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The uncertainty with nanosafety: Validity and reliability of published data

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ABSTRACT

Use and production of chemicals and new materials are always reasons for concern especially with regard to human health and the environmental impacts. Over the past few decades occupational safety is a greater focus for toxicologists and of national and international registration programs for new products. Thus, the careful investigation of the biological effects of new chemicals and materials is critical.

However, the hype around "The Nanotechnology" has boosted a competition for public funds and thereby the number of publications on this "nanotoxicology" topic has exploded. For more than two decades the public discussion around the special effects of nanomaterials or nanoparticles is ongoing without a final conclusion regarding an existing issue of a "nano-specific effect". Facing the situation of a dramatic increase in the number of publications (> 4400 PubMed references in 2017 alone!); the quality of the findings appears to be questionable, particularly with regard to the implementation of risk assessment for nanomaterials.

Most of the published nanotoxicology studies are associated with fundamental deficiencies in the experimental design of these investigations, including 1) a lack of rigorous and adequate physicochemical characterization of the test materials; 2) the absence of adequate particle controls; and 3) the implementation of high dose experiments, designed to produce toxicological effects - which are publishable (and sensational). As a consequence, the "toxicology" results have limited utility, and therefore must be critically (re)evaluated. This service is provided by the internet knowledge base DaNa (www.nanoobjects.info). On this website a criteria catalogue for the re-evaluation of scientific publications has been published and if these criteria are utilized > 60 70% of reported study findings are not acceptable and cannot be taken into consideration for risk assessment criteria.

1. Introduction

New chemicals and new materials alwaysgive rise of concern, as the past has shown that health related effects as well as influences on the environment cannot be excluded during production and use of new products. This is the reason for many national programs and international agreements on occupational and consumer safety. The latest challenge for occupational health and environmental safety comes together with the development of nanotechnology. The possibility to manipulate materials on the level of atoms and molecules raises the question around such new nanomaterials and their possible biological effects. The fact is that these new materials have new properties related to their chemical and physical behaviour in contact with their environment. Optical, electrical and electronical, magnetic as well as catalytic properties change when the particle size is reduced under specific outer dimensions which normally are below 30 nm [1]. This is not only restricted to their physico-chemical properties but also to their behaviour in biological environments [2]. Taken together, due to these new properties we face a totally new situation in toxicology, because the interactions of such nanomaterials with both biological organisms and the environment creates entirely new requirements with regard to the technical equipment, the analytical tools and the detailed knowledge around the chemical and physical background of such nanomaterials. Although the knowledge of nanoparticles and their use is relatively old, since nearly 2000 years metal nanoparticles have been used for colouring glass, the intentional production of nanomaterials commenced only around 150 years ago. At that time, Thomas Graham did his famous investigation (1851–1864) for his contribution "Liquid diffusion applied to analysis" demonstrating the behaviour of ultrasmall particles in suspension. This article, which was first published in the Philosophical Transactions and later also in the well-known "Annalen der Chemie und Pharmacie" [3] marked the beginning of colloidal

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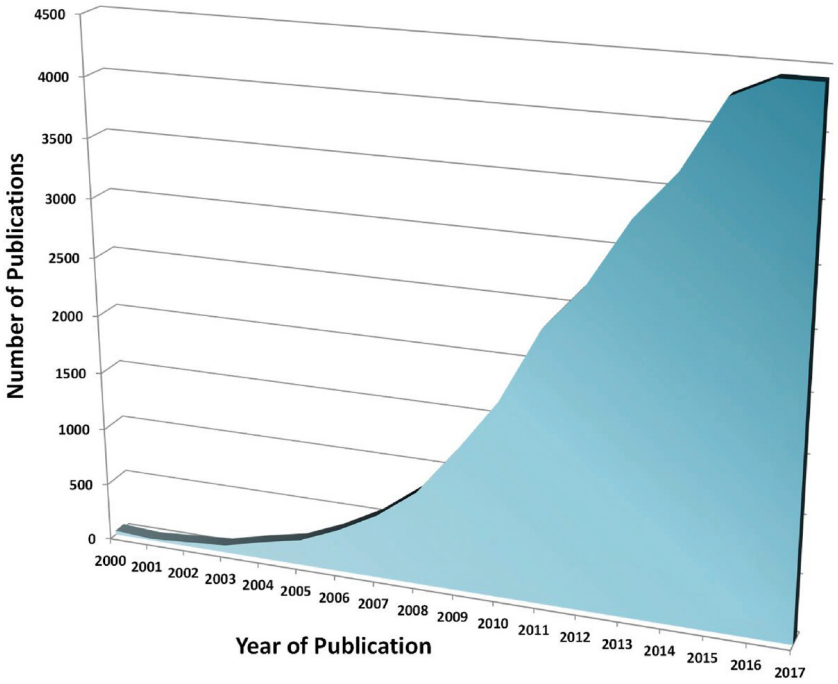

Fig. 1. Number of published studies in the field of "nanotoxicology" for the years.2000–2017.

chemistry. The first "mass use" of nanoparticles had been described for silver nanoparticles which have been used as a biocidal material for more than 120 years [4]. This short historical summary should demonstrate that use and investigation on nanomaterials, especially nanoparticles, is not a new issue. Nevertheless, nanotechnology provides the possibility to produce and manipulate these very small entities in a totally new way which leads us into a century with new expectations, hopes and fears around the term "Nano".

The interest in new materials and chemicals has been followed by an increase of published studies for the use of nanomaterials or nanotechnologies. In parallel or better slightly delayed we noticed an increase in publications on nanotoxicology as well (Fig. 1). The figure illustrates that the number of publications has dramatically increased during the last 10 years, which correlates nicely with the existence of national and international funding programs on nanotoxicology. Facing such a high number of 30,439 publications only in the database of Pubmed it should be possible to generally come to a reliable opinion about nanomaterials and their impact to trigger adverse effects in biological systems and whether this represents a potential hazard for the investigated materials. However, it is still difficult to obtain suitable information on the toxicity of nanomaterials from these publications and without careful re-evaluation of the published experiments it will be highly probable to be misled by incorrect relevance interpretation of the data. The reason for this will be further discussed within the following sections.

2. Quality criteria for toxicological studies

It is now more than 10 years ago that several scientists including our group have pointed to specific problems when investigating the biological (toxic) effects of nanomaterials. Within the various influences and sources of errors, specifically the interference of nanomaterials with the assay systems (analytes, measurement principle *etc.*) [5–8]; the adsorption of nutrients and other essential medium ingredients by the nanomaterials [9]; as well as the contamination of cells and tissues with nanoparticle-bound bacterial endotoxin [10,11] are prominent examples for misinterpretation of results in toxicological experiments with nanomaterials. In such cases the publications report on false-positive as well as on false-negative results and a faithful picture of the situation of the nanotoxicological effects cannot be recognised. At the same time it was clearly stated that "Current methods lack the desired sensitivity, reliability…" and "Therefore, improved physicochemical nanomaterial assays are needed to provide accurate exposure risk assessments…." [12].

There are numerous pitfalls and sources of error hidden within the study designs for experiments with nanomaterials as mentioned above. It starts just with characterising [13] and dispersing nanoparticles in physiological media [14] followed by many subsequent steps of the overall procedure in the lab [15]. We have analysed these steps for a simple toxicity assay and were able to demonstrate that the MTS assay used in many labs all around the world may result in an invalid outcome when specific procedures are not respected [16]. We demonstrated clearly in an interlaboratory comparison study by using the cause-and-effect diagram that only exact descriptions of the overall experimental scheme can be repeated and lead to comparable results [17;18]. Moreover, for other assays it has been described that for certain materials the outcome is not reliable. This has been demonstrated for the comet assay [19] which tests for DNA damage, for microscopic imaging [20] as well as for assays which test the immunomodulatory effects of nanoparticles [10]. Taken together, in analyzing these critical points for the experimental procedure it becomes obvious that likely many of the published data may present inaccurate results. This is the reason that we defined a "literature criteria checklist" for publications which shouldbe fulfilled to judge a published study as "acceptable" for our database which is open to every user in the internet [21,22]. We have announced on our webpage: "Particularly with respect to toxicological publications (human and eco toxicology) all described experiments and results were extensively assessed by the DaNa experts using this literature criteria checklist, a customised methodology to evaluate scientific literature prior to admission to the knowledge base." This "knowledge base for nanomaterials" which is available at www.nanoobjects.info currently covers the information on 26 nanomaterial-types used already in various products on the market (as of February 2018). The criteria checklist is also published on this website to clearly make the process of selection transparent and comprehensible. The checklist discriminates between mandatory and desirable assessment