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Original Article

Sneezing and Allergic Dermatitis were Increased in Engineered Nanomaterial Handling Workers

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Abstract: The aim of this study was to survey the work-relatedness of symptoms and diseases among engineered nanomaterials handling workers by questionnaire. A total of 258 exposed workers and 200 comparison workers were recruited from 14 nanomaterials handling factories in Taiwan. In addition to current disease status (prevalence), we classified the diseases worsened by employment (worsened by work). The control banding nanotool risk level matrix was adopted to categorize the severity and probability of nanomaterial exposure. The work-relatedness of symptoms was also self-reported in the questionnaire. The only symptom identified as significantly work-related was sneezing (5.88% in risk level 2 and 7.91% in risk level 1 vs. 2.00% in controls, *p*=0.04). The prevalences of work-related dry cough (*p*=0.06) and productive cough (*p*=0.09) in nanomaterials handling workers were also higher than those in controls. The only disease significantly worsened by work was allergic dermatitis (4.20% in risk level 2, 0% in risk level 1 vs. 0.50% in control, *p*=0.01). The incidence of angina in nanoworkers was also higher than in controls (*p*=0.06). In addition to allergic diseases, cardiopulmonary symptoms such as cough and angina may be used as screening tools for medical surveillance of people handling engineered nanomaterials.

Key words: Allergic dermatitis, Sneezing, Risk levels, Nanomaterial handling workers, Questionnaire

Introduction

Potential routes of nanoparticle exposure include inhalation, ingestion, and dermal absorption. Among them, inhalation is the most important exposure route[1–3]. Previous studies revealed that nanoparticles less than 100 nm in size have several toxic characteristics, including nanoparticles depositing mainly in the alveoli, nanoparticles clearing from the lungs slower than fine particles, and inhaled nanoparticles migrating from the lungs into the circulation, brain, interstitial tissues, and regional lymph nodes[1–3]. Even so, the health effects of engineered nanoparticles are uncertain. Evidence of human toxicity of nanoparticles, for example, oxidative damage, lung inflammation, asthma, possibly lung cancer, atherosclerosis, and worsening of heart disease, came from epidemiological studies of unintentionally or naturally produced ultrafine particles generated from traffic pollution and combustion processes such as diesel exhaust and welding fumes[4–9]. Epidemiological studies have shown positive correlation between the particulate matter in air pollution and increased morbidity and mortality in adults and children[4, 5]. Epidemiological studies also show links between respiratory illnesses and the number of ambient ultrafine particles[4, 5].

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Little was known about exposure assessment and health risk assessment of people exposed to engineered nanoparticles until suspected occupational diseases due to polyacrylate nanoparticles were reported in China[10]. Although health hazards induced by engineered nanoparticles have never been confirmed in humans, there is cumulative evidence from animal studies that exposure to some nanomaterials is harmful. The health effects induced by engineered nanoparticles in animal inhalation studies included oxidative stress, pulmonary inflammation, granuloma formation, lung fibrosis, cardiovascular effects, pleural plaque formation, mesothelioma-like effects, and lung cancer[1–5].

There are increasing public, governmental, and scientific concerns about the potential adverse health effects of nanoparticle exposure. Depression of antioxidant enzymes (superoxide dismutase and glutathione peroxidase) and increased expression of cardiovascular markers (fibrinogen and intercellular adhesion molecules) have been found among workers handling nanomaterials[11]. Although no human illness to date is confirmed to be attributed to engineered nanoparticles, occupational epidemiological study is needed to verify the health effects of engineered nanoparticles. We emphasize that our survey of workers handling engineered nanomaterials is not to answer "What are the health effects of nanoparticles?" Instead, we sought to answer "What are the potential health hazards among workers handling nanomaterials who are exposed to nanoparticles?" Therefore, the objective of this study was to survey symptoms complained and diseases that developed or worsened after work among workers handling engineered nanomaterials.

Subjects and Methods

Study population

We have conducted a survey of the nanotechnology factories in Taiwan. Among the lists of nanomaterials handling factories from the Environment, Health and Safety project, some were selling nanomaterials only but not handling raw nanomaterials, were shut-down, were not currently using nanomaterials, or had never used nanomaterials. We estimated that about 70 factories were manufacturing or applying nanomaterials in Taiwan. The total number of workers handling nanomaterials was estimated to be about 1,000 workers.

Among the 70 factories manufacturing or applying nanomaterials, we visited 39 factories and collected brief industrial hygiene information. There were 14 factories that agreed to participate in this study and provide detailed information. The basic information of these 13 factories except for one research institute is listed in Table 1. Among them, 5 factories manufacture nanomaterials and 12 factories use nanomaterials to manufacture other products. The physicochemical properties of nanomaterials manufactured and/or used in these factories are also listed in Table 1.

This is a cross-sectional study design. Both nanomaterial handling workers and non-exposed controls were recruited from 14 above-mentioned nanomaterial handling factories. In order to have comparable geographic area and socioeconomic status, the controls were selected from volunteers at the same factories as the exposed workers, but who did not handle nanomaterials. We recruited 258 nanomaterial handling workers and 200 non-exposed controls to participate in this cross-sectional study.

Work-relatedness of symptoms and diseases worsened by work

For each participant, a self-administered questionnaire was distributed to collect work history, personal habits, detailed symptom history, and detailed past and current disease history after informed consent. This study has been reviewed and approved by our institution's ethics review board. Health examinations were then performed and the symptom complained or the diseases developed were checked by an occupational medicine physician.

The symptom complained and diseases developed before (I had this symptom or disease before doing the job) or after (I didn't have this symptom or disease before doing the job) working in nanomaterial handling factories in this study population were collected by questionnaire. The symptom complaints collected included respiratory, cardiovascular, skin, and neurological symptoms. Work-relatedness of symptoms was self-reported in the questionnaire, along with current status (prevalence). The diseases collected included respiratory, cardiovascular, and skin diseases. In addition to current disease status (prevalence), participants further reported I had this disease after doing the job (incidence), as well as this disease got worse after doing the job (worsened by work).

Exposure assessment

Due to a lack of harmonization of measurement strategies for exposure to engineered nanoparticles, we adopted the control banding nanotool risk level matrix proposed by Dr. Paik and his colleagues[12–14] to categorize the risk level for each participant. An example elaborated detailed calculation of severity score, probability score and risk

Table 1 The characteristics of nanomaterials used or manufactured in these 13 factories

Factory number	Type of nanomaterial handling	Nanomaterial used/mfg	Major nanomaterial used/mfg	Size (nm)	Amount used/mfg (mg/time)	Duration of use/mfg (hour/time)	Frequency of use/mfg (times/week)	Type of nanomaterials used/mfg
1	Use	Nano-silver	Nano-silver	Unknown	20	5	5	Liquid solution
2	Use	Fe_2O_3	Fe_2O_3	6–10	5,000	2	1	Liquid solution
		Nano-gold		3–40	19	0.1	1	Liquid solution
		Nano-silver		5–10	2.1	0.1	1	Liquid solution
	Mfg	Fe_2O_3	Fe_2O_3	6–10	5,000	0.2	8	Liquid solution
		Nano-gold		3–40	10	0.25	8	Liquid solution
		Nano-silver		5–10	21	0.1	8	Liquid solution
3	Use	Titanium dioxide	Titanium dioxide	15–20	10,000	2.5	2.5	Powder and liquid solution
	Mfg	Titanium dioxide	Titanium dioxide	15–20	1,000,000	1	8	Powder and liquid solution
4	Use	Nano-silver	Nano-silver	Commercial secret	Commercial secret	3	7	Liquid solution
	Mfg	Nano-silver	Nano-silver	Commercial secret	Commercial secret	7	3	Liquid solution
5	Use	Titanium dioxide	Titanium dioxide	20	50,000	4	1	Liquid solution
6	Use	Silicon dioxide	Silicon dioxide	10	50,000	1	1	Liquid solution
		Nano-silver		100	50	1	1	Liquid solution
7	Use	Carbon nanotube	Carbon nanotube	40	100	1	1	Powder and liquid solution
		Silicon dioxide	Silicon dioxide	100	50,000	1	1	Powder
8	Use	Carbon nanotube	Carbon nanotube	0.5	Commercial secret	Commercial secret	Commercial secret	Liquid solution
9	Use	Silicon dioxide	Silicon dioxide	12–17	300	0.2	4	Powder
10	Mfg	Silicon dioxide		160	2,500	5	1	Liquid solution
		Silicon dioxide	Silicon dioxide	100–200	60,000	5	8	Colloid
11	Use	Carbon nanotube	Carbon nanotube	110	5,000	0.5	4.5	Powder, liquid solution, and gel
	Mfg	Carbon nanotube	Carbon nanotube	110	4,000,000	4	12	Powder and liquid solution
12	Use	Carbon nanotube	Carbon nanotube	100	>20	1	3.5	Powder
		Nano-silver		>100	>40	1	3.5	Liquid solution
13	Use	Titanium dioxide	Titanium dioxide	Unknown	5	6	0.33	Liquid solution

mfg: manufacturing

level was shown in Appendix 1.

Briefly, the risk level matrix was calculated based on the severity score of the nanomaterial toxicity and the score of the exposure probability. The factors considered in the calculation of the severity score included nanomaterial (70% of severity score) and parent material (30% of severity score). The factors considered in the calculation of the severity score of the nanomaterials included surface chemistry (10 points), particle shape (10 points), particle diameter (10 points), solubility (10 points), carcinogenicity (6 points), reproductive toxicity (6 points), mutagenicity (6 points), dermal toxicity (6 points), and asthmagenicity (6 points). The factors considered in the calculation of the severity score of parent material included occupational exposure limit (10 points), carcinogenicity (4 points), reproductive toxicity (4 points), mutagenicity (4 points), dermal toxicity (4 points), and asthmagenicity (4 points). The variables considered in the exposure probability included the estimated amount of material used (25 points), dustiness/mistiness (30 points), number of employees with similar exposure (15 points), frequency of operation (15 points), and duration of operation (15 points).

The exposure probability scores were collected by questionnaire from personal interview of individual workers exposed to the various nanomaterials. In order to obtain consistent scores, the nanomaterial toxicity severity score was based on the summary reports of a review document[15]. The cross-table of the severity scores and prob-

ability scores was used to generate the risk levels (1 to 4) for each individual. The higher the risk level, the higher the severity of nanomaterial toxicity and/or the higher the exposure probability.

Data analysis

Percentages were used to describe the distributions of categorical variables. The χ^2 test was used to test differences among categorical variables. In the data analysis, we compared the differences of prevalence, incidence and worsen by work among risk level 2 (RL2) workers (we combined RL3 and RL2 into RL2 in the data analysis), risk level 1 (RL1) workers, and non-exposed control workers. We also performed a trend analysis to test the dose-response gradients among control, RL1, and RL2 groups.

After identification of significant outcomes, multivariate logistic regression was used to adjust for confounders, including age, gender, smoking, history of respiratory diseases, and history of dust exposure. In addition to variables mentioned above, we also collected some other circumstance with potential exposed to incidential ultrafine particles. We found that there was no difference among RL2, RL1 and control groups in the distribution of frequency of types of transportation, resident closed to traffic roads, resident closed to factories within 50 meters, burning incense in the house, and burning anti-mosquito coil in the house. Therefore, the incidental ultrafine particles or nanoparticles exposure was not adjusted in our model.

Results

Distribution of risk levels and nanomaterials handled

The distribution of risk levels among the exposed study population (n=258) were 139 (53.9%) subjects in RL1, 110 (42.6%) in RL2, and 9 (3.5%) in RL 3. Since RL3 had such a small number of subjects, we combined RL3 and RL2 into RL2 (n=119, 46.1%) for the data analysis.

The types of nanomaterials handled by the 258 exposed individuals were carbon nanotubes, titanium dioxide, silica dioxide, nanosilver, and other nanomaterials including nanoresins, nanogold, nanoclay, nanoalumina, and metal oxides. Since most factories used several types of nanomaterials, most of our study population were multiple exposure to mixed types of nanomaterials (n=99, 38.4%) (Table 1). Besides, carbon nanotube was the most prevalent single exposure nanomaterial (n=60, 23.3%), followed by silica dioxide (n=37, 14.3%), titanium dioxide (n=21, 8.1%), nanosilver (n=15, 5.8%), and others (including nanoresin, nanoclay, etc.) (n=26, 10.1%).

Distribution of characteristics among the study population

The distribution of characteristics among the study population stratified by risk levels is shown in Table 2. The distribution of gender, education, alcohol drinking, and betel nut chewing differed significantly by risk level. RL2 had more men, high educational level, more alcohol drinkers, and more betel nut chewers, while the control group had more women, more university educated subjects, fewer alcohol drinkers, and fewer betel nut chewers. The difference in age distribution and smoking status among the three groups were not significant.

Prevalence of work-related symptoms

The prevalence of self-reported respiratory and cardiovascular symptoms and work-related symptoms are listed in Table 3 (The dematological and neurological symtoms were shown in Appendix 2). The prevalence of unexpected chest pain without resolution after 10 to 15 min of rest in the RL2 group (5.88%) was significantly higher than that of the control (0.51%) and RL1 groups (0.72%) ($p<0.001$). In contrast, the prevalence of shortness of breath in the exposed workers (1.45% in RL1 and 2.52% in RL2) were significantly lower than that of the controls (7.04%).

Sneezing was the only work-related symptom complained by the nanomaterials handling workers (7.9% in RL1 and 5.9% in RL2 vs. 2.0% in control, $p=0.04$) (Table 3). Sneezing symptoms revealed a dose-dependent gradient by risk levels ($p=0.05$). Multivariate logistic regression was used to adjust for confounders, including age, gender, smoking, history of respiratory diseases, and history of dust exposure (Table 4). The adjusted odds ratio of sneezing in RL1 was 4.99 (95% CI = 1.47–16.90), while it was 3.58 (95% CI = 0.97–13.25) in RL2. If duration of exposure to nanomaterials was used as surrogate of exposure, the regression models after adjusting for confounders showed that there was no significant association between work-related sneezing and duration of exposure (data not shown). If stratified by types of nanomaterial handling, we found sneezing was increased in workers handling carbon nanotube, titanium dioxide, and silicon dioxide, but not in workers handling nanosilver and other nanomaterials (data not shown). Therefore, sneezing was associated with nanomaterials handling in total population and in workers who handled specific nanomaterials.

The self-reporting work-related prevalence of dry cough (5.8% in RL2, 5.9% in RL1, vs. 1.5% in the control group) ($p=0.06$) and productive cough (2.5% in RL2, 2.2% in RL1, vs. 0% in controls) ($p=0.09$) was higher in exposed workers than in controls (Table 3). The self-reporting

Table 2. Distribution of characteristics among study population stratified by risk levels

Variables	Risk Levels						*p*-value*
	Control (n=200)		Risk Level 1 (n=139)		Risk Level 2 (n=119)		
	n	(%)	n	(%)	n	(%)	
Age							
≤40	135	67.5	101	72.7	93	78.2	0.12
>40	65	32.5	38	27.3	26	21.9	
Gender							
Female	80	40.0	35	25.2	26	21.9	<0.01
Male	120	60.0	104	74.8	93	78.2	
Ethnicity							
Taiwanese	157	79.3	109	78.4	92	77.3	0.55
Hakka	22	11.1	15	10.8	19	16.0	
Mainlander and Aborigine	19	9.6	15	10.8	8	6.7	
Education							
High school and less	38	19.2	18	13.1	20	16.8	0.03
University	104	52.5	62	45.3	47	39.5	
Graduate school	56	28.3	57	41.6	52	43.7	
Smoking							
No	174	87.9	118	85.5	97	81.5	0.30
Yes	24	12.1	20	14.5	22	18.5	
Alcohol drinking							
No	180	90.5	133	95.7	103	86.6	0.04
Yes	19	9.6	6	4.3	16	13.5	
Betel nut chewing							
No	196	98.5	139	100.0	112	94.1	<0.01
Yes	3	1.5	0	0.0	7	5.9	

**p* value for χ^2 test

work-related cardiovascular symptoms, skin symptoms and neurological symptoms (Appendix 2) were not statistically different between the exposed and control groups.

Prevalence of diseases and diseases worsened by nanomaterials work

The prevalence of diseases and diseases worsened by work in the nanomaterials handling factories (worsened by work) are shown in the Table 5, diseases that developed after employment in the nanomaterials handling factories (incidence), and the combination of incidence and worsened by work are shown in the Appendix 3. The prevalence of arrhythmia (5.88% in RL2, and 3.60% in RL1 vs. 1.01% in control, p=0.05), angina (4.20% in RL2 and 0% in RL1 vs. 0% in control, p<0.001), and allergic dermatitis (15.13% in RL2 and 5.76% in RL1 vs. 9.55% in control, p=0.04) were significantly higher in nanomaterials handling workers than in the controls (Table 5).

However, the only disease significantly worsened by work was allergic dermatitis (4.20% in RL2 and 0% in RL1 vs. 0.50% in the control group, p=0.01) (Table 5). Allergic dermatitis revealed a dose-dependent gradient by risk levels (p=0.02). Multivariate logistic regression was used to adjust for confounders, including age, gender, smoking, history of respiratory diseases, and history of dust exposure (Table 6). The adjusted odds ratio was 11.12 (95% CI = 1.18–104.51) in RL2 (there were no allergic dermatitis worsened by work in risk level 1). If duration of exposure to nanomaterials was used as surrogate of exposure, allergic dermatitis worsened by work was significantly associated with duration of exposure, either by 3 yr cut-point or 5 yr cut-point (data not shown). If stratified by types of nanomaterial handled, the prevalence of worsened by work allergic dermatitis in any nanomaterial handled was not significantly higher than in controls (data not shown).

When the diseases that developed after employment (incidence) and incidence plus the diseases worsened by the employment (incidence plus worsened by work) are listed separately (Appendix 3), there was no significant difference between exposed workers and controls for any disease surveyed. However, the incidence as well as the

Table 3. Self-reporting work-related respiratory and cardiovascular symptoms developed after employed in nanomaterials handling plants stratified by risk levels

Variables	Prevalence							Self-reporting work-related						
	Control (n=200)		Risk Level 1 (n=139)		Risk Level 2 (n=119)		*p*-value*	Control (n=200)		Risk Level 1 (n=139)		Risk Level 2 (n=119)		*p*-value*
	n	(%)	n	(%)	n	(%)		n	%	n	%	n	%	
Respiratory symptoms (not related to URI)														
Dry cough	24	12.1%	19	13.7%	20	16.8%	0.49	3	1.5%	8	5.8%	7	5.9%	0.06
Productive cough	14	7.0%	16	11.6%	11	9.2%	0.35	0	0.0%	3	2.2%	3	2.5%	0.09
Wheezing	4	2.0%	1	0.7%	1	0.8%	0.51	0	0.0%	0	0.0%	1	0.8%	0.24
Chest tightness	20	10.1%	8	5.8%	10	8.4%	0.37	7	3.5%	3	2.2%	4	3.4%	0.76
Shortness of breath	14	7.0%	2	1.5%	3	2.5%	0.02	2	1.0%	1	0.7%	2	1.7%	0.75
Sneezing	35	17.6%	25	18.0%	23	19.3%	0.93	4	2.0%	11	7.9%	7	5.9%	0.04
Rhinitis	22	11.1%	14	10.1%	15	12.6%	0.81	2	1.0%	6	4.3%	3	2.5%	0.15
Nose obstruction	30	15.1%	23	16.6%	21	17.7%	0.83	5	2.5%	7	5.0%	4	3.4%	0.46
Rhinorrhea	30	15.1%	18	13.0%	19	16.0%	0.77	3	1.5%	8	5.8%	5	4.2%	0.10
Cardiovascular symptoms														
Chest oppression, pain, burning sensation	10	5.1%	7	5.0%	8	6.7%	0.79	3	1.5%	1	0.7%	3	2.5%	0.50
Chest pain with radiation to left arm, shoulder, chin or back	6	3.0%	5	3.6%	4	3.4%	0.96	4	2.0%	3	2.2%	3	2.5%	0.95
Sweating, nausea, vomiting, dizziness and irritable, in addition to chest pain	5	2.5%	1	0.7%	6	5.1%	0.09	2	1.0%	1	0.7%	4	3.4%	0.16
Unexpected chest pain, without resolve after 10 to 15 min rest	1	0.5%	1	0.7%	7	5.9%	<0.001	0	0.0%	1	0.7%	1	0.8%	0.45

*p value for χ^2 test

Table 4. Multiple logistic regression of risk levels on work-related sneezing adjusted for confounders

Variables	B	SE	Exp(B) (Odds ratio)	95% CI for Odds ratio		*p* value
Age	0.03	0.02	1.03	0.98	1.08	0.21
Gender (male vs. female)	0.24	0.56	1.27	0.42	3.80	0.67
Smoking (yes vs. no)	–0.27	0.69	0.77	0.20	2.95	0.70
Respiratory disease history (yes vs. no)	2.22	0.49	9.16	3.54	23.71	<0.001
Dust exposure history (yes vs. no)	0.35	0.88	1.41	0.25	7.98	0.69
Risk Levels						
Risk Level 1 vs. control	1.61	0.62	4.99	1.47	16.90	0.01
Risk Level 2 vs. control	1.28	0.67	3.58	0.97	13.25	0.06
Constant	–6.26	1.23		–	–	–

Table 5. The prevalence of diseases or diseases worsened by nanomaterials handling work stratified by risk levels

Variables	Prevalence							Worsened by work						
	Control (n=200)		Risk Level 1 (n=139)		Risk Level 2 (n=119)		*p*-value*	Control (n=200)		Risk Level 1 (n=139)		Risk Level 2 (n=119)		*p*-value*
	N	(%)	N	(%)	N	(%)		N	(%)	N	(%)	N	(%)	
Respiratory Diseases														
Chronic Bronchitis	11	5.5%	8	5.8%	6	5.0%	0.96	0	0.0%	3	2.2%	2	1.7%	0.13
Emphysema	0	0.0%	0	0.0%	0	0.0%	.	0	0.0%	0	0.0%	0	0.0%	.
Asthma	7	3.5%	4	2.9%	2	1.7%	0.63	0	0.0%	1	0.7%	1	0.8%	0.46
Tuberculosis	1	0.5%	0	0.0%	0	0.0%	0.52	0	0.0%	0	0.0%	0	0.0%	.
Lung cancer	1	0.5%	0	0.0%	0	0.0%	0.52	0	0.0%	0	0.0%	0	0.0%	.
Rhinitis	37	18.7%	27	19.4%	23	19.3%	0.98	1	0.5%	5	3.6%	2	1.7%	0.10
Cardiovascular diseases														
Stroke	0	0.0%	0	0.0%	0	0.0%	.	0	0.0%	0	0.0%	0	0.0%	.
Arrhythmia	2	1.0%	5	3.6%	7	5.9%	0.05	0	0.0%	0	0.0%	1	0.8%	0.24
Ischemic heart dis	0	0.0%	0	0.0%	1	0.8%	0.24	0	0.0%	0	0.0%	0	0.0%	.
Angina	0	0.0%	0	0.0%	5	4.2%	<0.01	0	0.0%	0	0.0%	0	0.0%	.
Valve heart dis.	3	1.5%	2	1.4%	2	1.7%	0.99	0	0.0%	0	0.0%	0	0.0%	.
Hyperlipidemia	13	6.6%	9	6.5%	11	9.2%	0.62	1	0.5%	1	0.7%	1	0.8%	0.93
Hypertension	12	6.1%	9	6.5%	11	9.2%	0.54	2	1.0%	2	1.4%	0	0.0%	0.45
Skin Diseases														
Atopic dermatitis	9	4.5%	11	7.9%	9	7.6%	0.37	0	0.0%	1	0.7%	1	0.8%	0.46
Allergic dermatitis	19	9.6%	8	5.8%	18	15.1%	0.04	1	0.5%	0	0.0%	5	4.2%	0.01
Pigmentation	3	1.5%	2	1.4%	5	4.2%	0.22	0	0.0%	0	0.0%	0	0.0%	.
Skin cancer	0	0.0%	2	1.4%	1	0.8%	0.26	0	0.0%	0	0.0%	0	0.0%	.
Folliculitis	9	4.5%	7	5.0%	7	5.9%	0.87	0	0.0%	0	0.0%	1	0.8%	0.24

*χ^2 *p*-value

incidence plus worsened by work for angina was higher in exposed workers than in controls (1.68% in RL2, 0% in RL1 and. 0% in control group) (p=0.06) (Appendix 3). The incidence plus worsened by work for allergic dermatitis was also higher in exposed workers than in controls (10.92% in RL2, 4.32% in RL1 and 5.53% in the control group) (p=0.07) (Appendix 3).

Discussion

Recently, several cases of illnesses suspected of being caused by nanoparticles were reported in the medical literature. Two cases were reported in Germany and one in China. In the first case, in late March 2006, six people were admitted to the hospital with serious respiratory problems after using a new German bathroom cleaning

Table 6. Multiple logistic regression of risk levels on worsened by work allergic dermatitis adjusted for confounders

Variables	B	SE	Exp (B) (Odds ratio)	95% CI for odds ratio		*p* value
Age	–0.01	0.05	0.99	0.90	1.10	0.91
Gender (male vs. female)	–0.30	0.94	0.74	0.12	4.65	0.75
Smoking (yes vs. no)	–	–	–	–	–	–
Respiratory disease history (yes vs. no)	2.09	0.90	8.10	1.39	47.13	0.02
Dust exposure history (yes vs. no)	–	–	–	–	–	–
Risk Levels						
Risk Level 1 vs. control*	–	–	–	–	–	–
Risk Level 2 vs. control	2.41	1.14	11.12	1.18	104.51	0.04
Constant	–5.72	2.23		–	–	–

*There were 0 allergic dermatitis worsened by work in risk level 1 and 5 allergic dermatitis cases in risk level 2.

product called Magic Nano[16, 17]. The second case was pleural effusion, pulmonary fibrosis, and granuloma development in a printing plant worker in China[10]. The third case was a female office worker with toner dust exposure from laser printers who developed submesothelial deposition of carbon nanoparticles in the peritoneum[18]. Although the above-mentioned cases have never been confirmed to be caused by inhalation of nanoparticles, the primary target organ affected by nanoparticles seems to be the lungs, with acute irritation to chronic inflammation, pulmonary fibrosis, and granuloma formation[10, 16–18]. In this cross-sectional survey, we found that sneezing was significantly increased in nanomaterials handling workers and was reported as work-related. In addition to sneezing, dry cough and productive cough was the second and the third most frequently reported work-related symptoms (Table 3). Our findings are compatible with previous reports and support the notion that the primary target organ affected by nanoparticles is the lungs.

Detrimental cardiovascular consequences due to ultrafine particles exposure are reported in several epidemiological studies[19–25]. Cardiovascular diseases could likely be explained by translocation of nanoparticles from the respiratory epithelium into the circulation, with subsequent toxicity to the vascular endothelium, alteration of blood coagulation, eventually leading to atherosclerosis[23–25]. Nanoparticles can also trigger autonomic nervous system reflexes and alter cardiac frequency and function[20, 21]. Although cardiovascular diseases significantly worsen by work were not revealed in this study, the prevalence of arrhythmia and angina were significantly higher in nanomaterials handling workers than in the controls (Table 5). Also, the incidence as well as the incidence plus worsened by work for angina was higher in exposed workers than in controls (p=0.06) (Appendix 3). Our previous study has shown increased expression of blood coagulation markers (i.e. fibrinogen) and vascular endothelial damage marker (i.e. intercellular adhesion molecules) among workers handling nanomaterials[11]. The association between nanomaterials exposure and cardiovascular diseases and its exact mechanism need further investigation.

While interaction between nanoparticles and the immune system has been demonstrated, the details of this interaction are limited. Certain nanoparticles have been shown to accumulate in regional lymph nodes, where nanoparticles can be taken up and processed by dendritic cells, interact with self-proteins and, hence, modify their antigenicity and elicit altered immune responses and even autoimmunity[26]. Some nanoparticles have also been found to induce allergic sensitization, for example, allergic contact dermatitis induced by palladium[26]. These findings suggested that nanoparticles acted as adjuvants and induce specific patterns of cytokines, antibodies, and cells that favored allergic sensitization to environmental allergens, but nanoparticles unlikely acted as haptens, inducing specific immunoglobulin E production[26]. In addition, the immunotoxicity of both airborne and engineered nanoparticles may act as exacerbating factors in hypersusceptible subjects[27]. Our findings that allergic dermatitis being worsened by nanomaterials handling work but not being significantly increased in nanomaterials handling workers were consistent with the above-mentioned findings. A review article concluded that further mechanistic studies were required to improve our understanding of the physicochemical parameters of nanoparticles and their effects on the immune system[28].

There are several limitations to this epidemiologic study. First, the significant findings found in this study

may be due to chance or by random. Second, self-reported questionnaire cannot avoid misclassification and overestimation of health hazards. Third, the heterogeneity of nanomaterials made it difficult to find a sufficiently large group of workers exposed to the same particles to represent potential health effects of any individual nanomaterial. Fourth, validation of the control banding tools for nanomaterials exposure needs to be clarified[13]. Four of the five operations evaluated in that study were found to have implemented controls consistent with what was recommended by the Control Banding Nanotool[13]. The CB Nano Tool outcomes have been also compared with occupational hygienists' evaluations and showed a good agreement[14]. By developing this dynamic Control Banding Nanotool within the realm of the scientific information available, this application of control banding appears to be a useful approach for assessing the risk of nanomaterial operations, providing recommendations for appropriate engineering controls and facilitating the allocation of resources to the activities that most need them[13].

Until recently, information regarding the health hazards of nanoparticles has been lacking. In order to prevent the hazards of handling nanomaterials, the introduction of strict preventive measures, such as local ventilation and personal protective equipment, is currently the only way to prevent any risk of occupational disease in workers who handle nanomaterials. Periodic health examinations of workers handling nanomaterials, allergic diseases such as allergic dermatitis and angina as well as cardiopulmonary symptoms such as sneezing and cough may be used as screening tool. However, most of the symptoms identified in this study are not specific for nanoparticle exposure. A more sophisticated study design is needed to validate the sensitivity and specificity of these symptoms used for screening.

Conclusions

Sneezing and allergic dermatitis were significantly increased in engineered nanomaterials handling workers. In addition to allergic diseases, cardiopulmonary symptoms such as cough and angina may be used as screening tools for medical surveillance of people handling engineered nanomaterials.

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Appendix 1. Example of risk level calculation

A male staff worked in a light emission device (LED) company for 3 years. The main nanomaterial used is carbon nanotubes (CNT). The particle size of CNT is 20nm. He handled the CNT once a week, and about 1.5 hours weekly. The total amount of CNT used per week is about 15mg. He has 3 co-workers. He reported that little CNT leaks into the workplace during his works.

What is the risk level of this staff?

- **Severity score is based on the type of handled nanomaterial, CNT.**
- **Probability score is based on the dustiness of workplace and the frequency of handling nanomaterials.**

Severity Factors considered in the calculation of severity score

⦿ Nanomaterial: 70% of Severity Score

1. Surface Chemistry (10 pts)
2. Particle Shape (10 pts)
3. Particle Diameter (10 pts)
4. Solubility (10 pts)
5. Carcinogenicity (6 pts)
6. Reproductive Toxicity (6 pts)
7. Mutagenicity (6 pts)
8. Dermal Toxicity (6 pts)
9. Asthmagen (6 pts)

◎ Parent Material: 30% of Severity Score

10. Occupational Exposure Limit (10 pts)
11. Carcinogenicity (4 pts)
12. Reproductive Toxicity (4 pts)
13. Mutagenicity (4 pts)
14. Dermal Toxicity (4 pts)
15. Asthmagen (4 pts)

(Maximum points indicated in parentheses)

I. Score for Severity of nanomaterials

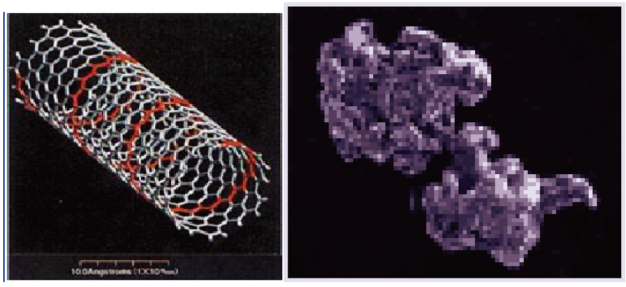
1. Surface Chemistry (nanomaterial)

Particle surface free radical activity

- Surface Chemistry (10 pts)
- Ability to generate reactive oxygen species, oxidative stress responses
- Toxicological studies – Bronchoalveolar lavage fluid collected from rodents: analyzed for markers of inflammation, lung tissue damage, antioxidant status, etc.
- Auger spectroscopy

High: 10 pts Medium: 5 pts Low: 0 pts Unknown: 7.5 pts

2. Particle Shape (nanomaterial)



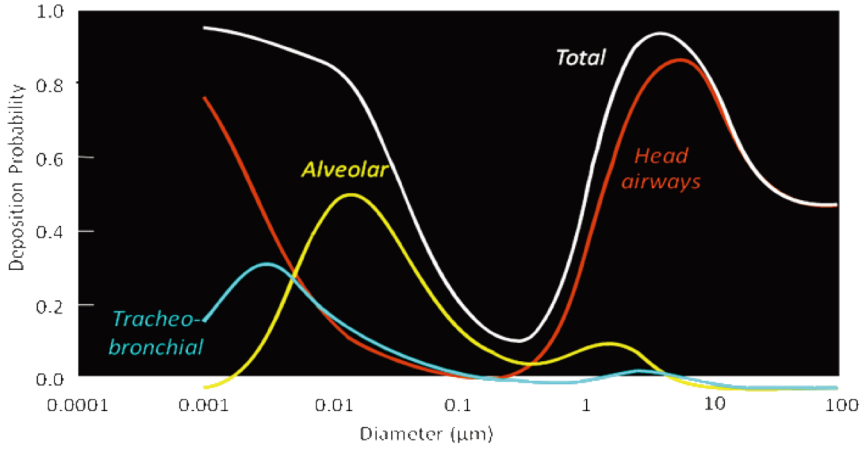
Tubular/fibrous: high aspect ratio particles (e.g., carbon nanotubes)

Irregular shapes: generally more surface area than compact (e.g., iron powders)

Tubular/fibrous: 10 pts Anisotropic: 5 pts Compact/spherical: 0 pts

Unknown: 7.5 pts

3. Particle Diameter (nanomaterial)



1–10 nm: 10 pts 11–40 nm: 5 pts >41 nm: 0 pts Unknown: 7.5 pts

ICRP (1994) model: adult, nose breathing, at rest. Courtesy of CDC-NIOSH.

4. Solubility (nanomaterial)

Insoluble particles

- Titanium dioxide, PTFE, $BaSO_4$
- Causes inflammatory response
- May penetrate skin, may translocate into brain

Soluble particles

- Potential systemic effects through absorption into blood

Insoluble: 10 pts Soluble: 5 pts Unknown: 7.5 pts

Other Toxicological Effects (nanomaterial)

5. Carcinogenicity

– e.g., Titanium dioxide (IARC Group 2B potential carcinogen)

Yes: 6 pts No: 0 pts Unknown: 4.5 pts

6. Reproductive toxicity – mostly unknown

Yes: 6 pts No: 0 pts Unknown: 4.5 pts

7. Mutagenicity – mostly unknown

Yes: 6 pts No: 0 pts Unknown: 4.5 pts

8. Dermal toxicity – mostly unknown

– Either cutaneous or through skin absorption

Yes: 6 pts No: 0 pts Unknown: 4.5 pts

9. Asthmagen – mostly unknown

Yes: 6 pts No: 0 pts Unknown: 4.5 pts

MOST TOXICOLOGICAL DATA PERTAINING TO NANOSCALE IS UNKNOWN

II. Score for Severity Factors of Parent Material

Toxicological properties of parent material may provide insight into nanomaterial toxicity

– 30% of total severity score is based on parent material characteristics

10. Bulk hazard (Parent material)

– Is there an established occupational exposure limit?

<10 μg/m^3: 10 pts 10–100 μg/m^3 : 5 pts 101–1000 μg/m^3 : 2.5 pts
>1 mg/m^3: 0 pts Unknown: 7.5 pts

11. Carcinogenicity

Yes: 4 pts No: 0 pts Unknown: 3 pts

12. Reproductive toxicity

Yes: 4 pts No: 0 pts Unknown: 3 pts

13. Mutagenicity

Yes: 4 pts No: 0 pts Unknown: 3 pts

14. Dermal toxicity

– Either cutaneous or through skin absorption

Yes: 4 pts No: 0 pts Unknown: 3 pts

Severity Factors and scores -- For example : CNT

Variables/scores	10 pts	7.5 pts	6 pts	5 pts	4.5 pts	4 pts	3 pts	2.5 pts	0 pts
Nanomaterial									
Surface chemistry [1]	High	Unknown	---	Medium	---		---		Low
Particle Shape [2]	Tubular / fibrous	Unknown	---	Anisotropic	---		---		Compact/spherical
Particle Diameter [2]	1-10nm	Unknown	---	11-40nm	---		---		>41nm
Solubility [2]	insoluble	Unknown	---	soluble	---		---		---
Carcinogenicity [2]	---	---	yes	---	Unknown		---		No
Reproductive Toxicity [2]	---	---	yes	---	Unknown		---		No
Mutagenicity [2]	---	---	yes	---	Unknown		---		No
Dermal Toxicity [2]	---	---	yes	---	Unknown		---		No
Asthmagen [2]	---	---	yes	---	Unknown		---		No
Parent Material									
Occupational exposure limit [3]	<10 μ g/m^3	Unknown	---	10-100 μ g/m^3	---		---	101-1000 μ g/m^3	---
Carcinogenicity [4]	---	---	---	---		yes	Unknown	---	No
Reproductive Toxicity [4]	---	---	---	---		yes	Unknown	---	No
Mutagenicity [4]	---	---	---	---		yes	Unknown	---	No
Dermal Toxicity [4]	---	---	---	---		yes	Unknown	---	No

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4.Permissible exposure limits-Taiwan IOSH

Severity score=38

III. Probability Factors considered in the calculation of probability score

- Pertain to probability of exposure, irrespective of toxicological effects

1. Estimated amount of material used

>100 mg: 25 pts 11–100 mg: 12.5 pts 0–10 mg: 6.25 pts Unknown: 18.75 pts

2. Dustiness/mistiness

High: 30 pts Medium: 15 pts Low: 7.5 pts None: 0 pts Unknown: 22.5 pts

3. Number of employees with similar exposure

>15: 15 pts 11–15: 10 pts 6–10: 5 pts 1–5: 0 pts Unknown: 11.25 pts

4. Frequency of operation

Daily: 15 pts Weekly: 10 pts Monthly: 5 pts Less than monthly: 0 pts

5. Duration of operation

>4 h: 15 pts 1–4 h: 10 pts 30–60: 5 pts <30 min: 0 pts Unknown: 11.25 pts

Probability Scores---For example : CNT

Variables/scores	30 pts	25 pts	22.5 pts	18.75 pts	15 pts	12.5 pts	11.25 pts	10 pts	7.5 pts	6.25 pts	5 pts	0 pts
Estimated amount of material used	---	>100 mg	---	Unknown	---	11-100mg	---	---	---	0-10mg	---	---
Dustiness/mistiness	High	---	Unknown	---	Medium	---	---	---	Low	---	---	None
Number of employees with similar exposure	---	---	---	---	>15	---	Unknown	11-15	---	---	6-10	1-5
Frequency of operation	---	---	---	---	Daily	---	---	Weekly	---	---	Monthly	Less than monthly
Duration of operation	---	---	---	---	>4hrs	---	Unknown	1-4hrs	---	---	30-60min	<30min

Probability score=40

Conclusion: this staff is classified as Risk Level 1 by Control Banding

Probability

Severity

	Extremely Unlikely (0-25)	Less Likely (26-50)	Likely (51-75)	Probable (76-100)
Very High (76-100)	RL 3	RL 3	RL 4	RL 4
High (51-75)	RL 2	RL 2	RL 3	RL 4
Medium (26-50)	RL 1	RL 1	RL 2	RL 3
Low (0-25)	RL 1	RL 1	RL 1	RL 2

Control Banding Approach to Safe Handing of Nanopaeticles.Samuel Paik.EH&S Challenges of the Nanotechnology Revolution.2009. 13

Appendix 2. Self-reporting work-related dermatological and neurological symptoms developed after employed in nanomaterials handling plants stratified by risk levels (Table A1)

Variables	Prevalence							Self-reporting work-related						
	Control (n=200)		Risk Level 1 (n=139)		Risk Level 2 (n=119)		*p*-value*	Control (n=200)		Risk Level 1 (n=139)		Risk Level 2 (n=119)		*p*-value*
	n	(%)	n	(%)	n	(%)		n	%	n	%	n	%	
Dermatological symptoms														
Itching	34	17.26%	27	19.42%	26	21.85%	0.60	10	5.00%	8	5.76%	13	10.92%	0.11
Red swelling	11	5.58%	10	7.19%	7	5.88%	0.82	4	2.00%	4	2.88%	6	5.04%	0.31
Papule	4	2.03%	1	0.72%	3	2.52%	0.51	3	1.50%	1	0.72%	1	0.84%	0.76
Loss of hair	28	14.14%	17	12.23%	14	11.76%	0.79	7	3.50%	9	6.47%	4	3.36%	0.35
Neurological symptoms														
Dizziness	25	12.56%	18	12.95%	20	16.81%	0.54	8	4.00%	11	7.91%	11	9.24%	0.14
Headache	35	17.59%	23	16.67%	27	22.69%	0.41	12	6.00%	11	7.91%	9	7.56%	0.76
Fatigue	60	30.15%	41	29.71%	39	32.77%	0.85	34	17.00%	23	16.55%	23	19.33%	0.82
Anxiety	39	19.80%	18	12.95%	21	17.65%	0.26	24	12.00%	13	9.35%	12	10.08%	0.72
Loss of memory	46	23.12%	34	24.46%	27	22.69%	0.94	12	6.00%	8	5.76%	10	8.40%	0.63
Insomnia	26	13.13%	18	12.95%	12	10.08%	0.70	18	9.00%	9	6.47%	5	4.20%	0.26
Nightmare	8	4.02%	11	7.97%	4	3.36%	0.16	2	1.00%	6	4.32%	3	2.52%	0.15
Night sweating	3	1.51%	4	2.90%	2	1.68%	0.64	2	1.00%	3	2.16%	1	0.84%	0.57

*χ^2 *p*-value

Appendix 3. The incidence of respiratory, cardiovascular and skin diseases or incidence plus worsened by nanomaterials handling work stratified by risk levels (Table A2)

Variables	Incidence							Incidence + worsened by work						
	Control (n=200)		Risk Level 1 (n=139)		Risk Level 2 (n=119)		*p*-value*	Control (n=200)		Risk Level 1 (n=139)		Risk Level 2 (n=119)		*p*-value*
	n	(%)	n	(%)	n	(%)		n	(%)	n	(%)	n	(%)	
Respiratory Diseases														
Chronic Bronchitis	4	2.01%	2	1.45%	1	0.84%	0.71	4	2.01%	5	3.62%	3	2.52%	0.66
Emphysema	0	0.00%	0	0.00%	0	0.00%	.	0	0.00%	0	0.00%	0	0.00%	.
Asthma	0	0.00%	0	0.00%	0	0.00%	.	0	0.00%	1	0.72%	1	0.84%	0.46
Tuberculosis	0	0.00%	0	0.00%	0	0.00%	.	0	0.00%	0	0.00%	0	0.00%	.
Lung cancer	1	0.51%	0	0.00%	0	0.00%	0.52	1	0.51%	0	0.00%	0	0.00%	0.52
Rhinitis	11	5.56%	6	4.32%	2	1.68%	0.25	12	6.06%	11	7.91%	4	3.36%	0.30
Cardiovascular diseases														
Stroke	0	0.00%	0	0.00%	0	0.00%	.	0	0.00%	0	0.00%	0	0.00%	.
Arrhythmia	2	1.01%	2	1.44%	3	2.52%	0.56	2	1.01%	2	1.44%	4	3.36%	0.28
Ischemic heart dis	0	0.00%	0	0.00%	0	0.00%	.	0	0.00%	0	0.00%	0	0.00%	.
Angina	0	0.00%	0	0.00%	2	1.68%	0.06	0	0.00%	0	0.00%	2	1.68%	0.06
Valve heart dis.	1	0.51%	1	0.72%	1	0.84%	0.93	1	0.51%	1	0.72%	1	0.84%	0.93
Hyperlipidemia	9	4.55%	6	4.32%	5	4.20%	0.99	10	5.05%	7	5.04%	6	5.04%	1.00
Hypertension	7	3.55%	5	3.60%	8	6.72%	0.35	9	4.57%	7	5.04%	8	6.72%	0.70
Skin Diseases														
Atopic dermatitis	4	2.01%	4	2.88%	3	2.52%	0.87	4	2.01%	5	3.60%	4	3.36%	0.64
Allergic dermatitis	10	5.03%	6	4.32%	8	6.72%	0.68	11	5.53%	6	4.32%	13	10.92%	0.07
Pigmentation	1	0.50%	1	0.72%	3	2.52%	0.22	1	0.50%	1	0.72%	3	2.52%	0.22
Skin cancer	0	0.00%	1	0.72%	0	0.00%	0.32	0	0.00%	1	0.72%	0	0.00%	0.32
Folliculitis	4	2.01%	3	2.16%	3	2.52%	0.96	4	2.01%	3	2.16%	4	3.36%	0.73

*χ^2 *p*-value