Case Report

Occupational Handling of Nickel Nanoparticles: A Case Report

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A 26-year-old female chemist formulated polymers and coatings usually using silver ink particles. When she later began working with nickel nanoparticle powder weighed out and handled on a lab bench with no protective measures, she developed throat irritation, nasal congestion, "post nasal drip," facial flushing, and new skin reactions to her earrings and belt buckle which were temporally related to working with the nanoparticles. Subsequently she was found to have a positive reaction to nickel on the T.R.U.E. patch test, and a normal range FEV1 that increased by 16% post bronchodilator. It was difficult returning her to work even in other parts of the building due to recurrence of symptoms. This incident triggered the company to make plans for better control measures for working with nickel nanoparticles. In conclusion, a worker developed nickel sensitization when working with nanoparticle nickel powder in a setting without any special respiratory protection or control measures. Am. J. Ind. Med. 57:1073–1076, 2014. *© 2014 Wiley Periodicals, Inc.*

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INTRODUCTION

Nanotechnology applications continue to be used in an increasingly diverse manner in the workplace resulting in engineered nanoparticles with unique properties. The science of nanotoxicology is also developing as the unique physicochemical properties of nanoscale materials are discovered [Nel et al., 2006; Castranova, 2011]. Nanosized particles (sometimes referred to as "ultrafine particles") may be found mixed in traditional bulk materials as well as in ambient particulate matter. However, materials engineered with specific size dependent properties are growing in quantity for industrial applications [NIOSH, 2013]. Engineered nanoparticles are created using innovative methods and technologies to be 1–100 nm in size, and at these dimensions, may exhibit new physicochemical properties. It is difficult to assess the number of workers handling nanoparticles given the complex lifecycle of nanomaterials, however the National Science Foundation has estimated that by 2020 nanotechnology will employ 6 million workers with 2 million located in the United States [IEEE, 2011; NIOSH, 2013]. The implementation of nanotechnology into the workplace poses a challenge for occupational risk assessment because of difficulty isolating exposures to specific types of nanoparticles and determining the presence or absence of nanoparticle toxicity.

The regulatory challenge pertaining to substances, such as nanoscale nickel, is whether to implement protective

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controls based upon the properties of a traditional bulk sample or upon what might be limited toxicity data related to the engineered nanoscale form of the substance [vanTassel and Goldman, 2011; Hamburg, 2012]. Occupational medicine is now challenged with revisiting these traditional (bulk) materials that may have new properties on the nanoscale which alter their toxicity and therefore the approach to risk assessment and control of exposures. From our review of the literature, there is a paucity of human toxicity data on a wide array of nanomaterials currently being used in industry.

Prior reports of nanoparticle induced effects in humans have had limitations that have made it difficult to draw definitive conclusions of causation about specific particles with well defined properties. Nevertheless, some case reports raise concerns. For example Song et al. [2009] published a report of seven previously healthy non-smoking young female workers in China who developed shortness of breath and pleural effusions after months of working with polyacrylate nanoparticles. Examination of lung tissue samples showed non-specific pulmonary inflammation, pulmonary fibrosis, foreign body granulomas of the pleura and nanoparticles in cells and chest fluid. Other infectious and immunological studies were negative. This case series was initially limited by the lack of workplace environmental monitoring data and information on the actual composition of the polyacrylate mixture. Song and Tang [2011] subsequently obtained information about the product, including analysis of the powder component in the raw materials. They found that the nanoparticles (particularly silica nanoparticles) found in the patients' pulmonary tissues and pleural effusions, were the same as the raw materials used by these workers.

Nickel is a silvery hard metal with properties that enable it to combine with other substances to form compounds that have many industrial applications [ATSDR, 2005; Zhao et al., 2009]. It exists as various compounds including nickel salts, nickel carbonyl, nickel oxide, nickel sulfide, nickel hydroxide, as well as newer nanoscale formulations. The most common and recognized reactions to traditional nickel are sensitizer-mediated reactions including allergic dermatitis, allergic rhinitis, and occupational asthma. Persons breathing nickel dust have also developed respiratory irritation, bronchitis and increased risks of lung and sinus cancer related to certain nickel compounds [ATSDR, 2005; Zhao et al., 2009].

Nanosized metallic nickel has properties which include a high surface energy, high magnetism, low melting point, high surface area and low burning point which makes it ideal for a number of industrial processes [Zhao et al., 2009]. There is some data to indicate that nanosized metallic nickel (20 nm) is more toxic than standard sized nickel (5 μm) in a rat model of lung toxicity [Zhang et al., 2003]. It has also been shown that among nanosized nickel, cobalt and titanium dioxide instilled into the lungs of rats that nano nickel has the greatest toxicity which has been attributed to differences in free radical generation [Zhang et al., 1998]. There is also one human post mortem case report of an individual who had a high level nickel exposure during an arc welding process and was found to have nanoscale nickel particles (<25 nm) in the lungs on autopsy [Phillips et al., 2010].

We present a case of a woman handling metallic nanoscale nickel powder in a manner more consistent with how bulk nickel powder might be handled who then develops symptoms. This case highlights issues related to lack of appreciation of differences in handling nanoparticle forms of a substance, the difficulty in assessing workers who present with suspected health effects from nanomaterials, and the challenges related to job accommodations in the setting of potential sensitization.

CASE REPORT

Written informed consent was obtained from the patient to publish this case report.

The 26-year-old non-smoking female patient worked as a formulation chemist for 3 years in an industry involved with making metallic inks for various applications. She had no symptoms doing work that involved formulating polymers and making coatings, nor when working in the same laboratory with metal plating baths. In 2010, she then started on a new project that involved making formulations involving micron-sized silver particles for inks. The patient then described the introduction of a new work task as measuring out 1–2 g quantities of dry nano nickel powder on the lab bench which would then later be added to a jar with water or ethylene glycol. She would then pipette this liquid material into open containers which were then covered. Small glass balls were then added to the mixed material for "ball milling" (in a closed container) to create even smaller nano-sized particles. She would then pour the mixture into an open funnel into a (closed) vacuum filtration set up. She then described using syringes to inject the material through small holes into other small containers. She also described cleaning the filtration flask, funnel, and ball mill container by triple rinsing with water into an open container to avoid any metals going down a sink drain. She wore latex gloves at that time, and no respiratory protection. Weighing of nickel nanoscale powder was done on the open lab bench and not in a glove box or fume hood. This was the first time she had directly handled any type of nickel powder.

Within 1 week of the transition to using the nickel nanoparticles the patient noted the onset of throat congestion with "post nasal drip" and flushing of the face daily. She denied any wheezing. Additionally she experienced skin reactions to earrings and her belt buckle that she was previously able to wear without any reactions. These items were not pure gold and were made from metal amalgams. She was initially seen by her primary care physician, who treated her for a sinus infection with amoxicillin with no improvement. She also had a chest x-ray which was normal. The patient was seen by an allergist who did T.R.U.E. patch testing and noted positive reactions to nickel as well as to molds, cat dander, ragweed and fragrance mix paraban. Spirometry showed normal range for forced expiratory volume in one second (FEV1) but there was 16% improvement after administration of bronchodilators. A CT was also performed of the facial bones and sinuses which demonstrated a deviated nasal septum and some findings which could suggest some mucosal thickening of the right maxillary sinus but was otherwise unremarkable.

Due to concerns about work-related symptoms, she was moved to a different floor. Here, she personally did not weigh out the nickel powder directly, but others did and she continued to have symptoms. She requested an occupational and environmental medicine consultation since she was not sure what she should do next. In general, when she was not in the building or near her work station her symptoms were markedly reduced.

She was seen in the occupational medicine clinic about 3 months after she stopped weighing out the powder directly, but she was still having indirect exposure in the workplace. On physical examination her vital signs were normal, she had no visible skin rashes. Eyes were clear and not injected. The nose showed some turbinate swelling and she also had a deviated septum and narrowing of the left nasal passage. There was a trace of post-nasal discharge. Her lungs were clear with no wheezing or rales. The rest of the examination was unremarkable. She provided a Material Safety Data Sheet (MSDS) for the substance she was handling: The MSDS from the supplier listed the nanomaterial as Nickel powder of 99.9+% purity. The aerodynamic particle size was 20 nm with a surface area of 40–60 m^2/g. The particle morphology was spherical. It was not clear whether the particles existed in aggregates or agglomerates.

The occupational medicine consultant also spoke with the company physician about the need for further assessment and change in how the nanoparticles were being handled, and he said that the company was planning to institute changes. Airborne nanoparticle sampling was not performed and therefore was not available to report. Eventually she had to move to another lab that had no metal chemistry work and her symptoms were much better.

DISCUSSION

We present an occupational scenario involving the handling of nanoscale nickel particles and the development of clinical symptoms in the worker. One key issue highlighted is whether the worker was handling the nanoscale nickel powder in a safe and prudent manner and whether acute and future health effects can be mitigated. Over the past decade concerns have been raised about how to protect workers who handle nanoparticles, particularly when there are still gaps in toxicity data as well as scientific data guiding the choice of protective clothing and types of respirators [NIOSH, 2013]. Occupational health groups have presented guidelines on appropriate methods to work with nanoparticles [NIOSH, 2012] and there has been some early work suggesting the need to implement surveillance as nanotechnology based materials become more pervasive in the workplace [Dahm et al., 2011; Sng et al., 2011; Lee et al., 2012].

Despite significant concern over the use of nanomaterials in consumer products, it is workers handling and producing raw types of nanomaterials who are thought to have the greatest potential for exposure at present [Dahm et al., 2011]. The worker in this case was not working with nanoscale nickel under a hood, or in a glove box, nor was she using personal protective equipment (PPE). Research is still being conducted on the efficacy of PPE for various types of nanomaterials [NIOSH, 2013]. For example, studies have suggested that an N95 mask might be sufficient to trap certain types of nanoparticulate [Shaffer and Rengasamy, 2009; Groso et al., 2010]. Indeed, engineering controls and personal protection were identified as one of the 10 critical topic areas that NIOSH has identified for research to address data gaps by stating the needs of: “Evaluating the effectiveness of engineering controls in reducing occupational exposures to nanoaerosols and developing new controls where needed; and Evaluating and improving current personal protective equipment” [CDC, 2013].

This case demonstrates a strong temporal relationship between the introduction of nano nickel powder to the patient’s work environment and the development of her symptoms. Of note the patient had findings clinically consistent with allergic rhinitis and a reaction to metal alloy jewellery which was later supported by a positive reaction to Nickel on the T.R.U.E. patch test. The nickel used in this patch test is traditional sized $NiSO_4$ and has been the standard in patch testing for many years. We do not know if her handling of the nanoparticle nickel increased her potential for sensitization, or her subsequent reaction to re-exposure if she was previously sensitized to nickel. It is also not known if she would have had a greater (or lesser) reaction to the metal if the patch test was conducted with a nanoparticle format. However, she did not report prior skin reactions to metal alloy jewellery prior to working with the nickel nanopowder at work, even though she had previously been working on the same floor in which bulk nickel powder was used. It is possible that that she may have developed the same symptoms if she had been working directly with bulk preparation of nickel powder. However, the nanoscale nickel has different properties than traditional larger sized particles [Zhang et al., 2003; Zhao et al., 2009] that might enhance the propensity to become airborne as well as the immunogenicity and/or irritant effects. While the total mass of the particles handled seems small the novel properties of nanoscale particles might lead to reactions at much lower mass based doses. One of the unique properties of some nanoscale particles is the high surface area [Wittmaack, 2007]. Whether or not nanoscale nickel particles have greater allergenicity than traditional sized nickel is not known. We presume that whatever amount of nickel this patient was exposed to that the absolute particle number per gram and total surface area of nickel nanoparticles would exceed that of traditional bulk nickel particles. The mechanisms by which these nanoscale properties influence toxicity are still being investigated.

The patient also had symptoms of throat irritation and post nasal drip, and a suggestion of bronchial hyperresponsiveness on her spirometry testing. It is difficult to say how much of a contribution to her throat clearing, coughing and bronchial hyperresponsiveness stemmed from her previous diagnosis of gastroesophageal reflux and/or to the irritant and/or allergic effects of the nano nickel powder exposures. The temporal relationship between the development of her skin symptoms, throat clearing, and nasal congestion with the new work place exposures is suggestive of a work-related relationship. Furthermore nickel exposure has been reported as a cause for occupational asthma [Zhao et al., 2009]. There is some evidence, in general, linking occupational contact dermatitis and occupational asthma [Arrandale et al., 2012]. It is possible that nanoparticles might increase the risk for allergic and irritant symptoms since there is a significant deposition fraction in the upper and lower airways relative to larger particles [Oberdorster et al., 2005].

From her description, it did not appear that appropriate engineering controls or personal protection were used in this lab area when workers were handling the nanomaterials. This is of particular concern given that nanoparticles may have a greater propensity to become airborne and may have more adverse health effects than simply handling the bulk product. Although specific aspects of engineering controls and toxicity continue to be researched, NIOSH has published a preliminary general guide to safe practices when working with nanoparticles in lab environments [NIOSH, 2012].

In summary, we present a case of a worker who developed sensitization while handling nickel nanoparticle powder with no special precautions. The case highlights the growing need to appreciate the differences between bulk and engineered nanoparticle materials, and to institute the proper exposure controls. This case also illustrates the need for more research to better define the nanotoxicological mechanisms by which nanoparticles can cause adverse health effects and the best ways to protect workers.

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