Nanomaterials, and Occupational Health and Safety—A Literature Review About Control Banding and a Semi-Quantitative Method Proposed for Hazard Assessment.

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Abstract. In recent decades, the control banding (CB) approach has been recognised as a hazard assessment methodology because of its increased importance in the occupational safety, health and hygiene (OSHH) industry. According to the American Industrial Hygiene Association, this approach originates from the pharmaceutical industry in the United Kingdom. The aim of the CB approach is to protect more than 90% (or approximately 2.7 billion) of the world’s workers who do not have access to OSHH professionals and traditional quantitative risk assessment methods. In other words, CB is a qualitative or semi-quantitative tool designed to prevent occupational accidents by controlling worker exposures to potentially hazardous chemicals in the absence of comprehensive toxicological and exposure data. These criteria correspond very precisely to the development and production of engineered nanomaterials (ENMs). Considering the significant lack of scientific knowledge about work-related health risks because of ENMs, CB is, in general, appropriate for these issues. Currently, CB can be adapted to the specificities of ENMs; hundreds of nanotechnology products containing ENMs are already on the market. In this context, this qualitative or semi-quantitative approach appears to be relevant for characterising and quantifying the degree of physico-chemical and biological reactivities of ENMs, leading towards better control of human health effects and the safe handling of ENMs in workplaces. The need to greater understand the CB approach is important to further manage the risks related to handling hazardous substances, such as ENMs, without established occupational exposure limits. In recent years, this topic has garnered much interest, including discussions in many technical papers. Several CB models have been developed, and many countries have created their own nano-specific CB instruments. The aims of this research were to perform a literature review about CBs, to classify the main approaches that were developed worldwide, and then to suggest an original methodology based on the characterisation of the hazard. These considerations will lead to the proposal of an original hazard assessment method based on physico-chemical and biological characteristics. Such a method should help the entire industry better understand the ability of the CB approach to limit workers’ exposure, while identifying the strengths and weaknesses of the approach. Developing this practice method will help to provide relevant recommendations to workers who handle hazardous chemicals such as ENMs and to the general population.
1. Introduction
Since 2000, nanotechnology has grown dramatically in all industrialised countries. Back then and even now, the advent of the infinitely small particle through nanotechnology is considered to be the industrial revolution of the twenty-first century [1]. However, the idea to manipulate matter at the atomic and molecular levels was raised explicitly by American physicist Richard Feynman during his famous lecture from 1959 that was titled “There Is Plenty of Room at the Bottom” [2]. In 1974, Japanese professor Norio Taniguchi coined the term “nanotechnology” [3]. However, the era of nanotechnology really arrived in 1986, thanks to the development of new sophisticated tools such as the scanning tunnelling microscope and the atomic force microscope [4, 5]. Therefore, remarkable progress is being made in a variety of fields such as energy, environment and health [6].

Nowadays, nanotechnology is a multidisciplinary research field in which an increasing variety of engineered ENMs are synthesised [7]. According to International Organization for Standardization (ISO)/TS 80004-1, one or more external dimensions of ENMs are in the size range of 1 nm to 100 nm. At the nanoscale level, ENMs have unique physical and chemical properties, which make them an attractive candidate for a wide range applications in a variety of revolutionary scientific fields [8]. Most industrialised countries are investing heavily in nanoscience and nanotechnology research and development around the world (in the United States of America, China, Japan, Russia and European countries) [7, 9]. Nevertheless, rapidly developing nanotechnology and the growing utilisation of ENMs in consumer and industrial products have led to a potential increase of human exposure, thus raising concerns of many scientists and governments regarding health risks to workers and the public [10-12]. Investigators supported some initiatives to implement the industry’s and researchers’ use of ENMs in nanotechnology. A survey was initiated among industries and researchers working in different specialties that were potentially involved in the development, production, distribution and integration of ENMs and use of ENMs-containing products [13, 14]. Indeed, the fear among public health institutions in several countries has increased regarding the quantitative health risk assessment of ENMs [7].

In 1983, the National Research Council first proposed a health risk assessment [15]. The four steps of this approach include source characterisation, hazard characterisation, exposure characterisation and risk characterisation. The principle of the health risk assessment is based on “the use of the factual base to define the health effects of exposure of individuals or populations to hazardous materials and situations” [15]. In the case of ENMs specifically, it will be virtually impossible to assess the potential occupational health hazard, given the almost limitless uncertainties of ENMs [16]. In such an uncertain context, in which current data regarding the toxicity of ENMs remain fragmented [17], quantitative health risk assessment (QHRA) is purely hypothetical. Thus, a risk assessment method for controlling ENMs exposures remains mainly qualitative or semi-quantitative in nature [18]. The qualitative risk assessment method, known as “control banding (CB),” is an alternative approach to QHRA that has some drawbacks that limit its use in nanotechnology; therefore, the current work is in this context. It is important to develop an approach of CB based on characterisation of potential hazards posed by ENMs. Characterisation is necessary to identify and quantify the degree of hazardousness of ENMs to establish a better framing of their health implications and to ensure safe handling of these ENMs. Emond et al. [19, 20] designed the first portion of the methodology to integrate QHRA and CB, thereby integrating a semi-quantitative approach for the assessment of ENMs. The second portion of the methodology is underway and is a part of the initiative in this current paper.

The core structure of this paper is organised in a step-wise manner. In Section 2 (Methods), we provide the literature search strategy that includes the study selection and data collection processes. This review provides the information that we observed regarding why these matrices were developed and their limitations. In Section 2, we also discuss the CB strategy and describe the main CB tools that have been developed specifically for ENMs. This synthesis is important in understanding the key concepts for CB and the implications of this approach’s overall effectiveness, and then for proposing our approach. In
Section 3 (Result and Discussion), we present the results from the literature search and our proposed assessment tool of ENMs based on physico-chemical and biological characteristics. In Section 3, we also briefly discuss the approach developed as an innovative hazard assessment method, which is different from the previously developed approaches. This paper discusses the ongoing project, addressing where we are so far, and the perspective of this project. Section 4 (Conclusion) of this paper presents an overview of the state of the project and describes the future work needed to complete it.

The aims of this research were to perform a literature review about CBs, to classify the main CB approaches that were developed worldwide and then to suggest an inventive methodology based on the characterisation of the hazard.

2. Methods
2.1. Literature Search Strategy
The study was conducted to cover the period from January 1996 to November 2016. The review was limited to only French and English papers. The following databases were searched: Toxline, PubMed, Web of Science, ScienceDirect and Google Scholar. The research strategy was based on four major concepts: CB, ENMs, physico-chemical characteristics and biological characteristics. Many keywords were used that referred to different complementary concepts that all linked to ENMs. The keywords were as follows: agglomerate and biological characterisation of ENMs, carbon nanotubes, CB tools, engineered ENMs, exposure banding, hazard assessment, nanotechnology, nanotoxicity, physicochemical parameters of ENMs, quantum dots and risk banding.

Furthermore, the governmental reports of recognised organisations were considered. Some of these organisations included the Robert-Sauvé Research Institute for Occupational Health and Safety (l'Institut de recherche Robert-Sauvé en Santé et en Sécurité du travail [IRSSST]), the National Agency for Food Safety, Environment and Labor (Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail [ANSES]) and NIOSH (the National Institute for Occupational Safety and Health). This review also considered conference abstracts (e.g. Nanosafe International Conferences on Safe Production and Use of ENMs) and theses and dissertations. This search also included specialised databases, taking to account primary and secondary, literature documents. The purpose of this work was not to conduct an exhaustive review of all of the studies published to date, but to identify the major documents, thereby obtaining a better understanding of the prioritisation of work regarding CB strategy, CB tools specifically developed for ENMs for ENMs and physicochemical and biological properties of ENMs. The aims of this review were to understand how the CD tools were developed and to identify the parameters in these matrices.

A total of 932 references were identified through bibliographic databases searches. An additional 50 references were obtained through other Internet sources. After removing duplicates, a total of 832 records were available for title review/abstract screening. Out of the 832 references, 91 (11%) records remained for a comprehensive review. After the comprehensive review of the 91 records, only 51 (6%) of these records were included in this literature review.

2.2. New Methodology Approach Based on CB, but for Health Hazard Characterisations of ENMs
The new method developed during the current work and discussed in this paper aims to evaluate the health hazards resulting from the use of ENMs, with the objective to protect workers and the general population from hazardous situations. This method is based on the CB approach that classifies several levels of toxicological hazards from ENMs; however, as discussed in this paper, our first intend in that project did not take exposure into consideration at this step. This approach is based exclusively on relevant physico-chemical and biological characteristics of ENMs. The levels of toxicological hazards used in the current method will combine four or five physico-chemical characteristics and the same
number for the toxicological tests. The combination of these hazard bands will lead to the development of a decision matrix tool to establish a control level, and then to make recommendations for the workers who handle hazardous chemicals such as ENMs and for members of the general population who might be exposed in the workplace.

We believe that the current method can be used to classify the ENMs according to their intrinsic reactivities with biological materials to establish a limit for the ENMs that currently do not have any reference values. It is important to mention that in this paper, we will discuss several potentials tests that could be used in this matrix. However, another exhaustive literature review will be necessary to identify the tests commonly used by different laboratories. All of these tests will be challenged by extensive criteria not discussed in this paper. A validation will then be required before a decision is made regarding the prioritisation of tests to be used to characterise the hazards. Thus, the validation component is not included in this current work.

3. Result and Discussion

3.1. Results from the Literature Search
These CB–type tools for ENMs that were developed between 2008 and 2012 have already been described in detail and reported in published studies for a comparative analysis [37, 38, 45, 46, 52]. The authors of these publications reviewed many of these CB tools for ENMs relating to their scope and applicability, hazard and exposure banding parameters and risk classification or control bands. It is evident from the scope of each of the strategies that they were developed for different purposes. For example, the CB Nanotool was created to protect nanotechnology researchers, whereas the Precautionary Matrix was created to identify and prioritise risks, considering the health of workers and consumers, as well as the environment. The CB methodology should not in any way be compared with the other tools because it is not a matrix that allocates hazard and exposure bands; instead, the methodology is only being used to determine whether there is a need for action. These Guidance were developed to help employers and workers with identifying the risks associated with different work situations. NanoSafer and the Stoffenmanager Nano were applied to assess and manage occupational risks during the synthesis and downstream use of ENMs in workplace settings and at laboratories.

3.2. Origins of the CB Strategy
CB, which is used as a risk management strategy, was developed as a simplified approach to conduct a qualitative risk assessment and to take measures to protect workers and the public. In a historical context, CB has grown from a number of qualitative risk assessment strategies that began to appear in the 1970s because of events that involved explosions, radiation, lasers and biological agents [21, 22]. In the early 1990s, the pharmaceutical industry implemented the CB method that was used to manage chemical risks to employees in the workplace [22]. In 1994, the Health and Safety Executive (HSE) in the United Kingdom initially developed the CB method, which was known as the Control of Substances Hazardous to Health Essentials (COSHH Essentials), primarily to benefit small- and medium-sized enterprises (SMEs) that may not have the expertise of a full-time occupational hygienist on staff or as a consultant [23, 24].

This approach was designed to help SME employers to carry out suitable and sufficient risk assessments for all chemicals used in the workplace and to take steps to ensure that exposure is adequately controlled [23, 25]. This regulation was intended to increase the emphasis on the use of risk assessments in the industry to protect human health [26]; however, many challenges were experienced regarding their effective implementation. An unpublished survey of 2000 companies revealed “widespread ignorance of the regulations and their implications”[27]. The main challenge was that the SMEs did not understand
the requirements of the COSHH Essentials and “wanted to be told exactly what they need and do not need to do” [21, 28]. However, there may be little practical use for occupational exposure limits (OELs) in small companies, given that SMEs often lack the financial and technical resources to conduct toxicological and epidemiological research to establish the OELs and collect and analyse samples [21]. With the challenge indicated, the SMEs have experienced increased difficulties with assessing and ensuring appropriate protection for their workers [29]; therefore, an alternative, user-friendly method to protect workers from adverse health effects of hazardous chemicals was needed. This concept was the origin of CB.

Strictly speaking, CB represents a qualitative strategy that originates from industrial hygiene and offers solutions and control measures to ensure the safety of workers who use new chemicals, for which reliable toxicological and exposure data are absent [25, 30]. These new chemicals were classified into “bands,” mainly defined according to the hazard level of known products similar to those used, taking into consideration exposure assessments. Each band corresponded to a risk control strategy [31]. In one of the least complex forms of CB, a four-level hierarchy of risk management options for controlling exposures to chemicals includes: (1) effective occupational hygiene practices, which may be supplemented by using appropriate personal protective equipment; (2) engineering controls, including local exhaust ventilation; (3) containment and (4) the need to seek advice from specialists [21].

To determine the appropriate control strategy, the exposure potential may be estimated by quantity of use, the volatility of liquids or dustiness of solids and the frequency and duration of exposure, and the potential hazard may be captured in what is known as a risk phrase [R-phrase] that were required by the European Union and used to rank the hazard of a chemical [21, 22]. The use of R-phrases or their equivalents in the Globally Harmonized System for Classification and Labelling of Chemicals in CB is helpful, but it is not intended to replace OELs, exposure assessments, or classic industrial hygiene protocols [21]. The majority of the CB methods focus the resources on preventing workers’ exposure to chemicals; however, the CB method was not intended to be a predictive exposure model, but rather a way to sort work processes into bands. Simply stated, the CB method was a way to link hazards to general control plans [21, 32]. The CB method is recognised by many national and international organisations and is being increasingly applied worldwide as a practical approach to meet the needs of SMEs and developing countries for addressing chemical hazards. CB has been internationalised by the International Labour Organization [25, 33]. Of all of the forces that drive the evolution of the CB model, there was an increasing recognition that the traditional process was losing ground. In fact, reliance on this approach has become increasingly difficult because of the growing number of potentially hazardous materials in the workplace that do not have OELs, specifically ENMs that are currently used in occupational settings [22, 34].

3.3. CB Tools for ENMs
Various countries have developed a variety of CB strategies [26]. In recent years, several nano-specific CB methodologies for different types of workplace environments (e.g. small and large industries and laboratories) have been developed and published, and each instrument has specific strengths and limitations [35]. The remainder of Section 3 of this review presents a brief summary and the purpose of each of the six instruments used for ENMs. These six instruments are the CB Nanotool, the Precautionary Matrix, the ANSES CB Tool for ENMs, NanoSafer, The Guidance and Stoffenmanager Nano.

3.3.1. CB Nanotool (United States of America)
In 2008, Paik et al. developed the CB Nanotool as a strategy for performing a risk assessment and protecting nanotechnology researchers at the Lawrence Livermore National Laboratory [36, 37]. The CB Nanotool is intended to be used by both experts and non-experts for providing recommendations for appropriate engineering controls [35, 36]. The CB Nanotool is a simplified approach based on the
paradigm established by the COSHH Essentials that uses a four-by-four factor risk matrix (Table 1) to determine the risk level (RL) [38-40]. The specific RL is determined by a “severity” score on one axis and by a “probability” score on the other axis [36]. The severity score is based on a mix of intrinsic properties of ENMs and on the presence or absence of health effects (four bands for the hazard). The probability score is based on interaction of the worker in the workplace and the ENMs (four bands for the exposure) [36]. The lack of data resulted in high scoring. The issue with this scoring, it is difficult to apply a summation of items that were different such as a dermal hazard and solubility or particle shape and carcinogenicity. The maximum probability/severity score is 100 (Table 1). In fact, the combination of severity and probability leads to an overall four possible RL control bands with corresponding specific control strategies that can be classified in RL 1 to RL 4 [36, 41].

Table 1: The CB Nanotool matrix (modified based on research from Paik et al. 2008)

| Severity     | Probability          |
|--------------|----------------------|
|              | Extremely unlikely   | Less likely | Likely | Probable |
|              | (0–25)               | (26–50)     | (51–75) | (76–100) |
| Very high (76–100) | RL 3 | RL 3 | RL 4 | RL 4 |
| High (51–75) | RL 2 | RL 2 | RL 3 | RL 4 |
| Medium (26–50) | RL 1 | RL 1 | RL 2 | RL 3 |
| Low (0–25) | RL 1 | RL 1 | RL 1 | RL 2 |

Note: RL 1 = general ventilation; RL 2 = fume hoods or local exhaust ventilation; RL 3 = containment; and RL 4 = seek specialist advice.

The severity scores are determined by using the physical-chemical characteristics of both the ENM and the parent material. The probability scores are determined by using the factors that determine the potential exposure of workers to ENMs [36]. The CB Nanotool provides indications regarding how to allocate scores for the severity factors and the probability factors. Then, the maximum scores can be attributed to each factor.

3.3.2. Precautionary Matrix (Switzerland)

The Swiss Federal Office of Public Health and the Federal Office for the Environment developed a Precautionary Matrix [42] in 2008 and revised the tool in 2010 [43]. The Precautionary Matrix was published almost at the same time as the CB Nanotool. The Precautionary Matrix is different from the CB Nanotool because the matrix also considers the workplace, consumers and the environment [43, 44]. This CB approach (i.e. the matrix) aims to guide SMEs to apply a precautionary method to identify possible sources of risk from the production, use and disposal of synthetic ENMs [42]. In contrast to the name, the Precautionary Matrix does not distinguish the bands for the hazard from the bands for exposure; however, the matrix does combine the hazard and exposure potential into a single score to determine whether there is a need for action [35, 45]. The total score is subdivided into two categories: Class A (lower score ≤20) and Class B (higher score ≥21) (see Table 2). The major issue is that the categories do not discriminate between the following: (1) hazard and exposure and (2) the sum of the pictograms based on different information about the amount of ENMs and work or consumer information that is related to the exposure. This approach requires some expertise to help ensure accurate interpretation. The precautionary matrix estimates the risk potentials—through the entire life cycle—for
the health of workers and consumers and for the environment. The applicability of this CB approach is difficult, and global.

| Score | Classification | Importance |
|-------|----------------|------------|
| ≤20   | A              | The nano-specific need for action can be rated as low, even without further clarification. |
| ≥20   | B              | The nano-specific action is needed. Existing measures should be reviewed, further clarification undertaken and, if necessary, measures to reduce the risk associated with manufacturing, use and disposal should be implemented. |

### 3.3.3. ANSES CB Tool for ENMs (France)

ANSES developed an operational CB approach for small- to large-sized enterprises during the synthesis and downstream use of ENMs in workplace settings and in laboratories [31, 35, 45]. The CB Tool for ENMs is only available as a paper version, and it is explicitly recommended that the users (academics and industrials) are adequately qualified to conduct work regarding chemical risk prevention [31, 39]. In the approach from ANSES, the control bands (levels) are determined by combining the bands for the hazard and the exposure (emission potential). ANSES uses five hazard bands that range from HB1 (very low [no significant risk to health]) to HB5 (very high [a severe hazard that requires an expert to perform a comprehensive hazard assessment]) [31]. The exposure bands are allocated based on the emission potential and can be grouped according to the following four levels: EP1 (solid), EP2 (liquid), EP3 (powder) and EP4 (aerosol) [31]. These five hazard bands and four exposure bands are directly linked to the five control bands associated with general recommendations that are ranked from lower CL1 (natural or mechanical general ventilation) to higher CL5 (full containment and review by a specialist are required) [31, 45, 46]. The hazard portion of the CB matrix (from ANSES) is based on the toxicity warning label that is associated with clinical observations. The issue regarding these criteria is that they are not specific enough; therefore, the criteria cannot be used to protect sensitive sub-populations. These criteria are based on general observations of large classifications and are not supported by quantitative data, with the exception of a large characteristic from the labelling that is used.

### 3.3.4. NanoSafer (Denmark)

 Developed by the Danish Technological Institute and National Research Center for the Working Environment, NanoSafer is an online CB tool that helps manage the risks resulting from the use of ENMs [37, 47]. Currently, there is only a Danish version of this tool, which is intended for SMEs and laboratories that do not have any or have limited experience in producing or working with ENMs [35, 47]. NanoSafer focuses on the work environment, and application of the tool is limited to assessing the handling of nanopowder products and fugitive and point-source emissions [35, 45]. In NanoSafer, four bands are allocated for the hazard and five bands are for the exposure. In addition, there are five RLs (control bands) [35] that range from RL1 (low hazard and low exposure potential) to RL5 (high hazard and/or moderate to very high exposure potential) [47]. NanoSafer uses its e-learning tool to make recommendations that are suitable control measures for each RL [47]. Because NanoSafer relies on the size of the ENMs, such as nanopowder, and the OEL of the application, it is relatively accepted that the sizes of ENMs are proportional to the toxicity and related to the surface. However, it also true that two ENMs of the same size may have vastly different toxicities. It is important to note that only considering...
the size of the ENMs will provide an indication, but this criterion will not be strong enough to ensure an accurate and valid assessment. The issue regarding hazards is much more complex than that.

3.3.5. The Guidance (The Netherlands)
The Guidance was developed by the Confederation of Netherlands Industry and Employers (Verbond van Nederlandse Ondernemingen-Nederlands Christelijk Werkgeversverbond [VNO-NCW]) and two Dutch trade associations, the Dutch Federation Vakbeweiging (Federatie Nederlandse Vakbeweiging [FNV]) and the Christian National Trade Union (Christelijk Nationaalvakverbond [CNV]). The purpose of The Guidance is to guide employers and employees in identifying the risks associated with the use of ENMs and nanoproducts during different work situations [48]. The Guidance has a list of 10 generic activities for making an inventory of ENMs that are produced or used along their life cycle within a company [35, 48]. In The Guidance, the following three hazard categories for ENMs and nanoproducts are identified: 1 (soluble nanoparticles), 2 (synthetic, persistent nanoparticles) and 3 (fibrous, nonsoluble nanoparticles) [48]. The exposure bands are allocated based on the emission potential from the different activities related to the production of polymeric nanocomposites: I (there are no emissions of free nanoparticles due to working in full containment), II (emissions of nanoparticles embedded in a matrix are possible) and III (emissions of free nanoparticles are possible) [48, 49]. Hazard and exposure data are collected and combined in a decision matrix to establish a control level (Table 3).

Table 3: The decision matrix to determine the risk management class and the control level for activities with ENMs and nano-enabled products (adapted from The Guidance, Version 4.2 dated August 2012)

| Description of the hazard category for each nano-enabled product | Hazard category 1 Rigid, biopersistent nanofibers for which asbestos-like effects are not excluded | Hazard categories 2a and 2b Biopersistent granular and fibre-form ENMs with excluded asbestos-like effects | Hazard category 3 Non-biopersistent granular or (water) soluble ENM |
|----------------------|----------------------------------|--------------------------------------------------------|---------------------------------------------------------|
| Probability of exposure to nanoparticles during activities | | | |
| Exposure category I: Emission of primary nanoparticles is possible. | A | A | C |
| Exposure category II: Emission of nanoparticles embedded in a larger solid (>100 nm) or liquid matrix is possible. | A | B | C |
| Exposure category III: Emission of free nanoparticles is minimised due to working in full containment | B | C | C |

A The hierarchic Occupational Hygienic Strategy will be strictly applied, and all protective measures that are both technically and organisationally feasible will be implemented. The reasonableness principle is not used.

B According to the hierarchic Occupational Hygienic Strategy, the technical and organisational feasible protective measures are evaluated regarding their economic feasibility. Control measures will be based on this evaluation.

C Sufficient (room) ventilation, if needed, is applied to local exhaust ventilation and/or containment of the emission source and use appropriate personal protective equipment.

3.3.6. Stoffenmanager Nano (The Netherlands)
Developed by the Netherlands’ Organisation for Applied Scientific Research (Nederlandse Organisatie voor Toegestuurd Natuurwetenschappelijk Onderzoek [TNO]) and Arbo Unie, Holland, the Dutch Stoffenmanager Nano [50] is a generic tool that has both Dutch and English versions. The
Stoffenmanager Nano was initially developed as a practical approach for scanning electron microscopy (SEMs) and also for laboratory work to support researchers with assessing, prioritising and controlling occupational risks during the synthesis and downstream use of ENMs [46, 50]. This CB approach is intended to be used by non-expert employees at SMEs [45]. The Stoffenmanager Nano combines five hazard bands (i.e. low, average, high, very high or extreme); the highest band is associated with the highest risk priority, irrespective of the exposure band [50]. The potential hazard level is assessed based on how it relates to the ENMs properties (i.e. size, shape and solubility) and the toxicological data available, together with the properties of the parent material [50, 51]. The Stoffenmanager Nano uses five exposure bands that are expressed by using a sophisticated algorithm and includes the most important exposure parameters, taking into account various aspects from the source of the ENM in the breathing zone of the workers [39, 51]. The combination of these hazard and exposure bands leads to three overall risk prioritisation bands that can be classified as 1 (the highest priority) to 3 (the lowest priority) [50].

The results of the literature review provided interesting information about how and where CB originated, how CB has been used in the past, and how CB is organised or structured. From this review, it was observed that each CB matrix described one or a few parameters related to the exposure. These parameters are usually related to a physical property of the ENMs (e.g. length, size, volatility, solubility). These physico-chemical properties integrated limited information that can be used to characterise the nanoparticles to help control risk. Other methods describe the CB approach that is used to determine the severity of a potential effect on the probability which depends on the manipulation of ENMs [36]. In this case, the matrix is a two-pronged account that is based on criteria of physical and health effects information to determine the severity and on the workplace information about exposure to derive the probability. This matrix is still fuzzy and needs an expert judgment to obtain a good interpretation. More effort should be made to improve the hazard characterisation of the nanoparticles. Thus, one way to improve this approach is to characterise the ENMs by using chemical and biological analysis tests, which, when combined, can provide a discriminate level of hazard. This characterisation of the hazard can be associated with a second banding graph, during which the hazard is correlated to the exposure classification, and then the risk assessment is estimated.

3.4. New Methodology Presented After the Literature Review

After reviewing the CB tools that have been developed specifically for ENMs, all of these tools are qualitative in nature and are based on the exposure. More specifically, all of the hazard criteria used in these different CB methods that were evaluated during this literature review missed the point of really characterising the ENMs based on their major characteristics. In fact, the series of parameters presented for each CB developed and reviewed as part of the current work is incomplete and based on classical occupational safety approaches. We believe that the literature review performed as part of our research about the CB approaches has revealed that the best thing that we can do to protect the workers and the general population exposed to ENMs is to use the established conventional occupational health methods. In fact, currently it is impossible to perform quantitative risk assessments because there is a lack of data. With that said, from the perspective of using a better and more relevant approach to conduct risk assessments, what can be done to improve the tool that is currently being used? This is why a new methodology to improve the hazard assessment is presented in this paper. The criteria of the tests selected for the new methodology are based on the availability of the analysis tools, the cost and the level of information that can be obtained from this analysis. The objectives are to maximise the information collected with tests and minimise the cost of the test. Of course, during the selection and prioritisation, more criteria may be added to obtain the best selection as possible, and then to characterise the reactivity of the ENMs.
This new approach is called a semi-quantitative hazard assessment method and is based on the CB approach and on the physico-chemical and toxicological tests of the ENMs. This new approach may help to quantify and interpret the levels of hazards from working with ENMs and with maximum confidence and minimum uncertainty regarding future recommendations to the workers who handle hazardous chemicals such as ENMs and to the general population.

The first phase of this work involved the development of an assessment tool of ENMs, based on the National Research Council’s (NRC’s) approach [20] in the publication titled “Integrated Approach to Design and Safe Handling of Nanomaterials—A Program Based on a Dialogue Between Industry and Evaluators of Health Risks,” which was published on the Web site for IRSST. The second phase of this work is underway (part of this initiative of the current paper). The second phase is needed to review the literature about the development of CB across time and to select the appropriate chemical and biological characterisation tests, which will be standardised and then assessment tools will be developed. Some examples of the potential tests that can be used are presented in Table 4.

For the physico-chemical characterisations, we have selected tests that describe the properties we want to measure. For example, there is a linkage between the size of the ENMs and toxicity. In general, the small nanoparticles have a higher toxicity, partly due to both the reactivity and to the proximity of the nucleus. Another example might be the surface chemistry of the nanoparticles. Therefore, two nanoparticles having the same size, but with different surface chemistries, will yield different toxicities. For each test, Table 4 also lists the equipment that can be used to perform analyses of this physical property. It is important to note that the list in Table 4 is not exhaustive because we are in the first step of this process.

### Table 4: Physico-chemical characteristics of ENMs and suitable evaluation equipment

| Physico-chemical characterisation | Instruments and methods                                      |
|----------------------------------|-------------------------------------------------------------|
| Size (size distribution, agglomeration) | Transmission electron microscopy (TEM), scanning electron microscopy and Raman scattering |
| Shape of nanoparticles           | TEM and near-field scanning optical microscopy              |
| Chemical composition             | Secondary ion mass spectrometry and nuclear magnetic resonance |
| Surface (surface charge, surface area) | Zeta potential, TEM and attenuated total reflection–Fourier transform infrared |
| Stability (colloidal stability, solubility) | Zeta potential, dynamic light scattering and circular dichroism |
| Crystal structure                | X-ray diffraction                                           |

The method also considers the biological characterisations of ENMs (Table 5). In this table, we tend to analyse the biological reactivity of the ENMs through interaction with the biology. In this characterisation, only the in vitro tests were considered because there is a budget issue regarding application in the industry. For example, the viability assay and the oxidative stress test are two major tests to analyse for toxicity. The right column in Table 5 lists some examples types of tests that are available to measure this toxicity.

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Table 5: Toxicological tests of nanoparticles (in vitro toxicity)

| Toxicological testing of ENMs | Tests available                                                                 |
|-------------------------------|---------------------------------------------------------------------------------|
| Viability assay               | Neutral red, resazurin test and Trypan blue exclusion assay (for cell counting) |
| Oxidative stress and inflammation tests | Superoxide dismutase activity, catalase, glutathione peroxidase, glutathione reductase, glutathione transferase, nuclear transcription factor–kappa B and interleukins (IL-1, IL-6, IL-8) |
| Apoptosis assay               | Caspase activity assay and membrane asymmetry                                    |
| Mitochondrial activity assay  | MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) or WST1 (water-soluble tetrazolium salts) assay |
| Metabolic activity test       | Sulforhodamine B (SRB) assay                                                    |
| Membrane integrity test       | Lactase dehydrogenase (LDH [or LD]) test                                         |

To determine which tests will be incorporated in the assessment tool, more work needs to be done during the third phase. In addition, a validation based on different criteria is required and will be explored during the second phase of the project. The results from the second phase will be presented in another paper.

The list of physical and biological tests selected will represent an original hazard assessment approach that can be used to characterise the ENMs. The selection and the analysis will be used to produce a hazard matrix (Table 6). Nevertheless, at this point, it is impossible to determine with some certainty which tests that correspond to the validation component will be used. To determine the list of tests, several criteria will be considered (e.g. widely used, inexpensive or free, easy to conduct and provides the information needed regarding the reactivity).

Table 6: Assessment tool of nanoparticles based on physico-chemical and biological characteristics

| Physicochemical | TEST A | TEST B | TEST C | TEST D | TEST E |
|-----------------|--------|--------|--------|--------|--------|
| Biological      |        |        |        |        |        |
| TEST A          |        |        |        |        |        |
| TEST B          |        |        |        |        |        |
| TEST C          |        |        |        |        |        |
| TEST D          |        |        |        |        |        |
| TEST E          |        |        |        |        |        |

Note: The risk factors are as follows: green = lower; yellow = moderate; orange = less high; and red = high.

The objectives of the literature review were to understand the CB tool and to understand the history of its development and how the CB tool has evolved over time. The goal of our new methodology is to provide a tool that uses an original hazard assessment method to compare the physico-chemical and biological characteristics of ENMs. The CB tool will be used by occupational safety workers who are in charge of conducting hazard evaluations for workers and the general population. The literature review has allowed us to understand what tools have been developed for CB to protect workers who have been potentially exposed to ENMs. The major observations were that the CB matrix is based on one physico-
chemical characteristic or on a cluster of physical or chemical properties and clinical observations. These parameters were then compared to the exposure scenario. reviewing these studies, we came at the conclusion that a better approach should be developed to improve the hazard characterisation of the ENMs.

The new approach developed to characterise the ENMs was very important step in this project. In fact, a comprehensive assessment of the physico-chemical and biological characterisations of ENMs is a key element of any ENM toxicity screening strategy. In this study, we were primarily interested in the characterisation of ENMs to analyse this reactivity with biological materials. Indeed, it is necessary to characterise the ENM that is intended for therapeutic use in both its originally manufactured condition and after its introduction into a physiological environment. The proposed method will contribute towards a better knowledge of ENMs to anticipate their potential effects on humans.

The proposed method discussed in this paper will require validation before it can be used as a semi-quantitative CB approach. It is important to remember that our aim in this paper was not to present the final version of proposed semi-quantitative method. We are currently selecting the most relevant physico-chemical and biological parameters of ENMs. The selection process and the findings will be discussed in upcoming paper. This method is not intended to be a substitution of existing methods currently in use to manage the hazards posed by chemicals. This proposed method is different from the approaches that have been developed by other agencies. The other approaches assess and characterise the risk for workers and the general population on a semi-quantitative basis. Nevertheless, it was important in this paper to identify a minimum number of in vitro studies that could generate a maximum amount of information. In vitro studies can generate reproducible results as quickly as possible at an affordable cost for industrialists. The toxicology and physico-chemical tests that will be selected will be the most suitable and commonly used in the nanotechnology field.

4. Conclusion
During the literature review, we evaluated how the CB models were developed and how they work. There were different observations regarding how the models were developed and how the parameters remained in each CB. The major problem with the CB models reviewed in this current paper is the hazard information required is not always available from the Material Safety Data Sheet; therefore, expert judgment is often required. Following the comprehension of CB, including the strengths and weaknesses, a new semi-quantitative methodology of CB is proposed for the Human Health Hazard Assessment based on physico-chemical and biological characteristics of ENMs. This new approach is original because it is dependent upon the structure of ENMs, but it is not based only on the exposure on the first intend. It is important to develop this CB approach based on the characterisation of potential health hazards posed by ENMs to identify and quantify the degree of hazardousness of ENMs to establish a better framing of their health implications and to ensure safe handling of these nanoparticles. In particular, this proposed method is a practical tool that will help provide relevant recommendations to the general population and particularly to the workers who handle ENMs and hazardous chemicals, thereby bolstering employees’ confidence in adopting a sophisticated hazard assessment approach by using objective and validated criteria. At this point, the limitation of this method is that all tests suggested in this paper must be validated before a decision is made regarding the prioritisation of tests to be used for characterising the hazards. This limitation corresponds to Step 3 of our certification process of this methodology, which was not presented during the Nanosafe 2016 meeting in Grenoble, France. Nevertheless, this CB method, based on characterisations of the potential hazards posed by ENMs, is required in order to develop better guidelines regarding health implications that will ensure safe handling by employees in workplace settings, as well for the general population, which could come into contact with ENMs. From this dependent hazardous assessment, it is possible to combine this assessment and the exposure assessment. The scientific knowledge of the risks associated with ENMs
is constantly changing, both with regard to physico-chemical characteristics and toxicology. Thus, it is therefore mandatory to update information regularly by integrating these new data into the CB method used in this study.

5. References

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