Case Studies on Chronic (Long term) Toxicity of Non-Degradable Nanomaterials

Jun Kanno

Division of Cellular and Molecular Toxicology
Biological Safety Research Center
National Institute of Health Sciences
Tokyo, Japan

Introduction:

It is quite reasonable to consider that the materials with new properties may lead to novel biological effects or unknown adverse health effects. To gather proper hazard information while exposure is not widespread, it is important to develop, in parallel, both in vivo experimental protocols and detection/measurement methods for nanomaterials in the body. Since 2005, we are running research multiple projects to develop methods to monitor health risk effects for the assessment of manufactured nanomaterials funded by the Ministry of Health, Labour and Welfare, Japan. In the projects, in vivo experiments (mainly focusing on long-term health implication) has been conducted on multi-walled carbon nanotube (MWCNT; long fiber-type), fullerene (C60), and titanium oxide, which were chosen as first three materials to be tested of their high production volume. Here, we report the chronic effects of long fiber MWCNT and fullerene.

Safety issue for new materials such as nanomaterials is a new paradigm. The key is that the full scale exposure to the public is not yet started. Therefore, there is a good chance that information from hazard identification studies can directly be fed back to the product development plan. Manufacturers can produce safer products without risking themselves waiting for the toxicology studies to be finished after their products are widely marketed.

Long fiber MWCNT:

A certain type of MWCNT was found to contain fibrous particles similar in dimension and shape to asbestos, and thus considered highly suspicious of its potential to induce mesothelioma according to the classical knowledge of "fiber carcinogenesis"(1,2,3,4,5). Here we report the study on mesotheliomagenesis of the long fiber MWCNT. The test material was MWCNT (MITSUI MWCNT-7, Lot NO. 060125-01k) (6). Here, we adopted a short-term bioassay, i.e., the p53 heterozygous mouse intraperitoneal exposure model reported to be sensitive to asbestos and develop mesotheliomas fast (7, 8). The first study showed that single i.p. injection of 1x109 of MWCNT particles (corresponding to 3 mg/kg) in 1 ml suspension induced mesothelioma. This result was supported by at least two studies (10, 11, 12). A follow up dose-response study was conducted with the MWCNT dosages 10 times, 100 times, and 1000 times lower than the first study (lowest dose group, 3microg/animal). It was followed up for one year, and the mesotheliomas were induced in all dosage groups in dose-dependent manner, including the low-dose group where no severe peritoneal adhesion was observed (manuscript in preparation). Detailed histological search of the fiber identified translocation of shorter fibers into organs remote from peritoneal cavity.

Fullerene (C60) chronic toxicity

During the first study of long fiber MWCNT mentioned above, we found a possible chronic toxicity of C60 which was used as a negative control for mesotheliomagenesis. A follow up study was conducted; a single injection of 3 mg of fullerene (a suspension of aggregates) was given i.p. to thirty wild type C57Bl/6 male mice. Another thirty mice were given vehicle solution. The body weight gain of the treated mice was significantly suppressed. At weeks 44, most of the C60 injected mice had macroscopic lesions of the kidney(s). It is noted that the peritoneal reaction was mild to minimum in both immune and foreign body reaction. Histopathological analysis indicates the

possible target of the chronic nephrotoxicity as renal tubular system. Detailed analysis is underway (manuscript in preparation).

Conclusion:

This series of studies aimed at feeding back the chronic toxicity information to the developers of nano-products before they are massively produced and consumed, or in other words, before they are exposed to the public in an uncontrollable fashion. Based on such information, the developers/ manufactures can produce safer product to foster the nano-industry with a sustainable market. In the 1980s and 1990s, a series of wrong risk assessment and management of asbestos had allowed its massive exposure to workers and various levels of exposure to a large indefinite number of non-worker population. This mistake should not be repeated by the champion of the high-technology "nanomaterials". The case studies strongly suggested that both long fiber MWCNT and fullerene should be used strictly within the controllable confined space in order to avoid contact with living organisms where chronic tissue reaction, even mild, can be induced.

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