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Employing Nanosafety Standards in a Nanomaterial Research Environment: Lessons Learned and Refinement Potential

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Abstract: Extensive research is currently being conducted on nanotechnologies worldwide, and the applications of nanomaterials are continuously expanding. Given their unique intrinsic characteristics, such as their small size and increased reactivity, nanomaterials may pose an occupational, environmental or consumer hazard. Therefore, a highly important aspect of ensuring the sustainable use of nanotechnologies is the establishment of proper health and safety practices. The area of nanosafety research has produced significant outcomes the last decades, and many of these achievements have been reflected in the standardization field. In this work, a discussion of prominent nanosafety standards (ISO/TS 12901-2:2014 and ISO/TR 12885:2018) is presented, based on the barriers faced during the endeavor to apply their principles within a research context. A critical viewpoint regarding their application is presented, and gaps faced in adapting the standards to the materials and processes applied are noted. Additionally, approaches that were followed to circumvent these gaps are also highlighted as suggestions to potentially overcome these barriers in future standardization efforts.

Keywords: nanosafety; occupational safety; standardization gaps; barriers; nanomaterial research; control banding

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1. Introduction

Nanotechnology, defined as "the understanding and control of matter at dimensions between 1 and 100 nm where unique phenomena enable novel applications", has been expanding considerably in the last decades, and a variety of industrial and scientific applications have been outlined for the future of nanomaterials [1]. The unique properties of nanomaterials are being exploited in a multitude of areas, such as in medicine and drug delivery [2], in the food industry [3], in agriculture [4], as pollutant removal agents in environmental remediation science [5] and as additives in polymeric coatings for applications such as corrosion protection [6].

While the prospect of extensive nanomaterial use in a large-scale level is highly promising from a technological point of view, the sustainability aspects of nanomaterials, such as environmental and human safety issues need to be thoroughly evaluated to facilitate the viable and undisrupted evolution of this domain. Regarding the human safety aspects in particular, nanomaterial toxicity concerns, which are greatly determined by the material's properties such as its size, shape, surface properties and charge have been expressed and documented in the literature [7]. Thus, nanomaterials can pose a potential exposure hazard within the occupational environment, since exposure through various routes such as inhalation, ingestion or skin contact is possible during the production, handling, processing or end-of-life treatment of the nanomaterial products [8]. Furthermore, safety concerns can be a substantial uncertainty factor in communicating the benefits of nanotechnology to the public [9], thus negatively impacting the commercial and market development of this technological field if not adequately examined and clarified.

The branch of nanosafety deals with the study of the safety aspects of nanomaterials. Nanosafety covers topics on an array of highly varying although interconnected sectors, ranging from nanotoxicology [10] to occupational exposure assessments [11], environmental exposure assessments [12] and evaluations of nanomaterials' environmental fate [13]. Several breakthrough developments have been realized in occupational nanosafety research over the last decade. Various prominent nanomaterial species that are extensively produced and applied have been mapped quite considerably in terms of their toxicological profiles; examples include carbon nanotubes [14] and graphene-family nanomaterials [15], both of which constitute highly promising cases in terms of their potential industrial applications. Although gaps still exist, basic guidelines on how to render these materials safer through structural modifications have been facilitated within the context of the safe-by-design concept [16]. Patterns of nanomaterials' emissions/release within an occupational context have been examined in the literature, supporting occupational exposure assessments. A series of on-site measurements, following defined protocols and using specialized equipment, is typically performed to examine airborne (nano)particle concentrations in the workplace and determine occupational exposure [17]. Additionally, an array of assistive tools (e.g., methodologies, guidance documents and web tools) to evaluate nanomaterials' safety have been developed, most of which are readily available for use. Extensive work has been carried out to compile and categorize all the various tools to enable easier access such as the publicly available NANoREG toolbox [18].

The development of nanosafety standards has closely followed the evolution of the research on nanomaterials' safety, with considerable milestones being accomplished in the last few years. In a recent review, Ramos et al. documented the status of nanosafety standardization, compiling the currently available standards that can be applied within the context of nanomaterial risk assessment and safety evaluations [19]. The authors show that particularly within the 2010–2020 decade, important nanosafety standards have been published on a European and worldwide level. These standards are related to the approaches of risk and exposure assessments, methodologies for defining appropriate safety controls, as well as supportive activities such as the preparation of safety data sheet (SDS) documents. These developments are quite important enablers in the application of standardized nanosafety principles in research projects.

In this context, the EU-funded project "DECOAT" (Grant Agreement 814505, Horizon 2020) [20] aims to enable the circular use of textiles and plastic parts with multilayer coatings, which are currently not recyclable. These coatings are composed of functional and performance coatings and paints, as well as adhesion layers. Therefore, novel triggerable smart polymer material systems and the corresponding recycling processes have been developed. The triggerable solutions are based on smart additives (microcapsules and engineered nanomaterials) for the coating formulations that are activated by a specific trigger (heat, steam, microwave or chemical). A continuous recycling pilot plant demonstrates the novel projects' principle that allows upgrades of the existing mechanical recycling by adding tools for activation of the trigger. The focus is on recycling the bulk materials, but reuse of the coating materials will also be performed. Through use of these recycling processes, circular use of a multitude of demonstrations has been validated. Finally, given the occupational and environmental hazards that the processes of developing nanomaterials have within the DECOAT project, the establishment of proper health and safety practices are deemed to be necessary for the sustainable use of these processes and nanotechnologies in general.

Within the DECOAT project, a risk evaluation process for the various developed nanomaterial solutions has been foreseen. This risk assessment aimed both to clarify the occupational safety concerns and to define the necessary controls, as well as identifying the comparatively safest solutions out of all the material alternatives. Since the research project also aimed to upscale the process, this comparative assessment had substantial importance for the overall viability of the final solutions proposed. This risk evaluation process has been undertaken on the basis of the principles of two of the most widely used nanosafety standards by the International Organization for Standardization (ISO) (ISO/TS 12901-2:2014, ISO/TR 12885:2018). Through the process of applying the standards for the materials and applications in question, several barriers have been faced, most of which are attributed to the novelty and uniqueness of the materials. The purpose of this work was to discuss these barriers, present potential ways to circumvent them and argue for refinements that could potentially mitigate these gaps in nanosafety standardization applications. This work is therefore relevant to experienced users of the standards, as well as researchers in the relevant fields who are investigating the potential for the application of standardized approaches in the study of nanosafety elements.

2. Materials and Methods

Standardization on nanotechnologies should contribute to improving the quality of life, and to protect public health and the environment. The introduction of nanomaterials into the workplace raises questions concerning occupational safety and health, and nanosafety standards can serve as important facilitators for properly identifying and addressing such occupational risks. In this section, the two standards consulted to perform the risk evaluation and safety recommendation process will be briefly presented.

ISO/TR 12885:2018 [21] assembles useful knowledge on occupational safety and health practices in the context of nanotechnologies. Use of the information included in ISO/TR 12885:2018 could help companies, researchers, workers and individuals to prevent potential adverse health and safety consequences during the production, handling, use and disposal of manufactured nanoobjects, and their aggregates and agglomerates (NOAA). Moreover, ISO/TR 12885:2018 focuses on the occupational manufacture and use of manufactured NOAA; it does not address the health and safety issues or practices associated with nanoobjects generated by natural processes and other standard operations which unintentionally generate them, or potential consumer exposures or uses, though some of the information included can be relevant to those areas.

The purpose of ISO/TS 12901-2:2014 [22] is to describe the use of a control banding approach for controlling the risks associated with occupational exposures to NOAA greater than 100 nm, even if knowledge regarding their toxicity and quantitative exposure estimations is limited or lacking. It is focused on intentionally produced nanoobjects such as nanoparticles, nanopowders, nanofibres, nanotubes and nanowires, as well as their aggregates and agglomerates in their original form or incorporated into materials or preparations from which they could be released during their lifecycle. Moreover, as for many other industrial processes, nanotechnological processes can generate by-products in the form of unintentionally produced nanoparticles which might be linked to health and safety issues that need to be addressed as well. According to the current state of knowledge [22], nanoobjects can exhibit toxicological properties, which are different from those of non-nanoscale (bulk) materials. Therefore, the current occupational exposure limits (OELs), which have mostly been established for bulk materials, might not be appropriate for them. In the absence of relevant regulatory specifications, the control banding approach can be used as the first approach to controlling workplace exposure to nanoobjects and their aggregates.

In addition, control banding is an approach which can be used for controlling workplace exposure to possibly hazardous agents with unknown or uncertain toxicological properties and for which quantitative exposure estimations are lacking. It may complement the traditional quantitative methods based on air sampling and analysis with reference to OELs when they exist, and can provide an alternative risk assessment and risk management process. The ultimate purpose of the control banding approach is to control exposure to prevent any possible adverse effects on workers' health. The methodology described is specifically designed for inhalation control, but some guidance for skin and eye protection is also given. Control banding applies to issues related to occupational health in the development, manufacturing and use of engineered nanomaterials under normal or reasonably predictable conditions, including maintenance and cleaning operations. ISO/TS 12901-2:2014 aims to help businesses and others, including research organizations engaged in the manufacturing, processing or handling of engineered nanomaterials, by providing an easy-to-understand approach to the control of occupational exposures.

An example of the ISO banding approach [22] is demonstrated in the Supplementary Information, featuring the banding of four materials used in the DECOAT project:

- Core–shell PMMA@PMAA (poly(methyl methacrylate)/poly(methacrylic acid)) nanoparticles based on Goulis et al. [23];
- Super-absorbent polymers (SAPs) based on Kartsonakis et al. [24];
- Magnetite (Fe_3O_4) nanoparticles based on Yazdani et al. [25];
- SiO_2@CNTs (silica/carbon nanotubes) microparticles synthesized through chemical vapor deposition, based on Kainourgios et al. [26].

Table 1 presents the basic characteristics of the materials and processes applied to synthesize them. These fundamental aspects were required as data to apply the methodology of the ISO/TS 12901-2:2014 standard, as well as our supportive assessments.

Table 1. Basic characteristics of the studied materials and their processes.

		Attributes of Materials and Processes				Reference
		Synthesis Method	**Primary Particle Size**	**Density**	**Reagents**	
Materials	**Core–shell PMMA@PMAA**	Wet chemistry	160–210 nm	0.94 g/cm^3	Methacrylic acid, methyl methacrylate, ethylene glycol dimethacrylate, potassium persulphate	Goulis et al. [23]
	Super-absorbent polymers (SAPs)	Wet chemistry	170–360 nm	1.02 g/cm^3	Potassium persulfate, acetonitrile, ammonium hydroxide, tetraethyl orthosilicate, ethylene glycol dimethacrylate, methacrylic acid	Kartsonakis et al. [24]
	Magnetite (Fe_3O_4) nanoparticles	Wet chemistry	5–50 nm	5.2 g/cm^3	Ferrous chloride tetrahydrate, ferric chloride, ferrous sulfate heptahydrate, ferric nitrate nonahydrate, ferric sulfate, sodium hydroxide	Yazdani et al. [25]
	Hybrid SiO_2@CNTs	Stöber method (wet chemistry), chemical vapor deposition (CVD)	SiO_2: 350 nm; iron oxide: 15–20 nm; MWCNTs: 50 nm in diameter	1.7–2.1 g/cm^3	Ethanol, tetraethyl orthosilicate, ammonia, ferrous chloride tetrahydrate, hydrogen, acetylene (compressed gas cylinders)	Kainourgios et al. [26]

3. Results and Discussion

3.1. Barriers Faced in Applying ISO/TS 12901-2:2014

This section documents the barriers faced in applying the ISO/TS 12901-2:2014 standard, as well as the proposed ways to address them. It is worth mentioning that, at the time of the composition of the present work, ISO/TS 12901-2:2014 was under the process of being updated. Therefore, various new features may be added to the methodology in the next version, which could potentially address some of the aspects discussed.

3.1.1. Hazard Classification of Hybrid and Core–Shell Materials

In the ISO control banding process, the hazard band is considered to be uniform for a given material; however, in DECOAT, there was a synthesis of the various materials of a hybrid nature, and such a case is not considered in the standard. The project involved the synthesis of organic core–shell copolymers [23] and super-absorbent polymers based on a polymeric core and an SiO_2 shell [24]. Additionally, magnetite nanoparticles and hybrid nanomaterials based on carbon nanotubes (CNTs) were produced.

In the risk assessment process, it was considered reasonable to apply the highest hazard band of the constituent materials as the defining hazard band for the hybrid material, following a precautionary approach. This was a straightforward choice for the hybrid materials containing CNTs, which are flagged as highly hazardous based on the banding rules, as a material whose toxicity is potentially driven by the fiber paradigm [22]. For cases of increased complexity, a standardized method to characterize the hazard of hybrid nanomaterials or nanocomposites involving multiple nanomaterials would be beneficial. A possible way to approach this would be to apply the precautionary principle and preserve the highest band of the constituent materials and also introduce additional criteria such as the relative volume/mass or the inner/outer material in core–shell particles. Indeed, in the cases of dermal hazard in core–shell particles, the properties of the shell were considered to be predominant, since it would be expected that this layer would be in contact with the skin in cases of exposure.

The practice of coating nanomaterials with a capping agent is very common, and its predominant role is to prevent aggregation of the nanoparticles [27]. Some coating agents are applied with the specific objective of reducing the toxicity of the nanoparticles [27]. This approach has been implemented and its efficiency has been confirmed in materials such as magnetite nanoparticles [28] through coating them with polyethylene glycol (PEG) and dextran, as well as in CNTs [29] through coating them with PEG. The possibility of the nanomaterials having a capping agent is not included in the standard, and it can be a hindrance in terms of output accuracy, since the capping agent may display an important role in determining the hazard. Although the precise definition of the effect of a capping agent would be quite difficult to feature in a banding approach, it could be reasonable to include it as an additional informative element within the standard's methodology to indicate potential uncertainty (e.g., as a footnote).

3.1.2. Dermal Hazard

The information for hazard categorization in the standard is based on inhalation toxicity/hazard and size-dependent dermal hazards are not considered. It would also be reasonable to consider dermal hazards, especially for nanomaterials with a very small primary particle size. A standardized banding system for allocating the materials in terms of dermal penetration or skin irritation concerns would be valuable, enabling consistency in comparing the results for a variety of different materials. However, this is not present in the standard, and consulting the nanosafety literature could provide supporting information to this approach.

In a study by Larese Filon et al., after reviewing various studies based on the effects of nanomaterials on the skin, a size range classification was proposed by the authors in order to assess the NP skin hazard in terms of the possibility of penetration [30] as follows.

- NPs < 4 nm: penetration has been demonstrated.
- NPs 4–20 nm: skin penetration/permeation is possible.
- NPs 21–45 nm: skin absorption can be possible only on damaged skin.
- NPs > 45 nm: skin absorption is unlikely in healthy skin.

Therefore, by considering the threshold of 20 nm as an indication of increased dermal hazard concerns, a practical banding approach to dermal penetration potential was introduced. Dermal hazard was assessed as an additional parameter in the material risk classification, and if primary particle size was less than 20 nm, the material was flagged as having a high dermal hazard potential.

3.1.3. Consideration of the Primary Particle Size

The utilization of bulk material OEL or globally harmonized system (GHS) hazard statements is defined in the standard as a method to derive the hazard bands of the nanomaterials. The size of the nanomaterials is not considered. However, primary particle size has been reported in the literature to be a determinant factor for a nanomaterial's toxicity and hazard, predominantly due to the increase in the specific surface area [31]. The threshold of 50 nm is commonly applied to consider an increased hazard for particles below than this size and has been implemented in other prominent control banding-based nanosafety tools, such as Stoffenmanager Nano [32]. Therefore, it would be reasonable to include an additional level of standardized hazard categorization, enquiring about the size of the primary nanomaterial particles, and recommend an increase in the hazard by one band in cases where the primary particle size is <50 nm.

The concept of increased hazard when the primary particles' size is lower is also consistent with the respiratory deposition potential of very small particles, which is known to be considerably increased in terms of alveolar and total respiratory system deposition compared with larger particles [33]. An additional tool, namely the multiple-path particle dosimetry (MPPD) model [34], was applied to provide insights for safer materials in connection with their size. The MPPD model is a computational model that can be used for estimating human and laboratory animal inhalation particle dosimetry and can be used in the context of risk assessments. The basic characteristics that are used as input in the model are the particles' size, density and aspect ratio. Based on the characterization results for the various nanomaterials (e.g., scanning electron microscope (SEM) particle size characterization), different scenarios for varying particle sizes were input into the model, and the expected respiratory deposition pattern after exposure was calculated. The materials with the lowest potential for alveolar and total deposition were defined as comparatively safer, given that lower respiratory deposition leads to lower potential for adverse health effects [33]. It is therefore a suggestion to also use respiratory deposition models as a supplementary aid in the banding process.

3.1.4. The Nanomaterials' Physical State

In the standard approach, the exposure band is derived by firstly defining the physical state of the nanomaterial and then providing the basic characteristics of the process. The available physical states are "powder", "suspension" or "bound in a solid matrix". It is possible that nanomaterials may be present in other forms as well, most notably as a "paste". There are several studies in the literature, and applications as well, where nanomaterials in the form of a "paste" have been used. Xiao et al. [35] studied a magnetic nanocomposite paste for the development of inductors that will be used in high-frequency electronic applications. Moreover, Tajik et al. [36], in his study, reviewed the progress that had been made the past few years in the field of electrochemical sensing using nanomaterial-based carbon paste electrodes.

Nanomaterials in the form of paste constitute a stabler suspension which is efficient at preventing releases that could be possible in the case of using powder. However, in this case, there is ambiguity about how to characterize the material within the standard's scope, since the user may define the material as both a "suspension" or "bound in a solid matrix". Therefore, we suggest introducing "nanomaterial in paste form" as an additional standardized physical state for nanoproducts within the relevant standards, since a paste has a distinct set of structural characteristics influencing the safety of the material and process (a category between "suspension" and "bound in a solid matrix").

3.1.5. Quantity Scaling

In the ISO control banding approach, quantity is considered when deriving the control bands. For nanomaterial powders, there are three groups in terms of quantity at <0.1 g, 0.1 g–1 kg and >1 kg. For nanosuspensions, the criteria are:

- Whether the quantity of nanomaterial is larger or lower than 1 g;
- Whether the quantity of the liquid is larger or lower than 1 L.

The control band is scaled accordingly, classifying greater exposure levels when higher quantities are observed. This criterion has validity for most laboratory processes and highlights some exposure hotspots. However, particularly in the case of nanosuspensions, it is not clear what the scaling of the exposure bands would be if the scale were to increase more in upscaled experiments on a pilot-line level (e.g., 100 g to 500 g), since there are no criteria for classifying quantities larger than 1 g/1 L in higher exposure bands. It is suggested that a standardized method of scaling of the quantities towards characterizing the hazards could have a greater quantity of classifications reaching larger scales for the case of nanosuspensions (e.g., hundreds of g, kg). This would help in accurately classifying cases of upscaled or pilot-line level production/processing.

3.2. Barriers Faced in Applying ISO/TR 12885:2018

While the basic information on the controls needed to mitigate exposure is provided by the control banding approach, more detailed information for safety controls is given in ISO/TR 12885:2018 (Nanotechnologies—Health and safety practices in occupational settings) [21]. Within this standard, a specific strategy for occupational nanosafety is presented in the form of the hierarchy of controls [37], giving engineering controls (e.g., ventilation) higher priority and efficiency levels than personal protective equipment or the administrative setup of the workplace. Within this framework, for hazardous materials such as CNTs, full enclosure of the process is recommended, using ventilated enclosures such as gloveboxes.

The scale and type of the process may be important to define, since some of these high-level controls may be totally inapplicable for some cases. Gloveboxes may interfere with the practical requirements of the process. An important example may be pilot-lines, which involve a set of processes that ought to work in a defined sequence. Additionally, large-scale processes may not be able to be enclosed whatsoever. Therefore, an additional mode of operations which may not allow enclosed systems should be considered. A different set of recommended controls for pilot- to industrial-scale processes would be beneficial, placing the focus primarily on partial enclosure, local or movable ventilation systems, general dilution ventilation, applying closed systems from the design phase, or designing for automation and less operator involvement. This is consistent with the remark made about the banding of deficient classes for exposure banding based on the quantity of nanomaterials used (an upper limit of 1 g for nanosuspensions, as discussed in Section 3.1.5). This can be attributed to the standards being more focused on a research/laboratory setting as opposed to a larger-scale/industrial setting, given the current state of nanomaterial technologies being applied. However, facilitation of more industrially focused safety controls within the nanosafety standards would be a beneficial element towards more widespread upscaling of nanotechnologies.

3.3. ISO/TS 12901-2:2014 Banding Example

An example of the banding results is presented in this section to aid in understanding the barriers and gaps, and to showcase how specific modifications to the approach can have a beneficial effect for assessments. As highlighted in the Materials and Methods section, the four materials examined were based on materials and processes commonly used and described in literature studies, and which correspond to cases of materials in the DECOAT project.

The detailed step-by-step information on the banding process (e.g., reagent hazard statements, MPPD model settings and more) is provided in the Supplementary Materials. The following paragraphs discuss how the assessment can be improved by introducing the aspects highlighted in this work, while Table 2 presents a summary of the banding results as well as our proposed complementary assessment outcomes. Overall, the basic steps followed to perform the assessment were as follows.

1. Investigation of the bulk material hazard statements in the European Chemicals Agency (ECHA) database;
2. Derivation of the nanomaterial hazard band, based on the ISO/TS 12901-2:2014 hazard banding rules;
3. Derivation of the exposure band of the synthesis process, taking the characteristics of the process into account (e.g., physical state of the material, quantities), on the basis of the ISO/TS 12901-2:2014 exposure banding rules;
4. Derivation of the control band, based on ISO/TS 12901-2:2014 control banding rules;
5. Hazard assessment of the process's reagents using the Control of Substances Hazardous to Health tool (e-COSHH tool) [38];
6. Application of the MPPD model based on the basic characteristics of the nanomaterial (size, density) [34];
7. Application of dermal penetration criteria to the nanomaterials;
8. Documentation of any notable additional hazards of the process (unrelated to exposure).

Table 2. Summary of the control banding results and additional assessment elements.

Material	Nano-hazard band	Nano-exposure band (EB)	Control band (CB)	Engineering control recommendations	MPPD * alveolar deposition fraction	Dermal penetration	Additional hazards and reagents' chemical hazards	Synthesis process hazards
PMMA@ PMAA	C	EB1 (wet phase synthesis)	CB2	Local ventilation: extractor hood, slot hood, arm hood, table hood, etc.	0.1313	Unlikely on healthy skin	H334 respiratory sensitization 1; H317 skin sensitization 1; H311 acute toxicity; 3 dermal; H314 skin corrosion 1A; H318 serious eye damage 1	Wet chemistry process
(SAPs) $PMAA@SiO_2$	C	EB1 (wet phase synthesis)	CB2	Local ventilation: extractor hood, slot hood, arm hood, table hood, etc.	0.1202	Unlikely on healthy skin	H334 respiratory sensitization 1; H317 skin sensitization 1; H311 acute toxicity; 3 dermal; H314 skin corrosion 1A; H318 serious eye damage 1	Wet chemistry process
SiO_2@CNTs	C E	EB4 (Chemical vapor condensation)	CB5	Full containment and review by a specialist: seek expert advice. On-site visit and measurements	0.0479 *	Possible (via healthy and injured skin)	Nanomaterials used as catalysts/precursors	Pressurized vessel use, high temperatures, high pressure, flammable gases
Fe_3O_4 nanoparticles	D	EB1 (wet phase synthesis)	CB3	Enclosed ventilation: ventilated booth, fume hood, closed reactor with regular openings	0.2982	Possible (via healthy and injured skin)	H314 skin corrosion 1A; H318 serious eye damage 1; H351 carcinogenicity 2	Wet chemistry process

* Toxicity is driven by the fiber paradigm.

An important point that comes up from Table 2's results is that the ISO banding rules for the CB derivation were fully followed in all cases excluding the magnetite particles, for which a +1 hazard band over the ISO rule-derived band was defined. Based on the ISO standard rules, the magnetite nanoparticles would be categorized in BC as a result of the hazard statements that the equivalent bulk material displayed (Supplementary Materials). For our assessment, the band was increased and, as discussed previously, this was on the grounds that the very small size (5–50 nm in the specific example studied) was adequate to raise concerns about an increased hazard. If this rule were not to be followed, these materials would be allocated to the same control band as the core–shell and SAP materials, and a lower level of control would have been proposed by the standard. This was emphasized further by the other added elements of our approach.

The results of the MPPD model [34] serve as a complementary aspect of the size concerns. According to these results, the magnetite nanoparticles present the highest potential for alveolar deposition (Supplementary Information), further reinforcing the argument for their increased hazard potential compared with the polymeric materials. Interestingly, the deposition fraction was slightly lower for the SAPs compared with the core–shell particles, which is an argument towards their comparatively safer profile. The CNT materials displayed low deposition potential, although their high hazard ranking, due to their fibrous nature, shows that this is not a cause to alleviate any hazard concerns on the basis of this low deposition potential only.

The dermal hazard concerns are an additional factor pointing towards the higher comparative hazard potential of the magnetite particles. These are the only particles that are $\leq$10 nm, and thus the only material capable of potential dermal penetration. This leads to the classification of the hybrid Fe_3O_4/CNT materials as hazardous in terms of dermal exposure as well, in line with the precautionary approach, since they contain the magnetite nanoparticles. The core–shell and SAP materials are too large to cause concern in terms of dermal penetration (>100 nm) [30]. This part would have been totally absent from the assessment were the rules of the standard to be followed with no additions.

The classification of the hybrid materials themselves (SiO_2/CNT) was somewhat ambiguous, since a material of hazard Band C (SiO_2), a material of Band D (magnetite) and a material of hazard Band E (CNTs) constituted the hybrid material. As discussed, there is no clause to guide users on how to classify the hazard of such a material in the standard. Additionally, the banding would be C for the magnetite particles if our approach was not followed, potentially causing higher uncertainty to the user of the standard on how to allocate the hazard band. Our suggestion is to use the highest hazard band of the constituent materials.

In terms of the material quantities and their impact on the banding, in the particular cases examined in this example, the banding was performed solely on the basis of the synthesis method, following the ISO standards' rules. However, particularly for the wet phase synthesis methods, the banding would not be scaled higher if the processes were to be upscaled further, since EB3 is the highest applicable exposure band for quantities of >1 g and 1 L. Therefore, the need for additional classes in terms of the quantities used is highlighted.

The documentation of the reagent hazards is also quite important. This can be seen in the first two materials (core–shell and SAPs), where a specific reagent was categorized in the highest hazard band (KPS, the initiator, as seen in the Supplementary Materials). Therefore, relatively benign nanomaterials require the use of a hazardous substance within the context of the synthesis process. While not directly affecting the hazard of the material, the potential substitution of this substance with another (provided that the process is not disrupted) could be an additional element within the overall safer-by-process design framework. This intervention is also in line with the hierarchy of controls paradigm, in which substitution is one of the predominant control modes [37].

In terms of processing hazards, only the synthesis of CVD presented any notable process safety issues, since pressurized vessels were applied to supply the auxiliary gases required for the CVD process, such as argon [39]. Additionally, the process involves high temperatures and pressure to arrive at the conditions required to synthesize carbon nanotubes [39]. On the contrary, the synthesis of the other materials takes place via wet phase synthesis, with only low levels of energy applied (e.g., stirring) and no high temperatures used, and thus no significant safety issues. While this is reflected in the lower exposure band, it would be useful to display this information from a process hazard viewpoint as well.

It is important to note that within the context of this study, we examined only the synthesis processes of the nanomaterials. The assessment could be complemented by additional steps of the nanomaterial's life cycle (i.e., processing, handling, incorporation in products, etc.), in which widely different risk factors may be in place (e.g., drying of the materials and use in powder form). Overall, it can be observed that the additional examinations that we propose add various new dimensions to the assessment and can alleviate some of the barriers that render the ISO standards difficult to use or inapplicable in some cases. It should be mentioned that the arguments presented in this work are much more beneficial primarily in cases where a comparative assessment of various materials is being performed (e.g., to decide on the safest solution for upscaling). While these additional aspects of the assessment have value for cases of risk assessments of isolated materials/processes, their added utility is most prominent when performing comparative assessments, since these extra dimensionalities reveal differences in the risk potential which the sole ISO standard assessment could not have identified. Although the current study is limited to case-specific nanomaterials, the proposed amendments to the ISO standard focus on the global research and manufacturing field around nanotechnology. Therefore, the proposed additions can be extrapolated and applied to other NOAA, enhancing the risk assessments during handling and usage of the nanomaterials.

4. Applications of ISO/TS 12901-2:2014 in the Literature

There are several studies where nanosafety standards such as ISO/TS 12901-2:2014 were used to perform a risk assessment and contribute to the risk management process. Ramos et al. [40] presented a case study where nanomaterials were applied to textiles by means of textile finishing. A finishing company produced two chemical finishes incorporating nanomaterials: a mosquito repellent and an antibacterial finish. The risk analysis mainly concerned four workers involved in the preparation of the finishing baths. Following the application of the control banding approach, measures to mitigate the risks were proposed, such as appropriate ventilation and the use of adequate personal protective equipment. They also concluded that the hazards related to one of the chemicals were higher and required the use of a closed booth and a smoke extractor to further reduce the risk. This is consistent with our suggestion to also assess the precursor or auxiliary chemicals used for the process in parallel to the ISO/TS 12901-2:2014 application, since vital safety-related information may be missed, should they not be assessed.

Furthermore, Boccuni et al. [41] studied and proposed a multimetric approach for measuring and sampling engineered nanomaterials in the workplace, applied to three case studies in laboratories dedicated to materials with different shapes and dimensionalities: graphene, nanowires and nanoparticles. The study was part of a larger project with the aim of improving the risk management tools in nanomaterial research laboratories. The harmonized methodology proposed by the Organization for Economic Cooperation and Development (OECD) was applied, including gathering information about the materials and processes, taking measurements with easy-to-use and hand-held real-time devices, air sampling with personal samplers and off-line analysis using scanning electron microscopy. Based on the OECD guidelines, in parallel to the measurements, the authors applied a control banding scheme to the various processes examined, based on ISO/TS 12901-2:2014. Interestingly, one of the three case studies examined in their study included Au/SiO_2 core–shell particles, which, as argued previously, can constitute a barrier to applying the standard. The overall risk banding of the synthesis process, which was described as a wet chemical method, was defined as having moderate risk, although the method used to define the hazard band of the core–shell materials was not documented.

Moreover, Van Hoornick et al. [42] studied and contributed to a risk assessment within the research facilities of Imec (a large research center for semiconductor nanotechnology) performed by the institute's environment, health and safety team. Since there was a lack of sufficient toxicological information about the engineered nanomaterials and since within the semiconductor research and manufacturing sector, nanomaterials are used to a great extent, a control banding technique to determine the risks associated with the nanomaterial research was applied, based on various control banding approach tools, such as ISO/TS 12901-2:2014, Stoffenmanager Nano and NanoSafer, but geared for application within the semiconductor research and development field. Thus, within their risk control approach, they targeted the hazard and exposure potential of the engineered nanomaterials used during specific activities. Both aspects were divided into groups of low, moderate and high potential. Through this classification, the appropriate risk control bands were defined, and several appropriate control measures were proposed in order for the employees to work safely when performing the activities. The authors recognized that the different banding approaches examined used a different ranking system (e.g., decision trees, binary systems and scoring systems) and that the proposed approach for dealing with uncertainty in the ISO approach is to use the precautionary approach. Although the aspect of limitations was not discussed, it is reasonable to argue that linear decision tree systems such as the one presented in ISO/TS 12901-2:2014 constitute a practical and easily applied method; however, they may lack flexibility compared with scoring-system-based ranking schemes, which was the focal point of our study. Therefore, some of the deficiencies discussed in the present work have direct relevance to other applications of the control banding standard.

5. Conclusions

In this study, several arguments have been presented regarding the barriers faced in applying a set of prominent nanosafety ISO standards within an EU-funded research project context (DECOAT). These barriers were discussed, and suggestions for their alleviation were proposed, while an example was used to highlight the benefits offered by introducing additional elements to circumvent these gaps. After applying the ISO/TS 12901-2:2014 standard and encountering these gaps, we suggest the following aspects as complementary to the standard's approach: (a) consideration of the primary nanoparticles' size as part of the hazard data, (b) assessment of the dermal penetration potential, (c) the application of respiratory deposition models to generate supportive risk-related data, (d) use of the precautionary approach in any cases of uncertainty regarding how to apply the standard's rules (e.g., hybrid nanomaterials), and (e) documentation of the process's hazards. These additional elements of the assessment are quite useful in comparative studies, as they reveal aspects that would not be highlighted by the application of the standard's rules only. As a consideration for further endeavors towards standardization, we have identified deficiencies in describing large-scale processes within the methodological framework of the standards and suggest complementing of the standards with aspects that relate to the safety of larger-scale nanomaterial processes. Expanded work on studies with a similar concept that could discuss more barriers to the application of nanosafety standards could refine the research community's understanding of the application of standards of nanosafety.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/standards2040034/s1. Table S1: ECHA's most reported hazard statements for bulk PMMA. Table S2: CB allocation for core–shell PMMA@PMAA nanoparticles. Table S3: Hazard assessment of the process reagents for the synthesis of core–shell PMMA@PMAA nanoparticles. Table S4: ECHA's most reported hazard statements for SiO_2 nanoparticles. Table S5: CB allocation for SAP nanoparticles. Table S6: Hazard assessment of the process reagents for the synthesis of SAP nanoparticles. Table S7: ECHA's most reported hazard statements for magnetite nanoparticles. Table S8: CB allocation for magnetite nanoparticles. Table S9: Hazard assessment of the process reagents for the synthesis of magnetite nanoparticles. Table S10: ECHA's most reported hazard statements for CNTs. Table S11: CB allocation for CNTs. Table S12: Hazard assessment of the process reagents for the synthesis of CNTs. Figure S1: Total deposition fraction results for core–shell

PMMA@PMAA nanoparticles. Figure S2: Total deposition fraction results for SAP nanoparticles. Figure S3: Total deposition fraction results for magnetite nanoparticles. Figure S4: Total deposition fraction results for SiO_2@CNTs.

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References

1. Hulla, J.; Sahu, S.; Hayes, A. Nanotechnology: History and Future. *Hum. Exp. Toxicol.* **2015**, *34*, 1318–1321. [CrossRef] [PubMed]
2. Sim, S.; Wong, N.K. Nanotechnology and Its Use in Imaging and Drug Delivery (Review). *Biomed. Rep.* **2021**, *14*, 42. [CrossRef] [PubMed]
3. Thiruvengadam, M.; Rajakumar, G.; Chung, I.-M. Nanotechnology: Current Uses and Future Applications in the Food Industry. *3 Biotech* **2018**, *8*, 74. [CrossRef] [PubMed]
4. Khot, L.R.; Sankaran, S.; Maja, J.M.; Ehsani, R.; Schuster, E.W. Applications of Nanomaterials in Agricultural Production and Crop Protection: A Review. *Crop Prot.* **2012**, *35*, 64–70. [CrossRef]
5. Khin, M.M.; Nair, A.S.; Babu, V.J.; Murugan, R.; Ramakrishna, S. A Review on Nanomaterials for Environmental Remediation. *Energy Environ. Sci.* **2012**, *5*, 8075–8109. [CrossRef]
6. Huang, H.; Sheng, X.; Tian, Y.; Zhang, L.; Chen, Y.; Zhang, X. Two-Dimensional Nanomaterials for Anticorrosive Polymeric Coatings: A Review. *Ind. Eng. Chem. Res.* **2020**, *59*, 15424–15446. [CrossRef]
7. Ganguly, P.; Breen, A.; Pillai, S.C. Toxicity of Nanomaterials: Exposure, Pathways, Assessment, and Recent Advances. *ACS Biomater. Sci. Eng.* **2018**, *4*, 2237–2275. [CrossRef]
8. Basinas, I.; Jiménez, A.S.; Galea, K.S.; van Tongeren, M.; Hurley, F. A Systematic Review of the Routes and Forms of Exposure to Engineered Nanomaterials. *Ann. Work. Expo. Health* **2018**, *62*, 639–662. [CrossRef]
9. Boholm, Å.; Larsson, S. What Is the Problem? A Literature Review on Challenges Facing the Communication of Nanotechnology to the Public. *J. Nanopart. Res.* **2019**, *21*, 86. [CrossRef]
10. Krug, H.F.; Wick, P. Nanotoxicology: An Interdisciplinary Challenge. *Angew. Chem. Int. Ed.* **2011**, *50*, 1260–1278. [CrossRef]
11. Kuhlbusch, T.A.J.; Wijnhoven, S.W.P.; Haase, A. Nanomaterial Exposures for Worker, Consumer and the General Public. *NanoImpact* **2018**, *10*, 11–25. [CrossRef]
12. Wigger, H.; Kägi, R.; Wiesner, M.; Nowack, B. Exposure and Possible Risks of Engineered Nanomaterials in the Environment—Current Knowledge and Directions for the Future. *Rev. Geophys.* **2020**, *58*, e2020RG000710. [CrossRef]
13. Suhendra, E.; Chang, C.-H.; Hou, W.-C.; Hsieh, Y.-C. A Review on the Environmental Fate Models for Predicting the Distribution of Engineered Nanomaterials in Surface Waters. *Int. J. Mol. Sci.* **2020**, *21*, 4554. [CrossRef]
14. Kobayashi, N.; Izumi, H.; Morimoto, Y. Review of Toxicity Studies of Carbon Nanotubes. *J. Occup. Health* **2017**, *59*, 394–407. [CrossRef]
15. Ou, L.; Song, B.; Liang, H.; Liu, J.; Feng, X.; Deng, B.; Sun, T.; Shao, L. Toxicity of Graphene-Family Nanoparticles: A General Review of the Origins and Mechanisms. *Part. Fibre Toxicol.* **2016**, *13*, 57. [CrossRef]
16. Yan, L.; Zhao, F.; Li, S.; Hu, Z.; Zhao, Y. Low-Toxic and Safe Nanomaterials by Surface-Chemical Design, Carbon Nanotubes, Fullerenes, Metallofullerenes, and Graphenes. *Nanoscale* **2011**, *3*, 362–382. [CrossRef]
17. McCormick, S.; Niang, M.; Dahm, M.M. Occupational Exposures to Engineered Nanomaterials: A Review of Workplace Exposure Assessment Methods. *Curr. Environ. Health Rep.* **2021**, *8*, 223–234. [CrossRef]
18. Jantunen, A.P.K.; Gottardo, S.; Rasmussen, K.; Crutzen, H.P. An Inventory of Ready-to-Use and Publicly Available Tools for the Safety Assessment of Nanomaterials. *NanoImpact* **2018**, *12*, 18–28. [CrossRef]
19. Ramos, D.; Almeida, L. Overview of Standards Related to the Occupational Risk and Safety of Nanotechnologies. *Standards* **2022**, *2*, 83–89. [CrossRef]
20. Decoat—Recycling of Coated and Painted Textile and Plastic Materials. Available online: https://decoat.eu/project/ (accessed on 23 September 2022).

21. *ISO/TR 12885:2018*; Nanotechnologies—Health and Safety Practices in Occupational Settings. International Organization for Standardization: Geneva, Switzerland, 2018.
22. *ISO/TS 12901-2:2014*; Nanotechnologies—Occupational Risk Management Applied to Engineered Nanomaterials—Part 2: Use of the Control Banding Approach. International Organization for Standardization: Geneva, Switzerland, 2014.
23. Goulis, P.; Kartsonakis, I.A.; Charitidis, C.A. Synthesis and Characterization of a Core-Shell Copolymer with Different Glass Transition Temperatures. *Fibers* **2020**, *8*, 71. [CrossRef]
24. Kartsonakis, I.A.; Goulis, P.; Charitidis, C.A. Triggerable Super Absorbent Polymers for Coating Debonding Applications. *Polymers* **2021**, *13*, 1432. [CrossRef] [PubMed]
25. Yazdani, F.; Seddigh, M. Magnetite Nanoparticles Synthesized by Co-Precipitation Method: The Effects of Various Iron Anions on Specifications. *Mater. Chem. Phys.* **2016**, *184*, 318–323. [CrossRef]
26. Kainourgios, P.; Kartsonakis, I.A.; Charitidis, C.A. Synthesis and Characterization of SiO2@CNTs Microparticles: Evaluation of Microwave-Induced Heat Production. *Fibers* **2021**, *9*, 81. [CrossRef]
27. Javed, R.; Zia, M.; Naz, S.; Aisida, S.O.; ul Ain, N.; Ao, Q. Role of Capping Agents in the Application of Nanoparticles in Biomedicine and Environmental Remediation: Recent Trends and Future Prospects. *J. Nanobiotechnol.* **2020**, *18*, 172. [CrossRef] [PubMed]
28. Yu, M.; Huang, S.; Yu, K.J.; Clyne, A.M. Dextran and Polymer Polyethylene Glycol (PEG) Coating Reduce Both 5 and 30 Nm Iron Oxide Nanoparticle Cytotoxicity in 2D and 3D Cell Culture. *Int. J. Mol. Sci.* **2012**, *13*, 5554–5570. [CrossRef]
29. Bottini, M.; Rosato, N.; Bottini, N. PEG-Modified Carbon Nanotubes in Biomedicine: Current Status and Challenges Ahead. *Biomacromolecules* **2011**, *12*, 3381–3393. [CrossRef]
30. Larese Filon, F.; Mauro, M.; Adami, G.; Bovenzi, M.; Crosera, M. Nanoparticles Skin Absorption: New Aspects for a Safety Profile Evaluation. *Regul. Toxicol. Pharmacol.* **2015**, *72*, 310–322. [CrossRef]
31. Schmid, O.; Stoeger, T. Surface Area Is the Biologically Most Effective Dose Metric for Acute Nanoparticle Toxicity in the Lung. *J. Aerosol Sci.* **2016**, *99*, 133–143. [CrossRef]
32. Van Duuren-Stuurman, B.; Vink, S.R.; Verbist, K.J.M.; Heussen, H.G.A.; Brouwer, D.H.; Kroese, D.E.D.; Van Niftrik, M.F.J.; Tielemans, E.; Fransman, W. Stoffenmanager Nano Version 1.0: A Web-Based Tool for Risk Prioritization of Airborne Manufactured Nano Objects. *Ann. Occup. Hyg.* **2012**, *56*, 525–541. [CrossRef]
33. Oberdörster, G.; Oberdörster, E.; Oberdörster, J. Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles. *Environ. Health Perspect.* **2005**, *113*, 823–839. [CrossRef]
34. MPPD: Multiple-Path Particle Dosimetry Model—ARA. Available online: https://www.ara.com/mppd/ (accessed on 23 September 2022).
35. Xiao, T.; Ma, X.; Zhang, H.; Reisner, D.; Raj, P.; Wan, L.; Tummala, R. Magnetic Nanocomposite Paste: An Ideal High μ, k and Q Nanomaterial for Embedded Inductors in High Frequency Electronic Applications. In Proceedings of the WMSCI 2005—The 9th World Multi-Conference on Systemics, Cybernetics and Informatics, Orlando, FL, USA, 1 January 2005; Volume 9.
36. Tajik, S.; Beitollahi, H.; Nejad, F.G.; Safaei, M.; Zhang, K.; Le, Q.V.; Varma, R.S.; Jang, H.W.; Shokouhimehr, M. Developments and Applications of Nanomaterial-Based Carbon Paste Electrodes. *RSC Adv.* **2020**, *10*, 21561–21581. [CrossRef]
37. *ISO 45001:2018*; Occupational Health and Safety Management Systems—Requirements with Guidance for Use. International Organization for Standardization: Geneva, Switzerland, 2018.
38. Control of Substances Hazardous to Health (COSHH)—COSHH. Available online: https://www.hse.gov.uk/coshh/ (accessed on 26 September 2022).
39. Terranova, M.L.; Sessa, V.; Rossi, M. The World of Carbon Nanotubes: An Overview of CVD Growth Methodologies. *Chem. Vap. Depos.* **2006**, *12*, 315–325. [CrossRef]
40. Ramos, D.; Almeida, L.; Gomes, M. Application of Control Banding to Workplace Exposure to Nanomaterials in the Textile Industry. In *Occupational and Environmental Safety and Health*; Arezes, P.M., Baptista, J.S., Barroso, M.P., Carneiro, P., Cordeiro, P., Costa, N., Melo, R.B., Miguel, A.S., Perestrelo, G., Eds.; Studies in Systems, Decision and Control; Springer International Publishing: Cham, Switzerland, 2019; pp. 105–113. ISBN 978-3-030-14730-3.
41. Boccuni, F.; Ferrante, R.; Tombolini, F.; Lega, D.; Antonini, A.; Alvino, A.; Pingue, P.; Beltram, F.; Sorba, L.; Piazza, V.; et al. Workers' Exposure to Nano-Objects with Different Dimensionalities in R&D Laboratories: Measurement Strategy and Field Studies. *Int. J. Mol. Sci.* **2018**, *19*, 349. [CrossRef]
42. Hoornick, N.V.; Prodanov, D.; Pardon, A. Banding Approach for Engineered Nanomaterial Risk Assessment and Control. *J. Phys. Conf. Ser.* **2017**, *838*, 012017. [CrossRef]