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Managing Risks when Using Nanomaterials in Research

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As the number of engineered nanomaterials (ENM) used in research increases with an incredible speed, health and safety specialists are continuously faced with the challenge of evaluating the risks involved with these materials. Nowadays there is not enough information about their toxicology and new materials are continuously being developed. Preliminary scientific results indicate that ENM might have a damaging impact on human health, which makes it even more important to have the right mitigation measures in place.
To address this challenge, a practical risk management procedure for working with ENM is presented. The task of choosing preventive and protective measures is largely simplified with a schematic decision tree approach that allows for a simple determination of the hazard level and Nano classification of a laboratory with three control bands. The methodology is adaptive and learning based, and it takes into account both the hazard level of the ENM and the exposure.
The usefulness and completeness of the methodology is demonstrated with an extensive classification of the activities involving ENM in one of the EPFL research units. The research group handles inorganic nanomaterials both in powder form and in suspension. This classification allowed for a complete hazard and risk mapping, which facilitates resource allocation decision-making. This was demonstrated with the proposition of a set of technical, organizational and personal mitigation measures that has since then been implemented in the laboratories.

1. Introduction

Occupational safety and health (OSH) specialists analyze workplaces to ensure the safety and health of workers and the environment. The management of occupational health and safety in a research environment poses different challenges compared to industry. Research activities are in constant evolution with increasing multidisciplinary research projects and increasing population densities with a large turnover. A lot of effort has been put into improving the safety training and culture in the academic world, but despite the increased awareness of risks, risk management in this environment remains complex compared to industry and safety culture is hard to implement (Marendaz et al., 2013). In order to manage the risks related to scientific research activities, EPFL has created a specialized OHS team, the Safety Competence Center (SCC) that consists of researchers with a background in chemistry, biology and physics.
Nanotechnology is a very exciting field of investigation with a wide range of possible applications in materials science, medicine and many more, but little is known about the potential health effects of ENM (Oberdörster et al., 2005). Studies have shown that the health effects of ENM differ from those of the corresponding bulk material (NIOSH, 2011), and similar effects can be seen for materials that only exist in nanoform, such as carbon nanotubes and graphene (NIOSH, 2013). Recommendations on working safely with nanomaterials have been developed in the past decade by government agencies and occupational health organizations such as the World Health Organization (WHO, 2017).
Even though a lot of progress has been made in generating information on health effects and exposure data, the risk assessment and management of the hazards associated with the work with ENM remains one of the big challenges for the OHS community today. It is difficult to measure the emission from a particular procedure, in particular in a research setting where reactions are often run on a small scale (mg – g).

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To take up on this challenge, EPFL created a new safety team targeting ENM risks that includes health and safety specialists, nanoparticle users and public health representatives. This group developed a control banding methodology that ensures a satisfactory protection level for the collaborators without stifling innovation, as is sometimes feared among researchers. In the absence of dose-response relationships and quantitative exposure measurements, control banding has been widely adopted by OHS community as a pragmatic tool in implementing a risk management strategy based on a precautionary approach. Control banding was developed in the pharmaceutical industry as a practical tool to manage risks resulting from exposure to a wide variety of potentially hazardous substances in the absence of firm toxicological and exposure data (Brouwer, 2012). In this approach, hazards and exposure are estimated and combined into broad risk classes, the so-called bands (ISO12901-2:2014, 2014). Materials and processes with similar risks will thereby be treated in a similar manner, and a detailed risk analysis procedure is avoided. Control banding methods have started to gain traction for treatment of the occupational hazards involved with work with nanomaterials (Eastlake et al., 2016). At EPFL over 30 research groups (in basic sciences, engineering or life sciences) produce, modify or use ENM in approximately 100 laboratories with over 300 different associated production or characterization processes. This work demonstrates the field application of our risk management methodology in this academic setting.

2. The methodology

The nano-safety team has developed a control banding method for management of nanomaterial hazards. The first version of the methodology was published in 2010 (Groso et al., 2010), that is used to evaluate the risk involved with each process where nanomaterials are being produced or handled. After positive feedback from the research society, an improved methodology was published in 2016 (Groso et al., 2016), that takes both the hazard of the material and the exposure risk of the process into account. Instead of a detailed and complicated analysis of each material, and a subsequent search for toxicological information and implementation of specific corrective measures, the materials are classified in the groups, i.e. control bands. All materials that are found in the same control band, i.e. have similar hazardous properties, are then treated in the same way. The methodology is complete and easy to use. Researchers without any specific safety training can classify their materials and their processes by following the proposed steps in the form of “Yes, No, I do not know” questions. This procedure is based on a precautionary principle, which increases the hazard level if the answer to any given question is “I do not know”. This approach increases the importance of searching for as much information as possible before answering a question. A material whose hazardous properties are not fully known will thus be classified into a higher hazard group than one that is known to be nontoxic.

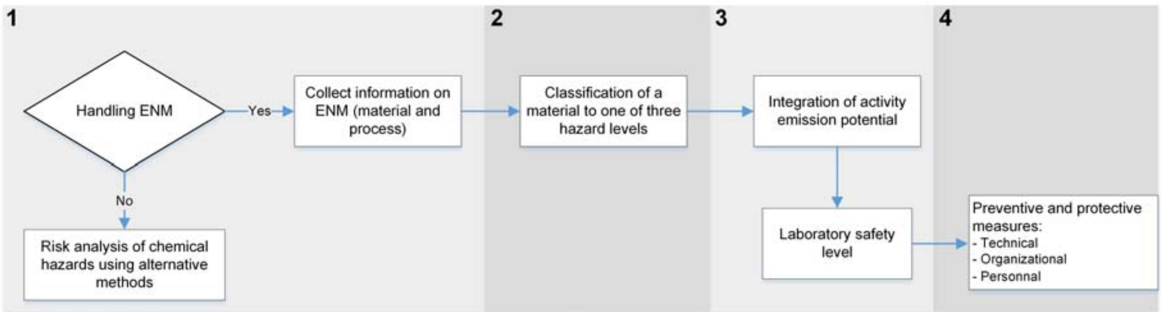

Figure 1: Flow chart of the process for classification of nanomaterial laboratories using the EPFL method.

2.1 Classification into hazard bands

If the nanomaterial or its corresponding bulk counterpart has already been classified by a relevant authority, it is automatically entered into one of the three control bands defined by the nano-safety team.
The hazard classification of a material using the EPFL methodology is based on the physicochemical properties of the compound. The researcher goes through a decision tree with a series of questions regarding the properties of the nanomaterials and reaches a classification. The first questions cover the solubility of the compound, since dissolved nanomaterials are prone to releasing toxic ions (Stohs, Bagchi, 1995), and then whether the material is a bio persistent or toxic nanofiber, since these are known to have a damaging effect on the lungs (Pacurari et al., 2016). The subsequent questions concern the composition of the material, whether it is a metal, an alloy or a pure carbon compound and if the material is amorphous. Finally, the last questions

are about the band gap energy of the material, since there is a link between the toxicity and the band gap energy of a nanomaterial. (Zhang et al., 2012)
The materials are distributed into three hazard bands as follows:

- H1 substances presumed not to be harmful to human health (there is no report to date showing adverse effect). Effect: no significant effect to health;
- H2 substances presumed to be harmful to human health. Effect: moderate or transient effects to health;
- H3 substances known or presumed to have significant toxicity in humans. Effect: significant or permanent effect to health.

2.2 Classification of processes

When analysing the exposure level of the process the state of the ENM plays an important role. When handling a material in powder form the risk of exposure is much higher than when working in a suspension. If there is a possibility of forming an aerosol when working with the suspension, the exposure risk increases dramatically again, since the aerosol droplets can be inhaled.
The exposure risk when working with ENM in a matrix, such as a fixed thin layer, is considered very low if there is no possibility to release powders. All these processes are therefore classified as Nano 1. Identically, processes that are confined in a glove box or another sealed chamber, are also considered Nano 1 due to the low risk of exposure. For the lower two hazard levels, H1 and H2, the time of exposure plays an important role. The longer the researcher is exposed to the ENM, the higher the risk of exposure. For materials of the highest hazard level, H3, the time of exposure is not taken into consideration as one dose is considered to be enough to cause serious health damage. Each step of the process is evaluated separately. Information about the form of the material and the possibility to release powders or aerosols is used to classify the process accordingly. The process that gives the highest Nano classification gives the classification for the whole laboratory, and all measures apply to everyone who enters in the premises.

2.3 Mitigation measures

When the laboratory has been classified, a series of predefined mitigation measures is proposed. One set of measures that apply to all ENM laboratories, which includes information on transport, reception and shipping of ENM; a waste handling procedure and protection of pregnant women. For the different levels of Nano laboratories, a set of technical, organizational and personal measures as well as specifications on who can perform cleaning, auditing and follow-up procedures is suggested.

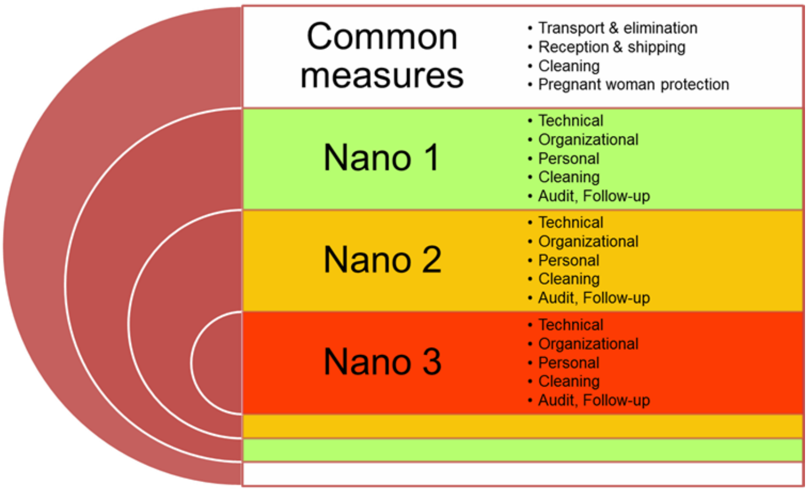

Figure 2: A schematic representation of the mitigation measures proposed for Nano classified laboratories.

3. Case study

To demonstrate the facility and usefulness of the published method, a step by step classification of the activities of one of the EPFL research groups is shown here. The group uses a great variety of different materials in the nano range and just above, and the researchers have different backgrounds and different education levels. No specific details on the research of the group is necessary for this classification, as long as there is the necessary information on the material and the main steps of the process. The chosen group worked in four laboratories, and the ENM activities were equally distributed between these laboratories.

3.1 Hazard classification of materials

In the first instance, the research group provided a complete list of materials that were used or present in their laboratories. A first screening was made to exclude all materials that did not fit the European Commission definition of a nanomaterial (European Commission, 2011). The remaining materials are listed in Table 1.
The materials that were investigated in this study are all metal or metalloid based. Metal oxides (Fe, Ti, Al and Cr) are produced and characterized in the laboratories, and finally used in various processes. Silica is used in characterization processes, as well as in interaction studies between nanomaterials and cells. Gold particles are synthesized in suspension and interactions between these nanoparticles and cells are being investigated.

Table 1: Representation of ENM used in the model research unit.

Entry	ENM	Size	Use
1	TiO_2	25 nm, mixture	Chemical treatment of nanomaterial
2	TiO_2	25 nm (agglomerated Dv50>500nm)	Doping
3	γ-Fe_2O_3	9-40 nm	Synthesis of iron oxide nanoparticles
4	Al_2O_3	10 nm à 600 nm	Characterization, various procedures
5	Cr_2O_3	10 nm à 600 nm	Characterization, various procedures
6	SiO_2	10 nm à 600 nm	Characterization, various procedures
7	SiO_2	10-80 nm	Interaction between nanomaterials and cells
8	Au	20 nm	Synthesis of nanoparticles in suspension
9	Au	10-80 nm	Interaction between nanomaterials and cells

The second step using the EPFL method was the hazard classification of the above-mentioned materials. The six materials were put through the hazard band decision tree and assigned into a hazard band.
Out of these six materials only one, γ-Fe_2O_3, was already classified by a relevant authority. γ-Fe_2O_3 is not classified as hazardous and was thereby assigned into the H1 category (Table 2, entry 2).
When the metals oxides were analysed with the questionnaire they were classified in the final set of questions. The first part of the questionnaire handles water soluble materials, nanofibers, pure carbon-based materials, and pure metals and alloys with metallic properties. The materials in question are semiconductors and could thereby be classified based on their band gap energy, more specifically the energy of the lower edge of the conductive band (Table 2, entries 1, 3 and 4).
The hazardousness of silica nanoparticles is known, and there is a question under the amorphous category that directly put silica in the H2 band (Table 2, entry 5). The same is true for gold, it is known that gold particles with a diameter of 5 nm can disrupt the function of DNA (Tsoli et al., 2005), while larger particles can be considered safe. Under the category of pure metals all materials that are not gold with a diameter below 10 nm are classified in the H1 band (Table 2, entry 6).

Table 2: List of hazard classifications of ENM used in model unit and a motivation for their classification.

Entry	ENM	Hazard class	Motivation
1	TiO_2	H2	Lower edge of conductive band -4.2 eV > E > -4.8 eV
2	γ-Fe_2O_3	H1	Classified by Globally Harmonized System of Classification and Labelling of Chemicals
3	Al_2O_3	H2	Lower edge of conductive band -4.2 eV > E > -4.8 eV
4	Cr_2O_3	H2	Lower edge of conductive band -4.2 eV > E > -4.8 eV
5	SiO_2	H2	Amorphous material, silica
6	Au	H1	Pure metal, Au with particle size >10 nm

3.2 Nano classification of processes

In the third step the processes where the ENM in Table 2 were used were evaluated using the second set of decision trees. Each process where the materials were used was evaluated separately. A comprehensive list of the processes of the model laboratory is found in table 3.
The metal oxides that were assigned H2 were classified using the decision tree specific for H2 materials. TiO_2 was used in powder form, which led to a set of questions for these and the amount used was above 200 nm (Table 3, entry 1). A frequency – duration calculation based on the occupational exposure limit for multiple inert particles was used to determine the final Nano level of the process. The matrix published by Groso et al.

(2016) put this process in the green area, and therefore as a Nano 2 classified process. The same result was found when classifying Al_2O_3, Cr_2O_3 and SiO_2 with the decision tree for H2 materials, all these processes were found to be Nano 2 (Table 3, entries 4, 5 and 6).
In the second process, TiO_2 remains in suspension during the entire process (Table 3, entry 2). The parts of the process where there is a possibility to release aerosols were confined in a closed milieu. Since the risk of exposure when working with ENM in suspension is much lower than when working with a powder, and there was no risk of the workers being exposed to aerosols, this process was classified as Nano 1.
The H1 classified materials Au and *γ-Fe_2O_3* were both used only in suspension and were classified as Nano 1 by using the decision tree for classification of H1 materials the processes (Table 3, entries 7 and 8).

Table 3: List of processes where ENM are used and their subsequent Nano classification.

Entry	ENM	Amount per batch	Process	Nano class
1	TiO_2	10 – 1000 mg	Used in powder form > 200 mg Low frequency, short duration	Nano 2
2	TiO_2	20 g	Work in suspension Aerosol released in closed milieu	Nano 1
3	γ-Fe_2O_3	< 250 mg	Work in suspension	Nano 1
4	Al_2O_3	10 – 1000 mg	Used in powder form > 200 mg Low frequency, short duration	Nano 2
5	Cr_2O_3	10 – 1000 mg	Used in powder form > 200 mg Low frequency, short duration	Nano 2
6	SiO_2	10 – 1000 mg	Used in powder form > 200 mg Low frequency, short duration	Nano 2
7	SiO_2	1 mg	Work in suspension	Nano 1
8	Au	< 250 mg	Work in suspension	Nano 1

After classification of all the processes, the S of the STOP (substitution, organizational, technical and personal) method for protective measures was applied on the parts of the processes with the highest classification in an attempt to lower the final classification. In this case none on the materials could be substituted, and the processes could not be confined completely, so the classifications of the processes remained unchanged and the highest classification that was reached, namely Nano 2, was assigned to the whole research unit.

3.3 Proposed mitigation measures

A Nano 1 classified laboratory remains, technically and operationally, a standard chemistry laboratory. No additional technical measures are being imposed for this kind of work. The personal protective equipment remains that of a standard chemistry laboratory i.e. safety glasses, a cotton laboratory coat and protective gloves that are adapted to the solvents and materials at hand.
A Nano 2 laboratory on the other hand, requires more extensive modifications to the safety infrastructure. Work in a fume hood is mandatory, and the extraction air must be filtered with an H14 filter to avoid contamination of the air outside the laboratory. In addition, the access to the laboratory must be restricted to authorized personnel and working procedures must be written down. On a personal protective level, all personnel who works in the laboratory must wear a non-woven lab coat, overshoes and two pairs of gloves. The cost of these measures is substantial. These expenses could be limited greatly by transferring all the Nano 2 classified processes into one laboratory, leaving the remaining three laboratories classified as Nano 1.

4. Conclusions

The methodology published by the Nano-safety team was used to classify the materials and processes of one of the research groups at EPFL to demonstrate its utility and simplicity of use. A representative research group was chosen, and the processes include work with powders and in suspension. The materials that were classified were readily assigned into one of the three hazard bands using the pre-set questions in the decision tree. All of the classified materials (metal oxides, silicon oxide and gold) were found to be in the H1 and H2 hazard bands, i.e. with low to moderate toxicity.

A series of processes using the previously classified materials on laboratory scale were successfully assigned into Nano levels using the subsequent decision trees designed for each hazard band. The work was conducted with up to 1 g of H2 material as a powder.

The proposed measures proved to be applicable, and with some additional effort on the part of the OHS team at EPFL, the costs could be reduced by some supplementary organizational measures. This work is a beautiful example of a collaborative approach, where OHS specialists can work together with researchers to find a solution that ensures optimum protection of the health of the researchers without for that sake imposing restrictions on their research projects.

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References

Brouwer Derk H. Control Banding Approaches for Nanomaterials [Journal] // The Annals of Occupational Hygiene. - 2012. - Vol. 56. - pp. 506-514.

Eastlake Adrienne, Zumwalde Ralph and Geraci Charles Can control banding be useful for the safe handling of nanomaterials? A systematic review [Journal] // Journal of Nanoparticle Research. - 22 6 2016. - Vol. 18. - p. 169. - ISSN: 1572-896X.

European Commission E. C. Commission Recommendation of 18 October 2011 on the definition of nanomaterial [Journal] // Official Journal of the European Union. - 20 10 2011.

Groso Amela [et al.] Engineered nanomaterials: toward effective safety management in research laboratories [Journal] // Journal of Nanobiotechnology. - 15 3 2016. - Vol. 14. - p. 21. - ISSN: 1477-3155.

Groso Amela [et al.] Management of nanomaterials safety in research environment [Journal] // Particle and Fibre Toxicology. - 10 12 2010. - Vol. 7. - p. 40. - ISSN: 1743-8977.

ISO12901-2:2014 Nanotechnologies -- Occupational risk management applied to engineered nanomaterials -- Part 2: Use of the control banding approach [Report] : Standard / International Organization for Standardization. - Geneva : [s.n.], 2014.

Marendaz Jean-Luc, Suard Jean-Claude and Meyer Thierry A systematic tool for Assessment and Classification of Hazards in Laboratories (ACHiL) [Journal] // Safety Science. - 2013. - Vol. 53. - pp. 168-176. - ISSN: 0925-7535.

Marendaz Jean-Luc, Suard Jean-Claude and Meyer Thierry A systematic tool for Assessment and Classification of Hazards in Laboratories (ACHiL) [Journal] // Safety Science. - 2013. - Vol. 53. - pp. 168-176. - ISSN: 0925-7535.

Nanotechnologies -- Occupational risk management applied to engineered nanomaterials -- Part 2: Use of the control banding approach [Report] : Standard / International Organization for Standardization. - Geneva : [s.n.], 2014.

NIOSH Current Intelligence Bulletin 63: Occupational Exposure to Titanium Dioxide. - 2011.

NIOSH Current Intelligence Bulletin 65: Occupational Exposure to Carbon Nanotubes and Nanofibers. - 2013.

Oberdörster Günter, Oberdörster Eva and Oberdörster Jan Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles [Journal] // Environmental Health Perspectives. - 2005. - Vol. 113. - pp. 823-839.

Pacurari Maricica [et al.] A review on the respiratory system toxicity of carbon nanoparticles [Journal] // International journal of environmental research and public health. - [s.l.] : Multidisciplinary Digital Publishing Institute, 2016. - Vol. 13. - p. 325.

Stohs S. J. and Bagchi D. Oxidative mechanisms in the toxicity of metal ions [Journal] // Free Radical Biology and Medicine. - 1995. - Vol. 18. - pp. 321-336. - ISSN: 0891-5849.

Tsoli Maria [et al.] Cellular Uptake and Toxicity of Au55 Clusters [Journal] // Small. - 2005. - Vol. 1. - pp. 841-844.

WHO WHO guidelines on protecting workers from potential risks of manufactured nanomaterials [Book]. - 2017.

Zhang Haiyuan [et al.] Use of Metal Oxide Nanoparticle Band Gap To Develop a Predictive Paradigm for Oxidative Stress and Acute Pulmonary Inflammation [Journal] // ACS Nano. - 2012. - Vol. 6. - pp. 4349-4368. - PMID: 22502734.

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