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Perspectives and interests in the construction of occupational health standards: the case of silver nanoparticles

Perspectivas e intereses en la construcción de normas de salud ocupacional: el caso de las nanopartículas de plata

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ABSTRACT

Introduction: The regulation of chemical substances involves a difficult negotiation between social actors, and requires the articulation between scientific analysis and its conversion into a legal norm. **Objective:** The article addresses the discussion elicited by a public consultation on a voluntary regulation guide on silver nanoparticles (AgNP) in workplaces. It examines the comments made from 2016 to 2018 by diverse social actors – business representatives, non-governmental organizations (NGO) and independent researchers – to two successive draft versions of a Recommended Exposure Limit (REL) in working environments with AgNP. The REL is a voluntary guideline on permissible exposure limits elaborated by the NIOSH in the United States. A guideline of this kind combines scientific information with its legal adjustment. **Method:** The methodology used was a content analysis of the comments, structured upon a historical and sociotechnical contextualization of nanotechnologies carried out through literature review and documental analysis. **Results:** The article shows how different social actors position themselves in the controversy over the risks of nanosilver, revealing a pattern of behavior consistent with their position in the research, production and commercialization of this new nanomaterial. While a group of actors, aligned with the interests of AgNP producers, proposed the restriction of mandatory and AgNP-specific regulation, another group of more heterogeneous actors, identified with the interests of workers and consumers, demanded for more scientific and technical information and stricter health protection measures. **Conclusions:** Within these divergent stands, the regulatory agency behaved in a transparent and receptive manner while conducting the public consultation and substantively modified the originally proposed exposure limits to AgNP.

KEYWORDS: Nanosilver; Risks; Recommended Exposure Limits; Regulation; Occupational Safety

RESUMEN

Introducción: La regulación de substancias químicas envuelve una difícil negociación entre actores sociales, y requiere de la articulación entre el análisis científico y su conversión en norma jurídica. **Objetivo:** El artículo aborda la discusión suscitada por la consulta pública sobre una propuesta de guía voluntaria de regulación de nanopartículas de plata (AgNP) en locales de trabajo en los Estados Unidos. Se examinan los comentarios realizados entre 2016 y 2018 por diversos actores sociales – representantes de empresas, organizaciones no gubernamentales (ONG) e investigadores independientes – a dos versiones sucesivas de borrador de *Recommended Exposure Limit* (REL) en ambientes de trabajo con AgNP. Se trata de una guía voluntaria de límites de exposición permisibles elaborada por el NIOSH de los Estados Unidos. Una guía de esta naturaleza combina información científica con su ajuste jurídico. **Método:** La metodología utilizada fue un análisis de contenido de los comentarios, estructurado a partir de la contextualización histórica y sociotécnica de las nanotecnologías realizada mediante revisión de literatura y análisis documental. **Resultados:** El artículo muestra la manera como los diferentes actores sociales se situaron en la controversia sobre los riesgos de la nanosilver, develando un patrón de comportamiento que es acorde con la posición que tienen en el proceso de investigación, producción y comercialización de este nuevo nanomaterial. Mientras un conjunto de actores, que responde a los intereses de los productores de AgNP, propuso restringir medidas regulatorias obligatorias y específicas para AgNP, otro grupo de actores, más heterogéneo, identificado con los intereses de trabajadores y consumidores, demandó ampliar la información científico-técnica y exigió medidas de protección a la salud más estrictas. **Conclusiones:** Entre estas posiciones divergentes, la agencia regulatoria se comportó de forma transparente y receptiva al conducir la consulta pública y modificó substancialmente los límites de exposición a las AgNP propuestos originalmente.

PALABRAS CLAVE: Nanoplata; Riesgos; *Recommended Exposure Limits*; Regulación; Seguridad Laboral

INTRODUCTION

The regulation of chemical substances involves a difficult negotiation between social actors, and requires the articulation between scientific analysis and its conversion into legal norm. When the regulation faces chemical substances with uncertain risk, as in many of the nanomaterials, the difficulties increase.

This article addresses the public discussion of a proposal for a voluntary guide to regulate exposure limits to silver nanoparticles (AgNP) in workplaces in the United States. The draft guide, known as *Recommended Exposure Limits* (REL), was prepared by *The National Institute for Occupational Safety and Health* (NIOSH) on demand from the *Centers for Disease Control and Prevention* (CDC), and went through two stages of discussion and rework during 2016-2018. The public discussion - *on line* - of both drafts by different social actors, basically academics, business organizations and non-governmental organizations (NGOs) is examined.

Examining this discussion requires placing nanotechnologies in their historical and socio-technical context. Nanotechnology is the intentional manipulation of matter to form new structures with a dimension smaller than 100 nanometers. The nanoparticles have particular physical-chemical properties (electrical, optical, magnetic, thermal, mechanical) and are different from the same material in larger size[1]. The interaction of nanoparticles with biological systems is highly unpredictable and their use may involve unknown risks[2].

From the 2000s there is an explosion of nanotechnology products in the market. Although there are no detailed records, StatNano[3] registers 8,452 products until November 2018, present in practically all economic sectors.

The development of these emerging technologies coincides with the wake-up call by the World Health Organization and the United Nations Environment Program on the global pandemic caused by toxic chemicals[4]. These organizations indicate that about five million people die annually from the exposure and handling of chemical substances and contact with consumer items that contain them[5, 6].

Silver is a metal known both for its toxicity and for its healing effects since ancient times[7]. Currently its use in the form of nanoparticles has been extended. The inventory of nanotechnology products of the *Woodrow Wilson International Center for Scholars* has identified 442 using AgNP, and reports that silver is the most commonly used nanomaterial in the product set[8, 9]. The antibacterial properties of AgNP justify its use in textiles, food packaging, paints, toys, environmental technologies, cosmetics, implants and other medical devices. They are also used in the electronics industry (semiconductor printing, radio frequency identifiers, flexible circuits, solar panels) [10, 11, 12]. The United States produced 20 tons of AgNP in 2010; and in 2014 between 450 and 542 tons were produced in word level[13].

The toxic effect of AgNP on the human organism has been detected when certain exposure levels are exceeded[14]. In the workplace, the AgNP enter the body mainly through inhalation. The final destination within the organism is uncertain. It was a consensus to consider that they were the lungs, but more recent research shows that they can move from the lungs to the liver and eventually to the spleen and kidneys, accumulating[12]. These characteristics of AgNP have raised the concern of CDC of United States, which has recommended to NIOSH the development of a voluntary guide (REL) of permissible exposure for AgNP[15].

The toxicity of silver in larger sizes, when certain exposure limits are exceeded, is already widely known, causing, for example, argyria, and there are safety regulations in this regard[16]. With the increasing use of AgNPs, a debate arises about whether, in smaller sizes, such as nanoparticles, the toxicity of silver remains the same, as some of the actors who participated in the public consultation discussed here argue, or if toxicity manifests itself differently, as other actors argue.

Regarding occupational safety, there are mandatory regulations and voluntary guides. In the United States, a chain of norms can be identified. The first are the *Occupational Exposure Limits* (OEL), which are scientific studies about the maximum acceptable limit of particles in workplaces of hazardous substances of certain material or class of materials. The OELs are established considering functional categories (exposure time period according to the degree of concentration, maximum exposure, and an emergency category when there is imminence of danger).

On the basis of OEL, standards called *Permissible Exposure Limit* (PEL) are developed, which are mandatory permissible exposure limits in workplaces. These are prepared by the *Occupational Safety and Health Administration* (OSHA). Voluntary standards can also be developed, often based on OELs. These are elaborated by NIOSH.

On December 18, 2015, the NIOSH placed the first REL draft for AgNP in public consultation, entitled *Current Intelligence Bulletin: Health Effects of Occupational Exposure to Silver Nanomaterials*[13]. This received comments from different institutions, organizations and scientists, from which a second draft was prepared[17] and made public on August 24, 2018. The latter also underwent public consultation, which ended in November 2018. This article examines the two drafts with their corresponding comments available on *website* of CDC (https://www.regulations.gov/docket?D=CDC-2016-0001). This article exclusively takes comments from the public, since the comments of peer reviewers are anonymous and not available.

The antecedent of this draft REL is the existence of a PEL based, in turn, on a 1988 OEL, which controls the exposure to silver in the workplace. The OSHA imposes a PEL of 10 μm/m^3 for soluble

and powdered silver. For AgNP, OEL or PEL do not exist. What is in elaboration and it is discussed here is a REL; so, the NIOSH, when using in the first rough draft the OEL of silver in larger size as the basis of the REL for nano size, implicitly orients to justify an equivalent regulatory treatment between silver and nanosilver. However, after the comments, the second draft of the NIOSH distinguishes nanoparticles in the air, establishing a maximum exposure of 0.9 µm/m^3 and leaving the limit of 10 µm/m^3 for particles in dust, smoke and soluble compounds. As will be seen, there are opposing positions regarding whether the OEL for silver is sufficient to elaborate a REL for nanosilver[11, 18].

The commentaries correspond to the following social actors: PISC, PBNS, NIA, CTA, SNWG, Faustman, Oberdörster and Fox, briefly described to follow.

- *PETA International Science Consortium Ltd* (PISC) is an international consortium aimed at promoting strategies to replace the use of animals in experiments[19].
- *Pennsylvania Bio Nano Systems* (PBNS) is a sole proprietorship that advises nanotechnology companies in technical-regulatory aspects[20].
- *Nanotechnology Industries Association* (NIA) is an association of companies and other sectors related to the production and commercialization of nanotechnology products. It advises national and international institutions and organisms, like the OECD and the ISO, and has as intention to promote the use nanotechnologies[21].
- *International for Center Technology Assessment* (CTA) is a oriented NGO oriented to assess the social impacts of technologies.
- *Silver Nanotechnology Working Group* (SNWG) is an enterprise organization which promotes scientific knowledge production and public information regarding the beneficial use of silver nanoparticles in industrial products and final consumption[23].
- *Elaine Faustman* is an investigator for the Institute *Risk Analysis and Risk Communication*, and the *Department of Environmental and Occupational Health Sciences*, of *University of Washington*, WA[24].
- *Guenter Oberdörster* is a recognized scientist specialized in toxicology of nanomaterials from the *Department of Environmental Medicine*, of *University of Rochester*, NY[18].
- *Mary A Fox* is assistant professor of *Johns Hopkins Bloomberg School of Public Health*, and *Co-director of the Risk Sciences and Public Policy Institute*[25].

METHOD

The investigation, of qualitative die, was elaborated in four stages, that go of the general to the individual, placing of four stages, that go from the general to the particular, placing the problem to analyze, the regulation of AgNP, within a broather historical and socio-technical perspective. The three first were based on revision of literature from consultations to the Scopus, *Web of Science* and PubMEd databases on products that use nanotechnologies. The last stage was developed through content analysis of the REL document and the interventions of the different actors in the public consultation.

The first stage consisted of drawing up the historical and socio-technical context in which nanotechnologies arise. It allowed heightening two aspects. In the first place, the fast growth of the products of nanotechnologies since the beguining of the century, most of them without regulation. Secondly, it allowed placing the entry of new chemical products such as silver nanoparticles to the market, without prior assessment of their risks, in the context of the pandemic caused by toxic chemicals used in everyday consumer goods, as stated by the Organization World Health (WHO) and UNDP (United Nations Development Program).

The second stage aimed to identify the main characteristics of the AgNP, both in technical terms, and in relation to their potential risks.

The third stage was to describe the object of study, that is, the voluntary guideline for AgNP regulation in preparation. This required explaining the main aspects and restrictions of the preparation of a voluntary guide such as the REL, which led to the identification of the contradictory nature of the process of transforming technical-scientific risk criteria into legal norms. Next, the actors (organizations or individuals) who commented on the drafts were identified.

The fourth stage then consisted of an analysis of the content of the NIOSH draft document and the comments made by the various actors in the public consultation. The content analysis was structured based on the information obtained in the previous stages. A voluntary guide such as the REL adapts scientific-technical information to a legal drafting of a legal nature. In this case the scientific-technical information responds to the danger / risk in a work environment with AgNP, while the regulations respond to the relationship between the State, private companies and workers. The first actor creates the regulation; the second is the target group of the same, and the last group is the main subject of risk and beneficiary of the regulation. From the two fields of interaction, scientific-technical and normative, three dimensions of content analysis were derived, which translate into three specific questions to challenge the positions of the different actors who participated in the discussion of the voluntary guide drafts. These are:

I. Based on the available methods, techniques and information, the standards, both mandatory (PEL) and voluntary (REL), conform to a given state of knowledge, feasible for further extension or revision, which, in turn, would lead to the updating of the rules. This raises the problem of how and when to regulate and limit (or expand) the production and market entry of new chemicals. In the case at hand, the

question is stated as follows: *From what moment in relation to the progress in research and development (R&D), the production and commercialization of AgNP are REL and/or PEL elaborated?*

II. Since the knowledge on danger/risk is always incomplete and subject to controversies, *How is solved the conflict between insufficient knowledge and administration of the risk?*

III. Being the main involved actors the State, the companies, and the workers, *Which is the opinion of the actors respect to the responsibility hierarchy on the risk (the producer, the regulatory organ, or the worker) and the degree of access to the information (confidential or public)?*

RESULTS AND DISCUSSION

When examining the actors who commented on the document, the different relative distance between them and the subject is highlighted. NIA and SNWG are industrial representatives and PBNS business advisor. This group of three actors has a conflict of interest on the subject, because its final objective is the production and incorporation of AgNP in consumer products and their commercialization. PISC is an animal rights defender organization; therefore, it has a conflict of interest regarding the methods *in vivo* of risk assessment. Oberdörster, Faustman and Fox are researchers from research centers who have declared no conflict of interest in articles published on the subject. CTA is an NGO, based in the United States, aimed at assessing and advising society on the economic, ethical, social, environmental and political impacts that result from the application of technologies, without a conflict of interest denounced, although manifestly in favor of workers and consumers. This different location of the actors regarding the subject necessarily determines their perspectives.

To follow, the arguments used by the actors are examined, organizing them arround the three questions formulated in the methodology.

I As of what moment, in relation to the I&D, production and commercialization of the AgNP, are REL and/or PEL elaborated?

Despite the enormous variety of nanoparticles, and that each one can imply different health risks for workers, there is an element in common to all of them: the matter in nanoscale shows different biological and physical-chemical properties than the same matter in larger scale. Even more: the same material behaves differently within the range of 1 to 100 nm, depending on its shape, crystallography, number of dimensions in the nanoscale and other characteristics. Its behavior also varies according to the route of introduction to the organism and the exposure time. Regarding silver, and without considering the nano size, there are several studies that indicate different toxicity depending on the way it is presented (dust, soluble etc.) [26], which already warns that size is associated to different toxic effects. So, there is a prior question to that stated: why do new chemicals enter the market without toxicity analysis, or with analyzes carried out based on methodologies developed for the matter in larger size - in the case of nanoparticles? Considering the context of the global pandemic caused by toxic chemicals, the uncertainty about the risks derived from the properties of the nano-sized matter, and the existence of sophisticated risk assessment techniques, it is necessary to understand why there is such a temporary lag between market entry of products with AgNP and its regulation[a].

In the REL discussion, NIOSH presents a first draft newsletter in 2016, then corrected in 2018. In none of them mention is made of the contradiction between the elaboration of a REL while the material (AgNP) continues to enter the market in various products without specific regulation. In this way, the NIOSH is implicitly manifested by the approach of "managing the existing situation" (*effective risk management*) without mentioning the possibility of modifying the orientation of production and consumption by controlling the market. There is also no mention of the delay in considering the regulation of products already marketed.

Of the commenters, only the CTA refers to the need for a marketing moratorium until there is no information confirming security: "*No data should mean no new production* [...] *companies should stop manufacturing unapproved nanosilver products*" (CTA, 2016, p. 1-2)[22].

Except for this actor, the NIOSH proposals and most of the comments take as a natural fact the existence of products in the market that may not be safe. In doing so, they promote a policy *ex post* regarding the market, instead of a preventive policy, generating background for other cases.

II How is solved the conflict between insufficient knowledge and administration of risk? The problem of uncertainty.

Three areas of conflict on the uncertainties in knowledge about the dangers and risks of AgNP can be distinguished here.

A first area of controversy is the distinction between the effects of silver and nanoplate. For the purpose of preparing a REL on AgNP, industrial actors and advisors affirm that nanoplate has the same toxicological behavior as silver in larger size, and that there is already a PEL issued by OSHA on silver in the United States. Remember that the first rough draft of the NIOSH considered an equivalent risk for the silver in nanoscale and in larger sizes. Already in the second draft (2018), NIOSH changes the criteria and formally declares the different intrinsic risk that results from the difference between silver in nano size and larger size [28]. The AgNP industry working group writes:

[a] It is not a place here to develop this issue, but the reader must consider both the economic and political power of the chemical industry and the neoliberal phase of capitalism that has been replacing the control of the State over private enterprise by business self-responsibility, a transition from regulation to governance, from *hard to soft law*[27].

> *SNWG is extending support of the Agency's recommendation that effective risk management control practices be implemented so that worker exposures to all forms of silver, including silver nanomaterials, do not exceed the NIOSH REL of 10 µg/m3 (8-hour time-weighted average) for silver metal dust, fume, and soluble compounds measured as a total airborne mass concentration. […] workers will be more than adequately protected from any potential harmful exposures to all forms of silver, including nanosilver. […] In light of some of the uncertainties concerning nanosilver, the SNWG believes that the toxicity of nanosilver is not significantly different from bulk or dissolved Ag (colloidal silver) (p. 4-6)23.*

It can be noted that this industry working group begins by supporting the NIOSH recommendation, but the support is in relation to the first draft of the document where the limit of 10 µg / m3 was suggested, which is the limit that OSHA uses for silver in larger size In the following paragraph, the comment is explicit in identifying silver as equal to nanoplate; and, in the last one, it emphasizes that the potential uncertainties are not different between silver and those that can be found in the nanoplate. In summary, SNWG argues that there is no need for a specific norm for nanoplate.

From the same opinion is the NIA,

> […] *the Association insists that silver nanomaterials do not present a different toxicological profile to other forms of silver, including colloidal silver. The antimicrobial action of silver, and therefore its toxicological profile, originates in silver ions (Ag+) and may not be attributed to the nanoparticles themselves* (p.1)[21].

For its part, PBNS, an industry consultant, considers argyria as the final point in the organism of the potential health risks of silver, and argues that the maximum permissible contemplate all types of particles, so there would be no difference between nano and non-nano, and, since there is an OSHA PEL for the larger size, the NIOSH should not insist on the specificity of the nano size. Contradictorily, PBNS recognizes that nanomaterials can present "unexpected properties" but, if NIOSH recognized that the end point of silver is argyria, there would be, according to PBNS, novel effect, and using the nano concept would be incorrect: "*In selecting argyria as the valid endpoint, there is then no novel use, nor first time exposure nor unexpected property. Yet, using the term nanomaterial implies that there should be a particle size dependence*". The entire PBNS comment goes in the direction of invalidating the specificity of nano and bringing the regulation to OSHA's already approved criteria based on larger size [20].

Note that the three industrial actors do not rebut the scientific articles published over the past two decades where the different behavior of AgNP with respect to silver in larger size is noted (see for example the systematic review of Akter et al. [14]), thereby ignoring that available scientific information that does not fit your interests. They also do not question the uncertainty, considered a crucial aspect in the first draft of the NIOSH, and on which it demands great attention when asking if the particles in the air imply a different risk to the particles in solid or liquid, due to the different route of introduction to the organism

The animal defense NGO (PISC), for its part, only emphasizes the need to substitute analysis methods *in vivo* with *in vitro* and *in silico*, indirectly supports the spirit of the business position, in the sense of identity between nano size and larger size with respect to risks.

The other sectors, the NGO and independent researchers, recognize that nanoplate implies a different risk than silver in larger size. Independent researchers, for example, explicitly call attention to the particular risks associated with nano size. Faustman argues that: "*While an OEL for micro-sized silver dust and silver fumes of 10µg/m3 is in place, we believe that the physicochemical properties of AgNPs allow for additional health risks not observed from exposure to micro-sized particles*" (p. 1)[24].

Oberdörster also emphasizes the specificity of AgNP by emphasizing the different risk of inhaled nanoparticles and the liver as the final point of destination in the organism [18]. CTA, meanwhile, shows that there is a much wider variety of AgNP on the market than what the NIOSH draft points out, and that each of these modalities may have different risks, so a specific REL is necessary for each case [22]. Fox, on the other hand, points out the need to specify that it is pure AgNP, and perhaps to establish different RELs according to whether they are nanoparticles soluble or not[25].

A second area of controversy regarding uncertainties has to do with the degree of correspondence between the scientific references provided by the NIOSH (bibliography) and its normative conclusions; that is, between scientific-technical information and its legal adaptation.

The NIA claims to reduce the scope of the regulation to a form of nanoparticles, spherical not covered; and this because the support bibliography of the NIOSH draft only includes this modality.

> […] *document scope should be revised to reflect the data presented in the Draft Bulletin. While NIOSH mentions the ISO definition of a nanomaterial, which includes particles, plates and wires, studies mentioned in the Draft Bulletin mostly address spherical silver nanoparticles. In addition, the studies in the document mostly focus on uncoated silver nanoparticles. As a result, the Draft Bulletin should explicitly focus on health effects of uncoated spherical silver nanoparticles* (p. 1)[21].

There is a huge variety of nanoparticles, and the regulations cannot deal one by one, but the industry takes refuge in this limitation of the literature to avoid or reduce the scope of the regulations. The same opinion on restricting the scope of the REL to strictly comply with bibliographic references, says the industrial consultant PNBS,

> *Narrow the current REL (10 µg/m3) to substantively spherical primary particles, their aggregates and agglomerates, and caution that the REL does not extend to shapes with high aspect ratios* […]
>
> *Narrow the current REL to uncoated silver-metal-particles* (p. 1)[20].

In the opposite direction, proposing to expand the scope of the REL, the CTA claims that the intended maximum of 100 nanometers established by the REL should be extended to 1,000 nm [22] and, to that end, introduces the argument that other agencies Government, as is the case of the FDA, have extended the analysis [29] to 1000 nm when it merits:

> *WHAT SIZE IS NANO? This review simply uses the narrow US government definition for "nano," i.e. 1-100nm. The NIOSH definition would be enhanced if it used the expanded standard used by the FDA, i.e. companies are asked to report as "nano" any change in size below 1000nm that changes the properties of the chemical* (p. 2)[22].

The industry remains at 100 nm, and emphasizes that analyzes of silver in larger size are sufficient. SNW, for example, supports the NIOSH based on the exposure categories of the existing PEL of OSHA. In doing so, it agrees with the first draft of the NIOSH in equivalent toxicity assessments between nano size and larger size[23]

So while independent scientists and the environmental NGO are pronounced to expand the bibliographic references and question the ones used [25], companies prefer to keep the existing bibliographic references and seek to restrict their scope.

A third area of controversy over uncertainties is in relation to the validity of scientific methods and their restrictions. Currently, most risk analyzes include various techniques (*in vitro, in vivo, in silico*). The analyzes *in silico* have expanded due to the speed, economy and possibility of standardizing the procedures; and also for ethical reasons to avoid tests on animals. PISC, for example, suggests that NIOSH replace analyzes *in vivo* with *in vitro* and *in silico*[19] and justifies this demand not only for ethical reasons, but also methodological, in relation to the validity of extrapolating information from animals to humans:

> *The dissolution of silver nanoparticles (AgNPs) in different physiological environments can be addressed using alternative methods (including in vitro and ex vivo), which are considered a vital tool in understanding AgNP behavior in vivo.*
>
> […] *Of note here is that there are many uncertainties in extrapolating toxicity outcomes from animals to humans, including variations in responses to chemicals in different species and strains of animals, gender differences within species of animals, as well as different toxic thresholds between species including humans* (p. 1-3)[19].

Some independent researchers have criticized NIOSH's preference for the application of the PBPK method to AgNP, rather than relying on research with methods *in vivo*. While the PBPK method is *in silico*, the one used as the basis for independent studies extrapolates results of an analysis *in vivo*[11]that, among other things, it suggests as a toxicological endpoint the liver instead of, or in addition to, the lungs, as the base article of the NIOSH argument suggests [24]. Also, the methods *in silico* have been criticized by many epidemiologists, basically because they use a number of variables that, however extensive, is always less than the amount that acts in the case of a living organism [30]. In addition, the selection of the variables to be considered may be subject to manipulation.[31, 32]. The Oberdörster researcher suggests that PBPK should not be used due to lack of reliability: "*REL are not well justified, because of either questionable PBPK modeling using disputed data or of rather simplistic unscientific extrapolation*" (p. 1)[18].

In the opposite position, SNWG applauds the use of the PBKP on which the NIOSH relied:

> *In light of these standards based on argyria, the endpoint of concern, the SNWG applauds the use of the Bachler et al., 2013 PBPK model for silver nanoparticles to evaluate the potential adverse effects of working lifetime exposure to silver nanoparticles at the current NIOSH REL for silver (10 ug/m3, 8-hr TWA concentration of soluble or insoluble silver, total airborne particle mass sampling). This PBPK model was developed based on data in rats, extrapolated to humans, and validated with limited bioassay data in humans* (p. 5)[23].

As the examples show, many of the arguments are not based on scientific information but on how participants use the inconsistencies of the draft to limit, extend or reject conclusions.

III What is the opinion of the actors regarding the hierarchy of responsibility for risk (producer, regulatory body, worker) and the degree of access to information (confidentiality or disclosure)?

The risk analysis considers the potential danger and the degree of exposure of the worker[33, 34]. Exposure can be reduced by an uncontaminated environment or by the use of protective equipment. The legislation aims to avoid danger, maintaining a pollution-free environment in the first instance, and, when this is not possible, to use personal protective equipment[35]. The REL draft reproduces this hierarchy of controls in its recommendations. Although this hierarchy of protection procedures is a widely established legal fact, the emphasis on one or another alternative is significant in the position of the different actors. Thus, for example, CTA is explicit in emphasizing hazard control: "*workplace controls, not respirators are needed*" [22] and extensively:

> *NIOSH, however, needs to stress even more strongly that in the absence of sufficient data on the inhaled toxicity of nanosilver products, that it is EXTREMELY important that workplaces implement a hierarchy of controls that keep*

> *workers from breathing any nanosilver. NIOSH needs to strengthen its risk management control practices to note that respirators will not be adequate to protect workers and that avoiding exposures is the best way to protect workers* (p. 2)[22].

The demand is valid because the REL is a voluntary guide, and, as long as there is no PEL from which the State can impose a firmer measure, the different approaches on how to avoid hazards lead to different responsibilities. Maintaining the work environment without risk is the responsibility of the employer, while the use of personal protective equipment places the responsibility on the worker. This criticism was assumed by NIOSH in the second draft:

> *The revised document recommends using the hierarchy of controls, encouraging the elimination or substitution of silver nanomaterials before employment of engineering controls, with PPE, including respirators, being the final and least preferable control* (p. 5)[36].

Responsibility for risk is closely linked to the availability of information. If workers do not have information about the materials they handle, their hazards, and the risks to which they are subjected, they can hardly adopt a preventive attitude towards illnesses and accidents at work. The publicity or confidentiality of the information that the companies handle is a point of contention. The CTA asks NIOSH to use information from other government agencies such as the EPA and the FDA about the effects of AgNP; information that these agencies have because they have authorized the entry into the market of products with AgNP [22]. The answer given reveals that there are confidentiality clauses that frequently prevent it: "*NIOSH collaborates with other Federal agencies* when possible *on chemical assessments to avoid a duplication of effort*" (p. 6, highlight own) [36].

SNWG insists on the confidentiality of potential requests for information by the NIOSH:

> *In regard to the research needs discussed in Section 8 of the NIOSH document, one of the functions of the Silver Nanotechnology Working Group is to identify, gather and consolidate industry data in an anonymous manner to protect CBI (Confidential Business Information). If such a mechanism is needed by NIOSH to bring forth needed data as listed on p. 120-121 of the External Review Draft [3] in a manner consistent with CBI, the SNWG would be glad to serve in such a capacity* (p. 9)[23].

The analytical answer to the third question leads to the same grouping as the answers to the previous two. The three industrial actors agree to reduce the available scientific information, or raise doubts about its relevance, to ensure the confidentiality of data on the materials used in production. In the opposite position are the independent researchers, who insist on expanding the range of literature and methods related to the subject, and on sustaining the differences between silver and nanoplate, and the environmental NGO, which demands to consolidate the responsibility in the employer instead of the worker and Disseminate business technical information.

CONCLUSIONS

The analysis of the voluntary guide to exposure to risk of AgNP in work environments, and the comments made by various actors allow us to draw some conclusions. The first and most general is that, with exceptions - only one commentator - both government institutions and other actors consider the issue under discussion as part of a larger context that cannot be modified, so that the proposals are reduced to administering the existing state of affairs. In this case, the existing state of affairs is the production and placing on the market of chemicals in the form of AgNP and the merchandise that incorporates them, notwithstanding the existence of scientific evidence of risk for the workers operating in its production. So the regulation faces an economic dynamic that exceeds it.

The second conclusion is that the commentators, despite responding to the draft NIOSH regulation guide individually, can be grouped analytically into two large groups, according to the coincidence of opinions. The first responds to the interests of AgNP producers and their opinions are in the sense of restricting as much as possible the advent of mandatory regulatory measures. This is explicit in the arguments to treat AgNP as well as silver, by reducing the forms of AgNP and assuming that the health effects of workers are the same in the case of silver and nanoplate; also, by raising doubts about potential risks, by giving priority to confidentiality over the dissemination of information on production processes, and by deriving responsibility for risk control to workers. The second group, with less cohesion, demands to broaden the spectrum of scientific-technical information, and demands limits on the production of articles with AgNP in order to protect workers and, indirectly, final consumers. The first group, more compact and convergent in their opinions, is clearly identified with positions of the business class. The second, more dispersed, is identified with the interests of workers and consumers, as well as independent intellectuals who demand further investigation.

The third conclusion of the analysis is the role, largely transparent and responsive, of the government agency that conducts the process, in this case the NIOSH. The transparency lies in the opening for public comments of the drafts, as well as the flexibility demonstrated in the changes made in the document from the comments. They included modifying the originally proposed exposure limit of 10.0 µg/m ^{3}for all particulate forms, to 0.9 µg/m3 in the specific case of AgNP in the air. It is also relevant to highlight that the second draft includes a specific mention of the hierarchy of risk responsibility, placing the producer first and secondarily the worker, specifying that the priority is to avoid the danger in the work environment, and only then individual protection must play its role.

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.