Health impact of nanomaterials?

To the editor:

The Perspective in the October issue on "the potential environmental impact of engineered nanomaterials" by Vicki Colvin (*Nat. Biotechnol.* **21**, 1166–1170, 2003) is a welcome contribution to the recent debate on the issue of nanoparticle exposure and possible health effects. The main strength of the Perspective is that the author, as a 'nanotechnology researcher' rather than a toxicologist or health scientist, openly addresses the potential impact of nanomaterials on the health of workers or consumers (and not so much on the environment). However, in our opinion, the article and its conclusion suffer from a rather pro-technology bias. Though we agree with Colvin that the paucity of sound data renders it premature to formulate any definitive risk assessment about engineered nanomaterials, several other important issues require close attention.

Engineered nanomaterials must not be considered as a uniform group of substances. Differences in size, shape, surface area, chemical composition and biopersistence require that the possible environmental and health impact be assessed for each type of nanomaterial in its own right. This statement may sound simplistic, but many years of toxicological research and experience have shown that closely similar compounds may induce substantially different health effects. This is a well-known feature of, for example, metallic agents, the speciation of which may strongly influence biological effects[1,2]. Agents that seemed to be innocuous when administered by the oral or dermal routes have proven surprisingly toxic to the lungs[3]. Numerous studies have shown that biological interactions between solid-state materials and cellular targets depend on the size, surface area and surface activity of the particles[4], and this is particularly true for nanosized materials. Nanoparticles, even when they aggregate, are likely to exert biological effects different from those caused by micron-sized particles[5].

The potential health risks of inhaled nanofibers cannot be dissociated from the well-known adverse effects of asbestos fibers[4]. The concern is particularly applicable to fibers with high biopersistence. In this respect, we feel that Colvin is too optimistic in her interpretation of the two recent articles[6,7] that have reported on the pulmonary effects of a single intratracheal instillation of single-walled carbon nanotubes in experimental animals. Although one of the articles cited expressed serious concern about the finding of pulmonary inflammation and granulomas in mice[6], Colvin espouses the hasty conclusions of the other article, which plays down similar observations in rats[7]. Admittedly, some aspects of these animal experiments, such as the mode of administration and the high doses given, preclude reaching definitive conclusions. However, the fact that "granulomas are not commonly observed in pulmonary toxicology" is not a serious reason for dismissing this type of response (especially when it appears to be so pronounced), and stating that "their medical significance has not been established" completely ignores the existence of a large array of granulomatous lung disorders[8].

It has been recently shown not only that inhaled ultrafine particles exert respiratory effects, but that they may also translocate, at least to some extent, from the lung into the systemic circulation[9,10] and this may result in cardiovascular and other extrapulmonary effects[11]. These observations are probably of general relevance for assessing the health risk of nanomaterials.

Colvin also sounds reassuring about the poor water solubility of nanomaterials. However, low aqueous solubility (generally expressed as a high octanol-water partition coefficient) generally favors the persistence of a chemical in the environment and its absorption by biological systems, where it can persist for long periods of time and even bioaccumulate, as has been shown for DDT (di(*para*-chlorophenyl)-trichloroethane) or dioxins. Whether this is relevant for nanomaterials is not established, but our point is that the poor water solubility of nanomaterials is not necessarily a reason for complacency.

In conclusion, we consider that producers of nanomaterials have a duty to provide relevant toxicity test results for any new material, according to prevailing international guidelines on risk assessment. Even some 'old' chemical agents may need to be reassessed if their physical state is substantially different from that which existed when they were assessed initially. Thus, if pulmonary exposure of the nanomaterial is expected, but the bulk material was never tested via inhalation, then appropriate tests are needed to evaluate its toxicity. Obviously, the actual health risk will depend not only on the intrinsic hazard of the agent but also on the likely exposure. However, one should not conclude too rapidly that exposure will be negligible, certainly not if the material proves to be highly toxic. In view of the fact that many nanomaterials, new and/or miniaturized bulk particles, are ready to enter the market, it is probably wise that authorities and legislators support fundamental research to construct a scientifically valid, low-cost, fast-throughput toxicity test battery to screen nanomaterials for toxicity and biopersistence.

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