

discussed in the study [1], the major reason for illness may be due to the powder in the coating, which contains nanoparticles.

As for the rashes the patients experienced on their faces, these may show the physical damage caused by polyacrylate nanoparticles to skin. It is not appropriate to link them to pre-existing atopy or immunological impairment. The rashes on the face of patients, characterised by skin itching, pachylosis and breakage, varied greatly from the rashes experienced in patients with immune-related disorders, such as systemic lupus erythematosus, which were characterised by no itching but smooth and intact skin. Moreover, detailed clinical examinations and follow-up excluded the immune-related disorders or pre-existing atopy.

Y. Song\*, X. Li<sup>#</sup> and X. Du\*

Depts of \*Occupational Medicine and Clinical Toxicology, and <sup>#</sup>Pathology, Beijing Chaoyang Hospital, Capital University of Medical Sciences, Beijing, China.

**Correspondence:** Y. Song, Dept of Occupational Medicine and Clinical Toxicology, Beijing Chaoyang Hospital, Capital University of Medical Sciences, No. 8 Baijiazhuang Road, Chaoyang District, Beijing, 100020, China. E-mail: songrain123@hotmail.com

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To the Editors:

We are writing to express concern about the recent paper by SONG *et al.* [1], which was published in a recent issue of the *European Respiratory Journal*. We read the paper with great interest, as it would constitute the first report of human nanoparticle-related disease and death. The title attracted our

attention, as well as that of the international media: “Exposure to nanoparticles is related to pleural effusion, pulmonary fibrosis and granuloma.” Note the use of the word “is.” The title appears to state a fact. We object.

We write as individuals committed to the science of nanotoxicology. It is known that nanomaterials have unusual physical and chemical properties [2] and that these unusual characteristics, combined with the ever expanding use of nanomaterials, deserve careful investigation [3, 4]. It is not the time for complacency. Serious methodical investigations of potential toxicity from nanoparticles and nanofibers are clearly warranted. We believe wholeheartedly in the cautionary principle and in providing the best possible data to protect workers and consumers.

This paper, however, draws premature conclusions and does not add objective evidence permitting us to evaluate the possibility of adverse health effects of nanoparticles in humans [1]. We do not agree with the implied conclusion that it was nanoparticles which caused the pulmonary problems and the deaths of two workers. The study by SONG *et al.* [1] clearly describes a primitive workplace characterised by a total lack of even the most rudimentary precautions. In the face of dangerous activities, including air spraying and curing polymers with heat, exposure controls were absent. SONG *et al.* [1] state, “It is estimated that the air flow or turn over rates of indoor air would be very slow, or quiescent due to the lack of windows and the closed door”.

Moreover, adequate exposure assessment is utterly lacking. We are especially concerned about a variety of hazards in this workplace. Yes, there is some evidence for the existence of nanoparticles, but the list of chemicals and dusts to which these workers were exposed is extensive. Many chemicals were used in this space where ventilation was inadequate or even absent. During spraying and related procedures, indoor concentrations of a variety of toxic materials were probably very high. All seven females who worked there for 5–13 months had a variety of symptoms; there is convincing evidence of that. The title of this article should have read, “Poor working conditions cause pleural effusion, pulmonary fibrosis and granuloma”. It would have been appropriate if the presence of nanoparticles had been mentioned, and even speculations made that they may have contributed to the resulting pathology. But the current message that nanoparticle exposure is primarily responsible is not warranted. SONG *et al.* [1] fail to provide any information about other respirable toxic agents which were inhaled both as solid aerosols and in the gas phase. Hence, the conclusion that nanoparticles are causally related to these pulmonary diseases is much too premature and scientifically not acceptable.

The outcome is certainly tragic and deserves the attention of the public and the international community of chest physicians, pneumologists and lung biologists. But this study primarily emphasises the importance of implementing appropriate industrial hygiene practices. It fails to provide evidence about unusual risks posed by nanoparticles. We simply do not know to what extent exposures to nanoparticles in this workplace contributed to the evident pulmonary pathology and to the documented unfortunate consequences.

We encourage careful studies of nanotoxicology, both in the laboratory and in the workplace. But we ask that excellent

journals, such as the *European Respiratory Journal*, critically review papers like this. Eliciting concerns through provocative but unfounded titles and conclusions which are not justified by the data does not enhance the reputation of the *European Respiratory Journal*, its reviewers or its editors.

J.D. Brain\*, W. Kreyling<sup>#</sup> and P. Gehr<sup>†</sup>

\*Dept of Environmental Health, Harvard School of Public Health, Boston, MA, USA. <sup>#</sup>Institute of Lung Biology and Disease, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany. <sup>†</sup>Institute of Anatomy, University of Bern, Bern, Switzerland.

**Correspondence:** J.D. Brain, Dept of Environmental Health, Harvard School of Public Health, 665 Huntington Avenue, Building 1, Room 1308, Boston, MA 02115, USA. E-mail: brain@hsph.harvard.edu

**Statement of Interest:** A statement of interest for P. Gehr can be found at [www.erj.ersjournals.com/misc/statements.dtl](http://www.erj.ersjournals.com/misc/statements.dtl)

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### From the Editors:

The editorial decision to publish the second revision of the study by SONG *et al.* [1] on nanoparticle toxicity was extremely difficult and the points of J.D. Brain and co-workers are well made. There is no formal proof that nanoparticle exposure at this workplace caused pulmonary disease in and the death of several workers in a primitive workplace without any occupational safety measures. However, SONG *et al.* [1] excluded a number of fateful differential diagnoses and came to the conclusion that nanoparticles were the most likely cause.

Conclusions by analogy were made from what is known about quartz, asbestos and air pollution to nanoparticle toxicity and the available peer-reviewed literature suggests that nanoparticles have unusual toxicological properties. They induce the release of pro-inflammatory and chemotactic mediators by

type II alveolar epithelial cells [2], stimulate mesenchymal cell growth, and cause fibrogenesis and granuloma formation, all of which have been reviewed elsewhere [3]; and all these pathomechanisms have most probably been taking place in the reported cases. Many national authorities remind the absence of systematic toxicological studies and, therefore, publish warnings regarding the use of nanoparticles within industry. Moreover, bioaccumulation in the food chain is currently under debate [4] and regulations to reduce or remove nanoparticles from waste streams are missing. The National Institute for Occupational Safety and Health in the USA is investigating the toxicity and health risks associated with occupational nanoparticle exposure and some research is also being funded by the European Commission and some European governments. However, under the assumption that most nanoparticles have to be estimated individually, and in view of the evidence of their effects beyond the organ of entry [5], and possible carcinogenesis [6], balanced and comprehensive toxicological statements will not be available in the near future. In this context the *European Respiratory Journal* decided to publish the work of SONG *et al.* [1] to stimulate awareness in both established and emerging industrialised nations, to serve our readers in the diagnostic work-up of granulomatous disorders, and to demonstrate to the authorities where action is needed.

The title and the discussion might overstress the finding but we felt that the circumstances at the workplace were well enough described to allow the reader to draw their own conclusion on the likelihood of nanoparticle toxicity.

## The European Respiratory Journal Editors

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