SYMPOSIUM PRESENTATION

Risk Assessment Studies of Nanomaterials in Japan and Other Countries

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Abstract

Recent developments in nanoparticle (NP) technology and their commercial production have raised concern regarding NP risk to health and the environment. The toxicological characteristics of NP may not be similar to that observed in pre-NP materials because of the enormous differences in size and surface area. Thus, careful risk evaluation studies are required. Since some NP have already been produced and introduced into the market, before a suitable framework enabling risk management has been firmly established, toxicological studies based on the specificity of NP which are not subordinate to their commercial production are indispensable. The summary of nanotoxicology studies shown below clearly indicates that compared with the UK, EU, USA, and other countries, Japanese studies regarding metals and SWCNT are far from sufficient to evaluate risk.

Key Words: Nanoparticles - toxicology - carcinogenicity - titanium dioxide - carbon black

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Introduction

The safety of our living environment can be secured by the balanced function of three elements: risk assessment, risk management and risk communication. The first of these elements, risk assessment, must be addressed first, since without reliable risk assessment, risk communication and risk management can not function. Importantly, for reliable risk assessment long-term animal studies are indispensable.

These principles, of course, hold true for engineered nanoparticles. Unfortunately, the risk assessment data for engineered nanoparticles are rather fragmentary. However, the available findings do present a disturbing picture of potential carcinogens entering the market place. Engineered nanoparticles included in this review include nano-size titanium dioxide ($nTiO_2$), carbon black (nCB), single-walled carbon nanotubes (SWCNT), multiple-walled carbon nanotubes (MWCNT) and fullerenes (C60). A summary of the testing so far performed shows that data are limited and Japan is not putting the priority this subject deserves (see Table 1) and Tsuda et al (2009), for a review.

Table 1. Number of Subacute/Chronic Toxicity Tests (PubMed, ~2007)

				Total
TiO_2		2	2[a]	4
S/MW-CNT				0
Fullerenes		1		1
Uf-Carbon black			4[a]	4
Total	0	3	6	9

[a]Carcinogenic

Overall Evaluation and Proposal for the Future

During the development and marketing of nanomaterials, risk assessment of these new products has been perfunctory at best. While nanomaterials have undeniable benefits, their use also has undeniable potential risk. This risk must be addressed in an unbiased and thorough manner. Only after the toxicity of the various nanomaterials is understood can their true benefits be realized.

In rodent studies, $nTiO_2$ whether administered by inhalation or intratracheal instillation was shown to induce lung tumors with characteristic squamous cell morphology in female rats. These nanomaterials did not induce lung tumors in male rats. Our own studies have also shown that instillation of $nTiO_2$ into the lungs of female rats showed tumor promoting activity and resulted in elevated ROS-mediated damage and production of inflammatory cytokines. It is reasonable to assume that other metal-derived nanoparticles, such as aluminium and copper nanoparticles, and metal containing nanoparticles, for example nCB-metal mixtures and SWCNT and MWCNT preparations, are also capable of producing these effects. Nanoparticles such as $nTiO_2$, nCB, SWCNT and MWCNT when intratracheally administered, were detected by light microscope as aggregates or agglomerates and these forms are reported to induce foreign body granulation tissue with various degrees of inflammatory reaction. Although the

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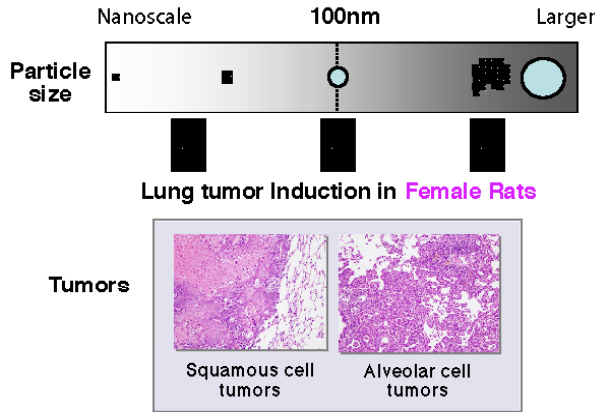

Figure 1. Schematic Presentation of Carcinogenic Effects of TiO_2, Carbon Black. Carcinogenic effects were elicited by both nano-scale and larger sized particles

relevance of foreign body-induced chronic inflammation to carcinogenesis is not clearly established, it is possible that reactive oxygen species (ROS) produced by macrophages attempting to destroy the foreign material in the inflammation site may cause DNA damage associated with carcinogenesis. Another possible contributing factor is metal, for example from metal-derived nanoparticles such as TiO_2 or from metal contaminants: these metals could also be involved in ROS production. Thus, it is possible that the observed carcinogenic effect is not specific to nanoparticles but rather associated with their ability to induce persistent foreign body-induced chronic inflammation and/or introduce metals into susceptible sites. For example, TiO_2 and carbon blacks larger than 100nm in diameter are known to induce lung tumors including similar squamous cell morphology (Nikula, 2000); (Pott and Roller, 2005) and both of these materials (larger than nano size) are classified as into group 2B (possibly carcinogenic to humans) by WHO/IARC (see Figure 1).

Mechanisms for mesothelioma induction by MWCNT in mice and rats have not been elucidated yet. A possible contributing factor is metal: Transition metals, such as iron, are commonly used as a catalytic center in the formation of CNTs, and contaminating metal in SWCNT and MWCNT particles could catalyze the formation of ROS by the Fenton reaction (Liu and Okada, 1994). One example of this type of toxicity is that human keratinocytes exposed to SWCNT were killed by ROS in the media (Shvedova et al., 2003). Another possible contributing factor is the length of the MWCNT (Pott and Roller, 2005; Muller et al., 2009; Sakamoto et al., 2009).

As noted at the beginning of this review, for reliable risk assessment long-term animal studies are indispensable. This is particularly true for risk assessment of potential carcinogens. The standard for the evaluation of the carcinogenic potential of a test chemical is testing in two rodent species, generally rats and mice, of each sex, at 3 doses (0, low and high) of the test chemical for up to two years. In the studies conducted to date concerning the carcinogenic risk presented by nanoparticles, there is a noticeable lack of long term testing: No long-term tests of any type have been reported for either SWCNT or fullerenes. Importantly, the primary goal of risk assessment is not to simply ban a product from the market place, but rather to determine product safety and establish guidelines lines for its production and use and promote consumer confidence. Given the known ability of many nanomaterials to induce mechanisms which are active in humans that are risk factors for carcinogenesis, for example ROS and inflammatory cytokine production, the continued introduction of these materials into the market is alarming. Establishing the safety of these materials is urgently needed.

In this short review, available in vivo data concerning the carcinogenic effects of $nTiO_2$, nCB, SWCNT and MWCNT, and Fullerenes is outlined. Of these, $nTiO_2$ and nCB are classified as possibly carcinogenic to humans. Testing of the carcinogenic activity of MWCNT produced mixed results. SWCNT and fullerenes have no carcinogenic activity in the studies conducted to date, however, toxicity testing of these materials has been quite limited and both of these materials have the potential to produce ROS. The observations noted here may apply to possible carcinogenic risk of other nanoparticles because of shared mechanisms of induction of inflammatory lesions and ROS generation. Our conclusions are that nanoparticles are clearly potentially toxic/carcinogenic to humans and their toxicity must be assessed, and their production and use managed appropriately.

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