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Invited Mini-Review

Adverse effects of nanoparticles on humans

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Abstract

It was previously thought that the particles inhaled by humans and having adverse effects were micron-sized; particles with a particularly high content of crystalline silica were thought to have harmful effects. In recent years, manufactured materials have been further refined to nano-level particles, and it has been reported that these ultrafine particles have different adverse effects, making it necessary to perform occupational health management for chemicals that differ from micron-sized particles. Here we report the adverse effects of carbon nanotubes, welding fumes, and organic substances as examples of nanoparticles.

Key points

In recent years, many reports have been published on the adverse effects of ultrafine particles such as nanoparticles. Initially, most of the reports were about artificially produced manufactured nanomaterials, but reports have now begun to be published on organic polymer compounds and welding fumes unintentionally generated during the manufacturing process. We believe that the adverse effects of nanoparticles on humans are worthy of attention.

Keywords: nanoparticle; worker; polyacrylic acid; carbon nanotube; welding fume; lung.

It was previously thought that the particles that humans inhale and have adverse effects were micron-sized; notably, particles with a high content of crystalline silica were thought to be harmful. In recent years, manufactured materials have been further refined to nano-level particles, and these ultrafine particles reportedly have different adverse effects, making it necessary for occupational health management to consider these chemicals that differ from ordinary micron-sized particles. Here we report the adverse effects of carbon nanotubes, welding fumes, and organic substances as examples of nanoparticles.

1. Manufactured nanomaterials

Manufactured nanomaterials were developed as a result of advances in nanotechnology; that is, the technology to manufacture materials with new functions by reducing the particle size to the nano level. Nanomaterials have allowed for functions such as photocatalytic reactions, enhanced wear resistance, minimization of magnetic domains, and minimization of circuit currents, and are used in environmental purification, strengthening of coating materials, miniaturization of hard disks, high-speed computers, etc. On the other hand, reports have been published on the adverse effects of nanomaterials. In mice, such as P53 heterozygous mice,[1] exposure to carbon nanotubes caused a high incidence of malignant mesothelioma. This raised concerns that nanomaterials may also cause lung disorders like asbestos does, and research on their biological effects began to be conducted.

National projects were carried out in Japan, undertaken by bodies such as the New Energy and Industrial Technology Development Organization (NEDO), the Ministry of Economy, Trade and Industry, and the Ministry of Health, Labour and Welfare.[2] At that time, because the aggregation of nanoparticles is very strong, the biological effects of aggregated nanoparticles were reported, but doubts arose as to whether the aggregates really reflected the true effects of nanoparticles. Concerns could not be dispelled as to whether the biological reactions of aggregated nanoparticles were truly representative of nanoparticles, and whether further biological reactions would occur if the aggregate size became smaller. In the NEDO project, inhalation exposure studies and intratracheal instillation studies were conducted using fullerenes and multi-walled carbon nanotubes (MWCNTs) that were monodispersed or close to monodispersed, as well as nickel oxide and single-walled carbon nanotubes (SWCNTs) that were dispersed to an unprecedentedly low level, making full use of dispersion technology. It was found that the pulmonary response caused by monodispersed or highly dispersed nanomaterials was not significantly different from that caused by aggregated materials (aggregates that can be inhaled), and the pulmonary response reactions of aggregated

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Table 1. Basic data for the occupational exposure limit in inhalation studies of multi-walled carbon nanotubes[3-6].

CNT	MWCNT (Baytubes)	MWCNT (Nanocyl Com. NC7000)	MWCNT (Graphistrength Com. C100)	MWNT-7[a]	MWNT-7
Physicochemical properties	Diameter: 10 nm Medium-length: range 200-300 nm	Diameter (range): 5-15 nm Length (range): 0.1-10 μm	Ave. diameter: 12 ± 4 nm Ave. length: 1.07 ± 1.10 μm	Ave. diameter: 94.1-98 nm Ave. length: 5.53-6.19 μm	Ave. diameter: 94.1-98 nm Ave. length: 5.53-6.19 μm
Exposure period	13 wk (6 h/d, 5 d/wk)	13 wk (6 h/d, 5 d/wk)	90 d	13 wk (6 h/d, 5 d/wk)	104 wk (6 h/d, 5 d/wk)
Concentration of CNT, mg/m^3	0, 0.1, 0.4, 1.5, 6.0	0, 0.1, 0.5, 2.5	0, 0.05, 0.25, 5.0	0, 0.2, 1.0, 5.0	0, 0.02, 0.2, 2.0
Observation period	26 wk	0 d	90 d	0 d, 14 d	0 d
Endpoint	Inflammation/fibrosis	Inflammation/fibrosis	Inflammation/fibrosis	Inflammation/fibrosis	Lung tumor, fibrosis
NOAEL, mg/m^3	0.1		0.05		0.02
LOAEL, mg/m^3		0.1		0.2	
Reference	Pauluhn, 2010	Ma-Hock et al, 2009	Pothmann et al, 2015	Kasai et al, 2015	Kasai et al, 2016

Abbreviations: Ave, average; CNT, carbon nanotube; LOAEL, lowest observed adverse effect level; MWCNT, multi-walled carbon nanotube; NOAEL, no observed adverse effect level. [a]MWCNTs manufactured by Hodogaya Chemical Co, Ltd.

nanomaterials were subsequently considered to be nano-level reactions. Carbon nanotubes have been the subject of most of the research on such effects on humans.

Carbon nanotubes are coaxial tubular materials formed by rolling up a 6-membered carbon ring structure into a cylindrical shape. SWCNTs comprise a single layer, whereas MWCNTs have multiple layers. Because they are poorly soluble, they have almost no acute reactions, but there are many reports of chronic effects such as tumors and fibrosis. There are few human studies or epidemiological studies that have evaluated the link with tumors and fibrosis, and most of studies are in vivo and in vitro studies. Inhalation exposure studies are the main animal exposure studies for evaluating biological effects. Among inhalation studies, the 104-week (2-year) inhalation exposure studies to evaluate carcinogenicity and the 13-week inhalation exposure studies to evaluate fibrotic potential, etc, are considered important because they are often used as basic data for the occupational exposure limit (Table 1).

The 104-week (2-year) inhalation exposure studies were the only ones conducted at the National Institute of Occupational Safety and Health Japan (previously Japan Bioassay Research Center).[3] Male and female F344 rats were exposed to MWCNTs (MWNT-7 manufactured by Hodogaya Chemical Co, Ltd: length 1-19 μm, diameter 70-170 nm, discontinued production) at 0, 0.02, 0.2, and 2 mg/m^3 for 104 weeks, and pathological examination was performed. The incidence of lung tumors (adenoma and lung cancer) was significantly high at 0.2 mg/m^3 in males and at 2 mg/m^3 in females. No significant incidence of mesothelioma was observed in either males or females. Based on the above, the no observed adverse effect level (NOAEL) for the occurrence of lung tumors was 0.02 mg/m^3. Since no pulmonary fibrosis occurred, the NOAEL for pulmonary fibrosis was also 0.02 mg/m^3.

Thirteen-week inhalation exposure studies have been reported for MWCNTs from different manufacturers, and the overall NOAEL for inflammation and fibrosis was 0.05-0.1 mg/m^3.[4-6]

Pauluhn[4] exposed rats to MWCNTs (manufactured by Baytube Com; diameter in the range of 10 nm, median length 200-300 nm) by nasal inhalation at 0, 0.1, 0.4, 1.5, and 6.0 mg/m^3 for 13 weeks, and examined them for pulmonary inflammation and fibrosis. At 0.1 mg/m^3, no signs of inflammation or fibrosis were observed; at levels up from 0.4 mg/m^3, neutrophil infiltration in the lung (a sign of inflammation) and thickening of the alveoli and interstitium (a sign of pulmonary fibrosis) were observed; and at 6.0 mg/m^3, pleural thickening was observed.

Table 2. The occupational exposure limits for fine particles, including nanoparticles, proposed by the Japan Society for Occupational Health.

Materials	Occupational exposure limit, mg/m^3
Zinc oxide nanoparticle	0.5
Titanium oxide nanoparticle	0.3
Multi-walled carbon nanotube	0.01

Ma-Hock et al[5] exposed rats to MWCNTs (NC 7000; Nanocyl: 90% carbon, 10% metal oxide, 5-15 nm diameter, 0.1-10 μm length) at 0, 0.1, 0.5, and 2.5 mg/m^3 via nasal inhalation for 13 weeks to examine pulmonary inflammation and fibrosis. Pathological findings in the lungs showed multiple neutrophil-dominated granulomatous inflammation and alveolar proteinosis-like lesions at 0.5 mg/m^3 and above. The authors concluded that an NOAEL could not be proposed because minimal granulomatous inflammation was observed even at 0.1 mg/m^3.

Pothmann et al[6] also exposed male and female rats to MWCNTs (Graphistrength C100 MWCNT: average diameter 11-12 nm, average length ~1 μm) at 0, 0.05, 0.25, and 5 mg/m^3 via nasal inhalation for 90 days, and examined for pulmonary inflammation after a maximum observation period of 90 days. No findings were observed at 0.05 mg/m^3 but inflammatory findings such as neutrophil infiltration were observed from 0.25 mg/m^3 upwards, and there was persistent inflammation at 5 mg/m^3, along with collagen deposition in the interstitium, a sign of fibrosis.

In Japan, the occupational exposure limit of the Japan Society for Occupational Health for MWCNTs is 0.01 mg/m^3, which was proposed based on a comprehensive consideration of the results of lung tumors and fibrosis in a 104-week inhalation exposure study and the results of inflammation and fibrosis in a 13-week inhalation exposure study (Table 2).

The physicochemical properties of carbon nanotubes that are related to lung disorders, such as fibrosis and cancer, are thought to be associated with their geometric shape, such as their length. It has been reported that the presence of many long fibers is more

toxic to lung tissue, especially when their length is 5 to 10 μm or more. MWCNTs with long fibers, such as Mitsui 7, cause prolonged pulmonary inflammation and fibrosis, whereas short MWCNTs tend to cause only temporary inflammation and fibrosis.

Seven types of MWCNTs and carbon fibers with different lengths and diameters (fibers with geometric mean diameters of 13-103 nm and arithmetic mean lengths of 0.8 to 7.64 μm) were instilled into the larynx of mice at dose of 40 μg to investigate inflammation/fibrosis in the lungs.[7] Granulomatous inflammation and interstitial fibrosis were observed in the lungs for all fibers, but the longer the fibers, the more severe the fibrosis. In a study in which 3 carbon fibers with submicron diameters but different lengths were injected intratracheally into rats,[8] reported that inflammation with the short carbon fiber (6.7 μm) was transient whereas inflammation with the 2 longer fibers (11.7 μm and 13.7 μm) was persistent.

It has also been reported that pulmonary inflammation and fibrosis are weaker and more temporary with short fibers than with long fibers. Relatively short, single-fiber MWCNTs [MWNT-7; manufactured by Hodogaya Chemical Co, Ltd: diameter ~60 nm, length ~1.5 μm (fibers longer than 10 μm are curled fibers)] were administered intratracheally to CD male rats at 0, 0.04, 0.2, and 1 mg/kg (positive control: crystalline silica 5 mg/kg),[9] and lung inflammation was evaluated over a maximum observation period of 6 months. Inflammatory cell infiltration was observed in the lungs after MWCNT injection, but it was transient. Short fibers of MWNT-7 also tended to cause inflammation to disappear.

It has been reported that if the diameter is small, even long fibers will bend and not be in a straight line like thick fibers, so lung injury will be reduced. Moreover, it has been reported that some thin fibers are cleared from the lungs faster and inflammation and fibrosis are reduced, although there are also reports that thinner fibers are more likely to cause inflammation and fibrosis. No consensus has been reached at present.

In any case, because carbon nanotubes have a long half-life in the lung, we consider that once deposited in the lungs, carbon nanotubes will not be expelled, like asbestos. It is necessary to impose strict limits on concentrations in the workplace and personal exposures, and to use appropriate respirators.

It has also been reported that carbon nanotubes have the effect of enhancing allergies, especially respiratory allergies. In a study in mice exposed to MWCNTs and an extract of house dust mites by oropharyngeal aspiration,[10] the combination of MWCNTs and house dust mites significantly enhanced eosinophil counts, protein concentration, and lactate dehydrogenase concentration in broncho-alveolar lavage fluid (BALF) compared with exposure to either nanotubes or mites alone. It was concluded that carbon nanotubes enhanced the asthmatic allergic response in the lungs of mice. These responses have also been reported in inhalation exposure studies of carbon nanotubes. Mice were exposed for 30 days to MWCNTs by inhalation and to house dust mite extract by intranasal instillation,[11] and the exposure to both increased serum immunoglobulin E levels, elevated interleukin-13 levels in BALF, and enhanced mucin production in the bronchi. Exposure to carbon nanotubes by inhalation, which is close to physiological exposure, also enhanced the pulmonary allergic response.

No reports in humans have shown a relationship between workers with asthma and carbon nanotube exposure. A cross-sectional study was conducted on workers at 12 carbon nanotube/carbon nanofiber (CNT/F) facilities in the United States,[12] and it was reported that self-reported chest symptoms and respiratory illness, including respiratory allergy symptoms, were positively associated with inhaled elemental carbon concentration in the workplace. However, no workers developed new respiratory diseases such as asthma or chronic obstructive pulmonary disease (COPD) after starting work.

2. Welding fumes

Welding fumes are aerosols that are generated as a gas after a metal rod melts due to high heat, such as during arc welding work, and are cooled by air and solidified. These particles are finer than those generated in normal working environments, and are at the nano level. Unlike materials that are intentionally manufactured to have new functions, such as manufactured nanomaterials, welding fumes are unintentionally generated nanoparticles. Adverse effects of these fumes on humans have also been reported. They are one of the main causes of pneumoconiosis, and have lung tumor potential. Welding fumes are also highly soluble, and deposit in other organs via the bloodstream, causing organ disorder, mainly in the basal ganglia. This latter disorder induces pathological conditions accompanied by extrapyramidal symptoms similar to Parkinson syndrome.

Welder's lung disease, a type of pneumoconiosis that causes pulmonary fibrosis due to exposure to welding fumes, often has no subjective symptoms, and is often discovered through abnormalities in chest x-rays during a health examination. Bronchiolitis develops in the respiratory bronchioles when welding fumes are deposited in the lungs, and bronchiolitis is thought to progress to interstitial pneumonia. Chest x-rays show diffuse, faint, fine, multiple granular shadows; lung function is rarely severely impaired and is usually normal. It is generally believed that the shadows of pneumoconiosis do not improve, but even if welder's lung disease does develop, it has been reported that the welder's lung itself improves with better work management, making it a relatively benign form of pneumoconiosis.

There have been reports of metal analysis of the lungs of welder's lung to verify whether welding fumes cause pulmonary fibrosis. x-Ray microfluorescence of the lung tissue of 21 welder's lung patients with fibrosis revealed depositions of Fe, Zn, Ti, Mn, Cr, Cu, Ni, Si, etc. Furthermore, a large number of metal nanoparticles (Fe, Cr, Mn, Cu) were found as aggregates at higher magnification of a macrophage-containing fibrous region when observed with a transmission electron microscope.[13]

It has been shown that the risk of onset of occupational respiratory bronchiolitis increases at a cumulative level of welding fumes of 100 mg.year/mL, and interstitial pneumonia may develop at 200 mg.year/mL.[14] To prevent welder's lung, it is important to ensure that workers do not reach the cumulative exposure level for individuals in the work environment, for example, by using the dust reduction effect of respiratory protective equipment (with a designated protection factor).

Various epidemiological studies have been conducted on lung cancer caused by welding fumes. Both case–control and cohort studies have confirmed an increased risk of lung cancer due to exposure to welding fumes. The International Agency for Research on Cancer (IARC), a global assessment body for chemicals, has classified welding fumes as Group 1 (carcinogenic to humans) based on the findings of human epidemiological surveys providing sufficient evidence for cancer in humans; also, pharyngeal aspiration and inhalation exposure studies[15] provide limited evidence for cancer in experimental animals. The Japan Society for Occupational Health has also re-evaluated the papers used in the IARC's assessment and, finding a similar risk of carcinogenicity, has proposed classifying welding fumes as Group 1 (carcinogenic to humans). Pneumoconiosis examinations are

mandatory in Japan for the early detection and treatment of lung diseases associated with welding work, but it may be necessary to estimate the occupational exposure limit to prevent the onset of welder's lung disease and lung cancer.

One of the adverse effects of welding fumes eluting from the lungs is fume fever. The clinical characteristics of fume fever are those caused by exposure to highly soluble metal fumes: shortness of breath and sore throat occur within a few hours, and systemic symptoms such as fever, muscle pain, and chills; symptoms usually last for 2-4 days. Metal fume fever in welders is reported to occur repeatedly in 31% of welders, and in a longitudinal study of several hundred welders, the prevalence of metal fume fever exceeded 35% after an average of 15 months. It has also been reported that inhaling yet higher concentrations of fumes for a short period of time can cause chemical pneumonia. Additional exposure to cadmium, chromium, cobalt, mercury, and nickel fumes have also caused chemical pneumonia. Prolonged exposure to fume fever, as with insufficient indoor ventilation or not wearing a mask, may progress to pneumonia.[16] Caution is required if respiratory or systemic symptoms persist after exposure to welding fumes, including the possibility of progression to pneumonia.

Among the metals that dissolve in welding fumes, manganese accumulates in the liver, muscles, and brain, especially the basal ganglia, when excessively dissolved, causing neurological disorders characterized by behavioral disorders and significant extrapyramidal syndromes similar to dystonia and Parkinson disease.[17] In manual metal arc welding workers, 55.8% of cases showed T1 hyperintensity in the basal ganglia on magnetic resonance imaging, and it has been reported that T1 hyperintensity correlates with blood manganese concentration, suggesting that manganese accumulates in the basal ganglia and causes disorders.

A study was conducted on 189 Japanese welders and non-welders to examine the relationship between blood manganese levels and the Wechsler Adult Intelligence Scale-IV, an intelligence test. The odds ratio between blood manganese levels and working memory index (WMI) in welders was high, at 3.73 (95% CI, 1.04-13.38),[18] and there was a positive correlation between blood manganese levels and WMI scores. This suggests that increased manganese levels are related to intellectual disability.

In Japan, manganese levels in the work environment and blood are monitored during welding work, which suggests that this is useful for preventing the development of brain diseases caused by manganese accumulation. However, whether monitoring manganese in the environment alone can lead to early detection of welder's lung is controversial.

There have been few reports of manganese-related pulmonary fibrosis or tumor development, and fumes also contain carcinogens such as chromium, so concentration control of substances other than manganese may also be necessary.[17] Welder's lung is a common pneumoconiosis in welding work, and it has recently been reported that it can also induce COPD. Reports have been published on the physicochemical properties of fumes from welding work, and most of the particles that were investigated are nanoparticles.

3. Organic substances

Chemical substances consist of inorganic and organic chemicals. Basically, organic substances are compounds of carbon and hydrogen combined (excluding compounds such as carbon dioxide, which is a simple carbon compound), whereas inorganic substances consist of other substances. Traditionally, pulmonary fibrosis such as pneumoconiosis was thought to develop from inorganic substances, whereas organic substances, although they can cause lung cancer and allergic diseases, were not thought directly to cause pulmonary fibrosis or interstitial pneumonia (excluding fibrosis caused by chronic allergic diseases such as hypersensitivity pneumonitis). In recent years, organic substances with lung fibrosis potential greater than that of asbestos or crystalline silica have been reported in Korea and Japan.[19] Cross-linked polyacrylic acids (CL-PAAs) are a representative example, and the Japanese Ministry of Health, Labor and Welfare issued a notification regarding the occurrence of a group of cases of pulmonary fibrosis in small and medium-sized enterprises handling CL-PAAs. According to a report on a company that handles the polymers,[20] the exposure period until pneumoconiosis develops is very short, at 2-5 years, whereas even with asbestos, a typical substance that causes pneumoconiosis, the disease takes more than 20 years to develop, suggesting that CL-PAAs may have a greater pulmonary fibrosis potential than asbestos clinically.

Animal exposure studies for CL-PAAs have been conducted. In particular, intratracheal instillation studies using polyacrylic acid, the basic structural component of CL-PAAs, have been reported to show a greater pulmonary inflammation and fibrosis potential than asbestos or crystalline silica.[21] In a 13-week inhalation exposure study for acrylic acid–based polymers,[22,23] NOAELs of 0.2 and 0.3 mg/m^3 (acrylic acid-based polymers) were reported, and it is thought that these data may become the basis for the occupational exposure limit in the future, which will improve occupational health management.

Studies have been conducted to determine what physicochemical properties of polyacrylic acid are involved in lung disorder, and these point to molecular weight and degree of crosslinking. In a study in which polyacrylic acids of different molecular weights were instilled intratracheally, it was reported that those with larger molecular weights caused more lung inflammation and fibrosis potential than acrylic acids with smaller molecular weights.[24] In addition, it has been reported that at a cross-linking degree of around 0.1%, found in polyacrylic acid used as a thickening material, fibrosis is enhanced; conversely, with no cross-linking fibrosis is reduced.[25] In addition to this, the presence of carbonyl groups is also thought to be related to viscosity through the capacity to retain water molecules, so there is interest in lung damage. Future research progress is expected.

Author contributions

C.N. and H.H. provided interpretation and support for engineering findings regarding nanoparticles. H.I. and T.T. also provided interpretation and support for findings on the basic science of nanoparticles. Y.M. summarized findings of the effects of nanoparticles on humans and wrote the manuscript.

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Conflicts of interest

None declared.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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