Human Risk Assessment and Its Application to Nanotechnology: A Challenge for Assessors

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Abstract. Scientific literature suggests that exposure to nanoparticles (NPs) might be associated with adverse health effects. A well-developed human risk assessment (HRA) that applies to NPs has never been established and optimized—until now. Furthermore, no government regulations are in place that establish what is considered to be an adequate and secure level of exposure and supported by a strong scientific approach for nanotechnology. It is important to implement the HRA to ensure that workers producing NPs, users of NPs and the general population are protected from deleterious issues related to NPs. In this work, a methodology is described based on the HRA. An effort is required during synthesis before the commercialization phase to evaluate the results of a systematic and rigorous assessment because this could significantly reduce the health risks of those exposed to NPs, including workers and the population.

1. Introduction
Nanotechnology use is currently growing at a rapid pace around the world [1] and is expected to further increase in the coming years, especially in the industrial and economical fields. Scientific literature suggests that exposure to nanoparticles (NPs) might be associated with adverse health effects [2-6]. The literature also suggests that the current data on the toxicity of nanomaterials remain fragmented and do not provide quantitative health risk assessment of exposures. Therefore, to help reduce the risk of exposure to nanomaterials, an alternative is to use a methodology to determine safety assessment (qualitative) exposures to nanomaterials. Despite some characterization initiatives, limited strategies on potential toxicities of nanomaterials are available. A well-developed health risk assessment (HRA) that applies to NPs has never been recognized and optimized—until now. In addition, no government regulations are in place that establish what is considered to be an adequate and secure level of exposure or are supported by a strong scientific approach for nanotechnology. It is mandatory to implement the...
HRA to ensure that workers producing NPs, users of NPs and the general population are protected from deleterious issues related to NPs. The aim of this work was to review the different characterization steps of the HRA and to discuss the current limitations that apply to them regarding nanotechnology. An international collaboration team was assembled to develop a methodology to improve the health risk assessment. The methodology is described in Section 2 [7]. This work will have an impact because governments and industries can use the information to improve their regulations and to protect workers and the general population from overexposure.

2. Methods
This section describes a general strategy that the Nanotechnology Health Risk Assessment Working Group should use to evaluate the risk factors that could potentially affect quality, efficacy and safety when using nanomaterials to develop and manufacture products or to assess the potential risk for the general population. The methodology described in this paper was initially discussed in a book (commonly referred to as the Red Book) published by the National Research Council (NRC) in 1983 and was adapted for nanotechnology [8]. The approach divided the HRA into four different characterization steps: Source Identification Characterization (SIC), Exposure Assessment Characterization (EAC), Hazard Assessment Characterization (HAC) and Risk Assessment Characterization (RAC) [8, 9] (Figure 1).

The **Source Identification Characterization (SIC)** is a straightforward step regarding the occupational point of view because it is relatively well understood.

The **Exposure Assessment Characterization (EAC)** is a challenge regarding methodology because existing equipment and instrumentation used for fine particulate matter are not always adequate for NPs.

The **Hazard Assessment Characterization (HAC)** is an important issue because no consensus exists on many points of view such as the physical and chemical characterizations of the NPs, dosimetry, and toxicological reference points.

The **Risk Assessment Characterization (RAC)** is a combination of the HAC and EAC. The RAC interprets the level of risk based on the exposure level affecting the exposed workers or the general population, as well as the level of HAC, corresponding to the sensitivity of the NPs to react with biological tissue.

*Figure 1: A schematic representation of the health risk assessment step proposed in this methodology, which is based on the NRC’s Red Book.*

The SIC represents a straightforward step regarding the occupational point of view because it is relatively well understood. Nevertheless, that may represent a challenge for the general population
because NPs are found in many different consumer products. Without a labelling regulation in place, it is difficult to determine whether NPs are in consumer products.

The purpose of the EAC step is to understand whether there is a potential interaction between NPs and biological materials. If no exposure has occurred, then there is a negligible risk (close to the risk = 0). To understand this issue, it is important to ask many different questions. The first set of questions should be as follows: Where in the vector or media can we find the NPs? Is it in food (liquid or solid media); in the air (primarily in the occupational area, but not exclusively); in cosmetics, which include sunscreens; or in other consumer products? Identifying the media will help to define the best approaches for characterizing NPs. The second set of questions should be as follows: In which NPs are we interested? Are they neutral NPs or ionic NPs? Are the NPs lipophilic or hydrophilic? It is important to characterize the size, the surface, the chemistry and the phenomenon of agglomeration and aggregations, which are all influenced by the chemistry of surface [10]. Answering the second set of questions will provide understanding of the speculated or generated hypothesis regarding the NP, the deposition site and the route of exposure. The third set of questions should be as follows: How can we understand the surface chemistry? How can we understand the behaviour of NPs? Once these questions are answered, then the question about exposure assessment characterization of the NPs can be answered. During the EAC step, the potential exposure is measured, which determines whether the NPs can be exposed to or interact with biological tissues. To determine whether there is any potential for an interaction, a scientific instrument is needed to measure and characterize the exposure. However, this important step is a challenge for metrology because existing equipment and instrumentation are often not adequate for NPs. However, new instruments are constantly being developed, which will help to improve real-time measurements and provide better accuracy for size assessments and for surface characterizations. Nevertheless, developers of the new instruments should ensure that the NPs are not destroyed during exposure assessments.

Of the four steps, the HAC step is the most challenging because no consensus currently exists on several points of view (e.g. the biological and chemical characterizations of the NPs, dosimetry) and about toxicological reference protocols [11]. Moreover, there is an important requirement to develop comparable toxicological protocols adapted to NPs [12]. In fact, publications focusing on an in vitro cellular assay frequently reported that the same NP in two different culture media can generate completely different toxicity profiles. In one case, the result revealed a toxicity, but in another case, the finding showed a weak toxicity or no toxicity [13]. For assessors, not enough information exists to replicate in vivo pharmacokinetics data or even comparable or published data [5]. We cannot just wait for the Organization for Economic Co-operation and Development protocols to be developed. There is also a requirement to develop an in silico model (i.e. physiologically based pharmacokinetic model [PBPK]) that can support the pharmacokinetics to gain a better understanding of the kinetic behaviour and to generate hypotheses [14-16]. In fact, the PBPK model proved that it was useful and sometimes essential in the environmental contaminant field of toxicology [17]. Consequently, there is an important requirement to develop or identify toxicological protocols that are adapted to specifically discuss the interaction of NPs with biological tissues. A response to that problem is difficult because better understandings of the NP and of the interaction with its actual environment are needed.

The RAC step, which represents the combination of the HAC and EAC steps, interprets the level of risk based on the exposure level assessment affecting the exposed workers or the general population and the level of HAC, corresponding to the potential reactivity of the NPs to react with biological tissues. This RAC step is problematic for risk assessors because there are several limitations, in the interpretations, or misunderstandings of the results. In addition, during the EAC and HAC steps, there are no concerns regarding replication, so the results cannot be interpreted and published.
3. Discussion and Conclusions

Nanotechnology is meant to play an essential role in the development of today’s modern societies. There are many great advantages associated with the use and application of NPs, but with that technology can come with serious potential concern to human health. Therefore, the main objective of this paper is to present a four-step methodology to assess the toxicity for NPs that uses developed health risk assessment strategy methods to consider diverse physicochemical and biological properties [8]. Our international collaboration team has conducted some work to fill gaps regarding nanosafety assessment by measuring the impacts earlier in the process than when the products appear on the market [12]. In fact, greater effort is required during synthesis and before the commercialization phase to evaluate the results of a systematic and rigorous assessment because this could significantly reduce the health risks of those exposed to NPs, including workers and the general population. Although future work still needs to be done regarding nanotechnology, the international collaboration team is steadfast in its goal to protect and develop secure NPs in a nanosafe environment.

4. References

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