  - Handling
  - Synthesizing
  - Waste collection
- A well-defined question helps to prevent finding widely differing studies

10. Quality of evidence GRADE

- ***Across studies !!!!***

- ***Overall*** judgement of quality of evidence: high to very low
- Randomized trials start at high quality but downgraded when
  1. limitations in study design or implementation
  2. inconsistency of results
  3. indirectness of evidence
  4. imprecision of estimates (wide confidence intervals)
  5. publication bias

- Observational studies start at low quality but upgraded when
  6. a very large magnitude of effect
  7. a dose-response gradient
  8. if all plausible biases would reduce an apparent treatment effect

Why Nanomaterials in WHO?

- Nanotechnology is an **emerging technology** with increasing use patterns worldwide
- **Risks** are not fully evaluated
- **Information** is not always available in an equal and equitable manner
- There is need to provide the **same level of protection** to workers dealing with manufactured nanomaterials (MNM) across the world
- **Global, science-based guidelines** provide foundation for health protection activities in countries

Contributors

- *In kind contributions by institutions within the Global Network of WHO CC on OH:*
  - Institut de recherche Robert-Sauvé en santé et en sécurité du travail (**IRSST**), Canada (reviewers from University of Montréal)
  - National Institute for Occupational Safety and Health (**NIOSH**), USA (reviewers, Chair)
  - Fundacentro, Brazil (reviewers, GDG member)
  - Italian National Insurance for Work Accidents and Occupational Diseases (**INAIL**), Italy (reviewers)
  - Finnish Institute of Occupational Health (**FIOH**), Finland (reviewers and methodologist)
  - National Institute of Occupational Health (**NIOH**), South Africa (reviewers, GDG member)
  - University of Occupational and Environment Health (**UEOH**), Japan (reviewers, GDG member)
  - Korean Occupational Health and Safety Agency (**KOSHA**), Republic of Korea (reviewers, GDG member)

- *Other contributors:*
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  - National Institute of Occupational Health (**STAMI**), Norway (reviewers)
  - Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**) (reviewers)
  - **Hoseo** University, South Korea (reviewers)
  - **ETUI** (Vice-Chair)
  - Members of the **Guideline Development Group**
  - Members of the **External Review Group**
  - WHO Steering Group members (2 from HQ, 1 from EURO)